Textbook of Traditional Japanese Medicine

Part 1 : Kampo

Health and Labour Sciences Research Grant
Research on the standardization of traditional Japanese medicine
promoting integrated medicine

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Standardization of Traditional Japanese Medicine for the Promotion of Integrated Medical Practice
- Traditional Japanese Medicine Textbook Project -
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Foreword

In September 1978, a declaration on primary health care (PHC) was adopted in Alma-Ata in Kazakhstan (then part of the Soviet Union) under the guidance of the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF). This is known as the Alma-Ata Declaration. PHC is defined as 'essential health care based on practical, scientifically sound and socially acceptable methods and technology.' Article VII of the Declaration states that PHC relies 'at local and referral levels, on health workers, including physicians, nurses, midwives, auxiliaries and community workers as applicable, as well as traditional practitioners as needed, suitably trained socially and technically to work as a health team and to respond to the expressed health needs of the community.' Roughly three decades later at the 56th World Health Assembly held in Geneva in 2003, the 192 participating countries and regions recommended that traditional methods of healthcare should be integrated into governmental public health systems and its harmonization with contemporary Western Medicine should be promoted. Thanks to this, Traditional Medicine spread rapidly over recent decades and its presence has become recognized. The significance of this change is important. Traditional Medicine is a comprehensive system of healthcare with its own theoretical basis and practical experience as determined by specific regional circumstances (indigenous culture, climate, natural resources, etc.). It includes Herbal Medicine, Acupuncture, and other non-drug therapies.

In this context, the profile of Traditional Medicine is rapidly rising globally and attracting interest and demand as a form of medicine that is useful and free of adverse effects. The standardization of the theoretical framework, terminology, and other aspects of Traditional Medicine has become a matter of urgency. It was 1965 when WHO took the lead in proposing the standardization of the locations and names of acupuncture points. In 1991, Standard International Acupuncture Nomenclature was adopted by the WHO in Geneva. Work on the standardization of Traditional Medicine has since spread globally. Japan, on its part, has embarked on several projects starting in 2004 in cooperation with the WHO West Pacific Regional Office. Our focus is on "standardization based on an evidence-based approach" and our aim is to promote the appropriate utilization of Traditional Medicine.

Because standards in Traditional Medicine are diverse (i.e., the position of acupuncture points, information about them, and actual clinical practice vary), the development of an internationally standardized system of terminology was the first step towards the overall standardization of Traditional Medicine. The Japanese Traditional Medicine community cooperated in the publication of WHO/WPRO's "*WHO International Standard Terminologies on Traditional Medicine in the Western Pacific Region* (IST)" in 2007 and of the "*Standard Acupuncture Point Locations in the Western Pacific Region*" in 2008. Based on the experience gained from such international collaboration, we have learned that the terminology of Traditional Medicine belonging to other nations should be derived from reference documents of the respective nations: it

is not for us to judge or refute. The Japanese healthcare system was overhauled in the Meiji Era, when all physicians were made to learn Western medicine and pass national examinations in order to qualify as practitioners. To practice Traditional Medicine, would-be practitioners were required to study Western Medicine before Kampo Medicine. The result was that Japan became unique among developed nations in being the only country to practice Western Medicine and Traditional Medicine simultaneously within the same healthcare system. What sets medicine in Japan apart from Traditional Chinese Medicine or Traditional Korean Medicine is that practitioners of Western Medicine in Japan, which meets the world's highest standards, also practice Kampo Medicine.

Since 1976, many Kampo formulations have been added to the government health insurance reimbursement list in Japan. About 80% of physicians are said to be using Kampo medicines. Kampo Medicine, which forms the core of Traditional Japanese Medicine, has been put to use and has contributed greatly to the health of the nation. Japan is the only county that can investigate Kampo Medicine from the vantage points of both Kampo Medicine and contemporary Western Medicine, in other words from the perspective of both Western Medicine and Oriental Medicine, and that can disseminate information not only within Japan but to the the outside world while upholding the uniqueness, usefulness, and diversity of Kampo Medicine.

The standardization of Kampo terminology is an important task that encompasses all aspects of education, research, and clinical practice. What is more, one of its significant roles is to upgrade the quality, safety, reliability, efficiency, and compatibility, which are the most important aspects of medicine and needless to say, of Traditional Medicine also. We believe we can make great contributions internationally by forming a Standard Textbook Committee to implement and complete the actions listed below and fulfill the purpose of our research project, which is the compilation of a standard textbook on Traditional Japanese Medicine. These actions are: 1. Writing standard textbooks on Traditional Japanese Medicine, including Acupuncture, and Kampo medicines and crude drugs; 2. Fact-finding with a focus on local community healthcare; 3. Standardization of Traditional Medicine internationally. There will also be benefits within Japan. Kampo will be given a sound footing within the medical school curriculum. We may expect to see questions about Kampo on the National Medical Licensing Examination. For this to happen, efforts to standardize Traditional Japanese Medicine is of great import, including the compilation of standard textbooks, textbooks for medical students, and guidelines for the training of pedagogical staff.

The Japan Society for Oriental Medicine (JSOM) was founded in 1950 to support education, research, and the clinical practice of traditional medicine. It has engaged in many activities resulting in many publications. JSOM has published handbooks on the terminology of traditional medicine including "*Toyo Igaku Yogoshu I* (*Glossary of Oriental Medicine I*)" in 1969, "*Toyo Igaku Yogoshu II* (*Glossary of Oriental Medicine II*)" in 1980, and "*Toyo Igaku Yogoshu* (*Glossary of Oriental Medicine*)" in 1999. For clinical practitioners, JSOM published "*Kampo Hoken Shinryo Shishin* (*Guidelines for Kampo Treatment under the National Health Insurance System*)" in 1986 and "*Kampo Hoken Shinryo Handobukku* (*Handbook on Kampo Treatment under the National Health Insurance System*)" in 1994. JSOM published the following standard textbooks: "*Nyumon Kampo Igaku*" in 2002 and its English version "*Introduction to KAMPO Japanese Traditional Medicine*" in 2005, "*Gakusei no tameno Kampo Igaku Tekisuto* (*Student Textbook on Kampo Medicine*)" in 2007, and "*Senmon-I no tameno Kampo Igaku Tekisuto: Senmon-I Kenshu Curriculum Junkyo*

(*Kampo Medicine Textbook for Specialists: Specialist Training Curriculum Reference*)" in 2010.

What was essential for our standardization project on Traditional Medicine was that not only JSOM, but many other organizations concerned with the project had to cooperate and participate by setting up working groups and liaison councils to deal appropriately with the status of Traditional Medicine in Japan and internationally. The members naturally have to be representatives of all participating organizations. Because of this, the standardization of Traditional Japanese Medicine will require creation of an academic platform. The working groups focusing on three domains (Kampo, Acupuncture/Moxibustion, and Pharmacy) will need to work together. The terminology will be from the Kampo publications of the JSOM mentioned above. For Acupuncture and Moxibustion, terminology from the Japan College Association of Oriental Medicine's "*Shinkyu Riron* (*Theory of Acupuncture and Moxibustion*)" and "*Toyo Igaku Gairon* (*Outline of Oriental Medicine*)" will provide the backbone. We need to ensure that terms used in both the Kampo and Acupuncture/Moxibustion domains are consistent.

Surveying the trends in traditional medicine around the world has alerted us to the threat of chaos in the healthcare system in Japan and its attendant threat to the health of the nation. We must prevent and circumvent such chaos. Also, in the context of the re-evaluation of integrative medicine by the West, Japan must dedicate its energy to safeguarding its own independent Traditional Medicine.

What lies at the heart of Traditional Medicine will not be changed by time or schools of practice. However, medicine and medical care must develop in line with advances in science and technology. Only then can the tradition be kept alive. More than thirty years have passed since the introduction of Kampo formulations for medical use into our world-class national health insurance system. At this juncture, it is meaningful internationally to standardize the terminology of Traditional Medicine so that it can be comprehended from the standpoints of Oriental and Western Medicine. This is truly what the Kampo community in Japan had long desired and attempted to achieve. In terms of education in Traditional Medicine, teaching now begins at the undergraduate level 'to be able to outline Wakan-yaku (Kampo medicine)' and 'to study chemistry-based pharmacy: naturally produced medicines' (i.e., the Medical and Pharmacy Education Model Core Curriculum). In the medical specialist system, the Kampo specialist is now an established category. Training in acupuncture/moxibustion is improving in colleges and universities. Various organizations have been actively pursuing education and research. These are all achievements that we must recognize and endorse.

The Traditional Medicine community in Japan has overcome numerous obstacles in its path. We look to the future with the publication of this textbook, which we hope will assist in serving the health of the Japanese people.

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Contents

Explanatory Notes

○Since the following books are mentioned throughout this text, they are not cited in the main text.

- The Japan Society for Oriental Medicine (ed). Senmon'i no tameno Kampo Tekisuto (Kampo Medicine Textbook for Specialists). Tokyo: Nankodo. 2010
- The Japan Society for Oriental Medicine Home Page pertaining to Evidence Based Medicine
  URL: http://www.jsom.or.jp/medical/ebm/ere/index.html

○Since standard Kampo terminology is now under discussion by a task force of the World Health Organization International Classification of Traditional Medicine (WHO-ICTM), some Kampo terms are tentatively transcribed into Roman letters (e.g., 'Yin' and 'Yo' for '陰陽', qi [Ki] for '気', and '*Kyokyo Kuman* [hypochondrium resistance and discomfort]' for '胸脇苦満').

○Section 4 "Therapy Details" basically describes ethical Kampo preparations in the Drug Tariff, and (*) depicts Kampo preparations not available as ethical Kampo preparations (explanatory note indicated at the end of the section).

○ Flow charts used in the "Therapy Details" section are reproduced from the reference given below:

- Cyong JC, Kikutani T. How to prescribe Kampo formulations (covered by health insurance). In: Yamaguchi T, et al (eds). Today's Therapy (2010). Tokyo: Igakushoin. pp. 1394–1404, 2010

Chapter 1

History of Kampo

Diversity in Japanese Kampo Medicine and Japanizationfrom a Perspective of Medical History

Hiroshi Kosoto (revised by Makoto Arai)

What is ‘Kampo medicine’?

Kampo medicine has a long history. Traditional medicine originating in ancient China spread from the Korean Peninsula to Japan and other East Asian countries, resulting in peculiar developments.

‘Kam’ of ‘Kampo’ means ‘China.’ Primarily the Kanji, or Chinese character, ‘*Kam*/*Kan* (漢)’ (Han in Chinese) is the name of dynasty or era (the Former Han dynasty [202 BC–9 AD] and the Later Han dynasty [25–220]). Since ancient times, Japanese people have used ‘*Kam*’ as a pronoun of China, and also used ‘*To* (唐)’ (Tang in Chinese) as another pronoun of China. Furthermore, to express things Chinese, Japanese people used to employ the Kanji ‘*Kam*/*Kan*’ or ‘*To*’, and the Kanji ‘*Wa* (和, 倭)’ or ‘*Koku* (国)’ to express things Japanese. Examples are ‘*Kanji* (漢字, Chinese character)’ versus ‘*Kokuji* (国字, Japan-originated Kanji character),’ ‘*Kambun* (漢文, Chinese literary)’ versus ‘*Kokubun* (国文, Japanese literary)’ or ‘*Wabun* (和文),’ ‘*Kango* (漢語, Chinese language)’ versus ‘*Kokugo* (国語, Japanese language)’ or ‘*Wago* (和語),’ and ‘*Kanseki* (漢籍, Chinese books)’ versus ‘*Kokusho* (国書, Japanese books).’ Kampo is not exceptional, and is used versus ‘*Waho* (和方, traditional Japanese folk medicine)’ and ‘*Rampo* (蘭方, the Western medicine).’

What is ‘*Ho/Po* (方)’? ‘*Ho/Po*’ means a means, measure(s), method(s), or skill(s) and may refer to ‘*Hogi* (方技),’ ‘*Hojutsu* (方術)’ and ‘*Iho* (医方).’

Many occupations require special skills. Among them, medicine has been thought to need the highest skills and techniques, because it treats human life. Accordingly, ‘*Hogi*’ and ‘*Hojutsu*’ have been used as the words to specifically refer to medical techniques since the ancient China (in the Han dynasty). In "*HanShu YiWenZhi* (漢書芸文志)," ‘*Hogi*’ is used as a generic name of medical books, divided into four categories: *Ikei*, *Keiho, Bochu*, and *Shinsen* (医経・経方・房中・神仙) mean general medical doctrine, herbal treatment book/formulary, sexual practice manual, and books about the pursuit of immortality, respectively. In “*HanShu PingDiJi* (漢書平帝紀), the words ‘*Shihen*, *Hojutsu*, and *Honzo* (史篇・方術・本草)’ appear. “*HouHanShu* (後漢書)” contains the history of medical techniques and physicians, *Hojutsuden*, or ‘*FanShuChuan* (方術伝).’ ‘*Hojutsu*’ or ‘*Hogi* (方技)’ includes acupuncture and moxibustion. The most famous medical text, however, is “*HuangDiNeiJing* (黄帝内経)”.

The word ‘*Iho*’ often appears and includes acupuncture and moxibustion in books following the historical book “*Shiji* (史記),”which particularly refers to secret medical techniques as ‘*Kimpo* (禁方) (*XiaoWuJi –BianCangYun* [孝武紀・扁倉伝]).

Thus, ‘*Kampo* (漢方)’ means Han medical techniques expressed as ‘*Kampogi* (漢方技),’ ‘*Kampojutsu* (漢方術),’ or ‘*Kan’iho* (漢医方)’, and is a synonym for ‘Chinese medical techniques,’ as is understood. More accurately, Kampo is the term referred to by Japanese for the medical techniques introduced from China. As far as I know, the term ‘*Kampo*’ was first used in a book authored by Sohaku Asada around the end of the

Edo period (1603-1868) or the early Meiji period (1868-1912). He seems to have employed '*Kampo*' as *Koho*, namely *Chochukei-ho*, which means medical care principles conducted by *Zhang Zhongjing* (張仲景, *Chochukei* in Japanese). Some people believe Kampo is limited to pharmacotherapy because '*Ho*' reminds them of '*Hozai* (方剤)' or '*Hoyaku* (方薬) (both formulation[s]).' In fact, however, it should be emphasized that '*Ho*' primarily means 'medicine.'

In China, it was not necessary that they call their own medicine '*Kampo*.' Rather, since the introduction of Western medicine, their own medicine has been called '*GuoYi* (国医) and after the establishment of People's Republic of China, '*ZhongYiXie* (中医学),' the abbreviation of '*ZhongGuoYiXue* (中国医学)' has been and is adopted. Given these circumstances, japanized traditional Chinese medicine can be called 'Kampo medicine.'

Some people maintain that Japanese Kampo medicine was established in the early stage of Showa period (1926–1989) and should be limited to the Koho school advocating 'formula versus pattern (*Hoshosotai*)' adhered to "*ShangHanLun* (傷寒論)." However, their thoughts do not cover the entire Japanese traditional Kampo medicine so that they cannot consider its diversity. Japanese Kampo medicine ascends to "*Ishimpo* (医心方)" in the Heian period (794–1192), and had been cultivated via the Kamakura, Nambokucho, and Muromachi periods through the Edo period (from 12th to 19th centuries). Japanese Kampo medicine cannot be discussed by somebody who has never surveyed the books authored by the Japanese physicians listed in "*Kinsei Kampo Igakusho Shusei* (近世漢方医学書集成)" (chiefly compiled by Keisetsu Otsuka and Domei Yakazu in 1979–1984). The compilation itself is the message of the recent pioneers who established Showa Kampo medicine.

Traditional medicine in China

Traditional medicine in China has an about 3,000-year history, which is twice as long as that in Japan.

In China, its intrinsic medicine began to be formed under accumulated vast experience and knowledge in the ancient China (i.e. Yin and Zhou dynasties, and through the Chunqiu and Zhanguo periods). The process of formation in the pre-Qin period can be imaged from classics written in ancient Chinese (inscriptions on bone and tortoise shell) including "*ZhouLi* (周礼)," "*LuShiChunQiu* (呂氏春秋)," "*HuaiNanZi* (淮南子)," "*ShiJi BianQueCangGongYun* (史記扁鵲倉公伝)," and "*HanShuYiWenZhi*" and from newly excavated medical history-related materials such as *ChangSha MaWangDui* Han Tomb (長沙馬王堆漢墓).

In the Han dynasty (206 BC), Chinese medicine was systematized and consolidated. Three great medical classics descending from the Han period are "*HuangDiNeiJing*," "*ShenNong BenCao Jing* (神農本草経)," and "*ShangHanLun*." These are still most highly appreciated as fundamental textbooks of Kampo medicine in Japan as well as in China. The source of Kampo medicine is in these classics. In other words, we cannot understand Kampo medicine without understanding these classics. Accordingly, a large number of books for annotation and research on "*HuangDiNeijing*," "*ShangHanLun*," and *BenCao* (本草, *Honzo*; Chinese materia medica; mainly *BenCaoGangMu* [本草綱目] after the early modern period) have been published in Japan as well.

"HuangDiNeiJing"

This is also known as '*Ikei* (医経),' a medical book that describes general doctrines of medicine and physiotherapies (acupuncture and moxibustion). This corpus that collects medical literatures written or spoken in the Chunqiu and Zhanguo periods (from the 8th to 3rd centuries BC) consists of two texts: "*SuWen* (素問)" and "*LingShu* (霊枢)." The former focuses on basic theories while the latter deals with clinical medicine, although there is a consistent philosophical doctrine through the two texts, China-specific YinYo and five-element doctrine (陰陽五行論). There is no need to explain the YinYo theory in detail. In the medical field, however, Yin and Yo are assigned to deficiency and excess; cold and heat; interior and exterior; chronic and acute; solid and hollow viscera, respectively. Based on the assignment, physiology and pathology are explained. In the five-element doctrine, five major elements of the universe (wood, fire, earth, metal, and water) are assigned to five solid viscera (liver [TM], heart [TM], spleen [TM], lung [TM], and kidney [TM]), five hollow viscera (gallbladder, small intestine, stomach, large intestine, and bladder), five sense organs (eye, tongue, lip, nose, and ear), five tissues (muscle, blood vessel, skin, hair, and bone), five emotions (anger, joy, thought, anxiety, and fear), and five tastes (sourness, bitterness, sweetness, pungency, and saltiness). Each set of five follows the principles of five elements in the way of productive/engendering (相生, *Sojo*) (wood→fire→earth→metal→water→wood) and conflicting/restraining (相剋, *Sokoku*) relationships (wood←metal←water←fire←metal←wood) to keep physiological functions. The well-balanced status is regarded as healthy, whereas the imbalanced status due to a pathogen or disturbed qi (Ki) is a disease. Accordingly, diagnosis is to determine which region and how the region is imbalanced, and treatment is to restore the imbalance by means of a drug(s) and/or acupuncture/moxibustion technique(s). Based on these concepts, it is said that the merits of Kampo medicine comprise viewing the whole, not a local or regional site, and thereby aiming on the restoration of spontaneous healing capability rather than attacking and eliminating the pathogen and/or lesion.

"ShenNongBenCaoJing"

This is a book of pharmacology/pharmacognosy, the source of so-called *BenCao*, that describes individual Kampo formulae and their effects as well as characteristics. *ShenNong* (神農, God of Agriculture) is one of the three legendary emperors (along with *HuangDi* [黄帝] and *FuXi* [伏羲].) and has been called the father of Chinese medicine (医薬神祖). The book contains a total of 365 entries of animal, plant, and mineral crude drugs divided in three classes: the top (上品, *johon*), medium (中品, *chuhon*), and low (下品, *gehon*) grades. This is referred to as the three-grade classification of *BenCao.* The top grade (also called 上薬, *joyaku*) crude drugs are life-nourishing medicines (養命薬) that are non-toxic and should be taken for a long-term period. The medium grade crude drugs are medicines nourishing physical strength (養性薬) that are toxic or non-toxic and therefore should be taken carefully. The top grade crude drugs are therapeutic medicines (治病薬) and that are toxic and thus should not be taken for a long-term period. These are the basic rules for medication. The concept of drugs in Western medicine corresponds to the low grade. The *BenCao* medicines are in a broader range of concept than Western drugs. The fundamental principles for use are that health should be kept with intake of the top or medium grade medicines, whereas taking the low grade medicines is a last resort not so favorable. In addition, another characteristic feature of Chinese traditional *BenCao* is valuing their combination. For composition of a formula, component crude drugs are selected according to a certain

rule of proportion, as each drug has a specific role (sovereign [君, top grade medicines exhibiting the main efficacy of the formula], minister [臣, medium grade medicines assisting the sovereign drug], assistant [佐, low grade medicines assisting the subject drug(s) or suppressing adverse/side effects of the formula], or courier [使, low grade medicines suppressing or neutralizing adverse/side effects of the formula]). There are also combination principles in which combination of two crude drugs (A and B) alter efficacy in a way that cause seven emotions (七情, s*hichijo*): single use of A or B [単行, *tanko*], mutual support between A and B [相須, *sosu*], B assisting A [相使, *soshi*], mutual repulsion between A and B [相反, *sohan*], A repulsing B [相悪, *soaku*], mutual killing [相殺, *sosatsu*], and B neutralizing A (with remaining B efficacy) [相畏, *soi*]. *Sohan* and *Soaku* mean contraindications. Based on these concepts, it is considered that Chinese crude drugs in single use are merely materials and that actual treatment needs formulation comprising several crude drugs. Thus formulae have extensively developed in China. Crude drugs as materials were sometimes processed to modulate efficacy. The medicinal processing is referred to as *XiuZhi* (修治, *shuji*) or *PaoZhi* (炮炙, *hosha*). Furthermore, dosage form varies from pill (丸, *gan*), powder (散, *san*), decoction (湯, *to*) to alcoholic tincture (酒漬, *shuseki*), and oil decoction (膏煎, *kosen*), which were devised in formulation, depending on efficacy and usage. The drug efficacy or effects described in *BenCao* are still good references for ingredient–related and pharmacological studies in pharmacognosy. In ancient China, everything in nature may have been regarded as medicinal. Chinese pharmacology/pharmacognosy has thus gradually developed to natural history. In pharmacological books prepared in the contemporary ancient Europe, plants are classified from a natural morphological viewpoint, contrasted with a perspective of efficacy for humans in China. A comparison in plant classification between Europe and China reveals an intrinsic difference in thinking pattern between the West and Orient: non-human-oriented or human-oriented. Following the "*ShenNongBenCaoJing,*" *"MingYiBieLu* (名医別録)*"* newly listing 365 crude drugs was published as an additional *BenCao* book in the end of the Han dynasty (early 3rd century). Thereafter, "*BenCaoJingJiZhu"* (本草経集注; 730 items)" revised by *Tao Hongjing* (陶弘景) around 500 CE in the Liang dynasty, "*XinXiuBenCao* (新修本草; 830 items)" in 659 in the Tang dynasty (618-907), "*KaiBaoBenCao* (開宝本草; 984 items)" in 974, "*JiaYouBenCao* (嘉祐本草; 1,084 items)" in 1061, "*ZhengLeiBenCao* (証類本草; 1,774 items)" in 1108 in the Song dynasty (960-1279), "*BenCaoPinHuiJingYao* (本草品彙精要; 1,815 items)" in 1505, and "*BenCaoGangMu*; 1,892 items)" in 1590 in the Ming period (1368-1644) were compiled.

"ShangHanLun"

This is a book of therapeutic medicine using drug formulations, each well composed of multiple crude drugs, for various pathological conditions. The source was one book consisting of "*JinGuiYaoLue* (金匱要略)" for various diseases and "*ShangHanLun"* for cold damage disease. The author is said to be *Zhang Zhongjing* who was a sovereign of Changsha in the end of the Later Han dynasty. *ShangHan* (傷寒) means cold-damaged acute febrile disease like typhoid fever. Its pathological conditions are divided into six stages of disease progression or transformation in "*ShangHanLun*." These six stages are three Yin and three Yo stages (six-meridian disease); for each stage, appropriate formulae are set up. For example, kakkonto (葛根湯) is one of the appropriate formulations for the first stage and shosaikoto (小柴胡湯), for the third stage. Therefore, accurate differentiation of the stage of disease, or absence of diagnostic mistake, will always lead to effective formulae. This mechanism by which diagnosis is directly linked to treatment is extensively interpreted by

Japanese Kampo physicians, resulting in creation of the concept of "pattern (*Sho*)." "*Sho*" is thought to be applicable to every type of disease. This concept was the goal of Koho school, the mainstream of Japanese Kampo medicine in the late Edo period. In other words, the conception that Kampo medicine does not employ the treatment based on the name of a disease, but uses so-called *hoshosotai* or pattern-based treatment (随証治療) is derived from here.

Medieval to Modern times

Many medical books that had been authored before the Tang dynasty were principally all in the line of the three medical classics. Representative medical books in the Tang dynasty included "*QianJinFang* (千金方)" by *Sun Simiao* (孫思邈) in 650–660 and "*WaiTaiMiYaoFang* (外台秘要方)" by *Wang Tao* (王燾) in 752.

In the Song dynasty, a considerable amount of medical books and formularies were published, including "*TaiPingShengHuiFang* (太平聖恵方)" by *Wang Huaiyin* et al. in 992, "*ShengJiZongLu* (聖済総録)" compiled by imperial command in 1111 to 1118, and "*HeJiJuFang* (和剤局方)." Particularly, "*TaiPingHuiMinHeJiJufang* (太平恵民和剤局方)" authored by *Chen Shiwen* (陳師文) et al. in 1170–1210 contains the Kampo formulae being well used even today.

In the Jin and Yuan Dynasties, innovative medical theories were developed and extended by the four famous doctors from four different schools of medicine: *Liu Wansu* (劉完素 [*Liu Hejian*, 劉河間], 12 century), *Zhang Zihe* (張子和 [*Zhang Congzheng,* 張従正], 1156–1228), *Li Dongyuan* (李東垣 [*Li Gao*, 李杲], 1180–1251), and *Zhu Danxi* (朱丹溪 [*Zhu Zhengheng*, 朱震亨], 1281–1358). *Liu* created bofutsushosan (防風通聖散); *Li*, hochuekkito (補中益気湯); and *Zhu*, jiinkokato (滋陰降火湯). The Jin-Yuan medical theories were passed down from generation to generation, forming the theoretical platform of today's Chinese medicine.

Complying with the trend of Jin-Yuan medicine, many medical books were also published n the Ming and Qing Dynasties (1644-1912). The representative materia medica of the Ming dynasty is "*BenCaoGangMu*" authored by *Li Shizhen* (李時珍) in 1578, and the representative formulary is "*WanBingHuiChun* (万病回春)" which was authored by *Gong Tingxian* (龔廷賢) in 1587, and which has greatly influenced Japanese medicine. In the Qing Dynasty, a new medical theory of febrile disease theory (温病学) was developed and has supported the theoretical platform of today's Chinese medicine.

After the People's Republic of China was established via Republic of China, previous theories in traditional medicine were integrated and organized under the governmental direction, resulting in the today's theoretical system of traditional Chinese medicine. However, the system has not been completely unified but its academic level may have been lowered. Since People's Republic of China adopted script simplification policies to promote the spread of simplified Chinese characters, unfavorable effects were produced in the understanding of classics written in traditional Chinese characters. In the same way, undesirable effect may be produced in today's traditional Chinese medicine that is just simplified Chinese traditional medicine. Given that the history of culture is the history of diversification, there is a concern about the current trend toward easy unification, or globalization. Not only Western medicine but also traditional medicine is doomed to progress by trials and errors.

Development of Japanese Kampo medicine

Prior to the Nara period (710-794)

Continental medical culture was introduced into Japan in the same way as other continental cultures, mainly via the Korean Peninsula until around the sixth century. The first record of introduced medical books dates back to 562 CE, (slightly after the introduction of Buddhism), when a Chinese physician monk named *Zhi Cong* (智聡) brought "*Yakusho* (薬書, texts on medicines)," *Meidozu* (明堂図, chart of meridian points)," and others to Japan via Korea. *Meidozu* may be a diagram of acupuncture and moxibustion points in the body.

Since the 7th century, copious amounts of medical culture had become directly imported from China with the start of the formal exchange with China that was mediated by Japanese envoys to the Tang and Sui (581-618) Dynasties. The physician Enichi (恵日) and the student Fukuin (福因) played a major role in such exchanges. Eventually, the *Ritsuryo* system (律令制) was introduced and the *Taiho* Code (大宝律令) was enforced in 701 for administrative reorganization. A medical law known as the *Ishitsuryo* (医疾令) that stipulates the medical system designated as medical textbooks Chinese medical copybooks from six dynasties in the Han to Wei era (the 2nd century BC to the late 6th century AD), including "*MaiJing* (脈経)" written by *Wang Shuhe* (王叔和) in the late 3rd century, "*JiaYiJing* (甲乙経)" by *Huang Fumi* (皇甫謐) in the late 3rd century, "*BenCaoJingJiZhu," "XiaoPinFang* (小品方)" by *Chen Yanzhi* (陳延之) in the late 5th century, "*JiYanFang* (集験方)" by *Yao Sengyuan* (姚僧垣) in the 6th century, "*Suwen*," and "*ZhenJing* (針経)." This Japanese stipulation exactly follows that in the early Tang system, as the then Chinese system is imitated. The needling canon "*ZhenJing*" is the old name of "*LingShu,"* and the canon combined with *"SuWen"* composes "*HuangDiNeiJing*." "*SuWen*" plus "*LingShu"* plus "*Meido*" were integrated and recompiled into "*JiaYiJing,"* a clinical acupuncture text. "*HuangDiNeiJing*" and "*ShangHanLun*" plus other classics were integrated and recompiled into "*Maijing,"* the canon of the pulse. "*BenCaoJingJiZhu"* is revision of the "*ShenNongBenCaoJing." "XiaoPinFang" and "JiYanFang*" are formulary-focusing medical books based on the "*ShangHanLun*." Any of these books are in the line of the three great classics.

Heian period (794-1185)

In the late 8th century to 12th century, Japan-specific medical books were compiled with the elevated cultural consciousness, including "*Daido Ruijuho* (大同類聚方)" and "*Kinranho* (金蘭方)," which are said to have been selected by Hirosada Izumo in 808 and his son Minetsugu Fujiwara before 870, respectively, under the then emperor's command. But the two existent books are imitations.

Sending official envoys to the Tang dynasty was finally cancelled after 838. By that year, most of the main medical books had been imported into Japan. The inventory "*Nihonkoku Genzaisho Mokuroku* (日本国見在書目録)" (Sukeyo Fujiwara; around 898) contains 166 Han-made discrete medical books with a total of 1,309 volumes, implying a great appetite of Japanese people for Chinese medical culture.

In 984, making the best use of these introduced medical books, Yasuyori Tamba compiled "*Ishimpo*," the Japanese existent earliest medical corpus consisting of 30 volumes. The compiler was of the 8th generation offspring of naturalized Chinese. Almost all of the content consists of citations from 200 different Chinese books (some of them were from Korea). In this meaning, the Japanese medical corpus is really a Chinese medical corpus. Nevertheless, there are Japanese taste and touch in the selection of material books. Although

in China there are only classics passed down as printed copies in Song dynasty, the existent medical book is an old copy prepared soon after the creation and provides precious materials for the research of medical books originating in the six dynasties to the Sui and Tang dynasties.

Kamakura and Nanbokucho periods

In the early Kamakura period (1192-1338), medical books published in the Song Dynasties were introduced from China, the situation changed dramatically. An innovative development in printing technology was made in the Song period so that a large amount of printed, not hand-copied, medical classics after revisions became widely spread. This trend was epoch-making in terms of popularization of medical knowledge. In addition, as aforementioned, the huge medical corpuses "*TaiPingShengHuiFang*" and "*ShengJiZongLu*" as well as the government-designated formulary "*HejiJufang"* were compiled and published. In the early Southern Song period (1127-1279) as well, medical books were issued one after another. These printed books streamed in through Japan–Song trade, of which the part is evident in the descending old-edition medical books at the Kanazawa-Bunko Museum in Kanagawa Prefecture.

After the first half of the 14th century, the time of samurai worriers, new medicine-responsible persons shifted from doctors working at the imperial court to monk physicians working at Zen temples, while the main target of medical care also shifted from nobles to common people. Representative medical corpuses reflecting the features of the times include "*Ton'isho* (頓医抄; completed in 1303)" and "*Man'ampo* (万安方; completed in 1315)" authored by a monk-physician of Shozen Kajiwara and "*Fukudempo* (福田方)" by Yurin around 1363. Unlike the previous Japanese medical books that were just exactly excerpted from Chinese medical classics, "*Ton'isho*" and "*Fukudempo*" were both translated from *Kambun* to *Wabun* for easy understanding via extensive utilization of newly introduced medical books and were sprinkled with authors' unique viewpoints.

Muromachi period

Between Japan and China's Ming dynasty, Kango trade (using a tally or trading license) started in 1404 in the Muromachi period (1392-1575). Physicians who had studied for several years in Ming came home and became the leaders of the medical circle, including Shokei Takeda (in the end of the Nanbokucho period [1338-1392]), Gekko, Sanki Tashiro, Joun Saka, Akichika Nakarai, and Ian Yoshida.

The then up-to-date Ming's medicine was based on the innovative medical theory newly created in the Jin and Yuan dynasties (960-1367). In brief, Jin-Yuan medicine officially aimed at integrating the aforementioned theories of the three great medical classics, but actually resulted in opening a new window on Chinese medicine. The successors of the four famous physicians (*Liu Wansu*, *Zhang Zhangzihe*, *Li Dongyuan*, and *Zhu Danxi*) in the aforementioned Jin and Yuan periods took the initiative in respective schools characterized with therapeutic policy. Especially Li and Zhu medicine (focusing on complementing nutrition [補養]) became popular in the name of Li-Zhu medicine also in Japan.

Physicians in the educated class of the Muromachi period earnestly sought to learn and spread the new Li-Zhu medicine. In 1528 at a peak of the trend, a printed medical book was first published in Japan. The book is "*YiShuDaQuan* (医書大全)" that was compiled by *Xiong Zongli* in Ming and published there in 1446, then reprinted by Sozui Asaino (in Sakai, Japan) at his own expense. In Japan, medical books were printed and

published 500 years behind China. Furthermore 70 years later, the technique of printing with movable types was introduced from Korea, owing to troops dispatch to Korea by Hideyoshi Toyotomi. By using that technique, a great number of medical and pharmaceutical books (published mainly in the jin, Yuan, and Ming periods) were printed and widely distributed in Japan. These are so-called old type printed version. Japanese medical book-publishing culture started here.

Azuchimomoyama period

One of the skilled good physicians in the end of the Muromachi period to the Azuchimomoyama period (1575-1603) is Dosan Manase (1507–1594). He is a remarkable doctor as a contributor who established the then Chinese medicine in Japan. Dosan Manase learned medicine from Sanki Tashiro and founded a medical school named Keitekiin in Kyoto. In parallel, he consolidated and grouped medical books issued in the Song, Jin-Yuan, and Ming dynasties, then wrote many medical books, such as "*Keitekishu* (啓迪集)," to enlighten and educate medical students. His medical theory was based on Jin-Yuan medicine, especially the doctrine by *Zhu Danxi*, through Ming's medical books. Manase's medicine grounded on the YinYo and five-element doctrine and using experiential formulae flexibly was handed down to succeeding physicians, including Gensaku Manase. These followers actively adopted medical books (such as *WanBingHuiChun*) published in the later Ming period, and had flourished until the middle to end of the Edo period, via a peak in the early Edo period. This school is called Gosei school, versus Koho school that emerged later.

Gosei (Shimpo) school

There are a variety of Gosei schools, depending on adopted Chinese medical book. Among them, the most influential was *Li-Zhu* medicine, or two physicians: *Li Dongyuan* (*Li Gao*) and *Zhu Danxi* (*Zhu Zhengheng*). Gyuzan Katsuki (1656–1740), who was a Confucian physician and authored "*Gyuzanhoko* (牛山方考)," "*Gyuzankatto* (牛山活套)," "*Rojin Hitsuyo Yashinaigusa* (老人必用養草)," and others, is a typical member of the Gosei school in the middle of the Edo period. However, Gyuzan did not blindly believe Chinese medical books; he developed a theory of his own after digesting knowledge.

After Dosan Manase, Japanese Kampo medicine appears to have focused on the use of drug prescription that is regarded as the fundamental basis of medicine. In other words, it is said that Japan valued practice, whereas China respected theory (the view of Shutei Nakagawa in "*Iho Shinkoben* [医方新古弁]"). "*Shuhokiku* (衆方規矩)" by Dosan Manase in 1636, "*Iho Kuketsushu* (医方口訣集)" written by Doju Nagasawa, supplemented by Sanryu Nakayama, and annotated by Yushoshi Kitayama in 1681, and "*Kokonhoi* (古今方彙)" by Tsugen Koga in 1747 are included in extended Dosan medicine. Until the middle of the Edo period, Chinese medical books were well read, including "*YiXueZhengZhuan* (医学正伝)" by *Yu Tuan* (虞摶) in 1515, "*YiXueRuMen* (医学入門)" by *Li Chan* (李梴) in 1575, "*WanBingHuiChun*" by *Gong Tingxian* in 1587, and "*ShouShiBaoYuan* (寿世保元)" by *Gong Tingxian* in 1615. Furthermore, among "*Seiden Wakumon* (正伝或問)" that is only a part of the "*YiXueZhengZhuan*" published as one book, "*Iho Taiseiron* (医方大成論)" that is the extracted medical theory of the "*YiShuDaQuan* (by *Xiong Zongli* in 1446)," "*ShiSiJingFaHui* (十四経発揮)" written by *Hua Shou* (滑寿) in 1341, "*NanJingBenYi* (難経本義)" also by *Hua Shou* in 1361, "*YunQiLunAo* (運気論奥)" by *Liu Wenshu* (劉温舒) in 1099, "*YiJingSuHuiJi* (医経溯洄集)" by *Wang Lu* (王履) in the end of the Yuan dynasty or the beginning of the Ming dynasty, "*JuFangFaHui* (局方発揮)" by *Zhu*

Danxi in 1347, "*GeZhiYuLun* (格致余論)" also by *Zhu Danxi* in 1347, "*BenCaoXuLi* (本草序例) that is only the introduction part of the "*ZhengLeiBenCao*" and was published as one book, and "*SuWen XuanJiYuanBingShi* (素問玄機原病式) by *Liu Wansu* around 1154, seven physicians' books were selected and well sold as 'Seven physicians' book series'. Eminent Kampo physicians included Gensaku Manase (1549–1631) who authored "*Igaku Tenshoki* (医学天正記), "*Iho Meikan* (医法明鑑)," "*Enju Satsuyo* (延寿撮要), etc., Genya Okamoto (1587–1645) who wrote "*Kaden Yoyakushu* (家伝預薬集)," "*Genya Hoko* (玄冶方考), "*Tokashu* (灯下集)," etc., Kengi Furubayashi (1579–1657) who wrote "*Nikki Chutoho* (日記中棟方)," "*Myoyaku Sokkoho* (妙薬速効方)," etc., Doju Nagasawa (year of birth unknown–1637) who wrote "*Iho Kuketsushu*," "*Zoho Nodoku* (増補能毒)," etc., Yushoshi Kitayama (year of birth unknown–1701) "*Kitayama Ian* (北山医案)," "*Iho Kojoken* (医方考縄愆)," etc., and Sanryu Nakayama (1614–1684) who wrote "*Suisho Zakki* (遂生雑記)," and "*Byoka Yoran* (病家要覧), etc. In addition to aforementioned Gyuzan Katsuki, there were Kensai Kato (1669–1724) who is the author of "*Iryo Tebikigusa* (医療手引草), "*Hengyoku Rokuhachi Honzo* (片玉六八本草)," "*Hoteki* (方的)," etc., Gensen Tsuda (1737–1809) who authored "*Kangaku Chitai* (勧学治体)," "*Sekizan Igen* (積山遺言)", etc., Shumpo Kitao (1658–1741) who wrote "*Teijidan* (提耳談)," "*Tosoan Kahokukai* (当壮庵家方口解)," "*Sokan Idan* (桑韓医談)," etc., Futei Fukui (1725–1792) who wrote "*Surankan Shukenho* (崇蘭館集験方)," "*Hodoku Benkai* (方読弁解)," "*Hinko Myakkai* (瀕湖脈解)," etc., Tokaku Wada (1744–1803) who is an author of "*Shoso Zatsuwa* (蕉窓雑話)," "*Shoso Hoikai* (蕉窓方意解)," "*Dosui Sagen* (導水瑣言)," etc., and Kien Takashina (1773–1843) who wrote "*Kyukokan Ifu* (求古館医譜)," "*Kyukokan Hofu* (求古館方譜)," "*Denka Rekikenho* (伝家歴験方)," etc. Ippo Okamoto (1654–1716) translated and annotated a large number of Chinese medical books, including "*Igaku Sanzo Benkai* (医学三蔵弁解)," *"Ikei Sokaishu Wagosho* (医経溯洄集倭語鈔)," and "*Jushikeiraku Hakkiwage* (十四経絡発揮和解)"; in addition, he wrote medical books for enlightenment.

Koho school

In the latter half of the 17 century, while it was after the middle of the Edo period, a Kampo school adhering to the "*ShangHanLun*" for an ideal medicine was in the majority of the then Japanese Kampo circle. This school advocating the spirit of the "*ShangHanLun*" compiled in the Han dynasty was called Koho school. In China, "*ShangHanLun"* was re-evaluated in the Song dynasty, and its spirit was pursued by a group of reversionistic physicians in the Ming to Qing dynasty. They analyzed "*ShangHanLun"* in their own way, and divided its content into two parts: what meets their view (was admitted as the original classic described by *Zhang Zhongjing*) and what does not meet their view (was not admitted and excluded by regarding the view as additional inserts by descendants such as *Wang Shuhe*). They may be said to have been rather radical. Japanese Koho school members were inspired by them. Inspired Japanese physicians included Gen'i Nagoya (1628–1696; "*Igaku Gutoku* [医学愚得]," "*Iho Mon'yo* [医方問余]," "*Kaia Ittoku* [怪痾一得]," "*Kinki Yoryaku Chukai* [金匱要略註解]," "*Etsuho Shokumotsu Honzo* [閲甫食物本草]" and many others), Konzan Goto (1659–1733; "*Shisetsu Hikki* [師説筆記]," "*Konzan Sensei Isetsu* [艮山先生医説]," etc.), Shuan Kagawa (1683–1755; "*Iji Setsuyaku* [医事説約]," "*Ippondo Koyo Igen* [一本堂行余医言]," "*Ippondo Yakusen* [一本堂薬選]," etc.), Kitetsu Naito (1701–1735; "*Ikei Kaiwakuron* [医経解惑論]," "*Shokan Zatsubyoron Ruihen* [傷寒雑病論類編]), Toyo Yamawaki (1705–1762; "*Zoshi* [蔵志]," "*Yojuin Isoku* [養寿院医則]," "*Yojuin Hokan* [養寿院方函]," etc.), Todo Yoshimasu (1702–1773; "*Iji Wakumon* [医事或問],"

"*Idan* [医断]," "*Iho Bunryoko* [医方分量考]," "*Kenshuroku* [建殊録]," "*Kosho Igen* [古書医言]," "*Hoki* [方機]," "*Hokyoku* [方極]," "*Yakucho* [薬徴]," "*Ruijuho* [類聚方], and many others), Dokushoan Nagatomi (1732–1766; "*Tohoko* [吐方考]," "*Man'yu Zakki* [漫遊雑記]," "*Hoko Hiroku* [葆光秘録)]," etc.), Kinzan Murai (1733–1815; "*Ido Nisen'nen Ganmokuhen* [医道二千年眼目篇]," "*Yakucho Zokuhen* [薬徴続編]," "*Yakuryoko* [薬量考]," "*Ruijuhogi* [類聚方議]," "*Waho Ichimanho* [和方一万方]," etc.), and Nanmei Kamei (1741–1814; "*Kokonsai Irohauta* [古今斎以呂波歌], "*Nanmei Mondo* [南冥問答]," etc). They had different standpoints. Among them, Todo Yoshimasu was a Kampo physician with a remarkable perspective.

Todo Yoshimasu proposed a conception that all diseases are derived from one poison and a variety of pathologic conditions occur depending on the location of the poison (*Manbyo Ichidoku theory*). Claiming that since all drugs are poison, the physician should attack the causative poison with drug poisons, he instituted aggressive therapies. Todo asserted that even if a therapy failed to cure a patient, it is the patient's fate (*Tenmei theory*), which should not be attributed to the physician. His assertion evoked controversy in the then medical circle. Todo denied the concepts of Chinese natural philosophy including the YinYo and five-element doctrines. He thoroughly dissected the sentences of "*ShangHanLun*" to compile "*Ruijuho*" in 1764 followed by "*Yakucho*" in 1785. Thus Todo Yoshimasu became the most left-wing member of Koho school. At this time point, it may be said that a Japanese-taste concept or cause of pattern was formed. His straightaway medical theory swept through the physicians' world in the late Edo period, resulting in a great influence on today's Japanese Kampo medicine. His son named Nangai succeeded Todo and sought to revise father's radical conception by explaining pathology and treatment with the qi (Ki), blood and fluid (*Kiketsusui*) doctrine. Nangai's medical conception also underlies the contemporary Kampo medicine. Yodo Odai (1799–1870; "*Hogi Zasshi* [方伎雑誌]," "*Ruijuho Kogi* [類聚方広義]," and "*Iyo* [医余]," etc.) who was well known at Edo (the present Tokyo) in the end of the Edo Shogunate (around 1850s to 1860s) adhered to Todo's medical concept, and bridged between the Edo and Heisei (1989~) Kampo medicine.

Sechu school

While Chinese people respected logic, or abstract concepts, Japanese people valued practical and concrete images. These tendencies were true in medicine. Since Koho school physicians were apt to become extremists, a group of flexible physicians appeared who took first account of effective formulae and incorporated clinically good points of medical schools. This group was called Sechu school, comprising aforementioned Tokaku Wada, Gengai Ogino (1737–1806; "*Shirakuhen* [刺絡編], "*Tohohen* [吐法編]," etc.), Kinkei Nakagami (1744–1833; "*Seiseido Itan* [生々堂医譚]," "*Seiseido Yojoron* [生々堂養生論]," "*Seiseido Shokan Yakugen* [生々堂傷寒約言]," "*Seiseido Zakki* [生々堂雑記]," etc.), Nan'yo Hara (1752–1820; "*Keiketsu Ikai* [経穴彙解]," "*Kiki Hoki* [寄奇方記]," "*Shokanron Yawa* [傷寒論夜話]," "*Sokei Guki* [叢桂偶記]," "*Sokeitei Iji Shogen* [叢桂亭医事小言]," "*Toridegusa* [砦草], etc.), and Kakuryo Katakura (1751–1822; "*Shokan Keibi* [傷寒啓微]," "*Sanka Hatsumo* [産科発蒙]," "*Seikendo Chiken* [静倹堂治験]," "*Seino Satan* [青嚢瑣探]," "*Bairai Shinsho* [黴癘新書]," "*Hoei Suchi* [保嬰須知]," etc.). Even today, the clinical technique by Tokaku Wada is highly appreciated. Quite a few people tried to take the middle course between Rampo (蘭方) and Kampo medicine. Among them, one leader was Seishu Hanaoka (1760–1835; "*Shunrinken Gansan Binran* [春林軒丸散便覧]," "*Seishu Sensei Chikenroku* [青洲先生治験録]," and many others) from Kishu (the present

Wakayama). He is well known as the first surgeon on earth to have successfully achieved extraction of breast cancer by use of an anesthetic of crude drugs developed by himself. One of his successors is Soken Honma (1804–1872; "*Naika Hiroku* [内科秘録]," "*Yoka Hiroku* [瘍科秘録]," etc.) In the Kampo circle of the early Meiji period, Sohaku Asada (1815–1894; "*Futsugo Yakusitsuhokan* [勿誤薬室方函]" "*Futsugo Yakushitsuhokan Kuketsu* [勿誤薬室方函口訣]," "*Igaku Tenkei* [医学典刑]," "*Kisso Shoei* [橘窓書影]," "*Koho Yakugi* [古方薬議]," "*Myakuho Shigen* [脈法私言]," "*Shokanronshi* [傷寒論識]," "*Zatsubyoronshi* [雑病論識]," "*Kokoku Meiiden* [皇国名医伝]," "*Sentetsu Iwa* [先哲医話]," "*Igakuchikan* [医学智環]," and many others) amazingly flourished as a Sechu school physician. Sohaku played the lead in the last stage as a Kampo magnate in the end of the Edo period to the Meiji period. There are many lessons to be learned from his clinical achievement.

Kosho school

In the late Edo period, a new Kampo group of Kosho school emerged under criticism and reflection on the past selfish interpretation of literature, and thrived at the end of the Edo period. The Kosho school succeeded the academic tradition of historical investigation in the Qing dynasty and introduced it into the medical field to seek facts through objective analysis of Kampo classics. Genkan Taki (1755–1810; "*Shokanron Shugi* [傷寒論輯義]," "*Kinki Yoryaku Shugi* [金匱要略輯義], "*Somonshi* [素問識]," "*Reisushi* [霊枢識]," "*Henjyakusokoden Iko* [扁鵲倉公伝彙考]," "*Myakugaku Shuyo* [脈学輯要], "*Isho* [医賸]," etc.), one of his sons Mototane Taki (1789–1827; "*Isekiko* [医籍考]," "*Nankei Sosho* [難経疏証]," etc.), another son Gen'in Taki (1795–1857; "*Shokanron Jutsugi* [傷寒論述義]," "*Kinki Yoryaku Jutsugi* [金匱要略述義]," "*Somon Shoshiki* [素問紹識]," "*Yakuji Tsugi* [薬治通義]," "*Shokan Koyo* [傷寒広要]," "*Zatsubyo Koyo* [雑病広要], etc.) and others of Edo Igakukan (a medical school) were representative physicians of the Kosho school of Kampo medicine. Furthermore, there were many medical scholars such as Ranken Isawa (1777–1829; "*Ranken Iwa* [蘭軒医話]," "*Ranken Idan* [蘭軒医談]," etc.), *Chusai Shibue* (1805–1858; "*Reisu Kogi* [霊枢講義], etc.), Hoso Kojima (1797–1848; "*Kasei Guki* [河清寓記]," etc.), Risshi Mori (1807–1885); "*Honzokei Kochu* [本草経攷注]," "*Shokanron Kochu* [傷寒論攷注], "*Somon Kochu* [素問攷注], and many others), and Gyoko Yamada (1807–1881; "*Igaku Kansui* [医学管錐] and many others). Achievements of these Kosho school physicians were introduced to China, the Kampo originator, after the Meiji Restoration (1868) and even today is highly appreciated. Although it tends to be considered that Kosho scholars of historical investigation exclusively search literature, there were actually quite a few excellent clinicians such as Gyoko Yamada.

Herbalism

Of the Chinese books of herbalism, "*BenCaoJingJiZhu"* was first introduced into Japan in the Asuka period (592-710); "*XinXiuBenCao*," in the Nara period (710-794). In the late Heian period, "*ZhengLei BenCao*" came over and was in use as the standard book of herbalism through the Kamakura –Muromachi period. In the early Edo period, import of "*BenCaoGangMu*" gave immeasurable effects as the fundamental literature of herbalism. Japanese herbal books in the Edo period include "*Yakusho Nodoku* (薬性能毒)" written by Dosan Manase in the end of the 16th century, "*Etsuho Shokumotsu Honzo*" (Gen'i Nagoya, 1669), "*Hochubiyo (Wamyo) Honzo* (庖厨備用[倭名]本草)" (Gensho Mukai, 1671), "*Honzo Bengi* (本草弁疑)" (Genri Endo,

1681), "*Honcho Shokkan* (本朝食鑑)" (Hitsudai Hitomi, 1692), "*Koeki Honzo Taisei* (広益本草大成)" (Ippo Okamoto, 1698), "*Yamato Honzo* (大和本草)" (Ekken Kaibara, 1708), "*Yoyaku Suchi* (用薬須知)" (Gentatsu Matsuoka, 1726), "*Yakuro Honzo* (薬籠本草)" (Gyuzan Katsuki, 1727), "*Ippondo Yakusen*" (Shuan Kagawa, 1731–1738), "*Yakucho*" (Todo Yoshimasu, 1771), "*Honzo Komoku Keimo* (本草綱目啓蒙)" (Ranzan Ono, 1803–1805), and "*Koho Yakuhin Ko* (古方薬品考)" (Naokata Naito, 1840).

Attention should be paid to abdominal examination as a Kampo diagnostic method uniquely improved and developed in Japan. Abdominal examination, which is essential for Japanese Kampo medicine, sprouted in the Nanbokucho period, and propagated through the Edo period. However, since it is complex and remains to be fully clarified, it is not further referred to here.

In conclusion

Gosei, Koho, Sechu, and Kosho schools as well as the herbalism field have been outlined. These schools and field cannot be clearly discriminated. The Gosei school is thought to be based on Jin-Yuan medicine; however, Jin-Yuan medicine did not neglect *Zhang Zhongjing's Koho*. The Koho school, even Todo Yoshimasu, used medicines other than those described in the "*ShangHanLun*" and "*JinGuiYaoLue*." The Sechu school is a generic name for groups of physicians who accepted *Iho* of various schools, while the Kosho school refers to a group of physicians who introduced a method of studying old documents into desk research. Since the Sechu and Kosho schools are defined from different viewpoints, the two are difficult to discriminate. Some maintain that there was no exchange between schools in the Edo period, which is not correct. Actually there were occasional exchanges even between Rampo (Western medicine) and Kampo families. For another example, there was an intimate exchange even between Yodo Odai regarded as a true Koho physician and Sohaku Asada belonging to a Sechu or Kosho school. Some critics limit Japanese Kampo medicine to a particular school that emphasizes 'formula versus pattern' and avoids referring to etiology. Such a view, however, was merely established in the early Showa period. Japanese Kampo medicine is not comprehensible from such a limited perspective. Rather, in the Edo period, especially after the Genroku era (1688-1703), Japanese Kampo medicine covered a far broader field including Rangaku (the study of Dutch) and natural history than traditional Chinese medicine of the Qing dynasty. Comparison in the level of knowledge alone on traditional medicine reveals that the today's Kampo circle is far inferior to that in the Edo period.

From the Postwar Time until Today

Tetsuo Akiba

Summary from the Postwar Period until the Present Time

Japanese Kampo medicine was greatly affected by the Second World War lasting until 1945. Of promising young Kampo physicians, Chokyu Kimura and Keisaburo Mori were killed in the War, and Yudo Yakazu died from a disease at the front, not at home, after the War. Just before the end of the War, Shizuka Ayukawa and Kazuo Yumoto deceased in succession. And in 1946, Hisashi Koide was sadly missed in the postwar confusion.

Although the youth of abilities who were to lead the next generation were lost, Kampo medicine began to step on the road to restoration with the postwar reconstruction in Japan.

The first challenge was a request (to prohibit acupuncture and moxibustion) that was submitted to the then Japanese Ministry of Health and Welfare by the General Headquarters (GHQ) of Allied military forces in September, 1947. This surprise request drove a large-scale protesting movement among acupuncturists and moxibustionists concerned throughout Japan, resulting in successful rejection of the request, partly owing to efforts of Dr. Hidetsurumaru Ishikawa (Kyoto Imperial University Professor Emeritus) and Dr. Takeshi Itakura (former Director of the Eastern Therapeutics Institute [東亜治療研究所]). However, it is beyond question that the prejudice of the allied nations toward Oriental medicine threatened the Kampo physicians engaging in the treatment with Kampo medicines (湯液) other than acupuncture and moxibustion.

While the postwar confusion settled down and economic recovery began, public interest had been increasingly given to Kampo medicine. Drug poisoning and health hazards due to environmental contamination were also headlined frequently, possibly because the people became aware of the negative aspects of industrialization and associated economic growth. In the period of 1955-1964, there was a Kampo boom in which Kampo medicine and related matters were picked up in media almost every day.

Meanwhile, the national health insurance system for the whole nation was established in 1961 and thereafter has allowed the people living in Japan to receive medical treatment equally at inexpensive costs. In early days, most patients were not insured and Kampo medicines were not often used in clinical practice, although insured medical care had been legally allowed using the crude drugs listed in the drug tariff, or drug price list. Kampo therapy was greatly changed in the qualitative as well as quantitative perspectives in 1976, when a large number of Kampo medicines were added to the drug tariff. In parallel, medical education in universities and medical schools was also reformed enough to convert Kampo therapy — from a special therapeutic means by limited specialists to a universal therapeutic means by general practitioners. This change was obvious, as indicated by the fact that the physicians who prescribe Kampo medicines in the routine work account for 86.3% in 2010 today.

A 65-year history of Kampo medicine after the War will be described here, focusing on the treatment with Kampo medicines (湯液), in the realms of academy, medical care and education systems, and social

trend of thoughts.

Trend in the academic world

1. Restart toward modern Kampo

The Kampo world that had been collapsed by the unprecedented defeat of Japan began to do its own activities.

At the big turning point of the postwar period, Professor Yaeji Ito (Department of Ophthalmology, Chiba Medical College [Now Chiba University School of Medicine]) published an article entitled 'Foreign cultures that affected Meiji medicine' in the April issue of "*Nippon Rekishi* (日本歴史, *Japan History*)" in 1947. He pointed out irrationality in the medicine and medical care systems in the early Meiji era that excluded Kampo medicine, emphasizing the necessity of their reconstruction. He offered a non-credit course for Oriental medicine to open the door for participants outside the college, as part of the reconstruction.

In 1948, novel movements were generated, including publication of the book "*Wakan Yakuyoshokubutsu* (和漢薬用植物, *Medicinal plants in Japan and China*) by Tatsuo Kariyone and Yushiro Kimura. The first joint memorial service for the Kampo physicians who died during the wartime was held by the Association of East-Asian Medicine (東亜医学協会), which set up the preparatory committee comprising Keisetsu Otsuka, Domei Yakazu, and Rin'ichi Kiga. This was a symbolic event for restart after the War. In the same year, Tokyo Kampo Medical Society (東京漢方医学会) (Tomekichi Muto and Kenzo Okuda) and Yokohama Onchi Medicinal Society (横浜温知医会) (Itsuma Takagi and Kazuo Tatsuno) were established to initiate energetic activities.

The year of 1949 became the commemorative year for Japan Kampo medicine that slipped out of the postwar disorder to firmly advance toward the future. More specifically, in those days, arrangements remarkably progressed for establishment of the Japan Society for Oriental Medicine (JSOM) as the core organization for academic activities of Kampo medicine professionals. On March 15, Kazuo Tatsuno, Keisetsu Otsuka, Domei Yakazu, Yoshio Nagahama, Masaaki Maruyama, and Ken Fujihira gathered and formed a Kampo study group to hold monthly meetings. At the October meeting, agreements were made about the formation of the arrangement committee for the first JSOM meeting. Kazuo Tatsuno was elected as manager for arrangement general affairs. On November 17, the arrangement committee to hold the first JSOM meeting was established and the charter was formulated with the use of the Tatsuno's house as the tentative office. The committee comprised 11 members: Shiro Hosono, Keisetsu Otsuka, Masatsugu Wada, Kazuo Tatsuno, Yoshio Nagahama, Domei Yakazu, Jyun Yamazaki, Masaaki Maruyama, Yoshio Manaka, Ken Fujihira, and Yukihiro Morita.

In the same year, Totaro Shimizu issued the book "*Nippon Yakugakushi* (日本薬学史, *The History of Pharmaceutical Science in Japan*)", and Yaeji Ito (Professor of Chiba University) submitted to the Ministry of Education an application for the establishment of a national research institute for Oriental medicine. In addition, the 9th Kampo medicine course was revived in Koryo (former, Takusyoku) University, with listed lecturers including Kazuo Tatsuno, Keisetsu Otsuka, Domei Yakazu, Totaro Shimizu, and Sorei Yanagiya.

2. JSOM

With the advent of 1950, the organizing committee for the tentative JSOM was held to prepare and send the charter to the persons concerned. On March 12, the JSOM inaugural meeting was held in the meeting room of Kitasato Memorial Medical Library, Keio University School of Medicine. The name of the society was finally fixed after a brisk discussion. In the election of president, nominated candidates declined one after another because of health or age problems, resulting in vacancy for the post. Then, the new organization was launched with Kazuo Tatsuno (responsible for general affairs) as the chief executive. The number of JSOM members at inauguration was 93; 38 members were honorary who participated in response to requests from the secretariat, while 60 were regular who must pay the membership fee.

Since the inauguration, JSOM had aimed to join the Japanese Association of Medical Sciences (JAMS) as one of the member societies. In July, 1953, 4 years after the inauguration, JSOM submitted to JAMS the first entry application, which was rejected by 26 votes to 3 votes at the Liaison Committee of JAMS held in the meeting room of the Japan Medical Association on August 27. The second application submitted in 1961 was also rejected by 31 votes to 14 votes. However, under the president Kunio Matsuda, the fourth application in 1991 received a two-thirds favorable vote to pass: JSOM was approved as the 87th affiliated specialist medical society. One of the goals at the inauguration of JSOM was achieved 41 years later.

Since then, another important goal for JSOM as a society of clinical medicine has been establishment of the specialist system similar to that in other medical societies. JSOM had sought to frame its specialist system, in parallel to submission of entry application to JAMS. In1990, the specialist system was accreditated. However, once JSOM became a member of the Japanese Board of Medical Specialties, Kampo specialists have been and are authorized as sophisticated-field specialists after accreditation of base-field specialists. In 2005, the Ministry of Health, Labor, and Welfare approved JSOM as a specialist qualification organization that can publicize the Kampo specialist. The number of JSOM members increased from 98 at the start to 1035 in 1970, 9751 in 1990, and 8690 in 2010, favorably with some margin of error. In 2010, 2230 new Kampo specialists were registered and high-level Kampo therapy has been carried out in practice.

3. Medical and Pharmaceutical Society for WAKAN-YAKU

The Medical and Pharmaceutical Society for WAKAN-YAKU was born in 1984 from ‘the WAKAN-YAKU symposium,’ which was first organized in 1967 by Yuichi Yamamura and others, evolving to resolve. Its objectives were to discuss up-to-date information about the resources, quality control, mechanisms of action, and clinical studies of Wakan-yaku from the scientific perspective, and to bridge basic and clinical medicine. A notable point was that the Society claims to quest the harmony of natural science (based on elemental reductionism) and traditional medicine and pharmacy (being a complex and multicomponent system). For that purpose, medical and pharmaceutical scientists as well as medical doctors and pharmacists, all studying Wakan-yaku in various forms, should assemble to exchange information. Curiously, this concept was consistent with the historical background, in which therapeutic measures of non-Western medicine had been high-rated all over the world, although since the 1980s medical care costs had been elevated annually. Traditional medicine was highlighted globally in 1990s. The society may have been the first to propose the value of academic Wakan-yaku research.

4. Association of East-Asian Medicine

Since prewar periods, the Association of East-Asian Medicine had existed as an association of Kampo medicine, and has been widely known as the publisher of a monthly issued magazine "*Kampo to Kan-yaku* (漢方と漢薬, *Kampo and Kan-yaku*)." The magazine was started in May 1934, changed its name to "*Shoyaku Chiryo* (生薬治療, *Japanese Journal of Pharmacognosy*)" in 1944, and had been published until volume 125 (publication suspended) as the official magazine for the Japanese Society of Kampo Medicine (日本漢方医学会)." "*Kampo to Kan-yaku*" was a product of collective efforts for Kampo medicine by Kampo medicine professionals concerned in then Japan. The articles of choice appeared in the magazine every month, not only enough to imply the vigor in the newborn Japan's Kampo circle, but also to give vivid and evergreen impressions even now in the 21st century. Naturally, the call for resumption of publication of "*Kampo to Kan-yaku*" occurred among the Kampo professionals.

Although magazines related to Oriental medicine had been perpetually published since soon after the War, regrettably many had been immediately suspended and some had been eventually stopped. Such difficulty in continuous publication was believed to be unconquerable. Ultimately in 1953, there was no monthly magazine related to Kampo in Japan. This misfortune inspired a desire for an ideal monthly magazine that contains significant contents (presenting typical Japanese Kampo papers and latest related national and international news as well as provides good impression.) The desire was also a matter of honor for Japan.

Preceding cases of suspended publication were investigated in detail. As a result, the best way to assure continuous publication of the magazine was found: a publisher coterie of six persons led by Domei Yakazu was selected and was regarded as responsible for publication, while the publication funding was secured; the Association of East-Asian Medicine, which had issued "*Kampo to Kan-yaku*," served as the publisher; Rin'ichi Kiga of "*Kampo to Kan-yaku*" was recommended as the editor. Finally in September 1, 1954, "*Kampo no Rinsho* (漢方の臨床, *Journal of Kampo Medicine*)" vol.1, No.1 was released. Since then, this journal has been continuously and uneventfully issued, did reach Vol. 52 in 2011, and is highly evaluated as a typical Oriental medicine magazine in Japan.

5. Other academic activities

In 1976, a considerable number of Kampo formulations were included in the drug tariff, which triggered the successive launch of many workshops and associations based on Western medicine among general physicians. The Obstetric and Gynecologic Kampo Workshop (産婦人科漢方研究会) was first established in 1981, followed by Japanese Association of Oriental Psychosomatic Medicine (日本東洋心身医学研究会), Association of Kampo and Immuno-Allergy (漢方免疫アレルギー研究会), Urologic Kampo workshop (泌尿器科漢方研究会), Surgical Kampo Workshop (外科漢方研究会), Japanese Association of Kampo and Otorhinolaryngology (日本耳鼻咽喉科漢方研究会), Japanese Society of Pediatric Surgical Kampo Medicine (小児外科漢方研究会), Japanese Association of Pain and Kampo Medicine (日本疼痛漢方研究会), and Japanese Association of Children and Kampo (日本小児漢方交流会). These workshops and associations are all very active, indicating that Kampo is prevailing all over the medical world in Japan.

Establishment of education and research bases

It is evident that education and research facilities play an important role for Kampo medicine to develop as wisdom. Major facilities are picked up here in the order of establishment, and their activities are briefly summarized.

1. Oriental Medicine Research Center of Kitasato Institute (now Kitasato University Oriental Medicine Research Center)

The Center was established in 1972 as the first comprehensive research institute for Oriental medicine in Japan. The first Director was Keisetsu Otsuka. On March 8, 1986, the Center became the first Japanese institution to be designated as a WHO Collaborating Center for Traditional Medicine. Since then pioneering activities has been carried out.

2. Toyama Medical and Pharmaceutical University and Research Institute for Wakan-yaku (now Institute of Natural Medicine, University of Toyama)

The University and Research Institute were founded in 1975 and 1978, respectively, in the place of Toyama abundant in pharmaceutical industries with a long history and tradition. A Department of Japanese Oriental (Kampo) Medicine (和漢診療学講座) was originated here with the inaugural professor of Katsutoshi Terasawa. The Institute has been designated as a WHO Collaborating Center for Traditional Medicine.

3. Kinki University Research Institute of Oriental Medicine

The Institute started as a Kampo-specialized research institution under the direct control of Kinki University in Osakasayama, Osaka, in 1975, when Kinki University Hospital was also opened. The first professor for the Department of Oriental medicine was Shigeru Arichi. The Research Institute consisted of the basic research division (in which Oriental medicine [Kampo] is earnestly studied) and the clinical practice division (in which clinical treatment is conducted), aiming to contribute to the improvement and enhancement of medical care.

4. Hyogo Prefectural Institute of Oriental Medicine and Affiliated Clinic

With the aim at ‘applying Oriental medicine to health and welfare for Hyogo prefectural people,’ the then governor founded the Institute and Clinic in 1977. Kampo clinic and research as well as acupuncture and moxibustion therapy and basic research are carried out.

5. Ehime Prefectural Central Hospital Institute of Oriental Medicine

The Institute was established in 1989 with the inaugural director of Hidehiko Mitsufuji. Since then, clinical practice and research work of Oriental medicine (acupuncture, moxibustion and Kampo) have been carried out, under a unique policy that patients to be treated are ‘those who have had long-lasting health problems (agony and agony-derived anxiety), which have not resolved by any medical treatment at hand’, or ‘those with chronic health impairment.’

6. Institute of Oriental Medicine, Tokyo Women's Medical University School of Medicine

The Institute was opened in 1992 with Hiroshi Obata named inaugural Director, provided with a health improvement facility and a clinical facility for acupuncture and moxibustion. Its aim is to practice Kampo that bridges Oriental medicine and Western medicine.

Transition of the medical system and its background

The medical system that is the core of social security systems was greatly changed soon after the War: the national health insurance system was implemented in 1961. Since then, Kampo therapy had gradually grown up to create a Kampo boom, which started in 1976 and lasted for some time.

1. Realization of the national health insurance system

The most remarkable event in the Japan's medical and medical care systems after World War II was realization of a national health insurance system. For Japanese public medical insurance, the basic scheme was formulated in the end of the Taisho period, and was increasingly expanded in the Showa period, though to limited populations. The universal health insurance system benefitting the Japanese people started in 1961. Amazingly, 20 kinds of crude drugs were included in the drug tariff two years before, in 1959, which indicates that insured treatment with Kampo decoction (湯剤) using crude drugs (of limited kinds) has become possible.

Already prior to the start of the universal system, insurance benefits for Kampo therapy were frequently paid via consultation with the insurer. A "*Kampo to Kan-yaku* " in 1941 carried a request from the Japanese Society of Kampo Medicine (日本漢方医学会) that the then insurance system should be revised for the future because the official prices for drugs as well as acupuncture and moxibustion did not satisfy necessary expenses.

The crude drugs added to the drug price list increased to 43 kinds in 1965 and jumped to approximately 200 kinds — sufficient for daily clinical practice — in 2011 today.

2. Appearance of extracts

There was a trend that calls heightened for new and easy-to-handle dosage forms enabling oral dosing, not decoction. Reportedly Tadanao Nakayama, the author of "*Kampo Igaku no Shinkenkyu* (漢方医学の新研究, *Original research of Kampo medicine*)," insisted the development of Kampo extract powder instead of decoction before the War.

As the inaugural Director of the Eastern Therapeutics Institute (東亜治療研究所) set up in the Fraternity Memorial Hospital (同愛記念病院) in 1943, Takeshi Itakura tried to confirm the efficacy of an experimentally prepared Kampo extract formulation on tuberculous pleurisy in a comparative clinical trial. The trial, reported to have proceeded to the clinical administration stage, was discontinued by the defeat of Japan. However, undoubtedly his studies somehow contributed to the manufacture and research of Kampo extract products that have been developed since soon after the War.

Among private medical institutions, Seikoen Hosono Clinic (Director, Shiro Hosono) of Kyoto created practical Kampo formulations soon after the War, in great expectation for a bright future of extract

formulations. More specifically, as a Kampo institution based on modern medicine, the Clinic originally developed and prepared a lot of extract products in a convenient form that matched the life style desired by urban residents. Furthermore, the Clinic was truly ahead of the extract formulations era that began more than 20 years later, in 1976. This foresight has been highly praised. It is also noted that Seikoen Hosono Clinic produced not a few Kampo physicians.

In 1957, over-the-counter (OTC) Kampo extract formulations were released on a large scale. Ten years later in 1967, four kinds of ethical Kampo extract products were first listed in the drug tariff. These Kampo products were initially used only by a few Kampo physicians, but have been increasingly called for by ordinary people.

3. Drug tariff-listing of Kampo medicines

The situation changed completely in 1976, when as many as 42 kinds of Kampo extract products were listed in the drug tariff under a classification of 'ethical Kampo products.' This led general physicians unfamiliar to Kampo medicines to wide use of Kampo products, and also researchers in various fields to evaluation of the efficacy of those products. Kampo medicines became officially evaluated as drugs.

Thereafter, the number of tariff-listed Kampo products has increased progressively, reaching 148 prescriptions and a total of more than 800 products in 2000.

The number of crude drugs that were first listed in the drug tariff in 1960 also increased up to approximately 200 at the present time. These drugs are totally or partially covered by public health insurance under the Western medicine system. The possible reason is that the efficacy and safety of ethical Kampo products have become recognized as solid evidence and accepted among a large number of medical doctors who rely on Western medicine.

4. Drug tariff deletion problem

Increases in medical care and welfare costs had been noticed by the Japanese government since 1965, and became abruptly manifest in 1973, when free medical care for the elderly was introduced. Soon later in 1976, massive Kampo extract formulations were included in the drug tariff, as mentioned above. Under these integrated situations, the government attributed the cost increase partly to the increase in extract formulations. Concretely, as reported in 1983, the then subordinate officer Yoshimura announced that stomachic digestant (健胃消化剤), combination cold remedies (総合感冒薬), cataplasm (パップ剤) and Kampo products would be removed from the drug tariff. This proposal may have derived from the speculation that Kampo extract formulations were exempted from clinical trials usually required before the tariff listing because of their long-years use as therapeutics in Japan. It must have been considered that the conditions were unfair for Kampo products, as compared with Western new drugs that must pass through strict clinical studies. In addition, there was an institutional principle that since some of the OTC Kampo medicines available in pharmacy after the Meiji period are practically as efficacious as ethical Kampo medicines, such medicines should not be covered by the health insurance. These two reasons were repeatedly informed to medical care professionals and pharmaceutical industry association, which were forced to take measures each time.

5. Japanese Association of Clinical Kampo Physicians (日本臨床漢方医会)

The tariff deletion problem of Kampo products resurfaced in 1993. In the same year, when the Council on Medical Insurance announced 'how to provide the drugs analogous to OTC drugs' in a form of proposal, the movement toward deletion became more evident in the review of fiscal 1997 insurance benefits. To stop non-coverage by insurance, it was needed to take political measures. However, for the academic association JAOM to conduct political activities was difficult. Thus a profit organization of Japanese Association of Clinical Kampo Physicians was set up in November 1997 to act instead JAOM. In only one week, about 240 promoters gathered and two weeks later more than 1000 members joined, showing how many people are concerned about the crisis of insured Kampo clinical practice.

6. Adverse effects problem for shosaikoto (小柴胡湯)

In March 1, 1996, the Ministry of Health and Welfare announced the occurrence of interstitial pneumonia in 88 patients having taken shosaikoto since 1994, resulting in death of 10 patients. Shosaikoto had been mainly used for 'improvement of hepatic dysfunction and chronic gastrointestinal disturbance in chronic hepatitis.' The use of this Kampo medicine had been already reported to induce the onset of interstitial pneumonia in patients with chronic hepatitis. In April 1991, the package insert contained a sentence regarding possible onset of interstitial pneumonia in the section of adverse effects of precautions. In December 1992, precaution against interstitial pneumonia was mentioned more above in the section of 'general precaution.' Since March in 1992, indications for interferon α and β have been extended to chronic active hepatitis type C. Because their combined use with shosaikoto had been reported to cause interstitial pneumonia in several patients, the use of interferon α and shosaikoto was contraindicated in January 1994. Nevertheless, during the subsequent 2 years, the disease newly occurred in 88 patients, of whom 10 died. This led to the announcement mentioned above.

Usually, therapeutic drugs entail more or less adverse effects or reactions. However, the announcement regarding shosaikoto provoked sharp reactions from Japanese people as well as media, far beyond anticipation of the people concerned. This incidence suddenly awakened the consciousness of medical care professionals, who clearly realized the fact that they had been content with a myth that Kampo medicines are safe therapeutics.

This issue and the tariff deletion problem had the same root: ethical Kampo products, represented by shosaikoto, had been listed in the drug tariff without undergoing fundamental clinical trials. This historical fact may have amplified the severe public reactions in Japan after the announcement of accumulative data of adverse drug reactions.

7. Clinical evidence of Kampo therapy

The historical element common to the tariff deletion and shosaikoto adverse effects problems was obviously the tariff listing of Kampo medicines without efficacy evidence in clinical trials. In other words, clinical evidence of Kampo medicines as therapeutic drugs was demanded. This demand is clearly understood in consideration of the fact that therapeutics able to be covered by the existing insurance are not called for the deletion from the tariff due to increased medical care cost or adverse drug reactions (of which the incidences are within medical common sense). Kampo medicine professionals were required to make collective efforts to

present the results (i.e., evidence) demonstrating the efficacy of Kampo medicines in clinical studies.

Individual research institutions started conducting clinical studies actively. In 1991, the then Ministry of Health and Welfare notified the reevaluation of 8 items of ethical Kampo extract formulation: orengedokuto (黄連解毒湯), keisikashakuyakuto (桂枝加芍薬湯), shakuyakukanzoto (芍薬甘草湯), shosaikoto (小柴胡湯), shoseiryuto (小青竜湯), daiokanzoto (大黄甘草湯), byakkokaninjinto (白虎加人参湯), and rikkunshito (六君子湯). Sequentially, placebo-controlled double-blind comparative clinical studies of these Kampo medicines are being conducted.

8. Activities of JAOM Evidence-based Medicine Committee

In 2001, the evidence-based Medicine (EBM) Committee was constituted in JAOM. The aim was to show that already pervading clinical treatment with Kampo medicines is 'EBM,' by demonstrating the efficacy of Kampo therapy, which has been asked for by people living in Japan.

Prior to the set-up of the EBM Committee, many clinical studies had been conducted and most of their results had been reported in overseas as well as domestic medical journals. Therefore, the initial objective of the Committee was to compile a large body of evidence in a book via categorizing by defined clinical field, evaluating, and summarizing the results. Of 3014 reports published between 1986 and 2001, 833 reports were divided into the defined categories and each report was reviewed to finally select robust evidence reports, totaling 93. These 93 papers were then submitted to the JAOM board of directors, and the final EBM committee report was submitted to the Ministry of Health and Welfare and other agencies concerned in 2005. Thereafter, revisions have been continuously made. In 2011 today, structured abstracts and evaluations with signs of reviewers are published both in English and Japanese on the JAOM web site, free accessible for everybody everywhere in the world.

As a result of these efforts, clinical evidence of Kampo therapy became widely recognized and the Kampo products being used also became appreciated as drugs with established efficacy. In this respect, Kampo medicine in Japan is quite different from traditional medicine with different methodologies in China and culturally related countries as well as Korea. Japanese Kampo medicine stands out as evidence-based medicine.

9. Establishment of the Japan Liaison of Oriental Medicine (JLOM) and launch of the integrated medical care project team

The movement surrounding Japan's traditional medicine did not stay in Japan, but became involved in waves of latest globalization in traditional medicine of China and other East Asian countries. This was a historical trend. Since the 1990s, while expectation for complementary and alternative medicine has been heightened in the U.S. and Europe, worldwide expectation has been elevated for traditional medicine. China and Korea took a national policy of promoting the overseas presence of their own traditional medicine. In Japan, however, there was no administrative agency supervising traditional medicine in an academic manner. Thus as an international negotiator, the Japan Liaison of Oriental Medicine (JLOM) was born in 2005 from association of Japanese medical societies related to traditional medicine and WHO cooperative centers. JLOM became responsible for establishing a national support system for Japanese traditional medicine as well as cooperating in international standardization of WHO-related traditional medicine terminologies and information. In

addition, the ministry of Health, Welfare, and Labor launched an integrated medical care project team in 2010 to start an integrated medical care policy involving Kampo medicine. At last, for Japanese traditional medicine, the international negotiation basis was built up to enter the globalization age.

Revolution in the medical education system

1. Kampo education in universities

After the War, a Kampo-related regular course was first set up in Toyama Medical and Pharmaceutical University (now University of Toyama Faculty of Medicine) among medical universities and faculties/schools of medicine. Toyama Medical and Pharmaceutical University was founded in 1975, and 4 years later in 1979, Wakan Clinic (和漢診療室, wakan-shinryoshitsu) was opened in the University Hospital. The inaugural head of the clinic was Katsutoshi Terasawa who was invited from Chiba University. In 1983, the name of "Wakan Clinic" was changed to Wakan Shinryobu (和漢診療部), then to Department of Japanese Oriental Medicine (和漢診療科) in 2004.

In 1990, the professorship was placed in the University Hospital Wakan Shinryobu (1st professor Katsutoshi Terasawa). In 1993, Department of Japanese Oriental Medicine was set up in the Faculty of Medicine. Thereafter in 2005, the University was integrated with another university and a college and turned its name to the University of Toyama. Toyama is traditionally famous for pharmaceutical industry and characterized with promoting research and education of Kampo medicine, providing many persons with talent or skills to the world.

2. Medical Education Model Core Curriculum

The medical education model core curriculum issued in 2001 from the Ministry of Education, Culture, Sports, Science, and Technology was epoch-making in emphasizing the necessity that any schools/faculties of medicine and medical universities should offer to medical students a core curriculum in which 'ability to outline Wakan-yaku can be acquired' in an appropriate period until graduation. This led all of the 80 schools/faculties of medicine and medical universities in Japan to provide a proper education for Kampo medicines. The knowledge of Kampo medicines excluded by the Cabinet more than 130 years before was revived in medical education after a long absence.

In the 2011 revision, a revision of 'ability to outline the characteristics and use of Wakan-yaku (Kampo-medicines) can be acquired' was made. More than 10 years after the issue, the number of medical doctors experiencing lectures of Kampo medicine in universities has gradually increased in clinical settings. Ethical Kampo products, like Western drugs, have been smoothly accepted in clinical practice as therapeutics. However, Kampo lecture hours in universities are still insufficient and recently an increasing number of relevant persons have emphasized the importance of Kampo in postgraduate education.

3. Pharmaceutical Education Model Core Curriculum

In the field of pharmaceutical sciences as well, especially pharmacy, education of Kampo medicines and Kampo medicine is essential, as is described as 'crude drugs and Kampo medicines in modern medical care' in

the 2002 core curriculum of a pharmaceutical education model. As a result, learning a broader range of knowledge became needed in addition to conventional pharmacognosy, medical botany, and natural products chemistry. This consequence is reasonable, given that Kampo medicines and crude drugs are pharmaceutical products being used in medical practice. In 2006, pharmaceutical education for training pharmacists extended from 4 to 6 years, and greater emphasis has been placed on pharmaceutical health care including Kampo in pharmaceutical education.

4. Problems in prescription of Kampo medicines

Although the widespread use of ethical Kampo products is still in an initial stage, so-called abuse or disorder occurs in prescription. Kampo medicines are originally decoction, of which formulae were defined in a traditional 'manner' and did not deviate largely. However, with the appearance of simple and convenient extract formulations, combined use of more than two formulations (of which the necessity is doubtful) has occurred without difficulty. This situation will last until new 'manners' for prescription of extract formulations are established and are spread. Novel development or innovation is expected to utilize Kampo extract formulations — therapeutics derived from precious natural resources — efficiently and effectively.

Change in social thinking

In retrospect of the postwar history, the driving force that has pushed forward Kampo medicine is obviously the expectation of Japanese people for Kampo medicines. Facing disasters of environmental pollution and drug poisoning in the rapid economic growth period starting in around 1960, the people promptly found out the fragility of an industrialized society and sought to restore the deteriorating natural environment. Such a movement of mind was very common to the Japanese, consistent with the spirit of keeping health by combining natural products (crude drugs).

As a result of the so-called governmental screening of budget requests abruptly carried out in 2009, a designated working group was reported to have reached a conclusion that 'OTC drugs analogs should be excluded from the coverage of the national health insurance.' This action was regarded as a novel 'exclusion of Kampo medicines from the reimbursement,' and ignited the aspiration of people for Kampo therapy, as evidenced by a total of 924,808 signatures collected in a short period of about two weeks. People did not want to purchase Kampo medicines according to the instruction of a guide book, but did clearly express their desire to take Kampo medicines as the drugs prescribed on the basis of established diagnosis by experienced physicians. And they also have a confidence that Kampo therapy will be a medical treatment able to better protect their health, in the future perspective of higher–quality medical care in Japan. We must keenly realize our obligation to fulfill their expectations, as Kampo specialists. (Honorifics omitted)

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Appendix: A Chronology of Kampo History (after the War)

Takao Namiki

Oriental Medicine -related Activities		Main events in Japan	
1947	An order for acupuncture and moxibustion prohibition is issued from GHQ.（The ban is withdrawn 3 months later） The first lecture of the Voluntary Course of Oriental Medicine opens (Chiba Medical School in Chiba).	1945	End of the World War II
1950	The Japan Society for Oriental Medicine (JSOM) is established.		
1954	"*Kampo no Rinsho*(漢方の臨床, *Journal of Kampo Medicine*)" is launched by the East-Asian Medical Association in Japan.	1951	Treaty of Peace with Japan (Treaty of San Francisco)
1957	Kampo extracts are first marketed.		
1959	Twenty kinds of crude drugs are listed in drug price list.	1961	Medical service system for the whole nation (national health insurance system)
		1964	Tokyo Olympics
1967	1st meeting of Symposium on WAKAN-YAKU is held.		
		1970	Osaka Exposition
1972	Oriental Medicine Research Center, the Kitasato Institute is established		
		1973	The first oil crisis
1976	Kampo medicines are listed in drug price list.		
1978	Institute of Natural Medicine in Toyama Medical and Pharmaceutical University is established.		
		1979	The second oil crisis
1984	The Medical and Pharmaceutical Society for WAKAN-YAKU is established.		
1989	JSOM initiated a system called 'Board Certified Member of the Japanese Society Oriental Medicine' (establishes a specialist accreditation system)		
1991	JSOM becomes a Member of Japan Medical Association		

1992	Tokyo Women's Medical University sets up Institute of Oriental Medicine.		
1996	Interstitial pneumonia due to shosaikoto is published.		
1997	The Association of Clinical Kampo physicians is established.		
2001	'Ability to explain outline of Wakan-Yaku' is described in Model Core Curriculum for Medical education: (draft of Educational Guideline)		
2002	'Crude drugs and Kampo medicines in modern medicine' is stipulated in the revised Pharmaceutical Education Model Core Curriculum.	2004	Start of the new clinical training system
2005	The Japan Liaison of Oriental Medicine (JLOM) is established		
2010	The integrated medical care project team is launched by the Ministry of Health, Labour and Welfare.		

Future Perspective

Kenji Watanabe

Introduction

In the first volume entitled "*Otsuka Keisetsu Chosakushu* (大塚敬節著作集, *Collected works of Keisetsu Otsuka*)," Keisetsu Otsuka writes, 'Oriental medicine is now confronted with a difficult situation. One critical issue is the exhaustion of resources, namely herbal resources and practitioners with a deep knowledge of Kampo. A period of a few years to more than a dozen years is required to replenish these resources. ----- An increasing number of physicians are now prescribing Kampo medicines. However, the Kampo prescription by physicians of Western medicine without knowledge of Kampo diagnosis often adversely affects the medical condition of patients who then seek the help of Kampo physicians.'

Although the above alarming message was written more than thirty years ago, the situation has not improved, no appropriate measures have been taken to improve the situation, and the situation even seems to have deteriorated.

This section describes the direction that Kampo medicine should be heading and the issues needing attention. The problems of Kampo medicine are discussed in a separate section, here, I would like to discuss about the future direction of Kampo medicine and challenges for that direction.

Integration of Oriental and Western medicine to optimize medical care

Traditional medicine in Japan has focused on solving problems on a case-by-case basis without formulating a grand design for the future Kampo medicine. The goal should be to establish medical care that only Japan can offer.

To this end, it is necessary to continuously ask how Kampo practice can always take social needs into account. The perspective and goals of Kampo medicine may and should be adaptable to the needs of the times. Keisetsu Otsuka said, 'Why have long-established stores been able to survive? Because they have adapted themselves to the needs of the age and this is how tradition is built up.' Although what is written here in 2011 may not be valid in 2030, it is hoped that Kampo medicine will stand the test of time by transforming itself.

Among the many issues that Japan and the world are currently facing, the following two issues are discussed below.

1. Management of chronic diseases

Most routine medical practice is devoted to management of chronic diseases, which accounts for a substantial proportion of the medical care cost. Given the aging of the population and growth in medical spending, our immediate goals are to maintain the health of the elderly and to prevent diseases in the younger population.

Typical chronic diseases include lifestyle diseases such as obesity, hyperlipidemia (excluding familial hyperlipidemia), type II diabetes, hyperuricemia, and hypertension. Moreover, cancer, ischemic heart diseases, and cerebrovascular disorders (which cause 60% of the deaths in Japan) are closely associated with lifestyle.

In the cancer area, the demand for Kampo products ought to be greater in the field of cancer treatment, but are poorly utilized. One reason may be that conventional treatment focuses mainly on knocking the cancer out. However, in recent years there has been a slight shift of focus. More specifically, for the elderly, the focus is likely to be on improving quality of life (QOL) rather than combating cancer. Even though Kampo therapy has little anticancer effect, it can improve QOL by increasing appetite, enhancing immunity, etc. Kampo therapy will be appreciated not only for its palliative effect in poor prognosis cases but also for its preventive effect on relapse and metastasis.

Arteriosclerosis often underlies ischemic heart disease and cerebrovascular disorders. Since some studies show that Kampo formulations prevent arteriosclerosis, their use in this field is also expected.

Another factor affecting these vascular disorders which has drawn attention in recent years is diabetes. Some Kampo formulations and crude drugs are said to have an antihyperglycemic effect. However, a wide range of hypoglycemic agents have become available, and the use of insulin has become more sophisticated in these days. Incretin-related pharmaceuticals have been attracting attention over the last few years as they are unlikely to cause hypoglycemia. Nonetheless, the prevention and treatment of complications have not been adequately addressed. Kampo formulations with effects on diabetes complications, such as goshajinkigan (牛車腎気丸) for diabetic neuropathy, will draw increasing attention. Prevention of diabetic nephropathy requiring hemodialysis is another critical issue.

Among the chronic diseases, those causing pain are most prevalent in the elderly. Long-term administration of nonsteroid anti-inflammatory drugs (NSAIDs) in the elderly is not recommended because NSAIDs increase their risk of peptic ulcer or deterioration of renal function. Needless to say, Kampo formulations are useful in controlling pain, although acupuncture and moxibustion are particularly important tools in this area. Numerous studies worldwide have described the effect of acupuncture and moxibustion on knee arthropathy and low back pain.

Since various background factors contribute to the risk of these chronic diseases, a simple scheme such as use of antibiotics against the causative microorganism cannot be effective. In Western medicine, concomitant use of multiple agents is likely to cause adverse effects in the elderly. On the other hand, Kampo formulations as well as acupuncture and moxibustion offer treatment with lesser adverse effects.

2. Measures against emerging infectious diseases

Traditional medicine is generally considered to be effective solely for chronic diseases. However, in fact, it also has a profound effect on acute infectious diseases. Specifically, "*ShangHanLun* (傷寒論)," a must-read classic for students of Japanese Kampo medicine, focuses on the treatment of sexually transmitted diseases. Currently the particular focus is on the treatment of emerging infectious diseases. It is hard to say whether

Kampo therapy played an adequate role in coping with severe acute respiratory syndrome (SARS), avian flu, and the pandemic of swine flu in 2009. In China, 'Lianhua Qingwen (連花清瘟) capsules,' a combination of makyokansekito (麻杏甘石湯) and gingyosan (銀翹散), was designated as a Key National New Product. Clinical studies of the drug were vigorously promoted, yielding favorable results. Lianhua Qingwen capsules were also adopted as swine flu countermeasures by the Chinese government. Furthermore, the *Lancet* reported that glycyrrhizin, a constituent of Glycyrrhiza (甘草, kanzo) is a potent inhibitor of the SARS virus.

The advantage of Kampo therapy for emerging infectious diseases is that it lessens the possibility of viral resistance to therapy via eliminating the viral load through enhanced host immunity rather than the antiviral effect mediated by direct interaction. Also Kampo formulations can be used concomitantly with antiviral drugs without adverse reactions, as they work through a different mechanism.

3. Integration of traditional and Western medicine

In the world, traditional medicine and Western medicine do not antagonize but are evolving as agonists to be used together. In China where 'integration of Chinese and Western medicine' is actively promoted, half of the curriculum in universities of Chinese medicine focuses on Western medicine. Guangzhou University of Chinese Medicine, for example, has four affiliated hospitals where both cutting-edge Western medicine and traditional Chinese medicine are integrated, and graduates of this university administer anesthetics and perform surgery.

On the other hand, there is a growing concern that the decreasing number of authentic Chinese medicine practitioners will lead to the collapse of Chinese traditional medicine. Graduates of universities of Chinese medicine are qualified to practice Western medicine. Hence an increasing number of graduates choose to practice Western medicine because treatment is relatively easy to give once diagnosis is made, in comparison with Chinese medicine treatment that requires long-term learning. Additionally practicing Western medicine produces more income than practicing Chinese medicine. Unit prices for Chinese medical services, specifically acupuncture and moxibustion, are too low to make a living.

In Hong Kong, Chinese medicine practitioners are not permitted to practice Western medicine. According to the Department of Health of Hong Kong, the aim of this regulation is to preserve authentic Chinese traditional medicine. A similar situation can be seen in Korea. At one time conflicted, Oriental and Western medicines are now promoting harmony.

Japan presents a unique situation: acupuncturists and moxibustionists are prohibited from practicing Western medicine while certified physicians of Western medicine are permitted to practice Kampo medicine.

What type of integration is desirable will be determined by history. Presently in Japan, Kampo medicine is merging with cutting-edge Western medicine relatively easily since certified physicians of Western medicine can prescribe Kampo medicines.

4. Issues concerning the integration of Oriental with Western medicine

Japan, Korea, mainland China, and Hong Kong have been trying to integrate Oriental and Western medicine in different ways. In Japan, the practice of acupuncture and moxibustion is limited to non-medical settings, and their integration with Western medicine has hardly begun. Japan must step up its efforts to promote integration of Oriental and Western medicine.

Although understanding about how Kampo formulations can be used as remedies is increasing, most formulations are used as part of Western mainstream medicines. For examples, rikkunshito (六君子湯) and yokukansan (抑肝散) are considered along with Western drugs to be among the options for treatment of functional gastrointestinal disorders and peripheral symptoms of dementia, respectively. It seems that treatment using most Kampo formulations is from the perspective of Western medicine in Japan.

To promote the clinical use of Kampo medicines and take advantage of their distinct characteristics (individualization and holism), it is necessary to address the following issues:

4-1. Development of an easily comprehensible system of Kampo medicine and improvement of education

Kampo formulations have improved remarkably since 1976 when ethical Kampo formulations were first introduced. Strict quality control including inspection systems that check levels of agrochemicals and heavy metals has been put into place. The latest statistics show that 83.5% of physicians in Japan routinely use Kampo products.

However, taking into account that they prescribe only one or two Kampo products applicable to their specialized area, it is doubtful that Kampo medicine is practiced in the true sense. Keisetsu Otsuka said, 'Tradition is built up by adaptation to the needs of the times.' Since more than 30 years ago, Kampo formulae have evolved without doubt, but has Kampo medicine itself evolved?

The pursuit of Kampo medicine is currently more vigorous than ever before. Kampo medicine originated in ancient China, namely during the Han (漢) Dynasty, as the Chinese character for Kampo medicine (漢方医学) indicates. The ancient Chinese medicine which came to Japan uniquely evolved into Kampo medicine. The system of Chinese medicine of the Han Dynasty period was quite simple, specifying the use of a herbal combination for a specific symptom. However, the enthusiasm to identify the mechanism of action resulted in the primacy of theory over practice in China. In Japan, during the Edo Period (AD 1603 – 1868), the Gosei school of Kampo medicine was dominant until physicians influenced by the philosophy of Jinsai Ito, known as Kogigaku, established the Koho school (which excluded unnecessary theories and advocated practical medicine). The Sechu school which blends traditions from the Koho and Gosei schools emerged in the later Edo period and lasted to the Showa period (AD 1926 – 1989). Thanks to the Kampo medicine giants in the Showa period—Keisetsu Otsuka (Koho school), Domei Yakazu (Gosei school), and Shiro Hosono (Sechu school)—the basis for modern Kampo medicine was established free of conflicting interpretation. Today the practice of Kampo medicine extends beyond Kampo practice as advocated by these schools.

Over the past ten years, however, Chinese medicine has been actively practiced in Japan. Three types of Chinese medicine can be identified by their period: pre-Mao, Mao to national standardization (1995), and post-standardization.. The first is practiced in Taiwan and shares a number of characteristics with Japanese Kampo medicine despite their different theoretical underpinnings. Yet, the theoretical system was unified during the Mao to standardization period, the second developed into a different system, but practitioners retained some individual freedom. It was under 'GB95' in 1995 that the system was standardized. The 'GB95' was a classification system of sho, or patterns, established by the Chinese government in 1995, lists 2,300 'pattern' codes. In fact, these codes are not fully utilized clinically and some universities have established their own classification system. The Traditional Chinese Medicine (TCM) of post-standardization is well organized

(i.e., the system of medical education is standardized and under state control), but it does not seem to reflect the needs of healthcare professionals. The total number of the codes, including diagnoses made before the national classification system was established, is said to exceed 30,000 and even the Chinese government cannot determine the exact number.

What is the basic classification system of Japanese Kampo medicine? 'Sho' is uncommonly used on viscera, except for deficiency of upper abdominal region (*Hikyo*) and deficiency of lower abdominal region (*Jinkyo*). It is necessary to build a consensus about the basic classification system of Kampo medicine.

The currently undertaken World Health Organization International Classification of Traditional Medicine (WHO ICTM) Project aims to establish a classification system for the traditional medicines of East Asian countries. This system is expected to be the cornerstone of Japanese Kampo medicine in the future. This project has a critical role in determining the basic classification system of Japanese Kampo medicine.

4-2. Promotion of clinical research

The greatest obstacle to conducting clinical research on Kampo products is 'individualized medicine.' Conventional randomized controlled trials (RCTs) are based on an assumption that a population can be standardized to generate statistical significance by increasing the number of subjects. The Kampo medicine system assumes that individuals vary. Thus, the basic Kampo approach is different from that of other systems. Moreover, Kampo is based on the concept that each part of the body is connected to every other part to make up the whole system. For example, headache may be treated to resolve edema. What is called for is a methodology that facilitates the conduct of clinical research from this unique perspective.

One possible approach is multi-dimensional analysis: specifically, construction of a database from available data using a data mining method and then performing data analysis. Now the door to the age of genomic medicine is about to open. Since genome analysis using a data mining approach is based on the assumption that the genome varies among individuals, the same approach can be applied to analysis of Kampo treatment, which varies among individuals.

Conventional inclusion criteria used in the clinical trials of Western medicine will also be applied to trials where a) some results can be obtained without individualization (e.g., preventive effect of daikenchuto [大建中湯] on postoperative ileus) or b) diseases which present a specific pattern (e.g., the TaiYo stage [*Taiyobyo*] in early swine flu infection). By performing these randomized controlled trials, the system of Kampo medicine will become more comprehensible to physicians of Western medicine.

5. Global promotion of Kampo treatment as part of Japanese medical care by strengthening cooperation with the Japanese government

Strengthening cooperation with the Japanese government can help globally promote Kampo medicine in Japanese medical care and thereby lay a firm foundation for integration of Oriental and Western medicine and for coping with ongoing globalization. To this end, establishment of close public-private partnerships is essential.

Currently the Japan Liaison of Oriental Medicine (JLOM), in close partnership with Japanese medical societies related to traditional medicine and WHO cooperative centers, serves as an international negotiator. Global promotion of Kampo medicine should be national policy. By forming close public-private partnerships,

Japan can establish a firm system comparable to those of China and Korea.

6. Conclusion

Although Japanese Kampo medicine is confronted with a number of issues, none of them is insurmountable. Rather these issues are expected to expand future perspectives.

■ Column ■

Ikkando Kampo Medicine

Keido Yakazu, Yoshihide Yakazu

Origin of the name 'Ikkando'

Dohaku Mori (1867–1931) was a Kampo physician active in Japan from the Meiji period through the Taisho and into the early Showa period. The name of his clinic, '*Ikkando Ryoin* (一貫堂療院, Ikkando Clinic),' comes from Yusa Ikkando, the name of the pharmacy of Mori's teacher, Taishin Yusa (Note 1). The name 'Ikkando' is derived from the words of *Kong Zi* (孔子) in the "*LunYu* (論語, Analects)" － '*Godo Ikkan* (吾道一貫, the way that Master advocated is simply loyalty and forgiveness).' Kampo was in decline during that period, but Mori was determined to revive it and to do so demonstrated great determination, adhering resolutely to his convictions.

Ikkando medicine

In 1964, in Mori's later years, his therapeutic system was published as "*Ikkando Kampo Igaku* (一貫堂漢方医学)," compiled by his pupil Kaku Yakazu (Note 2). The book is largely comprised of explanations of the 'three main patterns' (blood stasis pattern [瘀血証体質], visceral poison pattern [臓毒証体質], and detoxication pattern [解毒証体質]) and their treatment, the 'five prescriptions (五方)' (tsudosan [通導散], bofutsushosan [防風通聖散], saikoseikansan [柴胡清肝散], keigairengyoto [荊芥連翹湯], and ryutanshakanto [竜胆瀉肝湯]). This is commonly referred to as Ikkando medicine, meaning the 'three main patterns and five prescriptions (三大証五方).' However, it was simply the therapeutic system that Mori employed in his later years. The five prescriptions were used frequently mainly because of the social climate of the times (see below).

Mori actually utilized a wide range of prescriptions, not just the "five prescriptions"; in fact, Ikkando's 'standard formulary' was the "*Kokon Hoi* (古今方彙)" (Note 3). So, Mori did not restrict himself to either the Koho [古方] or the Gosei [後世] school of Kampo medicine. He also used acupuncture and moxibustion in combination to enhance therapeutic efficacy. Mori's approach contrasts with that of Kyushin Yumoto (1876–1941), who focused on the ancient prescriptions (*Koho*) and made the "*ShangHanLun* (傷寒論)*"* his bible.

The three main patterns and five prescriptions

The three main patterns classification is a unique therapeutic system based on 'classification of constitutions.' In Mori's day, no treatment could cure tuberculosis and stroke (cerebrovascular disorder). He therefore devised a therapeutic system that combined elements of 'preventative medicine' in an attempt to prevent these diseases. Here is an outline of his system.

1. Blood stasis pattern

- Cause: Blood stasis
- Main targets for prevention: Stroke, stomach ulcer, hemorrhoids, gynecological diseases
- Treatment: Tsudosan (通導散) (Note 4) (In fact he used kyukichoketsuindaiichikagen [芎帰調血飲第一加減], botampisan [牡丹皮散], Saikosokanto [柴胡疎肝湯], and the ancient prescriptions tokishakuyakusan [当帰芍薬散], keishibukuryogan [桂枝茯苓丸], tokakujokito [桃核承気湯], daiobotampito [大黄牡丹皮湯], geoketsugan [下瘀血丸], daioshachugan [大黄䗪蟲丸], and teitogan [抵当丸], as well as tsudosan.)

2. Visceral poison pattern

- Cause: stomach poison (*Shokudoku,* metabolic disturbance accumulation) and fluid disturbance (*Suidoku*) (Note 5)
- Main targets for prevention: Lifestyle diseases (such as arteriosclerosis and stroke) and renal disease
- Treatment: Bofutsushosan

3. Detoxication pattern

- Cause: Given that 'in this context, poison means the poison rendered harmless by a detoxicant (shimotsuorengedokuto [四物黄連解毒湯]), not visceral poison,' the cause is most likely a heat toxin (熱毒) requiring a heat pattern-treating (*Seinetsu*) formulae. (Note 6)
- Main targets for prevention: Infectious diseases such as tuberculosis and syphilis
- Treatment: Shimotsuorengedokuto (Note 7) and associated prescriptions

shimotsuorengedokuto is combined shimotsuto (四物湯) with the heat pattern-treating (*Seinetsu*) formulae orengedokuto to allow for its long-term usage. Other prescriptions based on this include saikoseikanto (柴胡清肝湯), which is strengthened to nourish Yin (滋陰), treat heat pattern, and detoxify; keigairengyoto (荊芥連翹湯), strengthened to expel pus (排膿) and wind (祛風); and ryutanshakanto (竜胆瀉肝湯), strengthened to treat fluid disturbance (利水), clear the liver (清肝), and purge fire (瀉火).

Saikoseikanto is used in clinical practice for children susceptible to bronchitis, tonsillitis, pharyngitis, rhinitis, and otitis media. Keigairengyoto is good for adolescents susceptible to tuberculosis, chronic sinusitis, otitis media, and neurosis. Ryutanshakanto is used for adults susceptible to sexually transmitted diseases such as gonorrhea, as well as cystitis and female urological diseases.

These constitutional classifications and treatments are even now employed for various diseases. (For example, the formula used for detoxication pattern can also be used for allergic diseases such as atopic dermatitis.)

Changes in lifestyle and environment owing to prosperity and the Pacific war

The unprecedented prosperity in Japan following World War I changed eating habits and stimulated the consumption of nutritious foods, especially meat. This increased the prevalence of stroke. In other words, it

increased the prevalence of the visceral poison pattern. We can therefore surmise that Mori increasingly prescribed bofutsushosankagen (防風通聖散加減) in his later years.

Yet, after Mori's death and the start of World War II (the Pacific War), food became scarcer, nutrition worsened, and psychological fatigue added to the problem, which meant more frequent use of warm-tonifying formulae (温補剤). This prevented Mori's pupils from using the five prescriptions, which mainly purge cold and coolness (寒凉攻下). Although this situation continued after the war, Japan moved into a period of rapid growth, prompting increased use of the five prescriptions.

This demonstrates how pathological conditions vary with changes in lifestyle, environment, and diet. That is, patterns change, and inevitably so do therapies (prescriptions). This is a principle and general rule of Kampo medicine.

As mentioned above, 'the three main patterns and five prescriptions' were simply Mori's therapeutic system during his later years, and it was mainly contemporary social factors that led to the establishment of his system. The basis for this system was accumulated clinical experience, not theory, and as a uniquely Japanese therapeutic system, it is very interesting.

Treatment of Spanish flu

The Spanish influenza (Spanish flu) epidemic, which struck during World War I (1918), is historically notable for its devastating effects. Antibiotics and antiviral drugs had not yet been discovered. Worldwide fatalities were high.

Mori treated patients during this period according to his three-type classification system. He administered kososankahange (香蘇散加半夏) / Atractylodes Rhizome (白朮, byakujutsu) / Poria Sclerotium (茯苓, bukuryo) to gastrointestinal patients, shoseiryutokakyonin (小青竜湯加杏仁) / Gypsum (石膏, sekko) to pneumonia patients, and shomakakkontokabyakushi (升麻葛根湯加白芷) / Cnidium Rhizome (川芎, senkyu) / Asiasarum Root (細辛, saishin) to cerebral disease patients, thereby saving many lives.

Being a part of Mori's medical practices, this system too can be included under a broad definition of Ikkando medicine.

Extract formulations based on Ikkando prescriptions

- Saikoseikanto (柴胡清肝湯)
- Ryutanshakanto (竜胆瀉肝湯) (source differs among some Kampo extract formulations for prescription)
- Keigairengyoto (荊芥連翹湯)

NOTES

1. Taishin Yusa was an obstetrician from Miyagi prefecture. The suspicion that his name was actually Kaishin, not Taishin, is well founded.

2. In fact, based on verbal statements by Kaku Yakazu, his younger brother Yudo Yakazu systematized the three main patterns and Domei Yakazu completed the book.
3. Formulary compiled by Tsugen Koga (1745). Most prescriptions listed in this formulary are sourced from "*WanBingHuiChun* (万病回春)," but it also refers to 63 Chinese medical texts and records 1229 prescriptions. It was a favorite among doctors and became more popular than "*Shuho Kiku* (衆方規矩)" because it classifies most prescriptions by disease type, regardless of provenance (prescriptions by Koho or Gosei school of Kampo medicine).
4. Dohaku Mori established applications for tsudosan through his use of it for crush syndrome in victims of home collapse in the Great Kanto Earthquake.
5. Stomach poison (*Shokudoku*), wind toxin (*Fudoku*), fluid disturbance (*Suidoku*), and syphilis (*Baidoku*) are defined as visceral poisons (臓毒, *Zodoku*).
6. Constitution prone to inflammatory response to external irritation.
7. Shimotsuorengedokuto is close to unseiin (温清飲), but to be exact, it is shimotsutogoorengedokutokarengyo (四物湯合黄連解毒湯加連翹) / Bupleurum Root (柴胡, saiko) / Glycyrrhiza (甘草, kanzo)

Chapter 2

Distinctive features of Japanese Kampo medicine

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Medical theory proposed by Todo Yoshimasu

A system of knowledge bundled as Japanese Kampo medicine, as described in Chapter I, actually comprises a broad spectrum of wisdom obtained from historical and inevitable courses of development. Its characteristic backbone is "*Iron* (医論, *The Medical Theory*)" authored by Todo Yoshimasu (1702-1773) (1).

Todo Yoshimasu denied all doctrines of traditional Chinese medicine (Yin-Yo [陰陽] doctrine; five elements doctrine; solid and hollow viscera [*ZangFu*]; meridian and collateral), and proposed a unique medical theory on the basis of so-called an existential empiricism or structuralism-based recognition method (2). Its basic principles are as follows:

1) The physician must be able to cure the patient on the basis of exact observation without speculation or conjecture (such a physician is called '*Shitsui* [疾医]').

2) An ideal physician is *Bian Que* in the ancient times. Ancient literatures should be learned that show "a world in the raw" with no speculation, conjecture, or modification.

3) Existing Chinese medicine, in which diseases are classified in many categories and diagnosed, then various measures are discussed, is filled with speculation and conjecture. In reality, all diseases develop from only one poison, transform in the body, and merely are manifested in the form of various symptoms and signs. Accordingly this poison can be eliminated with another poison, a drug. Thus the phrase 'All kinds of disease are caused by one poison (*Manbyo Ichidoku*)' is born.

4) Kampo formulae closer to their ancient prototypes are preferable, because those ancient formulae were devised by *Shitsui* and actually have been and are very effective. Accordingly, it is recommended that treatment be fundamentally based on the "*ShangHanLun* (傷寒論)" and "*JinGuiYaoLue* (金匱要略)" earliest established by *Zhang Zhong Jing*. However, since many speculations, conjectures, and annotations were later added to these classics, the ancient original forms must be selected carefully. The most important is that each formulation should be administered via being matched to a specific form of poison, or 'pattern.' This is called 'formula versus pattern (*Hosho sotai*).'

5) Since a poison is attacked with another poison, violent reaction/response occurs in the healing process. This is called paradoxical healing response (*Mengen*). Even old people say that 'if administration of a medicine does not induce *Mengen*, the disease will not cure.' Fearing the *Mengen* is a step in the wrong direction to *Shitsui.*

6) The use of some poison may cause patient's death. However, the death is not due to the poison (drug). Precisely, life or death is decided by God, not by human being. Thus, the physician should realize that he/she cannot predict life or death, and devote to do his or her best for the treatment of disease, as there is a saying that 'we can do what is humanly possible and leave the rest to fate.'

7) Kampo formulations, whether being ancient formulations or subsequent formulations, must be directly tested via repeated trials in clinical settings to evaluate the form of illness (pattern) and efficacy. Such is the case with crude drugs. Then only the formulations and crude drugs for which the efficacy has been established are used in clinical practices. This process is called 'direct trial experiment (*Shinshi Jikken,* 親試実験).' Not ancient but subsequent formulations, if proved to be effective in *Shinshi Jikken*, can be utilized smoothly.

8) Unless the true form of poison is found out without any speculation or conjecture, optimal formulations

cannot be selected. For that purpose, the entity of poison must be gained, namely by abdominal examination that is clinically the most important medical examination. Tension, stiffness, muscle contracture, and palpitation manifest on the abdominal region must be closely and carefully palpated. Next important is check for the signs appearing on the body surface. Detailed observation and careful auscultation should be carried out for spontaneous sweating, heat sensation in the upper half body and coldness in the lower half body, redness, swelling, and edema, in addition to inquiry about the frequencies of urination and defecation as well as the properties of urine and stool. Skills concerning pattern diagnosis necessary for formula selection must be learned and acquired by the physician himself or herself in clinical practices, and cannot be inherited by offspring or in writing.

Behind this thought, there are 'tacit knowledge' and 'explicit knowledge', which was proposed by Ikujiro Nonaka (3). Clinical knowledge to determine the form of illness, or pattern, manifest in and on a patient corresponds to the former that cannot be expressed in language, rather than the latter that can be expressed.

This is mentioned in a sentence of 'Skills concerning pattern diagnosis necessary for formula selection must be learned and acquired by the physician himself or herself in clinical practices, and cannot be inherited to offspring or in writing' in the above (8).

Needless to say, the 'tacit knowledge' unable to be expressed in language could be explained logically by use of YinYo and five elements doctrines. However, 'language' cannot express all the entity of a matter and the methodology of categorizing all things into five elements cannot approach to the truth of the whole. Therefore, the greatest problem in the logical development based on element reductionism is that the logic cannot reach the starting point 'tacit knowledge' retrospectively.

What is the methodology able to grasp the 'tacit knowledge' itself on the whole? Todo Yoshimasu proposed abdominal signs or body surface signs—that are substantial physical findings—as a mediator for grasping the whole picture. Why such abdominal signs appear is not discussed. Based on system control theory, it is considered for problem resolution that an appropriate formulation (a black box) is adapted to the black-box form of illness grasped on the basis of structuralism. The reason why abdominal examination is particularly emphasized and valued in 'Japanese Kampo medicine' is that the abdominal signs obtained by abdominal examination provide very precise information for the recognition of the black-box form of illness.

The second great achievement of Todo Yoshimasu is to have established the 'independence of formulae', which actually resulted in the work "*Ruijuho* (類聚方)" (1). Until then, Kampo formulae had been perceived to be used for particular diseases classified. But Todo Yoshimasu disregarded the classified diseases and instead regarded formulae as being appropriately utilized depending on the pathological condition (the form of poison), insisting on '*Manbyo Ichidoku*.' A concrete example of Todo-developed methodology can be seen on saikokeishito (柴胡桂枝湯), which is used without inhibition in Japanese Kampo practice for a wide variety of disease, such as frequent headache, chronic hepatitis, chronic pancreatitis, spinal canal stenosis, irritable bowel syndrome, and subacute-phase common cold. For the use, it is essential that the presence of the pathological condition fit for saikokeishito, or saikokeishito pattern, is confirmed in parallel with the expression of proneness to have hot flashes, spontaneous-sweating tendency, hypochondrium resistance and discomfort (*Kyokyo Kuman*), tension of the rectus abdominis, and nervousness.

Todo's medical theory and the subsequent development

Japanese Kampo medicine has developed based on the Todo's medical theory. However, merely complying with the theory as a golden rule might force the Kampo beginners to navigate without a compass. Thus, the following generations have adopted some or all of the Todo-denied YinYo, qi (Ki)-blood-fluid, and five solid viscera doctrines when necessary. On such occasions, the most influential was the medical theory written by Dosan Manase (1507-93), which was then the medical mainstream. As described in the preceding Chapter, Dosan Manase added his unique devices to Chinese Jin-Yuan medicine. His medical textbook titled "*Keitekishu* (啓迪集)" (with the preface written in 1574) (4) contains the idealism-based, intricated, and detailed theory of Chinese medicine in an extremely simplified form and implies the direction to seek the form of illness fit for a certain formula. In belief, it reminds of the prototype of formula versus pattern (*Hosho Sotai*). This tendency is particularly notable in '*Chubumon* (the wind-impact field)' and '*Shokanmon* (the cold damage diseases field).'

To be pointed out here is that Dosan Manase and related school used YinYo and five-elements doctrines as a compass for formula selection adjunctively, whether they were obviously conscious of it or not. Specific examples can be seen in "*Igaku Tensho ki* (医学天正記, issued in 1627)" (5), the clinical notes of Gensaku Manase (1549–1631), adoptive heir of Dosan. There is no evidence of logical building based on element reductionism and of reaching the form of illness (pattern) fit for a particular formula, but a direct approach to the appropriate formula is shown.

A school based on the Todo's methodology was called Koho school, whereas a Dosan-headed school was named Gosei school. In the middle 18 century when Todo actively performed, both schools were dramatically opposed to each other. However, from a viewpoint of medical care practice and young people education, they came to realize that integrated use of the methodologies of both schools would be fruitful. Then a new school which worked on the eclectic medical ways was established chiefly by physicians of the Edo-Igakukan (medical school of the Shogunate government), and termed Sechu school. Sohaku Asada (1815-1894), one of the Sechu school, authored "*Futsugo Yakushitsuhokan Kuketsu* (勿誤薬室方函口訣, A collection of more than 600 prescriptions during long medical experiences)" (6), in which formulae are listed in the order of Japanese alphabet. This may succeed to the Todo's policy of "independency of formulae" that he proposed via setting formulae free from the restriction by disease name.

The content of Japanese Kampo medicine

Over the above-mentioned history, the Gosei, Koho, and Sechu schools of Kampo medicine were born and have grown up in Japan. In the Taisho and early Showa periods (before the War), there were four schools:

1) A school promoted by Keijuro Wada (1872-1916), Kyushin Yumoto (1876-1941), and Keisetsu Otsuka (1900-80), toward rediscovery of Koho → Kokan medical school (included in the Koho school)

2) A lineage traced by Kenzo Okuda (1884-1961), Masatsugu Wada, Ken Fujihira (1914-1997), Shigenari Ogura, and others → Koho school

3) A lineage from Dohaku Mori and Kaku Yakazu to Domei Yakazu (1905-2002) → Gosei school

4) A lineage from Sogoro Niizuma and Shiro Hosono (1899-1988) to Hiroshi Sakaguchi (1921-2003) → Sechu school

However, decisive differences from the Edo period are exchange and cooperative systems among schools due to the union for a common purpose created in 1930s. The period between 1931 and 1941 is considered to have been the early development stage for the current 'Japanese Kampo medicine.' After the War, the union for a common purpose transformed to the Japan Society for Oriental Medicine (established in 1950) and the Association of East-Asian Medicine (restarted in 1954).

Of 'Japanese Kampo medicine' having been grown in this way, the current distinctive features are listed as follows:

1) The basic principle is formula versus pattern (*Hosho Sotai*) theory (Sho [pattern]-based therapy).

2) Every school values abdominal examination.

3) Abdominal examination varies among schools: examination using three positions and nine indicators is likely to be adopted by both the Sechu and Gosei schools, but not by the Koho school.

4) Unlike traditional Chinese medicine which uses dialectic-assisted treatment comprising pattern determination via element-reductionism-based logical building, Japanese Kampo medicine prefers direct grasping of tacit knowledge based on the entity from a structuralism view, and uses Yin and Yo, qi (Ki)-blood-fluid, and five solid viscera doctrines.

5) Accordingly, Japanese Kampo medicine does not use disease names such as *Keppisho* (血痺症) and *Kan'yokyosho* (肝陽虚症), but adopts kakkonto pattern, saikokeishito pattern, and other patterns in classification of diseases.

6) Todo's medical theory excludes idealism and seeks a clue among substantial symptoms and signs. The current Japanese Kampo medicine also makes continuous efforts to establish pattern diagnoses with the aid of diagnostic tools (such as diagnostic imaging and pathological diagnosis) used in Western medicine.

7) In actual clinical scenes, appropriate and safe combination of Kampo medicines and Western drugs is being carried out depending on the occasion.

8) Objective evaluation of clinical efficacy and monitoring of adverse drug reactions are routinely conducted via blood biochemistry and other laboratory tests, if necessary.

Despite the above-mentioned common characteristics shared, the Japanese Kampo schools maintain their representative formulae for routine use. This is well understood by the Japanese health, labour, and welfare administration, whose adequate consideration is implied from the sources of the Kampo extract products listed in the National Health Insurance (NHI) drug tariff (Table 1).

Table 1 Classified sources of Kampo extract products listed in the NHI-covered-drug tariff

Sources are *ShangHanLun* and *JinGuiYaoLue*. Routine formulae being used in Koho school are as follows:

Inchinkoto (茵蔯蒿湯), inchingoreisan (茵蔯五苓散), unkeito (温経湯), eppikajutsuto (越婢加朮湯), ogikenchuto (黄耆建中湯), ogonto (黄芩湯), orento (黄連湯), kakkonto (葛根湯), kanzoto (甘草湯), kambakutaisoto (甘麦大棗湯), kikyoto (桔梗湯), kyukikyogaito (芎帰膠艾湯), keishikaogito (桂枝加黄耆湯), keishikakakkonto (桂枝加葛根湯), keishikakobokukyoninto (桂枝加厚朴杏仁湯), keishito (桂枝湯), keishikashakuyakuto (桂枝加芍薬湯),keishikashakuyakudaioto (桂枝加芍薬大黄湯), keishikaryukotsuboreito (桂枝加竜骨牡蛎湯), keishishakuyakuchimoto (桂枝芍薬知母湯), keishininjinto (桂枝人参湯),keishibukuryogan (桂枝茯苓丸), keimakakuhanto (桂麻各半湯), goshuyuto (呉茱萸湯), goreisan (五苓散), saikokaryukotsuboreito (柴胡加竜骨牡蛎湯),saikokeishito (柴胡桂枝湯), saikokeishikankyoto (柴胡桂枝乾姜湯), san'oshashinto (三黄瀉心湯), sansoninto (酸棗仁湯), sammotsuogonto (三物黄芩湯), shigyakusan (四逆散),shishihakuhito (梔子柏皮湯), shakanzoto (炙甘草湯), shakuyakukanzoto (芍薬甘草湯), shokenchuto (小建中湯), shosaikoto (小柴胡湯), shoseiryuto (小青竜湯), shohangekabukuryoto (小半夏加茯苓湯), shimbuto (真武湯), daiokanzoto (大黄甘草湯), daiobotampito (大黄牡丹皮湯), daikenchuto (大建中湯), daisaikoto (大柴胡湯),daijokito (大承気湯), choijokito (調胃承気湯), choreito (猪苓湯), tokakujokito (桃核承気湯), tokikenchuto (当帰建中湯), tokishigyakukagoshuyushokyoto (当帰四逆加呉茱萸生姜湯),tokishakuyakusan (当帰芍薬散), ninjinto (人参湯), hainosankyuto (排膿散及湯), bakumondoto (麦門冬湯), hachimijiogan (八味地黄丸), hangekobokuto (半夏厚朴湯),hangeshashinto (半夏瀉心湯), byakkokaninjinto (白虎加人参湯), bukuryoin (茯苓飲), boiogito (防已黄耆湯), maoto (麻黄湯), maobushisaishinto (麻黄附子細辛湯),makyokansekito (麻杏甘石湯), makyoyokukanto (麻杏薏甘湯), mashiningan (麻子仁丸), mokuboito (木防已湯), ryokankyomishingeninto (苓甘姜味辛夏仁湯),ryokyojutsukanto (苓姜朮甘湯), and ryokeijutsukanto (苓桂朮甘湯)

(69 formulae)

Sources are "*WaiTaiMiYaoFang* (外台秘要方)" and "*QianJinFang* (千金方)" (6th–8th century). Routine formulae being used in schools are:

orengedokuto (黄連解毒湯), shimpito (神秘湯), choyoto (腸癰湯), and tokito (当帰湯)

(4 formulae)

Sources are "*HeJiJuFang* (和剤局方)," "*WanBingHuiChun* (万病回春)," "*JiShengFang* (済生方)," "*NuKeCuoYao* (女科撮要)," and others. Routine formulae being used in Gosei and Sechu schools are:

anchusan (安中散), ireito (胃苓湯), unseiin (温清飲), kamikihito (加味帰脾湯), kamishoyosan (加味逍遥散), kihito (帰脾湯), kyukichoketsuin (芎帰調血飲),keihito (啓脾湯), kososan (香蘇散), gokoto (五虎湯), goshakusan (五積散), goshajinkigan (牛車腎気丸), gorinsan (五淋散), jiinkokato (滋陰降火湯),jiinshihoto (滋陰至宝湯), shikunshito (四君子湯), shimotsuto (四物湯), juzentaihoto (十全大補湯), junchoto (潤腸湯), shofusan (消風散), shomakakkonto (升麻葛根湯), shin'iseihaito

(辛夷清肺湯), jinsoin (参蘇飲), seijobofuto (清上防風湯), seishoekkito (清暑益気湯), seishinrenshiin (清心蓮子飲), seihaito (清肺湯), senkyuchachosan (川芎茶調散), sokeikakketsuto (疎経活血湯), daibofuto (大防風湯), chikujountanto (竹茹温胆湯), chitosan (釣藤散), tsudosan (通導散), tokiinshi (当帰飲子), nijutsuto (二朮湯), nichinto (二陳湯), nyoshinsan (女神散), ninjin'yoeito (人参養栄湯), hangebyakujutsutemmato (半夏白朮天麻湯), bushirichuto (附子理中湯), heiisan (平胃散), bofutsushosan (防風通聖散), hochuekkito (補中益気湯), yokuininto (薏苡仁湯), yokukansan (抑肝散), rikkunshito (六君子湯), ryutanshakanto (竜胆瀉肝湯), and rokumigan (六味丸)

(48 formulae)

Experiences in Japan. The formulae having been created in Japan and being used commonly among schools are:

otsujito (乙字湯), kakkonkajutsubuto (葛根加朮附湯), kakkontokasenkyushin'i (葛根湯加川芎辛夷), kumibinroto (九味檳榔湯), keigairengyoto (荊芥連翹湯), keishikajutsubuto (桂枝加朮附湯), keishikaryojutsubuto (桂枝加苓朮附湯), keishibukuryogankayokuinin (桂枝茯苓丸加薏苡仁), saikanto (柴陥湯), saikoseikanto (柴胡清肝湯), saibokuto (柴朴湯), saireito (柴苓湯), shichimotsukokato (七物降下湯), jumihaidokuto (十味敗毒湯), shosaikotokakikyosekko (小柴胡湯加桔梗石膏), jizusoippo (治頭瘡一方), jidabokuippo (治打撲一方), choreitogoshimotsuto (猪苓湯合四物湯), bukuryoingohangekobokuto (茯苓飲合半夏厚朴湯), yokukansankachimpihange (抑肝散加陳皮半夏), and rikkosan (立効散).

(21 formulae)

In addition, formulations other than the classical formulae, or *Zhong Jing*'s formulae (derived from "*ShangHanLun*" or "*JinGuiYaoLue*") listed in Table 1 are recognized as analogs of the classical formulae, and frequently used for pattern-based treatment. Five-solid- viscera and qi (Ki)-blood-fluid doctrines are also adopted if needed (Table 2).

Table 2 Handling for the formulae other than *Zhong Jing*'s (derived from "*ShangHanLun*" or "*JinGuiYaoLue*") (typical examples)

Group 1: The formulae recognized as analogs to *Zhong Jing*'s, based on formula versus pattern.
Orengedokuto (黄連解毒湯) → regard as an analog of san'oshashinto (三黄瀉心湯)
shimpito (神秘湯) → regard as fit to a dual pattern of makyokansekito (麻杏甘石湯) pattern plus *Kyokyo Kuman* pattern
tokikenchuto (当帰建中湯) → regard as an analog of shokenchuto (小建中湯)
goshajinkigan (牛車腎気丸) & rokumigan (六味丸) → regard as an analog of hachimigan (八味丸)
gokoto (五虎湯) → regard as an analog of makyokansekito (麻杏甘石湯)
kamishoyosan (加味逍遥散) → use based on abdominal pattern such as *Kyokyo Kuman*
Group 2: Application of five solid viscera doctrine
yokukansan (抑肝散)
kihito (帰脾湯) and kamikihito (加味帰脾湯)
hangebyakujutsutemmato (半夏白朮天麻湯)
Group 3: Application of qi (Ki)-blood-fluid doctrine
rikkunshito (六君子湯), shikunshito (四君子湯), juzentaihoto (十全大補湯), ninjin'yoeito (人参養栄湯), shimotsuto (四物湯), and goshakusan (五積散).

Summary

The characteristics of Japanese Kampo medicine have been discussed. The fundamental difference between the recent Western medicine and Japanese Kampo medicine paradigms may be an underlying thought: the former based on element reductionism versus the latter based on structuralism. From a structuralism perspective, disease-fighting reactions and responses expressed at random in a living body can be grasped in block as orderly patterns in mutual relationships.

Similar relationships are found between Chinese medicine and Japanese Kampo medicine. Namely five-elements doctrine represents reducing into five elements; YinYo doctrine, surely element reduction into dualism; qi (Ki)-blood-fluid doctrine, element reduction into trialism. Exactly as the element reductionism in modern science cannot fully explain all the human being whose mind and body as one (*Shinshin Ichijo*, 心身一如) exist dynamically, element reductionisms in Chinese medicine fail to express 'bare conditions of illness (*byosho*, 病症)'accurately.

Pattern diagnosis based on structuralism is 'tacit knowledge,' and essentially all tacit knowledge cannot be transformed to 'explicit knowledge.' As insisted by Todo, tacit knowledge should be acquired on one's own. Nevertheless, 'acquire a tacit knowledge of patterns on your own' should not be told in a place of education. Accordingly, as a compass indicating the rough direction, Yin and Yo, deficiency and excess, qi (Ki)-blood-fluid, and five-solid viscera doctrines are used for convenience. In addition, the mission loaded on people who take the lead in Japanese Kampo medicine is to carefully and closely describe the part of tacit knowledge in the raw as explicit knowledge, as far as possible.

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Chapter 3

Diagnosis and treatment

Pathology and Treatment

Hideki Adachi

Pathological conditions in Kampo medicine are described by the use of terminology and concepts different from those in Western medicine; for example, deficiency-excess (*Kyojitsu*), cold-heat (*Kan Netsu*), and exterior-interior. Appropriate use of these terms and concepts leads to a correct understanding of Kampo medicine. 'Yin (陰) and Yo (陽)' theory is an upper concept of these term groups.

Yin-Yo doctrine as an upper concept

Yin-Yo doctrine is a philosophical concept that tries to comprehend all the matters from the two opposite but complementary aspects in nature, such as 'Yin and Yo' and 'male and female.' This may be a common way of thinking in both Western and Oriental worlds. Under the superior concept 'Yin and Yo,' various combinations of inferior concepts can be assumed. Kampo medicine deals chiefly with the following concepts:

'Deficiency and excess (*Kyojitsu*)'
deficiency: hollow and weak : belongs to Yin
excess: full and strong : belongs to Yo

'Cold and heat (*Kannetsu*)'
cold: being cold : belongs to Yin
heat: being hot : belongs to Yo

'Exterior and interior (*Hyori*)'
exterior: able to be seen by the observer : belongs to Yo
interior: unable to be seen by the observer : belongs to Yin

'Qi (Ki), blood and fluid (*Kiketsusui*)'
qi (Ki): circulating energy that is invisible : belongs to Yo
blood and fluid: circulating elements that are visible : belongs to Yin
(A red element is blood, while a white element is fluid or body fluid)

These terms compose units of two opposite but complementary natures such as 'Yin and Yo.' However, the mutual relationships of these natures are relative, as it is implied that there is a shade gradation (gradual change, tone gradient) between the complete shade and complete sunshine; or it can be said that the shade and sunshine move to each other via such a gradation.

Terms under the concept 'Yin and Yo' possess such relativity and mutual transition.

Five solid viscera and five elements

In addition to Yin and Yo, five elements (wood, fire, earth, metal and water) and five solid viscera (liver [TM], heart [TM], spleen [TM], lung [TM] and kidney [TM]) are used as basic concepts in acupuncture and moxibustion as well as traditional Chinese medicine. The concepts of the engendering cycle '*Sojo*' and the restraining cycle '*Sokoku*' stipulating the mutual relationships among five elements are also used. At present, however, these concepts alone cannot explain clinical findings. Although these may be useful as background information to understand classical literature, their abuse and overuse should be avoided in clinical settings.

But as shown below, the terms including five solid viscera have been customarily employed. The customary terminology is explained here; for example, the concept kidney [TM] of the five solid viscera is different from the kidney in Western medicine, although the two have the same denomination.

So-called Kidney [TM] deficiency (*Jinkyo*)

Is an indication for hachimijiogan (八味地黄丸) (hachimijinkigan [八味腎気丸]) and the like in realistic settings. Generally, refers to impairment of the lower half body, characterized by abnormal urination, thirst, polyposia, edema, reduced reproductive function, low back pain, hearing impairment, visual loss, respiratory dysfunction, and other symptoms. Is often associated with an abdominal pattern of weakness of the lower abdominal region (*Shofuku Fujin*), lower abdominal muscle tension (*Shofuku Genkyu*) or the linea alba below the umbilicus (*Saika Seichusin*). Including the impairment of the lower half body, the term 'deficiency of lower abdominal region (*Gesho no Kyo*)' can be used alternatively.

So-called spleen [TM] deficiency (*Hikyo*), spleen [TM] and stomach [TM] deficiency (*Hii no Kyo*)

Spleen [TM], one of the five solid viscera, and stomach [TM], one of the six hollow viscera, symbolize digestive function. The condition expressed as spleen [TM] deficiency (*Hikyo*) or spleen [TM] and stomach [TM] deficiency (*Hii no Kyo*) can be paraphrased as reduced digestive function. This condition is a typical indication for rikkunshito (六君子湯) and shikunshito (四君子湯), and is characterized by digestive tract symptoms including anorexia, epigastric discomfort feeling, fullness feeling, nausea, and postprandial lethargy as well as reduced physical and mental strength. As abdominal signs, reduced abdominal strength and epigastric splashing sound (*Shinkabu Shinsuion,* 心窩部振水音) are often seen. Thus, this condition can be included in 'upper abdominal region deficiency (*Chusho no Kyo*).'

Liver [TM]

Yokukansan (抑肝散) is picked up. Target symptoms for yokukansan include hypersensitivity such that the patient is said to be excitable; increased irritability (and loss of temper); and increased muscle tone such that spasm is likely to occur. These imply that there are problems in the central nervous system or emotional stability. Such a condition may be liver [TM] abnormality (increased liver energy). The name of yokukansan means a formulation suppressing such an abnormal condition.

Deficiency and excess

A concept of deficiency and excess

Deficiency implies 'the inside is hollow,' whereas excess signifies 'the inside is filled with something.' Naturally, these are relative concepts that transform mutually.

These apparently simple concepts have been associated with confused interpretation, leading to the present conception.

1. Transition of deficiency-excess theory

Tonan (Seichin) Yamada, a physician and historical investigator of the middle Edo period, discussed about the term 'deficiency and excess' and pointed out that 'even '*SuWen* (素問)' contains several confused descriptions such as strong and weak (firm and flaccid) constitution (original: physical strength), and excessive deficiency (original: excess and deficiency) of pathogen and beneficial qi (Ki). Todo Yoshimasu, another physician of the early to middle Edo period (1702~1773), insisted that 'diseases are all seeds of evil' and can be treated only by eliminating the evil from the inside of the body.

2. Definition of deficiency and excess in Modern Japan

On the basis of these circumstances, Kampo experts of the Showa period interpreted deficiency and excess. According to their interpretation, we in the Heisei period can define 'deficiency and excess' as follows:

'Excess' is full physical strength underlying full resistivity and responsiveness.

'Deficiency' is reduced physical strength underlying reduced resistivity and responsiveness.

3. Characteristics of deficiency-excess doctrine in Japan

In Japanese Kampo medicine, a formula is determined on the basis of clinical findings of a patient. Characteristically, discrimination of deficiency or excess is very likely to depend on the degree of abdominal force (evaluated from abdominal potential and the degrees of development and tension of abdominal muscles) as well as the degree of fullness of 'qi (Ki)'—so-called 'being active or energetic.' Unlike traditional Chinese medicine in which deficiency-excess theory deals only with excess or deficiency of bad energy and good energy, Japanese Kampo medicine emphasizes the physical strength or resistivity against a disease or diseases at that time point. Between the two countries, the same term of 'deficiency and excess' represents different meanings.

Treatments appropriate to deficiency and excess

A. Principles

To deficiency, a complement is given, while to excess, the excess is excluded as a rule. However, it is not simple to determine the degree of deficiency or excess, and the determination-based therapeutic selection requires a certain level of experience and knowledge.

B. Specific examples

(1)Initial stage of a febrile disease

An example is the acute phase of febrile diseases such as influenza. The patient shivers with chills, and has a feverish feeling with a red face, in association with arthralgia, low back pain, and headache. Palpation reveals hot and dry skin with no sweat. In this case, pulse is floating and strong and abdominal strength is commonly favorable. These subjective symptoms and objective signs are regarded as reflecting intense resistance reactions to the pathologic process, and therefore judged as excess pattern or between deficiency and excess pattern (*Kyojitsu Chukan Sho*). For excess pattern, maoto (麻黄湯) and the like are offered. For between deficiency and excess pattern supported by the evidence of neck tension and upper umbilical tenderness (Otsuka's *Saitsuten* [pain point just above umblicus]), kakkonto (葛根湯) is often selected. Once maoto or kakkonto is orally taken, gradual sweating will occur and mostly lead to relief of body pain and chills as well as fever. If the patient presents with mild complaints of body pain, chills, and feverish feeling, associated with floating and weak pulse and spontaneous sweating, resistant reaction to the pathologic process is considered to be rather weak. In this case, the patient is diagnosed as having deficiency pattern, which is best treated with keishito (桂枝湯) and the like.

(2)In cases of chronic disease

As an example, menstruation difficulty is taken up. The patient has impatience and anger, associated with abnormal eating behaviors. If she has also solid physical and abdominal strength, hot flashes, a tendency toward constipation, and resistance, scraping pain, or hyperalgesia in the left lower abdominal region, she has excess pattern and is offered tokakujokito (桃核承気湯). If the patient has less intense psychological symptoms, but a prominent constipation tendency associated with eruption, and solid abdominal strength with resistance and tenderness in the right lower abdominal region, excess pattern is considered and will be effectively treated with daiobotampito (大黄牡丹皮湯). However, in the patient with moderate physical and abdominal strength, the presence of resistance and tenderness in or near the umbilicus as well as more or less hot flashes and impatience will lead to a diagnosis of between deficiency and excess pattern (*Kyojitsu Chukan Sho*), then to selection of keishibukuryogan (桂枝茯苓丸). If there is coldness with swelling and other symptoms in the patient having slightly weak abdominal strength, she will be diagnosed as having deficiency pattern, for which tokishakuyakusan (当帰芍薬散) is appropriate. The patient with many complaints who is impatient and has rather weak abdominal strength with weak hypochondrium resistance and

discomfort (*Kyokyo Kuman*) is regarded as having deficiency pattern that is best treated with kamishoyosan (加味逍遥散).

Given that the cases are associated with a pathological condition of blood stasis (*Oketsu*), it has been shown that Kampo formula varies according to deficiency and excess patterns. Actually, not only deficiency and excess patterns but also various parameters must be taken into account for formula making.

Cold and Heat (*Kan and Netsu*)

A concept of cold and heat

Needless to say, cold means being cold and heat, being hot. In Kampo medicine, to determine whether a pathological condition is 'cold' or 'heat' is very important along with differentiation of deficiency and excess. Differential diagnoses of cold and heat as well as deficiency and excess are the key factors for therapeutic strategy.

In reference to the acute febrile diseases described in "*ShangHanLun* (傷寒論)," Yo stages (TaiYo stage [*Taiyobyo,* 太陽病], ShoYo stage [*Shoyobyo,* 少陽病], and YoMei stage [*Yomeibyo,* 陽明病]) of disease transformation are characterized by the nature of heat, whereas Yin stages (TaiYin stage [*Taiyinbyo,* 大陰病], ShoYin stage [*Shoyinbyo,* 少陰病], and KetsuYin stage [*Ketsuyinbyo,* 厥陰病]) of disease transformation are featured by the nature of cold. Thus, Yo and heat are sometimes used in the same meaning, as seen for Yin and cold. However, use of the term heat pattern or cold pattern is rather recommended for the pathologic condition of 'heat' or 'cold,' respectively. The coexistence of cold and heat is referred to as tangled cold and heat (*Kannetsu Sakuzatsu*, 寒熱錯雑), and the presence of heat in the upper half body and cold in the lower half body, as upper heat and lower cold.

Treatments appropriate to cold and heat (*Kannetsu*)

A. Principles

Warming or cooling for a pathological condition of 'cold' or 'heat,' respectively, is the first principle. But, there are some cases in which whether the condition is cold or heat cannot be determined easily.

B. Specific examples

1. Heat

a. Febrile diseases

Of febrile diseases, pathologic conditions are diagnosed and treated according to "*ShangHanLun*," which describes the heat conditions as follows:

(1)Fever

In "*ShangHanLun*," 'fever' not only refers to elevation of body temperature, but also stands for 'heat on the exterior body surface, including feeling of chills or chills with wind as well as

sensation of heat, and conditions associated with body stiffness and pain.' Generally pulse is floating. Chills are a feeling of being cold even under a comforter; chills with wind (悪風) are a feeling of hoping to stay under a comforter despite no feeling of coldness.

The presence of 'fever' is indicative of TaiYo stage, as described in "*ShangHanLun*," and heat pattern is diagnosed. Treatment in this case is diffusing heat through sweating. Patients with floating and tight pulse and no sweating tendency are finally diagnosed as having heat pattern and excess pattern, then treated with maoto and the like, while those with floating and relaxed pulse and a spontaneous sweating tendency are regarded as having heat pattern and deficiency pattern, an indication of keishito.

In contrast, the presence of chills with sunken pulse and no feeling of heat are suggestive of ShoYin stage, as described in "*ShangHanLun*," and the patient is generally regarded as having cold pattern. In this case, maobushisaishinto (麻黄附子細辛湯) and the like are helpful. However, an observational study on the flu-like condition comprising fever and chills due to intravenous injection of interferon revealed that, in the very early stage, chills did not fail to occur with yet sunken pulse, which was followed by floating and tension pulse. This condition is effectively treated with maoto. It should be carefully determined whether fever developed in the very early stage or ShoYin stage of disease transformation.

(2)Alternating chills and fever (*Oraikannetsu*)

This is a comprehensive condition in which chills and fever alternately visit. Commonly, body temperature begins to rise in the afternoon, then via a peak, declines in the night. Such a heat type, unlike 'fever' that occurs in the very early stage of a disease, frequently develops several days after the onset, corresponding to the ShoYo stage of disease transformation described in "*ShangHanLun*." A diagnosis of heat pattern is made. The condition is frequently associated with *Kyokyo Kuman*, anorexia, sunken and string-like pulse, tongue fur, and taste abnormality. Effective therapy is available with Bupleurum Root-containing formulae such as shosaikoto (小柴胡湯).

(3)Whole body fever (*Shinnetsu*)

Is systemic fever with sunken pulse, not associated with sweating, as seen in ShoYo and YoMei stages, and combination of three Yo (*San'yo Gobyo*) described in "*ShangHanLun*." The patient is regarded as having heat pattern. He or she also has burning sensation and aversion to heat (suffering from heat), usually not associated with chills or chills with wind. However, chills are occasionally experienced on the back in combination of three Yo, and chills with wind sometimes develop in ShoYo stage. Shosaikoto and the like are appropriate for the ShoYo stage, while byakkoto (白虎湯) is of choice for YoMei stage and combination of three Yo (which is occasionally associated with sweating).

(4)Tidal fever (*Chonetsu*)

Body temperature rises at certain times in the day like a tide, associated with sweating in the

whole body. There are no chills or chills with wind, but aversion to heat (a condition in which the patient feels heat as torture) is evident. This medical condition corresponds to YoMei stage of disease transformation, as described in "*ShangHanLun,*" and is regarded as heat pattern. Treatment with jokito (承気湯) group including daijokito (大承気湯) is effective.

b. Non-febrile diseases

(1) Typical heat pattern

Patients are sensitive to heat even without elevation in body temperature, and have burning sensation (*Hoteri*) as revealed by palpation. Strain pulse tends to be frequent (tachycardia). Urine is characterized by dark color and strong odor; stool also has strong odor. Most patients experience thirst, and have thick and colored tongue fur.

(2) Fever-associated pathological conditions

A variety of fever-related pathological conditions are described in classics. Of them, main conditions are as follows:

(a) Dampness heat (*Shitsunetsu*)

Refers to the heat being retained with dampness in the body, and is associated with decreased urine volume. A diagnosis of heat pattern and excess pattern is considered. This condition is effectively treated with inchinkoto and the like.

(b) Deficiency and heat (*Kyonetsu*)

Are febrile symptoms induced by fatigue and debilitation. A diagnosis of heat pattern but deficiency pattern will be made. Deficiency pattern-treating formulae, such as hochuekkito, are helpful.

(c) Heat with agitation (*Hannetsu*)

Is uncomfortable sensation of heat, and occurs in various pathological conditions. Gypsum (石膏, sekko)-containing formulae, Coptis Rhizome (黄連, oren)-containing formulae, Rehmannia Root (梔子, shishi)-containing formulae, and Rehmannia Root (地黄, jio)-containing formulae may be used.

(d) Heat with agitation in hands and feet (*Shusoku Hannetsu*)

Refers to a condition that uncomfortable heat sensation is present in hands and feet, and described as a postpartum symptom in "*JinGuiYaoLue* (金匱要略)" Sammotsuogonto (三物黄芩湯) and shosaikoto are appropriate therapies.

(e) Heat with agitation in palms and soles (*Shusho Hannetsu*)

Refers to a condition in which uncomfortable heat sensation is present in palms and soles. Unkeito (温経湯) may be offered.

(f) Blood heat (*Ketsunetsu*)

Originally refers to a febrile symptom accompanying the medical condition related to blood stasis or hemorrhage. In the Edo period literature, the word of blood heat is occasionally used in the same meaning as heat with agitation or deficiency and heat. Under a diagnosis of blood heat, blood stasis-treating formulae (*Kuoketsuzai*), shimotsuto (四物湯) group, shosaikoto, or sammotsuogonto may be used.

2. Cold (*Kan*)

a. Febrile diseases

In "ShangHanLun," TaiYin, ShoYin, and KetsuYin stages of disease transformation are described, and included in Yin stages of disease transformation. Their common nature is 'cold' that should be treated by warming using any of the following formulae: maobushisaishinto, shimbuto (真武湯), shigyakuto (四逆湯), ninjinto (人参湯), keishikashakuyakuto (桂枝加芍薬湯), etc.

b. Non-febrile diseases

(1) Typical cold pattern

Even if the patient has elevated body temperature, he or she does not complain of hot sensation but does complain of coldness, as proven by palpation of the body and limbs. The patient has sunken and small pulse, likely to become moderate (bradycardia). Light colored and odorless urine and stools with little odor are evident. He or she often may suffer watery diarrhea, but mostly does not experience thirst, and has thin and watery saliva with the uniformly smooth and glossy tongue and lesser tongue fur.

(2) Cold-associated pathological condition

A variety of cold-related pathological conditions are described in classics. Of them, main conditions are as follows:

(a)Cold sensation of the extremities with qi (Ki) reverse (厥寒, Ketsukan)

"ShangHanLun" contains the medical condition in which the patient feels intense coldness in the extremities, and terms it coldness of the extremities with qi (Ki) reverse or cold sensation of the extremities with qi (Ki) reverse (厥寒, Ketsukan). Clinical findings include chilblains and sallow extremities, suggesting poor peripheral circulation. In this case, tokishigyakuto (当帰四逆湯) and tokishigyakukagoshuyushokyoto (当帰四逆加呉茱萸生姜湯) are used. Keisetsu Otsuka analyzed the cases in which these two Kampo formulae were effective and reported the conditions termed 'abdominal colic syndrome A (senki syndrome type A).' The condition is characterized by coldness-induced aggravation of the chronic pain (low back pain, lower abdominal pain, headache, etc.) and other various complaints triggered by past coldness or surgery of the lower abdominal region. Pulse is sunken and small or sunken and thin, and is often too weak to be palpable, frequently in association with tenderness in the inguinal region.

(b)True cold and false heat (exterior heat and interior cold, interior cold and outer heat)

Despite the presence of possible febrile symptoms or signs on the body surface, the entity of the pathological condition is coldness in the depth of the body. In other words, there is inconsistency between gross findings and pathological entity. For example, the patient is sensitive to heat (then, heat pattern is considered so that urine should be reddish, very cloudy, and strong smelling, and pulse should be tight), but presents with clear urine like water and faint and weak pulse. Essentially the condition is cold pattern, not heat pattern. Therapy should focus on warming with formulae containing Processed Aconite Root (附子, bushi), Ginseng (人参, ninjin), and Processed Ginger (乾姜, Kankyo), such as shigyakuto.

Exterior and interior (*Hyori*)

A concept of exterior and interior (location)

A. Exterior and interior, and exterior pattern and interior pattern

In Kampo medicine, the term exterior and interior is used to express the depth of the site where a disorder occurs. Exterior refers to the body surface, including the skin, mucous membrane, and throat. Interior stands for the body depth which generally comprises the digestive organs. In addition, the term halfway pattern (*Hanpyo Hanri Sho*: halfway pattern between exterior and interior) signifies the location between exterior and interior, and may include the bronchi, lungs, and liver. Originally, the location expressed by exterior or interior is very rough, and does not always represent specific viscera or tissue.

Exterior pattern refers to signs and symptoms indicating that a disorder is located in the exterior; for example, ‘chills (associated with heat sensation),’ ‘pains in the body and joints,’ ‘headache,’ and ‘sore throat’. Interior pattern means signs and symptoms indicating that a disorder is located in the interior; for example, ‘abdominal distention,’ ‘abdominal pain,’ and ‘diarrhea.’ Halfway pattern refers to signs and symptoms indicating that a disorder is located in the halfway pattern; for example, ‘alternating chills and fever,’ ‘*Kyokyo Kuman*,’ and ‘nausea and vomiting.’

B. Inner and outer (*Naigai*)

“*ShangHanLun*” also uses the terms inner and outer, such as ‘halfway between inner and outer (*Hangai Hanri*).” Regarding the interpretation of these terms, there is controversy. One group insists that exterior and outer have the same meaning, and interior and inner also the same meaning. The other maintains that inner and outer are a relative concept: when the location of a disorder is fixed in a stage of disease transformation—such as halfway between exterior and interior—at a given time, the part closer to the exterior is termed outer while the part closer to interior is called inner.

The latter interpretation is often used when relatively distinctive locations are expressed in a wide range of halfway pattern.

Treatment appropriate for exterior and interior

A. Six stages (six-meridian disease and three Yin and three Yo) of disease transformation and exterior

and interior

"*ShangHanLun*" is a book focusing on the transformation and treatment of acute febrile diseases. Disease transformation is roughly divided into Yo stages (with heat nature) and Yin stages (with cold nature). Furthermore, Yo stages of disease transformation comprise three stages: TaiYo stage (of heat at exterior location), ShoYo stage (of heat at halfway location), and YoMei stage (of heat at interior location). Yin stages of disease transformation, known to be characterized by cold at interior location and severity, are also divided into three stages: TaiYin stage of low severity, ShoYin stage of moderate severity, and KetsuYin stage of high severity.

B. Treatment appropriate for each stage of disease transformation

Of disease transformation, TaiYo stage (heat pattern at exterior) is often treated with sweat-inducing formulae such as keishito and maoto; ShoYo stage (heat at halfway pattern between exterior and interior), neutralizing formulae such as shosaikoto; and YoMei stage (heat pattern at interior), purgative formulae such as daijokito or formulae to treat heat pattern such as byakkoto.

In the treatment of Yin stages (TaiYin, ShoYin, and KetsuYin stages) of disease transformation, interior-warming is recommended with keishikashakuyakuto, shimbuto, shigyakuto, and the like.

Six stages (six-meridian disease and three Yin and three Yo) of disease transformation

A concept of six stages of disease transformation

A. What are six stages of disease transformation?

As described in Section Exterior and Interior [D]-[2]-A, "*ShangHanLun*" classifies acute febrile diseases into six typical stages of disease transformation, namely TaiYo, ShoYo, YoMei, TaiYin, ShoYin, and KetsuYin stages.

Yo stages of disease transformation are of heat-centered features, consisting of TaiYo (heat at exterior), ShoYo (heat at halfway between exterior and interior), and YoMei (heat at interior). Yin stages are of cold-based features, composed of TaiYin (cold at interior and mild), ShoYin (not only cold at interior but also occasionally cold at exterior and moderate), and KetsuYin (essentially cold at interior, but occasionally manifesting tangled conditions of upper heat and lower cold or true cold and fake heat [exterior heat and interior cold], and severe).

B. Transformation of six stages (*Rikubyoi*)

If a febrile disease occurs, it will begin with TaiYo stage, often followed a few days later by ShoYo stage. However, occasionally it begins with ShoYin stage (direct ShoYin stage, *Jikichu no ShoYin*) or TaiYo stage is followed by YoMei stage. In a variety of courses, the disease may be not cured but prolonged and result in Yin stages, finally leading to KetsuYin stage.

Treatment appropriate to six stages of disease transformation

A. Yo stages of disease transformation

1. TaiYo stage

This is a stage (with heat at exterior location) of disease transformation. The patient has heat sensation accompanying chills and chills with wind, headache, stiff neck and nape, and myalgia/ arthralgia, with floating pulse as a general rule. These symptoms and signs are collectively termed exterior pattern in a meaning that the disorder is seen at exterior location.

a. Wind impact and cold damage

In "*ShangHanLun,*" febrile diseases are collectively termed cold damage. Nevertheless, mild and severe febrile diseases are named 'wind impact' and 'cold damage,' respectively. This is a somewhat complex terminological usage. In other words, the term cold damage has two meanings: 1) a generic term for febrile diseases and 2) a particular name for severe cases. This should be kept in mind.

Wind impact refers to the state in which sensation of heat is accompanied by chills with wind and associated with spontaneous sweating, and floating and relaxed or floating and weak pulse that the physician feels slightly weak tension. This case will be successfully treated with keishito and other formulae that exert '*Geki* (解肌) action' of venting the wind impact by inducing relatively weak sweating (微似汗, *Bijikan*) and harmonizing/balancing the body surface.

Cold damage may be associated with intense chills (reflecting the intensity of disease) from the beginning, and coexistence of exterior pattern (body pain, etc.) and interior pattern (gastrointestinal symptom, e.g. vomiting, etc.) as well as floating and tension pulse (indicating a forceful condition). In such a case, appropriate treatment is the use of maoto and the like, as a rule, that intensely promote sweating, leading to cure via *Bijikan*.

It cannot be determined whether the terms of wind impact and cold damage are used only at TaiYo stage (the initial stage of a febrile disease) or throughout the whole course of a febrile disease according to severity. The term usage varies among books. Commentaries for "*ShangHanLun*" should be carefully red.

b. Like ague, much heat and less cold

If a disease that started with TaiYo stage (with heat at exterior) does not cure even via induced sweating, the disease will often transform to ShoYo stage (with heat at halfway between exterior and interior) in a few days. Sometimes, however, the disease may stay in TaiYo stage, and presents ague-like repeated rise and fall in body temperature as seen in malaria (ague-like manifestation). In this case, the characteristic feature of TaiYo stage that heat sensation is associated with chills is held.

This status is described in "*ShangHanLun*" as the state being like ague with much heat and less cold as well as fever and chills. Keisetsu Otsuka interpreted the sentence as follows: 'the duration of fever is long whereas the duration of chills is short.' From his own experiences, Ken Fujihira has

realized that while heat sensation is distributed throughout the whole body, chills are felt on the shoulders alone. Such a state of disease can be effectively treated with keishimaokakuhanto (桂枝麻黄各半湯), keishinimaoichito (桂枝二麻黄一湯), keishinieppiichito (桂枝二越婢一湯), and the like.

2. ShoYo stage

This is the stage of disease transformation with heat at halfway location between exterior and interior. In ShoYo stage, the disease is converted into a heat type of alternating chills and fever: body temperature rises with chills and the temperature rise subsides with appearance of heat sensation. Chills and heat sensation appear alternately. Actually, body temperature does not rise in the morning but rises gradually in the afternoon, reaches a peak in the evening, and subsides at midnight. Concurrently with alternating chills and fever, *Kyokyo Kuman* also appears that is a specific feature for this stage. The presence of *Kyokyo Kuman* is the target for the use of Bupleurum Root (柴胡, saiko)-containing formulae including shosaikoto. Patients have frequently sunken and string-like or thin pulse, white tongue fur, bitterness or taste change in the mouth, and reduced appetite (sometimes associated with nausea). Feeling of throat dryness, dizziness, and ear blocking also may occur.

Treatment is effective with Bupleurum Root-containing formulae (such as shosaikoto), hangeshashinto (半夏瀉心湯) group, shishikoto (梔子鼓湯) group, and others, each modulating and harmonizing the whole, under a harmonizing method (*Waho*) policy without use of strong cathartics or sweating inducers.

3. YoMei stage of disease transformation

This is a stage of disease transformation with heat **at** interior location.

a. Tidal fever and jokito-group

TaiYo stage comprises chills and fever pattern; ShoYo stage, alternating cold and heat pattern; and YoMei stage, tidal fever pattern. Tidal fever means fever occurring at a certain time, concurrently accompanying spontaneous sweating enough to moisturize the whole body. The patient has not chills but suffers heat (aversion to heat, *Onetsu*), associated with abdominal fullness and distension, constipation, and sunken excess (strong or powerful) pulse. In addition, the patient may talk in feverish delirium.

Basic treatment is purgation with jokito group such as daijokito and shojokito (小承気湯).

b. Combination of three Yo (*San'yo Gobyo*) and byakkoto

In addition to tidal fever that is treated with jokito group, YoMei stage comprises another characteristic feature, combination of three Yo, for which byakkoto is appropriate. In combination of three Yo, the patient has burning sensation, with no chills as a rule (though sometimes slight chills on the back), but aversion to heat and occasional spontaneous sweating—without spontaneous sweating, these manifestations are quite similar to those of a heat type of whole body fever as seen in ShoYo stage of disease transformation. He or she also has much facial sebum, rough mouth, and taste

dysfunction. The patient may talk in delirium owing to disturbed consciousness. Furthermore, the patient suffers severe thirst, not associated with decreased urine volume. The upper abdominal region is full and tense, along with sunken, smooth, and frequent pulse or large surge pulse, resulting in excess pulse. The emergence of these diverse symptoms and signs is condensed into the term 'Combination of three Yo.' However, the entity of the medical condition is heat at interior location and included in YoMei stage. Some physicians claim that heat develops not only at exterior, but also interior and halfway pattern. Effective treatment is treat heat pattern (*Seinetsu*) with byakkoto, as a rule, rather than jokito group (for tidal fever).

B. Yin stages

Of disease transformation, TaiYin, ShoYin, and KetsuYin stages are collectively referred to as Yin stages, of which the essential nature is cold at interior location.

1. TaiYin stage

This is a stage characterized by cold at interior location of disease transformation. Severity is mild but likely to be associated with gastrointestinal symptoms such as abdominal fullness and pain, vomiting, anorexia, and diarrhea. Sunken pulse is also evident, and may occasionally accompany rectus abdominis muscle tension and epigastric discomfort and resistance (*Shinka Hiko*), but often weak abdominal strength. Treatment with keishikashakuyakuto, ninjinto, or the like is effective.

2. ShoYin stage

This is a stage with cold at interior location of disease transformation, sometimes accompanying cold at exterior location. Severity is moderate and is featured by pale face. The patient is easy to be tired, wants to lie on his or her side, and complains of dizziness, diarrhea, systemic pain, and sometimes thirst (deficiency and thirst [*Kyo Katsu,* 虚渇]). Pulse is sunken and faint, sunken and thin, or sunken and small. Some febrile diseases begin with ShoYin stage, which is termed 'direct ShoYin stage.' Patients complain of sore throat and malaise, associated with chills rather than heat sensation even in some with elevated body temperature. Appropriate formulae include maobushisaishinto, shimbuto, bushito, and shigyakuto.

3. KetsuYin stage

This is also a stage with cold at interior location of disease transformation, but likely to be associated with febrile symptoms. For example, the patient may present with tangled cold and heat: true cold and false heat (*Shinkan Kanetsu*) or upper heat and lower cold. The medical condition is serious.

The patient suffers coldness from the distal to the proximal of the limbs (coldness of the limbs with qi [Ki] reverse) but feels heat in the trunk or cannot eat or may vomit even in hunger; or has indigestion diarrhea associated with sunken and slow pulse despite heat feeling on the body surface or upper body region. These tangled symptoms are best treated by warming the interior with the shigyakuto group (including shigyakuto, bukuryoshigyakuto, and tsumyakushigyakuto [通脈四逆湯]).

C. Combination (of stages) (*Gobyo*)

The patient is in one stage of disease transformation but presents with entanglement of symptoms and signs related to more than two stages. Such a condition should be treated, as a rule, with one formula appropriate for the fundamental stage. All combinations of stages described in "*ShangHanLun*" are heat-based Yo stages, as follows:

1. Combination of TaiYo and YoMei

The entity of disease transformation is TaiYo stage with exterior heat pattern (*Hyonetsusho*, 表熱証). Symptoms in the TaiYo stage are associated with gastrointestinal symptoms (diarrhea, vomiting, etc.).

Effective Kampo formulae include kakkonto, kakkonkahangeto, and maoto.

2. Combination of TaiYo and ShoYo

The entity of disease transformation is ShoYo stage with halfway heat pattern (*hanpyohanri Netsusho*, 半表半裏熱証), associated with diarrhea and vomiting. Ogonto, ogonkahangeshokyoto, and the like are used.

3. Combination of ShoYo and YoMei

The entity of disease transformation is YoMei stage with interior heat pattern associated with diarrhea. After confirmation of pulse signs, treatment with daijokito is given.

4. Combination of three Yo (*San'yo Gobyo*)

The entity of disease transformation is YoMei stage with interior heat pattern, but may be interpreted as with heat not only at interior but also at exterior and halfway locations between the interior and exterior. Recommended treatment is heat cooling with byakkoto.

D. Overlap (*Heibyo*)

Consider the course of a disease from the view point of six stages of disease transformation, and the onset commonly begins with TaiYo stage (exterior heat pattern); several days later when the disease has not yet cured, the disease frequently transforms from TaiYo stage to ShoYo stage (halfway heat pattern). In the transformation, the disease may stay in both TaiYo and ShoYo stages, which is called shifting of stages. In shifting, symptoms and signs specific to both stages develop, which is called overlap.

Overlap is treated with different types of therapy, depending on the type of overlap. Examples are the overlap of TaiYo and ShoYo in which saikokeishito (柴胡桂枝湯), a combination of keishito (a formula for TaiYo stage) and shosaikoto (a formula for ShoYo), can be used; and the overlap of TaiYo and YoMei in which inducing sweating to eliminate exterior pattern is followed by purgation with jokito or the like.

From different perspectives, there can be many overlap variations. This idea was widely applied by Ken Fujihira in clinical settings to yield successful outcomes. He proposed therapeutic strategies that exterior recovery should precede interior recovery and that improvement of abrupt and serious symptoms (often of interior pattern) should be followed by improvement of slow symptoms.

Chaotic (*or* destructive) stage

This is a chaotic condition in which usually observed pathological features have been changed owing to inappropriate treatment, a departure from the above-mentioned therapeutic principles based on combination and overlap as well as six stages of disease transformation (inducing sweating and '*Geki*' for TaiYo stage; harmonizing methods without sweating inducers for ShoYo stage; purgation or treating heat pattern for YoMei stage; interior-warming for Yin stages), or inappropriate dosage (excessive sweating, excessive purgation, etc). Analyzing the course to the chaotic stage to find a mistake and confirming the present pattern by physical examination are needed for successful treatment outcome.

Probably, chronic or intractable pathological conditions in the modern medical care environment may be in such chaotic stages. Careful check of the medical history and minute physical examination will help to diagnose the present pattern (among six stages of disease transformation, combination, and overlap) even for the chaotic stage, which will lead to appropriate treatment, as mentioned above, and then favorable outcome. Even very complicated medical conditions will be resolved if the theory of overlap proposed by Ken Fujihira, underlying symptoms (*Sensho* [潜証]: medical conditions apparently regarded as heat or excess pattern can be effectively treated by single or concurrent use of the formula appropriate for cold pattern) suggested by Shigenari Ogura, and other theories are taken into account. A breakthrough may be achieved by determination of cold or heat and deficiency or excess as well as examination of qi (Ki), blood, and fluid, as described next section, rather than diagnosis of six stages of disease transformation.

Qi (Ki), blood, and fluid (*Kiketsusui*)

[1] Qi (Ki)

A. A concept of Qi (Ki)

Qi (Ki) means invisible action, function, or working that circulates throughout the body.

B. Disorders of qi (Ki) and treatment

It is important that a certain volume of qi (Ki) circulates throughout the body. Disturbed circulation gives rise to various disorders.

1.Qi (Ki) deficiency (*Kikyo*)

The function qi (Ki) itself weakens and gives rise to various dysfunctions. This 'inactive or low-spirited' condition is termed qi (Ki) deficiency, which concurrently entails digestive dysfunction (deficiency of upper abdominal region [*Chusho no Kyo*]). The patient complains of feeling tired and lazy as well as presents with weaken pulse and soft abdominal regions enough to be often regarded as weak abdominal strength.

Treatment is the use of qi (Ki)-treating formulae (deficiency pattern-treating formulae), such as hochuekkito, shikunshito, and rikkunshito, which contain ginseng and Astragalus Root (黄耆,

ogi). These formulae are also able to treat deficiency of upper abdominal region.

2.Qi (Ki) stagnation (*Kitai*) and qi (Ki) depression (*Kiutsu*)

This is the condition in which circulation of qi (Ki) is disturbed. As implied by the fact that the word qi (Ki) also means gas, many patients complain of gas retention and associated fullness feeling. A depressive condition is expressed as 'qi (Ki) choked,' which suggests that stagnation of qi (Ki) may appear as depression. This condition is really termed qi (Ki) depression (*Kiutsu*), frequently associated with sunken and thin or small pulse, and occasionally with abdominal bloating and tympany due to gas retention. As a result of qi (Ki) stagnation (*Kitai*) or depression, the following symptoms may occur:

a. Foreign body sensation in the throat (*Inchu Sharen* or *Baikakuki*)

Is abnormal sensation in the laryngopharynx. The patient feels as if something like a piece of roasted beef or a plum kernel is caught in the throat, and cannot swallow it although wanting to swallow, and cannot vomit although wanting to vomit. The abnormal sensation may be due to qi (Ki) depression. Hangekobokuto (半夏厚朴湯) is effective for this condition.

b. Asthma

Occasionally qi (Ki) stagnation and depression may appear in a form of breathing difficulty like asthma, and may be favorably treated with saibokuto (柴朴湯), hangekobokuto combined makyokansekito (半夏厚朴湯合麻杏甘石湯), and the like.

c. Ear blocking

Ear blocking may appear as a symptom of qi (Ki) stagnation and depression, although it may also develop in ShoYo stage. Shisoin (柴蘇飲) (shosaikoto combined kososan [小柴胡湯合香蘇散]) is used in some patients.

d. Pain

Saibokuto is effective for thalamic pain following cerebrovascular disorder. For the pain of the knee joint that has not been relieved with boiogito (防已黄耆湯) or the like, concurrent use of saibokuto or hangekobokuto may be helpful.

e. Abdominal distension

Hangekobokuto may be effective in patients (with aerophagia) who complain of abdominal distension every afternoon after they swallowed the air owing to having been too attentive.

Generally, formulae appropriate for qi (Ki) stagnation and depression include hangekobokuto, saibokuto, kososan, kihito (帰脾湯), and kamikihito (加味帰脾湯). In addition, jokito group, kumibinroto (九味檳榔湯), shigyakusan (四逆散), daisaikoto (大柴胡湯) are also effective for this condition. Furthermore, Magnolia Bark (厚朴, koboku), Perilla

Herb(蘇葉, soyo), Immature Orange (枳実, kijitsu), Rhubarb (大黄, daio), and others are useful for qi (Ki) stagnation.

3. Qi (Ki) counterflow (*Kigyaku*) (or qi [Ki] rising)

When the mood of a patient is stable, he or she may be commonly aware of the center of qi (Ki) located around below the navel. However, when his or her mood becomes unstable, the center of qi (Ki) rises up to the upper half of the body. The patient experiences hot flashes, with a red flushed face and cold feet, frequently associated with dizziness and palpitation. Examples are as follows:

a. Honton

Is a symptom described in "*JinGuiYaoLue*." The patient seems to suffer something like attack toward the chest from the lower abdominal region in association with abdominal pain and fever, and to fall into unconsciousness. At present, something like attack is generally considered to be hysterical attack. Hontonto (奔豚湯), ryokeikansoto (苓桂甘棗湯), keishikakeito (桂枝加桂湯), and the like are effective.

b. Fire counterflow (*Kagyaku*, 火逆)

"*ShangHanLun*" describes a hypersensitive condition that occurs by thermal treatment or burn. Major symptoms are palpitation, qi (Ki) counterflow, and agitation and restlessness (*Hanso*, 煩躁), similar to those of Honton. Keishikakeito, keishikanzoryukotsuboreito (桂枝甘草竜骨牡蛎湯), keishikyoshakuyakukashokushitsuboreiryukotsukyugyakuto (桂枝去芍薬加蜀漆牡蛎竜骨救逆湯) are used.

c. Tangled fluid disturbance (*Suidoku*) and qi (Ki) counterflow (*Kigyaku*)

Patients complain of dizziness, palpitation, and others, for which ryokeijutsukanto (苓桂朮甘湯) is appropriate.

d. Tangled blood stasis and qi (Ki) counterflow

Among patients in whom keishibukuryogan or tokakujokito are effective, those with strong hot flashes are applicable.

Many of the formulae used in the treatment of qi (Ki) counterflow contain Cinnamon Twig (桂枝, keishi) or Glycyrrhiza (甘草, kanzo) combination; for example, keishikyoshakuyakuto and shakanzoto (炙甘草湯).

[2]Blood

A. The concept of blood

Blood, circulating the body, is visible and red-colored. While qi (Ki) is invisible action, function, and working, blood is a visible component of the body, reflecting the nutritional and circulatory states.

B. Disorders of blood and treatment

1. Blood deficiency (*Kekkyo*)

This is deficiency in blood, which not only appears as anemia, but also represents poor nutritional and circulatory conditions. The patient has the dry skin apt to atrophy, white and thin hairs apt to fall out; and the limbs that become lean enough to distinguish the tendons and joints. Unlike qi (Ki) deficiency characterized by fair skin, rather flabby body, soft and weak muscles as well as skin, and decreased activity. Blood deficiency (*Kekkyo*) is manifest by the dark skin, lean body with a dehydrating tendency, firm skin as well as muscles and tendons, and sustained activity.

Frequent formulae include shimotsuto, kyukikyogaito (芎帰膠艾湯), renjuin (連珠飲), and unseiin (温清飲), all of which contain shimotsuto (Japanese Angelica Root [当帰, toki], Lindera Root [芍薬, shakuyaku], Cnidium Rhizome [川芎, senkyu], and Rehmannia Root).

Juzentaihoto (十全大補湯), containing both shimotsuto and shikunshito which is effective for qi (Ki) deficiency, is used for dual deficiency of qi (Ki) and blood (namely, dual deficiency of qi [Ki] and blood [*Kiketsu Ryokyo*]). However, The components Rehmannia Root and Cnidium Rhizome of shimotsuto may induce gastric symptoms in patients with decreased digestive function (deficiency of upper abdominal region) In such a case, juzentaihoto may be preferable. Rather, before selection of juzentaihoto, shimotsuto is abandoned and deficiency of upper abdominal region should be well treated.

2. Blood stasis (*Oketsu*)

This means stagnant blood; specifically, stagnation of the venous system and capillary vascular system can be imaged. Blood stasis commonly occurs during and soon before and after menstruation, and in delivery, puerperium, and climacteric. Inflammation, bruise, hemorrhoid, and varix can also be included in blood stasis. In a febrile disease associated with blood stasis, confusion and bleeding are induced and may result in significant modification of the pathological condition. The patient has resistance and tenderness in the lower abdominal region (*Shofuku Koman* [lower abdominal resistance and fullness], *Shofuku Kyuketsu* [resistance and sharp tenderness in the left iliac region], etc.), with sunken and rough pulse. In addition, the presence of blood stasis seems to be suggested by the following manifestations: 1) dry mouth (*Kokan*: the mouth is dried without thirst), 2) subjective feeling of abdominal fullness (without objective distention), 3) feeling of heat with agitation, 4) purpura on the skin and mucosal membrane as well as capillary and venous distension, 5) dry and rough skin, 6) dark red or blue tongue, 7) purple spots on the lingual margin, 8) blue lips, 9) dark stool, 10) hemorrhagic tendency, 11) increased appetite, and 12) being impatient or irritable and blaming others.

Treatment of blood stasis uses blood stasis-treating formulae, such as tokishakuyakusan, kamishoyosan, keishibukuryogan, nyoshinsan (女神散), tsudosan (通導散), and tokakujokito, based on the characteristics of each formula. Attention should be paid to the use of such a formula on the occurrence of fever: avoiding the use in the presence of exterior pattern or

halfway pattern closer to the exterior pattern than the interior pattern and beginning the use after disappearance of the pattern. This strategy is a principle described in "*ShangHanLun*."

[3] Fluid

A. A concept of fluid

Fluid is visible and transparent, circulating the body. It can be imaged as humor.

B. Disorders of fluid and their treatments

There is a wide range of pathological conditions related to fluid, including edema and inflammation that are involved in fluid disorders. There are also many synonyms of the term fluid (fluid, sputum, -in [drink], dampness, etc.). In Japan, however, fluid-related disorders (deviation from the normal) are often collectively called fluid disturbance (*Suidoku*) or fluid retention (*Suitai*). These examples are as follows:

(1)Modulation of fluid metabolism

Manifest symptoms include edema, decreased urine volume, pollakiuria, vertigo or dizziness, orthostatic dizziness or syncope, dizziness or lightheadedness, headache, ear ringing, thirst, vomiting, and watery diarrhea. Pulse and abdominal pattern also vary widely. Treatment, depending on the feature of each patient, uses goreisan (五苓散), inchingoreisan (茵蔯五苓散), choreito (猪苓湯), ryokeijutsukanto, shimbuto, tokishakuyakusan, takushato (沢瀉湯), or others. These formulae commonly contain several crude drugs of Alisma Rhizome (沢瀉, takusha), Polyporus Sclerotium (猪苓, chorei), rhizomes of Atractylodes spp. (朮, jutsu), and Poria Sclerotium (茯苓, bukuryo), and therefore possess fluid balance-controlling or diuresis-inducing activity.

(2)Arthralgia, arthritis, and associated edema

Keishikaryojutsubuto (桂枝加苓朮附湯), eppikajutsuto (越婢加朮湯), makyoyokukanto (麻杏薏甘湯), boiogito, and the like are offered that contain Ephedra Herb, rhizomes of Atractylodes spp., and Astragalus Root as component crude drugs.

(3)Fluid retention in the stomach ([*Suiin*], [*Tan'in*])

Splashing sound in the epigastric region is evident, associated with belch, nausea, and/or vomiting. This condition is treated with shohangekabukuryoto (小半夏加茯苓湯), goreisan, ireito, bukuryoin (茯苓飲), bukuryoingohangekobokuto (茯苓飲合半夏厚朴湯), or bukuryotakushato (茯苓沢瀉湯). Fluid retention in the stomach not only appears as a sign of fluid disturbance, but also may develop as a reflection of reduced digestive function. In the latter case, ninjinto, shikunshito, rikkunshito, hangebyakujutsutemmato (半夏白朮天麻湯), and the like are effective.

(4)Asthma and rhinitis

Asthma and rhinitis are occasionally reflections of fluid disturbance. In such cases, shoseiryuto (小青竜湯), or ryokankyomishingeninto (苓甘姜味辛夏仁湯) are offered.

Concerning ‘fluid (body fluid)’ or ‘moisture,’ many problems remain to be studied.

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Diagnostics

Go Ito, Toshihiko Hanawa

For examinations, the office should be well illuminated by natural light, and the temperature should be maintained appropriately so that unclothed patients do not feel cold. Examinations are also part of the diagnostic and treatment processes.

Examinations (*Shishin*)

In Kampo, four diagnostic examinations called *Shishin* are performed: Inspection (*Boshin*), listening and smelling examination (*Bunshin*), inquiry (*Monshin*), and palpation (*Sesshin*).

Inspection (*Boshin*)

Inspection, in modern medicine, includes observation of the patient's movement, gait, and abnormal movement when he/she enters the office. General observations include the patient's nutritional status, body shape, size, posture, muscle tone, skeletal deformities, edema, skin color/tone, skin dryness/dampness, and sweats, followed by specific observations including the complexion, light in the eyes, facial expression, eye and conjunctival conditions, hair and nail conditions, intraoral and tongue conditions (tongue inspection), and oral mucosal and gingival conditions. Capillary dilatation, plum-colored skin and lips, dark circles under the eyes, and brown spots are important signs of blood stasis (*Oketsu*). Of the inspection methods, tongue inspection has a special role and is described elsewhere in this chapter.

Physical signs revealed by inspection alone may sometimes lead directly to prescription of formulae and crude drugs. Rehmannia Root (地黄, jio)-containing formulae such as hachimijiogan (八味地黄丸) may be somewhat suggested by dark skin with a tendency to dryness, and Ephedra Herb (麻黄, mao)-containing formulae are somewhat suggested by bluish skin. Rehmannia Root is commonly used for middle-aged or elderly patients or for the treatment of chronic debilitating diseases, and Ephedra Herb is commonly used for adolescents or treatment early in the course of disease. If redness of the face changes during examination of a patient with atopic dermatitis, qi (Ki) rising is suspected; in such cases, Cinnamon Twig (桂枝, keishi)-containing formulae may be used. If redness does not change during the examination, blood heat is suspected; in such cases, Coptis Rhizome (黄連, oren)-containing formulae, Gardenia Fruit (山梔子, sanshishi)-containing formulae, and/or Safflower (紅花, koka)-containing formulae may be used.

a. Inspection of movement and gait

To detect deficiency or excess of qi (Ki)-blood (気血, *Kiketsu*), it is important to know whether the patient moves or walks fast or awkwardly. If the patient moves too sluggishly when sitting down on or getting up from a chair or examining table, the degree of depression and dual insufficiency of qi (Ki) and blood can be

estimated. If the patient cannot sit still in the chair, moves the chair, gets closer to the doctor, rests his/her chin on one hand, and/or gives a sigh, he/she may be impatient and irritable.

b. Inspection of the skin

Skin conditions indicate the general nutritional status and blood circulation, and therefore should be observed carefully. Dry appearance is frequently linked to blood deficiency (*Kekkyo*). In such cases, formulae based on shimotsuto (四物湯) may be used. If skin pigmentation is evident, blood stasis is considered.

c. Inspection of light in the eyes

The brightness and emptiness of the eyes when the patient enters the office are important determinants of the degree of deficiency or excess of qi (Ki)-blood. Powerful eyes are suggestive of fullness of qi (Ki) and high sympathetic tone. Empty, faint eyes are suggestive of qi (Ki) insufficiency and depression. Slanted eyes or being impatient or irritable is suggestive of liver (TM) abnormality, and red eyes are suggestive of qi (Ki) counterflow (*Kigyaku*) and blood heat.

d. Inspection of the complexion and faces

Complexion is important determinant of the degree of deficiency or excess of qi (Ki)-blood. Flushing of the skin may be suggestive of conditions such as blood heat, qi (Ki) counterflow, and blood stasis. Pallor may be suggestive of conditions such as blood deficiency, Yin pattern (*Yinsho*), deficiency pattern (*Kyosho*), and fluid disturbance (*Suidoku*). Facial telangiectasia, pigmentation, and dark circles under the eyes are signs of blood stasis. Puffy eyes may be suggestive of fluid disturbance, and darkish eye circles may be suggestive of deficiency of lower abdominal region or kidney [TM] deficiency (*Jinkyo*) and blood stasis.

e. Inspection of scalp hair

Thin hair, lusterless hair, and excessive hair loss may be suggestive of blood deficiency.

f. Inspection of the nails

Fragile nails with vertical ridges may be suggestive of blood deficiency and dual deficiency of qi (Ki) and blood (*Kiketsu Ryokyo*). Changes in nail color may be suggestive of blood stasis.

g. Inspection of the lips and gingivae

Dry lips and angular stomatitis are linked to deficiency of upper abdominal region or spleen [TM] deficiency (*Hikyo*), blood deficiency, and fluid insufficiency. Weak children with dry lips are likely to present with a shokenchuto (小建中湯)-pattern (*Shokenchutosho*). Plum-colored lips and gingivae may be suggestive of blood stasis. In such cases, unkeito (温経湯) may be used if the lips are dry, and ninjin'yoeito (人参養栄湯) may be used if there is fluid insufficiency.

Tongue inspection (*Zesshin*)

a. History of tongue inspection in Japan

In 1835 (Edo period), Takayuki (Mosai) Tsuchida published the "*Zettai Zusetsu* (舌胎図説)," which divides tongue fur into four classifications on the basis of color (white, yellow, black, and red) and 35 subclassifications. Mosai emphasized the benefits of the tongue inspection, stating that 'signs of differences between Yin (陰) and Yo (陽), exterior and interior, deficiency and excess, and cold (*Kan*) and heat (*Netsu*) are always seen on the tongue, unlike '*Myakuho* (脈法, pulse examination method),' which is difficult to perform.' Mosai stated that 'The objective … is to develop standards for diagnosing diseases by not only observing the color, luster, thickness, and lesions of tongue fur, but also giving attention to the movement and tremors of the tongue.' This deserves special consideration.

In 1813, Gencho (Hoan) Nojo published the "*Kokuji Fukuzetsu Zukai* (国字腹舌図解)," which presents abdominal examination and tongue examination findings and the corresponding treatments (Kampo formulae). Hoan published volume one of the "*Kokuji Fukuzetsu Zukai*" for his disciples as a textbook of his lectures on abdominal and tongue examinations. He suggested that tongue fur is the first priority in diagnosing 'the symptoms and signs of cold damages (傷寒の候),' and yellow fur or black fur is always linked to fever and most of the cases should defecate. White fur is also commonly linked to fever, and thin white fur on paler tongue than normal is commonly linked to cold (*Kan*). Diagnosis requires careful evaluation. In "*Kokuji Fukuzetsu Zukai*," 91 Kampo formulae, mainly from "*ShangHanLun* (傷寒論)," are suggested by both 91 tongue examination findings and 91 abdominal examination findings.

In contemporary Japanese Kampo (Koho school) medicine and acupuncture and moxibustion medicine, comprehensive patterns are not determined solely by examination of the tongue.

b. Summary of tongue inspection

The upper and lower surfaces of the tongue are also known as the dorsal and ventral surfaces of the tongue, respectively. The dorsal surface is covered with several types of papillae including filiform, fungiform, vallate, and foliates. The tongue inspection focuses on filiform papillae, which are distributed evenly over the entire dorsal surface of the tongue, and fungiform papillae, which occur sporadically on the same surface. Only the surface of the epithelium (stratified squamous epithelium) of the filiform papillae (not the other papillae) is keratinized. Tongue fur is produced when the exfoliation of the epithelium of filiform papillae is stagnant and bacteria grow.

Tongue findings are called tongue signs. There are two major tongue inspection procedures: inspection of the tongue itself (tongue body) and inspection of the fur that covers the tongue (tongue fur). In the inspection of the tongue body, tongue color, tongue form, and tongue motility are assessed. In the inspection of tongue fur, fur texture and fur color are assessed.

c. Characteristics of the tongue

(1) Color of the tongue

The color of the tongue body excluding the tongue fur is evaluated.

(a) Pale

A tongue paler than normal pale red indicates the presence of circulatory disturbances such as ischemia and anemia, or edema.

(b) Pale red

A tongue of normal color; also called ‘slightly red’ in the classic literature written in the Edo period (1603–1868).

(c) Red

A tongue darker than normal pale red; also called ‘pure red’ and ‘vermilion’ in the classic literature written in the Edo period. It indicates fever, dehydration, and blood stasis, and is often linked to heat pattern (*Netsusho*), including both excess and heat (*Jitsunetsu*), and deficiency and heat (*Kyonetsu*). The common causes are telangiectasia, hyperemia, congestion, and hemoconcentration due to interstitial dehydration of the tongue. Red tongue such as mirror tongue may also be attributed to atrophy of the lingual papillae or tongue mucosa. Formulae containing Gypsum (石膏, sekko), Japanese Angelica Root (当帰, toki), and Rehmannia Root are indicated.

(d) Crimson

Crimson tongue has been attributed to the YoMei stage (陽明病, *Yomeibyo*) of acute febrile illnesses insufficiency of fluid and humor, but it is also observed in cases of heat pattern with dehydration or blood stasis. It may be caused by the concentration and stagnation of blood flow at the capillary level, which leads to oxygen desaturation of the blood and thereby to dark red color. Formulae containing Rehmannia Root, Ophiopogon Tuber (麦門冬, bakumondo), and Adenophora stricta Miq./A. tetraphylla (Thunb.) Fisch. (沙参, shajin) are considered.

(e) Purple and blue

Purple or blue tongue, also called slightly blue and light blue tongue in the classic literature of the Edo period, indicates poor blood circulation and blood stasis. It is frequently attributed to changes in the venous system such as venous dilation in the tongue, but also to cyanosis. Blue tongue often indicates sensitivity to coldness (*Hiesho*) and purple tongue often indicates blood stasis. Formulae containing Japanese Angelica Root, Peony Root (芍薬, shakuyaku), Cnidium Rhizome (川芎, senkyu), and Rehmannia Root are considered.

(2) Form of the tongue

The tongue consists of muscles that allow for food intake. In general, thick, large tongue has well-developed muscles and indicates a strong digestion, whereas thin, small tongue has small muscles and indicates a weak digestion.

(a) Enlarged tongue

An enlarged tongue is a thick and swollen tongue that is large enough to force the mouth open with margins that protrude beyond the lips and usually bear dental indentations. In Western medicine, it is known as macroglossia and is seen in patients with acromegaly, hypothyroidism, and Down's syndrome. It is attributed to hypertrophy of a group of muscles in the tongue and edema of tongue bodyand is considered to reflect conditions of qi (Ki) deficiency (*Kikyo*) and fluid disturbance. Formulae treating qi (Ki) disorders (*Kizai*) and fluid disturbance-treating (*Risui*) formulae are used.

(b) Thin tongue

Thin tongue reflects conditions of qi (Ki) deficiency and deficiency of blood and fluid. It usually results from poorly developed muscles in the tongue and tongue muscle atrophy. It may also be congenital.

(c) Dental indentations (歯痕)

Dental indentations along the maxillary or mandibular dental arch are observed in patients with deficiency of upper abdominal region, qi (Ki) deficiency, and fluid disturbance. Formulae containing Ginseng (人参, ninjin) and Astragalus Root (黄耆, ogi) and formulations to treat fluid disturbance are considered. Teeth-marked tongue may also be caused by thrusting the tongue forward against the teeth in anxious patients. In this case, the size of the tongue is normal.

(d) Fissures (皺裂)

Fissures on the surface of the tongue called *jinretsu* (人裂), *jinjiretsu* (人字裂), and *jinjimon* (人字紋) in the classic literature of the Edo period. Fissured tongue also called lingua plicata, scrotal tongue, and cerebriform tongue in Western medicine, because of the appearance of folds. It is associated with deficiency of blood and fluid. If the tongue is pale white in color, it indicates blood deficiency or dual deficiency of qi (Ki) and blood. Fissured tongue may be congenital or familial.

(e) Red spots (紅点)

A tongue with scattered red spots on its dorsal surface, especially at its tip. The tongue was called '*Kosei-zetsu* (紅星舌)' in the classic literature of the Edo period. Because fungiform papillae are not keratinized, their blood vessels are visible. If capillary vessels in the fungiform papillae become hyperemic, the papillae become redder and appear as red spots. The spots are commonly observed in patients presenting with heat pattern or blood stasis.

(f) Static spots (瘀点)

A tongue with minute, flat, dark brown to purplish black spots on its surface, which corresponds to "*Kokuten* (黒点)" in the classic literature of the Edo period. Static spots seen from the outside are capillary vessels that become rusty in color due to stagnation of blood in the fungiform papillae resulting in destroyed red blood cells with oxidized hemoglobin. It indicates blood stasis, and formulations to treat blood stasis (*Kuoketsuzai*) are used.

(g) Static macules (瘀斑)

A tongue with plum-colored macules. Flat, bluish purple to purplish black macules on the tongue surface are specifically called static macules. It indicates blood stasis, and formulations to treat blood stasis are used.

(h) Prickly tongue

A tongue with lingual papillae visible as thorn-like protrusions on its surface, especially along its central groove. Black protrusions are called black thorns. The protrusions are caused by proliferation and keratinization of filiform papillae, and are indicative of exuberant heat of the gastrointestinal tract or qi (Ki) aspect.

(i) Sublingual varicosis (静脈怒張)

The veins that run under the surface of the tongue that appear engorged and tortuous and small spots caused by congestion of venules are signs of blood stasis. Anatomical nomenclature of the vein is not sublingual vein but deep lingual vein. Sublingual vein is the vein that runs through the sublingual gland, etc.

(j) Dryness (*Kan*) and dampness (*Shitsu*)

In the Edo period, the term '*Jun* (潤)' was used to describe a 'moist condition.' Moist tongue and slippery fur (tongue surface wet with saliva) are signs of Yin pattern (*Yinsho*), for which ninjinto (人参湯) is commonly indicated. Dry tongue is a sign of Yo pattern (*Yosho*) and also seen in patients with fluid deficiency or blood stasis. Byakkoto (白虎湯) is often indicated for patients with dry tongue.

(3) Motility of the tongue

In the Edo period, a condition in which the tip of a tongue was repeatedly protruded from and retracted back into the mouth was called '*Rozetsu* (弄舌, tongue thrusting), and a tongue that appeared to be contracted was called a '*Tanshuku* (短縮, contracted tongue)'. Tongue tremor is associated with neuropathy of the brain such as Parkinson's disease.

e. Tongue fur

Formation of tongue fur is associated with factors such as sleep, drinking, smoking, constipation, and fever. The pH of saliva, amount of salivary secretion, oral flora, and condition of filiform papillae play roles in the growth of tongue fur.

(1) Fur thickness and peeling

(a) No fur

The color of the tongue body is clearly visible without any fur. The absence of tongue fur may be attributed to atrophic or immature filiform papillae.

(b) Thin fur (little fur)

A tongue with little exfoliation of cells from keratinized filiform papillae indicates that the condition of the patient is normal or that his illness is mild.

(c) Thick fur

Tongue fur is thick. In general, the thicker the fur, the longer the duration of illness. Thick fur indicates entry of an external pathogen into the interior (裏, *Ri*); retention of phlegm (痰, *Tan*), retained fluid (飲, *In*), and dampness; and food retention. Use of a denture, eating difficulty, and reduced ability to masticate may also contribute.

(d) Geographical tongue

A tongue with irregular peeling of fur; also called migratory glossitis in Western medicine. This is a disorder of keratinization of the mucosal epithelium of the tongue, caused by partial atrophy or disappearance of filiform papillae. Immature filiform papillae look red and depressed; mature filiform papillae look white and elevated. The tongue is commonly seen in patients with psychosomatic, immune, and allergic disorders. Lateralized tongue fur was called *Hentai* (邉苔) in the literature of the Edo period.

(2) Color of the tongue fur

(a) White fur

A tongue covered with epithelial cells of filiform papillae that are degraded by keratinization but remain on the tips of the papillae. It indicates conditions such as the ShoYo stage (小陽病, *Shoyobyo*) and stagnation or impairment of digestive function. Bupleurum Root (柴胡, saiko)-containing formulae including shosaikoto (小柴胡湯), and formulae containing Pinellia Tuber (半夏, hange), rhizomes of Atractylodes spp. (朮, jutsu), and Poria Sclerotium (茯苓, bukuryo) are considered. As a rule, laxatives are not used when white fur is present on the tongue.

Small amounts of keratinized epithelial cells that are exfoliated but remain on the tips of filiform papillae develop into a thin white fur (or whitish fur), which are commonly visible on the tongue of healthy persons.

(b) Yellow fur

Yellow fur indicates symptoms of stomach heat, such as heartburn, reflux of gastric acid, stomachache, and constipation. Yellowing of tongue fur is caused by further degradation of cells of filiform papillae and proliferation of bacteria. Cathartics may be used when yellow fur is thick. For the treatment of common chronic diseases without fever, however, the presence or absence of yellow or white fur does not always indicate whether daisaikoto (大柴胡湯) or shosaikoto should be used. In such cases, formulae containing Coptis Rhizome and Rhubarb (大黄, daio) are considered.

Yellowish white fur, a white of yellow fur and small amounts of yellow fur, corresponds to “yellowish fur” in the classic literature of the Edo period. It indicates impairment of the digestion caused by febrile disease, for which Bupleurum Root -containing formulae and Rhubarb-containing

formulae are considered.

(c) Gray fur

The tongue with pale black (gray) to dark brown fur, also called "*Kaizetsu* (灰舌)" in the literature of the Edo period. It indicates a worse condition than indicated by yellow fur and an interior pattern (*Risho*) characterized by interior heat, fluid retention (*Tan'in*), and cold-dampness.

(d) Black fur

Black fur, also called "black tongue" in the literature of the Edo period, is seen at the peak of fever and in serious stages of disease. Black fur indicates an interior pattern and is commonly seen in patients receiving long-term antibiotic therapy and terminally ill cancer patients. Bacteria producing black or brown water-soluble pigment and bacteria producing hydrogen sulfide (H_2S. which by binding to iron and calcium stains tongue fur) may contribute to the formation of black fur. Candida infection as a secondary infection may also be a cause.

In Kampo medicine, patients exhibit two fever patterns: An excess heat pattern (*Jitsunetsusho*) that requires purgation using Rhubarb-containing formulae such as daijokito (大承気湯) and a deficiency-cold pattern (*Kyokansho*) that must be treated with warm-tonifying (*Ompo*) formulae such as Processed Aconite Root (附子, bushi)-containing formulae including shigyakuto (四逆湯) and shimbuto (真武湯).

Listening and smelling examination (*Bunshin*)

'*Bunshin*' consists of both the 'smelling examination (*Kyushin*)' and 'listening examination (*Choshin*).'

In Kampo medicine, doctors directly listen to the patient's voice, sounds of breathing (shortness of breath (*Tanki*), shallow breathing (*Shoki*), etc.), cough, wheezing dyspnea, delirious speech, hiccup, belching, stomach growling sound, etc. to make diagnoses. In the abdominal examination, there are also sound-related findings such as splashing sounds (*Shinsuion*) and borborygmus (*Fukuchu Raimei*).

1) Smell

Odors such as body odor, breath odors (halitosis, alcohol odor, acetone odor, urinous odor, etc.), pus odor, discharge odor, stool odor, and urine odor may indicate abnormalities of the body.

2) Speech and voice

Vigorous, brisk speech indicates good coordination of qi (Ki), blood, and fluid (*Kiketsusui*). A clear, vigorous voice often indicates an excess pattern (*Jitsusho*); a high voice and incessant talking often indicate a heat pattern or excess pattern; a low voice and few words often indicate a cold pattern (*Kansho*) or deficiency pattern; a faint low voice often indicates a deficiency pattern. Speech in a hoarse or feeble voice may be a sign of qi (Ki) deficiency. A low, feeble voice (語言軽微, *Gogenkeibi*) is an indication for hochuekkito (補中益気湯).

3) Cough and breath sounds

Cough and wheezing can be easily heard during the listening examination. Moisturizing formulae such as bakumondoto (麦門冬湯) are used to treat dry cough, and formulae to treat fluid disturbance such as shoseiryuto (小青竜湯) are used to treat productive cough.

4) Borborygmus

Peristaltic sound that is heard even when the stomach is not empty is linked to gastrointestinal disorders and coldness of the upper abdominal region or spleen-stomach [TM]. It is treated with formulae such as hangeshashinto (半夏瀉心湯) and kanzoshashinto (甘草瀉心湯). If the stomach and intestines move erratically, use of daikenchuto (大建中湯) should be considered.

Inquiry (*Monshin*)

a. Inquiry in Kampo medicine

The primary goal of Kampo medicine is to help patients perform activities of daily living more comfortably by improving their subjective symptoms. Kampo practitioners should help patients describe in their own words their conditions and enter the words as heard into the medical record. It is not uncommon that signs that seem to be insignificant in modern medicine are important and diagnostic in Kampo medicine. Such signs include bitter taste in the mouth, dry mouth with no desire to drink water, craving for sweets, stress eating, sensation of a lump in the throat, growling sound in the stomach even when it is not empty, difficulty in speaking due to excessive salivation, cold feet even in the middle of summer with several socks on, insomnia due to hot feet, weather-sensitive pain, and severe sweating of the neck and face.

A history should be taken to identify the relationship between past events and current distress. A diet history, including food preferences and types of food consumed, should also be taken. Sweet cravings often indicate upper abdominal region (or spleen-stomach [TM]) deficiency.

b. Inquiry about symptoms

The following issues should be addressed:

(1) Fever and sensation of heat

In the past, before thermometers were available, local warmth, general warmth, and burning sensation (*Hoteri*) were assessed in patients with fever. Fever is a common manifestation of a Yo pattern and may also indicate a Yin pattern. There are two different types of heat: excess-heat, and deficiency-heat. Whole body fever refers to an elevation of body temperature without sweating and external pattern (*Gaisho*) of the YoMei stage (*Yomeibyo*). Aversion to heat (*Onetsu*) refers to a condition in which the patient suffers from high fever and interior excess pattern (*Rijitsusho*) of the YoMei stage (*Yomeibyo*). Alternating chills and fever (*Oraikannetsu*) refers to a condition in which chills and fever alternate and fever is of the ShoYo stage (少陽病, *Shoyobyo*). Other conditions include heat with agitation, which refers to a condition in which the patient suffers from fever and heaviness in the chest, tidal fever (*Chonetsu*: which refers to periodic rise and fall of body temperature in a tidal fashion), and blood heat (*Ketsunetsu*: which

refers to retention of heat in organs and resultant dysfunction).

(2) Chills (*Okan*) and aversion to wind (*Ofu*)

Chills refer to feeling of coldness and shivering, which commonly indicate an exterior pattern (*Hyosho*) and occasionally an interior pattern. Chills are also signs of Yo and Yin patterns. Aversion to wind refers to a dislike of wind and feeling of coldness.

(3) Appetite

Illness does not always reduce appetite. When blood stasis is prominent, for example, appetite may be excessive with increased food intake and recurrence of hunger sensation shortly after eating (消穀善飢, *Shokokuzenki*: swift digestion with rapid hungering) and craving for food. Also, premenstrual syndrome (PMS) may cause a significant increase in appetite, and patients with constipation may complain of increased appetite.

Poor appetite has numerous causes, such as gastrointestinal disorders, psychosomatic disorders, and febrile diseases. Even if it is considered to be an indication for hachimijiogan or Ephedra Herb-containing formulae, Rehmannia Root and Ephedra Herb should be used with caution. Formulae to enhance mucosal defense or promote gastric emptying, such as rikkunshito (六君子湯), are the first choice. When deficiency of upper abdominal region (spleen-stomach [TM]) and deficiency of lower abdominal region (kidney [TM]) occur, treatment should begin by fortifying deficiency of upper abdominal region. If the patient is unable to eat owing to a depressive tendency, qi (Ki)-regulating formulae (*RikiYaku*) such as kosharikkunshito (香砂六君子湯) may be the treatment of choice.

(4) Sleep

Psychophysiological insomnia and depressive insomnia are the major types of insomnia. Consumptive disease such as weakness and fatigue (*Kyoro*) (i.e. weakness with agitation [*Kyohan*]) is the major cause of psychophysiological insomnia; patients with this type of insomnia often complain of fatigue, difficulty in falling asleep, restlessness, and excessive night sweating (*Tokan*). Formulae such as sansoninto (酸棗仁湯) may be the indicated treatment.

For the treatment of depressive insomnia, Coptis Rhizome and Jujube Seed (酸棗仁, sansonin) are frequently added to untanto (温胆湯)-based formulae. Polygala Root (遠志, onji) and Jujube Seed are commonly added to formulae for the treatment of insomnia. The abdominal pattern for untanto is characterized by the absence of abdominal palpitation. Kanzoshashinto is effective in treating psychosomatic complaints such as gastrointestinal discomfort, stomach growling, sensation of a lump in the epigastric region, shoulder stiffness, and frequent dreaming. For robust patients with hypochondrium resistance and discomfort (*Kyokyo Kuman*), formulae such as saikokaryukotsuboreito (柴胡加竜骨牡蛎湯) are considered. For patients with reddened complexion, irritability, anger against anything, restlessness, and insomnia, treatment with san'oshashinto (三黄瀉心湯) or the like and orengedokuto (黄連解毒湯) may also be considered.

(5) Urination

In Kampo medicine, a defect in fluid excretion is called "fluid disturbance." An increase in urine volume

is called "spontaneous urination (*Shobenjiri*)," and decrease in urine volume is called 'inhibited urination (*Shobenfuri*).' Difficulty in urination is called 'difficult urination (*Shobennan*),' and urinary incontinence is called 'enuresis (*Inyo*).' If the color of urine is clear white, it indicates Yin and cold pattern. If the color of urine is yellow or reddish, it indicates Yo and heat pattern.

In relation to other symptoms, urination-related symptoms are treated as follows: goreisan (五苓散) for thirst, decreased urine volume (*Nyofuri*), and a spontaneous sweating tendency; choreito (猪苓湯) for thirst, decreased urine volume, and a tendency toward the absence of sweating; bukuryokanzoto (茯苓甘草湯) for decreased urine volume (similar to the indications for goreisan except thirst); byakkoto for thirst, increased urine volume, and excessive sweating; hachimijiogan for thirst, polyuria, drying tendency, and weakness of the lower abdominal region (*Shofuku Fujin*). Hachimijiogan is commonly used to treat polyuria, and dysuria and frequent urination caused by prostatic hyperplasia. Seishinrenshiin (清心蓮子飲) is preferred to treat frequent urination caused by aseptic cystitis.

Hochuekkito has been used to treat urinary incontinence, but hachimijiogan is preferred for patients with urinary incontinence accompanied by lower abdominal numbness. Urination pain is treated with formulae such as choreito and gorinsan (五淋散), and urination pain accompanied by hematuria is treated with formulae such as choreitoadded shimotsuto (猪苓湯合四物湯).

(6) Defecation

Constipation with hardened stools indicates Yo and excess pattern, and diarrhea and loose stools indicate Yi and deficiency pattern. However, heat dysentery (*Netsuri*; a diarrheal disease caused by fever) and lower-body heaviness (*Geju*; a sense of residual stool and urge to defecate with futile attempts to defecate) are signs of Yo and excess pattern. Tenesmus (*Rikyu Koju*) is a condition in which the patient feels an urge to defecate and abdominal pain and makes repeated but futile attempts to defecate. Functional diarrheas are called chronic diarrhea (*Sessha*), and acute infectious diarrheas are called '*Rishitsu*'.

Rhubarb is the preferred treatment for constipation, but patients with weak upper abdominal region (spleen-stomach [TM]) are often poor candidates. In such cases, Gardenia Fruit, Hemp Fruit (麻子仁, mashinin), and Zanthoxylum Fruit (山椒 [or 蜀椒], sansho) should be used appropriately. For the treatment of infections diarrhea (*Rishitsu*), Rhubarb-containing formulae are used briefly, followed by formulae that fortify upper abdominal region. Use of antibiotics may change the intestinal flora and thereby lower the cathartic activity of Rhubarb.

Chronic constitutional diarrhea (*Sessha*) is associated with deficiency of upper abdominal region and lower abdominal region. Ninjinto is considered when gastric manifestations are prominent. Shimbuto is used for diarrhea caused by coldness, and shokenchuto, ogikenchuto (黄耆建中湯), keihito (啓脾湯), and jinryobyakujutsusan (参苓白朮散) are used for dyspeptic diarrhea. For the treatment of diarrhea alternating with constipation, formulae that fortify liver (TM)-spleen (TM) (i.e. lower and upper abdominal regions), such as kamishoyosan (加味逍遥散) and goshakusan (五積散), are considered.

(7) Easy fatigability

Easy fatigability is the most common complaint. Various conditions, not only qi (Ki) deficiency but also

stress, depression, and deficiency of lower abdominal region, may play roles. It may be present as a feature of disease stages such as “inactivity and difficulty in moving (ShoYo stage [*Shoyobyo*])” and “overwhelming desire to sleep (ShoYin stage [少陰病, *Shoyinbyo*]).”

(8) Malaise

Malaise may be present in dampness, ShoYo stage (*Shoyobyo*), YoMei stage (Yomeibyo), and ShoYin stage (*Shoyinbyo*).

(9) Forgetfulness

Forgetfulness (*Kibo*) is regarded as a sign of blood stasis. Forgetfulness associated with cerebrovascular disorder may be treated with orengedokuto, and Alzheimer-type dementia may be treated with formulae such as chotosan (釣藤散), tokishakuyakusan (当帰芍薬散), kihito (帰脾湯), and kamiuntanto (加味温胆湯).

(10) Irritability

In general, irritability is regarded as a symptom of liver (TM) abnormality. Bupleurum Root-containing formulae such as kamishoyosan may be used. Frowning while speaking, irascibility, rashness, and insomnia may be treated with yokukansan (抑肝散).

(11) Sweating and night sweating

Sweats can be divided into spontaneous sweating (*Jikan*), night sweating (*Tokan*), sweating on the head (*Zukan*), cold sweating (*Kyokan*), absence of sweating when all other people are sweating (*Mukan*), and sweating from the hands and feet (*Teashikan*).

Patients who tend to spontaneously sweat may have exterior deficiency and fluid disturbance, which may be treated with Astragalus Root-containing formulae. Exterior deficiency may be treated with formulae such as keishito (桂枝湯), keishikaogito (桂枝加黄耆湯), and gyokuheifusan (玉屏風散). Patients may complain of coldness when exterior heat is removed. Night sweating is commonly caused by a tendency toward body fluid deficiency combined with febrile states and agitation. It is also seen in patients with a fluid disturbance tendency, weak patients, and those in a state of chronic exhaustion. Tokirikuoto (当帰六黄湯) and saikokeishikankyoto (柴胡桂枝乾姜湯) may be used.

(12) Headache and dull headache

Treatment for headache and dull headache is determined in association with treatment for conditions such as coldness, gastrointestinal symptoms, shoulder stiffness, and blood stasis. Formulae such as goshuyuto (呉茱萸湯), hangebyakujutsutemmato (半夏白朮天麻湯), chotosan, kamishoyosan, and hachimijiogan are used.

(13) Tinnitus and hearing loss

Bupleurum Root-containing formulae, qi (Ki)-regulating formulae such as soshikokito (蘇子降気湯),

and formulae treating deficiency of lower abdominal region (*Hojinzai*)such as jijintsujito (滋腎通耳湯) are considered.

(14) Vertigo, hot flashes (*Nobose*), and dizziness on standing up

These symptoms may be present in various conditions such as fluid disturbance, qi (Ki) counterflow, qi (Ki) deficiency, and blood deficiency.

(15) Decreased vision, eyestrain, blurred vision, photophobia, and dark circles under the eyes

These symptoms are often regarded as signs of qi (Ki) deficiency and liver (TM) abnormality. Dark circles under the eyes are a sign of blood stasis.

(16) Sensation of a lump in the throat

The symptom is known as 'foreign-body sensation in the throat (*Inchu Sharen*)' in Kampo medicine and treated with hangekobokuto (半夏厚朴湯). It is also called '*Baikakuki*.' If it is attributable to hypersensitivity of the mucous membrane, the application is extended.

(17) Thirst, dry mouth, and dry lips

In Kampo medicine, thirst (*Kokatsu*) (a feeling of dryness in the mouth with a desire to drink) is distinguished from dry mouth (a lack of fluid in the mouth without a desire to drink). Dry lips are signs of deficiency of upper abdominal region, fluid deficiency, and blood stasis, and treated with formulae such as shokenchuto, ninjin'yoeito, and unkeito.

(18) Cough

Bakumondoto is used to treat nonproductive cough, and seihaito (清肺湯) to treat productive cough. Bakumondoto is indicated for severe paroxysmal coughing, and seihaito for cough and expectoration caused by bronchiectasis.

(19) Bitter taste in the mouth

Bitter taste in the mouth is an indication for Bupleurum Root-containing formulae. According to "*ShangHanLun*," the ShoYo stage (*Shoyobyo*) is characterized by bitter taste in the mouth, thirst, and dizziness. Because it may also be caused by aging, tooth decay, gingivitis, dental prosthesis, or other drugs, care must be taken.

Insensitivity of the mouth (no taste, taste disorders) and harmony of the mouth (normal taste such as tobacco, kochuwa) indicate the ShoYin stage (*Shoyinbyo*).

(20) Salivation

Excessive saliva secretion is an indication for ninjinto (人参湯) and a sign of stomach coldness. It may also be caused by excessive strain.

(21) Belching, heartburn, sensation of a lump in the epigastric region, nausea, and vomiting

These symptoms are signs of stomach qi (Ki) disharmony, and treatment may be formulae such as

hangekobokuto and hangeshashinto. Vomiting may be a sign of fluid disturbance.

(22) Abdominal pain, abdominal distention, stomach growling, and excessive gas

Abdominal pain is a very common symptom. Formulae based on a combination of Peony Root and Glycyrrhiza (甘草, kanzo) are commonly used. Abdominal distention indicates a deficiency or excess pattern. Formulae such as kobokushokyohangekanzoninjinto (厚朴生姜半夏甘草人参湯) may be used for a deficiency pattern, and jokito (承気湯) group may be used for an excess pattern. Stomach growling is a good indication for hangeshashinto and kanzoshashinto. Excessive gas is an indication for hangekobokuto (半夏厚朴湯) and jokito-group.

(23) Decreased libido

Decreased libido is a sign of deficiency of lower abdominal region. Disorder of upper abdominal region (*Hii*), liver (TM) abnormality, or qi (Ki) deficiency may cause decreased libido in both men and women from adolescence to middle-age.

(24) Brittle nails, hair loss, and dry, scaly skin

These symptoms are generally regarded as signs of blood deficiency. Basic treatment is shimotsuto. If Rehmannia Root causes indigestion, treatment should begin by compensating for the deficiency of upper abdominal region. Formulae to treat qi (Ki) deficiency may also be effective.

(25) Skin itching

The patient's skin should be palpated to determine whether it is dry or moist.

(26) Chilblain

Chilblains are caused by poor peripheral circulation. If chronic exposure to cold stress is the cause, tokishigyakukagoshuyushokyoto (当帰四逆加呉茱萸生姜湯) may be used.

(27) Neck and shoulder stiffness

Stiffness as an indication for kakkonto (葛根湯) is often felt in the nape of the neck and all the way down the back. Stiffness effectively treated with Bupleurum Root-containing formulae extends from the shoulder along the trapezius and is explained in terms of the bladder meridian of foot-TaiYo and the gallbladder meridian of foot-ShoYo.

(28) Pain

Pain caused by blood stasis does not move and tends to become severe at night probably because peripheral circulation is poorer at night. Pain from qi (Ki) stagnation (*Kitai*) may frequently move, and pain from wind-dampness often responds to changes in weather. Symptoms of rheumatoid arthritis and migraine may worsen in response to reduced atmospheric pressure, which is attributed to 'mutual contention of wind and dampness' in Kampo medicine. Pain from qi (Ki) deficiency tends to increase during the day and subside during the night.

(29) Coldness

Coldness is a very important manifestation. According to "*ShangHanLun*," subjective coldness is '"*Kan* (寒)' and objective coldness is '"*Rei* (冷).' Coldness in the hands and feet is called reversal of qi (Ki) (*Ketsu*), and may be limited to the hands and feet in mild cases. Coldness can be explained by a combination of Yin and Yo patterns. A Yin pattern with cold extremities and watery diarrhea due to a deficiency cold (*Kyokan*) in the body is called cold syncope (*Kanketsu*). It is treated by warming. A Yin pattern with inflammation in the interior (in organs), heat trapped in the body, and cold hands and feet is called heat syncope (*Netsuketsu*). It is treated by cooling. In examination, an objective condition in which coldness spreads from the tips of the limbs in a retrograde manner causing a significant reversal of qi (Ki) (*Ketsu*) is called reversal cold of the extremities (*Shusoku Ketsurei*). A subjective sense of coldness at the tips of extremities caused by hypersensitivity to external cold stress is called reversal cold in the extremities (*Shusoku Ketsukan*).

A subjective sense of coldness (*Shusokukan*) is treated with bushito (附子湯); '*Shusoku Ketsukan*' is treated with tokishigyakuto (当帰四逆湯); '*Shusoku Kanrei*' is treated with shigyakuto or goshuyuto. Thus, treatment is determined according to the severity of coldness. A subjective sense of warmth in the extremities (*Shisokuon*; 'neither hot nor cold') is treated with shosaikoto, shishishito (梔子豉湯), and shakuyakukanzoto (芍薬甘草湯). Coldness caused by spontaneous sweating from exterior deficiency is not uncommon and may be treated with keishito, keishikaogito (桂枝加黄耆湯), and gyokuheifusan. In patients with mild aversion to cold in the back (*Sebi Okan*), an indication for bushito, coldness in the center of the body may be felt as coldness in the back. Patients with fluid disturbance may also complain of coldness in the back. Seishitsuketanto (清湿化痰湯) may be used to treat the condition in which internal fluid gathers to form phlegm. The condition is described as 'icy coldness confined to the back.'

It is important to identify the type of coldness, such as coldness at the tips of the limbs due to poor peripheral circulation, coldness of the entire body, true cold and false heat, and true heat and false cold.

(30) Burning sensation (*Hoteri*)

Burning sensation is a manifestation of qi (Ki) counterflow, blood deficiency, and blood heat. Sammotsuogonto (三物黄芩湯), a Rehmannia Root-containing formula to enrich Yin (*Jiyin*) and treat heat pattern (*Seinetsu*), may be effective in treating insomnia due to hot feet.

Palpation

Palpation is a method of examination in which practitioners touch the patient's body directly using their hands. Pulse examination and abdominal examination are vital parts of palpation. According to old Kampo medical sayings, it was said that diagnosis of external impact (acute febrile illness) should be based mainly on pulse examination, and diagnosis of internal damage (chronic constitutional illness) should be based mainly on abdominal examination. Thus, pulse examination is essential for the diagnosis of acute illness and abdominal examination is essential for the diagnosis of chronic illness.

Practitioners also palpate the limbs and back to determine, for example, whether coldness is subjective or

both objective and subjective. In Kampo medicine, burning sensation (*Hoteri*) is also a significant finding. Palpation of the limbs should always be performed.

Pulse examination

a. Pulse examination methods in Japanese Kampo

In Kampo medicine, pulse examination is performed not only to check the pulse and arrhythmias but also to obtain other information required to determine treatment. The pulse is taken at the radial artery (寸口 [*Sunko*], wrist pulse), and in more detail, three fingers (*Sunko* [寸口, the index finger], *Kanjo* [関上, the middle finger], and *Shakuchu* [尺中, the ring finger]) may also be used individually to feel the pulse. The pulse is taken by lightly pressing the site of measurement and then gradually increasing the pressure. During pulse examination, the condition of the radial artery and supporting tissues is also examined. In modern Kampo medicine, emphasis is rarely placed on differences in pulse between the left and right wrists or among the above three fingers. In cases of pulseless disease (aortic arch syndrome), however, the difference may be of great diagnostic significance. If there is a clear difference in pulse between the left and right wrists, the condition of the wrist with the weaker pulse may be used to diagnose chronic illness.

According to "*Ritsuen Ikun Gojyunanasoku* (栗園医訓五十七則)" in the first part of "*Kisso Shoei* (橘窓書影)" written by Sohaku Asada (1815–1894), floating (浮) and sunken (沈) pulse patterns should be studied first as the major warp. As the illness progresses and blood/qi changes, relaxed (緩), tight (緊), moderate (遅), frequent (数), smooth (滑), and rough (濇) pulse patterns should be studied as the weft, and the meanings of the pulses will become evident step by step.

b. Pulse findings

(1) Normal pulse (平脈)

The pulse of a healthy person is called a normal pulse.

(2) Floating and sunken pulses (浮・沈)

The pulse is taken by lightly pressing the site of measurement and then gradually increasing the pressure. In general, floating pulse indicates that the site of the anti-disease reaction is exterior, and sunken pulse indicates that it is interior. A floating pulse found in the early stages of acute febrile disease is suggestive of an exterior pattern, because the blood flow rate in the vessel is increased and the vessel wall is pushed up from the inside. A floating pulse detected in patients with chronic nonfebrile disease is suggestive of a deficiency pattern.

(3) Tight and relaxed pulses (緊・緩)

If the pulse is taut, it is called a tight pulse, and if not, it is called a relaxed pulse. A taut pulse is thin and strong, and indicates excess, pain, and cold patterns. A relaxed pulse is slow, but not slower than a moderate pulse (about 65 beats/min). The degree of tension should be measured at the depth at which the pulse is most clearly felt and indicates the intensity of the anti-disease reaction.

(4) Excess (strong) and deficiency (weak) pulses (実・虚、強・弱)

These pulses indicate the dynamism of qi (Ki). The overall strength is expressed as replete (strong) or vacuous (weak).

(5) String-like pulse (弦)

The term 'string-like pulse' is seen in the classic literature. It is a straight and taut pulse, like a string of a bow. In general, a pulse that is slightly less taut than a tight pulse is called a string-like pulse. In other references, however, it is stated that there are differences in the tight pulse (but not the string-like pulse) between the left and right wrist.

(6) Surging (large) or fine pulse (small) (洪[大]・細[小])

The pulse width is measured. A wide pulse is called a surging pulse (large) and indicates Yo (heat). A narrow pulse is called a fine pulse (small) and indicates Yin (cold).

(7) Frequent or moderate pulses (数・遅)

Concept regarding the extent of pulse rate. In cases of acute diseases, a 'frequent pulse' (≥ 6 beats per 1 respiration of the practitioner, or ≥ 90 beats/min in general) indicates heat, and a 'moderate pulse' (≤ 4 beats per 1 respiration of the practitioner, or ≤ 60 beats/min in general) indicates cold.

(8) Rough and smooth pulses (渋[濇]・滑)

When the pulse train felt by three fingers is sluggish and irregular, the pulse is called 'rough' and is associated with sluggish circulation, fluid retention, and blood stasis. Hypovolemia, decreased cardiac output, and increased blood viscosity are possible causes.

A slippery, smooth pulse indicates heat, excess, and Yo patterns. It may also indicate pregnancy.

(9) Hollow pulse (芤)

A hollow pulse that is clearly felt by light pressure but barely felt by slightly more pressure, like touching a scallion stalk, is a sign of prostration resulting from loss of blood.

(10) Moderate and skipping, and pace changing pulses (結・代)

Moderate and skipping, and pace changing pulses indicate arrhythmias. A moderate and skipping pulse is a slow (結微) pulse (≤ 60 beats/min) that pauses transiently or at irregular intervals. It corresponds to bradyarrhythmias, usually seen in patients with various blocks, certain extrasystoles, and sinus bradycardia with escape rhythms. A intermittent pulse (代脈) pauses at regular intervals and the duration of each pause may be very long and described as a '"pausing at regular intervals.' From the viewpoint of modern medicine, moderate and skipping, and pace changing pulses are usually seen in patients with second-degree atrioventricular block or premature ventricular contraction.

c. Common pulse shapes in everyday practice

(1) Acute diseases

(a) Floating, frequent, and tight pulse

A rapid high tension pulse that is strong on light pressure can be treated with Ephedra Herb-containing formulae such as maoto (麻黄湯) and kakkonto (葛根湯).

(b) Floating, frequent, and weak pulse
A rapid no tension pulse that is weak on light pressure and intermittent on heavy pressure can be treated with formulae such as keishito (桂枝湯).

(c) Fine pulse
A pulse that feels like a fine thread, unlike floating and sunken pulses, indicates a transition from the TaiYo stage (*Taiyobyo*) to ShoYo stage (*Shoyobyo*).

(d) Sunken and excess pulse
A pulse that is strong on heavy pressure indicates the need for purgation with Rhubarb-containing formulae, etc.

(e) Sunken and smooth pulse
A pulse indicating the presence of heat in the interior requires treatment with Gypsum-containing formulae.

(f) Sunken, weak pulse
Refers to a pulse that is not felt by light pressure and barely felt by heavy pressure. A sunken, moderate, weak pulse indicates an interior cold pattern. Such a pulse indicates impaired metabolism, for which Processed Aconite Root-containing formulae such as bushirichuto (附子理中湯) and shigyakuto (四逆湯) are indicated.

(2) Chronic diseases
(a) Floating and weak pulse
A pulse diagnostic for interior deficiency. 'Paradoxical large pulse and no strength (散大無力, *Sandai Muryoku*)' is an indication for hochuekkito (補中益気湯); floating, large, faint pulse is an indication for Processed Aconite Root-containing formulae; sunken, weak, moderate pulse is an indication for shokenchuto (小建中湯).

(b) Floating, excess pulse
A pulse indicating multiple simultaneous pathogens for which promotion of sweating, treatment of fluid disturbance, and purgation may be indicated. Painful disease may be treated by promoting sweating.

(c) String-like, fine pulse
A pulse indicating the ShoYo stage (*Shoyobyo*), fluid disturbance, or a prolonged but not significantly deficient condition. Shosaikoto (小柴胡湯） may be used, but formulae to promote sweating, cathartics,

or emetics must not be used.

(d) Sunken, moderate, excess pulse

A pulse suggestive of an interior excess pattern (e.g., constipation), for which purgative formulae such as choijokito (調胃承気湯), shojokito (小承気湯), daijokito (大承気湯), and daisaikoto (大柴胡湯) are indicated.

(e) Sunken, moderate, weak pulse

A pulse indicating an interior deficiency pattern (e.g., diarrhea), for which deficiency pattern-treating formulae (*Hozai*), such as ninjinto (人参湯), shimbuto (真武湯), daikenchuto (大建中湯), and shigyakuto (四逆湯), and Processed Aconite Root-containing formulae are indicated.

(f) Sunken, rough pulse

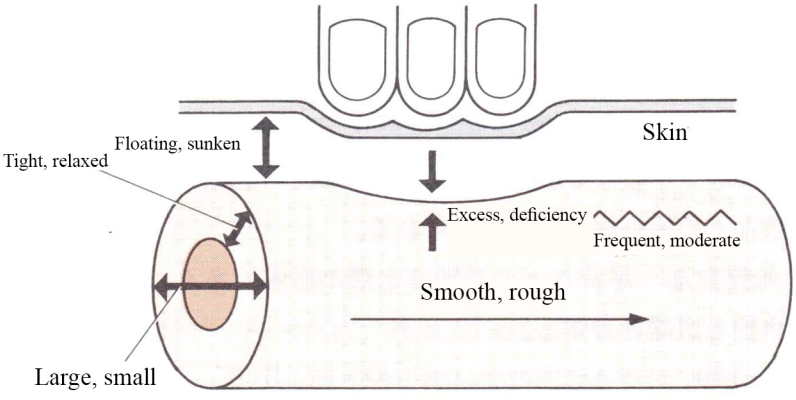
A pulse indicating blood stasis and pain and numbness pattern (痺証, *Hisho*). A sunken, excess, rough pulse is suggestive of blood stasis, for which formulae to treat blood stasis, such as tokakujokito (桃核承気湯), keishibukuryogan (桂枝茯苓丸), and teitoto (抵当湯), are indicated. A sunken, weak, rough pulse may also indicate blood deficiency.

(g) Fine, moderate pulse

A pulse indicating the presence of coldness in the extremities, for which formulae, such as tokishigyakuto (当帰四逆湯), goshuyuto (呉茱萸湯), bushirichuto (附子理中湯), shimbuto (真武湯), and keishikabushito (桂枝加附子湯), may be indicated.

(h) Large, weak pulse

A pulse indicating severe fatigue and loss of stamina, for which formulae such as juzentaihoto (十全大補湯) and hochuekkito (補中益気湯) may be indicated.



Source: Katsutoshi Terasawa: "*Shorei kara Manabu Wakan Shinryogaku* (症例から学ぶ和漢診療学, *Japanese Traditional [Kampo] Medicine, Learning from Case Studies*)"

Schematic diagram of pulse types used for diagnosis

Abdominal examination

a. History of abdominal examination in Japan

In Japan, abdominal examination has developed in a unique way and it is given particular emphasis in the practice of Kampo medicine. According to Keisetsu Otsuka, treatment similar to abdominal palpation (abdominal massage) was performed for patients by Zen priests in the Muromachi period (1392–1575). He speculated that the treatment influenced the techniques of abdominal palpation and abdominal examination in later generations. These techniques were summarized by Hoin Taga (多賀法印, Taga Kusushi Betto Hoin Kengi Hakugyoin), and documented in the book "*Fukushin no ho* (腹診の法)" stored in Taga Yakushi. It is said that Hoin Taga imparted the techniques of acupuncture and abdominal examination to a Zen priest named Mubunsai (夢分斎) (probably the same person as Mubun [無分], father of Isai Misono) in the Azuchi-Momoyama period (1575–1603). These techniques were then taught to Isai Misono (1557–1616) by Mubunsai. Isai developed a *dashin-ho* (needling with hammer) and had great success in the use of Isai-style acupuncture and Mubun-style abdominal examination. A book called "*Mubunryu Zofu Haitozu* (夢分流臓腑配当図)" describes the basic Mubun-style abdominal examination and is still used in some schools. These initial techniques of abdominal examination were based on "*NanJing* (難経)" and advocated mainly by acupuncture practitioners. It should be noted that Zen priests and acupuncture practitioners played important roles in the genesis of the abdominal examination. The techniques of *NanJing*-based abdominal examination were compiled and published as "*Shinbyo kikai* (診病奇侅)" by Genken Taki (多紀元堅) in Japan. The book was translated to Chinese by Misao Matsui (松井操) and published in China in 1888 as China's first book of Japanese Kampo medicine.

These *NanJing*-based techniques of abdominal examination had a great impact on Gosei school Kampo practitioners, whereas Koho school Kampo practitioners used *ShangHanLun*-based techniques of abdominal examination. The *ShangHanLun*-based abdominal examination was established by Konzan Goto (後藤艮山) who thought that abdominal patterns corresponded to abnormalities of the back. Konzan Goto was succeeded by Chinan Goto (後藤椿庵) (son of Konzan Goto and a Koho school practitioner) and Shuan Kagawa (香川修庵) (a disciple of Konzan). They emphasized the importance of back examination (kohai).

Then, Todo Yoshimasu (吉益東洞) (1702–1773), a leader of the Koho school, emphasized the importance of abdominal examination based on the belief that "the abdomen is the basis of human life and therefore shows signs of various diseases." This phrase is also seen in "*Hyakufuku Zusetsu* (百腹図説)" written by Dosan Manase (曲直瀬道三) (1507–1594). Various other abdominal examination methods were devised thereafter in the Edo period. In his "*Fukushinsho no Bunrui* (腹診書の分類), *Classification of Abdominal Examination*," Otsuka listed a total of 106 publications on abdominal examination (36 publications on *NanJing*-based methods, 37 on *ShangHanLun*-based methods, 5 on combinations of both mthods, and 28 which he did not read). Many of those publications were incomplete and presented only personal opinions. Of the publications on *ShangHanLun*-based abdominal examination methods, "*Fukushozui* (腹証図彙)" (1809) and "*Fukusho Kiran* (腹証奇覧)" (1801–1809) written by Bunrei Inaba (稲葉文礼), and "*Fukusho Kiranyoku* (腹証奇覧翼)" (1809–1853) written by Shukuko Wakuta (和久田叔虎), a disciple of Inaba, are outstanding. (Because Inaba died before seeing the completion of "*Fukusho kiran*," Wakuda took over and completed the job [i.e., the publication of "*Fukusho kiranyoku*"].) Their works have had a great impact on the abdominal

examination methods used in today's Kampo medicine.

b. Practice of abdominal examination

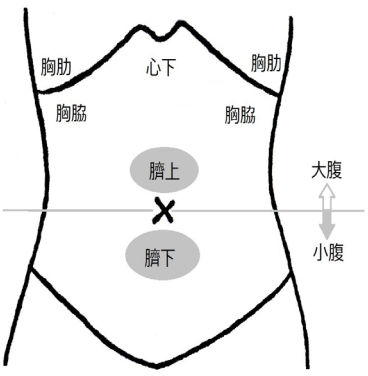
As a rule, abdominal examination is performed while the patient is supine with legs extended straight out in a relaxed manner, unlike the position for examination in Western medicine in which the patient is placed with knees bent. This is because the abdominal wall needs to be relaxed for abdominal examination in Western medicine to determine the characteristics of intra-abdominal organs, whereas abdominal examination in Kampo medicine is performed to investigate how abnormalities in intra-abdominal organs and the body appear on the surface of the abdomen. Abnormality is determined from the tension and nature of the abdominal wall and tenderness on pressure.

Abdominal examination should be done by softly touching the abdomen using one hand or both hands; if the hand(s) is pressed too hard against the abdomen, the patient may feel pain and become tense, thus hindering diagnosis. In general, for frail persons, it should be done by slowly stroking the abdomen with warm hands. For robust, middle-aged men, the tender points should be identified quickly using fingers. In abdominal examination, it is important to detect not only tenderness and resistance but also warmth, coldness, moistness, and dryness felt on the palm of the hand. If typical findings are obtained in abdominal examination, the patient should be asked again about symptoms associated with the findings for confirmation.

Tender points are areas on the skin that elicit pain when palpated, which show localization of lesions under the skin or in body cavities. If there are abnormalities (such as inflammation of the organ, peritoneum, or mesentery, nerve injury, and reduced blood flow), then visceral pain, somatic pain, or visceral motor reflex may cause involuntary twitches of skeletal muscles (muscle rigidity) in the abdomen innervated by a particular spinal nerve and hyperesthesia (hyperalgesia) in the spinal nerve. This may cause tenderness in local regions (skin and muscle) innervated by the nerve. In abdominal examination, it is possible to detect changes resulting from reduced blood flow in tissue, such as blood stasis and blood deficiency, based on the presence of tenderness.

c. Findings on abdominal examination

(1) Names of abdominal regions in Kampo medicine



Names of abdominal regions in Kampo medicine

Shinka (心下: similar to epigastrium) refers to the triangular region with the apex just below the xiphoid process and with the base connecting the intersections of the left and right breast lines and costal arches. *Daifuku* (大腹) refers to the upper abdomen (above the umbilicus), and *shofuku* (小腹) refers to the lower abdomen (below the umbilicus).

心下 *Shinka* (epigastric region)
胸肋 *Kyoroku* (sternocostal region)
胸脇 *Kyokyo* (hypochondriac region)
臍上 *Saijo* (supraumbilical region)
臍下 *Saika* (infraumbilical region)
大腹 *Daifuku* (upper abdominal region)
小腹 *Shofuku* (lower abdominal region)

(2) Abdominal strength (*Fukuryoku*)

The elasticity and tone of the abdomen are determined. The abdominal strength (*Fukuryoku*) is usually rated on a five-point scale of excessive, slightly excessive, moderate, slightly deficient, and deficient. The fullness of the anti-disease reaction is determined according to the deficiency or excess of the abdominal strength. In general, persons with a wide costal arch in the epigastric region are likely to have an excess pattern, and those with a narrow costal arch are likely to have a deficiency pattern. In fact, this examination is performed to investigate whether the patient has a strong abdomen. Persons with insufficient abdominal strength and low tension tend to have an insufficient anti-disease reaction, for whom purgative formulae containing Ephedra Herb, Rhubarb, and Gypsum may not be applicable. In such cases, deficiency pattern-treating formulae containing Ginseng, Astragalus Root, and Processed Aconite Root are commonly used.

(3) Abdominal distension (*Fukuman*)

Distention of the entire abdomen caused by retention of stool and gas in the digestive tract or ascites, often with a tympanitic note on percussion if the intestine is distended by gas. It is classified into two types: hard and tense distention (*Jitsuman*) and soft and forceless distention (*Kyoman*). *Jitsuman* is caused by ascites and severe constipation, and *Kyoman* is caused by relaxation of the intestines and retention of gas in the intestines due to a paralytic ileus.

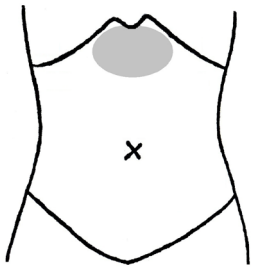
Jitsuman may be treated with jokito-group (承気湯類), and *Kyoman* may be treated with keishikashakuyakuto (桂枝加芍薬湯) and kobokushokyohangekanzoninjinto (厚朴生姜半夏甘草人参湯).

(4) Peristalsis unrest (*Zendo Fuon*)

The peristalsis of the intestines, often with abdominal pain, is visible through the thin abdominal wall. In ancient times, it was perceived as movement of a snake or eel. It is induced when gastrointestinal function is reduced by cold (or ileus occurs in severe cases), gas or fluid remains or moves in the intestinal tract, and the intestinal tract is distended by peristaltic movement. This movement occurs sporadically, and usually does not affect the passage of intestinal contents.

It may be treated with daikenchuto (大建中湯), or kaikyushokushoto (解急蜀椒湯), a combination of daikenchuto and bushikobeito (附子粳米湯) if pain is severe.

(5) Epigastric discomfort and resistance (*Shinka Hiko*)

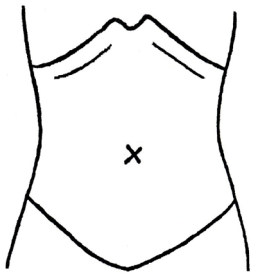


Epigastric discomfort and resistance (*Shinka Hiko*)

Resistance in the epigastric region. Stuffiness in the epigastric region (subjective symptom) alone is called *Shinka Hi*, and objective resistance on pressure is called *Shinka Hiko*. In practice, however, tenderness on pressure is commonly observed in patients diagnosed with *Shinka Hiko*. If tenderness is severe, it may also be called 'binding chest (*Kekkyo*).'

Formulae containing Coptis Rhizome, Ginseng, Bupleurum Root, and Pinellia Tuber, such as hangeshashinto (半夏瀉心湯) may be used.

(6) Hypochondrium resistance and discomfort (*Kyokyo Kuman*)



Hypochondrium resistance and discomfort (*Kyokyo Kuman*)

Resistance and tenderness in the hypochondrium. In classic literature, the term '*Kyokyo Kuman*' refers to abnormalities that are present mainly in the margins of both hypochondria and to extensive abnormalities that are present in both hypochondria, flanks, and outer parts of the chest. Abnormalities may also be present only in the left or right side of the body. In this case, the frequency of abnormalities only in the right side is slightly higher. *Kyokyo Kuman* is considered to be a typical finding of the ShoYo stage (*Shoyobyo*), and particular emphasis has been placed on it as an indication for Bupleurum Root (柴胡)-containing formulae in Japanese Kampo medicine.

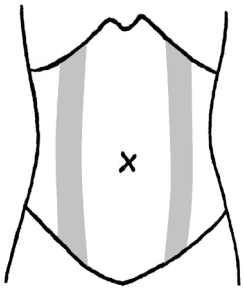
It has been pointed out that *Kyokyo Kuman* is associated with stress and diseases of organs that are located above and below the diaphragm, such as pleuritis, splenomegaly, chronic hepatitis, and hepatomegaly. It has also been reported that the more severe the symptoms of *Kyokyo Kuman*, the larger the left lobe of the liver in comparison with the right lobe.

In patients with *Kyokyo Kuman*, tenderness in the hypochondrium is considered to be induced as follows: Irritation of visceral afferent fibers caused by infection and inflammation such as pleuritis and hepatitis triggers hyperalgesia of afferent neurons of intercostal nerves, mediated by the reflex arcs in the 6th to 10th thoracic cord segments. Resistance is considered to be induced by involuntary contraction of the muscles in the subcostal region caused by efferent neurons. These hypotheses are in agreement with the theory proposed by Yoshio Nagahama that patients who are found have *Kyokyo Kuman* in abdominal examination are often found to have abnormalities such as tenderness at ganshu (BL18, 肝兪) and danshu (BL19, 胆兪) (acupuncture points of the bladder meridian) in back examination.

Kyokyo Kuman is an indication for Bupleurum Root-containing formulae such as shosaikoto (小柴胡湯), daisaikoto (大柴胡湯), shigyakusan (四逆散), and saikokaryukotsuboreito (柴胡加竜骨牡蛎湯).

(7) Contracture of rectus abdominis (*Fukuchokukin Renkyu*)

It indicates excessive strain of the rectus abdominis muscles. This change is usually bilateral, but may also be unilateral (left or right side of the body) or appear only on the upper abdomen. Strain of the upper rectus abdominis muscles is attributed to the middle thoracic cord, and strain of the lower rectus abdominis muscles is attributed to the lower thoracic cord. The strain may not be a muscle contraction caused by visceral motor reflex, but a compensatory excessive strain resulting from hypotonicity in the



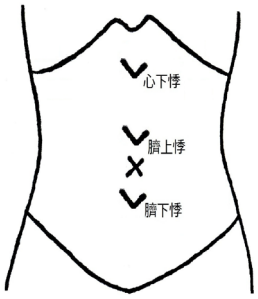
Rectus muscle tension (TM)

group of abdominal muscles (other than the rectus abdominis muscle) and from decreased abdominal pressure.

Shigyakusan (四逆散) may be used for patients with an excess pattern and shokenchuto (小建中湯) may be used for patients with a deficiency pattern.

(8) Palpable abdominal aortic pulsation (*Fukubu Doki*)

Palpable pulsation of the abdominal aorta in the peri-umbilical region. *Shinka Ki* refers to palpable pulsation in the epigastric region, *Seijo Ki* refers to palpable pulsation in the supraumbilical region, and *Seika Ki* refers to palpable pulsation in the infraumbilical region. It is caused by transmission of pulsation from the abdominal aorta to the abdominal wall, depending on the balance between the abdominal strength, abdominal wall tension, and sympathetic nerve tone. Pulsation of the abdominal aorta is felt by light pressure on the abdominal wall or can be seen through the abdominal wall in patients with a deficiency pattern characterized by a thin, relaxed abdominal wall (*Seijo Ki* or *Seika Ki*). In the elderly, the aortic bifurcation may be pulled downward due to spinal deformity and arteriosclerosis, which may cause a strong pulse felt in the infraumbilical region (*Seika Ki*). Pulsation of the abdominal aorta may be strong and readily transmitted to the abdominal wall in patients with an excess pattern characterized by high sympathetic tone (*Shinka Ki* or *Seijo Ki*).



Pulsation of the abdominal aorta

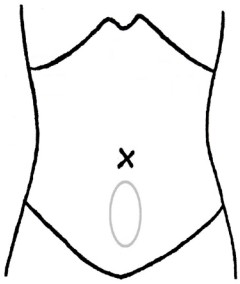
Shinka Ki may be treated with ryokeijutsukanto (苓桂朮甘湯). *Seijo Ki* may be treated with saikokaryukotsuboreito (柴胡加竜骨牡蛎湯) in the presence of an excess pattern and keishikaryukotsuboreito (桂枝加竜骨牡蛎湯) and shakanzoto (炙甘草湯) in the presence of a deficiency pattern. Hochuekkito (補中益気湯) may be used for cases of strong pulsation around the umbilicus, ryokeikansoto (苓桂甘棗湯) for cases of *Seika Ki*, and yokukansankachimpihange (抑肝散加陳皮半夏) for cases of strong pulsation between the umbilicus and the epigastric region.

心下悸：Pulsation in the epigastric region (*Shinka Ki*)

臍上悸：Pulsation in the supraumbilical region (*Seijo Ki)*

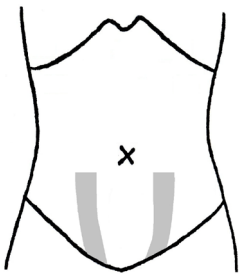
臍下悸：Pulsation in the infraumbilical region (*Seika Ki*)

(9) Weakness and muscle tension of lower abdominal region (*Shofuku Fujin* and *Shofuku Kokyu*) *Shofuku Fujin* and *Seika Fujin* usually refer to abnormal sensation in the infraumbilical region (numbness or supersensitivity), and often refer to weakness (soft and feeble) in the infraumbilical region in the presence of an abdominal pattern. The linea alba is composed of the fusion of abdominal muscle aponeuroses, such as the sarcolemmas of rectus abdominis muscles, which separates the left



Weakness of the lower abdominal region (*Shofuku Fujin*)

and right rectus abdominis muscles at the midline. The linea alba is thinner in the infraumbilical region than in the supraumbilical region. A decrease in the tone of the linea alba caused by aging or weakness may result in numbness in the infraumbilical region.



Lower Abdominal Muscle Tension (TM) (*Shofuku Kokyu*)

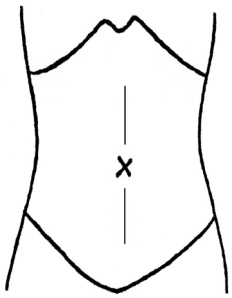
Shofuku Kokyu refers to contracture of the rectus abdominis muscles in the infraumbilical region.

The above findings on abdominal examination are indications for formulae containing Rehmannia Root and Processed Aconite Root. Hachimijiogan (八味地黄丸) may be used for patients with strong stomach, and shimbuto (真武湯) may be used for patients with weak stomach.

(10) Palpable thin line of linea alba (*Seichushin*)

Palatable cordlike hardness (like a pencil lead) runs down the center of linea alba. It tends to appear in skinny, frail individuals. It was named by Keisetsu Otsuka. In the literature on abdominal examination written in the Edo period, there are descriptions of tensional streak on the conception vessel.

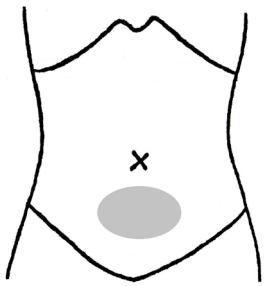
Anatomically, the palpable thin line of linea alba (*Seichushin*) that appears in the supraumbilical region is the falciform ligament including the round ligament (persistence of the umbilical vein and artery) of the liver, and *Seichushin* that appears in the infraumbilical region is the median umbilical fold including the median umbilical ligament (persistent urachus). The cordlike hardness may become palpable from the outside when the linea alba becomes loose and the surrounding connective and fat tissues decrease as a result of aging, etc.



Palpable thin line of linea alba (*Seichushin*)

Seichushin in the supraumbilical region may be an indication for formulae such as ninjinto (人参湯), and that in the infraumbilical region may be an indication for Processed Aconite Root-containing formulae.

(11) Lower abdominal fullness (TM) (*Shofuku Koman*)



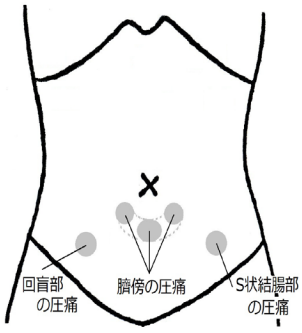
Lower abdominal hardness and fullness (*Shofuku Koman*)

Lower abdominal resistance and fullness, sometimes accompanied by tenderness, are evidence of blood stasis.

(12) Tenderness (圧痛): other tender points in the lower abdomen

(i) Tenderness in the peri-umbilical region

A tender point indicating blood stasis, including tenderness around the umbilicus and near the left and right coxal bones. There may be a horseshoe-shaped, raised area consisting of tender points below the umbilicus, especially in women. This is the site of pain referred to the region between the lower small intestine and transverse colon, and therefore considered to be associated with impairment of microcirculation in the small intestine and mesentery.



Tender points in the lower abdominal region

Formulae to treat blood stasis, such as keishibukuryogan (桂枝茯苓丸) and tokishakuyakusan (当帰芍薬散), may be used.

臍傍の圧痛：Tenderness in the peri-umbilical region
回盲部の圧痛：Tenderness in the ileocecal region
Ｓ状結腸部の圧痛：Tenderness in the sigmoid colon region

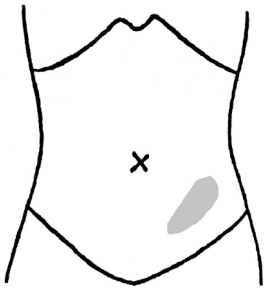
(ii) Tenderness in the ileocecal region

Tenderness in the ileocecal region may be a sign of appendicitis and evidence of blood stasis. Congestion or ischemia in the intestinal tract of the ileocecal region, adnexa, or venous plexus around the Fallopian tubes may also play a role.

Formulae to treat blood stasis, such as daiobotampito (大黄牡丹皮湯), may be used.

(iii) Tenderness in the sigmoid colon region

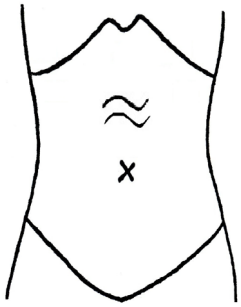
Tenderness in the sigmoid colon region. Mild to moderate cases of tenderness in this region may be evidence of blood stasis. Very severe cases may be perceived as scraping pain or resistance and sharp tenderness in the iliac region (*Shofuku Kyuketsu*). *Shofuku Kyuketsu* may be caused by hyperalgesia or increased abdominal wall tension resulting from referred visceral pain. It may also present as a band of hyperesthesia in the ovaries and uterine tubes suggesting that the tenderness may be caused by inflammation of the ovaries or uterine tubes.


Resistance and sharp tenderness in the iliac region (*Shofuku Kyuketsu*)

It may be an indication for keishibukuryogan (桂枝茯苓丸), or formulae to treat blood stasis such as tokakujokito (桃核承気湯) if the patient presents with constipation.

(13) Splashing sound (*Shinsuion*)

A splashing sound heard over the epigastric region when clapping with a flexible wrist. The sound is produced when the gastric wall is relaxed and there are certain amounts of gastric juice and air in the stomach; that is, when the smooth muscle of the stomach is relaxed and peristalsis is decreased, as in the case of gastroptosis, gastric juice and air are retained in the stomach instead of being excreted and thereby cause the sound. It is suggestive of vagus nerve dysfunction that is often accompanied by other autonomic signs. The sound


Splashing sound (*Shinsuion*)

may also be caused by fluid retention in the third portion of the duodenum or jejunum.

Formulae containing Poria Sclerotium, Atractylodes Rhizome (白朮, byakujutsu), and Pinellia Tuber, such as rikkunshito (六君子湯), may be used to treat fluid disturbance.

[Column] Umbilical pain

Pain on pressure immediately over the umbilical ring, also called 'Otsuka's umbilical pain' because it is one of the indications for kakkonto (葛根湯) proposed by Otsuka. Umbilical pain occurs everywhere immediately over the umbilical ring, including the center, left, right, and all other directions. It reflects excessive strain of the rectus abdominis muscles and stiffness of paravertebral muscles of the back. That is, this phenomenon occurs when hyperalgesia of the posterior branches of the spinal nerves, mainly around the 10th thoracic cord segment, is transferred to cutaneous nerves around the umbilical ring (both left and right sides) via intercostal nerves.

Back examination

Back examination may reveal abnormalities even when no abnormalities are found in the abdominal examination. In general, typical indications for kakkonto and keishito are back patterns such as stiffness of the neck and back (*Kohaikyo*), stiffness of the sides of the neck and occiput (*Keikokyo*), stiffness of the occiput (*Zukokyo*), and excessive strain of muscles extending from the shoulder to the back (*Kenpaikokyu*). In the back examination, it is also important to detect abnormalities such as hardness and tenderness of the transport points (兪穴) along the bladder meridian that runs in two rows parallel to the spine. The transport points are closely related to the distribution of sympathetic nerves in organs, and essential for the diagnosis and treatment of visceral diseases.

Persons with weak abdominal muscles may have thin, contracted back muscles. In such cases, stiffness in the scapulae and nape should also be palpated. Points that reflect responses of organs may appear on the back. Torsion should be checked by noting the symmetry between the left and right sides. Eruption on the back may be a manifestation of detoxification of the body. Coldness between the scapulae is a sign of interior cold or fluid disturbance.

Palpation of meridian and collateral (*Sekkei*)

According to Yoshio Nagahama, palpation of meridian and collateral (*Sekkei*) refers to a method to detect abnormalities by directly palpating meridian and collateral. *Sekkei* has an essential role not only in acupuncture practice but also in the practice of Gosei school in Kampo medicine, where it has been used as a diagnostic method.

According to "*Shinkyu Ijutsu no Mon* (鍼灸医術の門)" written by Sorei Yanagiya, the term 'excess', as used in *Sekkei*, refers to tactile change, for example tenderness on pressure, including linear induration, massive substance, muddy substance (blood stasis), aggregation of small masses, rodlike substance, platelike substance, and osteoid mass. The term 'deficiency', as used in *Sekkei*, refers to changes such as concavity, depression, pruritus induced by palpation, local softness or weakness, and points which (when pressed) causes

the patient to feel good. Abnormal findings include localized sense of coldness and warmth and skin abnormalities (e.g., moles, papules, pigmentation).

Acupuncture points of the twelve meridians are located symmetrically on both sides of the body, with respect to the spine, in two rows in each side. To detect tenderness and paresthesias in *Sekkei*, it is important to gently press each point and carefully compare each pair of points. It should also be noted that these points are treatment points in acupuncture practice.

Summary of the practice of Kampo medicine

a. Precautions for the four examinations (*Shishin*)

The examiner should be mindful of how the examination findings are related to the current illness and whether they are significant. Findings that change as treatment progresses are significant. However, some findings may change easily, some may not, and some may change spontaneously. For example, fissures and static macules on the tongue are often congenital and may not change during treatment. Whether findings change may also depend on the types of drugs the patient is taking. Antibiotic treatment is often a cause of tongue fur formation, and use of psychoactive drugs may cause erosion, redness, and spots on the tongue. Pulse types may also be modified by medication. Antihypertensives and tranquilizers often cause a sunken, slow pulse. Because the timing of meals may also influence findings, it is desirable to perform examinations at a similar time of day. In addition, findings on abdominal examination may be at variance with those on pulse examination. For example, pulse examination may reveal that treatment for a patient who has been diagnosed as having a pattern for Bupleurum Root-containing formulae by abdominal examination should receive deficiency pattern-treating formulae such as shokenchuto because of the presence of vacuous pulse.

b. Significance of findings in Kampo medicine

Needless to say, modern Kampo medicine, as a diagnostic modality, needs to be complemented by diagnostic techniques of modern Western medicine. For example, early cancers are not detectable by Kampo diagnostic methodology. It is self-evident that Kampo examinations, which rely on the five senses of the human body, have limited capabilities compared to the methods of modern Western medicine, which rely on state-of-the-art technology. Tongue patterns, pulse patterns, and abdominal patterns are not determined based solely on ‘local signs,’ but on distortion of the whole body, or on the body's response to disease and ability to normalize. These ‘anti-disease reactions’ may also be conceived of as a ‘reflection of visceral disease on the body wall,’ which we know from experience. In other words, various anti-disease reactions in the body may be thought to have reflections on the abdominal wall like images on a screen.

Chapter 4

Therapy Details

Headache

Shin-ichi Muramatsu

Overview of Disease

Headache is a frequent symptom, and the lifetime prevalence of tension-type headache, the most common type of headache, is regarded as 30-78%. The International Headache Society has classified headaches (ICHD-II) indicating the various diagnostic criteria for primary headache, which includes migraine, tension-type headache, and secondary headache. Secondary headache is caused by head and neck trauma, vascular impairment, tumor, infection, or psychoneurotic diseases.

The preceding signs of migraine include yawning, irritability, hunger sensation, and edema. In typical cases, signs of scintillating scotoma are found as visual aura. Intense pulsatile headache follows with nausea and vomiting, which may continue for several hours or up to 72 hours. Symptoms worsen with sound or light stimulation, movement, or posture change. Since walking, ascending/descending stairs and other daily living activities may worsen symptoms, patients commonly remain still in a darkened room.

Indications for Kampo Therapy

Primary headache — migraine and tension-type headache — is a good indication for Kampo medicines.
The drug of first choice in the treatment of migraine is triptan formulations, serotonin receptor ($5\text{-}HT_{1B/1D}$) agonists; however, triptans do not reduce the frequency of attacks and in one-third of cases are ineffective. Kampo medicines are appropriate even for drug abuse headache caused by overuse of triptans or various anti-inflammatory analgesics.

There are not many choices among Western drugs that can be used for symptomatic treatment of tension-type headache. Anti-anxiety agents and muscle relaxants are problematic because of drowsiness, lightheadedness and other adverse effects (so-called side effects). Kampo medicines increase treatment options remarkably.

Kampo medicines may be tried for secondary headache associated with organic diseases, particularly heavy headedness sensation associated with chronic subdural hematoma or brain tumor.

Frequent Formulae

1. Migraine

In migraine, preceding edema, vomiting during attacks and excess urination during recovery are considered to be the results of fluid disturbance (*Suidoku*). Therefore, the most appropriate is the use of fluid disturbance-treating (*Risui*) formulae (*Risuizai*) containing rhizomes of Atractylodes spp. (朮, jutsu), Poria

Sclerotium (茯苓, bukuryo), and Alisma Rhizome (沢瀉, takusha). On the onset of a migraine attack, the typical Kampo medicines to be administered are goreisan (五苓散) and goshuyuto (呉茱萸湯). Migraines bother many women and often worsen during menstruation; then, the use of blood stasis-treating (*Kuoketsu*) formulae containing Japanese Angelica Root (当帰, toki) and Peach Kernel (桃仁, tonin) may be helpful.

- **Goreisan (五苓散):** Indications include thirst, decreased urine volume (*Nyori Gensho*), vomiting at once after drinking (*Suigyaku*), and teeth-marked tongue (歯痕舌). However, not all symptoms need to be present. Goreisan (五苓散) is also used for hangover, nephritis-associated headaches and chronic subdural hematoma.
- **Goshuyuto (呉茱萸湯):** Used for vomiting-associated migraines in patients with a weak constitution who are prone to fatigue and suffer from coldness of limbs. This medication is considered to be effective for patients who suffer menstruation-related migraine, shoulder and neck stiffness before migraine attacks, or a epigastric distension by qi (Ki) counterflow (*Sinka Gyakuman*) during migraine attacks.
- **Keishininjinto (桂枝人参湯):** Used for headache in ninjinto (人参湯)-pattern (*Ninjintosho*) patients with interior cold (*Rikan*), characterized by weak digestive system, chronic indigestion and proneness to diarrhea. Patients often have epigastric discomfort (*Shinka Hi*).
- **Tokishakuyakusan (当帰芍薬散):** Normally used to treat heavy headedness. However, oral administration in between attacks can also reduce the frequency of attacks and severity of pain in menstruation-aggravated migraines. This medication is effective for women who have poor complexion and poor circulation, and complain of dizziness and shoulder stiffness.
- **Tokakujokito (桃核承気湯):** Used to treat headache in women with a good physique and who suffer from irregular menstruation and constipation. A specific abdominal pattern is resistance and sharp tenderness in the left iliac region (*Shofuku Kyuketsu*).

2. Tension-type headache

Tension-type headache sufferers complain of heaviness of the head, as though wearing something heavy on the head. In Kampo medicine, this symptom is termed “hat-wearing sensation” and many known formulae are used. Differentiation is made with consideration of coexisting symptoms including hypertension, dizziness, shoulder stiffness, and chill, in the deficiency, between deficiency and excess pattern (*Kyojitsu Chukan Sho*), and excess patterns.

a. Headache associated with shoulder stiffness and occipital pain

- **Kakkonto (葛根湯):** Used in patients with physical strength and whose digestive system is not weak. In cases of sinusitis, Magnolia Flower (辛夷, shin'i), senkyu (川芎, senkyu), Gypsum (石膏, sekko), and/or Platycodon Root (桔梗, kikyo) are added.
- **Hangebyakujutsutemmato (半夏白朮天麻湯):** Used for dizziness and headache in patients with constitutional gastrointestinal weakness. Also good for vertigo, feeling of shakiness, and light-headedness on standing. Low blood pressure is common.
- **Daisaikoto (大柴胡湯):** Appropriate for headache in excess pattern (*Jitsusho*) patients with good physique and tight abdominal muscles. Other symptoms include shoulder stiffness, insomnia, and

excitability.

- **Saikokaryukotsuboreito (柴胡加竜骨牡蛎湯):** Preferable to daisaikoto (大柴胡湯) for headache in patients with slight deficiency pattern. Other symptoms include palpitation, shortness of breath, and psychoneurotic symptoms such as irritability, insomnia, profuse dreaming, impatience, depression, and flightiness. Hypochondrium resistance and discomfort (*Kyokyo Kuman*) and palpable aortic pulsation in the paraumbilical region (*Saibo*).
- **Shigyakusan (四逆散):** Good for patients with a nervous introverted character and a tendency for depression.
- **Kamishoyosan (加味逍遥散):** Appropriate for patients with slight deficiency pattern (*Kyosho*). Used when there are many fluctuating complaints including headache, dizziness, tinnitus, palpitation, shoulder stiffness, low back pain, and insomnia.
- **Yokukansan (抑肝散):** Used for tension-type headache with oversensitivity such as irritability and short temper, or excitability and insomnia. In chronic cases, if the abdomen is soft and aortic pulsation is palpable, yokukansankachimpihange (抑肝散加陳皮半夏) is preferred.

b. Headache with dizziness

- **Ryokeijutsukanto (苓桂朮甘湯):** Broadly used for fluid disturbance in patients with deficiency pattern and frequently used for chronic dizziness including sensation of shakiness and orthostatic dizziness. Typical cases are characterized by decreased urination, cold limbs, and sunken and tight pulse. Abdominal examination reveals persistent fluid retention in the epigastric region (*Shinka Tan'in*), or splashing sound (*Shinsuion*), and *Shinka Gyakuman*). May be used as a combined formula renjuin (連珠飲) containing shimotsuto (四物湯).
- **Nyoshinsan (女神散):** Good for head heaviness sensation, hat-wearing sensation, dizziness, hot flashes, and shoulder stiffness in women with climacteric disorders. Symptoms are due to the between deficiency and excess pattern, and the indicators are hot flashes and dizziness.

c. Headache with high blood pressure

- **Orengedokuto (黄連解毒湯):** For excess pattern (*Jitsusho*) patients with facial redness and conjunctival congestion. Other symptoms include hot flashes, anxiety and uneasiness, insomnia, and nasal bleeding.
- **San'oshashinto (三黄瀉心湯):** Used for patients with orengedokuto (黄連解毒湯) pattern and remarkable *Shinka Hi* and constipation.
- **Shichimotsukokato (七物降下湯):** Used for deficiency-pattern patients with high blood pressure. Considered to be good for patients with protein-positive urine and those with high diastolic blood pressure.
- **Chotosan (釣藤散):** Used for hypertensive patients with slight deficiency pattern, associated with headache, hot flashes, bulbar conjunctiva congestion, shoulder stiffness, dizziness, or tinnitus. The skin is dry with less luster; the abdomen is weaker and slacker than that of yokukansan (抑肝散)-pattern (*Yokukansansho*) patients. Considered good for patients who suffer headache in the morning.

d. Headache with sensitivity to cold (*Hiesho*)

- **Goshakusan (五積散):** Used for coldness in the lower body and hot flashes in the upper body, or

upper heat and lower cold. Effective for anemia as well as headache or low back pain with *Hiesho* in patients with slight deficiency pattern.

3. Other headache - Facial pain

Cluster headache and closely related diseases comprising autonomic nerve symptoms such as severe headache clustering, conjunctival congestion, epiphora, nasal obstruction, and palpebral edema, are termed trigeminal autonomic cephalagia (TAC). Kampo medicines may be tried in cases associated with organic diseases including cerebello-pontine angle tumor.

- **Senkyuchachosan (川芎茶調散):** Used for headache in general, but is particularly good for headache following common cold.
- **Seijokentsuto (清上蠲痛湯):** Used for the headache and trigeminal neuralgia not relieved by other prescriptions.

Reference

International Headache Society. The International Classification of Headache Disorders, 2nd ed. Cephalalgia. 24 suppl 1: 1-160, 2004

Dizziness - Tinnitus

Akira Saito

Overview of Disease

Dizziness

The origins of dizziness vary and include inner ear disorder (such as Meniere's disease and benign paroxysmal positional vertigo), central nervous system diseases (such as cerebellar infarction), autonomic nerve abnormalities, and aging-related changes. In not a few cases, hearing and equilibrium function tests or brain MRI show no abnormality, and psychogenic elements such as stress contribute to the dizziness. Many drug therapies are available, but in some cases, psychotherapy or therapeutic exercise may be effective, while in others surgery is required. Improvement of daily habits is also important.

Tinnitus

The origins of tinnitus may often lie in the regions of the acoustic pathway from the outer ear to the central nervous system, in addition to the inner ear. Tinnitus associated with conduction hearing loss may improve with otological treatment or surgery. Drug therapies with vitamins, circulation-improving agents, and antianxiety drugs are widespread. Treatment may include counseling or sound therapy. When patients are told that tinnitus does not heal, their resistance to therapy increases. It is therefore important to explain that

although the tinnitus itself will not disappear, it is possible to lead daily life without noticing it. Improvement of daily habits is also important.

Indications for Kampo Therapy

When dosing is difficult in the acute phase of dizziness, dizziness is a life-threatening risk, or tinnitus is associated with acute sensory hearing loss, Western medical therapies are preferred. In other than those cases, dizziness and tinnitus are good targets for Kampo therapy.

Fundamentally there is no problem in combining Kampo therapy with Western drugs. Such combination therapy should be actively considered when symptoms worsen. For example, if Meniere's disease is being treated with Kampo medicines and attacks occur with aggravated hearing loss, administration of steroids or osmotic diuretic may be required.

Kampo medicines, of which the potential to act directly on the inner ear cannot be denied, are considered to alleviate dizziness and tinnitus by improving insomnia, psychological agitation, shoulder stiffness, and hot flashes.

Frequent Formulae

Although it is often said that the pathologic condition of dizziness is fluid retention (*Suitai*), dizziness is caused by abnormalities of qi (Ki) or blood as well as water. In blood stasis (*Oketsu*) or fluid disturbance (*Suidoku*), the smooth flow of qi (Ki) and blood to the brain is inhibited. Qi (Ki) deficiency (*Kikyo*) and blood deficiency (*Kekkyo*) mean nutrients are lacking, while qi (Ki) counterflow (*Kigyaku*) means excessive qi (Ki) is being supplied to the brain. Qi (Ki) depression (*Kiutsu*) means qi (Ki) is stagnant and does not circulate to the brain. Similarly, tinnitus may arise because of an abnormality of qi (Ki), blood, or water.

Most Kampo medicines prescribed for dizziness and tinnitus overlap.

- **Hangebyakujutsutemmato (半夏白朮天麻湯):** Used for dizziness associated with inner-ear dizziness and tinnitus, orthostatic dysregulation, and shoulder stiffness, as well as dizziness after eating. Patients also have debilitated digestive function, anorexia, coldness, and heavy headedness.
- **Ryokeijutsukanto (苓桂朮甘湯):** Used for inner ear dizziness and tinnitus, orthostatic dysregulation, and palpitation-associated dizziness. Patients also have poor physical strength, coldness in the limbs, palpitation, anxiety, shortness of breath, and decreased urine output.
- **Goreisan (五苓散):** Widely effective for dizziness in patients who have edema, thirst, decreased urine output, and diarrhea. Physical strength or weakness is not relevant.
- **Saireito (柴苓湯):** Offered for most types of dizziness (including inner ear disorder dizziness), and tinnitus associated with low-tone sensorineural hearing loss. Patients have middle physical strength, thirst, decreased urine output, and edema. Also appropriate for Meniere's disease unsuccessfully treated with an osmotic diuretic.
- **Takushato (沢瀉湯)*:** Used for most types of dizziness including inner ear disorder dizziness in

patients who have intermediate physical strength and decreased urine output.

- **Hochuekkito (補中益気湯):** Appropriate for dizziness associated with orthostatic dysregulation or fatigue-related lightheadedness. Patients also have various symptoms, including weak constitution, strong general malaise, reduced digestive function, low energy, proneness to fatigue, postprandial sleepiness, spontaneous sweating (*Jikan*), quiet voice, and headache.
- **Juzentaihoto (十全大補湯):** Offered for dizziness related to orthostatic dysregulation or fatigue. Patients also have reduced physical strength, anemia, fatigue and malaise, anorexia, poor complexion, and lusterless skin.
- **Ninjin'yoeito (人参養栄湯):** Used for dizziness in patients with depression tendency, proneness to palpitation, and stronger anxiety, in comparison with juzentaihoto (十全大補湯).
- **Shimotsuto (四物湯):** Appropriate for dizziness related with dysmenorrhea or delivery in women who have anemia and skin dryness. Frequently used in combination with ryokeijutsukanto (苓桂朮甘湯).
- **Shimbuto (真武湯):** Used for orthostatic dysregulation, dizziness with intense coldness in the upper and lower limbs, and dizziness in elderly people. Patients are associated with weakness, general malaise, diarrhea, and abdominal pain.
- **Kamishoyosan (加味逍遥散):** Used for dizziness coinciding with sexual cycle or menopause, in addition to highly psychogenic dizziness and tinnitus. Patients are relatively weak, associated with anxiety, irritability, insomnia, shoulder stiffness, paroxysmal sweating, and burning sensation.
- **Keishibukuryogan (桂枝茯苓丸):** Used for dizziness coinciding with sexual cycle or menopause. Patients' physical strength is intermediate or stronger, in association with hot flashes and coldness in the feet. Other indications include resistance and tenderness in the lower abdomen, and sublingual vein distension.
- **Tokishakuyakusan (当帰芍薬散):** Effective for menopausal dizziness as well as dizziness coinciding with sexual cycle. Patients have relatively reduced physical strength, associated with coldness and anemia.
- **Chotosan (釣藤散):** Frequently used for tinnitus as well as dizziness associated with high blood pressure and arteriosclerosis. Patients are middle aged or older and physical strength is middle to slightly weak. They complain of headache early in the morning or at arousal, hot flashes, and bulbar conjunctiva congestion.
- **Orengedokuto (黄連解毒湯):** Offered for hypertension-related as well as psychogenic dizziness. Also for patients with relatively strong bodies, hot flash tendency, facial redness, and psychoneurotic symptoms such as insomnia and irritability.
- **Saikokaryukotsuboreito (柴胡加竜骨牡蛎湯):** Good for highly psychogenic tinnitus and dizziness, associated with shoulder stiffness and high blood pressure. Patients are relatively strong and have nervousness symptoms such as palpitation, insomnia, short temper, and flightiness.
- **Daisaikoto (大柴胡湯):** Used for dizziness with shoulder stiffness and high blood pressure. Patients are relatively strong, associated with constipation, headache, irritability, and distended painful sensation in the upper abdomen. Contains crude drugs with a purgation effect, including Rhubarb (大黄, daio). Therefore, this formula should not be used for patients with weak abdominal strength or those with chronic diarrhea or gastrointestinal weakness.

- **Yokukansan (抑肝散):** Good for psychogenic dizziness and autonomic imbalance. Patients have intermediate physical strength, are nervous, short tempered and irritable, and complain of insomnia. Some patients also suffer eyelid twitching.
- **Yokukansankachimpihange (抑肝散加陳皮半夏):** Used for patients whose physical strength is weaker than that of yokukansan (抑肝散)-pattern (*Yokukansansho*) patients. Effective for tinnitus and dizziness associated with depression tendency.
- **Kamikihito (加味帰脾湯):** Used for highly psychogenic tinnitus and dizziness. Also effective for tinnitus related to patulous Eustachian tube. Patients have weak constitution with poor complexion, anemia, insomnia, and mental instability.
- **Hachimijiogan - Goshajinkigan (八味地黄丸・牛車腎気丸):** Appropriate for lightheadedness and tinnitus due to age-related changes. Frequently used in elderly patients. Patients have coldness in the low back and legs, numbness, and feeling of weakness, associated with nocturia and blurred vision.
- **Rokumigan (六味丸):** Used for tinnitus and dizziness associated with aging. Compared with hachimijiogan (八味地黄丸) and goshajinkigan (牛車腎気丸), rokumigan is appropriate for patients with less severe coldness but a burning sensation in the limbs.

* Not available as ethical Kampo extract formulation

Sneezing – Nasal Discharge – Nasal Occlusion Postnasal Drip

Toru Kaneko

Overview of Disease

In Western medical thinking, the acute diseases that cause sneezing, nasal discharge, nasal occlusion, and postnasal drip include the common cold, acute rhinitis, seasonal allergic rhinitis, and acute sinusitis. The chronic causative diseases include chronic rhinitis, perennial allergic rhinitis, and chronic sinusitis. Whether the cause is an allergy or an infection is determined on the basis of the properties of the nasal discharge. Sneezing, watery nasal discharge, and nasal occlusion are referred to as the three main signs of allergic rhinitis. If the nasal discharge is purulent, infectious sinusitis may be present. Unlike rhinorrhea (前鼻漏), postnasal drip is often responsible for cough, laryngopharyngeal discomfort, hoarseness, etc. Some elderly patients complain of watery nasal discharge only (particularly postnasal drip). A common cause is said to be fluid absorption disorder in the nasal mucosa due to nasal mucosal atrophy or reduced nasal mucosa temperature.

In Western medicine, the main treatments of allergic rhinitis are oral medication (typically antihistamines) and steroid nasal sprays. Radical therapies include hyposensitization. The acute-phase

treatment of sinusitis is antibacterial therapy chiefly using quinolones for adults (who show a good response) for adults; and quinolones and carbapenems (which have started to be used recently) as well as the relatively new cephems (which are generally considered helpful) for children. For chronic-phase treatment in both adults and children, long-term therapy using low-dose macrolide antibiotics is recommended.

In Kampo medicine, sneezing (or sternutation) is interpreted as a response of the body involving ciliary movement to eject the inhaled foreign matter via exhalation. It occurs with cold sensation and is associated with heat production. Nasal discharge is necessary for mucosal protection, warming, moistening, and dust removal, but when it becomes imbalanced, fluid disturbance (*Suidoku*) and fluid retention (*Suitai*) occur. Nasal occlusion involves fluid stagnation with nasal mucosa edematous change (fluid retention) and secretion gland enlargement (増生), followed by nasal discharge. Postnasal drip is a symptom in sinusitis. It is a condition of fluid retention and fluid disturbance and may also involve psychological factors (qi depression [*Kiutsu*] and qi stagnation [*Kitai*]).

Indications for Kampo Therapy

In classical Kampo thinking, nasal diseases are classified as *bikyu* (鼻鼽, allergic rhinitis) or *bien* (鼻淵, sinusitis), and nasal discharge is categorized as *seitei* (清涕, clear snivel) or *dakutei* (濁涕, turbid snivel). The putative diseases for *bikyu* include the present-day allergic rhinitis. The associated thin nasal discharge, including sputum, is termed *seitei*. On the other hand, *bien* can be considered as the present-day sinusitis with the associated purulent yellow nasal discharge termed *dakutei*.

In principle, Kampo therapy is used for unpleasant subjective symptoms. In both modern medicine and Kampo medicine, it is critical in the treatment of rhinitis to subdivide the disease according to the properties of nasal discharge. When symptoms are severe, treatment with Kampo medicines alone is difficult and concomitant use of Western drugs is often required.

Frequent Formulae

Watery Nasal Discharge

Commonly found in the early stage of allergic rhinitis and the common cold. The principal formulae in the acute phase are Ephedra Herb (麻黄, mao)-containing formulae such as kakkontokasenkyushin'i (葛根湯加川芎辛夷) and shoseiryuto (小青竜湯). Processed Aconite Root (附子, bushi)-containing formulae such as maobushisaishinto (麻黄附子細辛湯) may be selected for patients with more intense cold sensations and those having pallid nasal mucosa.

When symptoms are severe owing to cedar pollen allergy and the like, the quantity of Ephedra Herb may be increased. For example, gokoto (五虎湯) may be added to shoseiryuto (小青竜湯), or eppikajutsuto (越婢加朮湯) may be used. During the high pollen season, treatment with Kampo medicines alone is difficult. Concomitant use of Western drugs, such as oral antihistamines and steroid nasal sprays, is frequently required. The combined use of Ephedra Herbs-containing formulae on such occasions not only alleviates the symptoms

but can also be expected to reduce the adverse effect of sleepiness caused by the antihistamines. Naturally, attention must be paid to the adverse effects of Ephedra Herb-containing formulae (palpitation, stomach pain, etc.).

If the nasal discharge is accompanied by cough, shoseiryuto (小青竜湯) is helpful in mild cases, while makyokansekito (麻杏甘石湯), gokoto (五虎湯), or shimpito (神秘湯) is often required in severe cases. Bakumondoto (麦門冬湯) and jiinkokato (滋陰降火湯) are used either singly or concomitantly in patients with a strong tendency to dryness in the oral cavity.

The treatment of chronic-phase nasal occlusion is often very difficult in Western medicine as well. In this case, essential treatment (*Honchi*) according to pattern (*Zuisho*) is required rather than symptomatic treatment (*Hyochi*).

- **Kakkonto (葛根湯):** Effective for rhinitis found in the early stage of the common cold, particularly in patients also having neck and back (項背部) stiffness and headache. If systemic pain is present or symptoms are severe, maoto (麻黄湯) is more helpful.
- **Kakkontokasenkyushin'i (葛根湯加川芎辛夷):** Consists of kakkonto (葛根湯) with Cnidium Rhizome (川芎, senkyu) and Magnolia Flower (辛夷, shin'i). Effective for severe nasal occlusion and discharge, as well as the target symptoms for kakkonto (葛根湯). An important formula for sinusitis and allergic rhinitis associated with viscous nasal discharge. Combined use with long-term low-dose macrolide antibiotics is also effective.
- **Shoseiryuto (小青竜湯):** Effective for fluid disturbance symptoms such as watery nasal discharge, sneezing, and cough. Considered the first choice for allergic rhinitis.
- **Maobushisaishinto (麻黄附子細辛湯):** Target patients must have Yin pattern (*Yinsho*) or cold pattern (*Kansho*), comprising coldness and poor complexion. Effective for early-stage common cold and allergic rhinitis in elderly patients and patients with weak constitution.
- **Makyokansekito (麻杏甘石湯):** Effective for cough-associated rhinitis, and viscous sputum accompanied by bronchitis or pneumonia.
- **Gokoto (五虎湯)** Consists of makyokansekito (麻杏甘石湯) with Mulberry Bark (桑白皮, sohakuhi), which enhances the antitussive effect of the former.
- **Maoto (麻黄湯):** Effective for watery nasal discharge associated with headache, fever, chill, myalgia, and/or arthralgia. Often offered to children with severe nasal occlusion. Frequently used for influenza.
- **Shimpito (神秘湯):** Effective for allergic rhinitis accompanied by bronchial asthma or bronchitis.
- **Eppikajutsuto (越婢加朮湯):** A formula for facial, limb and joint edema and inflammation. Also appropriate for allergic rhinitis leading to palpebral edema.
- **Ryokankyomishingeninto (苓甘姜味辛夏仁湯):** A formula with a relatively mild effect used for allergic rhinitis in patients having no indications for Ephedra Herb (麻黄, mao)-containing formulae.

Purulent Nasal Discharge

Many patients with acute-phase sinusitis complain of pain and tension in the face, neck and back (項背部). For these symptoms and signs, Ephedra Herb (麻黄, mao)-containing formulae including kakkontokasenkyushin'i (葛根湯加川芎辛夷) are effective. Following that, the use of formulae such as

shin'iseihaito (辛夷清肺湯) containing gypsum (石膏, sekko) is common. For patients with concomitant comedo or tonsillitis, keigairengyoto (荊芥連翹湯) is frequently used. Combined use with antibacterials is effective and alleviates symptoms more rapidly than administration of either Kampo medicines or antibacterials alone.

- **Kakkonto (葛根湯)** and **Kakkontokasenkyushin'i (葛根湯加川芎辛夷):** (See above.)
- **Shin'iseihaito (辛夷清肺湯):** Appropriate for patients with localized inflammation and intense heat sensation. This formula, not containing Ephedra Herb (麻黄, mao), can be used for patients susceptible to the adverse effects of Ephedra Herb. Also helpful when used as a basic formula for postnasal drip. Can also be used for allergic rhinitis and is effective when used concomitantly with low-dose long-term macrolide antibiotics.
- **Keigairengyoto (荊芥連翹湯):** Effective for dermatological inflammatory diseases of the head and face, but also effective for otorhinological inflammatory diseases. Concomitant use with macrolides is effective.

Postnasal Drip

Treatment is carried out in cases in which the causative disease is clear. When the cause is not clear, even treatment with Western medicine is difficult.

- **Shin'iseihaito (辛夷清肺湯): (See above.)**
- **Chikujountanto (竹茹温胆湯):** Offered to patients with symptoms such as copious coughing and sputum, insomnia, and mental anxiety. Can be effective when combined with shin'iseihaito (辛夷清肺湯).

Oral Discomfort

Kojiro Yamaguchi

Overview of Disease

The functions of the oral cavity include mastication, swallowing, articulation, saliva secretion, and tasting. Recently there has been an increase in patients, mainly middle-aged to elderly, complaining of deterioration in these functions, as well as glossalgia and taste abnormality. This section explains five conditions responsible for oral discomfort: glossalgia, stomatitis, dryness of the mouth, taste abnormality, and atypical maxillofacial pain.

Glossalgia is a disease that tongue-confined pain occurs without organically abnormal findings in the oral mucosa. Its characteristic features are as follows. (1) It is common in women at a cancer-prone age (middle-age and above). Climacteric or post-menopausal hormone changes, stress, anxiety, nervousness, and

the like are involved in the aggravation and continuation of symptoms. (2) It occurs more frequently in the tip and margin of the tongue and infrequently in the back of the tongue. (3) The pain mitigates or resolves on talking or eating.

Stomatitis develops with inflammatory manifestations including reddening, erosion, and ulceration in the oral mucosa. Occasionally, stomatitis may be multiple or recurrent.

Dryness of the mouth may occur as a symptom due to reduced saliva secretion, or a sensation of dryness in the presence of saliva secretion. Prescriptions are selected according to the condition of dryness (thirst [*Kokatsu*], dry mouth [*Kokan*]).

The etiology of taste abnormality varies widely from dominant nerve disorder and taste abnormality related to systemic disease (zinc-deficiency disorder, drug-induced illness, endocrine abnormality, etc.) to oral mucosa abnormality (inflammation, oral dryness, tongue papilla atrophy, etc.) and psychogenic causes. Kampo medicines must be selected according to the patient's condition. Electrogustometry, qualitative taste testing, and serum zinc and copper testing should be carried out.

Atypical maxillofacial pain is the generic term for chronic persistent pain in the oral cavity, jaw, and face of which the organic or other cause is unidentified but is related to somatoform disorder and psychological factors. The pain is inconsistent with nerve tracts.

Indications for Kampo Therapy

Oral discomfort is generally a good target for Kampo therapy. However, oral candidiasis (thrush), which can often be seen in denture wearers and people with systemic immunosuppression, occurs with oral discomfort symptoms such as oral bitterness, glossalgia, stomatitis-like symptoms, and oral dryness. It is therefore necessary to carry out testing and rule it out beforehand.

Frequent Formulae

The oral cavity, of which the anatomical structure and nerve control are complex, is the initial digestive organ and is likely to be affected by various localized stimuli and microorganisms. Therefore, oral discomfort symptoms should be treated only after comprehensive examination of the anatomical factors, intraoral environmental factors (including cold [*Kan*], heat [*Netsu*], dampness [*Shitsu*], and dryness [*So*]), the relation between the oral cavity and the meridians of the body, and qi (Ki), blood, and fluid (*Kiketsusui*) abnormalities.

Glossalgia

Given the relation between the frequent onset sites for glossalgia and the reflecting the five parenchymatous viscera to the tongue, it seems that the tip of the tongue corresponds to the heart and lungs, the margin of the tongue to the liver and gallbladder, and the back of the tongue to the spleen and stomach. The causes include blood stasis (*Oketsu*), qi (Ki) depression (*Kiutsu*), and dryness due to lack of fluid (*Inbun*). Tongue inspection comprises dark-red punctate color change, sublingual vein distension, swollen tongue (*Handaizetsu*), tongue

fur dryness (*Zettai kanso*), geographical tongue, and teeth-marked tongue (*Shikonzetsu*). Abdominal examination often reveals paraumblical tenderness and resistance (*Saibo tenderness*), palpable aortic pulsation in the supraumblical region (*Saijo Ki*), hypochondrium resistance and discomfort (*Kyokyo Kuman*), as well as signs of static blood and qi (Ki) depression.

- **Kamishoyosan (加味逍遥散):** Used with most confidence for nonspecific women's complaints and coldness and hot flash (*Hienobose*) in deficiency-pattern (*Kyosho*) patients. Redness in the tip of the tongue indicates upper-body heat and is a good indication for this formula.
- **Hochuekkito (補中益気湯):** Effective for glossalgia in patients with deficiency pattern associated with qi (Ki) depression.
- **Saibokuto (柴朴湯):** Effective for glossalgia (including laryngopharyngeal discomfort) associated with fluid retention (*Suitai*) (fluid disturbance [*Suidoku*]) in ShoYo stage (*Shoyobyo*). Offered to patients who complain of pain in the median part of the back of the tongue (spleen [TM] and stomach [TM]) to the margin of the tongue (liver [TM] and gall bladder [TM]).
- **Tokishakuyakusan (当帰芍薬散):** Used for glossalgia associated with general malaise, fatigue proneness, menstrual disorder, palpitation, or autonomic nerve imbalance, particularly in patients who have white fur tongue and dark-red punctate color change, on the lingual tip and margin.
- **Byakkokaninjinto (白虎加人参湯):** Appropriate for patients with interior heat pattern (*Rinetsusho*) associated with oral dryness. Effective especially for glossalgia associated with nocturnal thirst.
- **Kikyoto (桔梗湯):** Anti-inflammatory and heat pattern-treating (*Seinetsu*) effects can be expected.
- **Rikkosan (立効散):** Effects can be expected through the analgesic action of Asiasarum Root (細辛, saishin) and Saposhnikovia Root and Rhizome (防風, bofu), and the anti-inflammatory action of Japanese Gentian (竜胆, ryutan) and Cimicifuga Rhizome (升麻, shoma).
- **Keishikajutsubuto (桂枝加朮附湯):** Used for fluid retention in patients with yin pattern (*Yinsho*) and deficiency pattern, because it contains Processed Aconite Root (附子, bushi), which is effective for water retention and exerts an analgesic effect under warming.
- **Other fomulae:** Kososan (香蘇散), yokukansankachimpihange (抑肝散加陳皮半夏), kambakutaisoto (甘麦大棗湯), saikokaryukotsuboreito (柴胡加竜骨牡蛎湯), and keishikaryukotsuboreito (桂枝加竜骨牡蛎湯) are used for psychogenic conditions.

Stomatitis

In Oriental medicine, stomatitis is most easily understood when roughly divided into two groups: cases of intense acute symptoms, and cases of chronic course.

Acute

Heat due to qi (Ki) rising (*Ki no Takaburi*) may affect the head, chest, and upper abdominal region. Therefore, treatment is required to cool the heat in the heart, stomach, and liver, with hangeshashinto (半夏瀉心湯), orento (黄連湯), orengedokuto (黄連解毒湯), byakkokaninjinto, Bupleurum Root (柴胡, saiko)-containing formulae, kamishoyosan, etc., Kanzoto (甘草湯) and kikyoto, possessing an anti-inflammatory and heat pattern-treating effects, are also useful as an oral rinse.

Chronic

Prolonged head, chest, and middle region heat causes fluid (*Inbun*) deficiency. Therefore, formulae are required not only to alleviate the heat, but also to treat qi (Ki) and blood, and to increase wetness by increasing fluid (*Inbun*). The following formulations can be selected: formulae treating deficiency of upper abdominal region (*Hojinzai*) including kenchuto (建中湯) group, rokumigan (六味丸) and hachimijiogan (八味地黄丸); qi (Ki) deficiency-treating formulae (*Hokizai*) including hochuekkito and rikkunshito (六君子湯); dual deficiency-treating formula(e) (*Kiketsu Sohozai*) including juzentaiho and ninjin'yoeito (人参養栄湯); and other formulations such as jiinkokato (滋陰降火湯), unseiin (温清飲), and tokishakuyakusan.

Dryness of the mouth

Kampo medicine divides dryness of the mouth into thirst and dry mouth.

Thirst (*Kokatsu*)

Patients are constantly thirsty and tend to gulp down water. Frequently they have thirst at night, and want to cool the mouth with ice, as is explained by the presence of heat pattern (*Ntesusho*) (interior heat [*Rinetsu*]) and fluid retention (*Suitai*). Byakkoto (白虎湯) containing Gypsum (石膏, sekko , byakkokaninjinto, shosaikotokakikyosekko (小柴胡湯加桔梗石膏), makyokansekito (麻杏甘石湯), and kikyoto (桔梗湯), which has a heat-pattern treating (*Seinetsu*) and saliva-secreting effect, are used. Rokumigan and hachimijiogan are effective for thirst due to deficiency of lower abdominal region (*Jinkyo*).

Dry mouth (*Kokan*)

Patients have dryness in the mouth, but what they want is to moisten or dampen the oral cavity rather than to drink much water. This condition is associated with dampness heat (*Shitsunetsu*), splashing sound (*Shinsuion*), qi (Ki) depression, dual deficiency of upper abdominal region (*Hii Ryokyo*), dual deficiency of qi (Ki) and blood (*Kiketsu Ryokyo*), dryness and heat due to lack of fluid (*Inbun*), and other symptoms. In addition to treating qi (Ki) and fluid (*Inbun*), dry mouth can be favorably treated with ninjin'yoeito, jiinkokato, unseiin, juzentaiho, seishoekkito (清暑益気湯) and bakumondoto (麦門冬湯), which all possess heat-pattern treating effects including the asthenic heat syndrome. Otherwise, goreisan (五苓散) can be used to regulate moisture content in the body and kamishoyosan and kamikihito (加味帰脾湯) are recommended for psychogenic or stress-induced dry mouth.

Taste abnormality

Intense bitterness

Shosaikoto (小柴胡湯), saikokeishito (柴胡桂枝湯), and other Bupleurum Root (柴胡, saiko)-containing formulae may be considered for intense bitterness in ShoYo stage (*Shoyobyo*) patients. Hangekobokuto (半夏厚朴湯) and saibokuto are appropriate for taste abnormality in patients with severe fluid retention.

Intense sweetness

Is a sign indicative of upper abdominal region (*Hii*) dampness heat (*Shitsunetsu*). Hangeshashinto (半夏

瀉心湯), inchinkoto (茵蔯蒿湯), and rikkunshito (六君子湯) are used.

Intense astringency

It has been considered that astringent substances interact with proteins in the tongue and oral mucosa, and via denaturation (astringent effect) intense astringency is produced. There is one hypothesis that such taste abnormality is close to pain and tactile sensation, and another proposes it is only a taste. Physiologically, astringency is also categorized as a kind of bitterness. This type of taste abnormality can therefore be regarded as a pathologic condition of ShoYo stage or glossalgia to be treated successfully with kamishoyosan (加味逍遥散).

Taste loss

Except for taste cell atrophy due to zinc deficiency, a loss of taste may be a sign of upper abdominal region deficiency (*Hiikyo*), for which rikkunshito and hochuekkito are effective. Juzentaiho, ninjin'yoeito and other deficiency pattern-treating formula(e) (*Hozai*) are helpful for lack of fluid (*Shineki*).

Miscellaneous

Other possible formulae include orengedokuto, byakkokaninjinto , saikokaryukotsuboreito , and saikokeishikankyoto (柴胡桂枝乾姜湯).

Atypical maxillofacial pain

In Kampo medicine, it is important to determine whether the pain is due to cold or heat, or lack or stagnation of qi (Ki), blood, or water. Warming and tonic formulations (温補剤), fluid disturbance-treating (*Risui*) formulae, and blood stasis-treating (*Kuoketsu*) formula(e) are used in treatment.

Dual deficiency of qi (Ki) and blood (*Kiketsu Ryokyo*)

For dual deficiency of qi (Ki) and blood with prolonged pain, mainly hochuekkitogotokishakuyakusan (補中益気湯合当帰芍薬散), renjuin (連珠飲), juzentaihoto , ninjin'yoeito, daibofuto (大防風湯), kamikihito, and other deficiency pattern-treating formulae are used.

Cold pattern (*Kansho*)

Processed Aconite Root (附子, bushi)-containing formulae such as keishikajutsubuto (桂枝加朮附湯) are effective.

Static blood (*Oketsu*)

Tokishakuyakusan, kamishoyosan, and keishibukuryogan are appropriate.

Qi depression (*Kiutsu*)

Keishiryukotsuboreito, saikokaryukotsuboreito, and yokukansan (抑肝散) are offered.

Fluid retention (*Suitai*)

Goreisan, ryokeijutsukanto (苓桂朮甘湯), etc. are used.

Common Cold Syndrome

Yukihiko Homma

Overview of Disease

Common cold syndrome (hereinafter, cold) comprises systemic symptoms such as chill, fever, and headache, with localized upper respiratory tract inflammation symptoms including pharyngeal pain, nasal discharge, and coughing. Viral infection is the most common origin. Anti-inflammatory analgesic and antipyretic drugs have conventionally been the main therapies. Recently it has been pointed out that these are symptomatic therapies in the broad sense and do not inherently cure colds.

In a controlled study involving febrile cold patients and comparing conventional anti-inflammatory analgesic and antipyretic drugs with a Kampo medicine possessing no direct antipyretic effect, the recovery time was significantly shorter with Kampo therapy. This has been interpreted as the result of the recovery time being prolonged by the defervescence-focusing pharmacotherapy, which activated the virus that is inherently cryophilic. Raising body temperature is important in the treatment of cold, because it is considered to inactivate the virus.

The antibacterial agents frequently used to prevent secondary infection cannot be expected to have a primary preventive effect. In addition, these agents may lower immunity by killing enterobacteria; and, antiallergenic as well as antitussive drugs also have the same potential to inhibit inherent biologic responses.

Indications for Kampo Therapy

Kampo therapy may be considered the first choice in the treatment of cold. Kakkonto (葛根湯), keishito (桂枝湯), and other Kampo medicines frequently used for cold all assist temperature elevation. Maoto (麻黄湯) in particular is frequently used for influenza owing to its strong warming action and has demonstrated as favorable as or more favorable results than antiviral drugs.

Frequent Formulae

"*ShangHanLun* (傷寒論)" may be described as a treatise focusing on therapeutic approaches to the cold, including influenza. It divides the cold into four stages: the TaiYo stage (*Taiyobyoki*), ShoYo stage (*Shoyobyoki*), YoMei stage (*Yomeibyoki*), and Yin stage (*Yinbyoki*).

Acute Phase

The stages equivalent to the acute phase are the TaiYo stage and the ShoYin stage (*Shoyinbyoki*). Generally this phase is the period from onset to approximately the third day. The chief symptoms include chill, fever,

pharyngeal pain, myalgia and arthralgia, which are termed the exterior pattern (*Hyosho*). During this phase, patients have either excess pattern (*Jitsusho*) with no sweating, or between deficiency and excess pattern (*Khojitsu Chukan Sho*) / deficiency pattern (*Kyosho*) with sweating.

Without sweating (excess pattern)

- **Maoto (麻黄湯):** Appropriate for severe symptoms, including high fever, severe myalgia/arthralgia, and low back pain, and floating and tight pulse.
- **Kakkonto (葛根湯):** Patients have pathognomonic symptoms such as headache, fever, and occipital stiffness, associated with floating pulse.

With sweating (between deficiency and excess pattern/ deficiency pattern)

- **Shoseiryuto (小青竜湯):** Used for allergic rhinitis symptoms including watery nasal discharge, sneezing, and nasal occlusion.
- **Keishito (桂枝湯):** Patients have weak constitution, associated with chills with wind (*Akufu*), headache, and low-grade fever. Pulse is floating and weak.
- **Keimakakuhanto (桂麻各半湯):** Effective for **s**trong heat sensation with fever and slight chill in patients whose face is flushed.
- **Keishinieppiichito (桂枝二越婢一湯)*:** Patients have fever, slight chill, and thirst.
- **Maobushisaishinto (麻黄附子細辛湯):** Offered to Yin pattern (*Yinsho*) patients, such as the elderly and frail, in the early phase of common cold. They have severe chill but weak heat sensation. If these conditions are prolonged, keishito (桂枝湯)-combined formula—keikyososo'oshinbuto (桂姜棗草黄辛附湯)*—is recommended.
- **Kososan (香蘇散):** Useful for patients with gastrointestinal weakness who cannot take keishito (桂枝湯), and have depression tendency with strong malaise and weakness sensation.
- **Kikyoto (桔梗湯):** The therapeutic target is common cold that starts with pharyngeal pain.
- **Goreisan (五苓散):** Used for fever associated with vomiting and diarrhea as seen in acute viral gastroenteritis. Often used in children.

Subacute Phase

The ShoYo stage equates to the subacute phase, which follows the fourth or fifth day of disease. Patients show halfway pattern (*Hampyo Hanri Sho*: halfway pattern between exterior and interior) characterized by coughs and sputum and/or interior pattern (*Risho*), comprising gastrointestinal symptoms.

- **Shosaikoto (小柴胡湯):** For between deficiency and excess pattern patients with bitter stickiness in the mouth and no appetite. Hypochondrium resistance and discomfort (*Kyokyo Kuman*) is the specific abdominal pattern.
- **Saikokeishito (柴胡桂枝湯):** Patients have rectus abdominis muscle tension and are weaker than those with shosaikoto (小柴胡湯) pattern .
- **Saikokeishikankyoto (柴胡桂枝乾姜湯):** Best suited to deficiency pattern patients, particularly the elderly and frail.
- **Jinsoin (参蘇飲):** Used in patients on prolonged kososan (香蘇散) therapy.

Chronic Phase – Recovery Phase

- **Chikujountanto (竹茹温胆湯):** Appropriate for patients who have coughing with sputum, continued low-grade fever, shallow sleep, and unpleasant mood.
- **Seihaito (清肺湯):** For patients who have large quantities of thick purulent sputum.
- **Hochuekkito (補中益気湯):** For recovery-phase patients with prolonged general malaise and anorexia.

Concomitant Symptoms

The following are often used in addition to the prescriptions mentioned in 1 to 3.

Coughing

- **Bakumondoto (麦門冬湯):** Patients complain of dry air passage and throat discomfort. The therapeutic target is paroxysmal coughing with severe bouts followed by flushing and ultimately severe vomiting (*Ogyaku*).
- **Jiinkokato (滋陰降火湯):** Appropriate for dry cough with viscous and thick sputum in patients who have fluid dryness, especially severe dryness in the throat at night. They also have dried and slightly dark skin.
- **Makyokansekito (麻杏甘石湯):** Effective for severe asthma-like cough and sputum in patients who have sweating and thirst during an attack. Often used in combination with shosaikoto (小柴胡湯).

Other symptoms

- **Saibokuto (柴朴湯):** Widely used for blocked-ear sensation due to cold.
- **Kososan-hangekobokuto combined formula** (香蘇散合半夏厚朴湯): Appropriate for blocked-ear sensation due to cold in deficiency-pattern patients.
- **Ryokankyomishingeninto (苓甘姜味辛夏仁湯):** Used for watery nasal discharge and sneezing in patients with gastrointestinal disorder due to Ephedra Herb (麻黄, mao). Termed the *Rishoho* (裏処方: formulae prescribed in a similar situation, but for patients of different constitution) to shoseiryuto (小青竜湯).
- **Keishikashakuyakuto (桂枝加芍薬湯):** Patients have abdominal pain, diarrhea, and fever.
- **Hangeshashinto (半夏瀉心湯):** Patients have nausea and diarrhea. Abdominal pattern comprises epigastric discomfort and resistance (*Shinka Hiko*).

* Not available as ethical Kampo extract formulation

Persistent Cough - Chronic Cough - Sputum

Koichiro Tatsumi

Overview of Disease

Cough Categorization by Duration

Cough is distinguished according to its duration: three weeks or less (acute cough), three to eight weeks (persistent cough), and eight weeks or more (chronic cough). The causes of acute cough mostly lie in respiratory tract infection. Non-infectious mechanisms are largely contributed to persistent or chronic cough, compared to acute cough. In cases of cough due to bacterial infection, Kampo therapy alone ought to be avoided: antibacterial drug administration is required. Combined use of antibacterial drugs and Kampo medicines is not considered problematic.

Cough Categorization by Sputum

Cough is categorized as either nonproductive or productive, according to the presence or absence of sputum. The key point in Kampo therapy for productive cough is whether the cough is infectious or not. Prior to initiation of Kampo therapy, it is similarly necessary to categorize the causal pathologic condition as either infectious or noninfectious.

Indications for Kampo Therapy

The causal pathologic conditions must be considered. Western medical therapy may be preferred, concurrent use of Western medical therapy and Kampo therapy may be helpful, or Kampo therapy alone may be effective, based on those considerations. Frequent formulae appear below according to pathologic condition.

Frequent Formulae

Persistent Cough Following Bronchitis

In cases of acute bronchitis, if it is not cured within a short period, cough may persist. Eppikahangeto (越婢加半夏湯)* and makyokansekito (麻杏甘石湯) are the medicines of choice for persistent violent cough.

- **Eppikahangeto (越婢加半夏湯)*:** Eppito (越婢湯)* is used for exterior (*Hyo*) fluid retention (*Suitai*), often associated with thirst. In addition, Pinellia Tuber (半夏, hange) has an expectorant effect. Combined use of eppikajutsuto (越婢加朮湯) with hangekobokuto (半夏厚朴湯) or shohangekabukuryoto (小半夏加茯苓湯) extract formulations is a possible alternative.
- **Makyokansekito (麻杏甘石湯):** Appropriate for cough that is not as violent as the cough for which eppikahangeto (越婢加半夏湯)* is used, but that is unfavorably improved by bakumondoto (麦門冬

湯). Combined use with shosaikoto (小柴胡湯) extract formulation is effective.

- **Gokoto (五虎湯):** Consists of makyokansekito (麻杏甘石湯) and sohakuhi (桑白皮), which has anti-inflammatory and antitussive actions**.** Accordingly, gokoto gives a slightly stronger antitussive effect than makyokansekito.

Persistent Cough with Chronic Respiratory Disease

- **Saibokuto (柴朴湯):** Is a combined formula of hangekobokuto (半夏厚朴湯), which improves qi (Ki) depression (*Kiutsu*), and shosaikoto (小柴胡湯), which has an anti-inflammatory action. In cases of bronchial asthma in which adequate Western drug therapy has not eliminated cough or sputum, concomitant use of saibokuto may offer reduction of inhaled steroid dosage.
- **Shimpito (神秘湯):** This prescription is like a combination of Bupleurum Root (柴胡, saiko) –related drugs with Ephedra Herb (麻黄, mao)-related drugs. Can be tried if saibokuto (柴朴湯) shows no effect.
- **Shosaikoto (小柴胡湯):** Should be tried at an early stage for idiopathic pulmonary fibrosis, if patient consent is obtained. Efficacy cannot be expected for late-stage honeycomb lung. If blood stasis (*Oketsu*) signs are present, use concurrently with keishibukuryogan (桂枝茯苓丸).

Persistent Cough

Formulae are used for mild cough, regardless of presence or absence of underlying disease.

- **Bakumondoto (麦門冬湯):** Can be used instead of expectorant if the throat and nasal meatus are mildly dry. Not effective for violent cough. Can be expected to moisten the airway, improve sputum expectoration, and soothe cough and dry mouth, so that it is effective as a basic therapeutic medicine for chronic respiratory tract disease.
- **Hangekobokuto (半夏厚朴湯):** In between deficiency and excess pattern (*Kyojitsu Chukan Sho*) patients, using this formula for laryngopharyngeal paresthesia (sense of stagnation in the pharynx region and foreign-body sensation in the throat [*Inchu Sharen*]) is an approach based on the Kampo classical texts. Has been shown to increase substance P in the laryngopharynx, improve swallowing and cough reflexes, and prevent aspiration pneumonia in elderly people.

Persistent Cough Associated with Sinusitis

- **Shin'iseihaito (辛夷清肺湯):** Magnolia Flower (辛夷, shin'i) is effective for nasal occlusion. If the use of shin'iseihaito alone cannot give sufficient efficacy, combination with shosaikoto (小柴胡湯) may be helpful.
- **Keigairengyoto (荊芥連翹湯):** May be used if shin'iseihaito (辛夷清肺湯) and shosaikoto (小柴胡湯) are not effective.
- **Kakkontokasenkyushin'i (葛根湯加川芎辛夷):** A formula consisting of kakkonto (葛根湯), Cnidium Rhizome (川芎, senkyu), which improves blood flow, and Magnolia Flower (辛夷, shin'i), which improves nasal occlusion. Used for short periods when sinusitis symptoms are severe.

Persistent Cough with Physical Weakness

- **Hochuekkito (補中益気湯):** Does not have a direct effect on cough or sputum, but improves general condition, resulting in effective reduction of common cold symptoms, improvement of respiratory infection condition, and decreases in cough and sputum.
- **Chikujountanto (竹茹温胆湯):** Used in expectation of its expectorant and tranquilizer effects, if mild cough and sputum continue with the onset of intense psychoneurotic symptoms such as insomnia, depression, and irritability.
- **Jiinkokato (滋陰降火湯):** A basic therapeutic medicine for blood deficiency (*Kekkyo*). A kind of nourishing tonic (滋養剤, *Jiyozai*) using shimotsuto (四物湯) with a blood-deficiency treating (*Hoketsu*) effect as the base. Better than bakumondoto (麦門冬湯) in patients who have highly dried general conditions (blood deficiency), including the skin, reduced physical strength, and difficulty in sputum expectoration.
- **Jiinshihoto (滋陰至宝湯):** Good for the pathologic conditions to which jiinkokato (滋陰降火湯) is indicated, particularly when cough is not strong enough for sputum expectoration in patients who have depression or other psychoneurotic symptoms.

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* Not available as ethical Kampo extract formulation

Wheezing dyspnea – Dyspnea

Takashi Ito

Overview of Disease

The primary or underlying diseases for dyspnea are asthma, chronic obstructive pulmonary disease, interstitial pneumonia, and chronic respiratory failure of the respiratory disease. Of the heart disease, heart failure may also be an underlying disease. In the treatment of these diseases, priority is given to Western medicine at least in Japan; however, in intractable cases, Kampo medicines are important because of their complementary role.

Indications for Kampo Therapy

Usefulness of Kampo medicines has been demonstrated in cases as stated below. In each case, Western medicine should be seriously considered, but might not be used in some cases.

Bronchial Asthma

Patients have resistance to inhaled corticosteroid therapy, low peak flow value, rhinitis complication, susceptibility to infection, mood disorder complication, and allergy to Western drugs.

Chronic Obstructive Pulmonary Disease, Chronic Respiratory Failure

Patients have recurrent lower respiratory tract infection despite long-term use of macrolide antibiotics, severe shortness of breath, anorexia, susceptibility to infection, and heart failure complication.

Frequent Formulae

Of the 1998 guidelines for the treatment of asthma, the Kampo therapy guidelines outline the general principles of Kampo formulae for dyspnea and wheezing dyspnea. (Figure) (1). More specifically, Ephedra Herb (麻黄, mao)-containing formulae are used in attacks, Bupleurum Root (柴胡, saiko)-containing formulae between attacks, and deficiency pattern-treating formulae (*Hozai*) in patients with weakness. The Ephedra Herb-containing formulae include makyokansekito (麻杏甘石湯) for heat pattern (*Netsusho*), shoseiryuto (小青竜湯) for cold pattern (*Kansho*), and bakumondoto (麦門冬湯) for severe dry cough. Bupleurum Root-containing formulae are appropriate for prevention of attack. Combined formulae of Bupleurum Root-containig formula and hangekobokuto (半夏厚朴湯) are helpful in patients with throat discomfort. Deficiency pattern-treating formulae offered to patients with weakness include hochuekkito (補中益気湯) for deficiency of upper abdominal region (*Hikyo*) and hachimijiogan (八味地黄丸) for deficiency of lower abdominal region (*Jinkyo*). Differentiated use of formulae in attacks (or when symptoms worsen) and between attacks is important.

In Japan today, the treatment of asthma focuses on inhaled corticosteroids, while Kampo therapy during attacks tends to be considered unimportant. Kampo specialists are expected to successfully prevent asthma attacks as well as aggravation of lower respiratory tract symptoms following viral infection by using not only routine Kampo formulae but special formulae containing Cinnamon Twig (桂枝, keishi) and Ephedra Herb during attacks.

When associated with rhinitis

It has been pointed out that respiratory discomfort is likely to occur concomitantly with rhinitis.

- **Kakkonto (葛根湯):** Helpful when used in patients having chronic sinusitis, neck and back stiffness, and little sweating.

- **Eppikajutsuto (越婢加朮湯):** Offered to patients having intense sneezing and nasal discharge. Helpful if mucous membrane redness and swelling are present.
- **Shoseiryuto (小青竜湯)**: Appropriate for patients with slight facial pallor and edema susceptibility. Effective for allergic rhinitis and asthma. However, it seems that increased severity of pollen allergy symptoms in recent Japan has decreased the number of effective cases.
- **Ryokankyomishingeninto (苓甘姜味辛夏仁湯):** Although target symptoms are almost the same as for shoseiryuto (小青竜湯), target patients are people who are intolerable to Ephedra Herb (麻黄, mao). Rhinitis commonly persists perennially, in association with coldness and edema.
- **Maobushisaishinto (麻黄附子細辛湯):** Good for patients with poor complexion and chills.

When associated with airway infection

Viral infection readily induces asthma attacks and aggravation of respiratory failure. If fever is present, Ephedra Herb (麻黄, mao)-containig formulae for TaiYo stage (*Taiyobyo*) are often prescribed. If the illness is persistent, Bupleurum Root (柴胡, saiko)-containing formulae for ShoYo stage (*Shoyobyo*) are recommended.

- **TaiYo stage (*Taiyobyo*) formulae:** Used within one to three days after infection. See "Common Cold Syndrome" for details.
- **Bupleurum Root (柴胡, saiko)-containing formulae:** Used from the fourth day after infection in cases of alternating chills and fever (*Orai Kannetsu*) and hypochondrium resistance and discomfort (*Kyokyo Kuman*). Includes shosaikoto (小柴胡湯), saikokeishito (柴胡桂枝湯), and saikokeishikankyoto (柴胡桂枝乾姜湯). See "Common Cold Syndrome" for details.
- **Kikyoto (桔梗湯):** Used for dyspnea in cases of sore throat without other infection symptoms (fever or chill). Helpful in the early phase of tonsillitis.
- **Maobushisaishinto (麻黄附子細辛湯):** Can prevent fever and purulent sputum as well as dyspnea when used in patients with chronic obstructive pulmonary disease in the early phase of infection, in which bronchitis aggravation starts with sore throat and chills.

When associated with asthma attacks

The following Ephedra Herb (麻黄, mao)-containing formulae are used, as a rule, at the time of an attack. In Japan today, priority is given to Western medicine, then if effects are unsatisfactory, the use of Kampo formulae is given consideration. However, depending on the timing of their use, Kampo medicines may exert efficacy equal to or superior to Western drugs. Nevertheless, if improvement is not evident, modern medicine should be considered to prevent the disease from proceeding.

- **Makyokansekito (麻杏甘石湯)**: Can control asthma attack when used on the onset of wheezing dyspnea and sweating in the early stage of the attack. Most patients have facial redness with heat pattern. If sweat is absent, dehydration is suspected, requiring caution.
- **Eppikahangeto (越婢加半夏湯)***: Effective for attacks with severe coughing (as if the eyes almost popped out) and vomiting at the peak of the attack.
- **Shimpito (神秘湯)**: Target symptoms are persistent cough with *Kyokyo Kuman*. Also effective for rather severe cough.

When associated with feeling of breathlessness in the pharynx

- **Hangekobokuto (半夏厚朴湯):** Appropriate for discomfort (foreign body sensation [*Sharen*]) from the throat to the chest. Patients commonly have background mental health imbalance, including anxiety and depressive condition. Frequently used for laryngopharyngeal neurosis.
- **Saibokuto (柴朴湯):** A combined formula of hangekobokuto (半夏厚朴湯) and shosaikoto (小柴胡湯). Used for patients with asthma or throat discomfort due to airway hypersensitivity. Effectiveness in steroid-dependent patients has been reported in a clinical trial using the envelope method (2).

When associated with feeling of breathlessness in the chest

Indications include chronic asthma, chronic heart failure, and pathologic conditions associated with secondary heart strain.

- **Mokuboito (木防已湯):** Appropriate for excess pattern (*Jitsusho*) patients with hard and broad resistance in the epigastric region (*Shinka Hiken*), thirst, and edema.
- **Mokuboikyosekkokabukuryoboshoto (木防已去石膏加茯苓芒硝湯)*:** Appropriate for patients who have constipation with no thirst and are of rather excess pattern than those with mokuboito (木防已湯) pattern.
- **Zosonmokuboito (増損木防已湯)*:** Used for severe cough in mokuboito (木防已湯)-pattern (*Mokuboitosho*) patients.
- **Bukuryokyoninkanzoto (茯苓杏仁甘草湯)***: Offered to deficiency pattern (*Kyosho*) patients with resistance below the heart, although such resistance is absent not infrequently.

Chronic Wheezing dyspnea

- **Hachimijiogan (八味地黄丸):** Appropriate for patients with deficiency of lower abdominal region (*Jinkyo*), specifically, weakness of the lower abdominal region (*Shofuku Fujin*), nocturia, lower body pain, numbness, and weakness. Effective in cases of low peak-flow value, but efficacy cannot be expected in severe cases of 250 L/minute or less (3).
- **Hochuekkito (補中益気湯)**: Main indication is qi deficiency (*Kikyo*) (deficiency of upper abdominal region); specifically, weak eyes, loss of spirit, loss of vigor, anorexia, low-grade fever tendency, susceptibility to colds, etc. In patients with chronic obstructive pulmonary disease, effective improvement of QOL, reduced incidence of common cold syndrome, and improvement in nutritional condition have been reported (4).

* Not available as ethical Kampo extract formulation

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Palpitation and Shortness of Breath

Shuji Yakubo

Overview of Disease

This overview deals with palpitation and shortness of breath associated with heart failure, and other palpitation.

Heart failure symptoms

Treatment must be carried out in consideration of the pathological condition and underlying diseases of heart failure.

For mild heart failure, treatment aims to avoid reductions in quality of life (QOL) by using diuretic, digitalis, catecholamine, and vasodilator drugs.

For severe heart failure, a catheter is inserted to measure cardiac index and pulmonary capillary wedge pressure. If the cardiac index is low, treatment should take pulmonary capillary wedge pressure into account with cardiac pumping ability maintained.

In cases of valve disease, hypertensive heart disease, cardiomyopathy, and ischemic heart diseases (such as cardiac infarction) that impair cardiac function, the necessary drug therapy, interventions, and surgical management should be carried out.

Palpitation

Treatment plans will differ according to the presence or absence of palpitation-linked arrhythmia and underlying diseases that cause arrhythmia. Arrhythmia is either tachycardia arrhythmia (tachyarrhythmia) or bradycardia arrhythmia (bradyarrythmia).

Dangerous tachyarrhythmia includes ventricular fibrillation and ventricular tachycardia. If these conditions are identified, or if long QT syndrome, Brugada syndrome, or late ventricular potential on signal-averaged electrocardiogram is found, aggressive treatment with anti-arrhythmic drugs should be given. Dangerous bradyarrhythmia requires therapy using a pacemaker.

Tachyarrhythmia that reduce QOL include paroxysmal arterial fibrillation and paroxysmal supraventricular tachycardia, both also treated with anti-arrhythmic drugs.

Excluding dangerous arrhythmias and QOL-reducing arrhythmias, non-dangerous arrhythmias that are not associated with underlying diseases are generally not treated with anti-arrhythmic drugs. Tranquilizers are administered for subjective symptoms such as palpitation. However, anti-arrhythmic drugs may be administered in cases in which significant subjective symptoms coincide with arrhythmia events.

Indications for Kampo Therapy

1. Heart failure symptoms

Modern intensive medical treatment is required for acute and severe life-threatening heart failure. Kampo therapy is used for chronic and non-severe pathologic conditions, which include New York Heart Association (NYHA) Functional Classification Class II and Class III heart failure involving the appearance of heart failure symptoms even with daily activities or light work.

2. Palpitation

Preference is given to modern medical treatment for dangerous arrhythmia.

Kampo medicines such as shakanzoto (炙甘草湯) are used for paroxysmal arterial fibrillation and paroxysmal supraventricular tachycardia, which reduce QOL. Mokuboito (木防已湯) is used for bradyarrhythmia.

Aggressive treatment with Kampo medicines may be considered for arrhythmia with strong subjective symptoms that does not require therapy with the anti-arrhythmic drugs of Western medicine.

Frequent Formulae

Kampo therapy for heart failure symptoms such as shortness of breath, palpitation, and edema includes the use of Kampo prescriptions using crude drugs with an effect treating fluid disturbance (*Risui*) combined with crude drugs with an effect treating qi (Ki) deficiency (*Hoki*).

Crude drugs with an effect treating heat pattern (*Seinetsu*) or antifebrile effect are appropriate for palpitation not associated with heart failure. For palpitation associated with blood deficiency (*Kekkyo*), prescriptions containing crude drugs with an effect treating blood statis (*Oketsu*) are recommended.

Heart failure symptoms

- **Mokuboito (木防已湯):** Used for heart failure symptoms such as respiratory distress, cough, and edema, associated with abdominal distension, thirst, and reduced urination. Specifically useful for patients with signs of blue-blackness in the face, wheezing, dyspnea, and abdominal swelling. The pulse is sunken and tight. Patients tend to have excess pattern and regardless of abdominal strength, abdominal examination shows a hard and broad resistance in the epigastric region (*Shinka Hiken*). There are reports that reduced serum concentrations of B-type natriuretic peptide (BNP), a heart failure marker, has improved with mokuboito (木防已湯).
- **Bukuryokyoninkanzoto (茯苓杏仁甘草湯)***: Target patients have a blockage sensation (*Hisokukan*) in the abdomen and signs of dyspnea, palpitation, and radiating chest-back pain; and may also be associated with respiratory distress and edema. They are of deficiency-pattern with sunken and faint pulse. Abdominal examination shows the abdomen is weak with soft resistance in the epigastric region. Thirst is absent.
- **Ryokankyomishingeninto (苓甘姜味辛夏仁湯)**: Contains the constituent crude drugs of bukuryokyoninkanzoto (茯苓杏仁甘草湯)*. Used for palpitation, shortness of breath, cough, and

sputum, specifically in deficiency-pattern patients with fatigue and sensitivity to coldness (*Hiesho*), also characterized by poor facial color, wheezing, and edema. The pulse is sunken and weak. Abdominal examination commonly shows weakness with splashing sound in the epigastric region (*Shinsuion*).

- **Ryokeijutsukanto (苓桂朮甘湯)**: Used for palpitation, shortness of breath, and dizziness. Deficiency pattern patients are targeted who have coldness in the lower limbs and reduced urination. The pulse is sunken and tight. Abdominal examination shows abdominal strength is intermediate or weaker. The abdomen shows palpable pulsation in the supraumblical region (*Saijo Ki*) and *Shinsuion*.
- **Tokishakuyakusan (当帰芍薬散)**: Specifically used in swelling-prone patients with *Hiesho* and other symptoms such as palpitation. They are deficiency pattern patients who are prone to fatigue and suffer from general malaise. Patients have anemia-like pallid facial color with soggy, slack skin; the pulse is sunken and weak. Abdominal examination shows weak abdominal strength, *Shinsuion* and paraumbilical tenderness and resistance (*Saibotenderness*).
- **Shimbuto (真武湯)**: Specifically used in deficiency pattern patients who have reduced metabolism and poor peripheral circulation. Patients complain of general malaise and leg and low-back coldness; and in addition to palpitations, they have dizziness, feeling of shakiness, edema and reduced urination. The pulse is sunken and weak. Abdominal examination shows the thin abdominal wall, reduced abdominal strength with *Shinsuion*. Occasionally there may be slight tension in the rectus abdominis muscles.

Palpitation

- **Keishininjinto (桂枝人参湯)**: Effective for hot flashes and palpitation. Administered to deficiency pattern patients with lower body coldness and who have gastrointestinal weakness and are prone to diarrhea. Abdominal examination shows slight weakness in the abdomen and abdominal strength is intermediate or weaker. Epigastric discomfort and resistance (*Shinka Hiko*) and *Shinsuion* are present. Occasionally the thin abdominal wall may have palpable tightness. The pulse is floating and weak.
- **Saikokaryukotsuboreito (柴胡加竜骨牡蛎湯)**: Targets stress-induced hypertension and palpitation. Used in excess pattern patients who are irritable, prone to anger, and anxious. Abdominal examination shows abdominal strength is intermediate or stronger. hypochondrium resistance and discomfort (*Kyokyo Kuman*), and resistance in the epigastric region are present, associated with *Saijo Ki*. The pulse is string like.
- **Orengedokuto (黄連解毒湯)**: Targets patients who are easily aroused and show palpitation and tachychardia when aroused. They are excess pattern patients who have signs of hot flashes with facial redness as well as psychoneurotic symptoms of anxiety and irritability. Abdominal examination shows distension in the abdomen and abdominal strength is intermediate or stronger. Resistance in the epigastric region is present.
- **Kamishoyosan (加味逍遙散)**: Specifically used in deficiency pattern patients who suffer coldness and have palpitation, anxiety, insomnia, and irritability, sometimes associated with a sensation of

hotness in the upper body, particularly the face, and paroxysmal sweating. The pulse is sunken and fine. Abdominal examination shows abdominal strength is intermediate or weaker. Slight resistance and tenderness in the epigastric region and slight *Kyokyo Kuman* are present, associated with *Saibotenderness*.

- **Shakanzoto (炙甘草湯)**: Also called fukumyakuto (復脈湯). Used for palpitation and shortness of breath in deficiency pattern patients, who have skin and mucous membrane dryness and atrophy; burning sensation (*Hoteri*) in the limbs; thirst and other blood deficiency symptoms; constipation and malaise. They are also prone to fatigue. The pulse is weak, sometimes frequent, irregular and intermittent.
- **Sansoninto (酸棗仁湯)**: Used for insomnia in mentally and physically fatigued deficiency pattern patients. They may have decreased physical strength, chest painfulness, and palpitation, associated with psychoneurotic symptoms such as anxiety and oversensitivity as well as dizziness, *Hoteri* in the limbs, and hot flash sensation. The skin tends to be dry. Abdominal examination shows reduced abdominal strength. *Saijo Ki* is not present.
- **Kihito (帰脾湯)**: Used for tachycardia, palpitation, insomnia and psychoneurotic symptoms (including anxiety, oversensitivity, overanxiety, and forgetfulness) in deficiency pattern patients with anemia and pale face. Sometimes fever attacks, night sweat (*Tokan*), and loss of appetite may be associated. Abdominal examination shows abdominal weakness with reduced abdominal strength.
- **Ninjinyoeito (人参養栄湯)**: Used for physical exhaustion after debilitating disease or surgery and for dual deficiency of qi (Ki) and blood (*Kiketsu Ryokyo*) due to weak constitution. General malaise, tachychardia, palpitation, night sweat, and coldness of limbs are present. The pulse is weak, and abdominal examination shows reduced abdominal strength.

* Not available as ethical Kampo extract formulation

Anorexia– Nausea – Vomiting – Heartburn

Tetsuro Oikawa

Overview of Disease

If patients have anorexia, nausea, vomiting, and heartburn originating in the upper digestive tract, and malignant tumor and peptic ulcer are ruled out in diagnosis, these symptoms often indicate a functional gastrointestinal disorder such as functional dyspepsia (FD). Functional gastrointestinal disorders are complex pathologic conditions. Western medicine having a singular site of action is often not completely effective. For such pathologic conditions, Kampo medicines considered to have multiple sites of action are as effective as, or

more effective than Western drug therapies. Actually, rikkunshito (六君子湯) is effective for chronic indigestion symptoms, and its various actions have been elucidated, including improvement of gastric emptying function and adaptive relaxation as well as stimulation of secretion of ghrelin, which has an appetite-increasing effect. Non-erosive reflux disease (NERD) is a pathologic condition of gastroesophageal reflux disease, a typical heartburn-causing disease. Proton pump inhibitors have not yielded adequate effect on NERD. However, recent attention has been paid on NERD, because it has been reported that concomitant use of rikkunshito (六君子湯) is helpful for this pathologic condition. As the limitations of Western medical approaches become apparent, the significance of complementary Kampo medicines comes to the front.

Indications for Kampo Therapy

In Kampo medicine, anorexia, nausea, vomiting, and heartburn tend to be associated with qi (Ki) deficiency (*Kikyo*). When anorexia, nausea, vomiting, and heartburn occur because of upper digestive tract dysfunction, digestion and absorption of essential nutrients are interrupted and the body's heat production level decreases, which then leads to a condition of qi (Ki) deficiency. At the same time, upper digestive tract dysfunction is often associated with decreased emptying function, which results in retention of fluids such as digestive juice in the stomach. This is termed fluid retention (*Suitai*) in the digestive tract, or '*Tan'in*.' Kampo medical treatment for anorexia, nausea, vomiting, and heartburn facilitates fluid retention drainage and qi (Ki) replenishment. Functional gastrointestinal disorder patients also suffer depression and anxiety and are often administered antianxiety drugs and antidepressants. In Kampo medicine, this condition is considered coexistence of qi (Ki) depression (*Kiutsu*). Active use of Kampo medicines, which often contain qi (Ki)-regulating formula(e) (*Rikiyaku*), is recommended.

Frequent Formulae

Anorexia

- **Rikkunshito (六君子湯)**: Widely used mainly in between deficiency and excess pattern- (*Kyojitsu Chukan Sho*) to deficiency pattern (*Kyosho*) patients. Especially effective for patients who complain of chronic indigestion and early satiety. Expected to exert efficacy on these symptoms in any pattern patients. Abdominal examination often shows epigastric discomfort and resistance (*Shinka Hiko*) and splashing sound (*Shinsuion*). This formula is one of the Kampo medicines whose action mechanisms have been intensively elucidated and there is a range of evidence for FD treatment and alleviation of psychoactive drug adverse effects.
- **Shikunshito (四君子湯)**: This is rikkunshito (六君子湯) without Citrus Unshiu Peel (陳皮, chimpi) and Pinellia Tuber (半夏, Hange). The removal of these ingredients weakens the efficacy for chronic indigestion and other symptoms due to fluid retention.
- **Ninjinto (人参湯)**: Patients have slender build and mostly have *Shinka Hiko*. They may also have plywood-like plate-shaped hardness in the upper abdomen. Combining with Glycyrrhiza (甘草,

kanzo) and Processed Ginger (乾姜, kankyo) eliminates interior cold (*Rikan*) and improves coldness in the feet and body.

- **Hangeshashinto (半夏瀉心湯)**: Patients often have subjective symptoms of gastric stuffiness (*Shinka no Hie*) and discomfort, with objective findings of *Shinka Hiko*. Patients may also have symptoms such as abdominal rumbling and diarrhea. Effective for stress gastritis in young patients.
- **Orengedokuto (黄連解毒湯)**: Patients often have gastric stuffiness and discomfort, with the abdominal pattern comprising *Shinka Hiko*. Used in patients with increased secretion of gastric acid who complain of heartburn and other symptoms such as gastric stuffiness and discomfort. Orengedokuto is similar to rikkunshito (六君子湯) and hangeshashinto (半夏瀉心湯) in target patients' abdominal findings of the *Shinka Hiko*, but is more often appropriate for excess-pattern (*Jitsusho*) patients. Also effective against facial redness and hot flash tendency.
- **Hochuekkito (補中益気湯):** This is a typical qi (Ki) deficiency-treating formulae (*Hokizai*) and is widely used for anorexia. It is especially effective in patients who have atonic constitution, characterized with gastroptosis, anal prolapse, and the like. Patients may have a tongue diagnosis of enlarged tongue (胖大舌); slight hypochondrium resistance and discomfort (*Kyokyo Kuman*) evident in abdominal examination; and a pulse diagnosis of dissipated and large pulse, a unique pulse.
- **Heiisan (平胃散):** This formula is used for dyspepsia symptoms such as stomach swelling after eating. More suited to excess pattern patients than rikkunshito (六君子湯).

Nausea and Vomiting

- **Shohangekabukuryoto (小半夏加茯苓湯)**: Often used for hyperemesis gravidarum. Also effective for similar symptoms. For severe symptoms, taking the formula cold (*Reifuku*) facilitates dosing.
- **Rikkunshito (六君子湯):** See Section C1-C-1 Anorexia.
- **Hangekobokuto (半夏厚朴湯):** A typical qi (Ki) medicine (*Kizai*). Appropriate for patients with neurosis tendency or digestive tract symptoms involving stress. Effective in patients with abdominal distension or laryngopharyngeal discomfort termed foreign-body sensation in the throat (*Inchu Sharen*). At a high rate, patients have a tongue diagnosis of teeth-marked tongue (歯痕舌) or white tongue fur with abdominal fullness (腹満) found in abdominal examination.
- **Bukuryoin (茯苓飲):** This formula drains fluid retention and is more effective than shohangekabukuryoto (小半夏加茯苓湯) against strong sensation that food does not move normally. Abdominal examination often shows splashing sound. Bukuryoin is often used as combined formula with hangekobokuto (半夏厚朴湯).
- **Goreisan (五苓散)**: A typical fluid disturbance-treating formula. Main target patients are who have thirst, sweating tendency, and decreased urine volume and urination frequency (*Nyori Gensho*). Widely used for nausea, vomiting, and diarrhea in acute gastroenteritis.
- **Shosaikoto (小柴胡湯)**: A typical formula for ShoYo stage (*Shoyobyo*), but nausea and vomiting are also target symptoms. In high frequency, patients have *Kyokyo Kuman* found in abdominal examination, with a tongue diagnosis of white fur. Given this, the formula may be used for various chronic digestive diseases.
- **Daisaikoto (大柴胡湯)**: More effective than shosaikoto (小柴胡湯) in patients with intense *Kyokyo*

Kuman, nausea, vomiting, and other symptoms, associated with constipation tendency.

- **Hangeshashinto (半夏瀉心湯)**: See Section C1-C-1 Anorexia.
- **Goshuyuto (呉茱萸湯)**: Known as a formula for headache, but it is very effective for nausea and vomiting associated with headache and coldness in the limbs. In high frequency, patients have coldness in the limbs and *Shinka Hiko* found in abdominal examination.

Heartburn

- **Rikkunshito (六君子湯):** See Sections C1-C-1 Anorexia, and C-C-2 Nausea & Vomiting.
- **Hangekobokuto (半夏厚朴湯)**: See Section C1-C-2 Nausea & Vomiting.
- **Hangeshashinto (半夏瀉心湯)**: See Sections C1-C-1 Anorexia, and C1-C-2 Nausea &Vomiting.
- **Orengedokuto (黄連解毒湯):** See Section C1-C-1 Anorexia.
- **Orento (黄連湯)**: Berberine contained in Coptis Rhizome (黄連, oren) possesses antiulcer, anti-inflammatory, and antibacterial activity. Effective for heartburn, sometimes associated with headache or stomach pain. Patients have the thick white fur tongue as well as *Shinka Hiko* or tenderness below the heart (*Shinka Attsu*) found in abdominal examination, at high frequency.
- **Anchusan (安中散)**: A combination of Cinnamon Bark (桂皮, keihi) with body-warming effect, Oyster Shell (牡蛎, borei) with acid-suppressing effect, and crude drugs such as Corydalis Tuber (延胡索, engosaku) with excellent analgesic effect. Appropriate for patients who have coldness and complain of abdominal pain and heartburn.
- **Shishishito (梔子豉湯)***: This formula, containing Gardenia Fruit (山梔子, sanshishi), is mainly used for heartburn, associated with indescribable pain and agony around the chest.

* Not available as ethical Kampo extract formulation

Constipation – Diarrhea – Abdominal pain Abdominal distension

Makoto Arai

Overview of Disease

It is believed that a healthy person defecates three times/day to three times/week and stool weight is 80 to 200 g. With constipation, moisture is excessively absorbed from intestine contents; defecation frequency as well as stool weight at each defecation decrease; and stools may harden. Discomfort such as difficulty defecating, incomplete evacuation sensation, and abdominal distension are characteristically associated with constipation. With diarrhea, patients show symptoms such as soft, muddy, or watery stool due to abnormal moisture increase in intestine contents. The cause may be inflammation or malignant tumor, but in most cases is an alimentary canal functional disorder such as irritable bowel syndrome. Similarly, in many cases, abdominal pain and abdominal distension are functional problems that become chronic, but in acute cases such as gallstone attack, acute pancreatitis, peritonitis, or strangulated ileus, emergency treatment may be required.

Indications for Kampo Therapy

Bowel movement disturbance, abdominal pain, and/or abdominal distension complained chronically or repeatedly correspond to the functional intestinal disorders or functional abdominal pain syndromes that fall within the classification of functional gastrointestinal disorders of the Rome III criteria. These symptoms are good indications for Kampo therapy. Causal therapy with Western medicine is preferred if the cause is clear, such as in the various systemic diseases associated with gastrointestinal infection, malignant tumor, inflammatory bowel diseases, or gastrointestinal symptoms, as well as the adverse effects (so-called side effects) or sequelae of Western medical therapies. However, even if the cause is clear, Kampo therapy often improves subjective symptoms in cases of acute viral gastroenteritis or postoperative intestinal adhesion. Targeting symptoms with Kampo therapy can be expected to result in improved alimentary canal function, enhanced physical strength and vitality, as well as improved general condition. The merits of improving subjective symptoms with Kampo therapy in the alimentary canal area are great and it is worthwhile actively using Kampo medicines in parallel with Western medical therapies, as necessary.

Frequent Formulae

Constipation (Figure)

Constipation is classified according to deficiency (*Kyo*) and excess (*Jitsu*) patterns.

Excess pattern constipation patients have strength in the abdomen and pulse, and will defecate normally with

laxatives such as Rhubarb (大黄, daio) or Mirabilite (芒硝, bosho). Deficiency pattern constipation patients might not defecate for several days or more than one week. Characteristically, when stool is passed, it is hard and rounded, and laxative use causes abdominal pain or severe diarrhea. Prescriptions for compounds containing crude drugs that improve alimentary canal function may be considered, but for extreme deficiency pattern constipation, it may be necessary to use prescriptions that do not contain Rhubarb or Mirabilite.

- **Daiokanzoto (大黄甘草湯)**: Used generally for excess pattern constipation.
- **Daisaikoto (大柴胡湯)**: Patients have stout physique, show strong hypochondrium resistance and discomfort (*Kyokyo Kuman*) and epigastric resistance and tight feeling (*Shinka Kyu*), and complain of shoulder stiffness and depressed mood.
- **Daijokito (大承気湯)**: Patients have abdominal distension with elasticity and tend to have accumulated gas.
- **San'oshashinto (三黄瀉心湯)**: Patients show epigastric discomfort and resistance (*Shinka Hiko*) and have hot flashes, irritability, insomnia and heavy headedness.
- **Tokakujokito (桃核承気湯)**: Patients have stout physique, associated with blood stasis (*Oketsu*) symptoms. Especially before menstruation, they complain of psychoneurotic symptoms such as irritability, hot flashes, and insomnia, and show resistance and sharp tenderness in the left iliac region (*Shofuku Kyuketsu*).
- **Bofutsushosan (防風通聖散)**: Patients are solidly built with a potbelly. Abdominal strength is substantial, particularly around the naval.
- **Otsujito (乙字湯)**: Patients have hemorrhoids.
- **Mashiningan (麻子仁丸)**: Patients are elderly or have weak constitution and pass hard rounded stools like rabbit droppings.
- **Junchoto (潤腸湯)**: Symptoms include skin dryness, and the degree of dryness is greater than for mashiningan (麻子仁丸).
- **Keishikashakuyakudaioto (桂枝加芍薬大黄湯)**: Patients complain of painful swollen abdomen and tenesmus (*Rikyu Koju*). Used for constipation as main symptom of irritable bowel syndrome.
- **Daikenchuto (大建中湯)**: Formulation not containing Rhubarb (非大黄剤, *hidaiozai*). Patients have extreme deficiency pattern constipation and abdominal gas retention or visible intestinal peristalsis.

Diarrhea

Diarrhea is classified from the Yin (陰) and Yo (陽) perspective.

The characteristics of Yin diarrhea include incompletely digested stool or watery stool with not strong odor. In most cases it is chronic diarrhea termed '*Sessha*,' which is not associated with tenesmus. Yin diarrhea becomes chronic and is a good indication for Kampo therapy. Yo diarrhea is inflammatory and symptoms are severe. Blood or pus may be discharged. It is commonly treated as bacterial enteritis and in most cases it is acute diarrhea termed '*Rishitsu*,' which is associated with tenesmus.

- **Shimbuto (真武湯)**: Used for yin diarrhea in patients whose abdomen is weak, pulse is weak, and have sensitivity to coldness (*Hiesho*) and poor complexion. Patients have no tenesmus. Even if stomach symptoms or abdominal pain are present, it is slight.
- **Ninjinto (人参湯)**: Indications are similar to those for shimbuto (真武湯), but are often associated

with stomach symptoms such as loss of appetite and indigestion.

- **Hangeshashinto (半夏瀉心湯)**: Patients have *Shinka Hiko*, associated with rumbling stomach.
- **Keishininjinto (桂枝人参湯)**: Appropriate for Ninjinto (人参湯)-pattern (*Ninjintosho*) diarrhea, associated with hot flashes, headache, and chills.
- **Keishikashakuyakuto (桂枝加芍薬湯)**: Used for patients with diarrhea-type irritable bowel syndrome, associated with abdominal pain and tenesmus.
- **Goreisan (五苓散)**: Patients are thirsty with reduced urination in comparison to water intake.
- **Ireito (胃苓湯)**: Patients have acute gastroenteritis, causing abdominal pain and diarrhea.
- **Keihito (啓脾湯)**: May be tried for Yin diarrhea, only if shimbuto (真武湯) or ninjinto (人参湯) are ineffective.

Abdominal pain

In general, prescriptions containing Peony Root (芍薬, shakuyaku) are used for abdominal colic caused by alimentary canal spasm. Bupleurum Root (柴胡, saiko)-containing formulae including saikokeishito (柴胡桂枝湯), daisaikoto (大柴胡湯), and shigyakusan (四逆散) are frequently used for epigastric pain, while kenchuto (建中湯) group such as daikenchuto (大建中湯) and shokenchuto (小建中湯) are frequently used for peri-umbilical pain and lower abdominal pain. Keishikashakuyakuto (桂枝加芍薬湯) is considered the first choice for irritable bowel syndrome. Shakuyakukanzoto (芍薬甘草湯) is effectively used at a single dose for sudden abdominal pain.

Chronic lower abdominal pain that is either induced or aggravated by exposure to cold is termed cold abdominal colic (*Kansen*). It may extend to the epigastric region, low back, mid back, perineal region, limbs and head and is treated with tokishigyakukagoshuyushokyoto (当帰四逆加呉茱萸生姜湯).

- **Keishikashakuyakuto (桂枝加芍薬湯)**: Specifically used for colic from the para-umbilical to the lower abdominal region caused by alimentary muscle tension (*Kokyu*).
- **Shokenchuto (小建中湯)**: Appropriate for keishikashakuyakuto (桂枝加芍薬湯)-pattern (*keishikashakuyakutosho*) patients with weak constitution or severe abdominal pain.
- **Daikenchuto (大建中湯)**: Effective for excessive intestinal peristalsis that can be seen through the thin abdominal wall, or for the distended entire abdomen due to gas retention.
- **Tokishigyakukagoshuyushokyoto (当帰四逆加呉茱萸生姜湯):** Prescription typically used for cold abdominal colic.
- **Shakuyakukanzoto (芍薬甘草湯):** Given for abdominal pain attack at a single dose.
- **Daisaikoto (大柴胡湯)**: Used for epigastric pain in patients who have stout physique with strong abdominal elasticity, and have remarkable *Kyokyo Kuman*.
- **Shigyakusan (四逆散)**: Patients are similar to daisaikoto (大柴胡湯)-pattern (*Daisaikotosho*) patients, but have no constipation and show rectus abdominis muscle tightness.
- **Saikokeishito (柴胡桂枝湯)**: Essentially used in between deficiency and excess pattern (*Kyojitsu Chukan Sho*) patients who have *Kyokyo Kuman* and epigastric abdominal muscle tightness. Widely used for epigastric pain.
- **Anchusan (安中散)**: For patients who complain of chronic dull epigastric pain, often associated with sour eructation symptoms such as heartburn.

Abdominal distension

Patients with elasticity and swelling in the entire abdomen are of excess pattern and the distension is relieved with jokito (承気湯) prescriptions such as daijokito (大承気湯). Patients who have a weak pulse and weak and powerless abdomen, or have slightly taut abdominal muscles and accumulated gas in the digestive tract, are diagnosed with deficiency pattern. Their alimentary canal function is improved by warming the abdomen with daikenchuto (大建中湯).

- **Daikenchuto (大建中湯)**: Patients have abdominal distension due to gas and visible intestinal peristalsis. Frequently used for abdominal distension due to post-operative digestive tract adhesion. If the outcome is inadequate, combined use of keishikashakuyakuto (桂枝加芍薬湯) may be effective.
- **Keishikashakuyakuto (桂枝加芍薬湯)**: Patients have bowel movement disturbance associated with abdominal pain.
- **Tokito (当帰湯)**: A Ginseng (人参, ninjin) and Astragalus Root (黄耆, ogi)-containing formula combining the characteristics of the three formulas daikenchuto (大建中湯), keishikashakuyakuto (桂枝加芍薬湯), or hangekobokuto (半夏厚朴湯).
- **Daijokito (大承気湯):** Patients have constipation and distension in the entire abdomen that is elastic.

Urination Disorder

Takao Ikeuchi

Overview of Disease

The lower urinary tract is responsible for two conflicting functions: urine storage over a given period and periodic urination. The associated abnormal symptoms are termed lower urinary tract symptoms, regardless of cause. The symptoms are classified into three types: urine storage symptoms, such as pollakiuria (diurnal pollakiuria, when urinary frequency during waking hours is eight times or more; and nocturnal pollakiuria, when urinary frequency during sleeping hours is twice or more), urge to urinate, and incontinence; urination symptoms, such as dysuria; and post-voiding symptoms, such as residual urine sensation. Other less frequent symptoms include painful urination, bladder (lower abdominal) pain, and indefinite urinary tract complaints.

The diseases that give rise to urination disorder include overactive bladder, incontinence, benign prostatic hypertrophy (BPH), lower urinary tract infection (cystitis), prostatitis syndrome, and unidentified clinical syndromes of the lower urinary tract such as psychogenic nervous pollakiuria and bladder neurosis. Furthermore, lower urinary tract symptoms may be associated with aging, sensitivity to coldness, menopausal syndrome, sleep disorder, habit polydipsia, and adverse reaction to Western drugs: the causes are highly varied.

Indications for Kampo Therapy

Elderly people account for the overwhelming majority of patients with urination disorder complaints; therefore, constitutional weakness, decreased anti-disease (抗病反応) response, and impaired biological defence mechanism are assumed as underlying factors. Most diseases follow a chronic course, and symptoms tend to become prolonged. Such pathological conditions, like psychogenic symptoms and indefinite complaints (that lack corresponding, or abnormal, objective findings), are ideal targets for Kampo therapy, which may offer great benefits. However, in some cases of advanced disease, surgical procedures may be required or Western drug therapy may be preferred. Physicians need to keep in mind the limitations of Kampo therapy and the fact that Kampo therapy cannot be used in some conditions.

Importantly, Kampo practitioners should address each of the varied urination disorder manifestations as a systemic symptom, without adhering to disease names in Western medicine. It is essential in Kampo medical practice to ascertain the patient's pattern(s) and then select the Kampo prescriptions suitable to the individual patient's physical strength and constitution.

Pathological Conditions in Kampo Medicine

In considering urination disorder from the Kampo medicine perspective, it is important to take into account innate life force, the cycle of predestined human life changes (growth, reproduction, aging), and fluid metabolism function. With aging come physiological decreases in sex hormones and reductions in urological functions. Moreover, qi (Ki), the energy that governs life, may become disordered and may develop into qi (Ki) deficiency (*Kikyo*) or qi (Ki) depression (*Kiutsu*) (qi [Ki] stagnation [*Kitai*]).

In the diseases originating in the renal-urinary system organs, a core pathological condition is fluid disturbance (*Suidoku*), or fluid retention (*Suitai*): abnormal fluid excretion underlies urination disorder. Since the bladder and the prostate gland, the prime organs that cause urination disorder, are located within the pelvic cavity, blood stasis (*Oketsu*) induced by anatomical changes is a key associated pathological condition. As life force decreases with aging, physical strength, immunity, and mental activity decrease. These decreases are accompanied by qi (Ki) abnormalities including qi (Ki) deficiency, qi (Ki) depression, and qi (Ki) counterflow (*Kigyaku*). Therefore, the Kampo pathological condition of urination disorder is presumed to be a pathological complex entangled by fluid disturbance, blood stasis and qi (Ki) abnormalities.

Frequent Formulae

Overactive bladder

If urge to urinate and pollakiuria（diurnal and nocturnal）are present, the condition is termed overactive bladder, which is associated with urge incontinence in half of the cases. The relevant Kampo pathological condition remains to be established; however, if Western medicines are insufficiently effective, there may be some benefit in trying Kampo medicines.

- Goshajinkigan (牛車腎気丸), Seishinrenshiin (清心蓮子飲): Formulae of first choice.
- Junchoto (潤腸湯), Keihito (啓脾湯): Formulae of second choice.

Blood stasis-treating (*Kuoketsu*) formulae are used for interior cold (*Rikan*) aggravated by cold, and blood deficiency-treating (*Hoketsu*) formulae are used if bladder ischemia is suspected.

Incontinence

The effective prescriptions for urinary incontinence differ because its pathological conditions differ according to the underlying mechanism. Urge incontinence associated with urge to urinate is dealt with in the section on overactive bladder. Stress urinary incontinence occurs with a sharp increase in abdominal pressure, resulting from muscle weakness and ligamentous laxity in the pelvic floor.

- **Hochuekkito (補中益気湯):** Used for Yo pattern (陽証, *Yosho*) patients. Combined formulae with kakkonto (葛根湯) containing Ephedra Herb (麻黄, mao) may also be offered.
- **Maobushisaishinto (麻黄附子細辛湯):** Formulae combining Ephedra Herb and Processed Aconite Root (附子, bushi) are used for Yin pattern (陰証, *Yinsho*) patients.
- **Goshajinkigan (牛車腎気丸), Hachimijiogan (八味地黄丸), Rokumigan (六味丸):** Used when reflex or total incontinence observed in neurogenic bladder is caused by spinal cord disease, or nervous system disease sequelae or complications.

Since overflow incontinence associated with large residual urine volume as observed in urinary retention occurs in end-stage BPH, it is dealt with in the following section.

Benign prostatic hypertrophy (BPH)

The presence of dysuria, nocturia, and residual urine sensation indicates BPH. Kampo medicines are best used at an early stage, and the appropriate prescriptions should be selected with consideration of both constitution (presence or absence of cold sensation in hands and feet) and physical strength (excess pattern [*Jitsusho*], between deficiency and excess pattern [*Kyojitsu Chukan Sho*], and deficiency pattern [*Kyosho*]).

- **Hachimijiogan (八味地黄丸), Rokumigan (六味丸) Goshajinkigan (牛車腎気丸):** Formulae treating deficiency of lower abdominal region (*Hojinzai*) are the first choice.
- **Choreito (猪苓湯), Ryutanshakanto (竜胆瀉肝湯), Gorinsan (五淋散):** Heat-treating (*Seinetsu*) and fluid disturbance-treating（*Risui*） formulae are the second choice.

For advanced BPH, which may cause blood stasis in the pelvic cavity, blood stasis-treating formula(e) are used.

Lower urinary tract infection

The presence of irritable bladder symptoms such as pollakiuria (diurnal and nocturnal) and painful urination indicates cystitis. The best indication for Kampo medicines is protracted chronic cystitis.

- **Choreito (猪苓湯), Choreitogoshimotsuto (猪苓湯合四物湯):** Heat-treating and fluid disturbance-treating formulae are the first choice.
- **Ryutanshakanto (竜胆瀉肝湯), Gorinsan (五淋散):** Second choice.
- **Others:** If the above prescriptions are ineffective, blood stasis-treating formulae may be effective for patients whose condition is aggravated by coldness, and qi (Ki) deficiency-treating formulae

(*Hokizai*) such as hochuekkito may be helpful if an underlying factor such as qi (Ki) deficiency associated with aging is suspected.

Prostatitis syndrome

Prostatitis syndrome is a number of pathological conditions including prostatitis and similar diseases. Patients may experience various symptoms other than urination disorder, or have indefinite complaints. Kampo medicines are most effective in the chronic cases that are intractable to Western medical treatment.

- **Keishibukuryogan (桂枝茯苓丸):** The most frequent form of prostatitis, intrapelvic venous congestion syndrome, corresponds to blood stasis in Kampo medicine.

Indefinite lower urinary tract complaints

The various lower urinary tract symptoms chiefly comprising indefinite complaints are regarded as a pattern (*Sho*) of indefinite lower urinary tract complaints in Kampo medicine. This pattern covers multiple disease names in Western medicine, such as nervous pollakiuria, bladder neurosis, chronic cystitis, urethritis, and prostatitis. In addition, several pathological conditions are also included that originate in coldness sensitivity and climacteric disorder. Accordingly, under Kampo therapy guidelines, a prescription should be selected that matches to a Kampo pathological condition (the basis of Kampo therapy). The therapeutic goal for indefinite complaints and psychogenic symptoms concerning the lower urinary tract is to improve qi (Ki) abnormalities (qi [Ki] deficiency, qi [Ki] depression, and qi [Ki] counterflow) caused by mental (psychological function and activity) imbalance. Then the practitioner may select the most appropriate qi (Ki) deficiency-treating or qi (Ki)-regulating (*Riki*) formula for the patient's symptoms and pathological condition.

Reference

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Menstruation Disorders – Climacteric Disorders

Takahisa Ushiroyama

Overview of Disease

Menstruation disorders, the common term for menstrual cycle disorders, are caused by pathological conditions of the endocrine environment. In Western medicine, the term refers to functional diseases triggered by organic or functional ovarian abnormality, or functional diencephalic/pituitary abnormality, not including the hemorrhage from the genital tract due to tumor or inflammation. Kampo medicine considers blood stasis (*Oketsu*) the main element of the pathological condition, and deficiency of lower abdominal region（*Jinkyo*） is partly responsible, according to the solid and five viscera (*ZangFu*) doctrine (五臓六腑論). Recently, dieting, unhealthy lifestyle, and excessive stress are suspected to be major factors in many menstruation disorder cases. Blood deficiency (*Kekkyo*), qi (Ki) deficiency (*Kikyo*), deficiency of upper abdominal region (脾胃虚, *Hiikyo*), or qi (Ki) stagnation (*Kitai*) lies at the core of the pathological condition in an increasing number of cases.

Climacteric disorder is, in the narrow definition, the endocrine climacteric disorder termed menopausal disorder. However, the general public is likely to think of climacteric disorders as the psychosomatic disorders that occur over a period of up to 10 years before, then again after, menopause. Therefore, the contemporary treatment of climacteric disorders falls within the scope of holistic medicine. Understanding the pathological condition from a Kampo medicine perspective enables selection of a therapeutic approach in many cases. These pathologies have appeared in all classic texts of Kampo medicine for many centuries, and in Japan have been treated by Kampo therapy as uterine bleeding and autonomic symptoms (*Chinomichisho*).

Climacteric disorders fitting the strict definition, which consist mainly of autonomic imbalance due to short-term abrupt changes in estrogen or pituitary gonadotropin, account for nearly 30% of cases and are generally well treated by hormone replacement therapy. Psychiatric disorders (depression, anxiety disorder, etc.) account for more than 40% of cases, requiring psychoneurotic drugs. The majority of the remainder involve autonomic nerve imbalance induced by psychosocial factors.

Indications for Kampo Therapy

Conditions such as severe ovulation disorder associated with weight loss; menstruation disorder associated with sensitivity to cold; menstruation disorder due to intense psychological stress; and ovulation disorder due to high blood LH level, including polycystic ovary syndrome, poorly respond to Western medications but best respond to Kampo therapy. In particular, unkeito (温経湯) is reported to have a regulatory effect on the pituitary gonadotropin secretory pattern, to stimulate follicle growth and luteal function, and to exert therapeutic effects in all types of menstrual cycle disorder. As mentioned in "*WanBingHuiChun* (万病回春)," the pathological conditions requiring 'menstrual regulation (調経, *Chokei*)' are "mostly diseases of qi (Ki)

excess (*Ki-sakan*) with blood deficiency", so that the therapy for blood or qi (Ki) deficiency is widely used as Kampo therapy for menstrual cycle disorders: Kyukichoketsuindaiichikagen (芎帰調血飲第一加減) is prescribed.

However, weight-gain diets or psychological therapy using behavioral stress management techniques take priority in cases of ovulation disorder caused by weight loss or exposure to excessive stress, respectively.

Kampo medication is the basis of holistic medicine for climacteric disorder. Obtaining a thorough understanding of the patient's social background and personality traits leads to successful outcomes of treatment. Blood stasis is observed in approximately one third, and qi (Ki) counterflow (*Kigyaku*) or qi (Ki) stagnation (*Kitai*) in approximately one quarter of climacteric disorder patients. Hot flashes, headache, heavy headedness, and vertigo/dizziness are various manifestations of qi (Ki), blood and fluid (*Kiketsusui*) pathological conditions. Under Western medical diagnostics, formulating a treatment strategy is difficult because a variety of symptoms are not organ-specific, and occasionally syndrome shift occurs. However, appropriate therapy can be given on the comprehensive diagnosis of various symptoms individually.

Frequent Formulae

Chokiyoketsuto (調気養血湯)* and senkinchokeito (千金調経湯)* were the formulae frequently used for 'menstrual regulation' before modern times. Senkinchokeito* is well known to contain the same crude drugs as unkeito (温経湯). Tsukeishimotsuto (通経四物湯)*, seikeishimotsuto (清経四物湯)*, and akyoshimotsuto (阿膠四物湯)* are unkeitokagen (温経湯加減) containing shimotsuto (四物湯) crude drugs. These formulae contain blood stasis-treating (*Kuoketsu*) crude drugs — including Peach Kernel (桃仁, tonin) and Safflower (紅花, koka) — since tonifying blood (*Hoketsu*), expelling blood (*Kuketsu*), and activating blood (*Kakketsu*) are considered the basic therapeutic approaches. Tokishakuyakusan (当帰芍薬散), keishibukuryogan (桂枝茯苓丸), and rikkunshito (六君子湯) are used very frequently in modern times, as well as unkeito (温経湯) and kyukichoketsuindaiichikagen (芎帰調血飲第一加減)*.

There is a bias among Western medicine specialties as to the most frequent formulae for climacteric disorder.

Gynecologists most frequently prescribe tokishakuyakusan, kamishoyosan, and keishibukuryogan, which account for half of their Kampo prescriptions. Tokishakuyakusan and keishibukuryogan are often used for shoulder stiffness, coldness, hot flashes, and numbness in the extremities, all being among the most frequently occurring symptoms in Japanese patients with climacteric disorder. The terms 'vexing heat in the chest, palms, and soles (五心煩熱, *Goshin Hannetsu*); cloudiness and heaviness in the head and eyes (頭目昏重, *Tomoku Konju*); uneasiness and facial redness (心悸頬赤, *Shinsho Kyoseki*; menstrual imbalance (月水調ワズ, *Gessui Totonowazu*); and ague-like symptoms with chills and fever (寒熱瘧ノ如ク, *Kannetsu Okorinogotoku*),' which appear among the indications for shoyosan (逍遥散)*, refer to symptoms commonly observed in climacteric disorder and suggest the presence of qi (Ki) counterflow and blood stasis.

Saikokeishikankyoto (柴胡桂枝乾姜湯), hangekobokuto (半夏厚朴湯), keishikaryukotsuboreito (桂枝加竜骨牡蛎湯), saikokaryukotsuboreito (柴胡加竜骨牡蛎湯), kamikihito (加味帰脾湯), and yokukansan (抑肝散) are being prescribed more frequently in recent times, reflecting the stressfulness of modern society.

Menstruation Disorders

- **Unkeito (温経湯):** May be used for all types of menstruation disorder and is sometimes offered to women with high blood LH, polycystic ovarian syndrome or luteal dysfunction. Appropriate for deficiency-pattern (*Kyosho*) patients who present with blood stasis signs including lower abdominal tenderness, as well as upper-body heat sensation and lip dryness.
- **Kyukichoketsuin daiichikagen (芎帰調血飲第一加減)***: Patients have dual deficiency of qi (Ki) and blood (*KiKetsu Ryokyo*) and complain of proneness to fatigue.
- **Tokishakuyakusan (当帰芍薬散):** Used in patients who have blood deficiency and fluid retention, as shown by anemia and edema.
- **Keishibukuryogan (桂枝茯苓丸):** Used for upper heat lower cold (*Hienobose*), in addition to lower abdominal tenderness associated with blood stasis.
- **Rikkunshito (六君子湯):** Offered to patients having decreased appetite, with an abdominal pattern of epigastric discomfort (*Shinka Hi*) and splashing sound (*Shinsuion*).
- **Kamishoyosan (加味逍遥散):** Appropriate for patients with qi (Ki) counterflow and blood stasis who have hypochondriac tendency (including palpitation) as well as coldness in the lower body.
- **Tokakujokito (桃核承気湯):** Effective for excess-pattern patients with constipation and intense psychoneurotic symptoms such as irritability, who are characterized by an abdominal pattern of chafing pain in the left lower abdomen (resistance and sharp tenderness in the left iliac region [*Shofuku Kyuketsu*]).
- **Shimotsuto (四物湯):** A basic formula for blood deficiency. May be sometimes combined with kamishoyosan.
- **Tokishigyakukagoshuyushokyoto (当帰四逆加呉茱萸生姜湯):** Good for patients with chilblains and intense coldness in the upper and lower limbs.
- **Kyukikyogaito (芎帰膠艾湯):** Used in deficiency-pattern patients in expectation of hemostatic potential. Very effective for anovulatory cycle.

Climacteric Disorders

- **Kamishoyosan (加味逍遥散):** Widely prescribed for climacteric disorders. The first choice for patients with pathological conditions mainly comprising qi (Ki) counterflow and blood stasis, and various complaints including irritability, insomnia, shoulder stiffness, and palpitations.
- **Keishibukuryogan (桂枝茯苓丸):** Appropriate for pathological conditions (including hot flashes) associated with blood stasis in excess-pattern patients. Also effective for deficiency-pattern patients as well, because this formula warms the lower body.
- **Tsudosan (通導散):** Used for psychoneurotic symptoms including irritability caused by qi (Ki) stagnation, as well as facial redness due to blood stasis in patients with rather high blood pressure and constipation tendency.
- **Tokishakuyakusan (当帰芍薬散):** Useful for fluid disturbance (*Suidoku*) associated with blood stasis in deficiency-pattern patients who have coldness in limbs, dizziness, and palpitations.
- **Unseiin (温清飲):** A typical formula for blood deficiency/blood heat pattern patients who have hot flashes and coldness, and may complain of headache. Their climacteric disorder is associated with

high blood pressure and not well treated with Western medicines.

- **Keishikaryukotsuboreito (桂枝加竜骨牡蛎湯):** Offered to patients with insomnia, oversensitivity, palpitations, and nervous imbalance, in addition to hair loss due to deficiency of lower abdominal region (*Jinkyo*).
- **Saikokaryukotsuboreito (柴胡加竜骨牡蛎湯):** Appropriate for patients with qi (Ki) stagnation and deficiency of upper abdominal region qi (Ki) (脾気虚, *Hikikyo*) who have psychoneurotic symptoms, including depression/anxiety complaints and insomnia tendency.
- **Hangekobokuto (半夏厚朴湯):** Effective for anxiety and depression due to qi (Ki) stagnation. This qi (Ki)-regulating formula (理気薬, *Rikiyaku*) is offered to patients with foreign-body sensation in the throat (*Inchu Sharen*) as well as palpitations and vertigo.

* Not available as ethical Kampo extract formulation

Edema

Kako Watanabe

Overview of Disease

Edema is a condition in which increased volume of body fluid and its abnormal distribution abnormally increase interstitial fluid. Various diseases cause edema, which can be divided into localized and generalized edema.

Localized edema is either unilateral or confined to a specific region. The ethiology is categorized as lymphatic, venoocclusive, allergic, inflammatory, or angioneurotic, including deep vein thrombosis, thrombophlebitis, varix, cellulitis, and lymphedema following surgery or radiotherapy.

Generalized edema is often found bilaterally. In mild cases, edema is readily found in the pretibial region, lateral malleolus, dorsum of the foot, upper eyelids, etc. In severe cases, edema appears as an abrupt increase in body weight gain, ascites fluid, and pleural effusion. It is categorized as renal, hepatic, cardiac, endocrine, dystrophic, gestational, or idiopathic. The primary diseases include nephrosis, kidney failure, acute glomerulonephritis, liver cirrhosis, congestive heart failure, hypothyroidism, hyperthyroidism, gestosis and idiopathic edema. Other cases include edema associated with pre-menstrual syndrome (PMS) and edema due to steroids or non-steroidal anti-inflammatory drugs (NSAIDs); enhanced activity of the renin-angiotensin-aldosterone system after long-term use of diuretics or laxatives, or repetitive intentional vomiting; pseudoaldosteronism as an adverse effect of Kampo medicines (Glycyrrhiza [甘草, kanzo]); maintaining the same posture for long periods; and lack of exercise. Edema is commonly induced by drugs and lifestyle.

Treatment consists of treating the primary disease and providing symptomatic therapy for edema, including rest, sodium restriction, fluid restriction, physiotherapy, and diuretics.

From the Kampo medicine perspective, edema is perceived as a fluid disturbance (*Suidoku*), involving generalized or localized retention of water (水), or fluid, other than blood. Symptoms specific to fluid disturbance are not only edema, but also dizziness, dizziness on standing up, headache, heavy headedness, tinnitus, watery nasal discharge, sputum, palpitation, thirst, feeling of sickness, nausea, abdominal rumbling, abdominal distension, diarrhea, coldness, arthralgia, and travel sickness. These symptoms are characteristically aggravated on rainy days, and by the approach of low-pressure systems or cold weather. Owing to water's cooling property, patients often complain of coldness symptoms such as cold sensation in the edema region.

Indications for Kampo Therapy

If an organic disease is present, treatment of that disease is preceded. Kampo therapy is considered helpful when the underlying disease is not known, the edema does not resolve despite the disease having been treated, or the swelling sensation is strong despite no edema being found by examination or abnormality being found in tests.

Kampo therapy focuses on fluid disturbance-treating (*Risui*) formulae, which regulate fluid distribution in the body. Fluid disturbance-treating formulae do not simply increase the excretion of urine, but are considered to correct uneven distribution of water in the body by regulating fluid through sweating as well as in the airway and digestive tract. Most diuretic formulations contain crude drugs such as Poria Sclerotium (茯苓, bukuryo), rhizomes of Atractylodes spp. (朮, jutsu), Alisma Rhizome (沢瀉, takusha), Polyporus Sclerotium (猪苓, chorei), Ephedra Herb (麻黄, mao), Akebia Stem (木通, mokutsu), Sinomenium Stem and Rhizome (防已, boi), Astragalus Root (黄耆, ogi), Pinellia Tuber (半夏, hange), Ginger (生姜, shokyo), Apricot Kernel (杏仁, kyonin), Asiasarum Root (細辛, saishin), Euodia Fruit (呉茱萸, goshuyu), and Processed Aconite Root (附子, bushi).

Many of the underlying diseases that cause edema have a long course of illness, as seen in chronic nephritis, chronic hepatitis, and autoimmune diseases as well as in cases of long-term steroid use. Therefore, in addition to fluid disturbance-treating formulae alone, blood stasis-treating (*Kuoketsu*) formulae (such as tokishakuyakusan [当帰芍薬散] and keishibukuryogan [桂枝茯苓丸]) and deficiency pattern-treating formulae (*Hozai*) (such as hochuekkito [補中益気湯], juzentaihoto [十全大補湯], hachimijiogan [八味地黄丸] and goshajinkigan [牛車腎気丸]) are often used either singly or in combination with fluid disturbance-treating formulae.

Treating edema such as postoperative lymphedema is frequently challenging, but there are reports that shinkoto (神効湯)* is effective in cases of repeated lymphangitis due to lower-limb lymphedema following radiotherapy or after uterine cancer surgery. Kampo medicines may be effective in some cases of edema intractable to modern medical therapy.

While selection of formulae is made on the principle of sho (pattern)-based therapy, they are often prescribed in clinical practice today, based on pharmacological knowledge.

Frequent Formulae

- **Goreisan (五苓散):** The first choice for edema and a typical fluid disturbance-treating formulae. Used for nephrosis and other renal diseases as well as nausea-associated headache, dizziness, and diarrhea in patients with thirst and reduced urine volume.
- **Saireito (柴苓湯)**: Widely used for renal diseases including chronic nephritis, nephrosis syndrome, and diabetic nephropathy as well as edema due to various causes. Originally this formula was used during hot weather when patients have thirst and reduced urine volume, but now is frequently used to alleviate adverse effects of steroids.
- **Choreito (猪苓湯)**: Frequently used for edema in the lower body associated with cystitis and other urological diseases, and symptoms including residual urine sensation, micturition pain, and hematuria. Widely used, except for extreme deficiency pattern (*Kyosho*) patients.
- **Ryokeijutsukanto (苓桂朮甘湯)**: Used for edema associated with palpitation, dizziness, dizziness on standing up, hot flashes, etc. Also frequently used for Meniere's disease (which results from fluid disturbance) and orthostatic dysregulation.
- **Boiogito (防已黄耆湯):** Used for edema associated with excessive sweating, coldness, reduced urine volume, arthralgia, and proneness to fatigue mainly in patients with soft subcutaneous fat and weak muscle tension, or the so-called flabby body type. Also effective for edema localized to the knee joint with osteoarthritis.
- **Shoseiryuto (小青竜湯):** A formula that corrects uneven distribution of water into the airway. Frequently used for asthma and allergic rhinitis. Also effective for facial edema due to cough or edema associated with headache, fever, chill, cough, and other symptoms in patients who have relatively strong stomach and intestines.
- **Shimbuto (真武湯):** Used for deficiency pattern edema associated with diarrhea, dizziness, sensation of shakiness, general malaise, and palpitation in patients having poor complexion and general coldness.
- **Hachimijiogan (八味地黄丸) and Goshajinkigan (牛車腎気丸):** Used for edema associated with urination disorder; coldness, numbness, and pain in the legs and low back; dysopia; and hearing impairment. Often effective for edema in lower limbs in patients with chronic disease and elderly people with deficiency of lower abdominal region (*Jinkyo*).
- **Inchinkoto (茵蔯蒿湯):** Well known as a jaundice medicament, but also has a diuretic effect. Used for edema with constipation, decreased urine volume (*Nyori Gensho*), and feeling of fullness in the epigastrium.
- **Inchingoreisan (茵蔯五苓散):** Used for post-radiotherapy regional edema as well as cirrhosis and nephrosis in patients with severely decreased urine volume and absence of constipation.
- **Keishibukuryogan (桂枝茯苓丸):** A typical, blood stasis-treating formula used for headache, shoulder stiffness, and hot flashes, but also improves edema by improving blood flow and eliminating excess fluid.
- **Tokishakuyakusan (当帰芍薬散):** Used for illness associated with coldness, heavy headedness, dizziness, and anemia. Has both diuretic and blood deficiency-treating (*Hoketsu*) effects and is

therefore effective for gestational edema, chronic nephritis, and nephrosis as well.

- **Hangekobokuto (半夏厚朴湯)**: Frequently used as a qi (Ki) depression-treating formula (*Kizai*), but in classical terms also has a diuretic effect. Patients have frequent complaints such as abdominal distension, anxiety, and foreign body sensation in the throat (*Inchu Sharen*).

* Not available as ethical Kampo extract formulation

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Arthralgia – Neuralgia

Toshiaki Kogure

Overview of Disease

Pain is generally classified as acute pain or chronic pain. Kampo therapy is principally used for chronic pain. Chronic pain is defined as pain that persists or recurs repeatedly for six months or more, has no clear correlation between the impairment degree and pain intensity, and has lost the alarm function that alerts tissue damage to the body. It is known that when inflammation in rheumatoid arthritis (RA) is not controlled and the pain becomes prolonged, a range of psychosocial factors arise and are involved in the pain. This pain complex is also considered as chronic pain.

Chronic nerve and joint pains are induced by a variety of factors including inflammation, ischemia, and post-traumatic or degenerative changes. Occasionally chronic pain may be experienced in a form of fibromyalgia (syndrome) of unknown causes. Before start of treatment, it is essential to gain a clear understanding of the etiology through clinical symptoms, hematological and serological findings, and diagnostic imaging.

Indications for Kampo Therapy

Kampo medicines are appropriate for simple low back pain, shoulder-arm-neck syndrome, osteoarthritis, RA and other nociceptive pain, postherpetic neuralgia, thalamic pain, and neuropathic pain, in addition to psychogenic pain.

For low back pain (of various causes), shoulder-arm-neck syndrome, and osteoarthritis, non-steroidal anti-inflammatory drugs (NSAIDs) and peripheral circulation improvement agents such as limaprost alfadex,

and vitamin E formulations may be tried in addition to physiotherapy. Surgical treatment may be required on occasion, but Kampo medicines are a therapy available throughout the course of the condition. In RA cases, if thorough understanding of disease activity cannot be obtained to control the inflammation, therapy including biological drugs may be needed. However, some patients respond to Kampo medicines. Especially for elderly patients and patients with tuberculosis history, liver and kidney damage, or interstitial pneumonia, the use of Kampo medicines can be recommended. Fybromyalgia is treated with salazosulfapyridine, gabapentine, or antianxiety drugs, according to the cluster classification, but Kampo medicines may be appropriate for all clusters.

Postherpetic neuralgia and idiopathic trigeminal neuralgia are both indications for Western medical therapy as well as Kampo medicines. For central neuralgia which is intractable, Kampo medicines may be tried to alleviate symptoms and improve the general condition.

Frequent Formulae

Arthralgia

The section on frequent formulae is divided here into arthralgia and neuralgia. In Kampo medicine terms, however, both arthralgia and neuralgia occur on external (*Hyo*) lesion sites. Accordingly, some of the appropriate Kampo prescriptions overlap. Yet, from the Western medical perspective, arthralgia is involved in a wide variety of pathologic conditions, from inflammatory diseases originating in the autoimmune mechanism such as RA, to diseases related with degenerative changes such as osteoarthritis. It is important to consider both the underlying pathologic condition and traditional medical approaches.

- **Eppikajutsuto (越婢加朮湯):** Used for severe arthralgia associated with joint swelling in Yo pattern (陽証, *Yosho*) patients with fluid retention (*Suitai*). For postherpetic neuralgia, administration in the stage when vesicles may or may not be appearing can relieve the pain after recovery from herpes zoster.
- **Makyoyokukanto (麻杏薏甘湯):**. Used for diverse arthralgia and neuralgia in patients with both skin dryness and blood deficiency (*Kekkyo*). As RA is referred to as morning stiffness, the pain intensifies in the early morning, but may worsen in the evening. This formula is offered to such RA patients.
- **Boiogito (防已黄耆湯):** Effective for osteoarthritis of the knee with joint swelling. According to qi (Ki), blood, and fluid (*Kiketsusui*) theory, joint swelling is considered as fluid retention. To improve fluid retention, this formula is in clinical use. An abdominal examination finding of middle-aged overweight indicates administration of this formula.
- **Yokuininto (薏苡仁湯):** Used for arthralgia and myalgia associated with heat sensation palpable in the painful part in patients having very slight coldness. Often effective for chronic osteoarthritis pain. May be helpful for RA patients who have somewhat advanced joint deformation but maintain activity of daily living.
- **Keishikajutsubuto (桂枝加朮附湯):** Appropriate for neuralgia and arthralgia aggravated by

coldness in patients with Yin pattern (陰証, *Yinsho*) associated with fluid retention.

- **Keishinieppiittokaryojutsubu (桂枝二越婢一湯加苓朮附)***: Often used for RA. Commonly used with addition of Sinomenium Stem and Rhizome (防已, boi) and Astragalus Root (黄耆, ogi).
- **Keishishakuyakuchimoto (桂枝芍薬知母湯):** Patients have Yin pattern constitution with deficiency pattern (*Kyosho*) pathologic condition. Effective for severe degeneration and intense pain in RA patients.
- **Daibofuto (大防風湯):** Used for dual deficiency of qi (Ki) and blood (*Kiketsu Ryokyo*) condition in patients with RA. Is similar to keishishakuyakuchimoto (桂枝芍薬知母湯), but the dual deficiency of qi (Ki) and blood condition is more prominent.
- **Ryokyojutsukanto (苓姜朮甘湯):** Offered to Yin pattern patients with deficiency pattern, especially those who have coldness in the lower body or complain of heavy low back pain. Helpful for patients who have a pathologic condition of fluid retention and complain of lower limb swelling in the evening, etc.
- **Hachimijiogan (八味地黄丸):** Administered to Yin pattern patients with deficiency pattern, especially targeting low back pain, lower limb numbness, coldness, and nocturia in elderly patients. For the same symptoms with edema tendency, goshajinkigan (牛車腎気丸) is better.
- **Tokishigyakukagoshuyushokyoto (当帰四逆加呉茱萸生姜湯):** Effective for patients who complain of coldness in the limbs with chronic low back pain. History of frostbitten fingers is also an indication. May be effective for patients with a subjective symptom of chronic headache.
- **Nijutsuto (二朮湯):** Widely used for shoulder and upper arm pain (frozen shoulder). Particularly effective for fluid retention signs with shoulder pain. Ephedra Herb (麻黄, mao) is added for Yo pattern patients, and Processed Aconite Root (附子, bushi) for Yin pattern patients.

Neuralgia

Yin and Yo (*Yinyo*) differentiation is important in the treatment of neuralgia. Most of the neuralgia patients who receive Kampo therapy have chronic pain, and include those who complain of pain over a long period. Among such patients, there are those who have Yo pattern (*Yosho*). These patients must be examined very carefully.

- **Kakkonto (葛根湯)**: Used in the early stages of peripheral neuralgia. Often patients have also stiffness in the posterior region of the neck.
- **Uyakujunkisan (鳥薬順気散)*:** Used for Yo pattern neuralgia, particularly effective in cases associated with qi (Ki) depression (*Kiutsu*).
- **Sokeikakketsuto (疎経活血湯):** Used for blood stasis (*Oketsu*) in Yo pattern patients. Commonly effective for lower limb pain and sciatica in particular.
- **Goreisan (五苓散):** Used for various forms of peripheral neuralgia. Considered a good formula for patients having pain with thirst, excessive sweating, and reduced urine volume.
- **Saireito (柴苓湯):** Appropriate for patients with the same findings as seen for goreisan (五苓散). The presence of hypochondrium resistance and discomfort (*Kyokyo Kuman*) in the abdominal pattern suggests the use of this formula.
- **Tokito (当帰湯):** Formula for deficiency pattern patients in TaiYin stage (*Taiyinbyo*). Frequently

effective for intercostal neuralgia in patients with both qi (Ki) deficiency (*Kikyo*) and blood deficiency.

- **Shozokumeito (小続命湯)*:** Used for Yin pattern neuralgia. Also effective for central neuralgia after cerebral infarction.
- **Bushito (附子湯)*:** Offered to patients with ShoYin stage (*Shoyobyo*) deficiency pattern who have fluid retention. Helpful for a complaint of coldness in the back.

* Not available as ethical Kampo extract formulation

Sensory Impairment – Motor Paralysis Involuntary Movement

Yutaka Shimada

Overview of Disease

The origins of sensory impairment, motor paralysis, and involuntary movement are diverse. These symptoms of nerve and muscle diseases may be found in all parts of the body, including the central and peripheral nerves, and muscles. Pathogenesis is also diverse, ranging from vascular disorder and degenerative, demyelinating, metabolic, and toxic diseases to trauma, tumor, and infection. These diseases are roughly classified into acute, sub-acute, and chronic phases, according to the period since onset; or may be progressive or recurrent.

Indications for Kampo Therapy

Since the effectiveness of Kampo therapy for sensory impairment and motor paralysis is determined by the primary disease, it is not possible to generalize about indications. However, when an effective Western medical therapeutic approach is available, it takes precedence. When there is not, Kampo therapy may be considered. Kampo therapy today is often used in the chronic phase.

Involuntary movement is classified into various types and the causes of the disease may differ; however, Kampo therapy is chiefly applied to trembling and tics, which have a strong psychogenetic element. Muscle spasm is an extremely good target for Kampo therapy. Epilepsy is mainly treated with Western therapies.

Frequent Formulae

Sensory Impairment and Motor Paralysis

The causes of sensory impairment and motor paralysis are regarded as external pathogens including wind, cold (*Kan*), dampness (*Shitsu*), and fire or heat (*Netsu*). From the qi (Ki), blood, and fluid (*Kiketsusui*) perspective, blood deficiency (*Kekkyo*) and blood stasis (*Oketsu*), qi (Ki) deficiency (*Kikyo*) and qi (Ki) stagnation (*Kitai*), and fluid retention (*Suitai*), or fluid disturbance (*Suidoku*), are important factors.

- **Keishikajutsubuto (桂枝加朮附湯):** Widely used for numbness and paralysis in deficiency pattern (*Kyosho*) patients with coldness (*Hie*). Rhizomes of Atractylodes spp. (朮, jutsu) with an effect treating fluid disturbance (*Risui*) and strongly warming (大熱, dainetsu) Processed Aconite Root (附子, bushi) are added to keishito (桂枝湯).
- **Keishikaryojutsubuto (桂枝加苓朮附湯)**: Poria Sclerotium (茯苓, bukuryo) with an effect treating fluid disturbance is added to keishikajutsubuto (桂枝加朮附湯), which further enhances the effect on dampness, or fluid disturbance.
- **Hachimijiogan (八味地黄丸)**: Appropriate for numbness and weakness in the low back and lower limbs in middle-aged and older patients, especially elderly patients, who are also likely to have fatigue, malaise, urination disorder, and weakness of the lower abdominal region (*Shofuku Fujin*). Hachimijiogan is a typical deficiency of lower abdominal region (*Jinkyo*) prescription, containing the warmth and heat crude drugs Cinnamon Twig (桂枝, keishi) and Processed Aconite Root (附子, bushi). This prescription is used for people with coldness in the upper and lower limbs, and can also be used in those with burning sensation.
- **Goshajinkigan (牛車腎気丸):** A prescription consisting of Achyranthes Root (牛膝, goshitsu) and Plantago Seed (車前子, shazenshi) added to hachimijiogan (八味地黄丸). Used for relatively strong numbness and pain in hachimijiogan (八味地黄丸)-pattern (*Hachimijiogansho*) patients with edema tendency.
- **Rokumigan (六味丸):** A prescription for which Cinnamon Twig and Processed Aconite Root are removed from hachimijiogan (八味地黄丸). Used for burning sensation in the upper and lower limbs in hachimijiogan-pattern patients.
- **Shimbuto (真武湯):** Used in deficiency-pattern patients who are sensitive to coldness (*Hiesho*), gastrointestinal weakness, diarrhea tendency, and strong malaise, associated with motor paralysis and sensory impairment. A Processed Aconite Root -containing formulation.
- **Ryokyojutsukanto (苓姜朮甘湯):** Appropriate for coldness and weakness from the low back to the lower limbs in deficiency pattern patients who have frequent urination tendency.
- **Kakkonto (葛根湯):** Used for abnormal skin sensation associated with common cold -like symptoms.
- **Goreisan (五苓散):** A typical fluid retention prescription. Also used for pathologic conditions including acute-phase neurological disorders in which localized edema may be assumed.
- **Tokishigyakukagoshuyushokyoto (当帰四逆加呉茱萸生姜湯):** Effective for numbness and paralysis in deficiency pattern patients who have remarkable coldness of the limbs.
- **Tokishakuyakusan (当帰芍薬散):** Used for limb numbness and weakness in deficiency pattern

patients who have anemia and swelling tendency. Patients also have blood deficiency, blood stasis, and water retention.

- **Keishibukuryogan (桂枝茯苓丸):** Used in middle or excess pattern patients who have hot flashes and facial redness tendency with signs of blood stasis, such as resistance and tenderness in the lower abdomen, as well as numbness of the limbs.
- **Tokakujokito (桃核承気湯):** Used for numbness of the limbs in excess pattern patients who have hot flash tendency with signs of blood stasis — such as resistance and tenderness in the left lower abdomen (*Shofuku Kyuketsu*) — and constipation.
- **Sokeikakketsuto (疎経活血湯):** Appropriate for numbness and paralysis of the limbs in middle pattern patients who either have no or only slight coldness. Patients also have signs of blood stasis, blood deficiency, and fluid retention.
- **Kamishoyosan (加味逍遥散):** Used in comparatively stronger deficiency pattern patients who have psychoneurotic symptoms (such as anxiety and irritability), and diverse autonomic nervous symptoms (such as episodic sweating and sensation of warmth), but complain of crawling, itchy and ticklish sensation in the skin.
- **Hochuekkito (補中益気湯):** Used for deficiency pattern patients who have motor paralysis, limb weakness, and proneness to fatigue, but have no appetite. A typical qi (Ki) deficiency prescription.
- **Juzentaihoto 十全大補湯):** Used for numbness, motor paralysis and weakness of the limbs in deficiency pattern patients who are prone to fatigue and have no appetite. A representative prescription in the coexistence of qi (Ki) deficiency and blood deficiency.
- **Daibofuto (大防風湯):** Used for motor paralysis, cramp, and numbness of the limbs in deficiency pattern patients who are sensitive to coldness. Patients also have signs of blood deficiency, qi (Ki) deficiency, and fluid retention. A Processed Aconite Root -containing formula (*Bushizai*).
- **Goshakusan (五積散):** Patients have upper heat and lower cold tendency. Used for numbness and paralysis in patients affected by coldness or dampness.
- **Unkeito (温経湯):** Used for burning sensation (*Hoteri*) in the palms in deficiency pattern patients with lip dryness, irregular menstruation, and pain in the lower abdomen.
- **Shokenchuto (小建中湯):** Used for *Hoteri* in the upper and lower limbs in deficiency pattern patients who are prone to fatigue with abdominal weakness and strong rectus abdominis muscle tension (*Kokyu*).
- **Sammotsuogonto (三物黄芩湯):** Used for patients who complain of heat and *Hoteri* in the limbs.
- **Shosaikoto (小柴胡湯):** Used for heat and *Hoteri* in the limbs in middle pattern patients who have hypochondrium resistance and discomfort (*Kyokyo Kuman*).
- **Orengedokuto (黄連解毒湯):** Used for sensory impairment such as numbness in the upper and lower limbs in excess pattern patients who have sensitivity to heat, hot flash, facial flushing, and nervous imbalance tendencies.
- **San'oshashinto (三黄瀉心湯):** Used in excess pattern patients with constipation who are irritable, cannot settle down, and complain of hot flashes, facial flushing, dizziness, and heavy headedness as well as sensory impairment (such as numbness of the upper and lower limbs).

Involuntary Movement

Muscle spasm is regarded as a symptom of blood deficiency and prescriptions are used which contains Peony Root (芍薬, shakuyaku) as the main ingredient, such as shakuyakukanzoto (芍薬甘草湯). There is an close relation between the muscles and liver and the spasms seen in epilepsy and the like are considered to be induced by liver abnormality; therefore, Bupleurum Root (柴胡, saiko)-containing formula and those containing Uncaria Hook (釣藤鈎, chotoko) are mainly used.

- **Shakuyakukanzoto (芍薬甘草湯):** Used for painful muscle spasm such as cramp in the leg. Addition of Processed Aconite Root (附子, bushi) to shakuyakukanzoto — shakuyakukanzobushito (芍薬甘草附子湯) — may be effective in patients with strong coldness and pain.
- **Yokukansan (抑肝散):** Used for involuntary movement such as epilepsy; epilepsy-like spasms; childhood febrile convulsion; eyelid, face and limb muscle cramp and spasm; and tremor and tics. Typical patients are oversensitive and short-tempered with irritability tendency. Yokukansankachimpihange (抑肝散加陳皮半夏) is effective for patients with gastrointestinal weakness and strongly palpable pulsation of the abdominal aorta (palpable pulsation in the supraumblical region [*Saijo Ki*]). Also effective for patients with intense muscle rigidity as seen in Parkinson's disease and Parkinsonian syndrome.
- **Saikokeishito (柴胡桂枝湯):** Appropriate for spasm observed in epilepsy and various involuntary movements. Typical patients have moderate deficiency pattern, with weak abdominal strength, *Kyokyo Kuman*, and *Saijo Ki*.
- **Chotosan (釣藤散):** Can be expected to improve microcirculatory disorder because containing Uncaria Hook that is effective for spasm. Used for vascular parkinsonism in relatively older patients with slight tremor and rigidity.
- **Keishikaryukotsuboreito (桂枝加竜骨牡蛎湯):** Used for spasm and tics aggravated by mental stress in deficiency-pattern patients with weak abdominal strength and strong *Saijo Ki*.
- **Saikokaryukotsuboreito (柴胡加竜骨牡蛎湯):** Used for epileptic seizures and involuntary movement in moderate excess pattern patients, with psychoneurotic symptoms (including anxiety and irritation), abdominal strength (that is intermediate or stronger), *Kyokyo Kuman*, and *Saijo Ki*.
- **Kambakutaisoto (甘麦大棗湯):** A prescription for hysteria attacks in women. Used for similar involuntary movement including spasms and tics.

Eczema – Urticaria – Pruritus

Masaru Natsuaki

Overview of Disease

Eczema

Precisely eczema is the general name for a group of diseases called 'the eczema/dermatitis group.' Clinically, it is associated with itchy sensation and emerges in various forms of exanthema, including erythema, papules, vesicles, pustules, erosion, crust, scale, and lichenification, and in various types of diseases, including contact dermatitis, seborrheic dermatitis, atopic dermatitis, nummular eczema, asteatotic dermatitis, stasis dermatitis, etc.

Urticaria

Urticaria (hives) is transiently developing wheal or erythema by activation of dermal mast cells, and is associated with severe itching. Individual exanthemas disappear within one to 24 hours. The causes include food, pathogenic microbes, and physical irritation. In most chronic cases, the triggers are mental stress and fatigue.

Pruritus

Pruritus is a condition with no eruption but associated with only itchy sensation. However, it may be associated with eczematous lesions due to intense scratching. Senile pruritus is common due to aging-related impaired skin function, but may reflect internal organ disease. Therefore, attention must be paid to diabetes, liver and kidney dysfunction, internal malignancy, etc.

Indications for Kampo Therapy

In every case, first the causes of the disease must be identified, then avoided and eliminated. In Western medicine, the basic treatments are the use of anti-histamines for itching and topical steroids for inflammation control. External antifungal medications are appropriate for seborrheic dermatitis and external tacrolimus medications for atopic dermatitis.

However, cases in which the cause is not identified, standard treatment is resisted, and the condition become chronic and intractable are targets for Kampo therapy. The approach to selection of formulae should not rely on deficiency or excess of physical strength, but rather focus on therapy for improvement of symptoms (*Hyochi*) by assessment of the symptoms (exanthema) appearing on the skin as the local pattern (*Sho*). Depending on the symptoms, two kinds of formulae are used concomitantly (combined formula). Then, the individual patient's constitution is determined as a general pattern and the patient's constitution (*Honchi*) is improved. Impaired autonomic nervous system and infection defense mechanism, regarded as qi (Ki)

deficiency (*Kikyo*), are treated with qi (Ki) deficiency-treating (*Hoki*) formulae, whereas blood deficiency-treating (*Hoketsu*) formulae and cold-dispelling (*Kyokan*) formulae are selected for blood deficiency (*Kekkyo*) and cold pattern (*Kansho*) constitutions. In cases in which symptoms do not improve with Kampo medicines alone, appropriate combined use of anti-histamines and topical steroids is preferable.

Frequent Formulae

Eczema

- **Byakkokaninjinto (白虎加人参湯):** Often used for facial erythema in atopic dermatitis associated with hot sensation (hot flush).
- **Orengedokuto (黄連解毒湯):** Appropriate for patients having erythema with severe itching and heat sensation.
- **Jumihaidokuto (十味敗毒湯):** Used for papules, pustules, etc. Also good for acne and folliculitis.
- **Eppikajutsuto (越婢加朮湯):** Effective for exanthema with exudative tendency, associated with erythema and vesicles.
- **Shofusan (消風散):** Used for erythema, vesicles, exudate, crust, scale, and skin dryness.
- **Keishibukuryogan (桂枝茯苓丸):** A typical blood stasis-treating formula, used for shoulder stiffness, coldness in the limbs, and irregular menstruation. Particularly effective for patients suffering from chronic exanthema with intense lichenification or pigmentation.
- **Tokakujokito (桃核承気湯):** Useful for patients with blood stasis (*Oketsu*) who have constipation, irregular menstruation or mental anxiety.
- **Hochuekkito (補中益気湯):** A typical qi (Ki) deficiency-treating formula (*Hokizai*) used to improve qi (Ki) deficiency constitution. The long-term oral use for atopic dermatitis can be expected to effectively reduce the amount of topical steroid.
- **Juzentaiho (十全大補湯):** Used to improve both qi (Ki) deficiency and blood deficiency constitutions, as well as loss of vigor, coldness in the limbs, and skin dryness.
- **Saikoseikanto (柴胡清肝湯):** Effective for chronic eczematous lesions in children who are prone to tonsillitis or lymphadenitis.
- **Ogikenchuto (黄耆建中湯):** Used to improve constitution in nervous infants and children with repetitive infection
- **Goreisan (五苓散):** Used for patients who have local exudate with general thirst, reduced urine volume, and edema tendency.

Urticaria

- **Makyokansekito (麻杏甘石湯):** Used for improvement of symptoms in acute urticaria.
- **Inchingoreisan (茵蔯五苓散):** Effective for urticaria with severe edema tendency in patients having thirst and reduced urine volume.
- **Maobushisaishinto (麻黄附子細辛湯):** First choice for cold urticaria.
- **Saikokaryukotsuboreito (柴胡加竜骨牡蛎湯):** Appropriate for patients with qi (Ki) stagnation

(*Kitai*) symptoms including insomnia and irritability.

Pruritus

- **Tokiinshi (当帰飲子):** First choice for senile pruritus. Appropriate for patients who have slight skin dryness and pruritus with poor inflammation findings (erythema or papules).
- **Goshajinkigan (牛車腎気丸):** Offered to elderly patients with proneness to cold in the lower body and lower abdominal weakness (weakness of the lower abdominal region [*Shofuku Fujin*]). Most appropriate for patients having diabetes-associated lower limb numbness and itching.
- **Orengedokuto (黄連解毒湯):** Sometimes used successfully for pruritus with underlying disease such as renal failure.

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Fatigue - Malaise

Shinji Nishida

Overview of Disease

The origins of fatigue and malaise are very diverse. Acute diseases involve infection, dehydration, and electrolyte abnormality. Chronic diseases involve organic pathologic changes as seen in visceral diseases（affecting the kidneys and liver, and the respiratory, endocrine and cardiovascular systems) as well as blood disease, malignant tumor, collagen disease, chronic inflammatory disease, and neuromuscular disease. Chronic diseases also comprise mood disorders (such as depression), and psychiatric disorders (such as anxiety disorder). However, there are many pathologic conditions (i.e. psychosomatic diseases) in which psychiatric and physical symptoms appear together and affect each other.

Recently a relevant concept of functional somatic syndrome (FSS) has been proposed. FSS is defined as ‘pathologic conditions in which the existence of organic diseases cannot be explained in specific terms, despite appropriate testing and examination.’ The chief symptoms include fatigue, pain (headache, joint pain, and muscle pain), palpitation, dizziness, and digestive symptoms. FSS covers irritable bowel syndrome,

dysmenorrhea, fibromyalgia, jaw arthropathy, multiple chemical sensitivity, tension-type headache, and chronic fatigue syndrome. FSS is also associated with a high incidence of psychoneurotic symptoms such as depression and anxiety. Many sufferers have complex psychosocial backgrounds, and find it difficult to build a satisfactory doctor-patient relationship. In many patients, FSS must be treated as psychosomatic diseases.

In patients who complain of chronic fatigue and malaise, it is therefore important not only to exclude organic disease, but also to take a dual approach to both the psychological and physical aspects.

Indications for Kampo Therapy

Kampo therapy is appropriate for people suffering chronic fatigue or malaise if no organic disease has been found. This is the disease group that is equal to FSS. Of those, the typical disease is chronic fatigue syndrome, for which the recommended therapies are pharmacotherapy with vitamin C, melatonin, and antidepressants, and nondrug therapy such as cognitive behavior therapy. Deficiency pattern-treating formulae (*Hozai*) such as hochuekkito (補中益気湯) and juzentaihoto (十全大補湯) are also considered effective.

In diseases that cause fatigue, there are not only the pathologic conditions of qi (Ki) deficiency (*Kikyo*) and blood deficiency (*Kekkyo*) that require deficiency pattern-treating formulae, but often other conditions of qi (Ki) depression (*Kiutsu*) and qi (Ki) counterflow (*Kigyaku*) as well.

On actual differentiation of diseases, patients with depression or irritability as well as fatigue may generally be considered to have qi (Ki) depression, while those who complain of fatigue alone rather than psychoneurotic symptoms may mostly be considered with qi (Ki) deficiency. A point to note on differentiation is that qi (Ki) depression often worsens during the morning and at the start of the week, whereas qi (Ki) deficiency commonly aggravates in the afternoon and at the end of the week.

In the treatment of qi (Ki) depression, antidepressants, tranquilizers, and the like as well as Kampo medicines do exhibit certain efficacy. There are no therapeutic drugs in Western medicine for qi (Ki) deficiency, which is a good target for Kampo therapy.

Frequent Formulae

Irritability or Depression-associated Fatigue and Malaise

- **Daisaikoto (大柴胡湯):** Patients have plump features. They appear to feel impatient but complain of their symptoms in a modest manner. Their complaints are mostly physical symptoms (malaise, shoulder stiffness, stomach pain, abdominal pain, constipation, etc.). Patients answer questions about psychoneurotic symptoms if asked, but relatively few patients regard psychoneurotic symptoms as their chief complaint. The abdominal pattern comprises extremely strong hypochondrium resistance and discomfort (*Kyokyo Kuman*), epigastric discomfort and resistance (*Shinka Hiko*), and rectus abdominis muscle tonus.
- **Saikokaryukotsuboreito (柴胡加竜骨牡蛎湯):** Patients complain of depressed mood, impatience, and other psychoneurotic symptoms as well as physical symptoms such as palpitation, lightheadedness, and headache. In many cases, patients are suffering stress from unavoidable life

situations including workplace relations and care problems. The abdominal pattern comprises strong *Kyokyo Kuman* and palpable pulsation of the abdominal aorta.

- **Saikokeishikankyoto (柴胡桂枝乾姜湯):** The abdominal pattern is characterized by weak abdominal strength, tenderness directly below the xiphoid process of the sternum, and palpable pulsation in the supraumblical region (*Saijo Ki*). *Kyokyo Kuman* is virtually imperceptible. Patients write about chief complaints, though extremely varied, in detail into the history-taking questionnaire. From a viewpoint of character tendency, this formula is considered effective for patients who say "I cheerfully look after guests when they visit, but feel exhausted after they leave". Many of these patients are resistant to taking psychoactive drugs or cannot take such drugs because of lightheadedness after medication.
- **Kamikihito (加味帰脾湯):** Used in patients with poor complexion and intense depressive symptoms rather than impatience. Patients characteristically have sleep disorder (especially profuse dreaming and light sleep).

Fatigue and Malaise with Few Psychoneurotic Symptoms

- **Hochuekkito (補中益気湯):** Used in patients who have symptoms such as sleepiness after meals, weak eyes, heavy feeling in the limbs as though they will fall off, atony, low-grade fever (unidentified fever), and proneness to colds. Abdominal strength is intermediate or weaker. Effective for chronic fatigue syndrome in patients who have absolutely no psychoneurotic problems; and elderly patients with mild depression who experience malaise after taking antidepressants.
- **Rikkunshito (六君子湯):** Used in patients who complain of early satiety after meals. Abdominal strength is feeble and splashing sound is heard. These findings are virtually equivalent to the postprandial distress syndrome of functional dyspepsia (FD).
- **Seishoekkito (清暑益気湯):** Used in patients who have heat sensation, thirst, diarrhea, and weight loss in summer. Abdominal strength is intermediate to slightly weak.
- **Juzentaihoto (十全大補湯):** Appropriate for patients with malaise who have also blurred vision, hair loss, and skin dryness; namely, with both qi (Ki) deficiency and blood deficiency. Often effective as an adjuvant therapy after malignant tumor surgery. Although juzentaihoto is used in patients with intermediate to weak abdominal strength, but that does not apply to the use as an adjuvant therapy for malignant tumor.
- **Ninjinyoeito (人参養栄湯):** Indications are similar to those for juzentaihoto (十全大補湯). However, the abdominal pattern often comprises *Shinka Hiko*. The constituent crude drugs suggest that the formula is more effective in patients with respiratory symptoms.
- **Tokishakuyakusan (当帰芍薬散):** Used in patients who have gastrointestinal weakness, blood deficiency symptoms such as hypomenorrhea and hair loss, as well as fluid disturbance (*Suidoku*) such as edema. The abdominal pattern often comprises splashing sound and tender points due to blood stasis (*Oketsu*).

Fatigue and Malaise Largely Affected by Constitution and Aging

- **Shokenchuto (小建中湯):** Used in patients who are likely to suffer stress-related stomach troubles

and cannot gain weight, as seen in irritable bowel syndrome cases. Abdominal examination shows elevated tonus of the rectus abdominis muscles.

- **Ogikenchuto (黄耆建中湯):** Used in patients with excessive sweating and chronic inflammation of the skin. Ogikenchuto may be used for pressure sores and the like in elderly patients, not only children. The abdominal pattern is the same as in shokenchuto (小建中湯).
- **Hachimijiogan (八味地黄丸):** Patients are elderly or have suffered a major illness. Abdominal examination characteristically shows lower abdominal numbness (*Shofuku Fujin*). Concomitant use in elderly patients who poorly respond to antidepressants may improve the effectiveness of the antidepressant.

Weak Constitution – Sensitivity to Coldness

Kenshu Lai

Weak Constitution

Overview of Disease

Modern medicine has no clear definition of the term "weak constitution". Causality lies in innate genetic predispositions and acquired predisposing factors derived from unhealthy lifestyle. Prior to modern times, causality lay in poor nutrition; however, with the changing times, the main causes now include digestive exhaustion due to overeating and cardiopulmonary hypokinesia due to physical inactivity or excessive/unbalanced nutrition. Increased stress, day-night reversal, and changed lifestyle patterns also worsen the pathological conditions.

Indications for Kampo Therapy

Counseling patients on correcting lifestyle factors such as diet and everyday habits is important: Kampo therapy alone is insufficient.

Frequent Formulae

Formulae for physical predispositions

- **Rokumigan (六味丸)**: Useful for slow-developing children and patients presenting with burning

sensation (*Hoteri*) due to fluid (津液) depletion

- **Hachimijiogan (八味地黄丸)**: Appropriate for patients with deficiency of lower abdominal region (*Jinkyo*) associated with aging and cold dampness (寒湿, *Kanshitsu*) (excessive fluid intake).
- **Shimbuto (真武湯)**: Used for symptoms caused by cold dampness (lightheadedness, diarrhea, etc.) or hypometabolism due to aging or chronic debilitating disease, in addition to gastrointestinal weakness.
- **Hangeshashinto (半夏瀉心湯)**: Target signs include epigastric discomfort (*Shinka Hi*), nausea/vomiting, and diarrhea with irritable bowel syndrome.
- **Hochuekkito (補中益気湯)**: Used for constitutional atony (visceroptosis), chronic debilitating conditions with general malaise, low-grade fever, nocturnal sweating, etc.
- **Shokenchuto (小建中湯)**: Effective for constitutional improvement in feeble patients, who have also lip dryness, nasal hemorrhage, and ticklishness tendencies.
- **Ninjinto (人参湯)**: Offered to patients who complain of anorexia, hypersalivation, watery nasal discharge, or stomach pain when exposed to coldness.
- **Shikunshito (四君子湯)/Rikkunshito (六君子湯)**: Good for anorexia or chronic indigestion.
- **Shosaikoto (小柴胡湯)**: Possesses a biological response modification (BRM) activity: long-term use is effective for improvement of constitution. Similar formulae include saibokuto (柴朴湯), saikokeishito (柴胡桂枝湯), and saikoseikanto (柴胡清肝湯).

Formulae for mental predispositions

- **Yokukansan (抑肝散)/Yokukansankachimpihange (抑肝散加陳皮半夏)**: Used for infantile neurosis (*Shonikansho*), tantrum, or irritability, and in short-tempered patients.
- **Kamishoyosan (加味逍遥散)**: A typical formula used to alleviate a range of symptoms including irritability, headache, and climacteric disorders.
- **Saikokeishikankyoto (柴胡桂枝乾姜湯)**: Effective for head sweating (*Zukan*), insomnia, and anxiety tendency.
- **Hangebyakujutsutemmato (半夏白朮天麻湯)**: For headache and vertigo/dizziness.
- **Kambakutaisoto (甘麦大棗湯)**: Good for emotional incontinence and hysteria.
- **Ryokeijutsukanto (苓桂朮甘湯)**: Used for autonomic imbalance, cardiac neurosis, and anxiety tendency.

Deficiency pattern-treating formulae (*Hozai*) for chronic fatigue

Ginseng (人参, ninjin) and Astragalus Root (黄耆, ogi)–containing formulae

- **Juzentaihoto (十全大補湯)**: A formula treating dual deficiency of qi (Ki) and blood (*KiKetsu Ryokyo*) by exerting immuno-enhancing/stimulating activity. Very useful for general malaise and low-grade fever in patients with chronic debilitating conditions.
- **Ninjinyoeito (人参養栄湯)**: Another formula for dual deficiency of qi (Ki) and blood. Appropriate for Juzentaihoto (十全大補湯)-pattern patients complaining of respiratory symptoms.
- **Hochuekkito (補中益気湯)**: As mentioned above.

Kenchuto (建中湯) group

- **Shokenchuto (小建中湯)**: As mentioned above.
- **Ogikenchuto (黄耆建中湯)**: Shokenchuto with Astragalus Root (黄耆, ogi) to treat qi (Ki) deficiency (*Hoki*). Effective for chronic fatigue in patients with hypertonic constitution caused by qi (Ki) deficiency (*Kikyo*).
- **Kigikenchuto (帰耆建中湯)**: Is ogikenchuto containing Japanese Angelica Root (当帰, toki) and useful for patients with dual deficiency of qi (Ki) and blood.

Sensitivity to Coldness

Overview of Disease

The concept of "sensitivity to coldness" does not exist in Western medicine. The temperature sensation of coldness (*Hie*) is precisely a kind of subjective biological response to external stimuli, while objectively there may be no coldness present at all. Conversely, the sufferer might not feel coldness despite the objective presence of coldness. Sensitivity to coldness is generally more prevalent among women; however, the incidence among men as well as younger age groups has increased remarkably in recent years.

Indications for Kampo Therapy

People whose energy production is low are prone to feeling coldness, while people whose gastrointestinal function is weak often feel coldness because energy is not properly supplemented or transported. Qi (Ki) depression (*Kiutsu*) may intensify psychogenic coldness and chills. In turn, fluid retention (*Suitai*) intensifies coldness in the lower body; and blood deficiency (*Kekkyo*) and blood stasis (*Oketsu*) result in coldness in the extremities.

Frequent Formulae

Patients should be counseled on lifestyle habits (appropriate exercise and redressing daily lifestyle factors including food, clothing, and home).

Whole body

The whole body cools when body energy is depleted, or when energy supplementation and transportation are compromised.

- **Shimbuto (真武湯), Hachimijiogan (八味地黄丸), Ninjinto (人参湯), Shokenchuto (小建中湯):** As mentioned above
- **Goshajinkigan (牛車腎気丸):** Useful for patients with edema who well respond to hachimigan.

- **Bushirichuto (附子理中湯):** Effective for patients with ninjinto (人参湯)-pattern and intense interior cold (*Rikan*).
- **Keishininjinto (桂枝人参湯):** For patients with ninjinto-pattern associated with chronic headache.
- **Ryokyojutsukanto (苓姜朮甘湯):** Used for low back and lower body coldness.
- **Goshuyuto (呉茱萸湯):** Offered to patients with gastrointestinal weakness who complain of headache, hiccup, vomiting, and shoulder stiffness.
- **Daikenchuto (大建中湯):** Used in patients with relatively strong abdominal pain and distension, or tympanites when the limbs and abdomen are cool.
- **Shigyakuto (四逆湯)*:** Used for coldness of the limbs and lientery (完穀下痢, *Kankokugeri*).
- **Bukuryoshigyakuto (茯苓四逆湯)*:** For shigyakuto (四逆湯)-pattern patients with agitation (煩躁, *Hanso*). Can be substituted by a combination of ryokyojutsukanto, ninjinto, and Processed Aconite Root powder (*Bushimatsu*) extract formulations.

Upper heat and lower cold

When the internal and lower parts of the body are cool, qi (Ki) rises, which requires a combination of Cinnamon Twig (桂枝, keishi) and Glycyrrhiza (甘草, kanzo). If fluid retention is also present, Poria Sclerotium (茯苓, bukuryo) is added. If blood stasis is present, blood stasis-treating (*Kuoketsu*) drugs are added. However, if the cause of the coldness is fluid disturbance (*Suidoku*) or dietary neglect, it must be rectified.

Qi (Ki) counterflow (*Kigyaku*)

- **Keishikanzoto (桂枝甘草湯)***: Effective for paroxysmal palpitation and chest distress.
- **Keishikaryukotsuboreito (桂枝加竜骨牡蛎湯)**: Good for patients with hot flashes and more intense anxiety and qi (Ki) abnormality than seen in keishikanzoto (桂枝甘草湯)-pattern.

Qi (Ki) counterflow and fluid retention

- **Ryokeimikanto (苓桂味甘湯)***: Used for blocked-ear sensation and hot flashes associated with coldness in the limbs.
- **Ryokeijutsukanto (苓桂朮甘湯)**: As mentioned above

Qi (*Ki*) counterflow and blood stasis

- **Tokakujokito (桃核承気湯)**: Patients have hot flashes and constipation tendency with remarkable psychoneurotic symptoms.
- **Keishibukuryogan (桂枝茯苓丸)**: Improves microcirculatory disorder throughout the body.
- **Unkeito (温経湯)**: Appropriate for lip dryness and vexing heat in the palms (手掌煩熱, *Shusho Hannetsu*).

Unhealthy diet and fluid disturbance

Overeating causes qi (Ki) to rise (hot flashes), which in turn results in fluid retention (*Tan'in*) whereby lower body coldness results in upper heat lower cold (*Hienobose*).

- **Goshakusan (五積散)**: Offered to patients who complain of lower abdominal pain, low back pain, myalgia, and arthralgia following exposure to cold dampness (*Kanshitsu*) (air conditioning and cool drinks), occasionally in association with upper heat lower cold.
- **Orento (黄連湯)**: Effective for patients with a similar pattern to hangeshashinto pattern. They also complain of hot flashes and gastric pain due to tangled cold and heat (*Kannetsu Sakuzatsu*)

conditions.

- **Choreito (猪苓湯)**: Approproate for hyperphagia/polydipsia patients complaining of lower body coldness and heaviness, lower abdominal discomfort, cystitis-like symptoms, and diarrhea tendency.
- **Ryutanshakanto (竜胆瀉肝湯)**: For hyperphagia/polydipsia patients complaining of lower body coldness and swelling, and leukorrhea/excessive menstrual bleeding.
- **Daisaikoto (大柴胡湯)**: Useful for patients complaining of upper heat lower cold, shoulder stiffness, abdominal pain/discomfort, and constipation tendency.

Extremities

Blood deficiency and blood stasis are the causes of vascular insufficiency in the extremities. The formulae containing Japanese Angelica Root (当帰, toki) should be selected for blood deficiency treatment, and blood stasis-treating formulae are used for blood stasis.

Blood deficiency

- **Shimotsuto (四物湯)**: Used for chronic debilitating disease or a variety of serious illnesses suspected of being related to immunity.
- **Tokishakuyakusan (当帰芍薬散)**: Appropriate for patients with blood deficiency, heavy headedness, swelling, and other fluid retention symptoms.
- **Tokishigyakukagoshuyushokyoto (当帰四逆加呉茱萸生姜湯)**: Used for various painful diseases induced by cold stimuli, especially effective for chilblains and Raynaud's symptoms.

Blood stasis

- **Keishibukuryogan (桂枝茯苓丸), Tokakujokito (桃核承気湯):** As mentioned above.

Others

- **Byakkoto (白虎湯)/Byakkokaninjinto (白虎加人参湯):** Body surface and limbs are cool despite interior heat (heat syncope [熱厥, netsuketsu]).

Autonomic imbalance

- **Kamishoyosan (加味逍遥散), Yokukansan (抑肝散)/Yokukansankachimpihange (抑肝散加陳皮半夏):** As mentioned above.

* Not available as ethical Kampo extract formulation

Depressive State – Anxiety – Insomnia

Hironobu Iguchi

Depressive State

Overview of Disease

According to the standardized diagnostic criteria (DSM-IV[1] and ICD-10[2]), a diagnosis of 'depressive state' is made if the state associated with core symptoms — such as a depressed mood, a loss of interest or pleasure, decreased energy, proneness to fatigue, and decreased activity, as well as pessimism, loss of concentration and determination, anxiety and agitation (不安焦燥), suicidal ideation, insomnia, and anorexia — lasts for at least two weeks, and if it hinders daily activities. Depressive state is commonly observed not only in so-called depression that primarily presents depressive state symptoms — major depressive disorder according to DSM-IV, but also in psychiatric disorders, physical disorders, and drug use. In the latter cases, treatment is preferred for the primary disease.

[1] DSM-IV: Diagnostic and Statistical Manual of Mental Disorders 4th edition

[2] ICD-10: International Statistical Classification of Diseases and Related Health Problems

Indications for Kampo Therapy

Of major depressive disorder, less severe conditions are considered good targets for Kampo therapy. These include considerably mild conditions in which patients have no suicidal ideation and are able to endeavor partially to do work and housework, and mild depressive states which do not meet the criteria for major depressive disorder (termed minor depressive disorder, for which the efficacy of general antidepressants have not been demonstrated). Once major depressive disorder becomes moderate or more severe, there is a particularly high risk of suicide. Therapy should not rely on Kampo medicines alone. However, combined use of antidepressants and Kampo medicines is possible under the supervision of a psychiatrist.

Frequent Formulae

The pathologic conditions considered to be the depressive state in Kampo medicine include those of which internal causes (sorrow [悲], anxiety [憂], worry [思], anger [怒], fear [恐]) were induced by overwork and worry, and in which qi (Ki) depression (*Kiutsu*) and qi (Ki) deficiency (*Kikyo*) appeared. Patients can be assumed to have blood as well as fluid imbalance; liver, spleen, or kidney problems; and in the six stages of disease transformation (*Rokubyoi*), pathologic conditions that are mainly in the ShoYo stage (*Shoyobyo*) to TaiYin stage (*Taiyinbyo*). In Kampo therapy, these pathologic conditions are taken into consideration in

deciding on the prescriptions suitable for the patient's pattern, which is the key to treatment.

- **Yokukansan (抑肝散):** Appropriate for patients who have marked sense of agitation (焦燥感), (including irritability and short temper), associated with eyelid twitching, trembling in the limbs (liver agitation [*Kan no Takaburi*]) and insomnia. Yokukansankachimpihange (抑肝散加陳皮半夏) is offered to patients with chronic symptoms.
- **Kamikihito (加味帰脾湯):** Effective for patients who have marked loss of vigor (気力低下), anxiety, palpitation, and insomnia. Kihito (帰脾湯) is an option if anxiety, agitation (焦燥), and heat sensation are not prominent.
- **Hangekobokuto (半夏厚朴湯):** Patients have qi (Ki) depression symptoms such as foreign-body sensation in the laryngopharynx and fullness sensation in the chest (胸満感, *Kyomankan*), in association with anxiety, palpitation, dizziness, insomnia, and a tendency toward splashing sound (*Shinsuion*) and epigastric discomfort (*Shinka Hi*). Kososan (香蘇散) may be used for patients with decreased physical strength.
- **Kamishoyosan (加味逍遥散):** Patients have various physical complaints including proneness to fatigue, headache, shoulder stiffness, as well as paroxysmal heat sensation in the upper body and sweating, in association with anxiety, agitation, and insomnia. They have also static blood (*Oketsu*).
- **Rikkunshito (六君子湯):** Patients have a feeling of enervation and postprandial bloating/fullness. If these symptoms are accompanied by anxiety and insomnia with cough and sputum, as well as a low-grade fever and hypochondrium resistance and discomfort (*Kyokyo Kuman*), chikujountanto (竹茹温胆湯) is offered. If general malaise is marked, hochuekkito (補中益気湯) is recommended.
- **Chotosan (釣藤散):** Effective for depressive state in patients with a hypertensive tendency, particularly in middle age or above, associated with chronic headache (often worsening in the morning), dizziness, and stiffness from the shoulders to the neck.
- **Hachimijiogan (八味地黄丸):** Appropriate for middle-aged or older patients who have proneness to fatigue, weakness and pain in the lower body, numbness, coldness and edema tendency, nocturia, and weakness of lower abdominal region (*Shofuku Fujin*). Rokumigan (六味丸) is used for younger patients with no coldness.
- **Saikokaryukotsuboreito (柴胡加竜骨牡蛎湯)**: Patients are relatively strong, but have anxiety, depression, insomnia, flightiness, irritability, and palpitation, with *Kyokyo Kuman*.
- **Daisaikoto (大柴胡湯):** Principally used for constipation, shoulder stiffness, nausea, etc. in relatively strong patients with prominent *Kyokyo Kuman*, but also can be expected to be effective for depression and insomnia.

Anxiety

Overview of Disease

According to conventional diagnosis, if anxiety is the basic symptom, it is not distinguished from "neurosis." However, DSM-IV classifies general neurosis as "anxiety disorder" [1) generalized anxiety disorder or 2)

panic disorder] or as “somatoform disorder” [3) somatization disorder, 4) non-differentiable somatoform disorder, or 5) hypochondria]. To simplify, 1) is anxiety neurosis, 2) repetitive anxiety attack with feeling of breathlessness and palpitation, 3) physical complaints throughout the body which have no identifiable organic cause and which have become chronic prior to 30 of age, 4) its milder form, and 5) hypochondriacal neurosis.

Indications for Kampo Therapy

Kampo therapy may be tried for mild cases; however, if its effects are unsatisfactory or symptoms worsen, the focus should shift to psychiatric therapy and Kampo should be used as an adjunctive therapy. Especially panic disorder is a debilitating disease and can often be accompanied by depression if the disease becomes chronic because of delayed treatment for attacks. In cases of somatization disorder, the frequency of association with depression, panic disorder, or personality disorder increases and requires appropriate psychiatric management.

Frequent Formulae

Because anxiety is often observed together with depression, most formulae listed in the section on depressive state can also be expected to be effective for anxiety. In Kampo terms, patients with anxiety state can be assumed to have qi (Ki) counterflow (*Kigyaku*) and heart abnormality.

- **Saikokaryukotsuboreito (柴胡加竜骨牡蛎湯):** Effective for patients who are relatively strong, but have anxiety, oversensitivity and palpitation with *Kyokyo Kuman*. Saikokeishikankyoto (柴胡桂枝乾姜湯) is more appropriate for patients with weaker physical strength, shortness of breath, coldness in the lower limbs, and nocturnal sweating.
- **Keishikaryukotsuboreito (桂枝加竜骨牡蛎湯):** Effective for anxiety associated with flightiness and palpitation, similarly to saikokaryukotsuboreito (柴胡加竜骨牡蛎湯), and in patients who have weaker physical strength, coldness in the lower limbs, and no *Kyokyo Kuman*.
- **Orengedokuto (黄連解毒湯):** Used for anxiety associated with agitation, irritability, and insomnia in patients who are relatively strong, characteristically with hypertensive tendency and facial redness. San’oshashinto (三黄瀉心湯) is recommended for patients also having constipation.
- **Hangeshashinto (半夏瀉心湯):** Patients have epigastric discomfort and resistance (*Shinka Hiko*) and increased borborygmus, associated with eructation, stomatitis, nausea, loose stool, diarrhea and other gastrointestinal symptoms.
- **Seishinrensahiin (清心蓮子飲):** Effective for anxiety, insomnia, and depression in patients with gastrointestinal weakness who chronically complain of worry strain, proneness to fatigue together with residual urine sensation, pollakiuria, and micturition pain. They also frequently have coldness in the lower limbs but facial redness.

Insomnia

Overview of Disease - Indications for Kampo Therapy

The causes of insomnia are commonly divided into five categories: physical disorder (cardiac disease, respiratory disease, sleep apnea syndrome, etc.), physiologic insomnia (shift work, inappropriate sleep hygiene, etc.), psychological insomnia (stress, nervousness and other personality traits, etc.), psychiatric disorder, and pharmacological insomnia (alcohol, caffeine, etc.). The top priorities are assessing the cause, and medical interventions according to identified causes. Then Kampo therapy is offered to several patients who have insomnia due to psychological causes or induced by psychiatric or physical disorder. When benzodiazepines are not satisfactorily effective, concurrent use of Kampo medicines may be helpful.

Frequent Formulae (Figure)

While Kampo medicines cannot be expected to have a direct hypnotic sedative action, continual oral use two to three times a day will demonstrate good indirect effects on sleep disorder. In selecting a formula, the following general categorization may be useful: sleep-onset insomnia (mainly due to nervousness and anxiety), sound-sleep disorder (mainly due to anxiety and depression), and early-morning awakening (mainly due to aging effects).

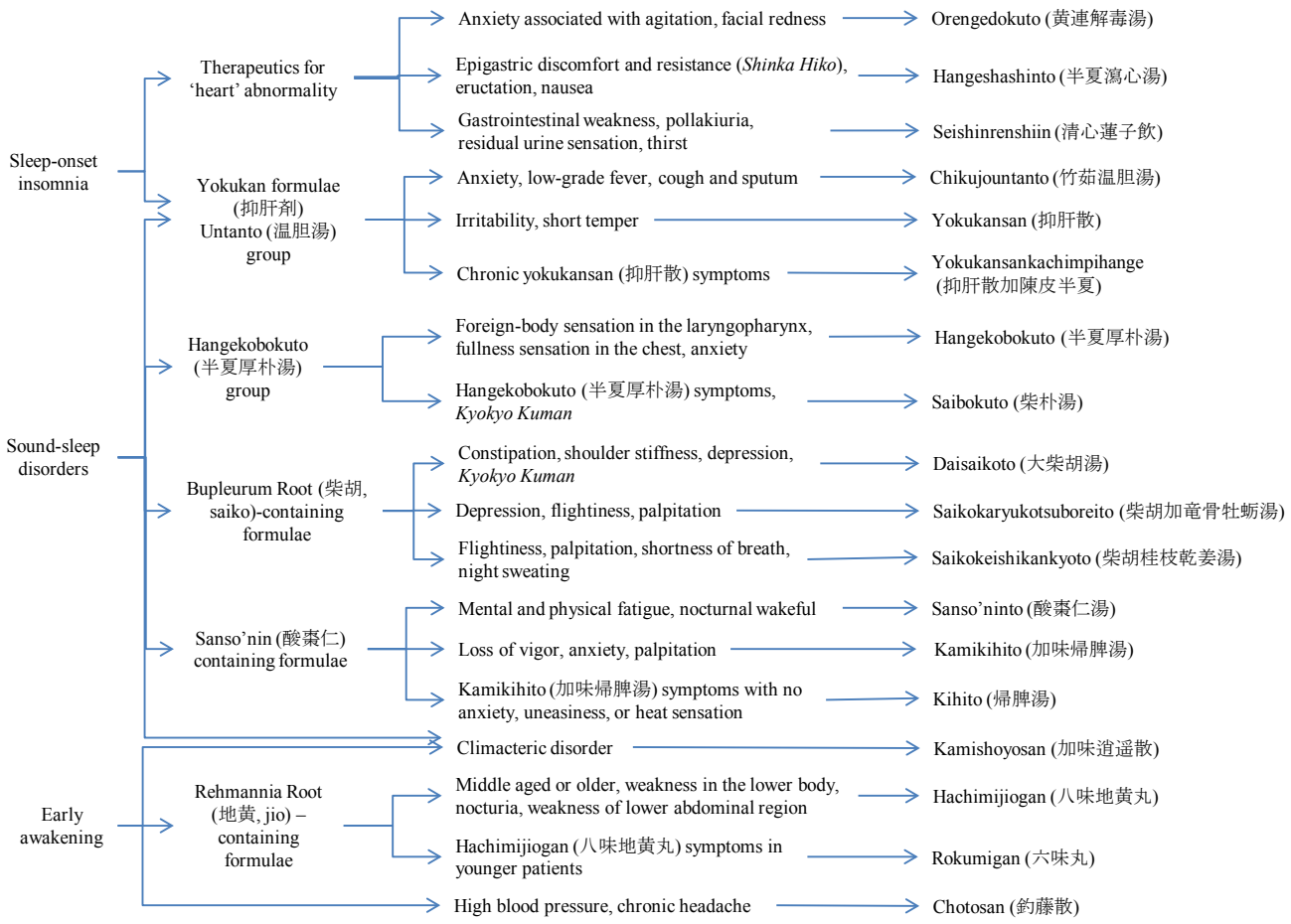

Figure: Frequent formulae for insomnia

Dementia – Abnormal Behavior

Eiichi Tahara

Overview of Disease

Dementia includes a range of diseases, primarily Alzheimer's disease, vascular dementia, and a mixed type of the two. The core symptoms are memory disorder, disorientation, reduced thinking and calculation ability, and impaired judgment. Peripheral symptoms, otherwise termed behavioral and psychological symptoms of dementia (BPSD), are gaining attention. They include (1) mood disorder (anxiety, agitation [興奮], depression, uneasiness [焦燥]); (2) hallucination, delusion, misidentification; and (3) behavioral disorder (wandering, sleep disorder, unhygienic behavior, feces handling, sexual deviation).

Indications for Kampo Therapy

Kampo medicines are used for dementia in general, but the best indication is BPSD. Formulations treating spleen and lower region deficiency (*Hohi Hojin Yaku*) such as hachimijiogan (八味地黄丸) and hochuekkito (補中益気湯) improve qi (Ki) deficiency (*Kikyo*) and qi (Ki) depression (*Kiutsu*) in depression tendency, mental anxiety, insomnia, impatience, and so on. Yokukansan (抑肝散) and orengedokuto (黄連解毒湯) are used for short temper and mental restlessness caused by liver (TM) and heart (TM) imbalance. Kampo medicines are extremely helpful in that, unlike Western medical therapy, they are free from central nervous system inhibition, aspiration pneumonia or fall risk.

Frequent Formulae

Dementia

- **Hachimijiogan (八味地黄丸):** A basic formula for Yin pattern (陰証, *Yinsho*) elderly patients. Effective for weak feeling, coldness, and numbness in the lower body; urination disorder (such as nocturnal urine); weakness of the lower abdominal region (*Shofuku Fujin*); slight edema tendency; coldness and heat vexation (*Hannetsu*) in the limbs. Sometimes taken in concurrent or combined form with ninjinto (人参湯). If coldness is marked, Processed Aconite Root (附子, bushi) is added.
- **Goshajinkigan (牛車腎気丸):** Patients have slightly prominent deficiency pattern (*Kyosho*) than those with hachimijiogan (八味地黄丸)-pattern (*Hachimijiogansho*), and also have obvious edema tendency.
- **Hochuekkito (補中益気湯):** Ginseng (人参, ninjin) and Astragalus Root (黄耆, ogi)-containing formula(e) (*Jingizai*). Offered for general malaise, anorexia, low-grade fever, night sweating (*Tokan*), visceral ptosis tendency, and lack of vigor in speech and eyes.

- **Rikkunshito (六君子湯):** Appropriate for Yin pattern and deficiency pattern patients. They have impaired gastrointestinal function, anorexia, epigastric fullness, thick tongue fur, and splashing sound (*Shinsuion*).
- **Shikunshito (四君子湯):** Offered to more prominent deficiency pattern patients than rikkunshito (六君子湯). They have general malaise, appetite loss, poor complexion, and impaired gastrointestinal function. Similar to rikkunshito but markedly effective in patients with qi (Ki) deficiency, associated with slight *Shinsuion* and tongue fur.
- **Tokishakuyakusan (当帰芍薬散):** Effective for patients with Yin pattern and deficiency pattern. They have signs of blood deficiency, static blood, and fluid disturbance, associated with headache, dizziness, or edema. May be used in combination with ninjinto (人参湯) or Processed Aconite Root (附子, bushi).
- **Keishibukuryogan (桂枝茯苓丸):** Appropriate for patients with Yo pattern (陽証, *Yosho*) and between deficiency and excess (*Kyojitsu Chukan*) to excess pattern (*Jitsusho*), who have commonly hot flashes with facial redness. Sometimes they have resistance and tenderness in the lower abdomen. Especially effective for patients suspected to have underlying cerebrovascular disorder.
- **Chotosan (釣藤散):** Offered to patients with Yo pattern and rather deficiency pattern. Generally used for shoulder stiffness and headache due to underlying high blood pressure. Especially effective for vascular dementia.
- **Shimbuto (真武湯):** Good for patients with Yin pattern and deficiency pattern, who have fluid disturbance signs including diarrhea, dizziness, sensation of shakiness, general malaise, and coldness in limbs.

Abnormal Behavior (Chiefly BPSD)

- **Yokukansan (抑肝散):** Appropriate for patients with middle Yo pattern, who are irritable, impatient, insomniac, and easily agitated. They may also have eyelid, face, or limb spasms. Sometimes used by caretakers as a form of stress care.
- **Yokukansankachimpihange (抑肝散加陳皮半夏):** Effective for patients with more prominent deficiency pattern than yokukansan (抑肝散).
- **Daisaikoto (大柴胡湯):** Offered to excess pattern patients, who have severe hypochondrium resistance and discomfort (*Kyokyo Kuman*) and constipation, sometimes associated with shoulder stiffness, heavy headedness, dizziness, tinnitus, nausea, vomiting, depressed mood, nervous tension, and/or rectus abdominis muscle cramp.
- **Saikokaryukotsuboreito (柴胡加竜骨牡蛎湯):** Effective for excess pattern patients, who have relatively severe *Kyokyo Kuman*, associated with anxiety, insomnia, and irritability. They may have palpable abdominal aortic pulsation, heavy headedness, headache, shoulder stiffness, or depressed mood.
- **Saikokeishikankyoto (柴胡桂枝乾姜湯):** Appropriate for deficiency pattern patients with fatigue and malaise, palpitation, shortness of breath, or insomnia. They may suffer from upper heat and lower cold, head sweating (*Zukan*), night sweating (*Tokan*), thirst, lip dryness, nightmare, or slight hypochondrium resistance (*Kyokyo Man Biketsu*).

- **Kamishoyosan (加味逍遥散):** Offered to deficiency pattern patients, who have prone to fatigue, nervous anxiety, insomnia, irritability, or short temper, associated with various symptoms including shoulder stiffness, headache, dizziness, burning sensation in the upper body, paroxysmal sweating, and skin formication. Proximate to saikokeishikankyoto (柴胡桂枝乾姜湯) but patients are differentiated by the presence of fever tendency and static blood.
- **Orengedokuto (黄連解毒湯):** Appropriate for patients with Yo pattern and excess pattern, who have hot flash tendency with facial redness, nervous anxiety, insomnia, and impatience, often associated with epigastric discomfort (*Shinka Hi*), nose bleed, or skin itch.
- **San'oshashinto (三黄瀉心湯):** Good for Yo pattern and excess pattern. Similar to orengedokuto (黄連解毒湯), patients have specifically constipation tendency.
- **Bushishashinto (附子瀉心湯)*:** Processed Aconite Root (附子, bushi)-containing san'oshashinto (三黄瀉心湯). Appropriate for patients with Yin pattern and excess-pattern, who have psychiatric symptoms similar to those in san'oshashinto-pattern (*san'oshashintosho*) patients, but with somewhat poor facial complexion and coldness in the limbs. On constipation, patients may complain of stuffiness in the epigastric region.
- **Unseiin (温清飲):** Appropriate for patients with Yo pattern and excess pattern, who have blood deficiency (*Kekkyo*) (composed of symptoms treated with shimotsuto [四物湯]) in addition to orengedokuto (黄連解毒湯)-pattern (*orengedokutosho*). They also have hot flashes and mental restlessness, with obviously dry and dark-red skin.
- **Kamiuntanto (加味温胆湯)*:** Offered to deficiency pattern patients, who have gastrointestinal weakness, difficulty in sleeping, easily startled, palpitation, etc. Effective against short temper, sense of urgency, and uneasiness.
- **Kamikihito (加味帰脾湯):** Appropriate for deficiency pattern patients with gastrointestinal weakness. They have fatigue-induced bleeding tendency and anemia, resulting in neurosis and amnesia, sometimes associated with fever tendency, and irritability, impatience, or anxiety.
- **Shishishito (梔子豉湯)*:** For deficiency pattern patients, who have precordial agony, insomnia, mental restlessness, and heat sensation in the chest. Some patients may complain of a downward pulling sensation from the shoulders, as though sinking, particularly in the morning. There are various shishishito (梔子豉湯) prescriptions for various coexisting symptoms: shishikankyoto (梔子乾姜湯)* for cold (*Kan*), shishikanzoto (梔子甘草湯)* for shallow breathing [*Shoki*], shishikobokuto (梔子厚朴湯)* for chest agitation (*Shimpan*) with abdominal fullness (*Fukuman*), shishishokyoshito (梔子生姜豉湯)* for nausea, and so on.
- **Kihito (帰脾湯):** Offered to deficiency pattern patients with gastrointestinal weakness, who are similar to those with kamikihito-pattern (*kamikihitosho*), but have no febrile sign. Patients are liable to have bleeding or anemia from overwork, resulting in neurosis and forgetfulness.
- **Kososan (香蘇散):** Appropriate for patients with deficiency pattern, associated with anorexia, gastrointestinal symptoms such as upper abdominal fullness sensation, anxiety, insomnia, headache, and qi (Ki) depression (*Kiutsu*) symptoms such as depressed mood.
- **Hangekobokuto (半夏厚朴湯):** Effective for –between deficiency and excess pattern patients with depression tendency. They complain of blocked throat sensation, broody mood, insomnia, nervous

anxiety, and so on. Often used concomitantly with Bupleurum Root (柴胡, saiko)-containing formulae.

- **Kambakutaisoto (甘麦大棗湯):** For patients with between deficiency and excess to deficiency pattern, who have oversensitivity, general or local muscle rigidity/spasm, yawning and insomnia, pessimism, or fits of agitation, etc.
- **Sansoninto (酸棗仁湯):** For deficiency pattern patients, who have insomnia which is induced by severe physical and mental fatigue due to underlying anemia tendency, and which is sometimes associated with mental anxiety, oversensitivity, and excitement.
- **Keishikaryukotsuboreito (桂枝加竜骨牡蛎湯):** For deficiency-pattern patients, who complain of oversensitivity or mental anxiety. They may also have palpable abdominal aortic pulsation, fatigue proneness, and night sweating. Also considered the prescription for different constitution (deficiency pattern) of saikokaryukotsuboreito (柴胡加竜骨牡蛎湯). May be effective for sexual deviation in elderly people. On such occasions, abdominal aortic pulsation is not necessarily palpable.
- **Tokakujokito (桃核承気湯):** A typical blood stasis-treating formula (*Kuoketsuzai*) for excess pattern patients, who have hot flashes, headache, dizziness, insomnia, agitation and other symptoms in addition to constipation. Tenderness in the sigmoid colon region, or resistance and sharp tenderness in the left iliac region (*Shofuku Kyuketsu*), is characteristic.

* Not available as ethical Kampo extract formulation

Metabolic Disease

Motoko Fukuzawa

Obesity

Overview of Disease

Obesity is a condition in which excessive adipose tissue is accumulated in the body. A person whose body mass index (BMI: body weight/body height as kg/m^2) is 25 or more is diagnosed as with obesity in japan. A BMI of 25 or over associated with visceral fat accumulation or with concomitant presence of hypertension, dyslipidemia, and abnormal glucose tolerance is diagnosed as obesity requiring treatment. Metabolic syndrome (visceral fat obesity plus concomitant hypertension, dyslipidemia, and abnormal glucose tolerance) patients are susceptible to arteriosclerotic disease such as ischemic heart disease and cerebral vascular disorder. In these patients, the treatment of obesity is very important.

Indications for Kampo Therapy

Drug therapy is offered for patients who do not respond to diet therapy and therapeutic exercise. The anorexiant mazindol is available in Western medicine, though its use is limited to patients with a BMI of 35 or more for a period of three months. Kampo medicines are not greatly effective in reducing weight, but can be used for long periods regardless of the degree of obesity, resulting in improvement of concomitant symptoms, quality of life (QOL), and weight loss outcomes. Bofutsushosan (防風通聖散) and boiogito (防已黄耆湯) have an anti-obesity effect enough to reduce visceral fat mass.

Frequent Formulae

The chief causes of obesity are food disturbance (食毒, *Shokudoku*) and fluid disturbance (*Suidoku*), frequently associated with blood stasis (*Oketsu*), qi (Ki) counterflow (*Kigyaku*), and qi (Ki) depression (*Kiutsu*). In patients who are solid build (regarded as an excess pattern [*Jitsusho*]), food disturbance plays a role and is often accompanied with constipation. Patients who are flabby build (a deficiency pattern [*Kyosho*]) are often related with fluid disturbance.

- **Bofutsushosan (防風通聖散):** Patients have excess pattern with solid build, potbelly, hot flashes, edema, and constipation.
- **Daisaikoto (大柴胡湯):** Patients have excess pattern with solid build, shoulder stiffness, headache, and constipation tendency, in addition to an abdominal pattern of hypochondrium resistance and discomfort (*Kyokyo Kuman*).
- **Boiogito (防已黄耆湯):** Patients have deficiency pattern with flabby build, excessive sweating, edema, and swelling and pain in the knee joint.
- **Saikokaryukotsuboreito (柴胡加竜骨牡蛎湯):** Patients have oversensitivity, palpitations, and insomnia, with an abdominal pattern of *Kyokyo Kuman* .
- **Tokakujokito (桃核承気湯):** Appropriate for constipation, hot flashes, irritability, insomnia, and menstruation disorder, associated with an abdominal pattern of resistance and sharp tenderness in the left iliac region (*Shofuku Kyuketsu*).
- **Keishibukuryogan (桂枝茯苓丸):** Offered for a slight excess pattern with hot flashes, facial redness, shoulder stiffness, headache, menstruation disorder, and signs of blood stasis.
- **Tokishakuyakusan (当帰芍薬散):** Effective for deficiency pattern with coldness in hands and feet, dizziness, edema, and menstrual disorder.
- **Eppikajutsuto (越婢加朮湯):** Offered to patients with swelling and pain in the joints (particularly the knees), edema, and reduced urine volume (*Nyori Gensho)*.
- **Kumibinroto (九味檳榔湯):** Useful for patients with coldness in hands and feet, joint stiffness, lower limb malaise, edema, and shortness of breath.
- **Kamishoyosan (加味逍遥散):** Used for upper heat lower cold (*Hienobose*) with irritability and insomnia.
- **Yokukansan (抑肝散):** Target patients have irritability, intense agitation, and insomnia.

- **Hangekobokuto (半夏厚朴湯):** Effective for patients having depression, anxiety, and insomnia.

Diabetes

Overview of Disease

Diabetes is a disease that results from inadequate insulin secretion or inadequate insulin response (due to insulin resistance) and leads to hyperglycemia. Diabetes is classified as type 1 or type 2.

Since complications such as retinopathy, nephropathy, and neuropathy reduce patients' QOL, preventing their onset and advance as well as controlling blood sugar are important treatment strategies. Diet therapy and therapeutic exercise are the basic treatments. Insulin treatment is used for type 1 diabetes. In type 2 diabetes, if glycemic improvement is inadequate, oral hypoglycemic drugs and insulin should be administered.

Indications for Kampo Therapy

Crude drugs such as Ginseng (人参, ninjin) and Rehmannia Root (地黄, jio), and formulae such as seishinrenshiin (清心蓮子飲) and hachimijiogan (八味地黄丸) reportedly have a hypoglycemic action; however, it is difficult to clinically achieve sufficient hypoglycemic effect with Kampo therapy alone. Thus, Western medicinal treatment is preferred for blood sugar control. Kampo is effective for the subjective symptoms of diabetes and its complications.

Frequent Formulae

Hyperglycemia treatment

Reportedly, crude drugs such as Ginseng, Rehmannia Root, Dioscorea Rhizome (山薬, san'yaku), Ophiopogon Tuber (麦門冬, bakumondo), Schisandra Fruit (五味子, gomishi), and Cornus Fruit (山茱萸, sanshuyu), as well as formulae such as seishinrenshiin, goreisan (五苓散), hachimijiogan, ninjinto (人参湯), byakkokaninjinto (白虎加人参湯), bakumondoto (麦門冬湯), chikuyosekkoto (竹葉石膏湯), and zokumeito (続命湯) give a hypoglycemic effect. In addition, bofutsushosan and goshajinkigan (牛車腎気丸) have been shown to improve insulin resistance, while bofutsushosan and boiogito have been demonstrated to ameliorate blood sugar values through their anti-obesity action.

Subjective symptom treatment

- **Byakkokaninjinto (白虎加人参湯):** Appropriate for excess-pattern patients who have thirst, polydipsia, and polyuria.
- **Bakumondoinshi (麦門冬飲子)*:** Offered to deficiency-pattern patients with thirst, polyuria, and dry skin.

- **Daisaikoto (大柴胡湯):** Used in obese patients with constipation and an abdominal pattern of *Kyokyo Kuman*.
- **Bofutsushosan (防風通聖散):** Effective for patients who have solid build with potbelly, hot flashes and constipation.
- **Goreisan (五苓散):** Useful for patients with thirst, reduced urine volume, edema, and dizziness.
- **Hachimijiogan (八味地黄丸):** Target patients have pollakiuria, nocturia, thirst, lower body cold and numbness, edema, and impotence.
- **Goshajinkigan (牛車腎気丸):** Patients have hachimijiogan pattern with remarkable chills and lower limb edema.
- **Rokumigan (六味丸):** Patients have hachimijiogan pattern without chills.
- **Seishinrenshiin (清心蓮子飲):** Effective for coldness sensitivity in patients with pollakiuria, gastrointestinal weakness, and oversensitivity.

Treatment of complications

a. Diabetic neuropathy

- **Hachimijiogan (八味地黄丸), Goshajinkigan (牛車腎気丸):** Effective for lower body chills, numbness, pain, and impotence. Goshajinkigan has been reported to exert an aldose reductase inhibitory effect, a vasodilatory effect, and an analgesic effect.
- **Keishikajutsubuto (桂枝加朮附湯):** Used in deficiency-pattern patients with sensitivity to coldness, low back pain, arthralgia, sciatica, and numbness in the hands and feet.
- **Sokeikakketsuto (疎経活血湯):** Offered to patients having sensitivity to coldness, lower body myalgia, arthralgia, and neuralgia (with more severe pain at night and dawn), in addition to blood stasis.

b. Diabetic nephropathy

- **Saireito (柴苓湯):** Appropriate for patients with thirst, reduced urine volume, edema, dizziness, and *Kyokyo Kuman*. Reportedly may improve urinary albumin excretion.
- **Tokishakuyakusan (当帰芍薬散):** Effective for deficiency-pattern patients with edema and sensitivity to coldness.
- **Seishinrenshiin (清心蓮子飲):** Used in patients who have gastrointestinal weakness and complain of pollakiuria and residual urine sensation.
- **Hachimijiogan (八味地黄丸), Goshajinkigan (牛車腎気丸):** Used for pollakiuria, nocturia, and edema.

c. Diabetic retinopathy

- **Keishibukuryogan (桂枝茯苓丸):** Patients have facial redness, hot flashes, and blood stasis symptoms.
- **Unseiin (温清飲):** Used for fundus hemorrhage in patients who have intermediate pattern with upper heat lower cold (*Hienobose*), irritability, insomnia, and itchy, dry skin.

Dyslipidemia

Overview of Disease

Dyslipidemia is a lifestyle disease that occurs when dietary habits, lack of exercise, and other lifestyle imbalances combine with genetic factors. Hypercholesterolemia, LDL hypercholesterolemia, HDL hypocholesterolemia, and hypertriglyceridemia are major risk factors for arteriosclerosis and are treated to prevent arteriosclerotic diseases such as ischemic heart disease and cerebrovascular disorder.

Indications for Kampo Therapy

A number of crude drugs and formulae have been demonstrated to improve blood lipid levels; however, their effectiveness is not as great as Western drugs. A fewer Kampo medicines are helpful when aiming to improve blood lipid levels alone. Kampo medicines are rather helpful when comprehensive treatment including improvement of concomitant symptoms is sought, and when used in patients who cannot take Western medicines because of adverse reactions.

Frequent Formulae

Bupleurum Root (柴胡, saiko)-containing formulae and blood stasis-treating (*Kuoketsu*) formulae are frequently used.

- **Daisaikoto (大柴胡湯):** Appropriate for excess-pattern patients who have solid build, shoulder stiffness, and constipation tendency, in addition to an abdominal pattern of *Kyokyo Kuman*.
- **Bofutsushosan (防風通聖散):** Useful for patients with excess pattern who have solid build, constipation, hot flashes, edema, and distended abdomen (potbelly).
- **Boiogito (防已黄耆湯):** Effective for flabby build, excessive sweating, edema, with swelling and pain in the knee joint.
- **Orengedokuto (黄連解毒湯):** Offered to slight excess-pattern patients with hot flashes, irritability, and insomnia.
- **San'oshashinto (三黄瀉心湯):** Good for orengedokuto-pattern patients with constipation.
- **Keishibukuryogan (桂枝茯苓丸):** Patients have shoulder stiffness, hot flashes, facial redness as well as blood stasis signs.
- **Tokakujokito (桃核承気湯):** Appropriate for hot flashes, headache, constipation, irritability, and insomnia, with an abdominal pattern of *Shofuku Kyuketsu*.
- **Tokishakuyakusan (当帰芍薬散):** Used in deficiency-pattern patients with coldness in hands and feet, dizziness, and edema.
- **Hachimijiogan (八味地黄丸):** Effective for coldness or heat vexation in hands and feet, associated with low back pain, lower limb numbness, sciatica, edema, and nocturia.

* Not available as ethical Kampo extract formulation

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Kidney and Urinary System Disorders

Tadamichi Mitsuma

Overview of Disease

With a sharp increase in terminal renal failure patients, including those with chronic dialysis, attention has been drawn to early detection and early therapy for chronic kidney disease (CKD). Efforts are being applied to prevent the progression of kidney disorder. Its underlying diseases vary and include diabetic nephropathy (the number one reason for dialysis commencement), primary glomerular disease (such as chronic nephritis, nephrotic syndrome), hypertension, and arteriosclerosis.

In the urinary system, infection is an ordinary disease; urinary stones and benign prostatic hyperplasia are common. Other disorders include chronic prostatitis, neurogenic bladder, and male infertility.

Malignant neoplasms are found in both the kidneys and the urinary system.

Indications for Kampo Therapy

Kampo medicines for kidney disease are chiefly used in the chronic phase. Clinical effects have been reported for glomerular diseases such as nephritis and nephrotic syndrome, as well as the prevention of kidney disorder progression in CKD. Kampo medicines have demonstrated inhibition and elimination effects on active oxygen as well as improvement of various symptoms, in chronic renal failure. Acute-phase treatment centers around Western medical therapies.

On urinary infection, Kampo medicines exert an immediate effect even in the acute phase. They are effective for prevention in chronic and recurrent infection, posing no risk of microbial substitution. In most cases, therapeutic targets are lower abdominal region heat (*Gesho no Netsu*, heat in the abdominal region under the navel) as well as urinary stones. Results concerning male infertility have also been reported.

Kampo medicines often serve as a supplementary therapy for malignant neoplasm; however, this facet will not be referred to here.

Frequent Formulae

1. Chronic Nephritis – Nephrotic Syndrome

fluid disturbance-treating (*Risui*) formulae (*Risuizai*)

These diseases often give rise to edema and overhydration, for which fluid disturbance-treating formulae are frequently used.

- **Goreisan** (五苓散): A typical fluid disturbance-treating formula for patients who have thirst and decreased urine volume (*Nyo Furi*), mostly associated with spontaneous sweating tendency. Primarily used for ShoYo stage (*Shoyobyo*) patients with between deficiency and excess pattern (*Kyojitsu Chukan Sho*), often in combination with Bupleurum Root (柴胡, saiko).
- **Choreito** (猪苓湯): Patients are similar to those with goreisan (五苓散)-pattern (*Goreisansho*) who have thirst with decreased urine volume. In a high frequency, patients have slight excess pattern (*Jitsusho*) with weak spontaneous sweating tendency. Patients also have lower abdominal region heat, sometimes associated with subjective and objective heat sensation in the lower abdomen, hematuria, and heat sensation in the genital region. May be combined with Bupleurum Root.
- **Others**: Bunshoto (分消湯)* is used for severe edema and abdominal distension in excess pattern patients with ShoYo stage. Hokikenchuto (補気建中湯)* gives similar effects to those of bunshoto*, but is markedly effective for ascites-associated pathologic conditions in deficiency pattern (*Kyosho*) patients.

Saiko (柴胡)-containing formulae

Shosaikoto (小柴胡湯) is the main prescription. The chief criteria for selection are ShoYo stage and deficiency (*Kyo*) or excess (*Jitsu*) pattern.

- **Shosaikoto** (小柴胡湯): Appropriate for patients with ShoYo stage who have between deficiency and excess to slight excess pattern. Is the central Bupleurum Root (柴胡, saiko)-containing formula for which the therapeutic target is hypochondrium resistance and discomfort (*Kyokyo Kuman*). Often used in combination with other prescriptions for ShoYo stage. There are many reports of multi-center trials[1)] using saireito (柴苓湯), combined with goreisan (五苓散), mainly for nephrotic syndrome. In addition, clinical results of saibokuto (柴朴湯), combined with hangekobokuto (半夏厚朴湯), have been reported in cases of recurrent upper respiratory infection. Often combined with blood stasis-treating (*Kuoketsu*) formula.
- **Other Bupleurum Root (柴胡, saiko)-containing formulae**: Used according to pattern. Daisaikoto (大柴胡湯) and saikokaryukotsuboreito (柴胡加竜骨牡蛎湯) is offered for excess pattern patients, and saikokeishito (柴胡桂枝湯) and saikokeishikankyoto (柴胡桂枝乾姜湯) for deficiency pattern patients. Also combined with other formulations.

Blood stasis-treating (*Kuoketsu*) formulae

Used for patients with blood stasis (*Oketsu*) findings, including dark-red tongue and lips, fine collateral vessels (*Sairaku*), and resistance and tenderness in the lower abdomen. Blood stasis readily worsens with steroid use. Can improve peripheral blood flow, and may be used concurrently with antiplatelet agent or anticoagulation therapy. Often used in combination or concomitantly with Bupleurum Root (柴胡, saiko) or other formulations.

- **Keishibukuryogan** (桂枝茯苓丸): A typical blood stasis-treating formula widely used mainly for excess pattern patients with ShoYo stage. Therapeutic target is tenderness (mostly left dominance) associated with induration two finger-widths diagonally below the umbilicus.
- **Tokishakuyakusan** (当帰芍薬散): Appropriate for pathologic conditions associated with fluid disturbance (*Suidoku*) in deficiency pattern (*Kyosho*) patients with ShoYo stage or TaiYin stage (*Taiyinbyo*). Patients have chief symptoms of coldness in the limbs and edema, while abdominal signs include poor abdominal strength, rectus abdominis muscle tone, splashing sound (*Sinsuion*) in the epigastric region and tenderness diagonally below the umbilicus (right dominance). Often used concomitantly with other formulations; for example, in combination with Bupleurum Root for deficiency pattern.

Formulae treating deficiency of lower abdominal region (*Hojinzai*)

- **Hachimijiogan** (八味地黄丸): Used in Yin pattern (*Yinsho*) patients. Not recommended for patients with gastrointestinal weakness. Appropriate for patients who have weakness of the lower abdominal region (*Shofuku Fujin*), coldness below the low back (especially below the knees), and lower limb edema. More frequently used in elderly, and often used concomitantly with Bupleurum Root or blood stasis-treating formulae. Hachimijiogan contains the heating medicine (熱薬, netsuyaku) Processed Aconite Root (附子, bushi) and is useful for pathologic conditions with cold (*Kan*).
- **Goshajinkigan** (牛車腎気丸): Often effective for hachimijiogan (八味地黄丸)-pattern (*Hachimijiogansho*) patients with prominent edema in the lower limbs.

2. Chronic Renal Failure – Renal Dysfunction

There are numerous research papers, from basic to clinical, concerning the effect of Kampo medicines principally for chronic renal impairment. In patients at pre-dialysis stage (serum creatinine value [Cr], 4.0 mg/dL or more), caution is required because hachimijiogan (八味地黄丸) or a fluid disturbance-treating formula containing Poria Sclerotium (茯苓, bukuryo) often accelerates renal impairment.

Rhubarb (大黄, daio)-containing formulae (大黄含有方剤)

Rhubarb (大黄, daio)-containing prescriptions have a laxation effect and in Kampo medicine, is said to improve metabolism by eliminating alimentary canal toxins. In effective cases, decreased BUN is evident within two weeks of administration.

- **Unpito (温脾湯)* or Shigyakukaninjinto (四逆加人参湯) added Rhubarb**: Consisting of shigyakuto (四逆湯)* (good for severe cold [*Kan*] with severe deficiency) , Ginseng (人参, ninjin) (enhances vigor by moistening fluid and activating stomach function), and Rhubarb (reported to have an anti-uremia effect). Appropriate for deficiency pattern patients. Has been found to improve the various symptoms of terminal-stage chronic renal failure and to effectively control the progression of renal dysfunction. If anorexia as well as epigastric discomfort and resistance (*Shinka Hiko*) are severe, Rhubarb can be added to bushirichuto (附子理中湯) which is ninjinto added Processed Aconite Root (附子, bushi), depending on the severity. Although no unpito (温脾湯)* extract preparations are available, bushirichuto added daio can be prescribed as extract preparations of two kinds, with the quantities of Processed Aconite Root (附子, bushi) and Rhubarb adjusted for coldness and bowel movement, respectively.

- **Daiokanzoto (大黄甘草湯)**: Rhubarb is used in expectation of its effect on renal failure, but its effects on cold and anorexia are often insufficient. Its inhibitory effect on the progression of kidney disorder has been recognized.

Astragalus Root (黄耆, ogi)-containig formulae

Astragalus Root (黄耆, ogi) -containing formulae, have been reported to lower Cr value in stable-stage patients.

- **Hochuekkito (補中益気湯)**: This prescription contains Bupleurum Root (柴胡, saiko), and is appropriate for ShoYo stage in deficiency pattern patients. The therapeutic target is qi (Ki) deficiency (*Kikyo*). Patients also have swollen tongue and mottled white fur; dissipated and large pulse (floating, large, and weak tendency); and fragile skin, which is an indication for Astragalus Root (黄耆, ogi) use. Even if other Bupleurum Root formulae may be effective, hochuekkito is used in many cases of terminal-stage chronic kidney failure and its efficacy is further enhanced with increased quantity of Astragalus Root. In effective cases, the Cr value tends to decrease after one or two weeks. If skin dryness is severe, the combined use with shimotsuto (四物湯) is favorable.
- **Other Astragalus Root-containing formulae**: There are reported cases in which other Astragalus Root-containing formulae— juzentaihoto (十全大補湯) and ogikenchuto (黄耆建中湯) — are effective for chronic renal failure.

Others

- **Hachimijiogan** (八味地黄丸): Effective for restless leg syndrome in maintenance dialysis patients and for pre-dialysis patients with a Cr value of 3.0 mg/dL or less.
- **Blood stasis-treating formulae**: Widely used to suppress renal impairment in stable stages and to reduce symptoms in the dialysis stage, independent of renal function level. Keishibukuryogan (桂枝茯苓丸) is also effective for prevention of shunt troubles. For severe cold (*Kan*), Processed Aconite Root (附子, bushi) is added to tokishakuyakusan (当帰芍薬散).
- **Dialysis complaints**: There are many reports of the rapid effectiveness of shakuyakukanzoto (芍薬甘草湯) for muscle cramp, or shakuyakukanzobushito (芍薬甘草附子湯) for cold (*Kan*) if any. For pruritus accompanied by dryness, tokiinshi (当帰飲子) is appropriate; orengedokuto (黄連解毒湯), if heat symptoms (熱候, nekko) are present; unseiin (温清飲), if heat symptoms and dryness are present.

3. Urinary Tract Diseases

Of urinary tract diseases, many pathologic conditions, including infection, stones, and nervous pollakiuria, often generate similar symptoms and signs. Appropriate Kampo prescriptions also overlap.

When 'lower abdominal region heat' symptoms are present

Subjective and objective findings indicative of lower abdominal region heat include lower abdominal and genital region heat sensation, hematuria, urination-related pain, burning sensation, and occasionally residual urine sensation as well as urination urgency.

- **Choreito** (猪苓湯): Typical prescription offered for lower abdominal region heat. Frequently used for acute and chronic cystitis (including similar conditions) and urinary stones. For recurrent urinary tract infection in elderly patients, one or two preventative doses per day are often effective.

- **Ryutanshakanto** (竜胆瀉肝湯): Patients have Yo pattern (陽証, *Yosho*) or excess pattern rather than choreito (猪苓湯)-pattern (*Choreitosho*) patients have. Effective for pathologic conditions involving severer heat symptoms.

Pathologic conditions associated with urination disorder

Prescriptions used for lower abdominal region heat are also offered. Other prescriptions are as follows.

- **Hachimijiogan - Goshajinkigan** (八味地黄丸・牛車腎気丸): Appropriate for pollakiuria, prolonged urination, and nocturnal urine. Also frequently used for prostate enlargement.
- **Seishinrenshiin** (清心蓮子飲): Used for urination urgency and nervous pollakiuria in deficiency pattern patients. Their pattern is similar to hachimijiogan (八味地黄丸)-pattern (*Hachimijiogansho*), but is associated with gastrointestinal weakness, nervousness, or depression tendency.
- **Others**: Shakuyakukanzoto (芍薬甘草湯) is used for colicky pain related to stones, but dosing is difficult for strong pain. Patients with intractable chronic prostatitis are likely to be stressed and frequently neurotic. Treatment with Bupleurum Root (柴胡, saiko) or blood stasis-treating formulae is effective in accordance with the patterns.

* Not available as ethical Kampo extract formulation

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Liver Dysfunction

Hiroshi Yamauchi

Overview of Disease

The diseases that cause liver dysfunction include viral hepatitis and cirrhosis, fatty liver, alcoholic liver disease, autoimmune hepatitis, primary biliary cirrhosis, drug-induced liver injury, cholelithiasis, and cholecystitis, etc. For chronic viral hepatitis, the current standards of care are advanced anti-viral therapies, using peginterferon (PEG-IFN), concurrent ribavirin (for chronic hepatitis C), and nucleotide analogues (for chronic hepatitis B), which have demonstrated marked sustained virological response (SVR). For intractable chronic hepatitis, which does not respond to anti-viral therapy or is not an indication of anti-viral treatment, liver-protecting and anti-inflammatory therapies are offered with stronger neo-minophagen C (a

glycyrrhizin-containig drug), ursodeoxycholic acid (UDCA drugs), etc.

Indications for Kampo Therapy

Acute hepatitis

Of the icteric diseases mentioned in the "*JinGuiYaoLue* (金匱要略)," dietary jaundice (穀疸) corresponds to acute viral hepatitis. Inchinkoto (茵蔯蒿湯) is used for moderate to severe jaundice, and heat-treating dampness-draining (*Seinetsu Rishitsu*) formulae such as inchingoreisan (茵蔯五苓散) are effective for mild jaundice. Bupleurum Root (柴胡, saiko)-containing formulae such as shosaikoto (小柴胡湯) and saikokeishito (柴胡桂枝湯) are offered if the patient presents with hypochondrium resistance and discomfort (*Kyokyo Kuman*), appetite loss, nausea, or fever.

Chronic hepatitis B and C

No anti-viral action is expected from Kampo formulae. During IFN treatment, qi (Ki) deficiency (*Kikyo*) and blood deficiency (*Kekkyo*) patterns (*Sho*) often develop as adverse reactions, so that concomitant use of deficiency pattern-treating formulae (*Hozai*) such as hochuekkito (補中益気湯) and juzentaihoto (十全大補湯) is often useful as supportive therapy for continuation or completion of IFN therapy. Deficiency pattern (*Kyosho*) is common among chronic hepatitis C patients of whom many are elderly, so that deficiency pattern-treating formulae often achieve a good response. Many patients also present with blood stasis (*Oketsu*) pattern, reflecting blood circulatory disorder: this pathological condition is considered to reflect primarily the progression to hepatic fibrosis stage or portal system congestion. A diagnosis of blood stasis is relatively easily made, on the basis of sublingual vein distension, palmar erythema, and paraumblical tenderness and resistance (*Saibo tenderness*) revealed by abdominal examination. To eliminate the blood stasis, blood stasis-treating (*Kuoketsu*) formulae such as keishibukuryogan (桂枝茯苓丸) and tokishakuyakusan (当帰芍薬散) are used in combination with deficiency pattern-treating formulae and Bupleurum Root (柴胡, saiko)-containing formulae.

Dampness heat pattern (*Shitsunetsusho*) is considered a pathological condition reflecting the necrosis and inflammation in hepatitis, and is readily observed when activity and ALT values are high. Heat-treating dampness-draining formulae such as inchinkoto and inchingoreisan may be used in combination.

Cirrhosis

Cirrhosis is a consequence of end-stage liver disease. As the condition is chronic and debilitating, it is generally considered a deficiency-pattern disease. Patients have a high incidence of deficiency of upper abdominal region (*Hikyo*) and qi (Ki) deficiency in particular, as well as fluid disturbance (*Suidoku*) and dual deficiency of qi (Ki) and blood. The main formulae are either qi (Ki) deficiency-treating formulae (*Hokizai*) or dual deficiency-treating formulae (*Kiketsu Sohozai*). Adding small quantities of a blood stasis-treating formula or a heat-treating dampness-draining formula may be effective. Diuretics are required in many cases of ascitic fluid in the decompensated cirrhosis patient; and combined formulae containing deficiency pattern-treating formulae and diuretics such as goreisan (五苓散) are useful. In many cases, a combination of formulae can

more easily control ascitic fluid and may offer the possibility of reducing the dosage of strong diuretics such as furosemide, when compared with diuretics alone.

Patients often suffer muscle cramp, which can be successfully treated with shakuyakukanzoto (芍薬甘草湯).

Fatty liver

Diet and therapeutic exercise are the basic therapies for both hypernutrition and simple fatty liver. Daisaikoto (大柴胡湯) or bofutsushosan (防風通聖散) is appropriate as ancillary therapy for obesity in excess heat pattern (*Jitsunetsusho*) cases.

Alcoholic liver disease

Abstaining or greatly reducing alcohol consumption is essential. Patients present with patterns such as fluid disturbance, dampness heat, *Kyokyo Kuman*, and upper abdominal region deficiency (*Hikyo*). Goreisan (五苓散), inchingoreisan (茵蔯五苓散), orengedokuto (黄連解毒湯), Bupleurum Root (柴胡, saiko)-containing formulae such as shosaikoto (小柴胡湯), and rikkunshito (六君子湯), etc. are offered on the basis of Kampo diagnosis.

Autoimmune hepatitis

The basic approach is steroid therapy. The combined use of shosaikoto or saireito (柴苓湯) with steroids enhances the efficacy of the steroids and allows dosage reduction, which is beneficial for long-term therapeutic use.

Primary biliary cirrhosis

Ursodeoxycholic acid is the only drug that has demonstrated effectiveness. Among the Kampo formulae, inchinkoto possesses choleretic, anti-inflammatory, and liver-cell protecting actions and is used in combination with ursodeoxycholic acid.

Cholelithiasis and cholecystitis

Daisaikoto (大柴胡湯) is used for excess-pattern (*Jitsusho*) cholelithiasis associated with obesity, and for excess-pattern acute cholecystitis and cholelithiasis, as well. Inchinkoto is offered for jaundice, and a single dose of shakuyakukanzoto, for upper abdominal pain. Saikokeishito is appropriate for deficiency-pattern cholelithiasis and biliary dyskinesia.

Frequent Formulae

The figure shows the main Kampo formulae used for liver disease. The formulae are divided into “chief formulae” and “combined formulae” to make treatment selection easier and more practical.

- **Shosaikoto (小柴胡湯):** A ShoYo stage (*Shoyobyo*)-harmonizing and releasing formula (和解剤, *Wakaizai*). It is representative of Bupleurum Root (柴胡, saiko)-containing formulae and has multiple

drug actions, including anti-inflammatory action (Bupleurum Root, Scutellaria Root [黄芩, ogon]), stomachic and anti-emetic action (Ginseng [人参, ninjin], Pinellia Tuber [半夏, hange], Jujube [大棗, taiso], Glycyrrhiza [甘草, kanzo], Ginger [生姜, shokyo]), and tranquilizer action (Bupleurum Root, Jujube, Glycyrrhiza). Target patients have moderate physical strength, *Kyokyo Kuman*, nausea, oral bitterness, and string-like pulse. Cirrhosis is a contraindication and combined use with IFN is also a contraindication. After an adverse reaction report of interstitial pneumonia due to shosaikoto (possibly a drug-induced allergy to the Scutellaria Root constituent), the frequency of shosaikoto use decreased, but in the 1980s researchers reported that the formula promotes chronic hepatitis B e-seroconversion.

- **Saikokeishito (柴胡桂枝湯):** Has a milder heat-treating effect than shosaikoto. Appropriate for chronic hepatitis patients who are liable to catch cold, and to suffer stress-induced abdominal pain or depressive condition. Patients also have gastrointestinal weakness and nervous tendency as well as moderate or weaker physical strength. Abdominal examination often shows tension in the rectus abdominis muscles of the upper abdomen (tightness below the heart [心下支結, *Shinka Shiketsu*]).
- **Daisaikoto (大柴胡湯):** Appropriate for excess-pattern patients who have remarkable *Kyokyo Kuman* or epigastric discomfort and resistance (*Shinka Hiko*) and ample physical strength. This formula has been very frequently used for fatty liver and cholelithiasis associated with obesity.
- **Kamishoyosan (加味逍遥散):** The most appropriate for deficiency-pattern patients with multiple complaints including susceptibility to irrtability, depressed mood, burning heat sensation in the upper body, and fatigue, specifically for female patients who have also climacteric disorder. Patients have commonly slight *Kyokyo Kuman* and blood stasis symptoms such as paraumblical tenderness and resistance (*Saibo tenderness*). This formula has been helpful for many female patients with deficiency-pattern chronic hepatitis and cirrhosis, indicating that it gives excellent autonomic tranquilizing effect.
- **Rikkunshito (六君子湯):** Formula of first choice for patients who have deficiency-pattern physical strength and symptoms of upper abdominal region deficiency (*Hikyo*) such as anorexia, chronic indigestion, and splashing sound (*Shinsuion*). This formula commonly increases appetite as well as feeling of wellbeing.
- **Ninjinto (人参湯):** Used in upper abdominal region deficiency (*Hikyo*) patients with sensitivity to cold, anorexia, and proneness to diarrhea and abdominal pain (deficiency cold of upper abdominal region [脾胃虚寒, *Hii Kyokan*]). Effective for more deficiency pattern than rikkunshito is.
- **Hochuekkito (補中益気湯):** Used in deficiency-pattern patients with reduced physical strength, especially those having qi (Ki) deficiency with strong fatigue and malaise, or visceroptosis. Widely offered as an essential treatment (*Honchi*) for deficiency pattern in both chronic hepatitis and cirrhosis patients. In a considerable number of patients who lack qi (Ki) deficiency symptoms including fatigue and malaise or fail to respond to Bupleurum Root -containing formulae, switching the chief formula to a deficiency pattern-treating formula such as hochuekkito can achieve satisfactory effects. Further, hochuekkito is often combined on a sho (pattern) basis with other formulae such as heat-treating dampness-draining formulae (inchingoreisan, inchinkoto), blood stasis-treating formulae (tokishakuyakusan [当帰芍薬散], keishibukuryogan [桂枝茯苓丸]) and

formulae treating deficiency of lower abdominal region (*Hojinzai*) such as rokumigan (六味丸) and hachimijiogan (八味地黄丸): the range of indications is broad.

- **Juzentaihoto (十全大補湯):** A dual deficiency-treating formula offered for patients with qi (Ki) deficiency including fatigue and malaise, anemia, as well as blood deficiency due to poor nutrition. Used for various pathological conditions associated with anemia and hypoproteinemia (hypoalbuminemia), and as an adjuvant to the various cancer therapies.

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Anemia – Bleeding Tendency

Takaaki Kosuge

Overview of Disease

Anemia

Anemia is defined as a condition of either absolute or relative reductions in erythrocyte count, hemoglobin level and hematocrit value.

In Western medicine, the main causes of anemia are (1) insufficient materials for erythrocyte production (hypoferric anemia), (2) hematopoietic disorder (aplastic anemia, pure red cell aplasia, myelofibrosis, myelodysplastic syndrome, etc.), (3) impaired cell maturation (renal anemia, megaloblastic anemia, etc.), and (4) excessive erythrocyte destruction (hemolytic anemia, hypersplenism, hemoglobinopathy, etc.).

Bleeding tendency

Bleeding diathesis (tendency) is an unusual susceptibility to bleeding on the skin or submucosal bleeding (1 and 2), or deep internal bleeding in joints, muscles, or organs (3 and 4): (1) skin or submucosal bleeding due to extravasation, as seen in allergic purpura, purpura simplex and senile purpura, (2) temporary hemostasis (thrombocyte hemostasis) disorder, as seen in petechial hemorrhagic lesion and purpura, epistaxis and ulorrhagia, gastrointestinal hemorrhage, and hypermenorrhea, (3) secondary hemostasis (blood coagulation factor-mediated hemostasis) disorder, and (4) abnormally accelerated coagulation or fibrinolytic system.

Indications for Kampo Therapy

Anemia

International standard therapies exist for the various classes of anemia. Once a definitive diagnosis has been made, replacement of iron, vitamin B12, folate, and/or erythropoietin as well as blood transfusion should start immediately. Kampo is not the first-choice therapy.

However, in Kampo terms, anemia is considered a blood-deficiency (*Kekkyo*) condition. Kampo formulae may improve symptoms caused by blood characteristics, not blood volume alone, as in (3) below.

(1) Cases in which Western medicine either is ineffective, or causes adverse effects

(2) Cases that, under the international standard therapy, only require monitoring without treatment: mild aplastic anemia, myelodysplastic syndrome (especially refractory anemia [RA] and refractory anemia with ringed sideroblasts [RARS]), and senile anemia

(3) Cases in which anemia symptoms continue despite blood values returning to normal.

Bleeding tendency

Western medical therapy is the first choice for (3) and (4) in section "Overview of Disease, Bleeding tendency" above, particularly for reasons of pathological condition severity. Kampo medicines demonstrate effectiveness for (1) and (2).

There are therapeutic guidelines for (2) idiopathic thrombocytopenic purpura (ITP), but not for other conditions.

In Kampo medicine, these symptoms are regarded as blood circulation abnormalities caused by the failure of blood control by qi (Ki).

Frequent Formulae

Anemia

Blood deficiency

Patients experience light-headedness and dizziness. The face becomes pallid and heart palpitations increase. In the limbs, heaviness and numbness develop. The skin loses its complexion and dries out, head-hair loss worsens, and anemia-like symptoms such as sleep disorders develop. The tongue becomes pale, and the pulse is fine.

- **Shimotsuto (四物湯):** The primary prescription for improving blood deficiency. Widely used as a combined formula or an addition to other formulae.
- **Kyukikyogaito (芎帰膠艾湯):** Used for bleeding associated with blood deficiency. Frequently effective for lower-body bleeding such as atypical genital bleeding, hemorrhoidal bleeding, and hematuria.
- **Tokishakuyakusan (当帰芍薬散):** Patients present with various symptoms, including blood deficiency and fluid disturbance (*Suidoku*). Effective for not only anemia but also gynecological disorder.

Dual deficiency of qi (Ki) and blood (*KiKetsu Ryokyo*)

Qi (Ki) deficiency (*Kikyo*) and blood deficiency are closely associated: many patients who have blood deficiency symptoms also suffer qi (Ki) deficiency. The tongue is pale, and the pulse is fine and vacuous.

- **Juzentaihoto (十全大補湯):** Shikunshito and shimotsuto fortified with Cinnamon Bark (桂皮, keihi) and Astragalus Root (黄耆, ogi). Most frequently used for anemia treatment. Effective for strong fatigue and malaise, general debility, night sweats, and coldness in hands and feet. In Western medicine, there is abundant evidence of myeloid stem cell differentiation-inducing activity.
- **Ninjinyoeito (人参養栄湯):** Similar to juzentaihoto, but appropriate for patients with more pronounced deficiency associated with coughing, sputum, shortness of breath, deficiency and heat (*Kyonetsu*), and nervous imbalance.
- **Kihito (帰脾湯):** Offered to patients with gastrointestinal and constitutional weakness who suffer bleeding or anemia as a result of overwork or nervous strain and who present with psychiatric symptoms including amnesia, insomnia, enervation and depressive tendency, in addition to strong blood deficiency symptoms.
- **Kamikihito (加味帰脾湯):** Useful for kihito (帰脾湯)-pattern patients suffering deficiency and heat with hot flashes, burning sensation, chest tightness, irritability and other nervous excitement. Often used as the first choice for ITP, based on the strong evidence, in Western medicine.

Qi (Ki) deficiency

Patients present with weak, shallow breathing, have little vocal force, and speak in a whispering tone. They are easily startled, and have facial pallor associated with intense limb or general malaise. Patients may also have anorexia, susceptibility to infection, and proneness to bleed. The tongue is pale and limp. Pulse is weak and soft, lacking vitality.

- **Shikunshito (四君子湯):** Typical prescription for qi (Ki) deficiency. Patients readily suffer painful abdominal distension, epigastric discomfort, nausea, vomiting, diarrhea, and other gastrointestinal weakness symptoms.
- **Rikkunshito (六君子湯):** Similar to shikunshito (四君子湯), but beneficial for stronger gastrointestinal symptoms, such as epigastric blockage sensation, than those in shikunshito-pattern patients.
- **Hochuekkito (補中益気湯):** Used in patients with remarkable general malaise, constitutional weakness, and weak digestion. Patients may also complain of sensation of visceroptosis or entire body ptosis, as well as taste disorder.
- **Ninjinto (人参湯):** Appropriate for patients having sensitivity to coldness as the chief symptom, and also gastrointestinal weakness symptoms as seen in shikunshito- and rikkunshito- pattern patients.

Bleeding Tendency

Excess heat (*Jitsunetsu*)

In pathological conditions with excess heat in all of the triple energizers, various symptoms associated with inflammation and congestion appear throughout the body. In mucous membranes, the most common manifestation is bleeding, which comes under the broad definition of bleeding diathesis. This includes epistaxis from nasal mucous membranes, hemoptysis from bronchial mucous membranes, and

hematemesis/melena from alimentary canal mucous membranes. Skin or submucosal bleeding in allergic purpura may also be included.

- **Orengedokuto (黄連解毒湯):** A typical heat-treating (*Seinetsu*) formula. Used in patients who are prone to hot flashes and irritability, and complain of epigastric discomfort (*Shinka Hi*) and chest tightness with palpitations. The pharmacological actions of Coptis Rhizome (黄連, oren) and Scutellaria Root (黄芩, ogon) help treat heat, cool blood (*Ryoketsu*) and arrest hemorrhage.
- **San'oshashinto (三黄瀉心湯):** Of the shashinto (瀉心湯) group, san'oshashinto is the leading prescription for the excess-pattern (*Jitsusho*). Its purgation effect helps eliminate the excess heat in the triple energizers and arrest hemorrhage. Used when patients have hot flashes, facial redness, nervous imbalance, and constipation tendency, in addition to stronger excess pattern than that in orengedokuto (黄連解毒湯)-pattern patients. Hemostasis may be effectively achieved with other shashinto-group formulae appropriate to the patient's pattern.

Deficiency of upper abdominal region (*Hikyo*)

In most cases of chronic bleeding tendency, deficiency of upper abdominal region (*Hikyo*) causes poor production of qi (Ki) and blood, disturbs blood circulation control, and leads to bleeding. In that sense, it is no exaggeration to say that the treatment of bleeding tendency is a matter of 'making up for the spleen'.

Qi (Ki)-treating (*Hoki*) and qi (Ki)- and blood-treating (*Hoketsu*) formulae are frequently used. See the previous section for details.

- Kihito (帰脾湯), Kamikihito (加味帰脾湯)
- Shikunshito (四君子湯), Rikkunshito (六君子湯), Hochuekkito (補中益気湯)
- Juzentaihoto (十全大補湯), Ninjinyoeito (人参養栄湯), Ninjinto (人参湯)
- Keihito (啓脾湯): Used when patients have stronger dyspepsia than in shikunshito (四君子湯)-pattern patients, and also remarkable watery or soft stool.

Other pathologies and formulae related to anemia and bleeding tendency

Blood stasis and qi (Ki) depression (*Kiutsu*), or stagnation (*Kitai*), may also be causes of anemia-like symptoms, submucosal hemorrhage or hemorrhage in the skin (瘀斑, ecchymosis), or localized bleeding. Blood stasis-treating (*Kuoketsu*) formulae and qi (Ki)-regulating (*Riki*) formulae may be useful.

- Hangekobokuto (半夏厚朴湯), Kososan (香蘇散): Qi (Ki)-regulating formulae.
- Kamishoyosan (加味逍遥散), Unkeito (温経湯), Nyoshinsan (女神散), etc.: Blood stasis-treating formulae.

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Cancer

Yoshiharu Motoo

Overview of Disease

Cancer occurs in various organs, with organ specificity. Its biological malignancy varies greatly according to histological type. Therefore, it is not possible to discuss the cancer in various forms as a single entity. In Japan, one out of two people will have some form of cancer during their lifetime and one out of three will die of it. Since 1981, cancer has been the top cause of death. By organ, lung cancer is number one on the list of cancer mortality among Japanese, followed by stomach, colorectal liver, and pancreas cancers in a descending order (2011/2012 National Public Health Trends). There have been sharp increases in prostate cancer in men, and breast cancer in women. Future measures require urgent attention. The three major cancer therapies are surgery, radiation, and chemotherapy. Each patient requires the most appropriate multidisciplinary treatments, including immunotherapy and palliative care. Less invasive surgical procedures have been and are being devised one after another; and especially remarkable advances have been made in endoscopic surgery. In radiotherapy, complications are decreasing as the irradiation field is narrowed to a pinpoint. In chemotherapy, the development of new anticancer agents and molecular-targeted drugs is demonstrating survival advantages, particularly in colorectal, breast, and renal cell cancers. Now, chemotherapy can render unresectable cancers amenable to potentially curable resection. Ultimately, some patients are freed from cancer.

Indications for Kampo Therapy

While Chinese medicine does use crude drugs termed “anticancer crude drugs”, in Japan it is virtually impossible to inhibit cancer growth with Kampo therapy alone within the framework of standard health insurance system. Instead, Kampo medicines offer much hope with their indirect antitumor effects through improvement of general condition. In the course of cancer management, Kampo may contribute to the following stages: treatment, follow-up, and palliative care. As mentioned above, Kampo is not expected to exert direct antitumor effects in cancer treatment; rather, it is intended to bring standard treatment to a successful conclusion with its chief goal being to reduce or prevent the adverse effects of various treatments. As mentioned below, Kampo can be used for symptoms that Western medicine finds difficult to deal with, such as peripheral neuropathy, anorexia, general malaise, and delayed diarrhea. This suggests that administering Kampo medicines with follow-up care for chronic (inflammatory) disease, especially liver disease, may lead to chemoprevention of hepatocellular cancer. Kampo can also be used in the follow-up after completion of postoperative adjuvant chemotherapy for all types of cancer. In palliative care, all kinds of Kampo medicines, especially prescriptions containing Processed Aconite Root (附子, bushi), can be used to reduce adverse effects and overcome resistance, as well as to increase the efficacy of the opioids used for pain relief. The rich variety of Kampo formulae offers many choices for psychoneurotic, digestive, and respiratory

symptoms, as well as pain.

Signs and symptoms not described in 'Frequent Formulae' will be summarized here.

For nausea and vomiting, there is no need to recommend Kampo medicines as the first choice. Rather, it is imperative to use 5-HT_3 and NK-1 receptor antagonists, dexamethasone, and others in accordance with the "Antiemetic Guidelines (2010)". However, in a recent randomized controlled trial (RCT), combined use of rikkunshito (六君子湯) significantly reduced nausea following chemotherapy on day 14 and tended to alleviate vomiting and anorexia as well.

Liver injury here refers to hepatic damage resulting from the use of anticancer agents (drug-induced liver injury), so that essential treatment includes discontinuation of medication and liver-supporting therapy. Ursodeoxycholic acid (UDCA) is often used in liver-supporting therapy, but inchinkoto (茵蔯蒿湯) is one of the possible measures for prolonged intrahepatic cholestasis. The level of evidence for its clinical effectiveness is not high, but there are detailed reports on the choleretic action mediated by the ingredient genipin in basic experiments.

What cancer patients and their families want is to enhance immune strength and to prevent its deterioration. Many patients want to maintain or enhance their immune strength while undergoing chemotherapy. That is also what attending physicians hope. However, there are only a few high-quality reports demonstrating the actual clinical effectiveness of Kampo formulations for prescription for tumor immunity improvement. Of those formulae, juzentaihoto (十全大補湯) has been reported to suppress inflammation after hepatectomy and prevent recurrence of hepatocellular carcinoma in RCTs, and also to suppress inflammatory cytokine and reactive oxygen species production by Kupffer cells on an experimental basis.

Frequent Formulae

Anorexia

- **Rikkunshito (六君子湯)**: The effectiveness of this prescription for anorexia following chemotherapy has been shown in basic studies and clinical trials. It has also been found that rikkunshito (六君子湯) reverses the blood acylghrelin decrease induced by chemotherapy (particularly cisplatin) and ghrelin receptor decrease in the hypothalamus.

Hematotoxicity

- **Kamikihito (加味帰脾湯):** Effectiveness has been demonstrated specifically for thrombocytopenia, though only in an observation study. The group treated with kamikihito showed milder thrombocytopenia and faster recovery than the untreated group.
- **Juzentaiho (十全大補湯):** Used for anemia and leukocytopenia, but only as an auxiliary role. Experimental studies have shown increases in spleen colony counts after irradiation, suggesting that juzentaihoto (十全大補湯) accelerates myeloid stem cell growth.

Stomatitis

- **Hangeshashinto (半夏瀉心湯):** It has been considered that chemotherapy-induced stomatitis

develops via the mechanism that oral mucosal cells with high cell turnover undergo apoptosis due to the increases in reactive oxygen species, cytokines, and prostaglandins that are induced by an anticancer agent. It is reported that hangeshashinto (半夏瀉心湯) is effective for chemotherapy-induced stomatitis through the action mechanisms involving inhibition of prostaglandin E2 induction and the antibacterial action of the ingredient crude drug Coptis Rhizome (黄連, oren).

Bowel Movement Disturbance

- **Daikenchuto (大建中湯):** This is used for prevention of postoperative ileus and intestinal hypomotility. The efficacy on opioid-induced constipation is also promising.
- **Hangeshashinto (半夏瀉心湯):** Effectiveness for delayed diarrhea due to irinotecan hydrochloride (CPT-11) is well known. Dosing prior to CPT-11 is recommended as a prophylactic.

Peripheral Neuropathy

- **Goshajinkigan (牛車腎気丸):** Appropriate for peripheral neuropathy due to paclitaxel and oxaliplatin. The chief symptom is numbness in the extremities. Chemotherapy must be discontinued before onset of functional disorder. However, these two anticancer drugs differ in the mechanism of inducing peripheral neuropathy. Paclitaxel induces axonopathy whereas oxaliplatin causes neuronopathy. Therefore, especially in the case of oxaliplatin, alternative Kampo preparations must be sought.

General Malaise - Cancer Cachexia

- **Hochuekkito (補中益気湯):** Of the Kampo preparations available, hochuekkito is most often administered to advanced and recurrent cancer patients with a complaint of general malaise as well as fatigue. While interleukin-6 (IL-6) is involved in cancer cachexia, the fact that hochuekkito has an IL-6 inhibiting activity is only mentioned in reports of invasive surgery and infection models, and it does not appear in cancer-related reports. Further elucidation of the action mechanisms of hochuekkito (補中益気湯) is expected, as activin receptor type IIB (ActRIIB) has recently been found to link with cancer cachexia.

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Chapter 5

Kampo Pharmacy

Kampo medicines

Masayuki Yoshikawa

Crude drugs composing Kampo medicines

Crude drugs have been selected from natural products, including animals, plants, and minerals, on the basis of long-year use experience by humans. The methods for selecting medicinal parts, and for preserving and processing them have well devised and passed down to today. Since crude drugs are derived from natural products, they have been called natural medicines; or since they possess folklore drug efficacies (伝承薬効) and are used in traditional medicine, they have been also referred to as traditional medicines. The Japanese Pharmacopoeia (JP) defines "Crude drugs include medicinal parts obtained from plants or animals, cell inclusions, secretes (separated from the origins), and their extracts, and minerals."

Classification and characteristics of crude drugs

There are a huge number of crude drugs over the world. Their comprehension and utilization require categorizing and compiling them. Crude drugs are, for example, categorized as shown in Table 1, and sometimes are arranged in an order of the Japanese (*kana*) syllabary or stroke count of Kanji.

It is known that since a large number of ingredients are contained in crude drugs, the combination of discrete activities from the ingredients induces diverse interactions to produce a variety of efficacy. In this context, crude drugs greatly differ from synthetic pharmaceutical products that consist of single compounds with limited drug efficacies. Even though some crude drugs are known as the same name, they may differ from each other in drug efficacy and quality, particularly in case of different original plants, and for identical original plants, depending on the source (affected by climate, soil, growth environment, and other factors), collection timing, and processing. Therefore, many kinds of commercial products are present on the market.

Table 1. Classification of crude drugs

Classification basis	Kind	Crude drugs, typical
1. Traditional Medicine (region)	Kanyaku (Traditional Chinese medicine)	Glycyrrhiza (甘草, kanzo), Rhubarb (大黄, daio)
	Wayaku (Japanese folk medicines)	Hypericum Erectum (otogiriso), Swertia Herb (senburi)
	Ayurvedic crude drugs (Traditional Indian medicine)	Rauwolfia (indojaboku), Gymnema Herb (gimunema)
	Western crude drugs (Traditional Western medicines)	Gentian, Belladonna Root (beradonnakon)
	Others including Unani crude drugs (Islamic medicine)and Jamu crude drugs (Traditional Indonesian medicine)	
2. Natural scientific classification (plant taxonomy)	Plant crude drugs → → → Crude drugs in Apiaceae	Bupleurum Root (柴胡, saiko), Japanese Angelica Root (当帰, toki)
	Animal crude drugs	Oriental Bezoar (牛黄, goo), Musk (麝香, jako)
	Mineral crude drugs	Gypsum (石膏, sekko), Longgu (竜骨, ryukotsu)
3. Parts for medicinal use	Crude drug leaves	Sweet Hydrangea tea (甘茶, amacha), Senna Leaf (senna)
	Crude drug fruits	Jujube (大棗, taiso), Forsythia Fruit (連翹, rengyo)
	Crude drug seeds	Plantago Seed (車前子, shazenshi), Peach Kernel (桃仁, tonin)
	Other crude drugs (barks, rhizomes, roots, whole herbs, etc)	
4. Contained ingredients	Saponin crude drugs	Platycodon Root (桔梗根, kikyokon), Ginseng (人参, ninjin)
	Alkaloid crude drugs	Coptis Rhizome (黄連, oren), Phellodendron Bark (黄柏, obaku)
	Tannin crude drugs	Gambir (阿仙薬, asen'yaku), Geranium Herb (gennoshoko)
	Other crude drugs containing anthraquinones, essential oils, or bitter	
5. Uses; drug efficacy	Cardiotonic crude drugs	Digitalis (jigitarisu), Toad Cake (蟾酥, senso)
	Stomachic crude drugs	Fennel Fruit (茴香, uikyo), Japanese Gentian (竜胆, ryutan)
	Other crude drugs (purgative, anti-diarrheal, tonic, and antiparasitic crude drugs, etc)	
	Exterior pattern-treating formulae	Cinnamon Bark (桂皮, keihi), Ephedra Herb (麻黄, mao)
	Heat pattern-treating formulae	Gardenia Fruit (山梔子, sanshishi), Gypsum (石膏, sekko)
	Other formulae (interior pattern-treating formulae (温裏薬), liver function-treating formulae (平肝薬), tonifying and replenishing formulae (補益薬), etc.)	

Production and Distribution of Crude Drugs

In Japan, since Kampo medicine has developed on the basis of traditional Chinese medicine, a large number of crude drugs for therapeutic purposes had been imported mainly from China. In the middle phase of the Edo period, the Tokugawa Shogunate promoted the cultivation of medicinal herbs and the establishment of a garden for medicinal herbs, advancing the cultivation of medicinal plants such as Ginseng (otaneninjin) and the development of alternative drugs including Panax Japonicus Rhizome (竹節人参, chikusetsuninjin). So far, the advanced cultivating technology is inherited but has become not profitable owing to elevated costs including personnel cost. Therefore, only a very small proportion of the needed crude drug plants are produced domestically, including Japanese Angelica Root (当帰, toki), Cnidium Rhizome (川芎, senkyu), Peony Root (芍薬, shakuyaku), Citrus Unshiu Peel (陳皮, chimpi), Magnolia Bark (厚朴, koboku), and Bupleurum Root (柴胡, saiko). The other crude drug plants are imported not only from China, Korea, India, and Indonesia, but also from Africa, Europe, and North and South America. However, even in China, Korea, and some of these crude drug plant-producing countries, steady production has become difficult. The reasons include the destruction of natural environment associated with modernization, decreases in the number of cultivation technicians, and sharply elevated costs. In 1973, an international agreement known as the Washington Convention (on international trade in endangered species of wild fauna and flora) was adopted and did prohibit the import of many crude drugs for Kampo, including Musk (麝香, jako) and Rhinoceros Horn (犀角, saikaku) from wild animals. In 2010, the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity was adopted at the 10th meeting of the Conference of the Parties to the Convention on Biological Diversity (COP10). An agreement was made between developed and developing countries. The future task to be tackled is utilization in consideration of preservation of crude drug resources.

Table 2 lists the import amount and domestic production amount of major crude drugs today. Higher import amounts are evident of Ginger (生姜, shokyo), Coix Seed (薏苡仁, yokuinin), Capsicum (番椒, togarashi), Turmeric (鬱金, ukon), and Glycyrrhiza (甘草, kanzo), which are used for eating as spices or sweetening, or as cosmetic raw materials as well as for medicinal use. Generally, crude drugs are imported from overseas by crude drug wholesalers; otherwise, are collected by domestic collectors of wild produce or from crude drug-cultivating farmers. Then these crude drugs are often delivered to pharmaceutical companies or transferred to pharmacies and hospitals via crude drug subdividers. A few pharmaceutical companies provide cultivation guidance to obtain crude drugs directly from foreign and domestic farmers. Part of those may be placed on the market via crude drug wholesalers and subdividers.

Table 2. Import amounts and domestic production amount of main crude drugs

Crude drug name	Import amount (kg)	Domestic production amount(kg)	Crude drug name	Import amount (Kg)	Domestic production amount (kg)
Ginger (生姜, shokyo)	23,804,000	3,000	Clove (丁子, choji)	220,000	
Coix Seed (薏苡仁, yokuinin)	6,971,000	50,000	Japanese Angelica Root (当帰, toki)	200,000	100,000
Capsicum (番椒, togarashi)	4,000,000		Bupleurum Root (柴胡, saiko)	200,000	40,000
Turmeric (鬱金, ukon)	3,727,000	10,000	Rhubarb Rhizome (大黄, daio)	170,000	35,000
Glycyrrhiza (甘草, kanzo)	2,016,000		Alisma Rhizome (沢瀉, takusha)	200,000	
Cinnamon Bark (桂皮, keihi)	1,259,000		Moutan Bark (牡丹皮, botampi)	130,000	1,000
Cassia Seed (決明子, ketsumeishi)	1,200,000	3,000	Atractylodes Rhizome (白朮, byakujutsu)	130,000	300
Safflower (Carthamus) (紅花, benibana)	1,053,000	2,000	Cnidium Rhizome (川芎, senkyu)		120,000
Ginseng (人参, ninjin)	621,000	8,000	Astragalus Root (黄耆, ogi)	100,000	12,000
Jujube (大棗, taiso)	550,000		Platycodon Root (桔梗, kikyo)	110,000	1,000
Ephedra Herb (麻黄, mao)	523,000		Peach Kernel (桃仁, tonin)	110,000	
Peony Root (芍薬, syakuyaku)	400,000	80,000	Discorea Rhizome (山薬, san'yaku)	100,000	3,000
Scutellaria Root (黄芩, ogon)	400,000		Apricot Kernel (杏仁, kyonin)	90,000	
Phellodendron Bark (黄柏, obaku)	350,000	35,000	Perilla Herb (蘇葉, soyo)	70,000	5,000
Citrus Unshiu Peel (陳皮, chimpi)	250,000	70,000	Magnolia Bark (厚朴, koboku)	10,000	60,000
Poria Sclerotium (茯苓, bukuryo)	300,000	1,000	Ophiopogon Tuber (麦門冬, bakumondo)	60,000	
Rehmannia Root (地黄, jio)	250,000	2,000	Sinomenium Stem (防已, boi)	20,000	40,000
Gardenia Fruit (山梔子, sanshishi)	250,000	1,000	Mentha Herb (薄荷, hakka)	50,000	2,000
Pinellia Tuber (半夏, hange)	250,000		Coptis Rhizome (黄連, oren)	35,000	2,000
Atractylodes Lancea Rhizome (蒼朮, sojutsu)	230,000		Processed Aconite Root (附子, bushi)	18,000	

Current Production Survey of Crude Drugs Union of crude drugs

Processing and manufacturing of crude drug products

Fresh intact materials of medicinal plants were used for the utilization of crude drugs in early days. With the development of medical care, processing such as removal of non-medicinal parts of the plants and drying for storage has been carried out to yield quality-controlled crude drug products. The JP specifies that 'Unless otherwise specified, crude drugs are used in dried form.' The drying is usually carried out at a temperature not exceeding 60℃. Crude drugs are usually stored in the form of whole, cut, or powdered crude drugs in cold and dark places. The JP also specifies that 'Crude drugs are preserved in well-closed containers unless otherwise specified.' Therefore, Powdered Cinnamon Bark containing volatile constituents is preserved in a tight container; Safflower containing light-sensitive constituents, in a well-closed light-shielding container; and Digitalis containing light- and moisture-sensitive constituents, in a light-shielding tight container. For protection from harmful insects and microbes, carbon dioxide, chloroform, carbon tetra chloride, and the like are used. For the treatment of large amounts of crude drugs in a storehouse, fumigation is conducted with sulfur, methyl bromide, ethylene oxide, and the like. In the JP, it is mentioned that 'In order to avoid insect damage, suitable fumigants may be used to preserve crude drugs," provided that the fumigants are so readily volatilized as to be harmless at the usual dosage of the crude drugs.

For medical necessity, secondary processing of crude drugs, a specific processing (修治, *shuji*) (also termed pao zhi [炮制], pao jiu [炮灸] and ziu shi [修事] in China) is also carried out. The purposes of this processing include 1) reducing adverse or side effects such as toxicity and irritability, 2) modifying traditional medicine-typical properties (ingredients [薬味, yakumi], nature [薬性, yakusei], and action [薬能, *yakuno*]) of crude drugs, 3) enhancing drug efficacy, 4) preventing deterioration and insect damage in storage, 5) adjusting the taste, flavor and color of crude drugs, 6) removing non-medicinal parts and improving crushing easiness. Specifically, the processing comprise various techniques of exposing to flowing water, dipping in drug solution(s), burning, steaming, boiling, fermenting and adding complementary crude drugs (補料, horyo). Today, the JP contains processed crude drugs, such as Powdered Processed Aconite Root (kako bushimatsu; Hobushi [炮附子], Processed Ginger (乾姜, kankyo), Red Ginseng (紅参, kojin), and Sweet Hydrangea Leaf (甘茶, amacha). In addition, Processed Rehmannia Root (熟地黄, jukujio), Processed Glycyrrhiza (炙甘草, shakanzo) and some processed crude drugs are employed in several Kampo hospitals.

Crude drugs, derived from wild or cultivated plants, are dealt with as agricultural produces until delivered to the storehouses of crude drug wholesalers, and thereafter become pharmaceuticals, which are dealt in accordance with the Good Manufacturing Practices (GMP) and manufactured via the following steps.

①After delivery of crude drug materials, a test for acceptance is carried out.

↓

②Sorting out of foreign matters

↓

③Cutting in pieces of crude drugs (Bupleurum Root [柴胡, saiko], Pinellia Tuber [半夏, hange], Ginseng [人参, ninjin], Glycyrrhiza [甘草, kanzo], Alisma Rhizome [沢瀉, takusha], etc. are soften with water, then cut in pieces, and dried at about 60ºC).

↓

④The crude drug pieces are sieved into different sizes (that serve as intermediate products), according to the specifications.

↓

⑤An intermediate test is conducted, according to the standards for intermediate products.

↓

⑥After the intermediate test, packaging is carried out before the final test including labeling check.

↓

⑦After the final test, appropriateness for shipment is determined to ship the crude drug products by the manager for drug manufacture.

In health service, crude drugs are roughly divided into three groups: ethical single crude drugs that are listed in the drug price list and are used under the supervision of physicians; OTC crude drug products that include Japanese folk medicines and are used by general consumers; and crude drugs that private companies use for manufacture of crude drug products.

i) Ethical single crude drugs: Are the crude drugs that are used by physicians or dentists themselves or under their guidance or supervision, and that are covered by the national health insurance (NHI), or listed in the NHI drug price list. As of August 2004, a total of 241 items are listed and mentioned to be used for dispensing of Kampo formulae.

ii) OTC crude drug products: Are the crude drugs that general consumers purchase at pharmacies or drug stores to use on their own decisions. Of these crude drugs, efficacies, effects, and administration and dosage are described. Twenty eight JP crude drug products are applicable, including Bearberry Leaf (uwaurushi).

iii) Crude drugs dedicated to manufacturing: Are the crude drugs that are used as raw materials for manufacture of pharmaceuticals or 212 pharmacy Kampo formulae. These crude drugs are labeled as ‘manufacture-only,’ with an additional mention that they are used as materials of Kampo products, or so.

Differentiation and quality assessment of crude drugs

The natural products of crude drugs entail many analogues. Frequently, the crude drugs named noble drugs are contaminated with non-noble sham drugs. Even though original animals or plants are identical, the contents of active ingredients may vary depending on the source, growth (cultivation) conditions, collecting timing, processing methods and storage state. In Japan, where many crude drugs are used after imported from China,

Korea, and other foreign countries, some of those imports may differ from Japanese not only in origin, name, processing method, but also in quality control and specification standards. Accordingly, there is a concern about possible contamination with some foreign matters not satisfying the JP requirements. Table 3 lists typical crude drugs whose original plants and medicinal sites vary between Japan and China. The crude drugs used in traditional Chinese medicine may contain original plants which are different from or allied to those stipulated in the JP, or for which the medicinal sites and processing methods (including the special processing [修治]) are different from those specified in JP.

Table 3. Typical crude drugs that differ in origin between Japan and China

Japanese Angelica Root (当帰, toki)	Japan: toki (*Angelica aculiloba*) or hokkaitoki (*A. aculiloba* var. *sugiyamae*) root (usually blanched or steamed) China: dang gui [当帰] (*A. sinensis*) root
Cnidium Rhizome (川芎, senkyu)	Japan: senkyu (*Cnidium officinale*) rhizome (usually blanched or steamed) China: chuan xiong [川芎] (*Ligusticum chuanxiong*) rhizome
Sinomenium Stem and Rhizome (防已, boi) 防己 (fang ji)	Japan: otuzurafuji (*Sinomenium acutum*） climbing stem and rhizome (used under the name of quing feng teng [清風藤] in China） China: fen fang ji [粉防己] (*Stephania tetrandra*) root (called kanboi［漢防己］in Japan)
Akebia Stem (木通, mokutsu) 川木通 (chuan mu tong)	Japan: akebi (*Akebia quinata*) or mitsubaakebi (*A. trifoliata*) climbing stem China: mu tong [木通] (*A. quinata*) ， san ye mu tong [三叶木通] (*A. trifoliata*), bai mu tong [白木通] (*A. trifoliata* var. *australis*) vine stem China: xiao mu tong [小木通] (*Clematis armandi*) ， xiu qiu teng [綉球藤] (*C. montana*) climbing stem
Zanthoxylum Fruit (山椒, sansho) 花椒 (hua jiao)	Japan: sansho (*Zanthoxylum piperitum*) ripe fruit peel China: hua jiao [花椒] (*Z. bungeanum*), qing jiao [青椒] (*Z. schinifolium*) fruit peel
Zedoary (莪述, gajyutsu) 莪朮 (e zhu)	Japan: gajyutsu (*Curcuma zedoaria*) rhizome (usually blanched) China: peng e zhu [蓬莪朮] (*C. phaeocaulis*), guang xi e zhu [广西莪朮] (*C. kwangsiensis*), wen yu jin [温郁金] (*C. wenyujin*) rhizome
Bupleurum Root (柴胡, saiko)	Japan: mishimasaiko (*Bupleurum falcatum*) root China: chai hu [柴胡] (*B. chinense*) (北柴胡), xia ye chai hu [狭叶柴胡] (*B. scorzonerifolium*) (南柴胡) root

Glycyrrhiza (甘草, kanzo)	Japan: *Glycyrrhiza uralensis or G. glabra* root and stolon China: Gan cao [甘草] (*G. uralensis*), guan guo gan cao [光果甘草] (*G. glabra*), zhang guo gan cao [脹果甘草] (*G. inflata*root and rhisome)
Artemisia Capillaris Flower (茵陳蒿, inchinko) 茵陳 (yin chen)	Japan: kawarayomogi (*Artemisia capillaris*) spike China: yin chen hao [茵陳蒿] (*A. capillaris*), bin hao [濱蒿] (*A. scoparia*) over-ground part (seedling: 綿茵陳)

＊Red species in the table are not listed in the Pharmacopeia of the People's Republic of China 2010.

Furthermore, several Kampo names are different between Japan and China. For example, the rhizome of *Curcuma longa* (akiukon) is called Turmeric in Japan, but jiang huang [姜黄] in China, where the root tubers of *C. phaeocaulis*, *C. kwangsiensis*, and *C. wenyujini* as well as *C. longa* are used as yu jin (郁金). Ginger (生姜, shokyo) is referred to as the dried rhizome of ginger in Japan, but means fresh rhizome in China. In contrast, Processed Ginger (乾姜, kankyo) is the blanched or steamed, and then dried rhizome of ginger in Japan, but in China, means the dried rhizome of ginger, which is identical to Ginger (shokyo) in Japan. Attention must be paid to the entity of these crude drugs. Thus, it is required that crude drugs be identified according to the morphology of raw material plant, and by comparison of ingredients, genetic analysis and other reliable means, and that their original plant sources and quality be confirmed in reference to the JP requirements for the supply to the clinical settings.

The JP was first issued in June 1886, since then has been repeatedly revised in association with development of new drugs and technological improvement for various tests. Most recently, the 16 version was published in March 2011, including the criteria for crude drugs that are used in medical care practice as well as for manufacturing medical materials— General Rules for Crude Drugs and Tests for Crude Drugs. General quality evaluations of crude drugs are as follows:

i) Origins of crude drugs:

Some are limited to one plant species; others are allowed to have multiple species of the same genus. (Confirmation of origin species by means of old literature, current status of production and distribution, plant classification, morphology, ingredient analysis, genetic analysis, and other techniques)

ii) Example tests for crude drugs:

a) Description and morphology test (appearance, sensory test, microscopic examination; b) Identification test; c) Purity test (residual pesticides, heavy metals, and arsenic limit tests); d) Test for total ash; e) Test for loss on drying; f) Test for acid-insoluble ash; g) Test for ingredient, extract, and essential oil contents (stipulation of the reference contents of specific ingredients, extracts extracted with diluted ethanol, and essential oils).

For each of the crude drugs and Kampo formulae contained in JP, description, identification test, and purity test are specified in the given article. A crude drug is discriminated and identified by morphological and

ingredient-mediated physicochemical techniques. The morphological approach comprises macroscopic and loupe-assisted observation of the external appearance, mainly for identification of a whole crude drug through five senses. Identification of cut or powdered crude drug requires microscopic observation of the internal structure, tissues and cell inclusions of the crude drug. The internal morphology is useful to discriminate the crude drug from foreign analogues or counterfeits if any.

The ingredient-mediated technique uses identification test for that crude drug. The test is based on the specific color reactions for alkaloids, flavonoids, phenolic compounds, triterpenes, steroids, saponins, and other compounds as well as functional groups; and the specific color presentation, precipitation, change in description for particular compounds.

For quality assessment of crude drugs, the JP specifies the purity test for non-medicinal parts of original plants or animals; limit tests for foreign matters, residual pesticides, heavy metals and arsenic; measurements for loss on drying, total ash, and extract content; and quantitative determination of particular ingredients by high performance liquid chromatography and gas chromatography.

Characteristics of Kampo products

So far, Kampo medicines have been used mainly as decoctions for the treatment of illness, and administered in the form of mixture of crude drug pieces for decoction. In home-made medicines, nostrums, and drugs for household delivery, pills and powder (powdered drugs) have played a main role. Kampo extract products were developed in 1957, and then have been in wide use for the sake of convenience. In 1967, Kampo extract products were first covered by the national health insurance and now a total of 148 formulae are listed as ethical Kampo extract products in the drug tariff. However, since Kampo medicines are the mixtures of crude drugs derived from natural products, and are used on the basis of Kampo-specific diagnoses and therapeutic methods, the active components and entity of Kampo medicines have not been fully clarified. In addition, quality control chiefly of active components, as seen in synthetic pharmaceuticals, and clinical verification of the efficacy were sometimes difficult. Thus, quality assurance of raw material crude drugs, verification of the equivalence to decoctions (湯液), and establishment of the standards for extract manufacturing processes are being carried out in parallel to elucidation of the efficacy and safety as well as quality assessment.

Differences between Kampo medicines and Western or folk medicines

Kampo is the traditional Japanese medicine that was introduced from China and has uniquely developed in Japan. One of its characteristics is to carry out the treatment for the whole man, which is expressed in the word '*shinshin-ichijyo* (心身一如)'. That is, in Kampo therapy, the individual constitution including the mental aspect as well and pathologic conditions are subjectively judged on the previous experiences, then therapeutic Kampo medicines are selected, and an overall medical care is administered aiming at harmonization of the whole body and maintenance of homeostasis. Since Kampo medicines are composed of diverse combinations of crude drugs, a variety of components, or mixed compounds, are considered to interact and exert various activities and effects.

In Western medicine, diagnosis is established on the basis of laboratory data analyzed and objective

judgment of affected site(s) and affection cause(s). Such a diagnosis is regarded as logical, reproducible and scientific. Then, single compounds of which the site of action and the mechanism of action have been clarified are universally applied to affected organs and tissues. In contrast, Kampo medicine may offer different therapies to patients with the same disease that was diagnosed according to Western medicine (*dobyo-ichi* [同病異治]), but the same therapy, or formula, to those with different diseases diagnosed by Western medicine (*ibyo-dochi* [異病同治]). Furthermore, in Kampo medicine, the state in which there are little affection is regarded as presymptomatic (*mibyo* [未病]) and early treatment of this state is recommended before the onset of full-scale affection, from the perspective of preventive medicine. This concept includes the view that diseases can be prevented by incorporation into eating habits of crude drugs abundant in dietetic elements, as is termed '*ishoku-dogen* (医食同源)'or '*yakushoku-dogen* (薬食同源)' (medicine and food coming from the same source).

. Folk medicines, unlike the crude medicines that are used in Kampo medicine and ayurveda, refer to such crude drugs that have no background of traditional medicine, which has been constructed theoretically and systematically. Folk medicines are found all over the world, and are being used as a symptomatic treatment, based on the empirical drug efficacy. Generally, folk medicines consist of single crude drugs and do not compose such formulae as Kampo medicines do, with unclear dosage and administration. In Japan as well, ancient books such as "*Kojiki* (古事記)", "*Nihonshoki* (日本書記)", "*Fudoki* (風土記)", and "*Engisiki* (延喜式)" suggest that there was a unique medical care system comprising peculiar medicines and incantations. For example, the Izumo myth of "*Inaba no shiro usagi* (因幡の白兎)" in "*Kojiki*" indicate that the ear of gama (蒲, *Typha latifolia*) was applied to wounds for hemostasis. Of such Japan-indigenous medicines and medical care systems, a scanty amount has been inherited as folklore therapies in the shadow of the development of Chinese and other foreign medicines and medical care systems. In Japan today, the crude drugs used as folklore therapies are called Japanese folk medicines. Table 4 presents typical Japanese folk medicines. Most of these use single crude drugs. However, Panax Japonicus Rhizome (竹節人参, chikusetsuninjin) and Glehnia Root and Rhizome (浜防風, hamabofu) were found as alternatives of the Kan-yaku Ginseng (人参, ninjin) and Saposhnikovia Root (防風, bofu), respectively, and each has been used in combinations for formulae. Cherry Bark (桜皮, Ohi) and Nuphar Rhizome (川骨, senkotsu) are component crude drugs for the Kampo formulae created in Japan.

Table 4. Typical Japanese folk medicines

Crude drug name	Origin	Use, history, and others
Sweet Hydrangea Tea (甘茶, amacha)	Fermented leaf of amacha *(Hydrangea macrophyla* [Thunb.] SER. VAR *thunbergii* [SIEB.] MAKINO).	Found as a sweet variety of yamaajisai (*H.macrophyla* [Thunb.] Ser. var. Acuminata [Sieb. et Zucc.] Makino) in the middle of the Edo period. A sweetener and flavoring agent. Listed in the JP.
Urajirogashi Oak (urajirogashi)	The leaf of urajirogashi (*Quercus salicina* BLUME)	Can suppress bladder stone formation, and can dissolve bladder stones. Used for cholecystolothiasis and nephrolithiasis.
Plectranthus (延命草, enmeiso)	The whole herb of hikiokoshi (*Rabdosia japonica* HARA)	An alternative of ryutan (竜胆) or senburi in the Edo period. A bitter stomachic.
Cherry Bark (桜皮, ohi)	The bark of yamazakura (*Prunus jamasakura* SIEB. ET OIDZ.)	A antitussive, expectorant, and antidotal agent in the Edo period. Contained in jumihaidokuto (十味敗毒湯) and jidabokuippo (治打撲一方).
Hypericum Erectum (otogiriso)	The whole herb of otogiriso (*Hypericum erectum* THUNB.)	Called xiao lian qiao (小連翹) in China． A hemostatic agent as well as astringent and mouthwash.
Catalpa Fruit (kisasage)	The root of kisasage (*Catalpa ovata* G. DON)	A diuretic. Listed in the JP.
Geranium Herb (Gennoshoko)	The whole herb of gennnosyoko (*Geranium thunbergii* SIEB. ET ZUCC.)	An astringent, antidiarrheal, stomachic and antiflatulent agent in the beginning of the Edo period. Reported to have trichogenic, analgesic, and anti-inflammatory effects, too. Listed in the JP.
Houttuynia Herb (十薬, juyaku)	The flower, leaf, and stem in bloom of dokudami (*Houttuynia* cordata THUNB.)	Called yu xing cao (魚腥草) in China. A diuretic, laxative, and antidortal agent. Listed in the JP.
Nuphar Rhizome (川骨, senkotsu)	The rhizome of kohone (*Nuphar japonicum* DC.)	An antipyretic, analgesic, antiphlogistic agent in the Heian period. Contained in jidabokuippo(治打撲一方) and jitsubosan (実母散). Listed in the JP.
Panax Japonicus Rhizome (竹節人参, chikusetsuninjin)	The rhizome of tochiba-ninjin (*Panax japonicus* C.A.MEYER)	Was contained as an alternative of ginseng in shosaikoto (小柴胡湯), and hangeshashinto (半夏瀉心湯), and the like in the beginning of the Edo period. A stomachic, antitussive, and expectorant agent. Listed in the JP.
Swertia Herb (senburi, 千振, 当薬)	The whole herb in bloom of sennburi (*Swertia japonica* MAKINO)	An alternative of the Kan-yaku "hu huang lian (胡黄連)" in the end of the Muromachi period. A bitter stomachic. Listed in the JP.
Nandina Fruit (南天実, nantenjitsu)	The mature fruit of nanten (*Nandina* domestica THUNB.)	A cold remedy with antitussive and expectorant effects.
Glehnia Root and Rhizome (浜防風, hamabofu)	The root and rhizome of hamabofu (*Glehnia littoralis* FR. SCHM.EX. MIQ.)	Was contained as an alternative of bofuin jumihaidokuto (十味敗毒湯), keigai-rengyoto (荊芥連翹湯), seijobofuto (清上防風湯), bofutushosan (防風通聖散) and the like. A perspirative, antipyretic, and analgesic agent.

Dosage form and kind for Kampo products

The conventional dosage forms of Kampo products have included decoction, pill, powder, and ointment, as listed below. However, preparation of a decoction has been a troublesome work and has burdened patients. It has also lacked convenience — not suitable for today's lifestyle — in preservation as well as carriage. Regarding pills and powders, safety and handling on medication have been problematic.

i) Decoction: Generally in Japan, a prescription per day is placed in about 600 ml of water and decocted for 30 – 60 minutes up to about the half of the volume. After decoction, the residue cooled to room temperature is filtered out through a tea strainer or gauze before the decoction is taken in three divided doses a day. As the vessel for decoction, an earthen (ware) tea pot or alumite (anodic oxidation-treated) pot is good, whereas no iron pot is used because it reacts to the tannin contained in some crude drugs. Decoction is called 'to-zai', 'to-eki' and 'senji-gusuri (kusuri)' in Japanese. As seen from hachimi(jio)ganryo (八味[地黄]丸料), the 'ganryo (丸料)' added to the prescription name indicates the conversion from pill or powder to decoction.

ii) Pill: Powdered crude drugs are mixed with honey and serial powder serving as a filler and binder and kneaded for preparation of pills. Such honey-coated pills can be preserved for longer periods than decoctions are.

iii) Powder: Mingled powder consisting of powdered crude drugs. This dosage form is suitable for crude drugs containing fat-soluble and/or heat-unstable ingredients.

iv) Ointment: Crude drug pieces for decoction that are combined according to the formula, extracted with lard, then filtered and kneaded. Siunko (紫雲膏) is a typical ointment for medical use.

For external use, there are suppositories, fumigants, bath preparations, dusting powders, detergents, and others of Kampo products.

Thus, regardless of the conventional dosage form, the formulae that had been used for decoctions were allowed to be realized as soft extract and dry extract formulations. Administratively, Kampo products including dry extracts are as follows:

i) Ehical Kampo formulations: Formulations that are produced by manufacturers and used by physicians or dentists directly or indirectly via prescriptions or directions. Extract products or extracted and formulated products. The formulations that are prepared by mixing of an extract and crude drug powder are not allowed to exist, because such mixing is regarded as a procedure for dispensing, not for formulating.

ii) OTC Kampo formulations: Formulations that are produced by manufacturers and sold at pharmacies and drug stores. Include extract products, pills, powdered products, and ointments. Mixture formulations consisting of extract and crude drug powder are also approved. For 236 formulae listed in the "Revised Guidance for OTC Kampo Formulae" and "For additional modification formulae, supplement issue", ingredients and their amounts, dosage and administration, and drug efficacy or effects have been set up in advance.

iii) In-pharmacy Kampo formulations: Formulations that are dispensed in pharmacies and are salable on the counter. Of the formulae listed in the Guidance for OTC Kampo Formulae, 192 formulae and 212 items are designated and the items contained in the Guidance have been set up in advance.

iv) Kampo formulations for household delivery: Formulations handled by drug salespersons. A total of 37 formulae are designated.

Kampo extract formulations and decoctions

For the extract (decoction) of extract preparations, water or water-containing ethanol (ethanol not exceeding 30%) is used. A mixture of crude drugs prepared according to a formula is extracted in a lump. The singly extracted extract of each component crude drug is not allowed to be mixed. Most of the ethical Kampo extract products are prepared into granules or fine granules after addition of fillers to the bulk powder extract. For the production of tablets, binders and lubricants are used. The fillers include milk sugar (lactose), potato or corn starch, and crystalline cellulose. As a binder, hydroxypropyl cellulose is used, and as a lubricant for tablet production using a compression method, stearic magnesium phosphate and the like are employed.

Table 5 shows merits and demerits of Kampo extract products versus decoctions. Kampo extract products are more favorable than the traditional dosage form of decoction in portability and convenience of use as well as storage and hygienic handling. Since the content of each ingredient of a Kampo extract formulation is fixed, certain levels of efficacy and quality are secured. In addition, since limit tests for heavy metals, arsenic, residual pesticides, harmful ingredients, and others are conducted, safety is also believed to be higher for Kampo extract products. In contrast, the former may be more unfavorable than the latter in the exertion of efficacy and the equivalence of fat-soluble ingredients such as essential oil (particularly in comparison between powder products or pills and extracted and formulated powder [散料] or pills [丸料]). Additional disadvantages of Kampo extract products include the onset of digestive tract system disorders due to fillers such as lactose; difficulty in the application to patients with lactose intolerance; and difficulties in the conduct of delicate methods for modification (increase/decrease of crude drugs) and combination.

Table 5. Comparison between Kampo extract products and decoctions

	Decoctions	Kampo extract products
Merits	1) Decoctions suitable for the constitution of each patient can be prepared by increase or decrease of crude drugs and a special processing (修治).	1) Portability is excellent and long-term storage is feasible.
	2) The decoction techniques (e.g., heating hours) can be adjusted for crude drugs containing sparingly water-soluble essential oil and heat-unstable cathartic ingredients.	2) Can be taken more smoothly than decoctions and can use oblate, in case of formulae containing a bitter-taste ingredient.
	3) Not only the effect of medication itself but also the temperature, smell, and taste of the decoction help to enhance the therapeutic efficacy.	3) Are not bulky and can be dispensed easily.
	4) Decocting by the patient helps to enhance his or her eagerness to recovery from the disease.	4) There is little variation in quality among products of the very same company.
	5) The component crude drugs of a decoction can be simply confirmed and tested.	
	6) Even though combination or component crude drugs increase, the dose of the decoction does not largely increase.	
Demerits	1) Decocting is troublesome and inconvenient.	1) The composition of a formula cannot be changed.
	2) Bitter taste (from some formulae) and decoction-specific taste and odor sometimes make medication difficult.	2) The test for the quality of crude drugs is difficult.
	3) The volume of a medicine is large and dispensing needs a considerable time.	3) In combination of formulae, some crude drugs may duplicate.
	4) Long-term storage is impossible and may lead to decomposition.	4) Large amounts of fillers may be contained in some products.
	5) If crude drugs are preserved in poor conditions, harmful insects or mold may develop.	5) Moisture is likely to be absorbed at opening of the package.
		6) Despite the very same formula, the component ratio and contents of component crude drugs vary from company to company.

Quality control for Kampo products

Of Kampo extract products, the equivalence to conventional decoctions must be secured chemically and biologically. Usually, in comparison with the standard decoction, chemical equivalence is assessed on the composition and contents of ingredients, while biological equivalence is evaluated in the studies of drug efficacy, absorption, metabolism and excretion. The standard decoction refers to the expert-prepared decoction which is highly reproducible and of which ingredients have been extracted at certain rates from crude drugs. For ordinary patients who are unfamiliar with preparation of decoctions, it is difficult to obtain the decoctions equivalent to the standard decoction. However, extract products provide the quality of the same level as the standard decoction. Concretely, among the index ingredients listed in Table 6, more than 2 ingredients per formula must meet the content specification for quality maintenance.

Table 6 Typical index ingredients used for quantification of ethical Kampo extract products

Crude drug name	Index ingredient(s)	Crude drug name	Index ingredient(s)
Donkey Glue (阿膠, akyo)	glycine, hydroxyproline	Peony Root (芍薬, shakuyaku)	paeoniflorin
Artemisia Capillaris Flower (茵陳蒿, inchinko)	capillarisin, dimethylesculetin	Ginger / Processed Ginger (生姜 [shokyo] / 乾姜 [kankyo])	6-gingerol, 6-shogaol
Scutellaria Root (黄芩, ogon)	baicalin, wogonin	Cnidium Rhizome (川芎, senkyu)	Ferulic acid, ligustilide
Phellodendron Bark / Coptis Rhizome (黄柏 [Obaku] / 黄連 [Oren])	berberine, coptisine, palmatine	Perilla Herb (蘇葉, soyo)	rosmarinic acid
Corydalis Tuber (延胡索, engosaku)	dehydrocorydaline, corydaline	Rhubarb (大黄, daio)	sennoside A, the anthraquinone derivatives
Pueraria Root (葛根, kakkon)	puerarin, daidzein	Jujube (大棗, taiso)	cyclic adenosine monophosphate (cAMP)
Glycyrrhiza (甘草, kanzo)	glycyrrhizin, liquiritin	Alisma Rhizome (沢瀉, takusha)	alisol B monoacetate, alisol C monoacetate, adenosine
Immature Orange / Orange Fruit (枳実 [kijitsu] / 枳殻 [kikoku])	hesperidin, naringin	Anemarrhena Rhizome (知母, chimo)	mangiferin
Apricot Kernel (杏仁 [kyonin])	amygdalin	Citrus Unshiu Peel (陳皮, chimpi)	hesperidin
Sophora Root (苦参, kujin)	matrine, oxymatrine	Peach Kernel (桃仁, tonin)	amygdalin
Cinnamon Bark (桂皮, keihi)	cinnamic acid	Japanese Angelica Root (当帰, toki)	ligustilide

Magnolia Bark (厚朴, koboku)	magnolol, honokiol	Ginseng (人参, ninjin)	ginsenoside-Rb1, ginsenoside-Rg1
Oriental Bezoar (牛黄, goo)	bilirubin	Pinellia Tuber (半夏, hange)	adenine, guanosine
Burdock Fruit (牛蒡子, goboshi)	arctiin	Poria Sclerotium (茯苓 bukuryo)	pachimic acid, dehydrotumolosic acid
Bupleurum Root (柴胡, saiko)	saikosaponin a (b1), d (b2)	Processed Aconite Root (附子, bushi)	aconitines (Purity test)
Asiasarum Root (細辛, saishin)	asarinin	Sinomenium Stem and Rhizome (防已, boi)	sinomenine
Gardenia Fruit (山梔子, sanshishi)	geniposide, gardenoside	Saposhnikovia Root and Rhizome (防風, bofu)	methylvisamminol
Cornus Fruit (山茱萸, sanshuyu)	loganin, morroniside	Moutan Bark (牡丹皮, botampi)	paeoniflorin, paeonol
Rehmannia Root (地黄, jio)	stachyose	Ephedra Herb (麻黄, mao)	ephedrine, pseudoephedrine

For ethical Kampo extract products, the following specifications and test items are set up by manufacturers.

Description test: To confirm the quality by formula-specific description, including shape, taste, and odor, and pH measurement.
Identification test: To identify ingredients from crude drugs in combined formulae by thin layer chromatography (TLC).
Ingredient quantification: To quantitatively determine the index ingredients in order to ensure the equivalency to the standard decoction.
Extract content: To obtain the total content of ingredients soluble in an appropriate solvent such as water, ethanol, or ethyl acetate, in the formulation in which ingredient composition is so complex that active ingredients cannot be identified.
Purity test (heavy metals, arsenic, total ash, acid-insoluble ash): To confirm the absence of contaminants/impurities derived from crude drugs or manufacturing processes.
Water: To stipulate the water content related to stability
Formulation test (disintegration, particle size, weight deviation, etc): To verify the function as a formulation.
Microbiological test: To confirm the hygienic management in manufacture.

For the ethical Kampo extract products listed in the JP, in addition to the stipulation of contained ingredients, the following stipulations are listed:

Method of preparation: Describes grams per daily dose of component crude drugs and preparing a dried extract as directed under Extracts.
Description: Describes color tone, odor and taste specific to extract preparations.
Identification (test): Identifies component crude drugs by the use of TLC.
Purity test: Confirms the limits of heavy metals (not exceeding 30ppm) and arsenic (not exceeding 3ppm)
Loss on drying: Stipulates the value of each extract preparation (1g), after 5–hour drying at 105℃.
Total ash: Stipulates the value of each extract preparation.

Thus, the quality of ethical Kampo extract products is secured by pharmaceutical companies, but may depend on the condition of storage. To prevent deterioration of the quality, these products should be kept under an appropriate environment free from moisture and direct sunlight.

Kampo pharmacology

Shin-ichi Tashiro

Before introduction of Western medicine

Kampo formulae, which came to Japan from China in ancient times, together with the preexisting Wayaku (Japanese traditional medicine) has significantly contributed to the maintenance of good health and management of diseases in Japanese people. At the center and leading-edge of medicine in Japan, Kampo evolved in daily practice through the development of new formulae, etc. to serve as Japan's dominant form of medicine. These practices are collectively called Wakan-yaku. In those days, what is currently called pharmacology did not exist. However, the effects of Kampo formulae, *sho* (pattern)-based therapy, interactions between crude drugs, and roles of special processing (修治, *shuji*) etc. have been established through clinical experience and observation and over time recorded. Medicine that can be called evidence-based (EBM) was practiced although the results of clinical experience and observation were not tested by statistical procedures. As a result, Kampo formulae were effective and maintained its predominance in Japan for a long time by not only preserving but also refining the tradition on a daily basis.

Research on active constituents in crude drugs

Among East Asian nations that have used “Kampo formulae,” Japan was the first to introduce the knowledge and technology of modern science, especially chemistry, from the Netherlands and Germany. As a result, researchers such as Nagayoshi Nagai were actively involved in isolation of active constituents from clinically effective traditional crude drugs, and discovered many such constituents including ephedrine in Ephedra Herb (麻黄, mao). These studies were not limited to crude drugs, but extended to all natural products including folk medicines and foods. These materials were then used for the development of pharmaceutical products, health foods, etc. and studied to determine their mechanisms of action. Japan has played a central role in natural products chemistry in the world, as reflected by the many compounds with Japanese names still in use, for instance, shogaol named for ginger (生姜, shoga: a common name of ginger) and shikimic acid named for ‘Illicium anisatum’ (梻, shikimi).

The aims of those studies were only to isolate active constituents from conventionally effective crude drugs, determine the structure of each constituent, use the compound as a seed to synthesize its related compounds, and find out more effective, safer compounds to develop a new drug, but never to clarify why multi-component Kampo formulations were effective.

Emergence of clinically based Kampo pharmaceutical sciences

Clinically-based pharmaceutical/pharmacological research of crude drugs has emerged from pharmacognosy. Their intention was to identify and isolate new substances from various plants with the aim of developing them as pharmaceutical products. For instance, the series of studies by Kitagawa and colleagues at Osaka University on the processing of crude drugs and their medicinal effects showed that the hyperthermic effect of Ginger (生姜, shokyo) is enhanced in steamed and dried ginger (Processed Ginger [乾姜, kankyo]) and depends on the change in the gingerol/shogaol ratio. The study by Kimura et al. at the University of Toyama showed that the mechanism of antispasmodic/analgesic action of shakuyakukanzoto (芍薬甘薬湯) is explained by the interaction between paeoniflorin in Peony Root (芍薬, shakuyaku) and glycyrrhizin in Glycyrrhiza (甘草, kanzo).

In these situations, the scientific method began to be applied to the study of Kampo formulae, which was not regarded by the Meiji government as mainstream medicine and continued to exist only because of the activities of so-called Kampo pharmacies. At the same time, extract formulations were developed with the use of superior Japanese drug-manufacturing technology. That is to say, easy-to-carry and simple-to-use Kampo formulations were developed and clinically tested, and an increasing number of medical professionals took another look at Kampo formulae. In addition, extract formulations because they were homogenous preparations could be tested nonclinically or clinically in Japan to determine their efficacy and pharmacology and to elucidate their mechanisms.

In this context, the WAKAN-YAKU Symposium was founded in 1967 as the first step in the pursuit of collaborative studies on Kampo pharmacology applied to clinical practices by both pharmaceutical sciences (pharmacists) and medicine (physicians). In 1984, the symposium evolved into Medical and Pharmaceutical Society for WAKAN-YAKU, achieving many successes.

The requirements for studying Kampo pharmacology

Kampo formulations have been increasingly used in clinical settings and become more and more important for medical treatment. Nonetheless, medical professionals are concerned about their use because much remains unknown including active constituents, mechanism of action, and interactions with new drugs. Appropriate research methods for the study of Kampo formulations have been developed recently to clarify the pharmacological mechanisms and proper usage.

Much remains unclear about their pharmacological effects unless the development of appropriate study methods takes into account the following characteristics of Kampo formulations: 1) multicomponent composition; 2) transformation or metabolism of constituents by digestive juices and/or the intestinal flora and excretion of others intact without being absorbed after oral administration, and 3) large difference in efficacy between individuals as indicated by the concept of ‘pattern (*sho*).’ Findings from studies based on these methodologies are summarized below.

Glycosides are prodrugs that require activation by intestinal bacteria

Plant constituents include many sugar-containing compounds called glycosides (Table), and many of the main constituents of major crude drugs are glycosides. These glycosides are highly soluble in water due to the presence of sugar, and most cannot penetrate the phospholipid-containing cell membrane or be absorbed. In the intestine, however, more than 100 trillion bacteria are actively involved in energy metabolism and proliferation, and bacteria that hydrolyze glycosides can remove sugars and utilize them as a source of energy. On the other hand, the aglycon, the suger-free portion of glycoside become lipophilic, can permeate the cell membrane made from phospholipid bilayer, and then act as the drug. Also, the compound is never active unless assimilating bacteria are present. These findings were from the studies by Kobashi et al. at the Toyama University and Tashiro et al. at Kyoto National Hospital.

Table Active constituents (glycosides) of major crude drugs.

Crude drug	Action	Main constituent	Aglycone
Glycyrrhiza (甘草、kanzo)	Anti-inflammatory	Glycyrrhizin	Glycyrrhetinic acid
Ginseng (人参, ninjin)	Metabolic activation	Ginsenoside	Protopanaxadiol
Rhubarb (大黄, daio)/ Senna Leaf (senna)	Purging	Sennoside	Rhein anthrone
Bupleurum Root (柴胡, Saiko)	Anti-inflammatory	Saikosaponin	Saikosapogenin
Scutellaria Root (黄芩, ogon)	Anti-allergic	Baicalin	Baicalein
Gardenia Fruit (山梔子, sanshishi)	Choleretic	Geniposide	Genipin
Peony Root (芍薬, shakuyaku)	Antispasmodic	Paeoniflorin	Paeonimetabolin

For instance, sennoside was conventionally considered to be a purging constituent of Rhubarb (大黄, daio)/Senna Leaf (senna). However, diarrhea is not induced after intravenous injection of sennoside. Sennoside is a prodrug (i.e., its activity and absorption require preliminary digestion). In the intestine, certain bifidobacteria, etc. release β-linked glucose from sennoside to produce sennidine, which is then cut in half to form rhein anthrone. The latter is then absorbed and functional. In a study, fecal samples from volunteers were anaerobically incubated with sennoside or sennidine, and the metabolism of each compound was monitored on a regular basis. In addition, the subjects were given Pursennid ™ (sennoside preparation) and checked for diarrhea the next morning. The product of the second reduction reaction was observed in fecal samples from all subjects with or without diarrhea. On the other hand, the sugar-releasing activity was detected in all subjects with diarrhea, but not in most of subjects without diarrhea. Those subjects in whom sugar-releasing activity was detected but who had no diarrhea were found to be daily users of Senna Leaf, etc., indicating that constant supply of sennoside resulted in the development of tolerance to rhein anthrone, which, in turn, resulted in ineffectiveness at the usual dose despite the presence of assimilating bacteria or induction of metabolic enzymes. The intestinal flora play a crucial role in the onset of medicinal effects.

If the importance of bacterial flora in prodrug therapy is understood, usage can be made more effective. Shakuyakukanzoto is a simple, fast-acting formula comprised of Peony Root and Glycyrrhiza. It is very

effective for pain due to muscle spasms. When used for menstrual pain on an as-needed basis, it was very effective in approximately 10% of women, effective to some degree in 50%, and ineffective in approximately 40%. Both paeoniflorin (the main constituent of Peony Root) and glycyrrhizin (the main constituent of Glycyrrhiza) are glycosides, indicating that the difference in the efficacy can be attributed to differences in the bacterial flora. Since the intestinal bacteria consume sugar as a source of energy, these assimilating bacteria should grow selectively, suggesting that the formulation may begin to work after repeated administration. Treatment was thus started 5 to 7 days before the expected onset of menstruation in the unresponsive and some moderately responsive women. One package per day rather than higher doses of the formulation were given in an attempt to increase the number of bacteria and induce enzyme synthesis. The efficacy was evaluated based on patient self-assessment of pain over time on a five-grade scale with "5" defined as conventional pain. As expected, daily low-dose premedication resulted in a much higher efficacy.

In conclusion, glycosides in Kampo formulations may be prodrugs that are activated by intestinal bacteria. If so, interindividual differences in the efficacy of Kampo formulations may be attributable to interindividual differences in bacterial flora, which reflect differences in diet and the intestinal environment. In addition, the onset of action of Kampo formulations may be prolonged because it takes time not only for ingested glycosides to reach the assimilating bacteria in the cecum, but also for the assimilating bacteria using glycoside sugar as a source of energy to grow to levels required to produce the adequate concentration of aglycones (the active constituents). The efficacy of Kampo formulations may be reduced when used in combination with antimicrobial agents because they reduce the number of assimilating bacteria. Kampo formulations should not be used concomitantly with antimicrobial agents without giving due consideration to this concern. Even in combination with antimicrobial agents, many constituents of Kampo formulations remain effective, and certain glycosides with a reduced efficacy are still useful in restoring the assimilating bacteria to normal levels as quickly as possible, indicating that Kampo formulations should be administered continuously. In addition, the start of treatment with Kampo formulations or switching to another formula leads to selective growth of those assimilating bacteria that can use the relevant constituents and thereby to changes in bacterial flora that may result in diarrhea or abdominal pain. It is thus desirable to instruct the patient about how to use the medicine prior to treatment.

From these viewpoints, it is unrealistic and therefore unscientific to apply constituents of Kampo formulations directly to cells or organs in pharmacological experiments. On the assumption that a truly active constituent would be transferred by blood to the site of action, Tashiro et al. designed a pharmacodynamic analysis system in which serum from patients receiving an orally administered Kampo formulation served as the drug applied directly to target cells, and presented their findings to the first meeting of Medical and Pharmaceutical Society for WAKAN-YAKU, which was founded in 1984. The pre-treatment serum was used as the control. Later, this approach was named "serum pharmacology" by Ogihara at Nagoya City University. Using the method, it was shown that Bupleurum Root (柴胡, Saiko)-containing formulae inhibits the proliferation of fibroblasts, Glycyrrhiza inhibits the leakage of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) from hepatocytes, san'oshashinto (三黄瀉心湯) inhibited the biosynthesis of fatty acids in the liver, and hochuekkito (補中益気湯) prolonged sperm motility.

Not all effects are mediated by serum

Serum pharmacology helped clarify the mechanism of action of Kampo formulations, but was not free of problems. Firstly, not all effects are mediated by serum. Some effects are direct, taste- or aroma-based, etc. In particular, the gastrointestinal tract is affected directly, for example, by anti-inflammatory substances such as Glycyrrhiza and glycyrrhizin, which are used to relieve stomatitis and gastritis.

It has also been reported that taste and aroma increase gastrointestinal motility. The methodology for clinical evaluation, especially preparation of the appropriate placebo for double-blind studies, is an issue requiring careful consideration.

As for the mechanism of immunostimulation shared by many Kampo formulations, Yamada et al. at Kitasato University reported not only that polymeric constituents such as polysaccharides may be absorbed, but also that Peyer's patch-mediated mucosal immunity may be involved. This is also interesting.

In addition, Tashiro et al. at Showa Pharmaceutical University reported that glycosides were absorbed intact after rectal administration, supporting the use of suppository formulations, which are sometimes employed clinically. Issues to be addressed include identification of new administration routes and the mode of site-dependent intestinal absorption.

In recent years, the number of interesting reports on absorption and excretion of constituents of Kampo formulations has been increasing and drug research including research on drug transporters has advanced. It has been reported that glycosides penetrate the cell membrane with their sugars intact. However, the aglycones (glycosides without sugars) for all of clinically important formula constituents present in large amounts (including glycyrrhizin in Glycyrrhiza, ginsenoside in Ginseng [人参, ninjin], sennoside in Rhubarb, and saikosaponin in Bupleurum Root) are detected in blood. Apart from their pharmacognostical interest, the absorption and activation of glycosides have been shown to be closely related to the intestinal flora in clinical pharmacokinetic findings.

Anyway, research on the intestine and intestinal flora is interesting basic research in Kampo pharmacology.

The importance of gastrointestinal pH for absorption of alkaloids

Alkaloids are also important crude drug constituents. Many alkaloids are alkaline and have strong effects at low doses. Alkaloids are biosynthesized by decarboxylation of amino acids, and are structurally and pharmacologically similar to physiologically active amines, which accounts for their strong effects. Crude drugs and Kampo formulations may be effective because the cause of disease (i.e., excess or deficiency of physiologically active substances) can be corrected by antagonists or agonists synthesized by biologically similar animals and plants from common precursors such as amino acids and sugars.

Ephedra Herb and Processed Aconite Root (附子, bushi) are the most common crude drugs containing an alkaloid as a main constituent. Ephedrine in Ephedra Herb is structurally and pharmacologically similar to adrenaline and has bronchodilator and vasopressor effects. It is contained in Ephedra Herb (麻黄,

mao)-containing formulae including: kakkonto (葛根湯); maoto (麻黄湯); and other formulae that are used for treating early symptoms of the common cold; makyokansekito (麻杏甘石湯), which is used for treating asthma attacks; and shoseiryuto (小青竜湯), which is indicated for allergic rhinitis.

The pH plays a critical role in absorption of alkaloids. Alkaloids are ionized in the acid stomach. Ionized alkaloids are soluble in water and less likely to be absorbed from the stomach because they cannot penetrate the lipid bilayer of the cell membrane. Monitoring the level of ephedrine in blood after intake of maoto showed that ephedrine was poorly absorbed under acidic conditions and blood ephedrine concentration was increased under basic conditions, as expected.

In Japan, kakkonto and maoto, which are used for treating early symptoms of the common cold, are traditionally taken with a large quantity of hot water or udon (Japanese noodle) soup. The intention is probably to warm the body for the purpose of heat retention, sweating, and pyretolysis and to replace fluid. However, considering the blood kinetics of ephedrine, this method of drug intake may also be pharmacokinetically meaningful. Intake of a large quantity of hot water dilutes gastric acid, resulting in increased absorption of ephedrine. A large quantity of fluid enlarges the stomach, increases the absorptive area, and accelerates transport to the high-pH duodenum. Hot drinks improve absorption by selectively dilating gastric blood vessels and increasing blood flow.

On the other hand, Ephedra Herb-containing formulae are sometimes associated with sympathomimetic symptoms such as palpitations and shortness of breath. In the event of sympathomimetic symptoms, it is necessary to rule out concurrent use of adrenergic agonists, anticholinergic agents, thyroid preparations, xanthine derivatives, etc.. If concomitant use of these drugs is ruled out, taking the formulation in divided doses can be recommended to decrease the blood ephedrine concentration. In order to minimize adverse effects while maintaining the efficacy, it is helpful to dissolve Kampo formulation in hot water and sip it as needed instead of drinking it all at once.

Since the introduction of extract formulations into the Japanese market, it has been recommended that Kampo formulation be taken on an empty stomach before or between meals. This instruction is probably based on the belief that active constituents would be better absorbed in the fasting state. In fact, this instruction is useful because alkaloids are not absorbed at once. Absorption depends on pH as theoretically predicted when decoctions and extracts are aqueous solutions. Many patients swallow the extract with water. As a result, two competing reactions (dissolution in water and dissolution in lipid) occur concurrently in the stomach, contrary to the theory. In order to improve compliance, patients are allowed to take Kampo formulation as they like, but due attention should be paid to how the medicine is taken if Ephedra Herb or Processed Aconite Root poisoning is suspected. In particular, concomitant use of stomach medicine containing antacid may result in higher pH and increased absorption and thereby symptoms of poisoning.

Kampo fomulae and allergy

Since Kampo formulations are natural products that contain polymeric constituents and many other compounds such as aldehydes (which react with the amino groups of proteins to form a Schiff's base and

potentially serve as allergenic haptens), it is possible for immune abnormalities, especially allergy, to occur. Notably, the main constituent of Cinnamon Twig (桂枝, keishi) and Perilla Herb (蘇葉, soyo), which often induce skin rash, etc., is cinnamic aldehyde and perillaldehyde, respectively. In addition, since some patients have allergies to environmental allergens including food and pollen, it is possible that Kampo formulations have antigens in common with these allergens. Theoretically, therefore, Kampo formulations should be used with due attention to allergy. Nonetheless, excessive concern is not necessary because the actual incidence is low.

Future pharmacological research

With the advancement of molecular biology, much has recently been learned about intra/extracellularly produced/released transmitters, intracellular signaling substances, drug transporters, etc., contributing to the clarification of the mechanisms by which Kampo formulations act. Further progress is expected.

Kampo formulae are very important to future medical care in Japan. Therefore, Kampo-specific pharmacological research based on the characteristics of Kampo formulations should be further investigated to verify their efficacy, safety, and usefulness non-clinically and clinically, and efforts should be made to ensure that patients are instructed or receive the information necessary for their proper use.

Precautions to Avoid the Adverse Reactions to Kampo products

Fumiyuki Kiuchi, Toshiaki Makino

Crude drugs and Kampo products are useful pharmaceuticals despite safety concerns (i.e., adverse reactions, contraindications, and drug interactions with concomitant drugs). Here, we provide instructions for the safe use of crude drugs and Kampo products in clinical settings.

Characteristics of crude drugs/Kampo products and precautions for crude drugs

(1) Variation in quality of crude drugs and Kampo products

Most crude drugs used in Kampo products are listed in the Japanese Pharmacopoeia (JP), with specifications established to ensure their quality as pharmaceuticals. However, it is impossible to control quality as strictly for naturally occurring crude drugs as for synthetic drugs, inevitably because they contain variable amounts and composition of ingredients. Furthermore, when several origin (or source) plants are used for one crude drug, the quantity, quality, and mix of ingredients may differ among these plants. The JP stipulates the contents (of minimum levels) of indicator ingredients, extracts, essential oils, and others in crude drugs. About the crude drugs actually used in the preparation, information should be obtained, including the origin plant, place of production, and ingredient composition.

Since a Kampo formula is a combination of several crude drugs, variation in ingredients of component crude drugs leads to variation in the formula. However, variation in Kampo extract products (the predominant Kampo products currently used clinically) is controlled by restricted content of indicator ingredients to a narrow range at the manufacture stage, provided that these extracts are from the same manufacturer. Nevertheless, Kampo formulae with the same name may vary in amount and composition, if they are from different manufacturers. The composition of ethical Kampo extract formulations are in compliance with the internal regulations on the review for approval of OTC Kampo products (210 formulae) (1), which were issued at 1975. The regulations, which contained the frequently used formulae, which were described in textbooks, were recently revised, and issued in September 2008 as a notification by the Evaluation & Licensing Division Chief, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labor & Welfare (MHLW) (Notification No. 0930001 of the PFSB ELD "Establishment of the Standards of Approval for OTC Kampo Products") (2). Since different manufacturers use different reference texts and therefore different formulae to produce currently used Kampo extract products, some products with the same formula name have different compositions. Table 1 shows the compositions of kakkonto (葛根湯) extracts included in the JP. Four different 'kakkonto' formulae are used to formulate four different Kampo extracts of the same name. Furthermore, kakkonto has two formulae containing Pueraria Root (葛根, kakkon) at a daily dose of 8 g and 4 g; thus, products with the same name may contain very different amounts of each

ingredient. The compositions of hochuekkito（補中益気湯）extracts included in the JP are shown in Table 2. In some of the formulae containing rhizomes of Atractylodes spp. (朮, jutsu), the content of Atractylodes Lancea Rhizome (蒼朮, sojutsu) or Atractylodes Rhizome (白朮, byakujutsu) are specified, but not in others. Atractylodes Lancea Rhizome and Atractylodes Rhizome are both listed in the JP, but differ in origin plant and therefore in composition. There are Ginger (生姜, shokyo)-based and Processed Ginger (乾姜, kankyo)-based formulae. Although both are included in the JP, Ginger is the dried rhizome of Zingiber officinale, whereas Processed Ginger is also the rhizome of Zingiber officinale, but is steamed or blanched (a heating process known to change ingredients) before dried. Although not listed in the JP, some formulae use ginger (fresh rhizome of Zingiber officinale) to manufacture Kampo extract formulations for prescription. Thus, Kampo extract products vary widely in content, even though their formulae have the same name. Furthermore, since the quality of raw material for crude drugs varies among manufacturers, awareness of the characteristics of individual products is important.

Table 1　Composition of Kakkonto Extract in JP

crude drug	composition 1	composition 2	composition 3	composition 4
Pueraria Root	8 g	4 g	4 g	4 g
Ephedra Herb	4 g	4 g	3 g	3 g
Jujube	4 g	3 g	3 g	3 g
Cinnamon Bark	3 g	2 g	2 g	2 g
Peony Root	3 g	2 g	2 g	2 g
Glycyrrhiza	2 g	2 g	2 g	2 g
Ginger	1 g	1 g	1 g	2 g

Table 2　Composition of Hochuekkito

crude drug	composition 1	composition 2	composition 3	composition 4	composition 5	composition 6
Ginseng	4 g	4 g	4 g	4 g	4 g	4 g
Atractylodes Rhizome	4 g	-	4 g	-	4 g	4 g
Atractylodes Lancea Rhizome	-	4 g	-	4 g	-	-
Astragalus Root	4 g	4 g	4 g	4 g	3 g	4 g
Japanese Angelica Root	3 g	3 g	3 g	3 g	3 g	3 g
Citrus Unshiu Peel	2 g	2 g	2 g	2 g	2 g	2 g
Jujube	2 g	2 g	2 g	2 g	2 g	2 g
Bupleurum Root	2 g	2 g	1 g	1 g	2 g	1 g

Glycyrrhiza	1.5 g	1.5 g	1.5 g	1.5 g	1.5 g	1.5 g
Ginger	0.5 g	0.5 g	0.5 g	0.5 g	0.5 g	-
Processed Ginger	-	-	-	-	-	0.5 g
Cimicifuga Rhizome	1 g	1 g	0.5 g	0.5 g	1 g	0.5 g

(2) Efficacy and adverse reactions to crude drugs

Generally, Kampo products are thought to be associated with no or minimal adverse reactions. However, no drugs are free of adverse reactions. Given that adverse reactions are effects other than therapeutic effects (efficacy), mixtures of many ingredients such as crude drugs/Kampo products may well produce unexpected adverse reactions, and Kampo products should be used with this in mind. Kampo medicine is highly individualized, with formulae tailored to patient constitution and condition. Adequate knowledge and extreme caution are needed to effectively use Kampo products while preventing adverse effects due to inappropriate usage. Crude drugs requiring warnings to protect against adverse reactions are listed below.

1) Glycyrrhiza (甘草, kanzo)

Glycyrrhiza, contained in many Kampo formulae, may cause symptoms of pseudoaldosteronism including increased blood pressure, hypokalemia, edema, hot flashes, and dizziness, as described later. Caution should be exercised when Glycyrrhiza is administered in patients with renal dysfunction, hypertension, or during treatment with a diuretic.

2) Ephedra Herb (麻黄, mao)

Ephedra Herb contains alkaloids including ephedrine, which has bronchodilatory activity and is used in the treatment of bronchial asthma. Since ephedrine with a structure similar to that of adrenalin, a neurotransmitter, has sympathetic and central nerve-stimulating activity, Ephedra Herb may cause excitation, increased blood pressure, palpitations, tachycardia, and impaired urination. Thus, Ephedra Herb-containing formulae (麻黄剤) may aggravate symptoms in patients with circulatory disease, severe renal disorder, or voiding disorder. Therefore, these formulations should be administered with caution in these patients and are contraindicated as a general rule in patients with a history of angina or myocardial infarction. The administration in the elderly should be with caution. Because of possible potentiation of adverse reactions, the following drugs should be co-administered with caution: monoamine oxidase inhibitors used as antidepressants, hypothyroidism-treating thyroid preparations, sympathetic stimulant catecholamines, and bronchodilator xanthines. Furthermore, since ephedrine may be excreted in breast milk, Ephedra Herb-containing formulae should not be given to nursing mothers.

3) Rhubarb (大黄, daio)

Rhubarb is commonly found in crude drug products for constipation, and also used for treating blood stasis (kuoketsu) and treating heat pattern (seinetsu) in Kampo medicine. Rhubarb exerts a cathartic effect when sennosides are converted by enterobacteria into rhein anthrone, which stimulates the large intestine. Formulae containing Rhubarb, as used for indications other than catharsis, may produce adverse reactions such as abdominal pain, diarrhea, and anorexia. The cathartic effect of Rhubarb depends on the action of the intestinal flora, and therefore its onset varies widely among individuals. Rhubarb-containing formulae should be administered with caution to debilitated patients, those with severe gastrointestinal weakness, and those with diarrhea or loose stools. In addition, Rhubarb may induce preterm delivery or miscarriage and is known to be excreted in breast milk; therefore, it should not be given to pregnant women or nursing mothers.

4) Processed Aconite Root (附子, bushi; 加工附子, processed bushi)

Processed Aconite Root is derived from aconite tuber, which is highly toxic, and is generally used after processed to reduce its toxicity (shuji [修治]: a special processing for safety). The toxin is a mixture of compounds called bushi diester alkaloids such as aconitin, which act on the sodium channel in nerve cells to enhance membrane permeability of Na+, thereby acting as a neurotoxin. Bushi diester alkaloids are converted by shuji into less toxic compounds (i.e., monoester alkaloid after removal of the acetyl group by hydrolysis and lipo-alkaloids after replacement of the acetyl group by long-chain fatty acid). Processed Aconite Root has an analgesic effect, which is attributable to aconitins, but an overdose causes symptoms such as palpitations, hot flashes, tongue numbness, and nausea. The JP has set the upper limit of content of bushi diester alkaloids; however, that limit varies among the three types of shuji. If necessary, crude drugs (not processed to reduce their toxicity) can be used but only with exercise of due caution against poisoning as indicated by sleepiness, perioral numbness, and burning sensation (hoteri).

5) Crude drugs requiring cautions during pregnancy

Since the safety of Kampo products in pregnant women has not been established, they should not be administered as a rule, particularly during early pregnancy in the period of fetal organogenesis. Caution must be taken in the use of some crude drugs including Rhubarb, which may cause preterm delivery or miscarriage, as mentioned above. Pregnant women should not be treated with the following crude drugs: Rhubarb and Mirabilite (芒硝, bosho) (which have uterotonic activity and may cause miscarriage or preterm delivery); Safflower (紅花, koka), Achyranthes Root (牛膝, goshitsu), Peach Kernel (桃仁, tonin), Moutan Bark (牡丹皮, botampi), and Coix Seed (薏苡仁, yokuinin) (which increase the risk of miscarriage/preterm delivery according to one report).

Beside these, Processed Aconite Root is likely to cause poisoning, requiring cautions against poisoning. Pregnant women should also avoid Job’s tears (Coix lacryma-jobi var. ma-yuen) for safety, since yokuinin is prepared by removal of the seed coat of Job’s tears, which is used in indigenous medicine. Trichosanthes Root (栝楼根, karokon) is a crude drug that previously had been used as an

abortient, and injection of the extract has been pharmacologically shown to induce abortion in animals; therefore, it should not be administered to pregnant women. In addition, the crude drugs that are not found in general obstetric or gynecologic formulations but are contraindicated in pregnant women are: Croton (巴豆, hazu: Croton tiglium L.), Euphorbia Pekinensis Root (大戟, taigeki; Euphorbia pekinensis RUPR.), Phytolacca Root (商陸, shoriku; Phytolacca esculenta VAN HOUTT), Sparganium Rhizome (山稜, sanryo; Sparganium stoloniferum BUCH.-HAM.), Zedoary (莪朮, gajutsu), and Pharbitis Seed (牽牛子, kengoshi).

6) Other crude drugs requiring cautions

In patients with gastrointestinal weakness, gastrointestinal symptoms such as anorexia, stomach discomfort, and vomiting are likely to occur. Therefore, caution should be exercised particularly against formulae containing the crude drugs such as Ephedra Herb, Rehmannia Root (地黄, jio), Japanese Angelica Root (当帰, toki), Cnidium Rhizome (川芎, senkyu), and Gypsum (石膏, sekko). Furthermore, since the crude drugs Cinnamon Bark (桂皮, keihi), Ginseng (人参, ninjin), and Rehmannia Root are sometimes associated with skin symptoms (rash, redness, and pruritus), particular caution should be given to patients with allergic constitution.

(3) Untoward interactions between Kampo products and Western drugs

Combinations of crude drugs or Kampo products and Western drugs may potentiate each other's positive effects, complement each other's deficiencies, yet adversely affect each other's efficacy.

1) Kampo formulae and drugs metabolized by the drug-metabolizing enzyme CYP3A4

Prenylated furanocoumarins contained in grapefruit juice have potent inhibitory action on the drug-metabolizing enzyme CYP3A4, which plays a role in metabolizing various drugs. Caution has been advised against coadministration of many drugs with grapefruit juice. Furanocoumarins occur in various plant species, especially in the Rutaceae (e.g., grapefruit), Apiaceae, and Leguminosae families. Prenylated furanocoumarin dimer, compared with their monomer, is highly potent and is found in only a few crude drugs including Notopterygium Rhizome (羌活, kyokatsu), whereas the monomer is more widely distributed and particularly plentiful in the crude drugs Bitter Orange Peel (橙皮, tohi) and Angelica Dahurica Root (白芷, byakushi), as revealed by enzyme linked immunosorbent assay (ELISA) (3). Furanocoumarins inhibit p-glycoprotein involved in drug efflux , as was suggested by the in vitro finding that overdoses of sokeikakketsuto (疎経活血湯) and senkyuchachosan (川芎茶調散) extracts suppressed absorption of digoxin from the gastrointestinal tract, possibly by acting on CYP3A4 and p-glycoprotein (4). St. John's wort (Hypericum perforatum L.), which has been traditionally used in Europe, has been shown to induce the activity of drug-metabolizing enzymes. The effects of Kampo formulae on drug metabolism remain to be clarified.

2) Kampo products and antibiotics

As described in the preceding section (B. Kampo Pharmacology), enterobacteria in the large intestine

change some ingredients of Kampo products into absorbable and active forms via hydrolysis and other processes. This suggests the possibility that coadministration of an antibiotic (by killing enterobacteria) may render the Kampo product ineffective, as demonstrated by the finding of antibiotic-mediated suppression of glycosides absorption in animals. However, recent reports have shown that the absorption of glycosides, which was thought to depend on detachment of the sugar portion by enterobacteria, occurred without involvement of enterobacteria, contradicting data that support the ban against coadministration of Kampo products and antibiotics. Many Kampo products have unidentified active ingredients, warranting further research including that involving enterobacteria.

3) Citrus Unshiu Peel (陳皮, chimpi) and Immature Orange (枳実, kijitsu)-containing formulae and drugs absorbed via organic anion-transporting polypeptide (OATP)

The anti-allergy drug fexofenadine interacts with grapefruit juice: fexofenadine taken with grapefruit juice decreases the blood concentration of fexofenadine. Fexofenadine is transported from the lumen to the epithelial cells of the gastrointestinal tract by OATP1A2, a transporter expressed on the outer membrane of small intestine epithelial cells. The decrease in blood concentration of fexofenadine is attributed to inhibition of the OATP1A2 by naringin and hesperidin, flavonoid glycosides contained in grapefruit juice (5). Citrus Unshiu Peel and Immature Orange present in Kampo products contain no furanocoumarins but do have sufficient concentrations of naringin and hesperidin to inhibit OATP1A2 in the gastrointestinal tract. The drug interactions with these Kampo products are therefore expected to be similar to the interaction of fexofenadine with grapefruit juice. It has been also reported that aglycone flavonoids such as apigenin, found in many crude drugs, inhibit not only OATP1A2 but also OATP2B1 (6). The drugs known to have such effects include the β-blockers (atenolol and celiprolol), the antibiotic revofloxacin, and the anti-hyperlipidemic agents (pravastatin and atorvastatin) (5). Although crude drugs as well as vegetables and fruits are rich in flavonoids, absorption of Western drugs but not Kampo medicines is assumed to be suppressed because the former are generally administered after meals, while the latter are generally administered before meals.

4) Gypsum (石膏, Sekko)-containing formulae and tetracycline antibiotics

Since gastrointestinal absorption of tetracycline and new quinolone antibiotics is suppressed by chelation with calcium ions and magnesium ions, these antibiotics should not be coadministered with calcium- or magnesium-containing dietary supplements or pharmaceutical products. A recent study in humans reported that byakkokaninjinto (白虎加人参湯) suppressed gastrointestinal absorption of tetracycline but not ciprofloxacin (7). Therefore, coadministration of Gypsum-containing formulae with tetracycline antibiotics should be avoided.

5) Ephedra Herb (麻黄, Mao)-containing Kampo formulae and common cold medicines

It is believed that common colds prevent the body from producing enough heat to fight the common cold virus. Maoto (麻黄湯) and kakkonto (葛根湯), which contain Ephedra Herb, may act by increasing body temperature to boost the immune system’s ability to eliminate virus and by stimulating sweating,

thereby decreasing body temperature. Thus, these Kampo formulae antagonize the antipyretic effect of compounds in commercially available combination cold remedies and PL granules, often used in the treatment of colds. Actually, some OTC drugs that contain both kakkonto and acetaminophen end up delaying recovery.

Information on adverse reactions to Kampo products

"Pharmaceuticals and Medical Devices Safety Information" contains information on adverse reactions to pharmaceuticals collected by the MHLW and is published on the website of the Pharmaceuticals and Medical Devices Agency. The information on the website (8) covers the period from 1997 to the present (No. 144 onward). There are main safety information on crude drugs/Kampo products and the information on significant adverse reactions mainly to Kampo products, both issued in the period from 1991 to the present.
The main adverse effect of Kampo products is interstitial pneumonia due to shosaikoto (小柴胡湯), prompting frequent bulletins on the Pharmaceuticals and Medical Devices Agency website. Hepatic dysfunction has also been associated, although infrequently, with many formulae. Given that information on adverse reactions has been increasing with expanded use of Kampo formulations, it is important to be alert to the latest information.

*Aristrochic-acid nephropathy

The Pharmaceuticals and Medical Devices Safety Information No. 161 provides information on crude drugs/Kampo products containing aristrochic acid, which causes renal disorders. A case of renal disorder (called Chinese herbs nephropathy and currently known as aristrochic-acid nephropathy) occurred in Belgium in 1993 (9). This renal disorder developed as a result of taking a diet aid product containing crude drugs imported from China, and the cause was identified as aristrochic acid present in guang fang ji (広防己; Aristorochia fangchi), an ingredient of this product. Aristrochic-acid nephropathy often rapidly progresses to the stage requiring dialysis and can progress even after discontinuation of the causative drug. From late 1996 to 1997, aristrochic-acid nephropathy, assumed to be due to Kampo products imported from China, occurred in Japan, leading to the issue of safety information in 2000. Moreover, a case of aristrochic-acid nephropathy caused by guang fang ji hat was erroneously imported and distributed as kanboi (漢防已; Stephania tetrandra) to be used as JP Sinomenium Stem and Rhizome (boi, 防己) was again reported in Pharmaceuticals and Medical Devices Safety Information No. 200 in 2004. Aristrochic acid, though present in some plants of the family Aristolochiaceae, is not present in crude drugs and Kampo formulations currently approved for pharmaceutical use in Japan. Asiasarum Root (細辛, saishin) included in the JP consists of the root and rhizome of Asiasarum sieboldi or A. heterotropoides var. mandshuricum in the Aristolochiaceae family. These parts of the plant do not contain aristrochic acid. However, since the epigeal parts of these plants do contain aristrochic acid, the JP requires a purity test using high performance liquid chromatography (HPLC) to confirm the absence of aristrochic acid in Asiasarum Root. In China, plants of the Aristolochiaceae family are sometimes used as crude drugs, e.g., guan mu tong (関木通; Aristolochia manshuriensis), guang fang ji (広防己), and qing mu xiang (青木香；Aristolochia contorara or A. debilis).

These may be confused with Coix Seed (木通, mokutsu; Akebia quinata or A. trifoliate), Sinomenium Stem and Rhizome (防己, boi; Sinomenium acutum), and Saussurea Root (木香, mokko; Saussurea lappa), which are used in Japan. Therefore, it is important to confirm that these crude drugs comply with the JP before use. Recently, the medicinal use of guan mu tong, guang fang ji, and qing mu xiang was prohibited in China as well, and they were not included in the 2010 Pharmacopeia of the People's Republic of China.

Adverse reactions to Kampo products and countermeasures

(1) Pseudoaldosteronism caused by Glycyrrhiza (甘草, kanzo)-containing Kampo formulae

Glycyrrhiza is an ingredient of many Kampo formulae used in Japan, rendering adverse reactions to Glycyrrhiza the most frequent adverse reactions to Kampo products.

Pseudoaldosteronism/pseudohyperaldosteronism is considered to develop through inhibition of type II 11β-hydroxysteroid dehydrogenase by 3-mono-glucuronyl glycyrrhetinic acid (a metabolite of glycyrrhetin, the principal ingredient in Glycyrrhiza). Type II 11β-hydroxysteroid dehydrogenase converts cortisol to its inactive form in the renal tubular epithelial cells. The inhibition of this enzyme causes cortisol to accumulate, leading to activation of aldosterone receptors (10) associated with edema, increased blood pressure, hypokalemia, and hypernatremia. Hypokalemia may manifest, resulting in myopathy and rhabdomyolysis.

Glycyrrhiza-containing Kampo products should not be coadministered with loop diuretics or thiazide diuretics. Since these diuretics also cause hypokalemia, their combination with Glycyrrhiza may increase the risk of myopathy and rhabdomyolysis. Also, coadministration with glycyrrhetin preparations which are used for hepatitis should be avoided, since these preparations and Glycyrrhiza share the same adverse reactions, and coadministration may enhance the risk toward these adverse reactions.

Since pseudoaldosteronism caused by Glycyrrhiza depends to some degree on the intake of Glycyrrhiza, daily Glycyrrhiza doses of 2.5 g or higher should be administered with extreme caution. However, even a trace of kanzo can cause symptoms in some patients and susceptibility to adverse reactions has been reported to vary among individuals. Even though the daily dose of Glycyrrhiza in an individual formula is below 2.5 g, the limit may be exceeded by combining several Glycyrrhiza-containing Kampo formulae or Glycyrrhiza -containing food additives. Every caution should be taken.

This adverse reaction, if mild, rapidly disappears within 2 days after discontinuation of Glycyrrhiza administration. Therefore, early detection is important. In the event of myolysis symptoms such as malaise, blood should be monitored for elevation in muscle enzymes. If edema or increased blood pressure is observed, Glycyrrhiza should be immediately discontinued. Since delayed detection may have a fatal outcome, it is important to carefully observe patients in the course of illness.

(2) Drug-induced liver disorder (jaundice) and drug-induced lung disorder (interstitial pneumonia)

Not so common but serious adverse reactions to Kampo products include drug-induced liver disorder and drug-induced lung disorder. To date, cases of liver disorder and lung disorder have been reported that are due

to approximately 40 and 20 Kampo formulae, respectively, including shosaikoto, hochuekkito, and bofutsushosan (防風通聖散) (see Table 4). These cases are considered to be relatively common in the elderly, but not necessarily related to old age, suggesting that idiosyncrasy such as allergic constitution may play a role. Accordingly, early detection and early treatment is the only way to prevent these adverse reactions besides careful history taking to pinpoint drug allergy before administration. As appropriate, blood tests should be performed periodically, 1 and 3 months after the first dose of a Kampo product, to check hepatic function. The assessment for interstitial pneumonia should include, if needed, serum KL-6 measurement and chest X-ray in addition to auscultation.

Pharmacoepidemiologic analysis has suggested Scutellaria Root (黄芩, ogon) as the crude drug producing these adverse reactions (11). Reports from several medical facilities indicate that liver disorders occurred in patients receiving a Scutellaria Root-containing Kampo formula, or that hepatic function was restored after removal of Scutellaria Root from a Kampo formula. The possible mechanism is sensitization by the Scutellaria Root relatively rich in baicalin, which interacts to albumin to form a hapten, a sensitizer. This is, however, just a hypothesis, warranting further research.

As described later, coadministration of shosaikoto and interferon preparations is contraindicated, since both are associated with interstitial pneumonia and are likely to increase the incidence of this adverse reaction when coadministered. Since interstitial pneumonia is an adverse reaction to many Kampo formulae, avoidance of coadministration of Kampo formulations and interferon preparations is recommended.

For general information about the above adverse reactions, see the Manual of Serious Adverse Reactions (pseudoaldosteronism, interstitial pneumonia, drug-induced liver disorder) compiled by the MHLW (available by download from the MHLW's website:
http://www.mhlw.go.jp/topics/2006/11/tp1122-1.html [in Japanese]).

List of Kampo products to be used with cautions

Contraindications, warnings, and significant adverse reactions are indicated in the respective package inserts of Kampo extract products.

Shosaikoto is contraindicated in patients under treatment with an interferon preparation, those with cirrhosis or liver cancer, and those with chronic hepatitis and platelet count (100,000/mm3 or lower) decreased owing to hepatic function disorder. The WARNING in the package insert states: 'This product may cause interstitial pneumonia, which may lead to serious outcomes such as death, unless early appropriate treatment is given. Patients should be carefully observed, and this product should be discontinued immediately in the event of symptoms such as fever, cough, and dyspnea as well as abnormal chest sounds (crepitations) and abnormal chest X-ray findings. Patients should be instructed to discontinue this product and consult a physician immediately in the event of symptoms such as fever, cough, and dyspnea.'

Since glycyrrhetinic acid contained in Glycyrrhiza is responsible for pseudoaldosteronism, as mentioned above, the package inserts of Glycyrrhiza-containing formulae designate pseudoaldosteronism and myopathy as serious adverse reactions. Glycyrrhiza-rich formulae such as shakuyakukanzoto are

contraindicated in patients with aldosteronism, myopathy, or hypokalemia. Serious adverse reactions to shakuyakukanzoto include congestive cardiac failure, ventricular fibrillation, and ventricular tachycardia (including Torsades de Pointes). Also, interstitial pneumonia, hepatic function disorder, and jaundice have been reported as adverse reactions to Kampo extract products, as aforementioned, and listed as serious adverse reactions in the package inserts of many formulae.

Other adverse reactions described in the package inserts of Kampo extract products are: hypersensitivity (rash, redness, pruritus, and urticaria), gastrointestinal reactions (anorexia, stomach discomfort, nausea, vomiting, abdominal pain, diarrhea, constipation, etc.), urological reactions (hematuria, feeling of residual urine, cystitis, pollakiuria, and painful urination), autonomic reactions (insomnia, excess sweating, tachycardia, palpitations, weakness generalized, mental excitement, etc.), liver function-related reactions (AST [GOT] increased, ALT [GPT] increased, etc.), hot flashes, tongue numbness, and nausea. Since only a limited number of ethical Kampo extract products have no adverse reactions in the respective package inserts, very careful attention should be paid to the contents in package inserts.

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Medical Science and the Effectiveness of Kampo Medicines

Foreword

Chizuko Hioki

The built of Kampo Pharmacy and the Development of Kampo Medicines

In Japan, the population is aging. The pace of ongoing reforms in the healthcare system is increasing around the globe. For these reforms to succeed, we need a medical science that is practical in nature and addresses the health issues of patients. Setting clear objectives and applying the best scientific information available, we must use medicines that best suit individual patients. Kampo formulations, which can be used widely to treat and prevent disease, are now attracting the attention of those involved in the healthcare reform process. Evidence-based medicine (EBM), an effort to evaluate efficacies using the methods and perspectives of Western Medicine and to identify the mechanisms of action, is starting to be applied in research and clinical practice contexts. The potential of Kampo to improve the quality of modern healthcare and to broaden the range of therapies is being explored. The Kampo formulations identified through such research as effective, such as cancer treatment formulations, are often used together with Western medicines. Thus the pharmacokinetics and pharmacodynamics of the main ingredients in Kampo and Western co-therapies is an important focus of research.

The theories of physiology and disease in Kampo are based on the concept of qi (Ki), blood and fluid (*Kiketsusui*)- life force, blood, and colorless bodily fluids (three elements that constitute an organism according to Chinese Traditional Medicine). Thus Kampo medicines act concurrently on the systems of the human body including the metabolic and nervous systems. Kampo medicines are prepared from multiple crude drugs so that just such an action can take place. These crude drugs originate from organisms and natural substances. Their constituents are metabolic products, which may be water or fat soluble and have different molecular weights. Many Kampo formulations are groups of substances extracted using water or ethanol. In crude drug research, efficacy evaluation is often conducted on the specific constituents of crude drugs, and results are obtained under more finely tuned conditions than those used in clinical practice. Then, different extract fractions sometimes lead to contradictory results; however, as these are crude drugs, variation in results is unavoidable. The diverse efficacies of Kampo medicines, which may at first seem unfavorable, make it possible to administer individual medical care. It is important that Kampo medicines are used with the support of the best possible knowledge in both chemistry and biology. Research also must be conducted from a broad perspective, which hopefully would lead to progress.

This chapter focuses on the efficacy and pharmacology of Kampo medicines whose efficacies are backed by good evidence. We have provided descriptions of the efficacy and pharmacology of crude drug

constituents that are ingredients of these Kampo medicines. The efficacies of all these medicines evaluated through clinical studies are those described in the classical writings that fundamentally define Kampo medical practice. EBM research clearly reflects the wisdom and insights of Kampo pioneers. We attempted a classification of Kampo formulations based on the combination of constituent crude drugs. The efficacy obtained by mixing crude drugs must be investigated in future. Research into Kampo is a relentless task. Outstanding research that is interdisciplinary, combines Western and Oriental Medicine, and draws upon knowledge gained from clinical practice may improve the health of the modern nation.

By judging the usefulness of Kampo medicines, we aim to build and establish the field of Kampo pharmaceuticals so that they can be used appropriately and safely in Japan.

Clinical efficacy and pharmacology

Kampo formulae containing Rhubarb (大黄, daio) and Gardenia Fruit (山梔子, sanshishi)

Inchinkoto (茵蔯蒿湯)

Jun-ichi Shoda

[Combination of crude drugs]

Artemisia Capillaris Flower (茵陳蒿, inchinko), Gardenia Fruit (山梔子, sanshishi) and Rhubarb (大黄, daio) all have choleretic action. Rhubarb (大黄, daio) adds cathartic action to heat pattern-treating (*Seinetsu*) and choleretic actions, and removes excess heat and solid waste, thereby promoting metabolism. Bofutsushosan (防風通聖散) also contains Gardenia Fruit (山梔子, sanshishi) and Rhubarb (大黄, daio).

[Component crude drugs]

Artemisia Capillaris Flower (茵陳蒿, inchinko), Gardenia Fruit (山梔子, sanshishi), Rhubarb (大黄, daio)

[Clinical efficacy and pharmacology in the gastrointestinal tract]

<Clinical effects> In clinical practice, we frequently encounter patients with cholestasis and jaundice. Cholestasis is a pathology characterized by impaired early-stage bile production in hepatocytes and impaired bile secretion. The accompanying oxidative stress may damage hepatocytes and thereby result in severe jaundice (hyperbilirubinemia), prolonging liver dysfunction.

Kampo formulation inchinkoto has long been widely used in China and Japan for treatment of cholestasis and jaundice. In Japan, inchinkoto has been empirically used for cases presenting with chronic cholestasis, including primary biliary cirrhosis, primary sclerosing cholangitis, postoperative congenital biliary atresia (1), and prolonged obstructive jaundice. Despite the many reports showing improvements by inchinkoto, including relief of liver dysfunction and hyperbilirubinemia in cholestasis, few have attempted to describe the molecular mechanism underlying these improvements. Although the pharmacological effects of Kampo formulae are recognized in clinical practice, the use of many Kampo formulae has failed to become widespread because of emphasis on evidence-based medicine and the lack of molecular mechanisms underlying these beneficial effects.

The results of randomized clinical trials on the usefulness of inchinkoto administration before hepatectomy for biliary tract cancer have been reported only recently (2). Biliary tract cancer is often accompanied by obstructive jaundice due to bile duct obstruction. Prolongation of obstructive jaundice leads to decreased liver function. In the study of Watanabe et al., hepatectomized patients with biliary tract cancer requiring preoperative biliary drainage for obstructive jaundice were randomly assigned to receive or not to receive inchinkoto to compare the clinical efficacy of inchinkoto. Patients receiving inchinkoto showed

marked pre- to post-treatment increases in bile flow, total bilirubin concentration in bile, and total bile acid concentration in bile (Figure 1). This was explained by the significant increase in the expression of multidrug resistance-associated protein 2 (Mrp2), a liver transporter protein for organic anions including bilirubin, located on the hepatocyte bile canalicular lumina membrane. The Western blotting method using liver homogenate also confirmed the significant increase in Mrp2 protein expression. It has been suggested that preoperative administration of inchinkoto increases Mrp2 expression in the liver and Mrp2 localization on the bile canalicular lateral membrane to promote excretion of bilirubin and bile acid in bile, thereby relieving preoperative liver dysfunction and reducing the operative risk of hepatectomy. Thus, these findings provided evidence for the clinical usefulness of inchinkoto.

<Basic research/actions of component crude drugs> Although the potent hepatocytes-protective and choleretic actions and main active ingredients of inchinkoto have long been known, it is only recently that the mechanism of action has been elucidated in detail (3,4).

Geniposide contained in Gardenia Fruit (山梔子, sanshishi) is hydrolyzed by the intestinal bacteria to be converted to the active form genipin, with the glucose portion detached. It was demonstrated that acute administration of genipin potently promotes translocation of Mrp2, a drug transporter functioning as a pump to excrete bilirubin, an anion, and reduced glutathione, from hepatocytes to the bile canalicular lumina, and localization on the bile canalicular membrane (Figure 2) (5). This results in enhanced ability to excrete bilirubin from the liver and to excrete reduced glutathione, thereby promoting bile secretion in a bile acid-independent manner. One-week oral administration of geniposide and genipin to rats (compared with control) significantly increased bile flow and also bile secretion of reduced glutathione (6). The concentration of reduced glutathione in the liver was also significantly increased by geniposide and genipin compared with the control (6).

In addition, 1-week oral administration of geniposide and genipin to chimeric mice with livers repopulated by human hepatocytes increased Mrp2 protein levels in human hepatocytes to that of mouse hepatocytes, as revealed by the immunostaining and Western blotting methods (6).

It has been reported that the main component of Artemisia Capillaris Flower, 6,7-dimethylesculetin, activates constitutive androstane receptor (CAR), the key regulator of bilirubin excretion, to increase expression of genes in hepatocytes involved in uptake, intracellular transport, glucuronate conjugation, and bilirubin excretion into the bile canalicular lumina (*Oatp2, Cyp2b10, Ugt1a1, Mrp2, Gsta1, Gsta2*), thereby potentiating bilirubin clearance from blood.7)

[Discussion]

The mechanism of the potent effect of inchinkoto on bile secretion (choleretic effect) is attributable to its component crude drug, genipin, which stimulates localization of the liver transporter protein Mrp2 located on the bile canalicular membranes of hepatocytes, thereby causing a bile acid-independent increase in bile secretion. Because of its pharmacological effects, inchinkoto is emerging as the second-line treatment for primary biliary cirrhosis resistant to ursodeoxycholic acid (8). In the future, inchinkoto may offer useful treatment for children with cholestatic liver disease and patients who undergo gastrointestinal surgery.

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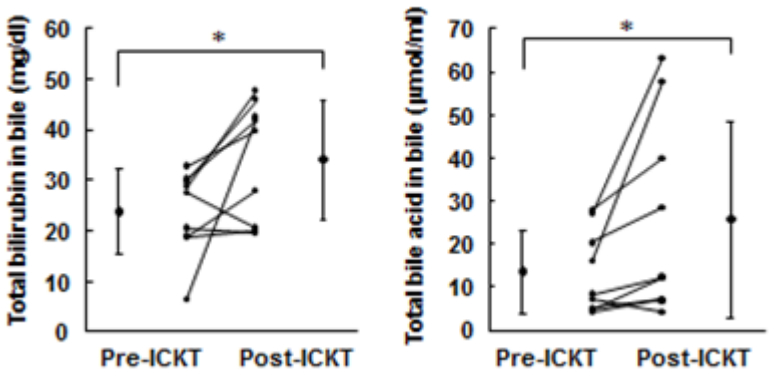

Figure 1

Comparison of total bilirubin concentration (A) and total bile acid concentration (B) in bile before and after inchinkoto administration.

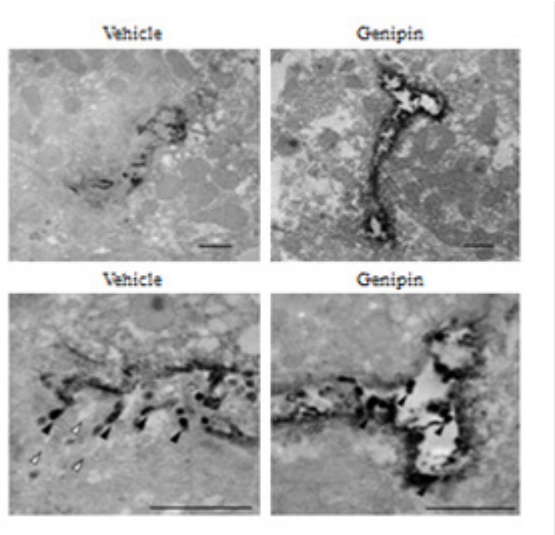

Figure 2

Changes in the level of expression of multidrug resistance-associated protein 2 (Mrp2) on bile canalicular membranes in inchinkoto-treated rats (immunoelectron micrograph).

Kampo formula containing Ephedra Herb (麻黄, mao), Cinnamon Bark (桂皮, keihi), and Glycyrrhiza (甘草, kanzo)

Chizuko Hioki

［Combination of crude drugs］

To Ephedra Herb (麻黄, mao) that increases body temperature and induces sweating, addition of Cinnamon Bark (桂皮, keihi) improving peripheral circulation, warming the body surface, and inducing sweating enhances sweating, which in turn inhibits proliferation of viruses and bacteria. Therefore, the combination of Ephedra Herb and Cinnamon Bark is used for symptoms amenable to diaphoretic treatment. This treatment is known as *Hakkangehyo* (発汗解表, promote sewating to release the exterior), since sweating eliminates exterior pattern (*hyosho*). Maoto (麻黄湯) and shoseiryuto (小青竜湯) have the same effect. Treatment is most effective when the patient takes such a medication with warm foods and remains in bed to keep the body temperature elevated.

Maoto（麻黄湯）

［Component crude drugs］

Ephedra Herb (麻黄, mao), Cinnamon Bark (桂皮, keihi), Apricot Kernel (杏仁, kyonin), Glycyrrhiza (甘草, kanzo)

According to "*ShangHanLun* (傷寒論)," the optimal pattern of Ephedra Herb (麻黄, mao) is 'the early-phase condition in which patients feel chilled with wind and experience severe symptoms such as high fever, cough, dyspnea, headache, back pain, and joint pain throughout the body without sweating.' These symptoms are observed at the onset of severe infectious diseases, such as pneumonia and influenza. Maoto has been, therefore, approved by the health insurance for the treatment of early-phase influenza. In 2004, it was reported that the antiviral agent oseltamivir (Tamiflu®; a neuraminidase inhibitor) should not be administered to less than 1-year-old infants because of uncertain safety for the immature blood-brain barrier of infants (1). In Japan, since the Ministry of Health, Labour and Welfare, Pharmaceutical and Food Safety Bureau, Safety Division, reported 'abnormal behavior after administration of oseltamivir' in 2007, physicians were cautioned to remain alert to abnormal behavior following administration of the drug. In addition, prescription of it to teenagers was banned in principle. An inhaled drug with the same clinical effect, zanamivir (Relenza®), can be administered only to patients more than 5 years old. By contrast, maoto is a health insurance approved therapy for congestion of the nose and poor sucking in infants. Recently, several reports showed the clinical effect of maoto during the acute phase of influenza in children.

［Efficacy pharmacology in respiratory system disease］

<Clinical effects> In 2007, patients aged less than 15 years old with type A influenza (n=81) and type B influenza (n=48) were included in a study comparing maoto extract (0.08–0.19 g/kg/day, for 2–8 days) with oseltamivir (4 mg/kg/day, for 2–5 days) and supportive care alone (during the 2002–2003 influenza season). In patients with type A influenza, the febrile period was shorter in both the maoto and oseltamivir arms than

in the supportive care arm, but similar in both of the drug-treatment arms. In patients with type B influenza, the febrile period was also shorter in both of the drug-treatment arms than in the supportive care arm, and the time to fever reduction was shorter in the maoto arm by 10.7 hours and the time to relief of systemic symptoms such as headache, general malaise, and loss of appetite was shorter in the maoto arm by 25.5 hours than in the oseltamivir arm ($p<0.05$) (2).

A study by Kubo et al. compared periods of fever (defined as body temperature above 37.2°C) in type A influenza patients assigned to three arms: maoto extract alone (n=17, 4.5±4.8 years, 0.06 g/kg/day), oseltamivir alone (n=18, 5.4±1.9 years, 2 mg/kg/day), and a combination of both medications (n=14, 5.2±1.9 years). The febrile period was significantly shorter in the maoto arm and combination arm (15 and 18 hours from the start of administration, respectively) than in the oseltamivir arm (24 hours). Neither disease progression nor adverse effects were observed during the treatment (3). Many clinical reports, including reports of adult cases, have shown that treatment with maoto extract for influenza is as beneficial as treatment with oseltamivir for influenza irrespective of the infecting virus type. Strictly speaking, however, there have been no randomized trials because influenza is an acute febrile disease. Therefore, further investigation is required to establish the usefulness of maoto.

<Basic research on the effects of crude drug ingredients> The mechanism of inhibition of influenza virus infection by maoto was investigated by use of Madin-Darby canine kidney (MDCK) cells infected with type A influenza virus PR-8 (A/PR/8/34(H1N1)(PR8)) strain (4). Mao solution (obtained by extraction of 50 g Ephedra Herb with 500 ml of water) was found to concentration-dependently inhibit replication of the virus, if added within 10 min of the time of infection, by preventing acidification within endosomes and lysosomes and thereby inhibiting viral uncoating. When added 15 minutes after infection, mao solution had no antiviral activity, suggesting that Ephedra Herb inhibits viral proliferation during the early phase of infection. In addition, the Ephedra Herb extract treated with $FeCl_3$ to remove tannin was a less effective concentration-dependent inhibitor of viral replication. This result suggests that tannin contained in the Ephedra Herb plays a role in the inhibition of viral proliferation.

When the infected cells were cultured in medium without Ephedra Herb after the Ephedra Herb extract treatment, virus count became comparable to that in untreated cells 15 hours after infection. This result indicates that the antiviral activity of Ephedra Herb persists 15 hours after treatment *in vitro*.

A similar effect was reported of Cinnamon Bark (5). Hayashi et al. added 40 μM of cinnamaldehyde (CA), a constituent of the extract of Cinnamon Bark, to MDCK cells infected with type A influenza virus PR-8 (A/PR/8/34(H1N1)(PR8)) strain every hour beginning immediately after the infection. CA added 3 hours after infection inhibited viral proliferation in as many as 29.7% of cells compared with untreated ones. CA (20–200 μM) added 3 hours after infection concentration-dependently inhibited viral proliferation, with the strongest effect observed at 200 μM. Comparison of mRNA expression in influenza virus between infected cells treated continuously with CA and untreated infected cells found no inhibition. But comparison of protein expression found concentration-dependent inhibition by CA addition 3 hours after infection. These results suggest that CA acts in an intermediate stage of viral proliferation, when viral proteins are synthesized in MDCK cells. When survival and viral load in alveolar lavage fluid were evaluated in two groups of mice

(one group infected with type A influenza virus PR-8 strain and treated intranasally with CA [250 mg/mouse/day] and the other group infected but untreated), the results showed that CA increased survival (80% of untreated mice died 8 days after infection) and inhibited virus proliferation by 10% 6 days after infection. Thus, Cinnamon Bark may inhibit synthesis of viral membrane proteins.

［Discussion］

Oseltamivir has replaced amantadine, an M2 inhibitor, which had been used in the treatment of type A influenza since 1998, because the latter promoted generation of resistant viruses. However, even oseltamivir, if administered at high doses, will facilitate the emergence of resistant viruses and, therefore, caution is still advised. If maoto allows us to reduce antiviral agent usage, it could prevent an outbreak of resistant viruses. In addition, this medication can be used in patients of all ages from infants to adults and be effective for fever, general malaise, muscle pain, headache, and stuffy nose, suggesting a favorable course of recovery. Further study is needed to clarify the role of Kampo formula ingredients other than those of Ephedra Herb and Cinnamon Bark in immune processes triggered by seasonal influenza infection.

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Kampo formula containing Ephedra Herb (麻黄, mao),
Cinnamon Bark (桂皮, keihi), and Glycyrrhiza (甘草, kanzo)

Kakkonto（葛根湯）

Chizuko Hioki

[Component crude drugs]

Pueraria Root (葛根, kakkon), Ephedra Herb (麻黄, mao), Cinnamon Bark (桂皮, keihi), Peony Root (芍薬, shakuyaku), Glycyrrhiza (甘草, kanzo), Ginger (生姜, shokyo), and Jujube (大棗, taiso)

“The Annual Report on Pharmaceutical Industry Production Vital Statistics 2007” issued by the Ministry of Health, Labour, and Welfare estimates total value of kakkonto (葛根湯) extract products at 2382 million yen, whose volume is in the top 20. “The Kampo Medicine Actual Use Research” report in the same year revealed that 72.4% of 713 randomly selected physicians routinely prescribe Kampo formulae with kakkonto as first-line therapy (Nikkei Medical, October 2007).

In Japan, since Sohaku Asada first recommended the use of kakkonto, it has been indicated for not only chills and tension of the trapezius region, but also for inflammation and hyperemia in the periphery of the

posterior cervical region and neuralgia in the upper body including stiff shoulder due to age, empyema, otitis media, mastitis, and urticaria. Although many recent studies have reported the efficacy of kakkonto for cold and influenza symptoms, including chills, headache, stiffness in the posterior neck and fever, and anhidrosis in the early stage of acute upper respiratory inflammation, the designs of these studies (including case studies) are all non-experimental or quasi-experimental.

[Clinical efficacy and pharmacology in respiratory disease]

<Clinical effects> In a study of cold syndrome, kakkonto (extract 7.5 g, containing 3.75 g of crude drug dry extract/day) and maoto (麻黄湯) (extract 7.5 g, containing 1.75 g of crude drug dry extract/day) were administered to 30 and 27 patients, respectively, and antipyretic effects were noted in 80% of the kakkonto group and 67% of the maoto group (1). A study of kakkonto (administered for 3 days) to 136 patients with cold syndrome reported improvement in systemic symptoms (slight or greater improvement in chills, feeling of warmth and diarrhea in 80% of patients) and respiratory symptoms (slight or greater improvement in nasal discharge, nasal congestion, sneezing, and sputum production in 60% of patients). Furthermore, effectiveness for pain (slight or greater improvement in muscle pain and stiff shoulder in 80% of patients) was also shown, with the rate of global improvement reported to be 79% (2).

<Basic research> Kakkonto (extract 0.005 g/day) was orally administered to 6-week-old fever-sensitive female DBA/2 Cr mice for 8 days, beginning on the day before infection with type A influenza virus PR-8 strain (A/PR/8/34[H1N1][PR8]) to evaluate its effects on symptom severity in comparison with those of distilled water as control. Measurement of the total area of inflammation or pneumonia in slices of lung from infected mice revealed that kakkonto reduced the size of the affected area. Kakkonto suppressed pneumonia symptoms, weight loss associated with influenza infection, andviral growth in alveolar lavage fluid on day 3 of infection, and improved survival. The effects of kakkonto on levels of IL-4, IL-10, IL-12, and IFN-γ in alveolar lavage fluid and serum from infected mice were evaluated on days 2, 4, and 6 of infection. The results showed a significant increase in the IL-12 level in alveolar lavage fluid on day 2 and a subsequent increase in the IFN-γ level in serum (3).

Oral administration of clarithromycin (20 mg/day, b.i.d.) to DBA/2 Cr mice for 7 days (beginning the day before infection) increased the IL-12 level in alveolar lavage fluid on day 2 of infection and the IFN-γ level in serum on day 3 of infection, and significantly decreased viral level in alveolar lavage fluid. Furthermore, nasal administration of IL-12 (20 ng/animal) produced a similar response only when administered on day 2 of infection. These studies demonstrated that kakkonto administration increases IL-12 level in alveolar lavage fluid and subsequently stimulates IFN-γ production, thereby inducing a cell-mediated (Th-1) immune response. Thus, it was demonstrated that kakkonto prevents pneumonia from becoming severe by enhancing cell-mediated immunity and suppressing viral growth, and suppresses fever by preventing excessive production of IL-1α (4, 5, 6).

<Action of component crude drugs> There is a report on the antipyretic action of kakkonto. Extracts resulting from 1-hr brewing of 50 g each of the following kakkonto component crude drugs in 1000 mL of

distilled water were administered to the above strain of mice to investigate antipyretic effects and production of IL-1α: Pueraria root (葛根, kakkon), ephedra herb (麻黄, mao), cinnamon bark (桂皮, keihi), peony root (芍薬, shakuyaku), glycyrrhiza (甘草, kanzo), ginger (生姜, shokyo), and jujube (大棗, taiso). The water extract of cinnamon bark exerted the most potent antipyretic effects and IL-1α production-suppressing effects. Thirteen cinnamyl compounds had these activities, whereas some others had the opposite effects. Infection with influenza triggers increase in interferon and IL-1α levels in serum, which act on the hypothalamus to activate cyclooxygenase (COX), thereby stimulating production of prostaglandin E2, leading to fever. Antipyretic mechanisms of aspirin and kakkonto differ: kakkonto suppresses fever by inhibiting IL-1α production, whereas aspirin resolves fever by inhibiting COX activity and prostaglandin E2 production. Cinnamyl compounds and kakkonto act similarly (3,7).

[Discussion]
Like macrolide antibiotics, kakkonto effectively limits influenza infection by promoting cytokine production in the respiratory epithelium and activating a protective response to infection. To have an even greater effect, it is crucial to stimulate a response in the host at an early stage of infection.

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Kampo products containing Ephedra Herb (麻黄, mao), Gypsum (石膏, sekko), Glycyrrhiza (甘草, kanzo)

Bofutsushosan (防風通聖散)

Chizuko Hioki

Mammals have white and brown fatty tissue. Both types generate fatty acid from neutral fat stored in cells. White adipose tissue (WAT) stores energy and releases fatty acid into the blood. Brown adipose tissue (BAT) takes up fatty acid and sugar then oxidizes them within the cells converting them into heat. Thereby energy is consumed but not stored (Fig. 3). Thus, BAT activation within the body promotes WAT lipolysis, which in turn reduces fat storage and may resolve symptoms associated with obesity.

Bofutsushosan (防風通聖散) is based on choijokito (調胃承気湯), which contains Rhubarb (大黄, daio), Mirabilite (芒消, bosho), and Glycyrrhiza (甘草, kanzo), giving it a purgation effect. It has also been investigated for the metabolic activation and anti-obesity effects that BAT activation promote.

[Components]

Rhubarb (大黄, daio), Mirabilite (芒消, bosho), Ephedra Herb (麻黄, mao), Schizonepeta Spike (荊芥, keigai), Saposhnikovia Root and Rhizome (防風, bofu), Aluminum Silicate Hydrate with Silicon Dioxide (滑石, kasseki), Gardenia Fruit (山梔子, sanshishi), Mentha Herb (薄荷, hakka), Forsythia Fruit (連翹, rengyo), Gypsum (石膏, sekko), Scutellaria Root (黄芩, ogon), Platycodon Root (桔梗, kikyo), Peony Root (芍薬, shakuyaku), Japanese Angelica Root (当帰, toki), Cnidium Rhizome (川芎, senkyu), Glycyrrhiza (甘草, kanzo), Atractylodes Rhizome (白朮, byakujutsu), and Ginger (生姜, shokyo)

[Evidence in the fields of endocrinology/glucose and urinary metabolism]

<Basic research> In an obese mouse model—hereditary obese KKA^{y} female mice injected with monosodium-L-glutamate (MSG) to destroy the hypothalamic region and accelerate the accumulation of body fat—administration of bofutsushosan was shown to activate the ability of BAT to bind guanosine-5'-diphosphate (GDP) in mitochondria, activate uncoupling protein (UCP1) on the mitochondrial inner membrane, generate heat, and promote lipolysis in WAT, thereby decreasing subcutaneous fat, visceral fat, and body weight1). Bofutsushosan is composed of 18 crude drugs. Its effects on the two types of fatty tissue are mainly attributed to *l*-ephedrine and *d*-pseudoephedrine in Ephedra Herb, which activate sympathetic nerves and potentiate the release of noradrenalin from the sympathetic nerve terminals to stimulate β-adrenalin receptors on brown and white adipose tissues. Furthermore, it was shown that the phosphodiesterase (PDE) inhibitory action, or caffeine-like action, of Glycyrrhiza, Schizonepeta Spike, and Forsythia Fruit acts additively to inhibit cAMP decomposition, thereby prolonging the effect of noradrenalin, resulting in fat decomposition in WAT and heat production in BAT (energy consumption) (Figs. 1 and 2).

<From basic to clinical research> The amount of BAT varies widely between species and decreases especially after puberty in large mammals such as humans and dogs unlike in small mammals such as rodents, then only a trace has been thought to remain in adults. Recently, it was reported that positron emission tomography (PET) with 2-[^{18}F]-fluoro-D-2-deoxy-D-glucose (FDG) can detect not only tumor tissue, but also brown adipose tissues in the bilateral cervical, supraclavicular, and paravertebral regions 3). Thus, the presence of BAT in adults can now be visualized 4). The verification of BAT activation by intramuscular administration of ephedrine in humans 5) suggests that ephedrine-induced BAT activation may be involved in the fat-decreasing effect of bofutsushosan.

In Japan, bofutsushosan is used to treat obesity-related ailments, diagnosed from the Kampo medicine perspective based on the "*sho* (pattern/syndrome)" concept. Although the criteria for diagnosis of obesity requiring treatment from the viewpoint of Western medicine were established in 2001, treatment of obesity had been covered by insurance before then. In this context, a double-blind study of bofutsushosan as treatment for obesity was performed in female outpatients to investigate whether the amount of visceral fat decreased and parameters of insulin resistance improved. The inclusion criteria were obesity, predisposition to constipation, and impaired glucose tolerance (IGT) defined as fasting blood glucose level <126 mg/dL and blood glucose level at 120 min after glucose loading ≥140 mg/dL and <200 mg/dL. Those with endocrine disorders, liver or heart disease, renal dysfunction, or receiving an antipsychotic were excluded 6).

The study followed a 2-month lifestyle-improvement intervention consisting of dietary restriction (1200 kcal/day) and advised exercise (5000 steps/day). Patients received bofutsushosan extract (bofutsushosan extract granules 7.5 g, containing 4.5 g of crude drug dry extract (生薬乾燥エキス) [1.5 g t.i.d]) before meals and control patients received a laxative. At the start of the study and 12 and 24 weeks thereafter, the following parameters were assessed: body weight; amount and distribution of fat; waist and hip circumference; resting metabolism; serum lipid and uric acid levels, and glucose level on the 75-g oral glucose tolerance test (OGTT). The study population consisted of 81 patients (BMI: 36.5±4.8 kg/m^2 [mean ± standard deviation]), with 41 patients (age: 52.6±14.0 years) assigned to the bofutsushosan group, and 40 (age: 54.8±12.5 years) to the control group. Comparison of abdominal fat by CT images demonstrated a decrease in visceral fat and subcutaneous fat at 24 weeks of treatment in both groups (bofutsushosan, –67.0±11.5 cm^2 and –103.0±13.3 cm^2, respectively; control, –34.7±11.0 cm^2 and –61.7±14.7 cm^2, respectively). The decrease in visceral fat was especially large in those receiving bofutsushosan. Waist circumference was also significantly lower in the bofutsushosan group (– 12.2±2.12 cm) than in the control group (–5.8±1.4 cm) (P<0.05).

Total cholesterol and neutral fat levels began decreasing at 12 weeks and uric acid level was decreased at 24 weeks in both groups. On the OGTT, glucose level at 90 min and thereafter was significantly decreased compared with the pretreatment level in both groups, confirming that dietary restriction and increase in exercise improve glucose and lipid metabolism. In the bofutsushosan group, insulin level at 120 min after glucose loading was significantly decreased (i.e., area under the insulin level-time curve was significantly decreased), confirming a decrease in fasting insulin level and improvement in the problem of delayed and excessive insulin release7). Homeostasis model assessment of insulin resistance (HOMA-IR) decreased from 3.8 to 2.1 in patients receiving bofutsushosan, indicating improvement in insulin resistance.

<Adverse drug reactions and social background> Thus, bofutsushosan was shown to improve insulin resistance by decreasing body weight and subcutaneous fat, especially abdominal visceral fat, without decreasing resting metabolic rate, in obese women with IGT. These findings suggested efficacy of this product for prevention and treatment of obesity and metabolic syndrome.

In addition, the schizophrenia drug olanzapine is an atypical antipsychotic drug (second-generation antipsychotic drug) with serotonin-dopamine antagonist (SDA) properties, that is, it blocks dopamine 2 (D2) and serotonin 2 (5-HT2) receptors in the brain. Olanzapine is also a multi-acting receptor-targeted antipsychotic (MARTA) since it acts on other receptors including adrenalin and histamine receptors. The adverse reactions are constipation, increased neutral fat, increased or decreased appetite, increased weight, and abnormal glucose tolerance. In the case of a 20-year-old female patient treated for schizophrenia with olanzapine (7.5 mg/day) and promethazine (75 mg/day) for 3 months reported in 2008, weight increased by 4.5 kg and BMI increased from 23.6 kg/m^2 to 25.4 kg/m^2, although psychiatric symptoms improved. The patient became reluctant to take the drugs after the weight gain, so bofutsushosan 7.5 g/day combined with these drugs was prescribed. The combination therapy decreased BMI to 24.3 kg/m^2 in 6 months without affecting appetite, demonstrating the effectiveness of bofutsushosan as a suppressor of olanzapine-induced weight gain 8). Drugs that block dopamine, serotonin, or other receptors, such as antipsychotics, affect eating

behavior by suppressing dopamine activity, which leads to the loss of a sense of fullness (satiety), causing overeating, and thus obesity and diabetes mellitus. This antipsychotic-induced obesity is difficult to treat because of uncontrollable appetite. On the other hand, bofutsushosan has not been shown to have appetite-suppressing effect, although sympathetic nerve activation has been noted.

There is an ever-increasing demand for bofutsushosan in both the over-the-counter (OTC) and prescription drug markets. For instance, the sales of bofutsushosan for prescription increased each year from 2005 to 2008 (1943 million yen in 2005, 2455 million yen in 2006, 2961 million yen in 2007, and 3452 million yen in 2008) (Strategic Decision Initiative, Inc. survey). Similarly, an increasing number of people are using OTC bofutsushosan. Underlying this increase in demand is the criteria used for the diagnosis of metabolic syndrome in Japan issued by eight academic societies (including the Japanese Society of Internal Medicine in April 2005) and the specific health examination established in 2008. The recommendation to self-medicate is driving people to purchase Kampo products, which are readily available and thought to be as safe as health food. With the rapid increase in users, however, cases of drug-induced liver disorder have been reported, although not frequently 9), requiring the establishment of precautions for the use of these products. One case was a 37-year-old woman who received OTC bofutsushosan extract granules 2.5 g/day (content of crude drug dry extract unknown) for 1 month from August 2006. She was hospitalized after jaundice and right hypochondrial pain developed. Liver function was abnormal (GOT 1210 IU/L, GPT 1592 IU/L, and T-Bil 18.0 mg/dL), but white blood tissue count and coagulation were normal, although platelet count was decreased, and eosinophilia was absent. Liver function steadily improved with treatment including hepatoprotective drugs (glycyrrhetin preparation and ursodeoxycholic acid). Although the patient suffered from acute hepatitis, drug-induced hepatic injury was diagnosed based on GOT/GPT ratio at her first visit and based on the “Diagnostic Criteria for Drug-induced Hepatic Injury by the DDW-J2004 Workshop on Drug-induced Hepatic Injury” 10). The drug-induced hepatic injury was judged to be caused by bofutsushosan. A drug lymphocyte stimulation test (DLST) was positive for bofutsushosan dry extract, Japanese Angelica Root, Cnidium Rhizome, and Mentha Herb.

[Discussion]

In one clinical study, some patients receiving bofutushosan dropped out prematurely owing to soft stool 6). Bofutsushosan (which contains Rhubarb [sennosides] and Mirabilite [Na_2SO_4]) should be used in patients with constipation, which is relieved through increase in bowel movement, but should not be used in patients with predisposition to diarrhea. This product should not be used if stool is soft, and measures such as adjustment of the dose of Mirabilite taken, if necessary. Furthermore, overeating due to the antipsychotic drug-induced increase in appetite may result in excess fat accumulation. Bofutsushosan enhances resting metabolism (almost equivalent to basal metabolism), which however reaches a plateau with extended use. Bofutsushosan decreases visceral fat and improves insulin resistance; however, to sustain these improvements, self-management including exercise and dietary restrictions is essential.

Bofutsushosan contains 18 crude drugs that not only activate the sympathetic nerve-adipose tissue system but also promote bile secretion, gastrointestinal function, excretion, and blood circulation, as described above. Since bofutsushosan can rapidly alter metabolism, this product should not be given to frail

patients.

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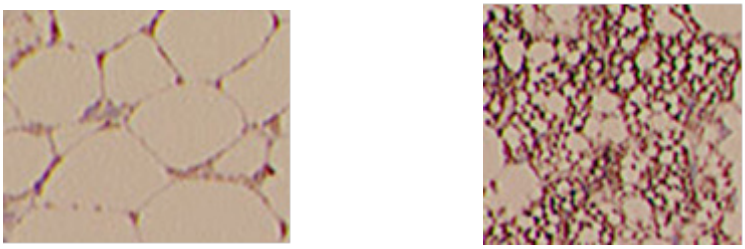

White adipose tissues Brown adipose tissues

Fig. 1. Mouse white and brown adipose tissues

White adipose tissues are relatively large and contain a single fat droplet. In contrast, brown adipose tissues (20–50 μm in diameter) have multilocular (many fat droplets) structure and contain many mitochondria. Uncoupling protein specifically expressed in the mitochondrial inner membrane of brown adipose tissues activates ATP synthesis-uncoupled respiration to generate a large amount of heat. Normally, under physiological conditions that increase sympathetic nerve activity including exposure to cold and polyphagia, heat production is promoted to maintain body temperature or to dissipate excess energy.

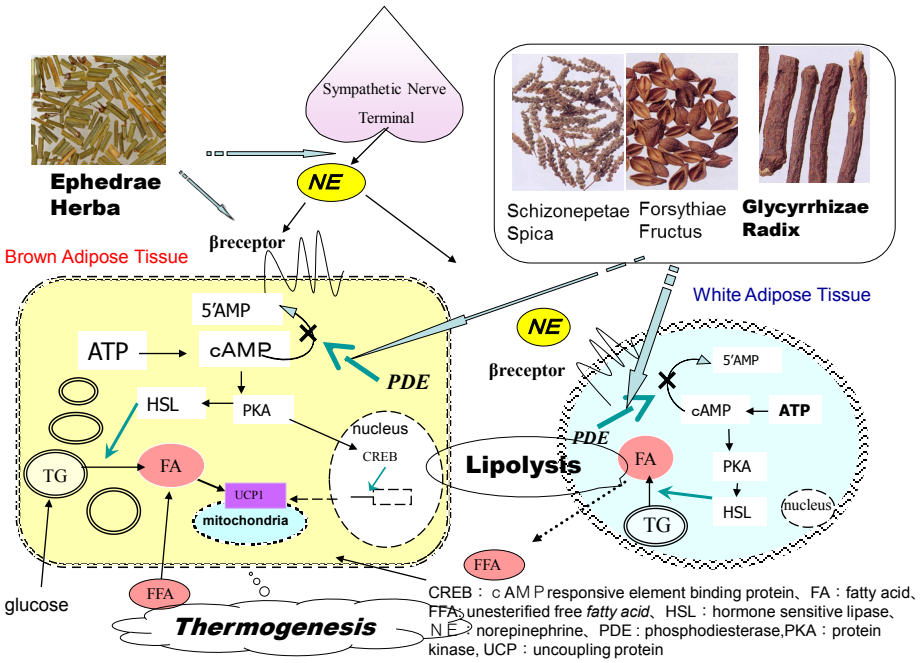

Fig. 2. Heat production from brown adipose tissue and breakdown of white adipose tissue induced by bofutsushosan

If hypofunction of the sympathetic nerve-white adipose and brown adipose systems underlies predisposition to obesity, activating the system may help prevent and treat obesity. Administration of bofutsushosan to obese mice decreased the amount of white adipose and activated brown adipose tissues. The same mechanism is considered to be responsible for the decrease in visceral fat and improvement of metabolism noted in obese patients receiving this product.

CREB, cAMP response element binding protein; FA, Fatty acid; FFA, free fatty acid; HSL, hormone-sensitive lipase; NA, noradrenaline; PDS, phosphodiesterase; PKA, protein kinase A; UCP, uncoupling protein

[Combination of crude drugs]
Processed Ginger (乾姜, kankyo) mainly warms the abdomen to treat abdominal pain and diarrhea caused by cold stimulus, whereas Ginseng (人参, ninjin) activates the upper abdominal region to restore appetite. Shoseiryuto (小青竜湯) and ninjinto (人参湯) (Ginseng [人参, ninjin], rhizomes of Atractylodes spp. [朮, jutsu], Processed Ginger [乾姜, kankyo], Glycyrrhiza [甘草, kanzo]) also have this combination.

Daikenchuto (大建中湯)

Chizuko Hioki

[Component crude drugs]
Zanthoxylum Fruit (山椒, sansho), Processed Ginger (乾姜, kankyo), Ginseng (人参, ninjin), *Koi* (膠飴 [a saccharized substance obtained by hydrolysis of starch])

The original text "*JinGuiYaoLue* (金匱要略)" gives the indications for daikenchuto as cold abdomen, abdominal pain, and intense gastrointestinal peristalsis. However, it is also effective for the opposite reasons such as no or weak peristalsis, and is used in western medicine for intestinal obstruction due to sub-ileus and intestinal adhesion. Since surgery for malignant tumor generally involves massive organ resection, the postoperative needs are to conserve functions of residual organs and to avoid complications. While conservative therapies to prevent and treat common post-laparotomy disorders and simple adhesive ileus include dehydration and electrolyte correction via transfusion, administration of antibiotics, reduction in intra-intestinal pressure via intubation and placement of an ileus tube, and resting the bowel by fasting the patient, it is suggested that daikenchuto combined with these therapies can enhance therapeutic outcome.

[Clinical efficacy and pharmacology in the gastrointestinal tract]
<Clinical effects> In 1993, an open-label trial conducted in 52 patients at 11 sites in the Kanto district, Japan, showed that daikenchuto improved postoperative bowel motility. Daikenchuto extract 5.0 g (containing 0.4 g of crude drug dry extract and 3.3 g of powder candy was dissolved in 20 mL of lukewarm water and administered for 5 days via a nasogastric tube or long tube to patients with simple adhesive ileus with complaints of abdominal pain and feeling of abdominal enlargement. The study excluded those with carcinomatous peritonitis, tumors, and inflammatory ileus. Feeling of abdominal enlargement was 'slightly improved' in 56.7% (n=30) and 76.6% (n=40) of patients at day 2 and day 5 of administration, respectively. Both abdominal pain in 65.4% and 78.2% of patients at day 2 and day 5, respectively, and nausea/vomiting in 81.8% and 90.5% of patients at day 2 and day 5, respectively, were 'slightly improved.' Diarrhea occurred in 18.2% and 66.7% of patients at day 1 and day 5 of administration, respectively; however, given that

watery or muddy stool is commonly noted immediately after resolution of ileus, the postdose diarrhea was considered to represent improved ileus, but not an adverse reaction (1).

In 1995, a study to compare daikenchuto treatment and non-treatment was conducted in patients with ileus, and found that daikenchuto improved symptoms and shortened duration until ileus tube extubation and hospitalization (2). A randomized controlled study reported in 2002 found that daikenchuto helped reduce postoperative ileus recurrence (3). Thereafter, the protective effect of daikenchuto on ileus development after intestinal surgery has been reported (4,5).

A gynecologic study used various routes of administration. Daikenchuto extract 10.0 g (containing 0.8 g of crude drug dry extract and 6.6 g of *Koi* [a saccharized substance obtained by hydrolysis of starch]) was dissolved in 100 mL of lukewarm water and given as an enema once daily to fasted patients with ileus (with air-fluid level in the left upper abdomen) that developed 1 year after hysterectomy and pelvic external radiotherapy (50.4 Gy) for cervical cancer. At day 5, a rapid reduction in serum c-reactive protein (CRP) level and movement of intestinal gas were noted. Patients received daikenchuto extract at the same dose via a nasogastric tube once at day 7 and daikenchuto extract 15.0 g (containing 1.25 g of crude drug dry extract and 10.0 g of *Koi*) following gastric tube extubation at day 10, and recovered from ileus at day 13. Thereafter, sub-ileus developed at day 21 of continuous oral administration, but favorably resolved following 1 day of fasting. Although for adhesive ileus, daikenchuto is often introduced into the small intestine via an ileus tube, enema administration also promotes intestinal peristalsis without causing local adverse reactions (6).

In a clinical study, daikenchuto extract (0.3 g/kg/day) was administered for 3–12 months to 10 pediatric patients with functional chronic constipation (8.6 years) and 5 pediatric patients with chronic constipation after surgery for anorectal malformation (11.5 years), to evaluate the following items: 4 items of awareness of defecation, constipation, incontinence, and soiling; intra-anorectal pressure; severity before and after administration; and defecation function. Both patient populations showed significant improvement in the 4 items and defecation function; particularly children with functional chronic constipation showed marked improvement in rectal retention ability, with the maximum tolerable volume decreased. It was concluded that administration of daikenchuto improved bowel motility to allow regular bowel movement. That is, it normalized bowel habits, and thereby improved rectal retention ability (7).

In 2010, the Mayo Clinic in the U.S. conducted a 5-day clinical study in which 60 healthy subjects received daikenchuto extract 7.5 g/day (n=19, 11 females; BMI, 25.3±1.1 kg/m^2) or 15 g/day (n=20, 10 females, BMI, 25.6±0.7 kg/m^2) or placebo (n=21, 11 females; BMI, 24.5±0.7 kg/m^2), to evaluate the changes in transit times in the stomach, small intestine, and large intestine by scintigraphy using technetium-99m and indium-111. Daikenchuto had no effect on stomach discharge function, but shortened small intestinal transit time ($p=0.04$) (compared with placebo) and the ascending colon emptying time ($p=0.07$). It was confirmed that administration of daikenchuto via the geometric center (GC) of the colon accelerated intestinal filling rate and content transit in each part of the large intestine.

Morphine suppresses intestinal peristalsis mainly by causing continuous contraction of the intestinal circular muscle. In addition, morphine increases anal sphincter tone, weakening rectal reflex relaxation. Furthermore, since suppressed intestinal secretion increases viscosity of gut content, continuous administration of morphine for pain control induces constipation at high frequency. Daikenchuto was

effective for such morphine-induced constipation, and it was noted that its effects are associated with not only stimulation of serotonin receptors and activation of cholinergic nerves, but also elevation in blood motilin concentration (9).

<Basic research>

[Enhancement of gastrointestinal motility via serotonin receptor-mediated release of acetylcholine from enterochromaffin (EC) cells in the gastrointestinal mucosa]

After daikenchuto administration to dogs equipped with strain gauge force transducers attached to the gastric antrum, duodenum, jejunum, and ileum, strong contractions moving toward the anus were detected at the site of injection and other parts of the digestive tract. This effect lasted a short time in fasting dogs and for approximately 20 min after a meal. Administration via gastrostomy also promoted contractile motility in the stomach, duodenum, and jejunum. This effect was not observed when daikenchuto was administered 5 min after anesthesia of the gastric mucosa with 10 mL of 1% xylocaine, suggesting that daikenchuto enhances upper gastrointestinal motility via mucosal stimulation. The contractile force triggered by daikenchuto administration was comparable to that of Interdigestive Migrating Contractions (IMCs; spontaneous strong contractions during fasting) and was not observed on the rostral side. Studies of the relationship between the effects of daikenchuto and neurotransmitters in the gastrointestinal and autonomic nervous systems have demonstrated that the increase in gastrointestinal motility stimulated by daikenchuto was suppressed by pretreatment with atropine (muscarinic acetylcholine receptor antagonist) and hexamethonium (nicotine receptor antagonist) in the gastric corpus, gastric antrum, duodenum, jejunum, and by pretreatment with ondansetron (5-HT3 receptor antagonist) in the gastric antrum and duodenum (10,11).

Daikenchuto extract and Zanthoxylum Fruit (山椒, sansho) extract induced contraction of the isolated ileum from guinea pigs. Daikenchuto and Zanthoxylum Fruit extract promoted release of acetylcholine from the intestine. Pretreatment with atropine and tetrodotoxin (neurotransmission blocker) suppressed the intestinal contraction, which was not suppressed by pretreatment with a 5-HT_3 receptor antagonist but was suppressed by pretreatment with a 5-HT_4 receptor antagonist (12, 13).

It was suggested that daikenchuto promotes release of acetylcholine via serotonin (5-HT_3, 5-HT_4) receptors at the cholinergic nerve terminal.

[Enhancement of gastrointestinal motility via motilin secretion from Mo cells in the gastrointestinal mucosa]

After administration of daikenchuto extract 7.5 g (containing 0.6 g of crude drug extract and 4.9 g ofKoi) to 24 male volunteers, the time-course of plasma concentration of brain-gut hormones (gastrin, somatostatin, and motilin) was measured. Motilin concentration was significantly increased, indicating that promotion of motilin secretion in the small intestinal mucosa is involved in the gastrointestinal motility promoted by daikenchuto (14).

[Enhancement of gastrointestinal motility via vanilloid receptor-mediated secretion of substance P]

Administration of capsazepine (vanilloid receptor antagonist), which inhibits capsaicin-sensitive sensory nerves, suppressed the increase in gastrointestinal contraction by daikenchuto.

Hydroxy-β-sanshool contained in Zanthoxylum Fruit binds to the vanilloid receptor TRPV1 (Transient Receptor Potential Vanilloid 1) occurring on the parasympathetic postganglionic fiber to stimulate capsaicin-sensitive sensory nerves. Substance P, which is released at the same time via vanilloid receptors, is also considered to be involved in enhancement of gastrointestinal motility (15,16).

[Vasodilation via vanilloid receptor-mediated release of calcitonin gene-related peptide (CGRP) and improvement in intestinal blood flow via adrenomedullin (AM)]

Kono et al. suggested that daikenchuto increases intestinal blood flow by releasing adrenomedullin (AM), which is a member of the CGRP superfamily.

The Transient Receptor Potential (TRP) protein is a calcium ion channel, and it activates the communication system in response to influx of calcium in cells. Hydroxy-α-sanshool and 6-shogaol contained in Processed Ginger (乾姜, kankyo) dilate vessels by stimulating the release of calcitonin gene-related peptide (CGRP) via activation of TRPV1. Daikenchuto caused release of CGRP and expression of regulatory protein familyRAMP1, 2, 3; receptor activity - modifying protein). RAMP1 binds to CRLR (calcitonin receptor-like receptor) causing it to change to CGRP receptor, which binds RAMP2 or RAMP3. Thereupon, CGRP receptor changes to AM receptor, suggesting the contribution of these calcitonin family members to vasodilation and blood flow improvement. Furthermore, AM suppresses IFN-γ and TNF-α production in a concentration-dependent manner, confirming that daikenchuto has anti-inflammatory and cytokine-suppressive effects (17,18).

< Action and pharmacokinetics of component crude drugs> It is empirically known that Zanthoxylum Fruit (山椒, sansho [蜀椒, shokusho]) and Processed Ginger have warming/heating and wind-expelling (expelling gas from the intestine) effects. It has been experimentally demonstrated that these crude drugs promote AM release (17). A study using rats revealed that after administration of Processed Ginger (150 mg/kg) and its constituent, 6-shogaol (2 mg/kg), Ginseng (人参, ninjin) (90 mg/kg), and Zanthoxylum Fruit (60 mg/kg), intestinal blood flow was increased, as measured with a laser Doppler blood-flowmeter. The effect of processed ginger and 6-shogaol on the increase in blood flow was especially significant. Two hundred forty minutes after undergoing surgery involving laparotomy followed by manipulation of the small intestine, rats received oral administration of daikenchuto (2.7 g/kg) and hydroxy-α-sanshool (0.3 mg/kg, 1.0 mg/kg), a zanthoxylum fruit constituent. Thirty minutes later, a mobile marker was administered to examine the peristaltic contractile waveform using a high-sensitivity pressure transducer. Daikenchuto and hydroxy-α-sanshool (1.0 mg/kg) improved gastrointestinal transport compared with distilled water (19). Thus, component crude drugs zanthoxylum fruit, ginseng, and processed ginger are all involved in bowel motility.

The pharmacokinetics of 44 crude drug-derived compounds from daikenchuto were examined by liquid chromatography-tandem mass spectrometry (LC-MS/MS). After administering daikenchuto extract (containing 1.25 g of dry extracts from 5.0 g of processed ginger, 3.0 g of ginseng, 2.0 g of zanthoxylum fruit, and 10.0 g of candy) to 4 healthy subjects (25.0 years old, 2 males and 2 females), plasma was sampled at 30, 60, 120, 240 and 480 min, and urine at 240 and 480 min. There was no sex difference in the composition of samples. Glucuronate conjugates of hydroxysanshool, shogaol, and gingerol, which are

processed ginger- and zanthoxylum fruit-derived constituents, were detected in plasma and urine. Hydroxy-α-sanshool and 6- shogaol in plasma reached the maximum concentration 30 min after administration and then declined rapidly. In contrast, plasma concentration of the active ingredient of Ginseng, ginsenoside Rb1, slowly increased with time (20).

[Discussion]
It was scientifically demonstrated that several daikenchuto component crude drugs have efficacy for 'patients complaining of relatively severe abdominal pain with poor physical strength and cold extremities and abdomen, or presenting with enlarged abdomen or flatulence and soft and weak abdominal wall and visible peristalsis' mediated via neurotransmitters in the gastrointestinal or autonomic nervous system. Further elucidation of the pharmacokinetics, or absorption, distribution, metabolism and excretion, of main constituents will lead to new developments in Kampo formulae.

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Kampo Formula containing Uncaria Hook (釣藤鈎, chotoko)

Yokukansan (抑肝散)

Chizuko Hioki

[Component crude drugs]
Uncaria Hook (釣藤鈎, chotoko), Bupleurum Root (柴胡, saiko), Glycyrrhiza (甘草, kanzo), Japanese Angelica Root (当帰, toki), Cnidium Rhizome (川芎, senkyu), rhizomes of Atractylodes spp. (朮, jutsu), Poria Sclerotium (茯苓, bukuryo).

[Combination of crude drugs]
Muscle tonus increases in the agitated, irritable, and over-emotional state. Uncaria Hook (釣藤鈎, chotoko),

Bupleurum Root (柴胡, saiko), and Glycyrrhiza (甘草, kanzo) suppress over-excitement of nervous system activity and reduce muscle hypertonus. Since the increase of qi (Ki) of the liver (TM) leads to dysfunction of the spleen (*Hi*) (TM). Rhizomes of Atractylodes spp. (朮, jutsu) and Poria Sclerotium (茯苓, bukuryo) are used to support splenic (TM) activity and remove dampness (*Shitsu*) for improvement of this condition. Japanese Angelica Root (当帰, toki) and Cnidium Rhizome (川芎, senkyu) improve circulation of the blood (resolve blood stasis [*Oketsu*]) and qi (Ki).

Yokukansan is used in children and the elderly for treatment of psychotic manifestations (mainly anger according to Dotaku Meguro and Sohaku Asada et al.). It modulates skeletal muscle tonus and autonomic nervous system activity, and also affects circulation and metabolism. These effects in turn suppress signs related to anger, irritation, and agitation due to insomnia or aggression. Therefore, it has been approved by the health insurance for treatment of neurosis or hot temper of children (小児疳症, *Shonikansho*). Patients with impaired cognitive function may manifest behavioral and psychological symptoms of dementia (BPSD) (e.g., anxiety, depression, irritability, wandering behaviors, hallucinations, delusions, and lack of motivation). A randomized trial of yokukansan evaluated its effect on BPSD (1).

Dementia with Lewy bodies (DLB), Alzheimer's disease (AD), and vascular dementia are three major categories of dementia. DLB patients have a tendency to present with psychological symptoms and BPSD, and Parkinsonism and BPSD in these patients are treated first. Thus, a clinical trial of yokukansan was performed in DLB patients as well as was done in AD patients.

[Efficacy pharmacology in patients with psychological disease]

<Clinical effects> Fifty-two patients having dementia (including DLB, AD, and vascular dementia; mean age, 80.3±9.0 years) and presenting with BPSD were randomly assigned to two groups: one group receiving yokukansan (extract 7.5 g, including crude drug dry extract 3.25 g/day; n=27) for 4 weeks and the other group (control group) not receiving medication (n=25). If the BPSD was uncontrollable enough to make care difficult, tiapride hydrochloride (benzamide antipsychotic) was added to their treatment. Neuropsychiatric inventory (NPI) score, Mini-mental State Examination (MMSE) score, and Barthel index were obtained at baseline and the end of the study period to evaluate the changes in BPSD, cognitive function, and activities of daily living (ADL). The NPI decreased ($p<0.01$) and Barthel index improved ($p<0.05$). There were no adverse events such as falling or misswallowing in the yokukansan group. There was no between-group difference in MMSE score. On the other hand, 11 patients (controls) were treated with 25 mg of tiapride hydrochloride; of them, 6 experienced dizziness, which was considered an adverse effect/adverse drug reaction.

In conclusion, yokukansan improved BPSD but not the cognitive function of elderly patients without causing extrapyramidal symptoms, which are seen as adverse effects of antipsychotic agents (2).

In 2009, it was reported that the dose of antipsychotics could be reduced by treatment with yokukansan for 12 weeks in elderly AD patients refractory to antipsychotics (3). These patients (mean age was 80.2±4.0) had MMSE score of 6–23, NPI score of ≥6 in at least one category (delusion, hallucination, agitation/aggression, disinhibition, irritability/lability, or aberrant motor behavior), and BPSD after 2 weeks

administration of sulpiride (50 mg daily). The patients continued to receive sulpiride (50 mg daily) and were randomly assigned to two groups. Yokukansan (extract 7.5 g, including crude drug extract 3.25 g/day) was administered to the first group (n = 10) but not the second group (n = 5). The dose of sulpiride was reduced if the NPI scores in the above categories were all < 4 during the 12-week treatment period, and was increased, if any of the scores was ≥ 8 in at least one category. The endpoints were NPI score and Barthel index at 4, 8, and 12 weeks and MMSE score at 12 weeks. The average dose of sulpiride at the end of the treatment period was lower in yokukansan arm than in the control arm and the average NPI score was improved at 8 and 12 weeks in yokukansan arm ($p<0.001$). There was no significant between-arm difference, however, in MMSE score and Barthel index at baseline and 12 weeks. Hypokalemia was observed in 2 patients of the yokukansan arm.

Iwasaki et al. reported that NPI score was decreased in 15 DLB patients who received yokukansan (extract 7.5 g, including crude drug dry extract 3.25 g/day) for 4 weeks. In addition, the scores in the categories of agitation/aggression, irritability/lability aberrant motor behavior, sleep disorder and hallucination were improved, reducing from 7.5 to 1.5 (4). Mizukami et al. published the result of a multicenter randomized crossover trial of yokukansan for BPSD in 106 patients with dementia (15 patients with DLB, 78 with AD, and 13 with mixed) and randomly assigned to two groups. Yokukansan was given for 4 weeks followed by a 4-week washout period in one group, and this sequence was reversed in the other group. Yokukansan was found to significantly decrease NPI score without rebound after discontinuation of the therapy. Although treatment was terminated in 3, 2, and 1 patient owing to gastrointestinal symptoms (such as nausea or uncomfortable feeling in the abdomen), hypokalemia, and edema of the lower limbs, respectively, it is suggested that yokukansan could improve BPSD in both AD and DLB (5).

<From clinic to bench>

One of the pathophysiological characteristics of dementia is nerve cell dysfunction due to accumulation of amyloid β proteins to form senile plaques. The result is not only memory dysfunction and cognitive function impairment due to loss of nerve cells but also BPSD related to functional changes of residual neurons. Since yokukansan shows clinical effects on the aberrant excitatory psychological symptoms of BPSD including irritability, insomnia, and aggression, studies seeking to elucidate the pharmacodynamics of yokukansan were performed.

Abnormal increase in the extracellular concentration of glutamate (caused by impairment of glutamatergic transmission) activates glutamate receptors and markedly increases calcium and zinc ion concentrations in postsynaptic neurons, leading to neuronal cell dysfunction. Glutamate excitotoxicity is observed only in glutamatergic neurons and is a common mechanism seen in not only acute neuronal injury such as brain ischemia and epileptic seizure, but also chronic neuronal diseases such as AD, amyotrophic lateral sclerosis, and Huntington's disease. Therefore, studies have been performed to test the hypothesis that yokukansan suppresses the hyperexcitability of glutamatergic neurons in the hippocampus. Hyperexcitability of these neurons is likely to be involved in BPSD of dementia.

<Basic research>

[Correcting extracellular glutamate concentration] Low-zinc diet increases sensitivity to the epileptic seizure activity induced by kainic acid and the rate of nerve cell death in the hippocampus of rats. This suggests lack of zinc could exacerbate glutamate excitotoxicity (6). In this zinc-deficient rat model, glutamate concentration in the extracellular fluid of the hippocampus was increased by perfusion of artificial cerebrospinal fluid containing 100 mM KCl. The concentration of glutamate was further elevated by the stress of a low-zinc diet for 4 weeks. However, oral administration of yokukansan extract (0.3 g/kg/day) for 10 days inhibited the elevation of the extracellular glutamate concentration. This effect was also observed when 100 μM zinc chloride was added to the fluid (7).

[Improvement of glutamatergic neuron function]
Four-week-old Wistar male rats were fed a normal diet or low zinc diet for 29 days. Yokukansan extract (0.3 g/kg/day) was orally administered from day 19 to day 28, and hippocampal tissue sections were prepared at day 29. Since glutamate and zinc are located in the synaptic vesicles of mossy fiber terminals, hippocampal tissue sections were stained with FM4-64 (a die [Molecular Probes] for detection of exocytosis) and ZnAF-2DA (a Zn-specific fluorescent probe for detection of fiber terminals). Exocytosis was determined by attenuation of fluorescent signals in dentate granule cells after tetanic stimulation. Glutamate release was increased in fiber terminals, and yokukansan inhibited this increase in the hippocampus of rats fed a low zinc diet but not in rats fed a normal diet. This increase was also seen after the administration of zinc, suggesting that zinc (together with glutamate, released from synapses into mossy fiber terminals) did regulate the process of exocytosis. These findings implied that yokukansan did not affect the process of exocytosis, but improved glutamatergic neuron function impaired by low zinc concentration (8).

[Glutamate uptake increased by activating the glutamate-aspartate transporter (GLAST) in astrocytes]
Glutamate that is released from nerve terminals into the synaptic cleft will bind to N-methyl-D-aspartate (NMDA) receptors on postsynaptic membranes to trigger activation of neuronal cells. To avoid the hyperexcitable state, astrocytes will incorporate glutamate through the GLAST and inactivate glutamate.

In thiamine-deficient rats, memory dysfunction and aggression develop, followed by epileptiform seizures with hypersensitivity or opisthotonus. Increased extracellular glutamate concentration and loss of nerve cells or hydropic degeneration of astrocytes were observed in the brain tissue of these rats (9). Yokukansan extract 0.5 g/kg or 1.0 g/kg once daily was administered orally for 28 days, resulting in inhibition of increase of extracellular glutamate concentration in the brain and preventing nerve cell degeneration in the 1.0 g/kg group (10).

In cultured astrocytes under thiamine-deficiency conditions, yokukansan decreased glutamate uptake by down-regulating GLAST activity and increased extracellular glutamate concentration. Yokukansan, however, increased levels of transporter protein and mRNA expression (11).

[Prevention of glutamate-induced cell death] Yokukansan binds strongly to the glutamate or glycine recognition sites on glutamate NMDA receptors in the postsynaptic membrane, and inhibits

glutamate-induced PC12 cell death (11). The death of PC12 cells, none of which express NMDA receptors, was due to oxidative stress caused by inhibition of cystine-glutamate antiporter system (Xc^-system) and production of glutathione (GSH; a free radical scavenger). In poly-IC (polyinosinic acid–polycytidylic acid)-treated mice, used in this study as a model of schizophrenia, yokukansan inhibited the decrease in GSH level in the hippocampus (12). This effect also suggested the involvement of yokukansan in the cell death sequence induced through oxidative stress. These results implied that yokukansan might contribute to inhibition of NMDA receptors and the Xc-system and in production of GHS, protecting cells from death.

[Partial agonist effect on 5-HT1A receptors and down-regulation effect on 5-HT2A receptors *in vitro*]
Binding to 5-HT receptors, serotonin (5-HT) acts as a neurotransmitter. There are 14 receptor subtypes. Of them, 5-HT1A receptors are most commonly expressed in the brain and have an inhibitory effect on nerve cells, while 5-HT2A receptors have an excitatory effect, which is thought to underlie psychological symptoms such as hallucination.

Yokukansan was reported to have a partial agonist effect on 5-HT1A receptors (13) and a down-regulation effect on 5-HT2A receptors (14).

Binding experiments using CHO cells expressing human 5-HT1A or 5-HT2A receptors showed that yokukansan inhibited the binding of radio-labeled ligands ([^{3}H]8-OH-DPAT) to 5-HT1A receptors but hardly inhibited the binding of ligands ([^{3}H] ketanserin) to 5-HT2A receptors. Examination using [^{35}S] GTPγS of yokukansan binding to 5-HT1A showed that yokukansan increased the binding of radio-labeled GTP to these receptors. However, elevation in yokukansan concentration did not proportionally increase neuronal cell activity, and the effect was approximately 50% of that of full-agonists such as serotonin. These results suggested that yokukansan was acting as a partial agonist for 5-HT1A receptors (13).

Effects of yokukansan extract on the frequency during a 5-minute period of head-twitch response induced by (2,5-dimethoxy-4-iodoamphetamine) (DOI, 5.0 mg/kg, i.p.), a 5-HT2A agonist, was examined in 4-week-old ddY male mice. Oral administration of yokukansan extract (0.1g, 0.3g/kg/day) at a single dose, before 55 minutes DOI administration, had no effects. In the same way, however, yokukansan continuous administration (0.3 g/kg/day) for 14 days yielded significantly inhibited the head-twitch response versus non-administrated mice. This study showed that decreasing of the expression of the protein on the 5-HT2A receptors in the frontal cortex (14).

In 8-week-old male rats injected with a single dose (5 mg/kg, i.p.) of parachloroamphetamine (PCA), an inhibitor of serotonin synthesis, serotonin concentration in the brain or reduction of its release was correlated with presentation of aggressive behavior. Aggression in PCA-treated rats was decreased by buspirone (5-HT1A agonist) and ketanserin (5-HT2A antagonist), but not by WAY-100635 (5-HT1A antagonist) or fluvoxamine (SSRI), and worsened by DOI. These experiments showed that stimulation of 5-HT2A receptors induces aggression in PCA-treated rats, and both 5-HT2A antagonists and 5-HT1A agonists have an aggression-improving effect. Repeated administration for 14 days, but not single-dose, of yokukansan (1.0 g/kg/day, p.o.) reduced aggression. Since 14-day administration of yokukansan did not increase serotonin concentration in the brain or its release, yokukansan was thought to act on the postsynaptic neuron (as a 5-HT2A antagonist or 5-HT1A agonist) (15).

<Activity of crude drug ingredients> Glycyrrhetinic acid contained in Glycyrrhiza, one of the components of yokukansan, inhibits protein kinase C (PKC) or acts on the metabotropic glutamate receptor (mGluRs) (16), and may affect the expression and activity of GLAST.

Constituents of Uncaria Hook, such as rhynchophylline and isorhynchophylline, act as antagonists of NMDA receptor (17). Additionally, geissoschizine methyl ether as an agonist of 5-HT1A receptor was reported in 1985 (18).

[Discussion] Stimulation of 5-HT1A receptors induces desensitization of 5-HT2A receptors (19). Yokukansan may mainly act as a partial agonist of 5-HT1A receptors and exert its effects through intracellular signaling.

A white paper on Aging Society issued, in 2010, by the Japanese Cabinet Office showed that the 29 million people were ≥65 years of age and the rate of aging in the population was 22.7% in 2009. The incidence of dementia, therefore, is expected to increase. In 2005, the U.S. Food and Drug Administration (FDA) warned that atypical antipsychotic agents used for supportive treatment of BPSD of dementia, especially agitation, aggression, and hallucination, increased the risk of heart failure (20), and in 2008 it warned that typical antipsychotic agents increased the risk of death. Yokukansan is therefore expected to contribute to the treatment of dementia.

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Kampo formulae containing Sinomenium Stem and Rhizome (防已, boi) and Astragalus Root (黄耆, ogi)

Boiogito (防已黄耆湯)

Masaki Aburada

[Components]

Sinomenium Stem and Rhizome (防已, boi), Astragalus Root (黄耆, ogi), Atractylodes (Lancea) Rhizome (白朮/蒼朮, byakujutsu/sojutu), Ginger (生姜, shokyo), Glycyrrhiza (甘草, kanzo), Jujube (大棗, taiso)

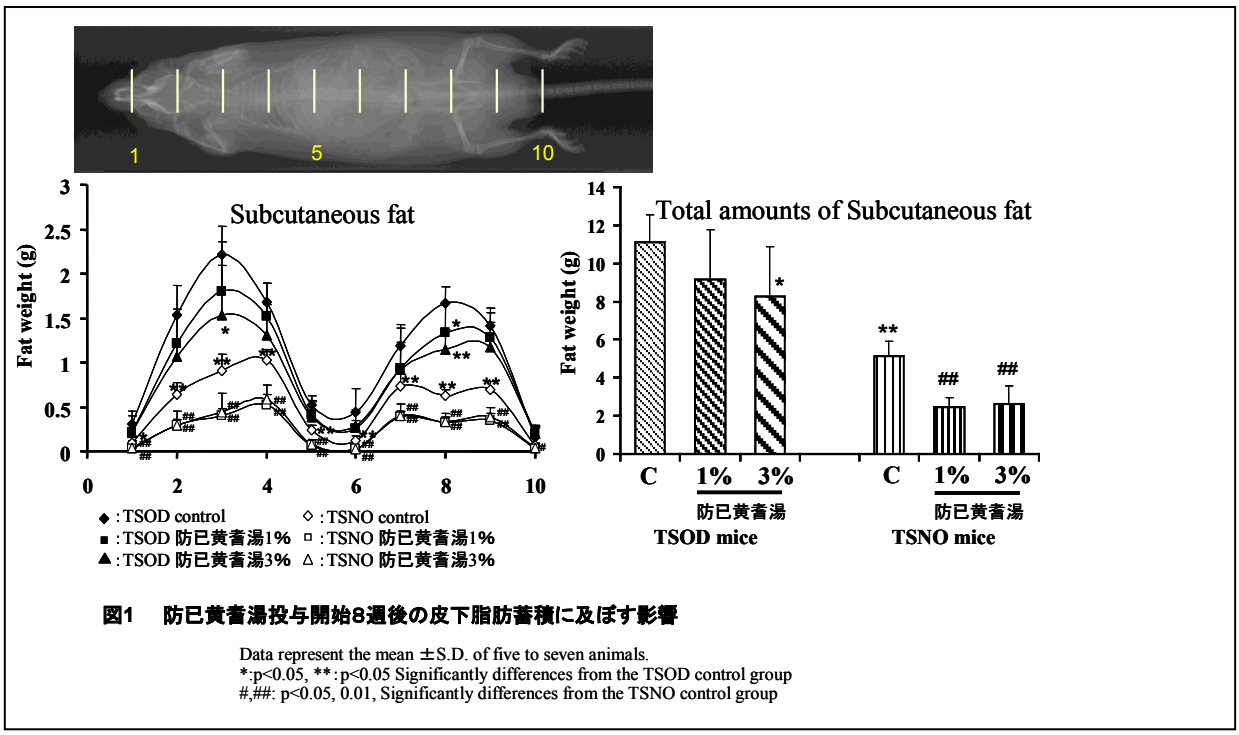
[Combination of crude drug]

Sinomenium Stem and Rhizome has potent aquaretic and edema-dispelling effects and also has a wind-dampness (*Fushitsu*)-dispelling effect, which is potentiated when combined with Astragalus Root. Astragalus Root has an anti-perspirant effect, which is potentiated when combined with Rhizomes of Atractylodes (朮, jutsu). Glycyrrhiza, Ginger, and Jujube enhance gastrointestinal function.

[Clinical efficacy on obesity]

Yoshida et al. divided 19 obese patients with non-insulin-dependent diabetes mellitus into two groups: a group that could not exercise because of retinopathy, nephropathy, or other diseases (n=11, 5 males and 6 females) and a group that could exercise (n=8, 3 males and 5 females). Dietary therapy in all patients was followed by 6 months of administration of boiogito (7.5 g of extract preparation containing 3.75 g of dry extract bulk powder per day) in the non-exercise group and 160 cal/day of aerobic exercise in the exercise group. Pre- to posttreatment changes in the following parameters were assessed: visceral fat (V), subcutaneous fat (S), body mass index (BMI), blood glucose, and lipid. In the boiogito group, serum cholesterol level and V/S ratio were significantly improved after treatment compared with baseline, whereas blood glucose, HDL, and TG levels tended to improve, but not significantly. In the exercise therapy group, all parameters showed improvement though the changes were not significant (1).

<Basic research> Shimada et al. investigated the anti-obesity effect of boiogito in the TSOD (Tsumura Suzuki Obese Diabetes), mouse a model of spontaneous obese type 2 diabetes mellitus. Boiogito (extract bulk powder) was shown to have a significant anti-obesity effect, suppressing weight gain in a dose-dependent manner and to significantly improve hyperinsulinemia, fasting hyperglycemia and abnormal lipid metabolism. However, subcutaneous (but not visceral) fat accumulation was suppressed (Figure 1), the researchers concluded that boiogito is effective for subcutaneous fat obesity, which is the deficiency pattern (*Kyosho*), but not for visceral fat obesity, which is the excess pattern (*Jitsusho*) (2).



Boiogito 1%

Boiogito 3%

Figure 1　Effects on the accumulation of subcutaneous fat after 8-week administration of boiogito

Yamakawa et al. investigated the anti-obesity effect of boiogito (extract bulk powder) in a ovariectomized rat model. Weight loss was significant 6 weeks after the start of the experiment. The researchers concluded that boiogito is useful for obesity associated with estrogen withdrawal, and potentially prevents the increase in obesity as estrogen level declines after menopause (3). Takakura et al. administered boiogito (extract bulk powder) with feed to rats for 8 weeks, and reported a decrease in Lee index [(weight on the day of sacrifice)$^{1/3}$÷(naso-anal length)], dose-dependent elevations in interscapular brown adipose tissue and rectal temperatures, and an elevation in plasma leptin level (4).

[Clinical efficacy on osteoarthritis of the knee]

Noguchi et al. investigated the effects of boiogito on osteoarthritis of the knee accompanied by hydrops in 84 patients, with the cooperation of 12 institutions. The patients were assigned to a boiogito (7.5 g of extract preparation containing 3.75 g of dry extract bulk powder per day) group (n=31), boiogito (7.5 g/day) + non-steroidal anti-inflammatory drugs (NSAIDs) combination group (n=33), and NSAIDs group (n=20), and observed for 8 weeks. The response rate, defined as improvement in clinical symptoms by 1 or more grades at 8 weeks of treatment, was 80.0%, 96.4%, and 57.9% for 'patellar ballottement,' 64.5%, 75.1%, and 42.1% for 'soft tissue swelling of the knee joint,' and 24.0%, 57.2%, and 21.1% for 'heat of the knee' in the boiogito group, boiogito + NSAIDs combination group, and NSAIDs group, respectively. Furthermore, group comparison revealed significant improvement of patellar ballottement and soft tissue swelling of the knee joints in the boiogito + NSAIDs combination group compared with the NSAIDs group, and significant

improvement of local heat in the boiogito + NSAIDs combination group compared with the NSAIDs group or boiogito group (5). Otani et al. evaluated the clinical efficacy of boiogito (5.0-7.5 g of extract preparation containing 205-3.75 g of dry extract bulk powder per day) on knee pain using a visual analogue scale (VAS) method in 137 patients with osteoarthritis of the knee for 6 months. Boiogito monotherapy improved knee pain in 4 of 20 males (20%), and 41 of 117 females (35%), for a total of 45 patients (33%) at 4 weeks, and in 6 of 20 males (30%), and 53 of 117 females (45%), for a total of 59 patients (43%) at 6 months (6).

[Discussion]

Boiogito is a formula for treating people who are fair-skinned, flabby, and easily fatigued, and who sweat excessively (i.e., people with the deficiency pattern). It is often used for treatment of obesity and osteoarthritis of the knee. The clinical efficacy of boiogito for 'visceral fat accumulation type obesity' has been reported. In a mouse model of obese type 2 diabetes mellitus, boiogito decreased subcutaneous fat accumulation as well as improved hyperinsulinemia, hyperglycemia, and abnormal lipid metabolism. The therapeutic effect on osteoarthritis of the knee has also been clinically confirmed, suggesting that boiogito is a useful drug that can be used alone or in combination with NSAIDs for conservative therapy.

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Kampo formulae containing Atractylodes (Lancea) Rhisome (白朮/蒼朮, byakujutsu/soujutu) and Poria Sclerotium (茯苓, bukuryo)

Goreisan (五苓散)

Masaki Aburada

[Component crude drugs]

Poria Sclerotium **(**茯苓, bukuryo), Polyporus Sclerotium (猪苓, chorei), Atractylodes (Lancea) Rhizome (白朮/蒼朮, byakujutsu/soujutu), Alisma Rhizome (沢瀉, takusha), Cinnamon Bark (桂枝, keishi)

[Combination of crude drugs]

Goreisan (五苓散) is a typical formula for treating fluid disturbance (*Suidoku*) by normalizing water metabolism. Alisma Rhizome, Polyporus Sclerotium, and Poria Sclerotium have a diuretic effect, Cinnamon Bark mildly suppresses central nervous system activity, promotes sweating and invigorating the stomach and modulates water metabolism. Atractylodes spp., including Atractylodes Rhizome and Atractylodes Lancea Rhizome, modulate water metabolism and promote invigorating the stomach, sweating, and diuresis.

[Clinical efficacy on orthostatic hypotension]

<Clinical effects> Nakamura et al. examined the effect of goreisan compared with placebo on orthostatic hypotension in 10 patients with diabetes mellitus (2 patients with type I and 8 patients with type II; 5 men and 5 women). In this trial, goreisan (extract tablets) or placebo was administered for 1 month and the Schellong test, measuring the change of blood pressure between the baseline and endpoint, was performed. Goreisan but not the placebo was found to significantly improve both the systolic and diastolic blood pressure in the upright position (1, 2).

[Clinical efficacy on vomiting]

<Clinical effects> Fukutomi et al. evaluated the effect of goreisan intestinal infusion on vomiting in children (6 months to 11 years old) with acute gastroenteritis. In this trial, 336 children suffering acute gastroenteritis with a chief complaint of vomiting received intestinal infusion of goreisan (7.5 g of extract preparation containing 1.5 g of dry extract bulk powder per day) dissolved in warm saline. Efficacy was assessed by subjective symptoms of vomiting after infusion. The overall efficacy rate was 79% and efficacy did not depend on age. There was significant correlation between the efficacy of goreisan and the frequency of vomiting before consultation (3, 4). Kawamura examined the effect of goreisan intestinal infusion in patients diagnosed as having gastroenteritis due to norovirus or rotavirus infection. A total of 398 patients who vomited twice or more during the 24 hours before consultation or presented with severe nausea and ill pallor were given intestinal infusion of goreisan followed 15 minutes later by oral-rehydration therapy. Within 15 minutes after the treatment, nausea and ill pallor were markedly improved in 340 patients (85%), moderately improved in 16 (4%), and not improved in 42 patients (11%). The 16 patients showing moderate improvement vomited again after they went home but received intestinal infusion of goreisan the next day, which relieved their symptoms again. Nearly 80% of the patients who vomited 10 times or more recovered without drip infusion, although the efficacy was lower in the patients who vomited more frequently within the 24 hours after infusion (5). Suzuki et al. conducted a similar trial of intestinal infusion of slightly warm goreisan solution in 84 infants (4 months–3.5 years old) diagnosed as having gastroenteritis caused by infection of rotavirus or adenovirus. 'Effective' was defined as recovery of normal skin pallor, absence of nausea or vomiting, and no worsening of diarrhea in the infants who were permitted intake of fluid within 1 hour after infusion, otherwise assessed as 'no effect.' Intestinal infusion of goreisan relieved nausea and vomiting in 84.5% of these infants and did not aggravate diarrhea in any infant. In 85% of patients in whom goreisan was effective, the clinical effect was apparent within 30 minutes and was more likely to be rapid in younger patients (6). Fukasawa et al. evaluated the effectiveness of goreisan (extract) suppositories—prepared in-house—dispensed to 66 children who complained of nausea and vomiting. Marked effect, moderate effect, mild effect, no effect, and exacerbation were seen in 15, 17, 21, 6, and 7 children, respectively. Efficacy rate (defined as the percentage of the patients whose response was either marked, moderate, or mild) was 80.3%, and the effect was immediate or occurred within 30 minutes in many cases (7). Nishi et al. compared goreisan (extract) suppositories with domperidone suppositories for treatment of vomiting in children. Children (12 boys and 8 girls; mean age, 4.5 years) who complained of

vomiting but did not have a high fever or dehydration requiring drip infusion were given goreisan or domperidone suppositories followed 30 minutes later by oral intake of water. Clinical effect was either moderate (defined as relief of both nausea and vomiting) or mild (defined as relief of vomiting but some relief of nausea). In the goreisan suppository arm, the treatment was effective (response moderate or mild) in 12 of 13 patients (92.3%), whereas in the domperidone arm, the treatment was effective in 5 of 7 patients (71.4%) and ineffective in 2 patients (28.6%). There was no significant between-arm difference and no adverse effects in all patients (8).

[Beneficial effect and pharmacology in gynecology and obstetrics]

<Clinical effects> Kanamaru examined the effect of goreisan on indefinite complaints in premenstrual syndrome (PMS) patients. Fifty patients who complained of physical symptoms including swelling, abdominal pain, breast tension, diarrhea, and headache in the premenstrual luteal phase were included. Patients received goreisan (extract preparation 5.0–7.5 g/day) beginning 5–7 days before the expected menstrual period and until the symptoms of PMS disappeared. Clinical effect was defined as the disappearance of subjective symptoms. The effect was significant in 54% of the patients, moderate in 34%, and mild in 10%. Only one patient reported no effect. In total, 88% of the patients reported at least moderate effect. PMS is associated with fluid disturbance (i.e., water retention caused by luteal hormone). Therefore, goreisan, which is used for fluid disturbance, was able to improve this condition (9).

<Basic research> The effect of goreisan on water metabolism has been studied. Nagai examined the effects of goreisan and its component crude drugs on plasma membrane osmotic water permeability using the murine lung epithelium cell line (MLE-12 cells) expressing aquaporin 5 (AQP5). Goreisan (bulk extract) was found to dose-dependently inhibit water permeability, similar to the inhibitory effect by AQP inhibitor, $HgCl_2$. Among the components of goreisan, Atractylodes Lancea Rhizome had the strongest inhibitory effect on water permeability. In addition, the activity was found in the 80% ethanol-insoluble fraction (10).

[Discussion]

Goreisan is a representative medication that improves fluid retention (*Suitai*) symptoms including nausea, vomiting, dizziness, orthostatic hypotension, and diarrhea. It is actually used for orthostatic hypotension and vomiting. Although goreisan's clinical effect on orthostatic hypotension is known, a large clinical trial will be required to provide scientific evidence of the effect. The clinical effect of goreisan intestinal infusion has been demonstrated mainly in children, and its efficacy has been documented. However, because intestinal infusion of Kampo extract is not covered by health insurance, licensing of this drug for administration via a new route will be needed before its use can be routinely recommended.

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Kampo formulae containing Coptis Rhizome (黄連, oren) and Scutellaria Root (黄芩, ogon)

Orengedokuto (黄連解毒湯)

Masaki Aburada

[Component crude drugs]
Coptis Rhizome (黄連, oren), Scutellaria Root (黄芩, ogon), Phellodendron Bark (黄柏, obaku), Gardenia Fruit (山梔子, sanshishi)

[Combination of crude drugs]
Orengedokuto (黄連解毒湯) is a formulation containing Scutellaria Root and Coptis Rhizome (芩連剤, gorenzai), and its component crude drugs all treat heat pattern (*Seinetsu*). The name comes from the principal agent 'oren' and refers to its anti-inflammatory and antidotal efficacy.

[Clinical efficacy and pharmacology in cerebrovascular disorder treatment]
<Clinical effects> Arakawa et al. conducted a placebo-controlled double-blind clinical trial to evaluate the efficacy, safety, and usefulness of orengedokuto (黄連解毒湯) for hypertension-associated symptoms. In their study, orengedokuto (7.5 g of extract preparation containing 1.5 g of dry extract bulk powder per day) and placebo were orally administered for 8 weeks to evaluate the degree of hypertension-associated symptoms including excitement (feeling irritated), anxiety, sleep disorder, feeling of warmth, and facial flushing; other subjective symptoms; changes in blood pressure/heart rate, etc. Of 265 patients enrolled in the study, 204 were included in the efficacy analysis population (orengedokuto group, n=103; placebo group, n=101). Rating of hypertension-associated symptoms, the primary endpoint, revealed significantly higher efficacy in the orengedokuto group. Orengedokuto was significantly more effective than placebo for reducing the feeling of hot flushes and facial flushing. As treatment for other subjective/objective symptoms, orengedokuto had significantly higher efficacy at 4 weeks of administration, a tendency toward higher efficacy at 8 weeks of administration, and no safety problems, confirming its great usefulness. In contrast, both orengedokuto and placebo resulted in similar blood pressure decrease and antihypertensive efficacy (1). Ushikubo et al. orally administered orengedokuto (7.5 g of extract preparation containing 1.5 g of dry extract bulk powder per day) for at least 8 weeks to 57 patients (31 males and 26 females) with cerebrovascular disease sequelae lasting at least 3 months, and evaluated changes in severity from baseline, to 4 weeks and 8 weeks after the start of administration, in the following variables: subjective symptoms; decreased motivation; emotional disorder; problem behavior; and intellectual behavior. Subjective symptoms (headache

and feeling of hot flushes) improved at least slightly in 57.1% and 52.6% of patients, respectively. Regarding decreased motivation, an average of 56.5% of patients showed at least slight improvement in activities not particularly requiring spontaneity, such as watching TV and reading books. For all emotional disorder items except affective incontinence, 68.8% of patients showed at least slight improvement. In addition, measurement of local cerebral blood flow in 21 patients showed an increase of an average of 1.71 mL/100 g/min, although this was not a statistically significant change (2). Otomo et al. studied the clinical usefulness of orengedokuto for cerebrovascular disorder using the envelope method and calcium hopantenate (which is considered to be ineffective as a cerebral metabolism stimulant, and therefore can be used as a placebo) as a control. In the study, orengedokuto (7.5 g of extract preparation containing 1.5 g of dry extract bulk powder per day; n=76) or calcium hopantenate (n=67) was administered for 12 weeks to 143 patients with psychiatric symptoms of cerebral infarction sequelae, cerebral hemorrhage sequelae, and undifferentiated stroke sequelae to evaluate the changes in severity of psychiatric signs, subjective symptoms, neurological signs, and daily living activity impairment. The percentage of patients with at least moderate global improvement in the orengedokuto group was 16.4%, 26.5%, and 37.1% after 4, 8, and 12 weeks of administration, respectively, and significantly higher than that in the calcium hopantenate group (1.5%, 1.6%, and 5.2%, respectively). Patients in the orengedokuto group compared with the calcium hopantenate group showed marked global improvement in psychiatric signs, in particular, but only a slight decrease in blood pressure (3).

<Basic research> To investigate the effects on cerebral ischemic disorder, Sato et al. administered orengedokuto (extract bulk powder) for 14 days before and 30 days after ischemia directly into the stomach of rats with permanent bilateral occlusion of the carotid arteries (an experimental model of ischemic cerebrovascular disorder). The acute-stage mortality was 23% in the orengedokuto group and 42% in the distilled water group. The final mortality did not differ between groups, and this was attributed to delayed death in the orengedokuto group. The percentage of surviving rats with infarcts was significantly lower in the orengedokuto group than the distilled water group (0% vs 71%) (4).

<Basic research on blood pressure reduction> Ozaki et al. used spontaneously hypertensive stroke-prone rats (SHRSP) to investigate the possible efficacy of orengedokuto for blood pressure and hypertensive lesions. Orengedokuto (extract bulk powder) exerted antihypertensive action, although weakly, as evidenced by serum biochemistry showing low values of urea nitrogen, neutral fat, and β-lipoprotein. Furthermore, in the 1% salt water-loaded SHRSR rat model of aggravated hypertension, orengedokuto significantly decreased neutral fat, relieved hypertensive lesions, and further prolonged life (5).

[Clinical efficacy and pharmacology in dermal pruritus treatment]

<Clinical effects>In the study by Okuma, dermal pruritus was significantly improved after oral administration of orengedokuto (7.5 g of extract preparation containing 1.5 g of dry extract bulk powder per day) to 10 patients, with complete response (itch completely or almost completely resolved), partial response (itch improved), and no change/progressive disease (itch unchanged or aggravated) in 13%, 50%, and 38%, respectively. Although the efficacies of orengedokuto and an antihistamine (n=35) were similar, orengedokuto had none of the adverse reactions to the antihistamine including sleepiness and malaise (6).

<Basic research> Nose et al. created an experimental pruritus model to investigate the possible efficacy of Kampo formulae including orengedokuto. In their study, oral pretreatment with orengedokuto (extract bulk powder) in mice significantly reduced the frequency of scratching a hind limb itch induced by subcutaneous administration of compound 48/80 and significantly suppressed severe degranulation in dermal mast cells. Repeated auricular administration of a hapten causes chronic dermatitis similar to human atopic dermatitis, eliciting scratching behavior. Oral administration of orengedokuto markedly and persistently suppressed such scratching behavior (7).

Oh et al. investigated the anti-inflammatory effects of unseiin (温清飲) and orengedokuto in rats and mice using assays of anti-carrageenin/egg albumin/formalin-induced paw edema, analgesia of acetic acid-induced writhing, and vascular permeability in mice with xylene-induced ear edema. In these experiments, oral administration of both unseiin (extract bulk powder) and orengedokuto (extract bulk powder) were demonstrated to have anti-edema, analgesic, and anti-vascular permeability promoting effects (8).

[Pharmacology in burning sensation (*Hoteri*) and facial hot flushes treatment]

<Basic research> Wakita et al. conducted a rat experiment and reported the possible clinical usefulness of orengedokuto for burning sensation (*Hoteri*) and facial hot flushes. In their study, auricular blood flow fell significantly and rapidly (by 15 min) to trough levels and then gradually recovered after intra-duodenal administration of orengedokuto (extract bulk powder, 1.0 g/kg) to anesthetized rats. In addition, orengedokuto significantly decreased blood pressure and heart rate as well as auricular blood flow in theophylline-treated rats. Since orengedokuto caused contraction of vascular smooth muscle in an *in vitro* experiment, the decrease in auricular blood flow was attributed to the contractile effect of orengedokuto on vascular smooth muscle (9).

[Discussion]

Orengedokuto, a medicine for treatment of sthenic heat (*Jitsunetsu*) associated with febrile disease, has long been used for facial hot flushes, headache, insomnia, anxiety, and various hemorrhages associated with feeling of hot flushes. In modern medicine, orengedokuto is used and effective for such conditions as hypertension-associated symptoms, burning sensation, facial hot flushes, and dermal pruritus, as mentioned above.

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Shosaikoto (小柴胡湯)

Masaki Aburada

[Component crude drugs]

Bupleurum Root (柴胡, saiko), Scutellaria Root (黄芩, ogon), Pinellia Tuber (半夏, hange), Ginseng (人参, ninjin), Ginger (生姜, shokyo), Glycyrrhiza (甘草, kanzo), Jujube (大棗, taiso)

[Combination of crude drugs]

Shosaikoto is a representative Bupleurum Root -containing formula and is indicated for the treatment of symptoms in the chest and upper gastrointestinal tract in ShoYo stage (*Shoyobyo*) including hypochondrium resistance and discomfort (*Kyokyo Kuman*) and anorexia. Saiko-containing formulae are primarily comprised of Bupleurum Root and Scutellaria Root, and include shosaikoto, daisaikoto (大柴胡湯), saikokeishito (柴胡桂枝湯), saikokeishikankyoto (柴胡桂枝乾姜湯), and saikokaryukotsuboreito (柴胡加竜骨牡蛎湯).

[Clinical efficacy on common cold syndrome]

<Clinical effects> In 1992, Hoshino et al. reported the results of a clinical (open-label) study conducted to evaluate the usefulness of 'shosaikoto (小柴胡湯)' in the treatment of persistent symptoms of the common cold. According to the report, treatment with shosaikoto (10.0 g of extract preparation containing 6.0 g of dry extract bulk powder per day) was effective at Week 1 in 16 of 20 patients (efficacy rate 80%) who presented with common cold syndrome persisting 7 or more days after the onset of the initial symptom and showed a 'shosaikoto-sho (pattern).' Respiratory tract symptoms (cough, sputum, nasal discharge, nasal congestion, sore throat) associated with common cold syndrome tended to improve within 1 to 4 days, and general symptoms (anorexia, taste alteration, general malaise, nausea, dizziness) tended to improve within 1 to 5 days (1). In 1995-1999, Kaji et al. conducted a multicenter placebo-controlled double-blind comparative study to objectively evaluate the efficacy and safety of shosaikoto in the treatment of cold. Patients were eligible to participate in the study if they had colds that persisted for 5 days or more after the onset together with cough and at least one of the following symptoms: oral discomfort (bitter taste in the mouth/stickiness in the mouth/taste alteration), anorexia, and malaise. The patients received oral doses of shosaikoto (7.5 g of extract containing 4.5 g of dry crude drug extract per day) or placebo three times daily before or between meals for 1 week. Of 331 patients enrolled in the study, 250 patients were included in the primary efficacy analysis set (per protocol set) (shosaikoto group, 131; placebo group, 119 patients), 268 patients were included in the safety analysis set, and 217 patients were included in the efficacy analysis set. The shosaikoto group had achieved significantly higher rates of overall improvement (the primary endpoint). At the end of the study treatment, the shosaikoto group had achieved significantly greater symptom-specific improvement in 'loose sputum' (respiratory symptom), 'appetite' (gastrointestinal symptom), and 'joint pain/muscle pain' (general symptom), and showed a tendency toward greater improvement in 'sputum amount' (respiratory symptom), 'stickiness in the mouth' (gastrointestinal symptom), and 'headache' (general symptom). For all

symptoms, the percentage of patients with 'improvement' or better outcome was higher in the shosaikoto group than in the placebo group, suggesting that shosaikoto is effective for prolonged symptoms of cold regardless of the patient's physical strength, *Kyokyo Kuman*, etc. in all patients except those who are inappropriate from the viewpoint of Kampo medicine. There were no significant between-group differences in the safety profile, demonstrating that shosaikoto is significantly more useful (2).

[Clinical efficacy and Pharmacology in hepatitis]

<Clinical effects> From May 1986 to April 1988, Hirayama et al. conducted a multicenter double-blind clinical study to evaluate the efficacy of shosaikoto for chronic active hepatitis. In- or out-patients with chronic hepatitis were eligible to participate in the study if they had abnormal alanine aminotransferase (ALT) levels and had been diagnosed by liver biopsy to have chronic active hepatitis requiring treatment within one year prior to the study. Patients were treated with shosaikoto (6.0 g of extract preparation containing 5.4 g of dry extract bulk powder per day) or placebo for 12 weeks. Of 231 patients collected from various treatment centers, 222 patients were included in the study: 116 patients in the shosaikoto group and 106 patients in the placebo group. In liver function tests (Table 1), aspartate transaminase (AST) was significantly decreased from baseline at Week 12 in the shosaikoto group and at Week 8 in the placebo group, but was significantly lower in the shosaikoto group than in the placebo group at Week 12.

Table 2 Changes in serum enzymatic activities over time during treatment with shosaikoto

Enzyme	Group	Treatment period (weeks)			
		0	4	8	12
AST (IU)	Shosaikoto	11±111 (116)	96±63 (112)	95 + 73 (104)	7±67* (104)
	Placebo	U7±123 (106)	110±93 (102)	92 ±58* (99)	108 + 76 (100)
	Intergroup comparison	N.S.	N.S.	N.S.	*
ALT (lU)	Shosaikoto	163 + 156 (116)	132±92* (112)	134±110 (104)	120±108** (104)
	Placebo	169±162 (106)	156±121 (102)	143±112 (99)	162±140 (100)
	Intergroup comparison	N.S.	N.S.	N.S.	*
r-GT (mu／ml)	Shosaikoto	62±48 (114)	57±46* (111)	53±64 (102)	53±43* (102)
	Placebo	62±37 (106)	61 + 46 (101)	56 ± 37* (98)	55±41 (99)
	Intergroup comparison	N.S.	N.S.	N.S.	N.S.

Abbreviations: AST, aspartate transaminase; ALT, alanine aminotransferase; r-GT, r-glutamyl transpeptidase.
Mean ± S. D. The figure in parentheses represents the number of subjects. * Indicates that the intra-group/intergroup difference is significant (*: $p<0.05$, **: $p<0.01$).

ALT was significantly decreased only in the shosaikoto group at Weeks 4 and 12, and was significantly lower in the shosaikoto group than in the placebo group at Week 12. These results indicate that shosaikoto significantly decreases serum AST and ALT in chronic active hepatitis, compared with placebo. Regardless of the type of disease (B or non-B [primarily C]) or histological activity (mild or severe), shosaikoto significantly decreased AST and ALT in the hepatitis B and mild groups, compared with placebo (3, 4, 5).

<Basic research> The alleviating effect of shosaikoto on experimental liver disorder was evaluated. Shosaikoto (extract bulk powder) inhibited consecutive carbon tetrachloride-induced liver fibrosis and carbon tetrachloride- or D-galactosamine-induced acute hepatic dysfunction in mice, and increased the hepatocyte mitotic index, liver weight, liver protein content, and liver RNA/DNA content in rats after partial hepatectomy (6, 7). Shimizu et al. reported that shosaikoto (extract bulk powder) decreased the hepatocellular concentrations of the hepatic stellate cell-activation marker α-smooth muscle actin (α-SMA), collagen, and the lipoperoxidation marker malondialdehyde (MDA) in a rat model of liver fibrosis induced by dimethylnitrosamine or pig serum (*in vivo*), and had the following effects *in vitro*: inhibition of MDA in hepatocytes; inhibition of collagen production, α-SMA expression, cellular proliferation, oxidative stress, etc. in hepatic stellate cells; lipoperoxidation inhibition and radical scavenging activity in liver mitochondria, indicating that shosaikoto acts as a fibrosis inhibitor by inhibiting lipoperoxidation in hepatocytes and hepatic stellate cells (8).

[Discussion]

Shosaikoto is indicated for the treatment of the common cold complicated by chest or respiratory symptoms and fever, and can be used to 'improve hepatic dysfunction in patients with chronic hepatitis.' These effects have been clinically demonstrated in open-label studies, double-blind studies, etc. In addition, many nonclinical studies have reported that shosaikoto acted in a protective manner to improve experimental liver disorders, promoted cytokine production, inhibited cytokine release, etc. Shosaikoto has no antiviral activity, but can be said to be a useful biological response modifier (BRM) that exerts its therapeutic effects by altering the biological defense mechanism.

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Saikokaryukotsuboreito (柴胡加竜骨牡蛎湯)

Masaki Aburada

[Component crude drugs]
Bupleurum Root (柴胡, saiko), Scutellaria Root (黄芩, ogon), Pinellia Tuber (半夏, hange), Ginseng (人参, ninjin), Ginger (生姜, shokyo), Jujube (大棗, taiso), Cinnamon Bark (桂皮, keihi), Poria Sclerotium (茯苓, bukuryo), Rhubarb (大黄, daio), Longgu (竜骨, ryukotsu), Oyster Shell (牡蛎, borei)

[Combination of crude drugs]
Saikokaryukotsuboreito (柴胡加竜骨牡蛎湯) is shosaikoto (小柴胡湯) minus Glycyrrhiza (甘草, kanzo) plus Cinnamon Bark / Poria Sclerotium / Rhubarb / Longgu / Oyster Shell. With sedative Longgu and Oyster Shell, this formula is indicated for shosaikoto-sho (pattern) with psychoneurotic symptoms.

[Clinical efficacy and pharmacology in metabolic disease]
<Clinical effects> Kosuge et al. evaluated the clinical effect of saikokaryukotsuboreito on vascular function. The study population (aged 40–79 years) was divided into a healthy group (n=258), sclerosis group (n=58), and treatment group (n=53) and followed up for 36 months. The subjects in the treatment group received saikokaryukotsuboreito (7.5 g of extract preparation containing 4.5 g of dry extract bulk powder per day). The aortic pulse wave velocity (PWV) was determined by the foot-to-foot method and the carotid (common carotid artery, carotid sinus artery, internal carotid artery, cervical vertebral artery) extensibility was determined by the ultrasonic velocity method (β method) every 12 months in all subjects. At Month 36, the mean PWV and β value of the four cervical arteries were significantly lower in the treatment group than in the sclerosis group. In many treated subjects, the PWV and β were decreased after treatment, suggesting the possibility that saikokaryukotsuboreito not only inhibits sclerosis, but also induces regression of sclerosis. Based on these results, it was concluded that saikokaryukotsuboreito has an anti-arteriosclerotic effect (1). In addition, Nomura et al. found that platelet activation markers (CD62P, PMPs, etc.), sE-selectin, anti-oxidized LDL antibody, etc. were decreased in 8 hyperlipidemia patients with high blood triglyceride levels after 8-week treatment with saikokaryukotsuboreito (7.5 g of extract preparation containing 4.5 g of dry extract bulk powder per day), concluding that saikokaryukotsuboreito prevents the progression of angiopathy in patients with hyperlipidemia (2).

<Basic research> Chung, H. J et al. reported that saikokaryukotsuboreito (extract bulk powder) inhibited carotid arterial intimal thickening and vascular smooth muscle proliferation, and decreased serum total cholesterol and LDL cholesterol levels, although not significantly, after oral administration to cholesterol diet-fed rats with balloon inflation injury of the carotid artery endothelium (3). Yoshie et al. reported that 24-week treatment with saikokaryukotsuboreito (extract bulk powder) in a rabbit model of hereditary hyperlipidemia decreased blood total cholesterol levels, inhibited the progression of atherosclerotic lesions in

the thoracic aortic arch, and significantly increased mRNA expression of ApoE and LDL receptors in the liver (4, 5). Ishikawa et al. found that 6-month oral administration of saikokaryukotsuboreito (extract bulk powder) significantly decreased serum lipoperoxide levels as well as triglyceride levels in serum, brain, and heart in mice (6). Furukawa et al. found that saikokaryukotsuboreito (extract bulk powder) inhibited the intracellular synthesis of cholesterol esters and triglycerides and decreased the secretion of ApoB in an in vitro experiment using HepG2 (a human hepatocellular liver carcinoma cell line) (7).

[Clinical efficacy on male sterility]

<Clinical effects> Ohashi et al. orally administered saikokaryukotsuboreito (7.5 g of extract preparation containing 4.5 g of dry extract bulk powder per day) to 30 patients with a chief complaint of idiopathic male sterility for at least 3 months and compared post-treatment seminal findings with baseline seminal findings. The efficacy rate for increasing sperm concentration was 50% in patients with oligozoospermia, 44% in patients with oligozoospermia/asthenozoospermia, and 46% in all patients, and the efficacy rate for increasing sperm motility was 71% in patients with asthenozoospermia, 56% in patients with oligozoospermia/asthenozoospermia, and 65% in all patients, respectively. No changes were observed in serum hormone levels before and after treatment (8). Komiya et al. administered saikokaryukotsuboreito (7.5 g of extract preparation containing 4.5 g of dry extract bulk powder per day) to 39 male patients with confirmed sterility and analyzed the therapeutic efficacy. After treatment, the seminal examination was performed in 25 patients. The seminal volume, sperm concentration, sperm motility, and normal sperm morphology rate were significantly increased after treatment with saikokaryukotsuboreito. Pregnancy occurred in 8 (21%) partners of 39 patients treated for 1 to 38 months (9).

[Clinical efficacy on neurosis]

<Clinical effects> Ohara et al. administered saikokaryukotsuboreito (7.5 g of extract preparation containing 4.5 g of dry extract bulk powder per day) to 23 outpatients (13 males and 10 females) with various neuroses for 3 weeks and assessed the change in clinical symptoms through an interview. The overall improvement was graded as marked in 1 patient, moderate or better in 4 patients, and mild or better in 18 patients (78%). General malaise, fatigability, anxiety, depression, hypochondriasis, irascibility, and cardiovascular symptoms were improved, and treatment was at least slightly effective in more than 50% of patients (10).

[Discussion]

Saikokaryukotsuboreito is used for hypertension with psychoneurotic symptoms, arteriosclerosis, neurasthenia, nervous palpitation, impotence, etc. Clinical studies have shown that it has an anti-arteriosclerotic effect and is effective for male sterility, various neuroses, etc. These clinical effects are supported by nonclinical studies showing that it inhibits the progression of vascular lesions and intracellular synthesis of lipids, indicating that it is a useful formula.

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Kampo formula containing Moutan Bark (牡丹皮, botampi)

Kamishoyosan (加味逍遥散)

Masaki Aburada

[Component crude drugs]
Bupleurum Root (柴胡, saiko), Japanese Angelica Root (当帰, toki), Peony Root (芍薬, shakuyaku), Atractylodes (Lancea) Rhizome (白朮/蒼朮, byakujutsu/soujutu), Poria Sclerotium **(**茯苓, bukuryo), Ginger (生姜, shokyo), Mentha Herb (薄荷, hakka), Gardenia Fruit (山梔子, sanshishi), Moutan Bark (牡丹皮, botampi)

[Clinical efficacy and pharmacology in climacteric disorder]
<Clinical effects> Takamatsu et al. investigated the efficacy of Kampo therapy vs. hormone replacement therapy (HRT) in menopausal/bilaterally oophorectomized patients visiting outpatient menopause clinics with a chief complaint of climacteric disorder. Their study used the Keio modified menopause index questionnaire to evaluate therapeutic efficacy. Patients were divided into those receiving tokishakuyakusan (当帰芍薬散) (7.5 g of extract preparation containing 4.0 g of dry extract bulk powder per day, n = 23), kamishoyosan (加味逍遥散) (7.5 g of extract preparation containing 4.0 g of dry extract bulk powder per day, n = 23), or keishibukuryogan (桂枝茯苓丸) (7.5 g of extract preparation containing 1.75 g of dry extract bulk powder per day, n = 24) as Kampo therapy and those mainly receiving conjugated estrogens as HRT (n = 110). Treatment was ‘effective’ in both patients receiving HRT and patients receiving Kampo therapy (78% vs 68.6%; no significant difference). HRT was superior to Kampo therapy in the degree of effectiveness. Comparison of overall efficacy between Kampo formulae disclosed no significant difference between groups. Evaluation of the efficacy of Kampo therapy by symptom revealed high effectiveness for nervousness, irritableness, anxiety, and worrying. Thus, these findings demonstrated the considerable efficacy of Kampo therapy for climacteric disorders, in particular, the high efficacy of kamishoyosan for psychological symptoms (1). Hidaka et al. investigated the efficacy of kamishoyosan and keishibukuryogan for the between deficiency and excess pattern (*Kyojitsu Chukan Sho*) of climacteric disorder. Specifically, patients were assigned to either kamishoyosan or keishibukuryogan based on Kampo ‘pattern (*Sho*)’ diagnosis, and received the assigned Kampo formulation for at least 4 weeks. The state of climacteric symptoms was evaluated before and after administration based on the Simplified Menopausal Index of Koyama et al. (SMI), subjective symptom improvement (rated on a Visual Analogue Scale [VAS]) and severity. Among SMI items,

the combination of 3 items [burning sensation (*Hoteri*), perspiration, and coldness (*Hie*)] was used to evaluate vasomotor symptoms and the combination of 4 items [insomnia, irritableness, depression, and headache] was used to evaluate psychoneurotic symptoms. In the kamishoyosan group, the pre- to post-treatment decreases in overall SMI total score and VAS score were significant, with treatment judged to be effective in 33 of 45 patients (clinical effectiveness rate: 73.3%). Moreover, vasomotor symptom and psychoneurotic symptom SMI total scores and VAS score were significantly decreased after treatment. The efficacy was similar in the keishibukuryogan group (2). Higuchi et al. investigated the efficacy of kamishoyosan vs. HRT for treatment of climacteric disorder. Specifically, kamishoyosan (7.5 g of extract preparation containing 4.0 g of dry extract bulk powder per day, n=12), oral conjugated estrogen or 17β-estradiol patch as HRT (n=11), or combination of these therapies (n=12) was administered to patients who were diagnosed with climacteric disorder uncomplicated by obvious psychoneurotic symptoms for 8 weeks to evaluate the severity of depression, anxiety, sleep disturbance, and climacteric symptoms before administration, and at weeks 4 and 8 of administration. The severities of depression, anxiety, sleep disturbance, and climacteric symptoms were scored and rated using the self-rating depression scale (SDS), the Hamilton anxiety scale (HAS), the Pittsburgh sleep quality index (PSQI), and the questionnaire for assessment of climacteric symptoms prepared by the Japan Society of Obstetrics and Gynecology, respectively. On the SDS, significant improvement was noted from week 4 in the kamishoyosan group and from week 8 in the HRT and combination groups, compared with baseline, although there was no significant between-group difference at each time point of measurement during treatment. The HAS score was significantly improved from week 4 compared with baseline in all treatment groups, and group comparison at week 4 revealed significantly more improvement in the kamishoyosan than in other groups. The PSQI score was significantly improved from week 4 in the kamishoyosan group and from week 8 in the HRT and combination groups, compared with baseline, although there was no significant between-group difference at each time point of measurement during treatment. Regarding climacteric symptoms, the items ‘burning sensation of head and upper body’ and ‘being sweaty’ showed significant improvement from week 4 in the HRT and combination groups, but only tendency for improvement in the kamishoyosan group.These findings suggested that kamishoyosan may reduce the severity of depression, anxiety, and sleep disturbance earlier than HRT and can be expected to also improve ‘hot flash’ to some degree, although there was no difference (3).

<Basic research> Terawaki et al. investigated the efficacy of Kampo prescriptions in ovariectomized rats, using the change in motor activity associated with intracerebroventricular corticotropin-releasing hormone CRF administration as the index, to elucidate the role of CRF in development of climacteric psychological symptoms and the therapeutic efficacy of Kampo prescriptions for the symptoms. Specifically, after 1-week oral administration of a Kampo prescription (powdered extracts of tokishakuyakusan, kamishoyosan, or keishibukuryogan) to ovariectomized rats, CRF was intracerebroventricularly administered, and motor activity was measured for 120 min from 60 min post-dose. CRF administration significantly increased motor activity, and only kamishoyosan suppressed the increase in motor activity in a dose-dependent manner (100–1,000 mg/kg). In addition, kamishoyosan had no effect on blood estradiol concentration and uterus

weight, suggesting that kamishoyosan exerts its effects on CRF receptors altered by estrogen decrease or CRF receptor antagonism, but not through the effect of estrogen replacement (4). Yuzurihara et al. investigated the efficacy of Kampo prescriptions (kamishoyosan and keishibukuryogan) and HRT in the model of luteinizing hormone-releasing hormone (LH-RH)-induced skin temperature elevation. Specifically, after 1-week oral administration of kamishoyosan (extract bulk powder, 2 g/kg) and keishibukuryogan (extract bulk powder, 1 g/kg) or 17ß-estradiol, to ovariectomized rats, LH-RH was intracerebroventricularly administered, and caudal skin temperature was measured until 90 min post-dose at 2-min intervals. Both kamishoyosan and estradiol were shown to significantly suppress the increase in skin temperature by intracerebroventricular LH-RH administration (5).

[Discussion]
These findings are evidence for the high clinical effectiveness of kamishoyosan especially for psychological symptoms in climacteric patients. Development of climacteric psychoneurotic symptoms is considered to involve increased CRF reactivity due to estrogen decline. The finding of basic research that kamishoyosan suppressed the increase in motor activity by CRF without affecting uterus weight and blood estradiol concentration suggests that kamishoyosan suppresses climacteric psychological symptoms by improving CRF reactive changes. A proposed theory attributes development of hot flashes to LH-RH in the body temperature center located in the hypothalamus. Some previous reports have suggested the possibility that kamishoyosan acts on the hypothalamus to suppress hot flashes. The basic research findings that kamishoyosan inhibited LH-RH-induced skin temperature elevation support the previous findings.

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Kampo formulae containing Rehmannia Root (地黄, jio), Cornus Fruit (山茱萸, sanshuyu) and Moutan Bark (牡丹皮, botampi)

Hiroaki Kiyohara

[Combination of crude drugs]
Hachimigan (八味丸) is a Kampo formula consisting of rokumigan (六味丸) plus Cinnamon Bark (桂皮, keihi) and Processed Aconite Root (附子, bushi). Whereas Goshajinkigan（牛車腎気丸） comprises Hachimigan plus Plantago Seed (車前子, shazenshi) and Achyranthes Root (牛膝, goshitsu) Hachimigan and goshajinkigan are both used for treatment of deficiency of lower abdominal region (*Jinkyo*). Yin deficiency (*Yinkyo*) is a state in which energy is exhausted with catabolism exceeding anabolism and a symptom of heat

is added to blood deficiency (*Kekkyo*). Rehmannia Root (地黄, jio) and Cornus Fruit (山茱萸, sanshuyu) supplement kidney [TM] yin (*Jinyin*) deficiency, whereas Moutan Bark (牡丹皮, botampi) resolves deficiency and heat (*Kyonetsu*).

Rokumigan: Rehmannia Root (地黄, jio), Cornus Fruit (山茱萸, sanshuyu), Moutan Bark (牡丹皮, botampi), Dioscorea Rhizome (山薬, sanyaku), Alisma Rhizome (沢瀉, takusha), Poria Sclerotium (茯苓, bukuryo)

Hachimijiogan (八味地黄丸)

[Component crude drugs]

Rehmannia Root (地黄, jio), Cornus Fruit (山茱萸, sanshuyu), Dioscorea Rhizome (山薬, sanyaku), Moutan Bark (牡丹皮, botampi), Cinnamon Bark (桂皮, keihi), Alisma Rhizome (沢瀉, takusha), Poria Sclerotium (茯苓, bukuryo), Processed Aconite Root (附子, bushi)

[Clinical efficacy and pharmacology in the lower urological tract]

<Clinical effects> Fuse et al. have reported improvements in subjective symptoms (delay in the start of urination, prolonged voiding time, decreased stream, feeling of residual urine, frequent urination in a short time, daytime and nocturnal frequent urination) by hachimijiogan (八味地黄丸) in patients with micturition disorder without organic disease or with prostatic hypertrophy (1). In the controlled clinical trial to investigate the efficacy of hachimijiogan for discomfort after uterine prolapse surgery conducted by Oribe et al., hachimijiogan significantly decreased residual urine volume, suggesting effects on tissue repair early after surgery (2). Moreover, Yoshimura et al. conducted a controlled clinical trial of hachimijiogan (extract 4 g/day, 2 weeks) in 41 untreated male patients with prostatic hypertrophy (estimated prostate volume not less than 20 cm^3). In the trial, hachimijiogan significantly improved subjective symptoms such as force of urinary stream and feeling of residual urine as well as improved objective indices including the International Prostate Symptom Score (I-PSS), quality of life (QOL) score, and Qmax to the degree comparable to that achieved by the control drug tamsulosin hydrochloride. Feeling of residual urine was the indication for this Kampo formula (3).

<Basic research> In the rat model of overactive bladder with decreased voiding interval, each voiding volume and bladder volume, which was created via continuous infusion of 0.1% acetic acid solution (5.0 mL/hr) using a bladder catheter, oral administration of hachimijiogan or its ethanol-soluble fraction significantly increased voiding interval, each voiding volume, and bladder volume 20–40 min later (4). Moreover, investigation of the ethanol-soluble fraction has demonstrated that hachimijiogan increased voiding volume and bladder volume, decreased residual urine volume, and prolonged intervals between urination in rats with partially obstructed lower urinary tracts (5), testosterone-induced prostatic hypertrophy (4), and cold stress-induced overactive bladder (4), suggesting that hachimijiogan acts on the bladder and parasympathetic nervous system by affecting unmyelinated C-fibers (4).

[Clinical efficacy and pharmacology in neuropsychiatric disorders]

<Clinical effects> Randomized double-blind studies in patients with senile dementia have demonstrated that hachimijiogan improves scores of the early-stage dementia diagnosis scale (Mini-Mental State Examination, MMSE) and independent daily living activity index (Barthel Index) (6). Furthermore, a controlled clinical trial in healthy people has demonstrated that hachimijiogan significantly increases systolic and diastolic blood flow velocity in the central retinal artery, offering promise of visual recovery and increased cerebral blood flow (7).

<Basic research> Hachimijiogan improved retention of radial maze learning, and increased acetylcholine content in the cerebral frontal cortex and choline acetyltransferase (ChAT) activity in the rat model of scopolamine-induced memory disorder (8). Furthermore, hachimijiogan prolonged survival and potentiated the anti-ischemic effect of physostigmine, which disappeared after atropine administration, in the mouse model of cerebral ischemia induced by exposure to potassium cyanide, suggesting that the central effect of hachimijiogan is mediated through the central cholinergic nervous system (9).

[Clinical efficacy and pharmacology in geriatric disorders]

<Clinical effects> Randomized controlled clinical trials of hachimijiogan have demonstrated significant global improvement in subjective symptoms (tinnitus, limb coldness [*Hie*] , low back pain, lumbar exercise pain, cramps of the lower extremities) and itchy skin related to hypertension with concomitant symptoms (10), senile skin pruritus (11,12), and lumbar spinal stenosis (13). Moreover, hachimijiogan has been reported to significantly decrease natural antibody titer against serum heat shock protein 60 (Hsp60), a damage-associated molecular pattern molecule involved in pathogenesis and progression of chronic inflammatory disease (14).

<Basic research> It has been demonstrated that hachimijiogan significantly decreases urinary protein level and blood antinuclear antibody titer and improves bone density in senescence-accelerated mice (SAM-P1 or SAM-P6) (15,16). In addition, hachimijiogan has been shown to elevate glutathione concentration in the lenses of aged rats and to delay lens opacification and normalize electrolyte (Na^+, K^+, Ca^{2+}) level through recovery of Na^+/ K^+-ATPase activity in the lenses of rats with cataracts induced by feeding 30% galactose and mice with hereditary cataracts (17,18,19). Furthermore, studies using rats with streptozotocin-induced diabetes as the model of type I diabetes mellitus (20), Otsuka Long-Evans Tokushima Fatty (OLETF) rats as the model of type II diabetes mellitus (21),and the high-fat diet-fed spontaneously diabetic rat model (WBN/Kob)(22) found that hachimijiogan improved renal function (suppression of blood urea nitrogen and creatinine clearance) by suppressing elevation in active oxygen and nitric oxide levels in blood, oxidized protein level in kidney mitochondria, and glycosylated protein level in the kidney, and protected renal function by suppressing TGF-β expression in the kidney, thereby decreasing fibronectin level(Fig). Experiments showing that hachimijiogan protects renal function in 3/4 nephrectomized rats provide evidence for the direct effect of hachimijiogan on renal disorder due to oxidative stress or other causes (23).

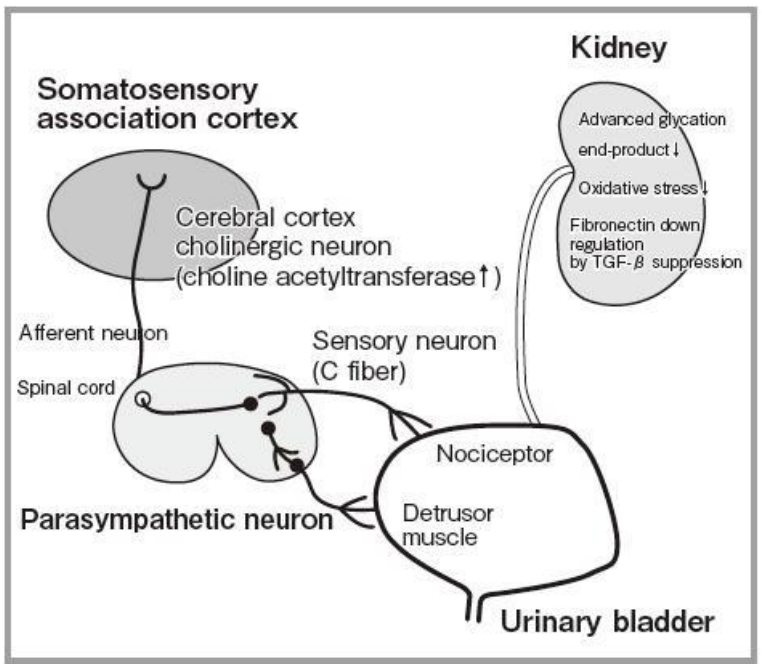

Fig:Summary of action mechanism of Hachimi-jio-gan for improvement of urinological impairment

<Action of component crude drugs > It has been demonstrated that morroniside, a Cornus Fruit (山茱萸, sanshuyu)-derived iridoid derivative suppressed an elevation in blood glucose, improved proteinuria, and reduced blood urea nitrogen (BUN) level in streptozotocin-treated rats. It was suggested that morroniside mediates these effects through suppression in the renal cortex of heme oxygenase-1 expression, an enzyme which induces oxidative stress. (24) Furthermore, 7-O-galloyl-D-sedoheptulose, a Cornus Fruit-derived low-molecular-weight tannin, has also been shown to decrease the neutral lipid levels in blood and liver in rats fed a high-fructose diet, by increasing the expression of peroxisome proliferators-activated receptor α (PPARα) (25).

[Discussion]

It has been reported that hachimijiogan suppresses progression of renal dysfunction in chronic renal failure during the conservative phase (serum creatinine level, 3.0 mg/dL or less), providing the promise of delaying the start of kidney dialysis in patients with chronic renal failure (26). Additionally, there is a case study showing the efficacy of this Kampo formula for Mikulicz disease, implicating induction of regulatory T lymphocytes in the mechanism of action (27). Since hachimijiogan decoction and extract formulations are currently used clinically, the combined efficacy of the decoction formulation and the original pill formulation will need to be analyzed in future studies investigating its effects including its effects on the immune system.

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Combination therapy with Kampo formulae and Western-style medications

Kiyoshi Sugiyama

Pharmacology of Kampo formulae used in combination with anticancer agents and steroids

Hochuekkito (補中益気湯)

[Component crude drugs]

Ginseng (人参, ninjin), rhizomes of Atractylodes spp. (朮, jyutsu), Astragalus Root (黄耆, ogi), Bupleurum Root (柴胡, Saiko), Japanese Angelica Root (当帰, toki), Glycyrrhiza (甘草, kanzo), Citrus Unshiu Peel (陳皮, chimpi), Jujube (大棗, taiso), Ginger (生姜, shokyo), Cimicifuga Rhizome (升麻, shoma)

[Clinical efficacy in cancer treatment]

<Clinical effects> In cancer treatment, Kampo formulae are used for ① direct cytotoxicity against cancer cells; ② immune modulation contributing to cancer regression, metastasis suppression, relapse prophylaxis, and the prevention of bacterial or viral infection; ③ improvement of pre/postoperative physical strength and amelioration of performance status (including anorexia), resolution of unidentified complaints, and stress relief; ④ enhancement of antitumor effects and reduction/prevention of side effects of adjuvant radiation and chemotherapy; and ⑤ pain relief. Hochuekkito (補中益気湯), which is an auxiliary agent, is used primarily for ②, ③, and ④ and exhibits specific effects.

One study reported that preoperative treatment with hochuekkito is effective for perioperative stress associated with esophageal cancer, gastric cancer, hepatocellular carcinoma, colorectal cancer, and others. (1) Patients were randomized to receive either 7.5 g of hochuekkito (2.5 g × 3, n=20) or no treatment (n=27) for 7 days preoperatively. Preoperative and postoperative levels of peripheral blood lymphocytes (PBLs), natural killer (NK) cells, blood interleukin (IL)-6, and noradrenaline were determined and compared between groups. Hochuekkito had no effect on the PBL count, but it significantly inhibited surgery-related decreases in the NK cell count and activity as well as decreased blood IL-6 and noradrenaline levels (stress indicators).

Chronic hepatitis C increases the risk of hepatic cancer. One study reported that hochuekkito was effective for chronic hepatitis C patients with 'qi (Ki) deficiency (*Kikyo*)' (2). A total of 25 patients with chronic hepatitis C were treated with hochuekkito for 6 months. Prior to treatment, 17 of these patients were diagnosed according to the traditional diagnostic criteria (pattern [*sho*]). After 6 months of treatment, the common symptoms, such as "malaise" or "fatigability," were significantly improved, whereas glutamic pyruvic transaminase (GPT), glutamic oxalacetic transaminase (GOT), total cholesterol (TC), platelet count (PLT), viral load (HCV-RNA), and fibrosis markers (type VI collagen 7s, hyaluronic acid) were not markedly affected in the study population. Interestingly, GPT and GOT were significantly lower in patients aged 60 years and older than in those aged 59 years and younger. In addition, improvement in hepatic

function was more marked in patients with “malaise,” “vulnerability to colds,” “weak pulse,” etc. than in those without these clinical characteristics, suggesting that a Kampo medical diagnosis of ‘qi (Ki) deficiency’ is important for the treatment of chronic hepatitis C. In another report, hochuekkito brought significant improvement to patients with ‘qi (Ki) deficiency,’ such as ‘anorexia,’ ‘general malaise,’ or ‘hypobulia’ (3), suggesting that it is effective in improving the common symptoms caused by cancer treatment (4).

[Clinical efficacy and pharmacology of hochuekkito in combination with steroids]

<Clinical effects> A Th1/Th2 imbalance with the predominance of Th2 T cells due to abnormal energy metabolism, aging, or stress results in impaired immunity against infection and cancer and aggravation of allergies. Hochuekkito is known to correct a Th1/Th2 imbalance. A recent multicenter placebo-controlled double-blind randomized comparative study found that hochuekkito was effective for refractory atopic dermatitis with ‘qi (Ki) deficiency’ (5). A total of 91 patients (age 20–40 years) with refractory disease that was unresponsive to 4 or more weeks of standard treatment and with ‘qi (Ki) deficiency’ received either hochuekkito (7.5 g) or placebo for 24 weeks, and the atopic dermatitis severity, change in topical medication usage (steroids, tacrolimus), and safety were assessed. The condition of the skin was improved at 3 and 6 months in both groups, but with no significant between-group difference. On the other hand, the topical medication usage was significantly reduced at 6 months in the hochuekkito group (with an increase from baseline in the placebo group, but no increase in the hochuekkito group). Moreover, in the hochuekkito group, the efficacy was excellent: skin eruptions disappeared in more patients, and the disease worsened in significantly fewer patients. There were no safety concerns. Allergic disease is difficult to cure. Reduced use of steroids and immunosuppressants when combined with hochuekkito indicates that allergies may be cured by the effective use of Kampo formulations and Western-style medications, which can be regarded as an alternative treatment option.

<Basic research> Substantial evidence indicates that hochuekkito inhibits carcinogenesis and regulates immunity. In a long-term study of N-methyl-N-nitrosourea (MNU) and estradiol-17β in mice with endometrial carcinogenesis, the incidence of adenocarcinoma was significantly decreased in the hochuekkito group (0.2% feeding, 29-week treatment). In a short-term study conducted to investigate the mechanism of carcinogenesis, hochuekkito inhibited the expression of the proto-oncogene c-jun, estrogen receptors (ER-α and ER-β), and tumor necrosis factor (TNF)-α (6).

It is suggested that the immunoregulatory function of hochuekkito is primarily attributable to its polysaccharides. An experiment using immortalized gastrointestinal endothelial cells (MCE 301 cells) showed that hochuekkito promoted the secretion of granulocyte colony-stimulating factors (G-CSFs) and that this effect was caused by polysaccharides (7). In response to myelosuppression caused by anticancer agents and radiation therapy, G-CSFs not only promote the proliferation of granulocytes but also correct a Th1/Th2 imbalance through cytokine production. The stimulation of G-CSF secretion may be essential to understand the pharmacological action of hochuekkito. The polysaccharides in hochuekkito play a role in immunoregulation by acting on Peyer’s patch immunocompetent cells (8). Information about bacteria and other antigens in the intestinal lumen is transmitted via T cells, B cells, and macrophages to a group of

immunocompetent cells in Peyer's patches. Complex information processing among Peyer's patch immunocompetent cells results in immunological tolerance that controls abnormal immune responses, such as the production of antigen-specific secretory IgA and allergic reactions. When Peyer's patch cells from hochuekkito-treated mice were stimulated by incubation with concanavalin A, cytokine production increased or decreased. Interestingly, the cytokine production pattern depended on the sugar side chains of the polysaccharides (9).

[Discussion]
In general, polysaccharides are less likely to be absorbed from the gastrointestinal tract. There has been no consistent view on the function of polysaccharides in Kampo formulations. To assess the function of Kampo formulations in the gastrointestinal tract, it may be an important finding that polysaccharides are active constituents of hochuekkito. In particular, the gastrointestinal tract may play an essential role in triggering hochuekkito activity, which is used for "qi (Ki) deficiency" related to the gastrointestinal function. Thus, gastrointestinal function is closely related to the onset of action of hochuekkito, and this relationship may suggest different ways of using hochuekkito.

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Juzentaihoto (十全大補湯)

[Component crude drugs] Ginseng (人参, ninjin), rhizomes of Atractylodes spp. (朮, jyutsu), Poria Sclerotium (茯苓, bukuryo), Japanese Angelica Root (当帰, toki), Glycyrrhiza (甘草, kanzo), Cnidium Rhizome (川芎, senkyu), Peony Root (芍薬, shakuyaku), Rehmannia Root (地黄, jio), Astragalus Root (黄耆, ogi), Cinnamon Bark (桂皮, keihi)

[Clinical efficacy and pharmacology in cancer treatment]
<Clinical effects> In cancer treatment, juzentaihoto (十全大補湯) is used for ① immune modulation contributing to cancer regression, metastasis suppression, relapse prophylaxis, and bacterial or viral infection prophylaxis; ② improvement of pre/postoperative physical strength, improvement of performance status (including anorexia), resolution of unidentified complaints, and stress relief; and ③ reduction/prevention of side effects from radiation and chemotherapy with certain effects.

As for purpose ①, suppression of cancer recurrence was assessed after long-term treatment with juzentaihoto in postoperative patients with hepatocellular carcinoma. In patients who received juzentaihoto

beginning 1 month after surgery (7.5 g, up to 6 years, n=10), cancer recurrence was significantly inhibited compared to untreated patients (n=38) (1). A long-term study conducted in mice to investigate the inhibition of hepatocellular carcinoma showed that juzentaihoto inhibited oxidative DNA damage, inflammatory cell infiltration in the liver, and the production of IL-1β, IL-6, and TNFα. It was also shown that these inhibitory effects stemmed from the inhibition of Kupffer cell activation (1). In addition, the efficacy of juzentaihoto was evaluated in patients with refractory type C chronic liver disease (chronic hepatitis, hepatic cirrhosis) that was unresponsive to conventional hepatoprotective agents (Stronger Neo-Minophagen C [SNMC], ursodeoxycholic acid [UDCA], SNMC + UDCA) with an inadequate decrease in the activated T lymphocyte (ATL) count (mean alanine aminotransferase [ALT] > 80 units). A total of 40 patients were treated for at least 6 months with a combination of SNMC/juzentaihoto (7.5 g), UDCA/juzentaihoto, or SNMC + UDCA/juzentaihoto. Treatment was considered to be effective in 23 patients (57.5%) as defined by at least a 25% decrease in ALT from baseline. The efficacy rate was higher in female patients (69.6%) than in male patients (41.2%). In 23 patients treated with juzentaihoto for 2 years, the ATL count was markedly decreased (2).

As for the purposes ② and ③, the usefulness of juzentaihoto was evaluated in advanced breast cancer. Patients were randomly assigned to Group A (n=58) or B (n=61) using the envelope method to compare the effects on survival, subjective symptoms, and laboratory values. Group A was treated with endocrine therapy, chemotherapy, and juzentaihoto (7.5 g). Group B was treated with only endocrine therapy and chemotherapy. No significant differences were observed in the baseline patient characteristics between the two groups. No significant differences were observed in the response to the anticancer agents or in the survival curve between the two groups. In the juzentaihoto-treated group, however, lymphopenia and subjective symptoms, such as anorexia or cold limbs, were improved (3). There were no adverse reactions to juzentaihoto. In addition, the efficacy of juzentaihoto was evaluated in patients with digestive system cancer who were scheduled to receive major surgery that could potentially decrease their physical strength postoperatively. The patients were randomly assigned to either a juzentaihoto-treated group (100 patients) or an untreated group (61 patients). In the juzentaihoto-treated group (7.5 g, 8–12 weeks), anorexia and leukopenia were improved (4).

<Basic research> Substantial evidence shows that juzentaihoto reduces the side effects of radiation and chemotherapy. Cisplatin exhibits potent antitumor effects by inhibiting DNA synthesis and inducing apoptosis, but it is associated with serious adverse effects, such as renal dysfunction and bone marrow disorder. Studies show that juzentaihoto improves these adverse effects. In a mouse model of cisplatin toxicity, a 12-day treatment with juzentaihoto resulted in a reduction of cisplatin nephrotoxicity, myelotoxicity (leukopenia, thrombopenia, etc.), and general toxicity (weight loss, loss of appetite, etc.) without attenuation of its antitumor effect. It was also found that these effects are attributable to sodium malate and macromolecular polysaccharides in juzentaihoto. Macromolecular polysaccharides in juzentaihoto were also shown to promote the proliferation of bone marrow stem cells (via the production of GM-CSF) (5–12).

It has been reported that juzentaihoto inhibits the metastasis (13) and proliferation (14) of cancer cells by

increasing NK cells, enhancing the NK cell activity, and inhibiting angiogenesis.

A partial hepatectomy due to hepatic cancer or other reasons may result in hyperammonemia. It has been reported that juzentaihoto improves hyperammonemia following a partial hepatectomy. Hyperammonemia was significantly improved in mice treated with juzentaihoto for 7 days (1.0 g/kg body weight) before a partial hepatectomy and for 3 days postoperatively. Approximately 50% of the ammonia in the body is formed from amino acids in the liver, and the remaining 50% is produced by ammonia-producing intestinal bacteria. The liver catabolizes ammonia to urea to maintain ammonia homeostasis. The disturbance in the intestinal flora balance associated with postoperative stress results in the proliferation of ammonia-producing bacteria, thus causing hyperammonemia. It was found that juzentaihoto prevents hyperammonemia by relieving or correcting this imbalance (15).

［Discussion］

Many reports show that juzentaihoto also improves adverse effects from anticancer agents, such as mitomycin C, 5-fluorouracil (5-FU), and cyclophosphamide, drawing attention to the usefulness of juzentaihoto for alleviating the side effects of anticancer agents. It has also been reported that juzentaihoto effectively reduces the side effects of steroids, raising expectations of new possible therapies by combining Western-style medications with Kampo formulae.

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Shakuyakukanzoto (芍薬甘草湯)

[Component crude drugs]

Peony Root (芍薬, shakuyaku), Glycyrrhiza (甘草, kanzo)

[Clinical efficacy and pharmacology in the treatment of muscle cramps]

<Clinical effects> Shakuyakukanzoto (芍薬甘草湯) is used clinically for relaxing skeletal and smooth muscles and relieving pain. Little evidence shows that shakuyakukanzoto is actively used in cancer treatment, but substantial evidence shows that it is very effective for muscle cramps, which often occurs in hepatic

cirrhosis, dialysis, diabetes, and other conditions.

A placebo-controlled double-blind comparative study was conducted to evaluate the efficacy and safety of shakuyakukanzoto in patients (20–70 years) from 23 treatment centers who were clinically diagnosed with hepatic cirrhosis and had at least 4 episodes of muscle cramps (calf cramps) during a 2-week observation period. A total of 90 patients were randomized to receive either shakuyakukanzoto (7.5 g) (49 patients) or placebo (41 patients) for 2 weeks, and muscle cramp symptoms were compared between the observation (pretreatment) and treatment periods. The percentage of patients with "improvement," defined as a 50% or less frequency of muscle cramps, was 67.3% in the shakuyakukanzoto group and 37.5% in the placebo group. In the overall assessment, including an assessment of pain severity and the frequency of muscle cramps, the percentage of patients with improvement was 69.2% in the shakuyakukanzoto group and 28.6% in the placebo group. However, the between-group difference in the incidence of adverse effects (14.3% in the shakuyakukanzoto group and 4.9% in the placebo group) was not significant. The most common adverse effect in the shakuyakukanzoto group was pseudoaldosteronism, which was mild in severity. Based on these results, it was concluded that shakuyakukanzoto is useful and safe for the treatment of muscle cramps associated with hepatic cirrhosis (1, 2).

The efficacy and safety of shakuyakukanzoto were evaluated in 37 patients who often had muscle cramps (calf cramps) due to sciatic nerve stimulation. The study population included 31 patients with sciatica or spinal column stenosis due to spinal osteoarthritis, 5 patients with lumbar disc herniations, and 1 patient with a spinal compression fracture. Thus, muscle cramps were attributable to sciatic nerve stimulation in most patients. Treatment with shakuyakukanzoto (mainly 7.5 g three times daily) was effective in 36 of 37 patients. The time to the onset of action was 1 day in 6 patients, 2–3 days in 9 patients, and 4–7 days in 12 patients, showing that treatment was beneficial in 73% of patients within the first week of treatment. Mild pseudoaldosteronism was observed in 2 patients under long-term treatment with shakuyakukanzoto (3).

Many reports have shown that shakuyakukanzoto is useful in the treatment of 'calf cramps,' including one report on the efficacy for leg muscle cramps in patients with type 2 diabetes (4) and several other reports on the efficacy for leg muscle cramps during dialysis (5, 6).

It has been reported that shakuyakukanzoto inhibits intestinal contraction during large bowel endoscopies. In a large bowel endoscopy, 0.5 g of shakuyakukanzoto dissolved in 50 mL of physiological saline was sprayed directly on the intestinal lumen surface via a forceps hole for approximately a 10-second period. The intestinal contraction and relaxation motion was videotaped for 3 minutes before spraying and 3 minutes after spraying. In 26 shakuyakukanzoto-treated subjects, the luminal area was significantly increased after spraying, suggesting that shakuyakukanzoto can be used to inhibit intestinal contraction during large bowel endoscopies (7, 8).

<Basic research> Cancer chemotherapy containing paclitaxel is associated with pain due to peripheral nerve disorder, often decreasing the quality of life of affected patients. It has been reported that shakuyakukanzoto relieves this pain. The efficacy of shakuyakukanzoto for pain was evaluated after oral administration of shakuyakukanzoto (1.75 mg/mouse) to mice engineered to develop allodynia (pain caused by slight touch that normally is not even noticed) and hyperalgesia after the administration of paclitaxel. Shakuyakukanzoto

markedly inhibited both allodynia and hyperalgesia. Interestingly, neither Peony Root (芍薬, shakuyaku) nor Glycyrrhiza (甘草, kanzo), both of which are constituent crude drugs, could inhibit allodynia or hyperalgesia when used alone (9).

The muscle relaxant effect of shakuyakukanzoto was attributable to the depolarization block caused by the combination of paeoniflorin in Peony Root and glycyrrhizin in Glycyrrhiza. Paeoniflorin inhibits the cellular influx of Ca ions, and glycyrrhizin promotes the outflow of K ions through the intracellular kinetics of K ion–Ca ion exchange. It was found that these constituents have a weak muscle relaxant effect individually but a more potent effect when combined at the blend ratio with shakuyakukanzoto (10).

[Discussion]

In an oral administration study of shakuyakukanzoto in mice, the time-to-maximum blood paeoniflorin concentration (Tmax) was as short as 17 minutes. It was also shown that glycyrrhetinic acid, a metabolite of glycyrrhizin, has no muscle relaxant effect (11, 12). These results are consistent with the finding that shakuyakukanzoto has a short onset of action.

Morphine is often used to reduce cancer pain. However, approximately 20% of patients (patients with neuropathic pain) are refractory to morphine. The recent report that shakuyakukanzoto is effective for neuropathic pain raises expectations of its use for this indication.

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Hangeshashinto (半夏瀉心湯)

[Component crude drugs]

Pinellia Tuber (半夏, hange), Scutellaria Root (黄芩, ogon), Ginseng (人参, ninjin), Glycyrrhiza (甘草, kanzo), Jujube (大棗, taiso), Processed Ginger (乾姜, kankyo), Coptis Rhizome (黄連, oren)

[Evidence for efficacy as a cancer therapy]

Hangeshashinto (半夏瀉心湯) is used in cancer therapy to relieve and prevent chemotherapy-caused adverse reactions, with certain efficacy.

Irinotecan hydrochloride exerts excellent anticancer effects by inhibiting topoisomerase I, an enzyme

that facilitates DNA replication. However, the associated leukopenia and serious diarrhea are dose-restricting factors. Relief of irinotecan hydrochloride-caused diarrhea by hangeshashinto (半夏瀉心湯) has been frequently reported. The efficacy of hangeshashinto was investigated in patients with non-small-cell lung cancer treated with a combination of irinotecan and cisplatin (IP therapy). Hangeshashinto 7.5 g (2.5 g t.i.d.) was administered for at least 21 days, beginning 3 days before the start of IP therapy. Patients receiving hangeshashinto in addition to IP therapy (n = 18) experienced significantly less frequent and less severe diarrhea than those receiving IP therapy alone (n = 23). Hangeshashinto administration was not associated with serious adverse reactions, although constipation was noted in 2 patients (1).

In another study, magnesium oxide was coadministered to relieve constipation associated with hangeshashinto administration. Small-cell or non-small-cell lung cancer patients receiving hangeshashinto combined with IP therapy were divided into 2 groups, one of which received magnesium oxide (1.0 to 2.0 g/day) in combination. Hangeshashinto 7.5 g (2.5 g t.i.d.) was administered before meals. Although there was no difference in the incidence and severity of diarrhea between the magnesium oxide combination group and control group (low incidences in both groups), the incidence of constipation was significantly decreased in the magnesium oxide combination group (2). It has been shown that hangeshashinto is more likely to cause constipation when the dose of coadministered irinotecan hydrochloride is higher, and that hangeshashinto does not cause constipation when administered alone (3).

[Evidence from basic research studies]

Irinotecan hydrochloride is converted to its active anticancer metabolite (SN-38) in the liver. SN-38 is conjugated to glucuronate in the liver and in turn converted to SN-38 glucuronide, an inactive form. SN-38 glucuronide is excreted via bile into the intestine, where it is deconjugated by β-glucuronidase from intestinal microflora to regenerate the active form of SN-38, which is considered to be a causative agent for late-onset diarrhea. Baicalin (derived from Scutellaria Root [黄芩, ogon]), a hangeshashinto component, inhibits β-glucuronidase activity. This may contribute to suppression of SN-38 regeneration in the intestine, thereby suppressing diarrhea (4—6).

[Discussion]

While hangeshashinto is widely used to suppress diarrhea caused by irinotecan hydrochloride in cancer therapy, it also has anti-inflammatory, anti-oxidative, apoptosis-inducing, and anti-bacterial/viral effects. Hangeshashinto may be useful for cancer treatment and recurrence prevention in the future.

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Saireito (柴苓湯)

[Component crude drugs]

Bupleurum Root (柴胡, saiko), Pinellia Tuber (半夏, hange), Scutellaria Root (黄芩, ogon), Ginseng (人参, ninjin), Glycyrrhiza (甘草, kanzo), Jujube (大棗, taiso), Ginger (生姜, shokyo), Alisma Rhizome (沢瀉, takusha), Polyporus Sclerotium (猪苓, chorei), Poria Sclerotium (茯苓, bukuryo), rhizomes of Atractylodes spp. (朮, jutsu), Cinnamon Twig (桂枝, keishi)

[Evidence for efficacy as a combination therapy with Western-style medications]

The indications of saireito (柴苓湯), which is shosaikoto (小柴胡湯) combined with goreisan (五苓散), include acute gastroenteritis, acute nephritis, chronic nephritis, cold, edema, sunstroke, swelling, cirrhosis, and nephrosis. Saireito is therefore often combined with western-style medications, particularly to relieve adverse reactions of western-style medications and to reduce steroid dose.

Saireito (2.5–5.0 g/day) was administered to idiopathic nephrotic syndrome patients treated with a steroid (n = 15, 3–17 years old) for 3–20 months. The addition of saireito enabled steroid dose reduction in 11 of 15 patients and was judged to be effective (1).

A study reported the efficacy of saireito for renal disorder associated with high-dose methotrexate administration. In primary central nervous system lymphoma patients receiving high-dose methotrexate (100 mg/kg) (n = 17, 42–82 years old), the severity of methotrexate-caused renal disorder was compared between patients treated with and without saireito (9.0 g/day, 3.0 g t.i.d.). Administration of methotrexate alone induced renal disorder characterized by increased blood urea nitrogen (BUN) and decreased creatinine clearance. In contrast, treatment with the saireito combination was hardly ever associated with increased BUN and decreased creatinine clearance. This was attributed to the inhibition of renal tubular reabsorption of water by saireito, leading to increased urine volume (2).

[Evidence for efficacy from basic research studies]

An experiment using rats has demonstrated the efficacy of saireito for the relief of adverse reactions to steroids or the reduction/withdrawal of steroid dose. The efficacy of saireito combined with dexamethasone for granulation tissue formed around implanted swabs was investigated in rats. The results showed that saireito can reduce the dexamethasone dose to approximately 1/3 (3).

The mouse model of cardiac transplantation with histocompatibility antigen-fully mismatched allografts was used to investigate the efficacy of saireito for transplantation immunity. The hearts of C57BL/6 mice were transplanted to recipient CBA mice. Saireito (2, 0.2, 0.02 and 0.002 g/kg) was administered for 8 consecutive days from the day of heart transplantation. In the saireito-untreated group, the cardiac allografts were rejected on days 7 and 8, leading to death of the mice. In contrast, saireito-treated group showed dose-dependent extension of survival. Mice receiving saireito at 2 g/kg and 0.2 g/kg survived for 100 days or longer and 41 days, respectively. Interestingly, shosaikoto (小柴胡湯) and goreisan (五苓散) did not prolong survival. Similarly, no component crude drugs had life-extending action comparable to that of saireito, when used alone. The mechanism was considered as follows: Saireito induced immunosuppressive

CD4+CD25+FOXP3+ regulatory T cells, thereby causing immunological tolerance (4).

[Discussion]
A study that reported the efficacy of saireito for ulcerative colitis identified ergosterol as the active component (5). Ergosterol has carcinogenesis-inhibiting and anti-tumor effects (6,7). Saireito, as a new application, may be useful for cancer treatment and recurrence prevention. Its potential as an immunosuppressant adjuvant raises the expectation that saireito will prove useful in organ transplantation procedures.

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Individual Crude Drugs

Makoto Inoue , Syunji Horie, Hisashi Matsuda
Yoshihiro Mimaki, Masayuki Yoshikawa

Artemisia Capillaris Flower (茵陳蒿, inchinko)★

[Origin]
Capitulum of kawarayomogi (*Artemisia capillaris* Thunberg) in the *Compositae* Family. In China, both *A. capillaris* and *A. scoparia* are used. The seedling harvested in the sprouting stage in spring is called 'Artemisia Capillaris seedling (綿茵蔯, men´inchin),' and the capitulium harvested in autumn is known as 'Artemisia Capillaris Flower (茵陳蒿, inchinko).'

[Principal ingredients]
Chromones such as capillarisin (principal ingredient), coumarins such as 6,7-dimethylesculetin = 6,7-dimethoxycoumarin = esculetin 6,7-dimethylether, essences such as capillin, capillen and capillone, phenylpropanoids, flavonoids, etc.

[Pharmacology]
The Artemisia Capillaris Flower in Kampo formulae includes inchinkoto (茵陳蒿湯) and inchingoreisan (茵陳五苓散) for indications of jaundice and liver and gallbladder symptoms. Its choleretic, liver-protective, and anti-inflammatory effects have been reported.

- **1) Choleretic effect:** Administration of inchinkoto ethanol extract to rat duodenum increases bile secretion. Also, 6,7-dimethylesculetin, capillarisin, and capillin (all present in inchinkoto extract) have been shown to increase bile secretion to a similar extent in various animal species, and to directly relax smooth muscle of the gallbladder and biliary duct terminal portions (1, 2). Capillarisin at high concentration has only a slight relaxant effect on isolated guinea pig gallbladder and Oddi's sphincter. However, capillarisin suppresses the activity of acetylcholine and the release of acetylcholine from the nerve terminals, suggesting that it acts not only directly on smooth muscle cells in the gallbladder and Oddi's sphincter but also indirectly on cholinergic nerve terminals (3). Studies on the choleretic effect of inchinkoto have revealed activation of the bile acid transporter (multidrug resistance-associated protein 2: Mrp2) and a nuclear receptor (constitutive androstane receptor: CAR) involved in bilirubin clearance, and identified genipin (which is produced by enterobacteria from geniposide contained in Gardenia Fruit [山梔子, sanshishi]) and 6,7-dimethylesculetin contained in Artemisia Capillaris Flower as active ingredients (see section 'Inchinkoto') (4, 5).
- **2) Hepatoprotective effect**: Capillarisin and 6,7-dimethylesculetin suppress carbon tetrachloride-

or D-galactosamine-induced liver disorder (6). A study on the efficacy of inchinkoto for concanavalin A-induced hepatitis in mice attributed its effect to suppression of interferon γ (IFN-γ) and interleukin (IL)-12 production, demonstrating the suppressive effects of components Artemisia Capillaris Flower and capillarisin on IFN-γ production (7).

- **3) Analgesic and anti-inflammatory effects:** There is a report that 6,7-dimethylesculetin suppresses acetic acid writhing, carrageenin-induced paw edema, etc. (8). Also reported are the suppressive effects on lipopolysaccharide-induced macrophage activation and the antioxidant effects of the essential oil and ethyl acetate fraction (9, 10).
- **4) Other effects:** 6,7-Dimethylesculetin significantly increased coronary vascular flow and heart rate in isolated rat hearts, and suppressed constriction of vascular smooth muscle isolated from rabbit thoracic aorta by noradrenalin, serotonin, and angiotensin II (11–13). It has been reported that 6,7- dimethylesculetin and capillarisin inhibit aldose reductase activity (14) and that the ethyl acetate fraction of Artemisia Capillaris Flower exerts its anti-obesity effect by stimulating the lipid metabolism (15).

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Astragalus Root (黄耆, ogi)

[Origin]

Root of *Astragalus membranaceus* Bunge or *Astragalus mongholicus* Bunge in the *Leguminosae* family

[Principal ingredients]

Triterpene saponins such as astragalosides I to VIII; amino acid derivatives; polysaccharides; isoflavones such as formononetin

[Pharmacology]

Astragalus root is a representative auxiliary agent which together with ginseng (人参, ninjin) is contained in

Kampo formulae for nutritional fortification, immunity enhancement, diuresis, and improvement of spontaneous/night sweating, edema, and suppuration. While few studies have examined its effect on diuresis or night sweating, many studies have examined its effect on immunity enhancement and resultant antitumor activity. Although not directly related to its principal medicinal effect, astragalus root reduces hypertension (an effect of γ-aminobutyric acid [GABA]) (1).

- **1) Tonic effect**: Continuous oral administration of the water extract of astragalus root (5 mg/kg) prolonged forced swimming in rats, and increased serum protein levels and liver uptake of leucine (2, 3).
- **2) Diuretic effect:** Compared to a placebo, the water extract of astragalus root significantly increased the urinary sodium level and fractional excretion of sodium within 4 hours after administration of a single dose (0.3 g/kg) in healthy male adults. This was due to an increase in serum atrial natriuretic peptide (ANP), with no involvement of the renin-angiotensin aldosterone system, but not due to an increase in blood pressure or glomerular filtration rate (4).
- **3) Effect on the immune system**: Astragalus root-derived polysaccharides (APS) inhibited the growth of solid Sarcoma 180 or ascites hepatoma implanted into mice. APS also enhanced the immune function in normal mice and inhibited cyclophosphamide- or prednisolone-induced immune impairment.

  After intraperitoneal administration of APS (500 mg/kg) in mice, there was a significant deposition of complement C3 in peripheral blood macrophages and an increase in peripheral blood macrophages, indicating that complement C3 activation is involved in the immunity-enhancing effect and resultant antitumor activity of APS (5). The water extract of astragalus root inhibited cyclophosphamide-induced decreases in the number and chemotactic activity of peritoneal macrophages in mice after oral administration for 7 days (10 mg/kg, as the crude drug). It also completely prevented cyclophosphamide-induced functional decline of natural killer (NK) cells (6).

  The oral administration of the crude polysaccharide fraction of astragalus root for 5 days (0.6 mg/mouse, 1.2 mg/mouse) significantly increased IgM production, which decreased with age (36 weeks old, 60 weeks old). The crude polysaccharide fraction was further separated by high-performance chromatography （HPLC） into two fractions. Both fractions were much more active than the starting crude polysaccharide fraction and contained polysaccharides (approximately 12,000 and 22,000 kDa, respectively) primarily composed of glucose molecules (7).

  In addition, the antitumor activity and stimulatory effect on macrophage phagocytosis (8), mechanism of macrophage activation by polysaccharides and triterpene glycosides in astragalus root (9, 10), stimulation of tumor-decreased immunity (11–14), etc. have been reported.
- **4) Antibacterial effect**: The methanol extract had antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* (15).
- **5) Other:** Oral administration of the water extract (10–20 mg/kg) every 8 hours for 2 days inhibited increases in serum urea nitrogen, creatinine, and sodium excretion rate and decrease in creatinine clearance in rats with glycerol-induced acute renal disorder (16).

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Scutellaria Root (黄芩, ogon)

[Origin]
Root of *Scutellaria baicalensis* Georgi in the *Labiatae* family, without periderm

[Principal ingredients]
Flavonoids such as baicalin (primary ingredient), baicalein, and wogonin
Content of baicalin: ≥10.0%

[Pharmacology]
Scutellaria root is contained in Kampo formulae stimulatory for antipyresis, analgesia, and anti-inflammatory action, anti-inflammation/pus discharge, antidiarrheal and intestinal regulation, gastric digestion, treatment of urinary tract disease, etc. The antipyretic, analgesic, anti-inflammatory, anti-allergic, anti-inflammatory and pus discharge, gastric, antidiarrheal and intestinal regulation properties, etc. of scutellaria root have been demonstrated in many pharmacological studies.

- **1) Anti-inflammatory effect**: The scutellaria root extract has an anti-inflammatory effect in inflammation models such as carrageenan-induced paw edema in rats, dextran sulfate-induced colitis, and zymosan-induced mouse air-pouch model (1–3), and inhibits lipopolysaccharide-stimulated production of nitric oxide, prostaglandin, and inflammatory cytokines in RAW264.7 macrophages (4). In addition, there have been many reports on anti-inflammatory effects of baicalin, baicalein, and wogonin in macrophages, endothelial cells, and neutrophils (5–7).
- **2)Anti-allergic effect**: The anti-allergic effect of baicalin and baicalein is well known. It has been reported that baicalein and baicalin inhibit asthma in an experimental animal model, inhibit picric acid-induced auricular edema and type IV allergic reaction after oral administration, and inhibit tracheal permeability in ovalbumin-sensitized guinea pigs (8–10). Baicalein also alleviates atopiform dermatitis symptoms in NC/Nga mice by inhibiting inflammatory cytokine production (TNF-α, IL-6, etc.) and immunocyte infiltration (11). It also inhibits eotaxin, an eosinophil

chemotactic factor deeply involved in induction of allergy, more potently than baicalin (12).

- **3) Antiviral effect:** Baicalein inhibits infection with influenza virus H1N1 in BALB/c mice and viral growth *in vitro* (13). Moreover, baicalin inhibits viral replication by inhibiting reverse transcriptase in cells infected with human T-cell leukemia virus (HTLV-1) or human immunodeficiency virus (HIV-1) (14, 15). In addition, baicalin may also prevent viral invasion by inhibiting HIV-1 envelope binding to chemokine receptors (16). The water extract of scutellaria root inhibits hepatitis B virus (HBV) production in human hepatic cancer cells (17), and wogonin inhibits HBV surface antigen production (18). The scutellaria root extract regulates the antiviral innate immune system by enhancing peripheral lymphocyte resistance to stomatitis viruses and controlling cytokine production (19). These actions may account for the immunoregulatory effect of bupleurum root (柴胡, saiko) formulations in ShoYo stage (*shoyobyoki*).
- **4) Antihepatopathic effect**: Scutellaria root (methanol extract) inhibits liver fibrosis in a bile duct ligation model (10), and baicalin inhibits ischemia-reperfusion injury (21), hemin/nitrite/hydrogen peroxide-induced liver disorder (22) and *tert*-butylhydroperoxide-induced liver disorder (23). Hepatoprotection has been attributed to elimination of active oxygen. In addition, baicalin inhibits fatty liver in high-fat diet-fed rats (24). Scutellaria root may have the abovementioned antihepatopathic effects in heat- and humidity-related hepatobiliary pathology, etc. although it causes gastric stuffiness (*Shinka Hi*).
- **5) Gastric effect**: Scutellaria root inhibits gastrointestinal disorder. Wogonin inhibits ethanol-induced gastric mucosal disorder, and this effect can be attributed to promotion of prostaglandin D_2 synthesis, inhibition of 5*S*-hydroxyeicosatetraenoic acid, or inhibition of apoptosis in the stomach (25). Furthermore, baicalein and the water extract of scutellaria root inhibit gastrointestinal adverse reactions such as nausea and vomiting caused by ritonavir, which is used for the treatment of acquired immune deficiency syndrome (26).
- **6) Antipruritic effect**: Scutellaria root suppresses inflammation and relieves itching in skin disease related to blood heat. The extract is reported to inhibit histamine- or compound 48/80-induced scratching behavior in mice (27). Baicalin, the primary ingredient, and its metabolites baicalein and oroxylin A have more potent antipruritic activity.
- **7) Analgesic effect**: Baicalin has an analgesic effect in a rat model of carrageenan-induced thermal hyperalgesia (28) and decreases the expression of capsaicin-sensitive vanilloid receptor, a pain receptor, in spinal ganglion neurons in primary cell culture (29).
- **8) Antispasmodic effect**: Wogonin and baicalein bind to the benzodiazepine site of γ-aminobutyric acid (GABA) receptor A (30) and have an anti-anxiety effect (31) and an antispasmodic effect mediated via GABA receptors (32).
- **9) Fetal protective effect**: The relaxant effect of oroxylin A, a metabolite of baicalin, on spontaneous or agonist-induced myometrial contraction (mediated through potassium channel activation) may protect the fetus (33).
- **10) Antidiarrheal effect**: In animal and clinical studies, hangeshashinto (半夏瀉心湯) showed efficacy for irinotecan (CPT-11)-induced delayed diarrhea, and the effect was due in part to baicalin

in scutellaria root. The CPT-11-induced delayed diarrhea itself may be attributed to an active metabolite of CPT-11, SN-38 glucuronide (with 200- to 1000-fold higher antitumor activity than CPT-11). SN-38 glucuronide is secreted into the bile and deconjugated by β-glucuronidase released from intestinal bacteria to form SN-38, which, in turn, damages luminal cells. It has been reported that baicalin inhibits β-glucuronidase (34, 35) and thereby SN-38 secretion into the lumen (36).

- **11) Other**: Total flavonoids in scutellaria root markedly inhibit cerebral ischemia-related or ischemia-reperfusion-related brain disorder as well as platelet aggregation (37). Many studies have reported the protective effects of baicalin and baicalein against drug-induced neuropathy, active oxygen-induced nerve disorder, and amyloid β-induced neuropathy (38). In addition, scutellaria root has an anti-arteriosclerotic effect.

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Coptis Rhizome (黄連, oren)

[Origin]

Rhizome of *Coptis japonica* Makino, *Coptis chinensis* Franchet, *Coptis deltoidea* C.Y. Cheng et Hsiao, or

Coptis teeta Wallich in the *Ranunculaceae* family, almost without root

[Principal ingredients]
Isoquinoline alkaloids such as berberine (primary ingredient), palmatine, and coptisine
Content of berberine (as berberine chloride): ≥4.2%

[Pharmacology]
Like phellodendron bark (黄柏, obaku), coptis rhizome contains berberine and other alkaloids and tastes very bitter. It is contained in Kampo formulae for gastric bitter taste, sedation, and antidiarrheal action. For the pharmacological effects of berberine, see the section on 'Phellodendron bark.'

- **1) Effect on the digestive system**: It is said that bitter taste stimulates the secretion of saliva, gastric juice, and pancreatic juice, but pharmacological verification of the stimulatory effect on gastric juice secretion is incomplete. Subcutaneous or oral administration of the extract inhibits various types of experimental gastric ulcers (1, 2). In addition, coptisine protects the gastric mucosa more effectively than berberine (3) and berberine inhibits barium chloride-induced diarrhea and intestinal peristalsis (see the section on 'Phellodendron bark'). One report indicates that the extract has antibacterial activity against *Helicobactor pylori* (4).
- **2) Bactericidal effect**: The 50% methanol extract has antibacterial activity against *Staphylococcus aureus*, *Shigella* spp., *Vibrio cholerae*, etc. (5). The infusion is effective for corneal herpes simplex infection in rabbits (6).
- **3) Effect on the central nervous system**: Berberine has central inhibitory, sedative, and antispasmodic effects after subcutaneous administration (see the section on 'Phellodendron bark').
- **4) Hypoglycemic effect**: Many reports indicate berberine has a hypoglycemic effect (see the section on 'Coptis rhizome').
- **5) Anti-inflammatory effect**: The water or methanol extract and berberine have anti-inflammatory effects such as inhibition of granulation tissue formation (7, 8), and berberine and coptisine inhibit collagenase (9).
- **6) Other effects**: Coptis rhizome stimulates the secretion of bile and pancreatic juice, lowers serum cholesterol, and relaxes blood vessels (10–12).

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Pueraria Root (葛根, kakkon)

[Origin]
Root of *Pueraria lobata* Ohwi in the *Leguminosae* family, without periderm

[Principal ingredients]
Isoflavones (primary ingredients) such as daidzin, daidzein, and puerarin; saponins; starch (10–14%)
Content of puerarin: ≥2.0%

[Pharmacology]
Pueraria Root is a mild diaphoretic that reduces fever and is used for insufficient sweating. It also alleviates inflammatory diarrhea. It is contained in Kampo formulae for diaphoresis, antipyresis, and spasmolysis. Pharmacologically, it has anti-inflammatory effects and efficacy for inflammation-related disease.

- **1) Antipyretic/analgesic/antispasmodic effect**: The efficacy of isoflavones in Pueraria Root was evaluated in a mouse model of subcutaneously injected lipopolysaccharide (LPS)-induced pyrexia. Daidzin and genistin (i.p.) were found to have a weak antipyretic effect. Interestingly, the antipyretic effect of daidzein and *p*-ethylphenol (i.p.), *in vivo* metabolites of daidzin, is more potent than that of daidzin. *p*-Ethylphenol has the most potent antipyretic effect (1). In the acetic acid writhing assay, the analgesic effect of daidzin and its metabolites daidzein, dihydrodaidzein, and *p*-ethylphenol was as potent as that of aminopyrine (1). In the rotarod performance test, *p*-ethylphenol and equol had a skeletal muscle relaxant effect (1). These effects may explain the antipyretic/antispasmodic effects of Pueraria Root.
- **2) Anti-inflammatory effect**: Puerarin inhibits tumor necrosis factor (TNF-α)-induced mRNA and protein expression of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) in human umbilical cord endothelial cells (2); inhibits intranuclear transfer of nuclear factor κB (NF-κB) and LPS-stimulated production of C-reactive protein by preventing phosphorylation and degradation of the inhibitor of NF-κB (I-κB) in mononuclear cells from angina patients (3); inhibits advanced glycation end product-induced inflammation in mesangial cells by inducing heme oxygenase-1 expression (4). The anti-inflammatory effect of puerarin may explain the antipyretic effect, inhibitory effect on inflammatory diarrhea, etc. of Pueraria Root.
- **3)Improvement of diabetes/insulin resistance**: In a rat model of streptozotocin-induced type I diabetes, oral administration of the ethanol extract of Pueraria Root lowered blood glucose and reduced oxidative stress (5). Likewise, intravenous administration of puerarin lowered blood glucose and improved insulin resistance by increasing glucose uptake in skeletal muscle cells and inducing glucose transporter 4 expression (6). It has also been reported that puerarin and genistein activate phospholipase C and protein kinase C through α_1-adrenoceptor activation and increase glucose uptake in C2C12 muscle cells (7, 8). These findings may account for the ability of Pueraria Root to alleviate thirst.
- **4) Other effects**: Pueraria Root has estrogen-like effects including inhibition of bone density decrease (9) and improvement in learning ability (10) and cardiovascular effects, including inhibition of myocardial infarction (puerarin), lowering of blood pressure (total flavone fraction),

and improvement of ischemia-reperfusion injury (11–13).

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Glycyrrhiza (甘草, kanzo)

[Origin]

Root and stolon of *Glycyrrhiza uralensis* Fischer or *Glycyrrhiza glabra* Linné in the *Leguminosae* family, with or without the periderm (i.e., with bark removed)

[Principal ingredients]

Triterpene glycosides (content: 3–6%) such as glycyrrhizinic acid (primary ingredient, also known as glycyrrhizin; source of sweet taste); flavonoids and their glycosides such as liquiritin, isoliquiritin, liquiritigenin, and isoliquiritigenin

There are also species-specific ingredients, including coumarins such as glycycoumarin from *G. uralensis* and isoflavones such as glabridin from *G. glabra*. In addition, *G. inflata*, which is used in China as a crude drug but not in Japan, contains chalcones such as licochalcone A.

Content of glycyrrhizinic acid: ≥2.5%

[Pharmacology]

Glycyrrhiza is one of the most commonly used Kampo crude drugs and present in more than 70% of 236 general Kampo formulae. It is frequently found in formulae used as an antitussive/expectorant, analgesic/expectorant, or antipyretic/analgesic/anti-inflammatory drug. Because it tastes sweet, glycyrrhiza may be added to reduce the bitter flavor of the whole formula. Many pharmacological studies of glycyrrhiza have been conducted, but only reports on the antitussive, analgesic/antispasmodic, anti-inflammatory, and anti-allergic effects of extracts and ingredients are described below in line with the primary objectives of use.

- **1) Antitussive effect**: In guinea pigs given oral doses (100 mg/kg) of a fraction of the water extract eluted from a Diaion HP-20 (a porous synthetic adsorbent) column by 50% methanol, the frequency of capsaicin-induced coughing was inhibited by 60%. In guinea pigs given oral doses of liquiritin apioside (LA; 3–30 mg/kg), one of the principal ingredients in the 50% methanol-eluted fraction, the frequency of coughing was inhibited in a dose-dependent manner, suggesting that the

antitussive effect of glycyrrhiza may be due to LA. In addition, the antitussive action of LA (30 mg/kg, oral administration) was antagonized by methysergide, but not by naloxone. On the other hand, pretreatment with glibenclamide, an ATP-sensitive K channel blocker, reduced the antitussive effect of LA. These findings indicate that LA has both peripheral and central antitussive effects (1). Intragastric administration of isoliquiritigenin (5–20 mg/kg) caused relaxation of acetylcholine-contacted guinea pig bronchial smooth muscle and inhibited bronchospasm in guinea pigs. In an *in vitro* experiment using guinea pig bronchial smooth muscle cells, on the other hand, isoliquiritigenin activated soluble guanylate cyclase (sGC) and inhibited phosphodiesterase 5 (PDE5). It also opened the BKCa channel by inducing the cyclic guanosine monophosphate/protein kinase G (cGMP/PKG) signaling cascade, indicating that the smooth muscle relaxant effect of isoliquiritigenin may be based on a decrease in the intracellular Ca^{2+} concentration (2).

- **2) Analgesic/antispasmodic effect**: Compared with orally administered water extract of rhubarb (大黄, daio) (500 mg/kg), orally administered daiokanzoto (大黄甘草湯, water extract of rhubarb and glycyrrhiza, equivalent to 500 and 125 mg/kg, respectively) significantly inhibited cathartic-induced intense colon contractions in rats. Oral administration of the rhubarb extract (500 mg/kg) with glycyrrhizinic acid (5 mg/kg), liquiritin (2.5 mg/kg), and glycyrrhizinic acid (5 mg/kg) + liquiritin (2.5 mg/kg) had the same inhibitory effect on colon contractions, indicating that glycyrrhiza in daiokanzoto inhibits rhubarb-related intense contractions of colon circular muscle and reduces cathartic-induced abdominal pain, and that these effects are due to glycyrrhizinic acid and liquiritin (3). Glycycoumarin and liquiritigenin inhibited carbamylcholine-induced contractions of isolated segments of mouse jejunum (4, 5).
- **3) Anti-inflammatory/anti-allergic effect**: The water extract of glycyrrhiza inhibited IgE-mediated auricular swelling in mice (6). Licochalcone A inhibited lipopolysaccharide (LPS)-stimulated production of nitric oxide (NO) and prostaglandin (PG) E_2 in RAW264.7 cells, and LPS-induced fatal endotoxin shock in mice after oral administration (1–10 mg/kg) (7). Glycyrol inhibited LPS-stimulated NO production in RAW264.7 cells and carrageenin-induced paw edema in mice after intraperitoneal administration (30, 100 mg/kg) (8). Liquiritigenin inhibited LPS-stimulated production of NO, interleukin (IL)-1β, and IL-6 in RAW264.7 cells, and this effect was shown to be partly due to inhibition of NF-κB activation (9). Glycyrrhizinic acid reduced experimental allergic asthma symptoms (10) and inhibited reactive oxygen species (ROS) production in neutrophils (11). 18β-Glycyrrhetinic acid and liquiritigenin potently inhibited IgE-induced degranulation in RBL-2H3 cells, compound 48/80-induced degranulation in rat peritoneal mast cells, and the passive cutaneous anaphylaxis (PCA) reaction (12).

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Schizonepeta Spike (荊芥穂 [荊芥], keigai)

[Origin]
Spike of *Schizonepeta tenuifolia* Briquet in the *Labiatae* family

[Principal ingredients]
Essential oil composed of monoterpenes (*d*-menthone [primary ingredient], *l*-pulegone, *d*-limonene, isopulegone, etc.) and sesquiterpenes (caryophyllene, β-elemene, etc.); monoterpene glycosides; flavone glycosides, etc.

[Pharmacology]
Schizonepeta spike is contained in Kampo formulae for anti-inflammation/pus discharge and skin disease. Anti-inflammatory/anti-allergic effects have been reported.

- **1) Effect on skin disease**: The water extract maintains skin moisture and inhibits hyaluronidase, which contributes to its anti-allergic effect (1). In an experiment using rat peritoneal mast cells, the water extract inhibited antigen- or compound 48/80-stimulated release of histamine and TNF-α (2). The methanol extract decreased the frequency of scratching in mice with substance P-induced pruritus (3).
- **2) Anti-inflammatory effect**: The water extract exerts its immunomodulatory effect by controlling the release of Th1 and Th2 cytokines from T cells (4). Schizonepeta spike inhibits lipopolysaccharide-stimulated production of COX-2, iNOS, TNF-α, and IL-6 in macrophages by blocking NF-κB activation and the MAP cascade (5–7). The *d*-menthone in schizonepeta spike inhibits intraperitoneally administered acetic acid-induced increase in vascular permeability and has an antinociceptive effect (8).

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Bupleurum root (柴胡, saiko)

[Origin]
Root of *Bupleurum falcatum* Linné in the *Umbelliferae* family

[Principal ingredients]
Triterpenoid saponins such as saikosaponins A, C, and D (primary ingredient); phytosterols
Content of total saponins (saikosaponins A and D): ≥0.35%

[Pharmacology]
Bupleurum root is present in Kampo formulae used as antipyretic/analgesic/anti-inflammatory drugs, anti-inflammatory/pus discharge drugs, stomachic digestant, anti-psychoneurotic drugs, etc. Pharmacological studies have been conducted to demonstrate these effects, and many studies on the immunoregulatory effect, anti-inflammatory/anti-allergic effect, hepatoprotective effect, anti-ulcer effect, etc. have been reported.

- 1) Immunoregulatory effect: Saikosaponin D inhibits concanavalin A- or phorbol ester (PMA)-induced T-cell activation (1, 2). This effect may be due to inhibition of the NF-κB transcriptional activity through inhibition of IKK and Akt, inhibition of intranuclear transfer of transcriptional factors NF-AT and AP-1, inhibition of activation of protein kinase C and JNK, etc. Saikosaponin A inhibits T-cell activation (3). A pectic polysaccharide isolated from bupleurum root, bupleuran 2IIb, promotes B-cell proliferation and interleukin-6 production (4, 5). In addition, intramuscular injection of saikosaponin D increased peritoneal macrophage phagocytosis, lysosome enzymatic activity, fungicidal activity against yeast, Fc receptor expression, and interleukin-1 production in mice (6). Bupleuran 2IIb also increased Fc receptor expression in macrophages (7). These findings indicate that bupleurum root is cardinal remedy for ShoYo stage (*shoyobyo*) and acts by regulating the immune response multilaterally.
- **2) Anti-inflammatory effect**: Oral or intramuscular administration of crude saikosaponin separated from bupleurum root inhibits cotton pellet-induced granulation (8), and intraperitoneal or oral administration of saikosaponins A and D and their metabolites stimulate the secretion of adrenocorticotropic hormone and corticosterone and inhibit inflammation (9, 10). These effects may contribute to bupleurum root-induced antipyresis and alleviation of hepatitis and nephritis.
- **3) Anti-allergic effect**: Intravenous administration of saikosaponin A dose-dependently inhibited passive cutaneous anaphylaxis and tracheal contraction in an ovalbumin-immunized guinea pig model of asthma (11).
- **4) Antinephritic effect**: Intramuscular administration of saikosaponin D inhibited aminonucleoside-induced proteinuria, suggesting that it may prevent proteinuria associated with nephrotic syndrome (12). Intraperitoneal injection of saikosaponins A and D improved proteinuria, high serum cholesterol, and histopathological changes in an antiglomerular basement membrane antibody nephritis model. These effects may be partly due to inhibition of platelet aggregation, increased corticosterone concentration, and inhibition of the decrease in active oxygen-scavenging

enzymes (13).

- **5) Hepatoprotective effect**: Saikosaponin D inhibits D-galactosamine- or carbon tetrachloride-induced experimental liver disorder (14, 15). This effect is partly due to marked inhibition of carbon tetrachloride-induced lipoperoxidation. It also reduces continuously administered carbon tetrachloride-induced liver cirrhosis, indicating that saikosaponin D is hepatoprotective.
- **6) Anti-ulcer effect**: The acid polysaccharide fraction from bupleurum root has an anti-ulcer effect in various experimental ulcer models including hydrochloric acid/ethanol-induced gastric ulcer and water immersion stress-induced gastric ulcer. This effect may be partly due to hydroxyl radical scavenging activity (16).
- **7) Effect on brain function**: The methanol extract of bupleurum root improves restraint stress-induced spatial organization deficit, possibly by preventing cholinergic nerve loss (17). It also has an antidepressant effect in tail suspension and open field tests, and the serotonin and noradrenaline nervous systems may be involved in the effect (18).
- **8) Other**: Crude saikosaponin has an anticholesteremic activity due in part to promotion of cholesterol excretion as bile acids (19). In addition, saikosaponin A inhibits platelet production of thromboxane and ADP-induced platelet aggregation, suggesting that it may be used to maintain circulatory system homeostasis (20).

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Gardenia Fruit (山梔子, sanshishi)

[Origin]

Fruit of *Gardenia jasminoides* Ellis in the *Rubiaceae* family

[Principal ingredients]

Iridoid glycosides such as geniposide (primary ingredient) and gardenoside; carotenoid pigments such as crocin and crocetin

Content of geniposide: ≥3.0%

[Pharmacology]

Gardenia fruit is present in Kampo formulae such as inchinkoto (茵陳蒿湯) and orengedokuto (黄連解毒湯) for choleresis, anti-inflammation, antipyresis, sedation, hemostasis, etc. Pharmacological studies have focused extensively on the choleretic and anti-inflammatory effects of gardenia fruit extract, geniposide (iridoid glycoside in gardenia fruit) and its aglycone genipin, and carotenoids (crocin and crocetin).

- **1) Choleretic effect**: The water and alcohol extracts increased bile secretion in rabbits after intravenous administration (1.0 g/kg) (1). The methanol extract increased bile secretion in rats after intraduodenal administration (1.5 g/kg) (2). Geniposide significantly stimulated bile secretion in rats 2 hours after intraduodenal administration (2.0 g/kg) and thereafter. Genipin significantly increased bile secretion in rats after intravenous administration (25 mg/kg), intraduodenal administration (25 mg/kg), and intraportal administration (2.5 mg/kg). In addition, genipin stimulated bile secretion more potently and more persistently in rats after oral administration (25 mg/kg), compared with dehydrocholic acid at the same dose. The choleretic effect of gardenia fruit may be caused by genipin, which is formed as a result of hydrolysis after gastrointestinal administration of geniposide (3–5). Crocin and crocetin stimulated bile secretion in rabbits after intravenous administration (crocin: 0.1 g/kg, crocetin: 0.01 g/kg) (6) (see the sections entitled ‘Artemisia Capillaris Flower [茵陳蒿, inchinko]’ and ‘Inchinkoto [茵陳蒿湯]’).
- **2) Anti-inflammatory effect**: Caerulein-induced acute pancreatitis was significantly inhibited in mice after oral administration of the water extrract (0.1 and 1 g/kg) for 7 days, compared with control mice (7). Crocin inhibited xylene-induced auricular edema in a dose-dependent manner in mice after oral administration (25, 50, and 100 mg/kg) and carrageenin-induced paw edema in a dose-dependent manner in rats after oral administration (25 and 50 mg/kg) (8). Genipin inhibited hydrochloric acid/ethanol-induced gastritis more effectively in rats after oral administration (50 and 100 mg/kg), compared with cimetidine, a positive control (9).
- **3) Sedative effect**: Geniposide and genipin prevented a decrease in learning behavior in mice exposed to stressful stimuli after oral administration (50 mg/kg) (10).
- **4) Hypotensive effect**: The methanol extract inhibited rabbit lung-derived angiotensin-converting enzyme (11).

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Ginger (生姜, shokyo) and Processed Ginger (乾姜, kankyo)

[Origin]

Ginger is the rhizome of *Zingiber officinale* Roscoe in the *Zingiberaceae* family. Processed ginger is the rhizome of *Zingiber officinale* Roscoe, after being processed through hot water or being steamed..

In Japan, steamed and then dried fresh rhizome is called processed ginger and used in formulae separately from ginger. In China, on the other hand, fresh rhizome of *Zingiber officinale* Roscoe is called ginger and used as an antiemetic, expectorant, antitussive, detoxicant, antipyretic, digestive system stimulant, etc. Dried rhizome of *Zingiber officinale* Roscoe, which is equivalent to ginger (shokyo) in Japan, is called 'qianjiang (乾姜)' (or 'baijiang (白姜),' 'junjiang (均姜),' 'qianshengjiang (乾生姜),' etc.) and present in formulae to reduce wheezing and improve abdominal pain, stomach ache, and gastrointestinal retention. In summary, the name, medicinal effects, and usage of medical *Zingiber officinale* Roscoe in Japanese Kampo medicine are different from those in traditional Chinese medicine.

[Principal ingredients]

Essential oil composed of pungent ingredients such as 6-,8-,10-gingerol (primary ingredient: 6-gingerol) and 6-shogaol (barely detectable in raw *Zingiber officinale* Roscoe); sesquiterpenes such as α-gingiberene; monoterpenes

[Pharmacology]

Ginger is contained in Kampo formulae for transpiration and antiemetic activity, and processed ginger is contained in Kampo formulae for eliminating interior cold and improving chill and pain and coughing and wheezing. Ginger and processed ginger have pharmacological effects including antiemetic, gastric mucosal protective, and anti-inflammatory and anti-allergic effects. Differences in the medicinal effects of 'ginger' and 'processed ginger' are related to differences in the contents of gingerols, shogaols, and essential oil constituents and their pharmacological effects and potency (1, 2). Gingerols, 6-dehydrogingerdione, and sesquiterpenes are markedly decreased during the processing of fresh ginger into dry ginger, indicating that differences in medicinal effects of 'ginger (shokyo)' and 'processed ginger (kankyo)' result from ingredient changes during the drying process (3, 4).

- **1) Effect on the digestive system**: Pressed ginger juice inhibits copper sulfate-induced vomiting, and pungent ingredients gingerols and shogaols are identified as the active ingredients responsible for this effect (1, 2), which has been attributed in part to antagonism of 5-hydroxytryptamine type 3 (5-HT_3) receptors (5, 6). 8-Gingerol, 6-shogaol, and galanolactone

(diterpene) antagonize the effects of serotonin (5-HT), and 6-gingerol, 6-shogaol, and 6-dehydrogingerdione inhibit 5-HT-induced hypothermia and diarrhea (5, 6). In addition, the extract prevents hydrochloric acid/ethanol-induced gastric mucosal damage after oral administration, and 6-gingerol, 6-shogaol, 6-gingesulfonic acid, and sesquiterpenes (*α*-gingiberene, β-sesquiphellandrene, β-bisabolene, and *ar*-curcumene) are inhibitory (7–10). Gingerols and 6-shogaol enhance small intestinal motility at low doses (11). Gastric mucosal protection, increased cardiac contractility, and bronchial smooth muscle contraction by pungent ingredients such as gingerols and shogaols are due to vanilloid receptor (TRPV1) stimulation, as is the case with capsaicin (12, 13).

Daikenchuto (大建中湯) is said to be effective for postoperative ileus and experimentally found to promote gastrointestinal motility and increase intestinal blood flow. Serotonin receptor (5-HT3 and 5-HT4)-mediated acetylcholine release is involved in gastrointestinal motility (14), and improvement in blood flow was found to result from TRPV1-stimulated release of calcitonin gene-related peptide (CGRP) from sensory nerve endings, TRPA1-stimulated release of adrenomedullin from intestinal mucosal epithelial cells, and mobilization of these receptor-related genes (15, 16). Furthermore, 6-shogaol in processed ginger, a crude drug comprising daikenchuto, stimulates not only TRPV1 but also TRPA1, and hydroxy-α-sanshool in zanthoxylum fruit (山椒, sansho), another constituent crude drug, stimulates TRPA1 (17).

- **2) Antipyretic/analgesic/anti-inflammatory effect**: The extract, 6-gingerol, and 6-shogaol have antipyretic, analgesic, and anti-inflammatory effects, all attributable to inhibition of prostaglandin synthesis. As for anti-allergic effects, it has been reported that 6-gingerol and 6-shogaol potently inhibit 5-lipoxygenase activity (1, 2, 18) and 6-shogaol inhibits passive cutaneous anaphylaxis and compound 48/80- or calcium ionophore A23187-stimulated histamine release in rat peritoneal mast cells (12).
- **3) Other effects**: The extract, gingerols, and shogaols induce bronchial smooth muscle contraction and increase the contractility of isolated atrium, with 6-shogaol having the highest activity (12, 13, 19, 20). The pungent effect in humans is strongest for 6-shogaol, followed by 6-gingerdione, 6-gingerol, and 6-gingesulfonic acid (10).

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Gypsum (石膏, sekko), Mirabilite (芒硝 [消], bosho), Aluminum Silicate Hydrate with Silicon Dioxide (滑石, kasseki)

Gypsum (石膏, sekko)

[Origin/ingredients]
It is natural occurring hydrous calcium sulfate composed almost completely of $CaSO_4 \cdot 2H_2O$.
[Pharmacology] Gypsum is contained in Kampo medicines for relieving fever and thirst with uneasiness, but few studies have provided evidence supporting this claim.

- **1) Thirst-reducing effect**: Gypsum water (decoction filtrate) decreased water intake in water-deprived rats, rats with fever, rats with diuretic-induced dehydration, and rats with salt-induced water deficit (1, 2).
- **2) Other effects**: Intestinal absorption of calcium is more efficient from calcium in gypsum than from calcium sulfate, calcium chloride, etc. (3). Byakkokaninjinto (白虎加人参湯)inhibited triphasic cutaneous reaction in anti-DNP IgE antibody-sensitized mice. This effect was attenuated in the absence of gypsum, glycyrrhiza, or brown rice （粳米, kobei）, but was not exhibited by gypsum (4). Gypsum enhances the release of ephedrine from ephedra herb (麻黄, mao) into hot water (5).

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Mirabilite (芒硝 [消], bosho)

[Origin/ingredients]
It is recrystallized from naturally occurring mirabilite. It is primarily composed of $Na_2SO_4 \cdot 10H_2O$ and also contains traces of magnesium sulfate, calcium sulfate, magnesium chloride, sodium chloride, etc.
Mirabilite stored in the Shosoin Treasure House is crystal magnesium sulfate, but apparently mirabilite was naturally occurring magnesium sulfate ($MgSO_4 \cdot 7H_2O$) at least until the Tang Dynasty.

[Pharmacology]
Its heat pattern-treating (*seinetsu*) and cathartic effects are utilized to alleviate gastrointestinal inflammation and loosen the bowels. It also has an aquaretic effect. It is often utilized in combination with rhubarb to produce internal heat pattern-treating and cathartic effects, and in combination with other aquaretic drugs to produce aquaresis. Few studies have been reported, except for those on its effects as a saline laxative.

Aluminum Silicate Hydrate with Silicon Dioxide (滑石, kasseki)

[Origin/ingredients]
It is a mineral composed of natural hydrous aluminum silicate, silicon dioxide, etc.
Silicate mineral ore: Hard aluminum silicate hydrate with silicon dioxide (primary ingredient [talc: $3MgO \cdot 4SiO_2 \cdot H_2O$]) and soft aluminum silicate hydrate with silicon dioxide (hydrated halloysite, etc.; primary ingredient [hydrous aluminum silicate]) are commercially available. Studies of drugs stored in the Shosoin Treasure House indicate that soft aluminum silicate hydrate with silicon dioxide was used in antient times. In modern China, hard aluminum silicate hydrate with silicon dioxide is used.

[Pharmacology]
It is contained in Kampo formulae for decreased urine volume (*shobenfuri*) and dry mouth (*kokan*). Its inhibitory effects on carcinogenesis promotion, cAMP phosphodiesterase activity, etc. (1–3), have been more widely investigated than its effects on oliguresis/anuria or thirst.

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Rhubarb (大黄, daio）

[Origin]
Usually rhizome of *Rheum palmatum* Linné, *Rheum tanguticum* Maximowicz, *Rheum officinale* Baillon, or *Rheum coreanum* Nakai in the *Polygonaceae* family, or their interspecific hybrids

[Principal ingredients]
Dianthrone (bis-anthrone) glycosides such as sennosides A and B (primary ingredient); anthrone glycosides such as rheinoside; anthraquinones and their glycosides such as rhein, aloe-emodin, and chrysophanol;

condensed and hydrolyzable tannin, etc.
Content of sennoside A: ≥0.25%

[Pharmacology]
Rhubarb is included in Kampo formulae not only for alleviating constipation and various accompanying symptoms, but also for treating blood stasis (*Kuoketsu*). The cathartic effect is dependent on the content of sennosides (which are converted into active compounds by intestinal bacteria), not on the production region or name (kinmondaio [錦紋大黄], gao [雅黄], etc.). The cathartic, anti-inflammatory and anti-blood-clotting effects of sennosides on blood flow and renal disease have been studied. Like artemisia capillaris flower and gardenia fruit, rhubarb is included in Kampo formulae for jaundice, but few studies support its efficacy for jaundice.

- **1) Cathartic effect**: Orally administered water and ethanol extracts in mice have a cathartic effect attributable primarily to sennosides A, B, C, D, E, F, etc. (1–5). Sennosides A and B are metabolized into rhein anthrone (a cathartic) by intestinal bacteria (6) and the onset of rhein anthrone activity in mice involves prostaglandin E_2 (7, 8). Free anthraquinones (rhein, emodin, aloe-emodin, chrysophanol, and physcion) have little cathartic effect (9, 10). In one study, the cathartic effect of rhubarb in rats was enhanced by glycyrrhiza (11).
- **2) Anti-inflammatory effect/hepatoprotective effect**: Lindleyin, aspirin, and phenylbutazone have similar analgesic/anti-inflammatory potencies (12). Also, emodin and chrysophanol inhibit an increase in serum transaminase (GPT) in carbon tetrachloride-induced liver disorder (13).
- **3) Inhibitory effect on blood coagulation**: The decoction inhibits thrombin formation, fibrinolysis, platelet aggregation *in vitro* (14, 15), and endotoxin-induced intravascular coagulation (DIC) in rats (16).
- **4) Blood urea nitrogen (BUN)-lowering effect**: The rhubarb-induced decreases noted in blood urea nitrogen (BUN), creatinine, portal blood ammonia, and hepatic and renal urea content in rats with experimental renal failure can be attibuted to rhatannin, a tannin derivative (17–29).
- **5) Other effects**: While rhubarb was found to suppress the locomotor activity and antagonize methamphetamine-induced increase in locomotor activity in rats (30), one clinical study concluded that the psychotropic effect of daiokanzoto (大黄甘草湯) is too weak to be of clinical significance (31). Rhubarb has antibacterial (32–34) and antiviral (herpes virus) effects (35), eliminates peroxynitrite ($ONOO^-$) and O_2^- (through inhibition of xanthine oxidase) (36), and inhibitsadvanced glycation end-product (AGE) formation (37).

Similar crude drugs: Rhubarb extracted from *R. undulatum* inhibits platelet aggregation, type I and IV allergy, and macrophage activation, and has antioxidant and vasodilatory effects, and stilbenes are responsible for these effects (38–45). Among various rhubarb preparations, those from Rhapontica containing rhaponticin are viewed as inferior to rhubarb. However, there is a view that rhubarb preparations rich in stilbene compounds are useful for improving blood flow (39, 42).

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Alisma Rhizome (沢瀉，takusha)

[Origin]

Tuber of *Alisma orientale* Juzepczuk in the *Alismataceae* family, from which periderm has been usually removed.

[Principal ingredients]

Sesquiterpenes such as alismol (primary ingredient); triterpenes such as alisol A monoacetate and alisol B monoacetate

[Pharmacology]

Alisma rhizome is contained in Kampo formulae for alleviating heaviness of the head, dizziness, and tinnitus due to abnormal water metabolism in the upper body. Many reports support the effects of alisma rhizome on the renal/urinary and circulatory systems but not many support its effects on the above.

- **1) Effect on the renal/urinary system**: Alisol A monoacetate and alisol B are mild diuretics and have been shown to significantly increase sodium excretion in rats (1). Alisma rhizome improved uremia and prolonged life in mice with experimental uremia (2) and inhibited urinary calculus formation. The inhibition of endothelin 1 production by saireto in a rat model of anti-GBM nephritis has been attributed to alisma rhizome and alisol B (3).
- **2) Anti-allergic effect**: The methanol extract and alisols inhibit complement activity (4).

  The methanol extract but not the water extract inhibited a type III allergic reaction in rats. This effect was caused by alismol, alismoxide, alisol A, alisol B, and monoacetates of alisol A and B (5). Alisma rhizome also inhibited urinary protein excretion in a rat model of immune complex nephritis (6).
- **3) Effect on lipid metabolism**: Alisma rhizome powder inhibits hepatic lipid accumulation, and alisol A monoacetate decreases plasma and liver cholesterol levels (7–9).
- **4) Effect on the circulatory system**: The hypotensive effect of alismol was shown by inhibition of angiotensin I-, calcium-, or adrenaline-induced vasoconstriction in isolated blood vessels (10–14). Alisols were also shown to have a vasorelaxant effect and antagonize vasopressin and angiotensin II receptors in isolated blood vessels (15, 16).
- **5) Other effects**: Alisols inhibit lipopolysaccharide-stimulated excessive nitric oxide production in macrophages, kill tumor cells, and have anti-HBV (hepatitis B virus) activity (17–21).

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Citrus Unshiu Peel (陳皮, chimpi)

[Origin]
Mature peel of *Citrus unshiu* Markovich or *Citrus reticulata* Blanco in the Rutaceae family

[Principal ingredients]
Essential oil composed of monoterpenes such as *d*-limonene (essential oil constituent present in citrus crude drugs); flavonoid glycosides such as hesperidin (primary ingredient), neohesperidin, and naringin; limonin, an amaroid, etc.
Content of essential oil: ≥0.2 mL per 50.0 g

[Pharmacology]
Citrus crude drugs (citrus unshiu peel [陳皮 chimpi], citrus peel [橘皮, kippi], immature orange [枳実, kijitsu], bitter orange peel [橙皮, tohi]), which have unique aroma and bitter taste, are used as aromatic bitter digestive tonics. Citrus unshiu peel is included in Kampo formulae for stimulating stomachic and antitussive/expectorant action. Many studies have examined the stomachic and anti-allergic effects of constituent flavonoids.

- **1) Effect on the digestive system**: The decoction mildly stimulated gastric juice secretion and enhanced the effect of lipase in fasted dogs with Pavlov's pouch after oral, supralingual, or oral mucosal administration (1–3). Intragastric administration stimulated stomach motility in rabbits (4). *d*-Limonene was found to stimulate intestinal motility and bile secretion (5–8).

  Rikkunshito (六君子湯) is effective for cisplatin-induced decrease in plasma ghrelin concentrations and accompanying anorexia. Decreased plasma ghrelin concentrations and anorexia, possibly due to increased release of serotonin that stimulates 5-$HT_{2B/2C}$ receptors, may be inhibited by methoxyflavones in citrus unshiu peel such as 3,3',4',5,6,7,8-heptamethoxyflavone, nobiletin, and tangeretin (9, 10). Rikkunshito also inhibited anorexia associated with increased plasma leptin concentrations in elderly mice. The inhibitory activity on phosphoinositide 3-kinase and phosphodiesterase (PDE)3, which are involved in hypothalamic leptin signaling, was assessed, and 3,3',4',5,6,7,8-heptamethoxyflavone and nobiletin in citrus unshiu peel were found to inhibit PDE3 (10, 11) (see the section entitled 'Rikkunshito').
- **2) Anti-allergic effect**: Citrus unshiu peel inhibits the passive cutaneous anaphylaxis reaction, a basic model of type I allergy, as well as type IV allergic reactions. The higher anti-allergy activity of the immature fruit of *Citrus unshiu* Markovich than the mature fruit has been attributed to the inhibitory effect of hesperidin and narirutin (which are more abundant in immature fruit) and on histamine release from mast cells (12–15). Likewise, flavonoids have been shown to inhibit the degranulation of RBL-2H3, cells derived from anti-DNP IgE antibody-sensitized basophils (16).
- **3) Effect on the respiratory system**: With regard to the antitussive effect, synephrine in citrus crude drugs has a bronchodilator effect. Synephrine inhibited the release of the slow-reacting substance of anaphylaxis from the lung and leukotriene-induced tracheal contraction in sensitized

guinea pigs (17).

- **4) Effect on the central nervous system**: Nobiletin improved cerebral Aβ accumulation and memory impairment in mice with amyloid β (Aβ)-induced memory impairment, olfactory bulbectomy-induced memory impairment, and *N*-methyl-D-aspartate receptor antagonist (MK-801)-induced memory impairment/learning disorder (18).
- **5) Effect on the circulatory system**: Synephrine is a sympathomimetic substance with not only a bronchodilator effect, but also vasoconstrictive and hypertensive effects (17, 19).
- **6) Other effects**: *d*-Limonene has sedative and central depressant effects, constricts the smooth muscle, and stimulates intestinal motility and bile secretion (5–8) Nobiletin inhibits cAMP phosphodiesterase (20), promotes adipocyte differentiation, enhances lipolysis in adipocytes (21), kills tumor cells, and inhibits tumor cell infiltration (22–26). In addition, polymethoxyflavones induce myeloid leukemia cell differentiation (27). Hesperidin is effective in a rat model of diabetes (28, 29).

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Ginseng (人参, ninjin)

[Origin]

Root or gently blanched root of *Panax ginseng* C. A. Meyer (*Panax schinseng* Nees) in the *Araliaceae* family,

from which rootlets have been removed, or the root tnat has been quickly passed through hot water.

[Principal ingredients]
Triterpenoid saponins (primary ingredient) such as ginsenosides Ro, Ra to Rh and malonylginsenosides; polyacetylene alcohols such as panaxynol (= falcarinol)

The genuine sapogenin of ginsenoside Ro is oleanolic acid, whereas the other ginsenosides are dammarane triterpenoid saponins, including those with 20*S*-protopanaxadiol as the aglycone (ginsenosides Rb_1, Rb_2, Rc, Rd, etc.) and those with 20*S*-protopanaxatriol as the aglycone (ginsenosides Re, Rf, Rg_1, Rg_2, etc.)

Content of ginsenoside Rg_1: ≥0.10%

Content of ginsenoside Rb_1: ≥0.2%

[Pharmacology]
Ginseng is included in Kampo formulae for frailty-related anorexia, impaired digestive function, diarrhea, chronic fatigue, mental instability, etc. It is characterized by its regulatory effect on the gastrointestinal and respiratory systems. It enhances immunity, metabolism, appetite, and alleviates diarrhea. It also has a tranquilizing effect on the central nervous system. These effects of ginseng have been extensively but not fully demonstrated in pharmacological studies.

- **1) Immunoregulatory effect**: The ginseng extract not only enhances humoral immunity, which results in an increase in antibody-producing cell concentration and blood antibody titer, but also enhances cellular immunity against viral antigens (1). It also promotes natural killer cell activation and restores immunosuppressive cyclophosphamide-impaired natural killer cell function (2). Total saponins in ginseng not only serve as an adjuvant to activate antigen-specific antibody production and cellular immunity in ovalbumin-immunized mice, but also reverse morphine-induced thymic and splenic atrophy (3, 4). Like the ginseng extract, ginsenoside Rg_1 (i.p.) activates humoral and cellular immunity and macrophages, and restores cyclophosphamide-suppressed immunity (5). As for other ginsenosides, Rb_1 and Re (when coadministered with inactivated virus) act as an adjuvant to enhance anti-viral antibody and cytokine production (13, 14). Also, the water extract of ginseng, total saponins, and ginsan (an acid polysaccharide) activate macrophages *in vitro*. As shown by these reports, ginseng has multiple immunoregulatory effects.
- **2) Effect on the nervous system**: Ginsenosides Rb_1 and Rg_1 serve as neurotrophic and neuroprotective factors to maintain dopaminergic neuron survival and neurite growth (8, 9). In addition, ginsenoside Rb_1 enhances nerve growth factor expression in the hippocampus (10), prevents ischemia-reperfusion- or neurotoxic glutamine-induced hippocampal CA1 neuron disorder (11, 12), and inhibits scopolamine-induced learning and memory impairment. The last effect may be explained by increased choline uptake in central nerve endings, acetylcholine release, and choline acetyltransferase expression (13). On the other hand, ginsenoside Rg_1 (i.p.) inhibits 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced nigral neuronal loss (14) and promotes axonal regeneration and functional recovery in rats with crushed sciatic nerve (15). In

addition, ginsenoside Rg_3 (i.c.v.) inhibits excitotoxic homocysteine-induced hippocampal disorder by inhibiting NMDA receptor activation (16). This effect is complemented by the inhibitory effect of ginsenoside Rg_3 on NMDA-induced intracellular calcium increase in cultured hippocampal neurons (17). Also, the neuroprotective effect of ginsenosides Rg_2, Re, 20 (*S*)-Rg_3, and Rb_2 has been demonstrated *in vitro*.

- **3) Anti-aging effect**: The extract reversed the decrease in learning ability in eight-arm radial arm maze task and passive avoidance test in elderly rats after intake for several weeks (18, 19). It also inhibited the decrease in nocturnal locomotor activity in elderly rats (20). In addition, it (i.p.) reversed the age-related decrease in atrial natriuretic peptide gene expression (21). These findings indicate that ginseng may inhibit or reverse age-related functional decline.
- **4) Anti-ulcer effect**: The effectiveness of ginseng and red ginseng (紅参) against ulcers has been demonstrated in an experimental model. The inhibitory effect of ginseng on ethanol-induced ulcer may be due to cytoprotection through expression induction of heat-shock proteins 70 and 27 (22, 23). Ginsenoside Rb_1 and acid polysaccharides have been identified as the active ingredients responsible for this effect (24, 25).
- **5) Antistress/anti-fatigue effect**: The ginseng extract markedly inhibits acute and chronic immobilization stress-induced increases in the gastric ulcer area, adrenal weight, and plasma corticosterone concentration (26). It also reduces fatigue and enhances endurance during the forced swimming test (27). Total saponins in ginseng and ginsenosides Rg_3 and Rb_1 (p.o.) have a neuroprotective effect by significantly decreasing the level of putrescine (a polyamine in the brain that increases in response to immobilization stress) (28).
- **6) Antidiabetic effect**: The water extract of ginseng markedly lowered blood glucose in mice with epinephrine-induced hyperglycemia after oral administration (29). This effect may be due to increased glucose uptake in the liver resulting from increased expression of glucose transporter 2. In addition, red ginseng improved insulin sensitivity and decreased visceral fat in Otsuka Long-Evans Tokushima Fatty (OLETF) rats with diabetes after oral administration (30). This effect is due to increase in the number of mitochondria and increased sugar utilization associated with AMP kinase activation in skeletal muscles. Also, the ethanol extract of ginseng markedly decreases levels of blood glucose and serum lipids in a mouse model of high-fat diet-induced hyperglycemia and obesity (31). Blood glucose is lowered or insulin resistance is improved by ginsenosides Rb_2, 20 (*S*)-Rg_3, and Re in rats with streptozotocin-induced diabetes (32, 33, 34), by ginsenoside Rh_2 in high-fructose diet-fed rats (35), and by panaxan in mice with alloxane-induced hyperglycemia (36).
- **7) Other effects**: These include antitumor, anti-arteriosclerotic, antiplatelet, hepatoprotective, anti-inflammatory effects, etc.

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Mentha Herb (薄荷, hakka)

[Origin]
Aerial part of *Mentha arvensis* Linné var. *piperascens* Malinvaud in the Labiatae family

[Principal ingredients]
Essential oil (approximately 1%) composed of monoterpenes such as *l*-menthol (primary ingredient) and *l*-menthone
Content of essential oil: ≥0.4 mL per 50.0 g

[Pharmacology]
Mentha herb is contained in Kampo formulae for heat detoxification (清熱解毒), analgesic detoxification, antitussive/expectorant action, stomachic action, etc. In addition, mentha herb oil and menthol are algefacients for external application to the oral cavity, nasal cavity, and skin. There have been reports on its algefacient, smooth muscle relaxant, anti-ulcer, analgesic, antibacterial effects, etc.

- **1) Algefacient effect**: Menthol acts on TRPM8, a cold and menthol receptor (1). TRPM8 is a temperature-sensitive sensor that is expressed in skin and visceral primary afferent sensory nerves and activated at or below 25°C. Menthol causes sensation of cold (pleasant cooling sensation) in the skin and oral cavity by activating TRPM8. The pharmacological effects of mentha herb may in

part be due to TRPM8, which is very subject to desensitization (depolarizing blocking).

- **2) Smooth muscle relaxant effect**: The mentha herb extract and menthol inhibit gastrointestinal motility of mouse small intestine (2, 3). Menthol (the primary ingredient) and menthone have an antispasmodic effect. Mentha herb also inhibits gastrointestinal smooth muscle excitation possibly by acting as a local anesthetic, but the mechanism of this effect has not been elucidated. Moreover, the extract caused vascular smooth muscle relaxation in rat thoracic aorta and mesenteric artery specimens (4). This effect has been attributed to nitric oxide (NO) release from the vascular endothelium. Mentha herb is thus expected to improve peripheral blood flow.
- **3) Anti-ulcer effect**: The extract inhibited gastric damage formation in models of pylorus ligation-induced gastric damage, ethanol-induced gastric damage, and hydrochloric acid-induced gastric damage (5). This gastric mucosal protective effect may contribute to the stomachic effect.
- **4) Analgesic effect**: The extract had an analgesic effect in the acetic acid writhing assay in mice (6). Menthol had analgesic and local anesthetic effects in experimental animals. Mentha herb may exert these analgesic, local anesthetic, and skin irritating effects via TRPM8.
- **5) Antibacterial effect**: Mentha herb oil has an antibacterial effect (7) and enhances the antibacterial activity of antibacterial agents such as kanamycin against multiresistant *Escherichia coli* (8).

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Atractylodes Rhizome (白朮, byakujutsu), Atractylodes Lancea Rhizome (蒼朮, sojutsu)

[Origin]

Byakujutsu: Rhizome of *Atractylodes japonica* Koidzumi ex Kitamura or *Atracylodes macrocephala* Koidzumi (*Atractylodes ovata* De Candolle) in the *Compositae* family

Atractylodes lancea rhizome: Rhizome of *Atractylodes lancea* De Candolle or *Atractylodes chinensis* Koidzumi in the *Compositae* family, or their hybrids

[Principal ingredients]

Atractylodes rhizome: Essential oil (1.5–3%) composed of sesquiterpenes such as atractylon (primary ingredient), 3β-hydroxyatractylon, etc.; polyacetylene compounds

Content of essential oil: ≥0.5 mL per 50.0 g

Atractylodes lancea rhizome: Essential oil (3.5%–7%) composed of sesquiterpenes such as β-eudesmol (primary ingredient) and hinesol; acetylene compounds such as atractylodin
Content of essential oil: ≥0.7 mL per 50.0 g

[Pharmacology]
The rhizomes of Atractylodes spp. (朮, jutsu) is contained in Kampo formulae for stomachic action, antidiarrheal action, diuresis, etc. The medicinal effects have been utilized since ancient times. They include the possible diaphoretic, diuretic, and anti-diarrhetic effects of atractylodes lancea rhizome, and the stomachic, aquaretic, and qi deficiency-treating effects of atractylodes rhizome. In Japan, atractylodes rhizome and atractylodes lancea rhizome are used without clear distinction and sometimes used separately depending on the brand name of preparations.

1) Effect on the renal/urinary system:

- **Atractylodes rhizome**: The ethanol extract slightly increased the urine volume in mice after intraperitoneal administration, but not after oral administration (1). (6*E*,12*E*)-tetradecadiene-8,10-diyne-1,3-diol and its diacetate derivative mildly inhibited dog kidney-derived Na^+/K^+-ATPase, but had no effect on the urine volume after oral administration (2). The essential oil increased urine volume and urine electrolytes in rats after oral administration (3). Neither goreisan containing atractylodes lancea rhizome nor goreisan containing atractylodes rhizome caused change in total body water or circulating plasma volume in rats compared with the control group, and only goreisan containing atractylodes rhizome decreased the urine volume in water-deprived rats (4).
- **Atractylodes lancea rhizome**: Atractylodes lancea rhizome promotes excretion of Na^+, K^+, and Cl^-, and inhibits the Na^+/K^+-ATPase activity (5). The inhibitory effect of goreisan and atractylodes lancea rhizome on plasma membrane water permeability has been attributed to aquaporin (AQP) inhibition, which may be related to manganese ion in the crude drug, and goreisan inhibited cerebral edema in a mouse model of water intoxication (6).

2)Effect on the digestive system:

- **Atractylodes rhizome**: It promotes intestinal transport and inhibits stress-induced ulcer but is not effective for gastric ulcer associated with excessive gastric juice secretion, indicating that those effects are anti-stress effects (7). Atractylon inhibits hydrochloric acid/ethanol-induced gastric mucosal damage (8). Both the hot water extract of goreisan containing atractylodes rhizome and that of goreisan containing atractylodes lancea rhizome had an antidiarrheal effect in a mouse model of magnesium sulfate-induced diarrhea. However, both goreisan not containing atractylodes rhizome and goreisan not containing atractylodes lancea rhizome had a decreased antidiarrheal effect, indicating that the antidiarrheal effect in this diarrhea model is not caused by a certain crude drug (9).
- **Atractylodes lancea rhizome**: For atractylodes lancea rhizome contained in Kampo formulae for gastrointestinal disease such as abdominal pain, the extract inhibits pylorus ligation-, aspirin-,

serotonin-, histamine-, acetic acid-, or water immersion stress-induced experimental ulcer. Atractylodes lancea rhizome was effective for various types of experimental gastric ulcer and gastric mucosal damage, whereas atractylodes rhizome was effective only for water immersion stress-induced ulcer (7). Atractylodes lancea rhizome was also found to inhibit gastric juice secretion and serotonin-induced decrease in gastric mucosal blood flow and to enhance gastric mucosal protective ability (10, 11). The essential oil or its main constituents β-eudesmol and hinesol were found to antagonize histamine H_2 receptors and protect the gastric mucosa (12). Hinesol inhibits high-concentration KCl-, carbachol-, or serotonin-induced contraction of isolated smooth muscles, especially ileal smooth muscles (13).

3) Anti-inflammatory effect:

- **Atractylodes rhizome**: The 50% ethanol or methanol extract inhibited acetic acid-induced increase in vascular permeability in mice, and eudesma-4(14),7(11)-dien-8-one and atractylenolide I were identified as the active ingredients responsible for this effect (14). The decoction extract inhibited adjuvant arthritis (15). Atractylodes rhizome also inhibited lipopolysaccharide-stimulated production of nitric oxide (NO) and prostaglandin E_2 and expression of inducible NO synthetase and cyclooxygenase-2 in macrophage-like RAW264.7 cells (16).

4)Other effects:

- **Atractylodes rhizome**: These effects include inhibition of experimental liver disorder (17, 18), lowering of blood glucose (19), and stimulation of early immune responses. Compared to atractylodes lancea rhizome, atractylodes rhizome is more effective in preventing carbon tetrachloride-induced liver disorder probably thanks to atractylon, whereas compared to atractylodes rhizome, atractylodes lancea rhizome is a more potent stimulator of bile production, possibly thanks to atractylodin (17). Goreisan powder and atractylodes rhizome powder prolonged life and inhibited the increase in blood pressure in 1%-salt diet-fed stroke-prone spontaneously hypertensive rats (SHRSP). Atractylodes rhizome has no apparent diuretic effect, but inhibits body weight gain, decreases neutral lipids, and reduces fat deposition (20, 21).

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Processed Aconite Root (附子, [Bushi]/烏頭, [uzu])

[Origin]

Processed aconite root in the Japanese Pharmacopoeia is made from the tuberous root of *Aconitum carmichaeli* Debeaux or *Aconitum japonicum* Thunberg in the *Ranunculaceae* family, which is processed as described below and called Processed Aconite Root 1, Processed Aconite Root 2, and Processed Aconite Root 3, respectively. The content of total alkaloids (as benzoylaconine [$C_{32}H_{45}NO_{10}$: 603.70]) is 0.7–1.5%, 0.1–0.6%, and 0.5–0.9%, respectively.

1) Treated with high-pressure steam
2) Immersed in an aqueous solution of salt, rock salt, or calcium chloride and then treated with heat or high-pressure steam
3) Immersed in an aqueous solution of salt and then treated with calcium hydroxide

The residual content of each of the highly toxic diester alkaloids aconitine, jesaconitine, hypaconitine, and mesaconitine are determined by HPLC and required to be (in μg/g) ≤60, ≤60, ≤280, and ≤140, respectively, for individual ingredients and ≤450 for total diester alkaloids.

In China, the mother root, which looks like the head of 'wu [u]' (crow), is called 'wutou [uzu]' (head of crow), and the daughter root is separately called 'fuzi [bushi].' In Japan, both mother and daughter roots are called processed aconite root (bushi) without distinction. The toxicity of the tuberous root is appropriately attenuated (by specific processing) before use because it is still highly toxic when it is just dried. It is said that bushi warms the body, and uzu relieves pain.

[Principal ingredients]

Diterpene (aconitine) alkaloids such as aconitine, jesaconitine, hypaconitine, and mesaconitine; benzylisoquinoline alkaloids such as higenamine

[Pharmacology]

Processed aconite root is contained in Kampo formulae for warming the body from the inside, eliminating coldness, and relieving pain. This is supported by evidence showing analgesic, thermogenic, and vasorelaxant effects, etc. In recent years, processed and unprocessed tuberous roots of aconite were often called bushi and uzu, respectively, creating confusion in the published literature.

- **1) Analgesic effect**: Bushi/uzu without specific processing has a potent analgesic effect attributable to mesaconitine in normal mice in the tail pinch test, etc. (1). The analgesic activity is markedly decreased by specific processing probably because mesaconitine is hydrolyzed into less

active benzoylmesaconine and then into mesaconine (2). Also, processed aconite root had a potent anti-allodynic effect in a rat model of neuropathic pain (3).

Although the mechanism of these analgesic effects has not been elucidated, μ-opioid receptor stimulation or spinal κ-opioid receptor activation through endogenous opioid (dynorphin, etc.) release may be involved (4, 5).

- **2) Thermogenic effect**: Bushi warms the chilled body from the inside. In mice maintained at 4°C for 10 days, rectal temperature decreased with body weight loss, but returned to the normal level with free access to diets containing processed bushi (6). It has been suggested that processed aconite root powder may increase heat production by increasing uncoupling protein 1 (UCP-1) in the inner mitochondrial membrane in the brown adipose tissue (6). These effects may explain why bushi enhances metabolism and eliminates coldness.
- **3) Vasorelaxant effect**: Bushi may improve 'cold hands and feet' not only by enhancing heat production, but also by improving peripheral blood circulation. It has been shown that mesaconitine, an alkaloid in bushi, relaxes the vascular smooth muscle by stimulating nitric oxide (NO) release from the vascular endothelium in rat aorta specimens and endothelium-derived hyperpolarizing factor (EDHF) release in rat gastric artery specimens (7, 8). Blood NO levels are higher in patients who take Kampo formulae containing bushi (9). These vasorelaxant effects may contribute to improvement in peripheral blood circulation.
- **4) Cardiotonic effect**: Bushi/uzu eliminates local water retention. A part of this effect is considered to be a cardiotonic effect. Higenamine, an alkaloid in bushi/uzu, has a positive inotropic effect in guinea pig papillary muscle specimens and a positive chronotropic effect in guinea pig ventricular specimens (10). Bushi/uzu may have a cardiotonic effect, which contributes to elimination of excess water.

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Sinomenium Stem (防已, Boi)

[Origin]

Climbing stem and rhizome of *Sinomenium acutum* Rehder et Wilson in the *Menispermaceae* family

[Principal ingredients]
Alkaloids such as sinomenine (primary ingredient) and disinomenine

[Pharmacology]
Sinomenium stem is contained in Kampo formulae such as boiogito, sokeikakketsuto, and mokuboito for diuresis/antiedematous action and analgesia. While many studies have demonstrated the bioactivity of sinomenine (an alkaloid structurally similar to morphine and the primary ingredient in sinomenium stem) after parenteral administration, few studies support the medicinal effects of sinomenium stem in Kampo medicines. In particular, the diuretic effect is denied in one report (1).

- **1) Antiedematous effect**: The 50% methanol extract of sinomenium stem significantly inhibited jugular vein ligation-induced congestive edema in rats after oral administration (2 g/kg), compared with the control group (2).
- **2) Analgesic effect**: Screening for analgesic activity using the hot plate test, sinomenine hydrochloride had an analgesic effect in mice after subcutaneous administration (2 mg/10 g). During once-daily treatment, the analgesic activity was increased to the maximum level after approximately 1 week. The effect persisted for several days after completion of treatment (3, 4).

  Sinomenine hydrochloride attenuated tactile stimulus- or needle stimulus-induced sensory afferent impulses in cats after local subcutaneous administration (0.75–1.0 mg). This effect reached the maximum level 30–60 minutes post dose, then gradually weakened 60–90 minutes post dose, and finally disappeared 2–3 hours post dose. In addition, complete anesthesia was produced 5–15 minutes after administration at a dose of 2.0 mg and persisted for several hours (5). Sinomenine competed against naloxone for μ-opioid receptors in Chinese hamster ovary cells, with an IC_{50} value of 109.5±51.0 nM. It also phosphorylated μ-opioid receptors at concentrations of 1 and 10 μM. In mice, it inhibited tail flick reflex dose-dependently after intraperitoneal administration at doses of 10–30 mg/kg. After subcutaneous administration to mice (30 mg/kg twice daily for 6 days), it inhibited the development of analgesic tolerance to morphine administered at a dose of 10 mg/kg in a similar manner (6).
- **3) Anti-inflammatory effect**: Tetrandrine, an alkaloid in sinomenium stem, inhibited carrageenin-induced hind footpad edema by approximately 20% in rats after intramuscular administration (200 mg/kg). The inhibitory effect of tetrandrine hydrochloride at a dose of 100 mg/kg was as potent as that of the control phenylbutazone, but did not increase at a dose of 200 mg/kg, showing no dose-dependency. Orally administered tetrandrine (200 mg/kg) inhibited ovalbumin-induced footpad edema (7). The water extract of sinomenium stem inhibited anaphylactic mediator release and had an antihistaminic effect (8). Several studies investigated the efficacy of sinomenine for rheumatoid arthritis and its mechanism of action (9–13), but their intention was to find a new antirheumatic drug that could be used in Western medicine.

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Saposhnikovia Root (防風, bofu)

[Origin]
Root and rhizome of *Saposhnikovia divaricata* Schischk in the *Umbelliferae* family

[Principal ingredients]
Coumarins such as deltoin, bergapten, psoralen, and imperatorin; chromone derivatives; polysaccharides; polyacetylene, etc.

[Pharmacology]
Saposhnikovia root is primarily contained in Kampo formulae for skin disease, inflammation/pus discharge, and fever/pain. However, few studies have assessed the medicinal effects of saposhnikovia root in Kampo medicines. The decoction of saposhnikovia root is very effective for fever caused by mixed typhoid bacilli after oral administration. It has also been reported that the 50% ethanol extract markedly increases pain threshold (1), but this is not a reliable report. The recent pharmacological studies supporting the antipyretic/analgesic effect and anti-inflammatory/anti-allergic effect of saposhnikovia root are described below.

- **1) Antipyretic/analgesic effect**: A sugar-free saposhnikovia root extract fraction (SIB; prepared by passing the 30% ethanol extract of saposhnikovia root through a porous synthetic adsorbent, Diaion HP-20) inhibited acetic acid-induced writhing in a dose-dependent manner (40–1000 mg/kg) in mice after oral administration (2). Polyacetylene compounds in saposhnikovia root such as falcarindiol and falcarinol inhibited thromboxane B_2 formation in human platelets in a dose-dependent manner (2–200 μg/mL) by inhibiting cyclooxygenase, suggesting that these polyacetylene compounds may be involved in the antipyretic, analgesic, and anti-inflammatory effects of saposhnikovia root (3). Oral administration of the methanol extract of saposhnikovia root (2 g/kg) inhibited acetic acid-induced writhing in mice. The ingredients responsible for this analgesic activity were chromone derivatives such as *sec-O*-glucosylhamaudol, cimifugin, hamaudol, ledebouriellol, and divaricatol. A significant analgesic activity was observed after oral administration of (in mg/kg) *sec-O*-glucosylhamaudol (40), cimifugin (80), hamaudol (1 and 10; the aglycone of *sec-O*-glucosylhamaudol), ledebouriellol (1 and 5), and divaricatol (1 and 5). Of

these compounds, *sec*-*O*-glucosylhamaudol (oral administration, 80 mg/kg), one of the main chromones in saposhnikovia root, showed a significant analgesic activity in mice using the tail pressure method as well as the Randall-Selitto method. The analgesic activity of *sec*-*O*-glucosylhamaudol was reversed by naloxone, suggesting that this analgesic activity may be mediated by opioid receptors (4).

- **2) Anti-inflammatory/anti-allergic effect**: The water extract of saposhnikovia root inhibited dried Bacillus Calmette-Guerin adjuvant-induced arthritis in rats after oral administration (extract equivalent to 1 g/kg raw crude drug) (5). The methanol extract of saposhnikovia root inhibited compound 48/80-stimulated histamine release from rat peritoneal mast cells by 50% or more at concentrations of 10 μg/mL or less (6). Imperatorin and deltoin, furocoumarin derivatives separated from saposhnikovia root, inhibited lipopolysaccharide (LPS)-stimulated expression of inducible nitric oxide synthetase (iNOS) protein and NO production in mouse RAW264.7 macrophages (IC_{50}: imperatorin: 17.3 μg/mL, deltoin: 11.6 μg/mL) (7). The ethyl acetate extract of saposhnikovia root inhibited LPS/IFN-γ-stimulated nitric oxide (NO) production by approximately 27% in C6 glioma cells at a concentration of 10 μg/mL. The ingredients responsible for this activity were polyacetylene compounds such as falcarindiol. Falcarindiol (10 μM) inhibited LPS/IFN-γ-stimulated iNOS and NO production by approximately 70% in C6 glioma cells (8).

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Ephedra herb (麻黄, mao)

[Origin]

Terrestrial stem of *Ephedra sinica* Stapf, *Ephedra intermedia* Schrenk et C.A. Meyer, or *Ephedra equisetina* Bunge in the *Ephedraceae* family

[Principal ingredients]

Alkaloids such as (–)ephedrine (primary ingredient), (+)-pseudoephedrine, (–)-norephedrine, and (–)-*N*-methylephedrine

Content of total alkaloids (ephedrine and pseudoephedrine): ≥0.7%

[Pharmacology]

Ephedra herb is used as a diaphoretic, antipyretic, and analgesic for chills, edema, headache, body pain, joint pain, etc. in TaiYo stage (*taiyobyo*). It is also used as an antitussive for cough, asthma, etc. Ephedrine, the primary ingredient, has sympathomimetic, central stimulatory, antitussive, thermogenic, and anti-obesity properties.

- **1) Anti-asthmatic effect**: The ephedra herb extract inhibited pulmonary production of IL-4 and leukotriene C4 in an asthma model of ovalbumin-immunized/sensitized mice (1). Ephedrine, the primary ingredient, was used for the treatment of asthma in 1929 (2) and shown to have a weak, persistent bronchodilator effect via β_2-adrenoceptors.
- **2) Anti-inflammatory effect**: The ethanol extract of ephedra herb markedly inhibited paw edema in rats with adjuvant arthritis after oral administration, showing that ephedra herb has an aquaretic/anti-swelling effect (3). Ephedrine and pseudoephedrine also inhibited carrageenan-induced paw edema, and this effect does not involve either the central nervous system or inhibition of prostaglandin E_2 biosynthesis (4). The maobushisaishinto extract and (–)-ephedrine inhibited passive cutaneous anaphylaxis immediately after administration, and this effect may involve the afferent and efferent nervous systems through gastric β_2-receptor stimulation (5–7).
- **3) Effect on the circulatory system**: The marked vasoconstriction induced by ephedra herb is mediated through α_1-adrenoceptor activation in the cat pulmonary vascular bed (8). Healthy humans who took the ephedra herb powder showed increased pulse rate but interindividual variation in blood pressure (9). Ephedrine gradually increases blood pressure because of its vasoconstrictive (α_1 adrenoceptor agonistic) and cardiac-stimulating (β_1 adrenoceptor agonistic) effects, and this hypertensive effect persists for several hours.
- **4) Effect on the nervous system**: In humans, the sympathetic nervous system dominates after intake of the ephedra herb dry extract (10). Ephedrine promotes heat production by stimulating fatty acid metabolism via β-oxidation, resulting in inhibition of fat accumulation. This heat production may be related to the diaphoretic effect of ephedra herb (11, 12). Ephedrine improved ischemic hypoxia-induced decrease in spatial cognitive ability by increasing synaptic connections (13). The effect of ephedrine on the central nervous system also enhanced motor performance and food intake, and these effects may be related to indirect activation of the dopaminergic nervous system (14).
- **5) Anti-obesity effect**: The ephedra herb extract decreased body mass index in premenopausal women on low-calorie diets in a double-blind randomized controlled study (15). This effect may be mediated by β-adrenoceptors. In addition, the water extract of ephedra herb has been found to reduce hypothalamic secretion of neuropeptide Y, an orexigenic factor, in the starvation state (16).
- **6) Other**: Deaths and serious adverse reactions such as stroke, arrhythmia, coronary infarction, cardiomyopathy, aneurysm, and nephrolithiasis have been attributed to ephedra herb taken alone or as the ephedra herb contained-supplement for enhancement of motor performance, fat combustion, weight loss, etc. (17, 18).

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Forsythia Fruit (蓮翹, rengyo)

[Origin]

Fruit of *Forsythia suspensa* Vahl or *Forsythia viridissima* Lindley in the *Oleaceae* family

[Principal ingredients]

Lignans such as arctigenin, arctiin, and (+)-pinoresinol; phenylethanoid glycosides such as forsythiaside

[Pharmacology]

Forsythia fruit is contained in Kampo formulae such as bofutsushosan (防風通聖散), jumihaidokuto (十味敗毒湯), and keigairengyoto (荊芥連翹湯)having potential anti-inflammatory, pus discharge, antidotal, antibacterial, diuretic effects, etc. Pharamacological studies evaluated mostly anti-allergic and anti-inflammatory effects and often succeeded in identifying the active ingredients. On the other hand, few studies have evaluated the antidotal, antibacterial, and diuretic effects.

7) Anti-allergic effect: Arctigenin inhibited ovalbumin-induced passive cutaneous anaphylaxis (PCA; type I reaction) and compound 48/80-induced histamine release from peritoneal mast cells (type I reaction) by approximately 30% in mice after oral administration (15 mg/kg). It also markedly inhibited reversed cutaneous anaphylaxis (RCA) reaction (type II reaction) in rats and inhibited sheep red blood cell (SRBC)-induced Arthus reaction (type III reaction) in mice after oral administration (15 mg/kg). In addition, it markedly inhibited SRBC-induced delayed type hypersensitivity and formation of SRBC rosettes in mice and inhibited picryl chloride- or dinitrofluorobenzene-induced contact dermatitis (type IV reaction) in mice after oral administration (15 mg/kg, 45 mg/kg) (1). The methanol extract of forsythia fruit inhibited compound 48/80-induced anaphylaxis and compound 48/80-induced auricular inflammation by approximately 30%, and inhibited anti-dinitrophenyl (DNP) IgE antibody-induced PCA reaction after oral administration in mice (1 g/kg) (2). The 80% methanol extract reduced anaphylactoid symptoms such as

coughing, vomiting, and gastric contraction in piglets with allergy induced by β-conglycinin, which accounts for approximately 30% of soybean proteins, after oral administration (100 mg/kg). It also inhibited the PCA reaction, degranulation in mast cells, and histamine release from mast cells (3). Triterpenes in forsythia fruit had an anti-asthmatic effect by decreasing specific airway resistance in immediate and delayed reactions, reducing erythropoietin activity and eosinophil infiltration, inhibiting inflammatory mediator release in the lung, etc. in a guinea pig model of ovalbumin-induced allergic asthma (4).

2) Anti-inflammatory effect: The 70% methanol extract inhibited acetic acid-induced increase in dye permeability after administration to mice, and this effect was attibutable to 3β-acetoxy-20,25-epoxydammarane-24-ol (5). The water extract markedly inhibited compound 48/80-induced edema and decreased vascular permeability by approximately 89% in mice after oral administration (100 mg/kg) (6). Phylligenin inhibited carrageenin-induced paw edema by approximately 22–35% in mice after intraperitoneal administration (12.5–100 mg/kg) (7).

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Kampo Formula Nomenclature

Japanese(Han character)	Roman alphabet	Structured notation
安中散	anchusan	Anchu-San
胃苓湯	ireito	I-rei-To
茵蔯蒿湯	inchinkoto	Inchinko-To
茵蔯五苓散	inchingoreisan	Inchin-gorei-San
温経湯	unkeito	Unkei-To
温清飲	unseiin	Unsei-In
越婢加朮湯	eppikajutsuto	Eppi-ka-jutsu-To
黄耆建中湯	ogikenchuto	Ogi-Kenchu-To
黄芩湯	ogonto	Ogon-To
黄連解毒湯	oregedokuto	Oren-gedoku-To
黄連湯	orento	Oren-To
乙字湯	otsujito	Otsuji-To
葛根加朮附湯	kakkonkajutsubuto	Kakkon-ka-jutsu-bu-To
葛根湯	kakkonto	Kakkon-To
葛根湯加川芎辛夷	kakkontokasenkyushin'i	Kakkon-To-ka-senkyu-shin'i
加味帰脾湯	kamikihito	Kami-kihi-To
加味逍遥散	kamishoyosan	Kami-shoyo-San
甘草湯	kanzoto	Kanzo-To
甘麦大棗湯	kanbakutaisoto	Kanbaku-taiso-To
桔梗湯	kikyoto	Kikyo-To
帰脾湯	kihito	Kihi-To
芎帰膠艾湯	kyukikyogaito	Kyu-ki-kyogai-To
芎帰調血飲	kyukichoketsuin	Kyu-ki-choketsu-In
九味檳榔湯	kumibinroto	Kumi-binro-To
荊芥連翹湯	keigairengyoto	Keigai-rengyo-To
桂枝加黄耆湯	keishikaogito	Keishi-ka-ogi-To
桂枝加葛根湯	keishikakakkonto	Keishi-ka-kakkon-To
桂枝加厚朴杏仁湯	keishikakobokukyoninto	Keishi-ka-koboku-kyonin-To
桂枝加芍薬大黄湯	keishikashakuyakudaioto	Keishi-ka-shakuyaku-daio-To
桂枝加芍薬湯	keishikashakuyakuto	Keishi-ka-shakuyaku-To
桂枝加朮附湯	keishikajutsubuto	Keishi-ka-jutsu-bu-To
桂枝加竜骨牡蛎湯	keishikaryukotsuboreito	Keishi-ka-ryukotsu-borei-To
桂枝加苓朮附湯	keishikaryoujutsubuto	Keishi-ka-ryo-jutsu-bu-To
桂枝芍薬知母湯	keishishakuyakuchimoto	Keishi-shakuyaku-chimo-To
桂枝湯	keishito	Keishi-To
桂枝人参湯	keishininjinto	Keishi-ninjin-To

桂枝茯苓丸	keishibukuryogan	Keishi-bukuryo-Gan
桂枝茯苓丸加薏苡仁	keishibukurogankayokuinin	Keishi-bukuryo-Gan-ka-yokuinin
啓脾湯	keihito	Keihi-To
桂麻各半湯	keimakakuhanto	Kei-ma-kakuhan-To
香蘇散	kososan	Ko-so-San
五虎湯	gokoto	Goko-To
五積散	goshakusan	Goshaku-San
牛車腎気丸	goshajinkigan	Go-sha-jinki-Gan
呉茱萸湯	goshuyuto	Goshuyu-To
五淋散	gorinsan	Gorin-San
五苓散	goreisan	Go-rei-San
柴陥湯	saikanto	Sai-kan-To
柴胡加竜骨牡蛎湯	saikokaryukotsuboreito	Saiko-ka-ryukotsu-borei-To
柴胡桂枝乾姜湯	saikokeishikankyoto	Saiko-keishi-kankyo-To
柴胡桂枝湯	saikokeishito	Saiko-keishi-To
柴胡清肝湯	saikoseikanto	Saiko-seikan-To
柴朴湯	saibokuto	Sai-boku-To
柴苓湯	saireito	Sai-rei-To
三黄瀉心湯	san'oshashinto	San-o-shashin-To
酸棗仁湯	sansoninto	Sansonin-To
三物黄芩湯	sammotsuogonto	Sammotsu-ogon-To
滋陰降火湯	jiinkokato	Jiin-koka-To
滋陰至宝湯	jiinshihoto	Jiin-shiho-To
紫雲膏	shiunko	Shiun-Ko
四逆散	shgyakusan	Shigyaku-San
四君子湯	shikunshito	Shikunshi-To
梔子柏皮湯	shishihakuhito	Shishi-hakuhi-To
七物降下湯	shichimotsukokato	Shichimotsu-koka-To
四物湯	shimotsuto	Shimotsu-To
炙甘草湯	shakanzoto	Sha-kanzo-To
芍薬甘草湯	shakuyakukanzoto	Shakuyaku-kanzo-To
芍薬甘草附子湯	shakuyakukanzobushito	Shakuyaku-kanzo-bushi-To
十全大補湯	juzentaihoto	Juzen-taiho-To
十味敗毒湯	jumihaidokuto	Jumi-haidoku-To
潤腸湯	junchoto	Juncho-To
小建中湯	shokenchuto	Sho-kenchu-To
小柴胡湯	shosaikoto	Sho-saiko-To
小柴胡湯加桔梗石膏	shosaikotokakikyosekko	Sho-saiko-To-ka-kikyo-sekko

小青竜湯	shoseiryuto	Sho-seiryu-To
小半夏加茯苓湯	shohangekabukuryoto	Sho-hange-ka-bukuryo-To
消風散	shofusan	Shofu-San
升麻葛根湯	shomakakkonto	Shoma-kakkon-To
四苓湯	shireist	Shi-rei-to
辛夷清肺湯	shin'iseihaito	Shin'i-seihai-To
参蘇飲	jinsoin	JIn-so-In
神秘湯	shimpito	Shimpi-To
真武湯	shimbuto	Shimbu-To
清上防風湯	seijobofuto	Seijo-bofu-To
清暑益気湯	seishoekkito	Seisho-ekki-To
清心蓮子飲	seishinrenshiin	Seishin-renshi-In
清肺湯	seihaito	Seihai-To
川芎茶調散	senkyuchachosan	Senkyu-Cha-cho-San
疎経活血湯	sokeikakketsuto	Sokei-kakketsu-To
大黄甘草湯	daiokanzoto	Daio-kanzo-To
大黄牡丹皮湯	daiobotanpito	Daio-botampi-To
大建中湯	daikenchuto	Dai-kenchu-To
大柴胡湯	daisaikoto	Dai-saiko-To
大柴胡湯去大黄	daisaikotokyodaio	Dai-saiko-To-kyo-daio
大承気湯	daijokito	Dai-joki-To
大防風湯	daibofuto	Dai-bofu-To
竹茹温胆湯	chikujountanto	Chikujo-untan-To
治頭瘡一方	jizusoippo	JI-zuso-Ippo
治打撲一方	jidabokuippo	Ji-daboku-Ippo
調胃承気湯	choijokito	Choi-joki-To
釣藤散	chotosan	Choto-San
腸癰湯	choyoto	Choyo-To
猪苓湯	choreito	Chorei-To
猪苓湯合四物湯	choreitogoshimotsuto	Chorei-To-go-Shimotsu-To
通導散	tsudosan	Tsudo-San
桃核承気湯	tokakujokito	Tokaku-joki-To
当帰飲子	tokiinshi	Toki-Inshi
当帰建中湯	tokikenchuto	Toki-kenchu-To
当帰四逆加呉茱萸生姜湯	tokishigyakukagoshuyushokyoto	Toki-shigyaku-ka-goshuyu-shokyo-To
当帰芍薬散	tokishakuyakusan	Toki-shakuyaku-San
当帰芍薬散加附子	tokishakuyakusankabushi	Toki-shakuyaku-San-ka-bushi
当帰湯	tokito	Toki-To

二朮湯	nijutsuto	Ni-jutsu-To
二陳湯	nichinto	Ni-chin-To
女神散	nyoshinsan	Nyoshin-San
人参湯	ninjinto	Ninjin-To
人参養栄湯	ninjinyoeito	Ninjin-yoei-To
排膿散及湯	hainosankyuto	Haino-sankyu-To
麦門冬湯	bakumondoto	Bakumondo-To
八味地黄丸	hachimijiogan	Hachimi-jio-Gan
半夏厚朴湯	hangekobokuto	Hange-koboku-To
半夏瀉心湯	hangeshoshinto	Hange-shashin-To
半夏白朮天麻湯	hangebyakujutsutemmato	Hange-byakujutsu-temma-To
白虎加人参湯	byakkokaninjinto	Byakko-ka-ninjin-To
茯苓飲	bukuryoin	Bukuryo-In
茯苓飲合半夏厚朴湯	bukuryoingohangekobokuto	Bukuyo-In-go-Hange-koboku-To
附子理中湯	bushirichuto	Bushi-richu-To
平胃散	heiisan	Heii-San
防已黄耆湯	boiohito	Boi-ogi-To
防風通聖散	bofutsushosan	Bofu-tsusho-San
補中益気湯	hochuekkito	Hochu-ekki-To
麻黄湯	maoto	Mao-To
麻黄附子細辛湯	maobushisaishinto	Mao-bushi-saishin-To
麻杏甘石湯	makyokansekito	Ma-kyo-kan-seki-To
麻杏薏甘湯	makyoyokukanto	Ma-kyo-yoku-kan-To
麻子仁丸	mashiningan	Mashinin-Gan
木防已湯	mokuboito	Mokuboi-To
薏苡仁湯	yokuininto	Yokuinin-To
抑肝散	yokukansan	Yokukan-San
抑肝散加陳皮半夏	yokukansankachinpihange	Yokukan-San-ka-chimpi-hange
六君子湯	rikkunshito	Rikkunshi-To
立効散	rikkosan	Rikko-San
竜胆瀉肝湯	ryutanshakanto	Ryutan-shakan-To
苓甘姜味辛夏仁湯	ryokankyomishingeninto	Ryo-kan-kyo-mi-shin-ge-nin-To
苓姜朮甘湯	ryokyojutsukanto	Ryo-kyo-jutsu-kan-To
苓桂朮甘湯	ryokeijutsukanto	Ryo-kei-jutsu-kan-To
六味丸	rokumigan	Rokumi-Gan