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Chapter 3

Herbal Drugs in Traditional Japanese Medicine

Tsutomu Hatano

Additional information is available at the end of the chapter

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1. Introduction

Medicinal herbs are used in the context of ethnic traditions in various regions of the world. Although modern medicine, based on Western medicine, is practiced in developed countries, traditional medicine is also an important part of treatment in Asian countries.

Traditional Chinese medicine (TCM) influences traditional medicine in Asian countries as a function of the cultural and historical relationships between each country and China. That is, traditional medicine has developed in each country under the influence of TCM in the context of its own cultural background.

This chapter examines traditional Japanese medicine (TJM), an alternative form of medicine used in Japan. Although acupuncture, moxibustion, and several related medical practices also play important roles in TJM, herbal medicine, as the most characteristic treatment within TJM, is the focus of this chapter.

2. Relationship between TJM and TCM

Western medicine often regards patients as sets of individual organs, and illnesses are often attributed to pathogens or morbid organs that should be removed. However, Asian traditional medicine, including TJM and TCM, understand patients from a holistic perspective that emphasizes the importance of balancing and harmonizing the entire patient, including her or his mind and body. Asian forms of medicine explain changes in symptoms in terms of causes, and treatments are prescribed based on a view of diseases as dynamic processes [1,2].

Basic medical concepts are common to both TJM and TCM, and practitioners of these disciplines arrive at diagnoses via four basic approaches.

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1. Visual examination: Observation of the status of the face, tongue, skin, and behavior of the patient.
2. Auditory examination: Auscultation of the patient speaking, sighing and wheezing and examination of the patient's olfaction.
3. Interview: Questions posed to the patient about the history of the illness.
4. Tactile examination: Evaluation of the pulse and determination of abdominal status.

However, differences between TCM and TJM exist with regard to how each makes diagnoses and prescribes treatment.

Diagnosis in the TCM treatment involves the following steps:

1. Gathering data about symptoms to determine a diagnosis. Ba-bang-bian-zheng (in Chinese, assignment of body conditions to one of the eight principal states) is an important step in the diagnostic process of TCM and is based on discriminating between members of pairs: ying (negativity/hypo-functioning) and yang (positivity/hyper-functioning), xu (deficiency) and shi (excessiveness), han (cold/chills) and re (heat/fever), and biao (exterior) and li (interior).
2. Identifying the cause of the illness based on the theory underpinning TCM, including the five-element theory described later.
3. Determining the appropriate prescription based on the theory underpinning TCM. According to TCM, herbal prescriptions are based on imbalances in the viscera and bowels.

In contrast, TJM diagnoses, particularly those based on the Koho school, involve selecting an appropriate prescription; each prescription corresponds to specific symptoms associated with the constituents of herbal drugs. The most characteristic feature of TJM is that diagnosis is directly linked to selection of a prescription. The differences between TJM and TCM became especially pronounced during the Edo era in the 17th–19th centuries. Indeed, important diagnostic concepts often have different meanings in TJM and TCM. Thus, different uses of the concepts result in confusion, even among apprentices in TJM.

3. Short history of TJM

Drug use has long been part of the ethnic traditions in Japan, and various folk medicines have been applied in these contexts. The Geranium herb (over-ground part of *Geranium thunbergii* Sieb. et Zucc.), which is used as an anti-diarrheic, and Mallotus bark (bark of *Mallotus japonicus* Muell.-Arg.), which is used for stomach disorders, are examples of herbal drugs introduced into the Japanese Pharmacopeia (Fig. 1). The leaf of *Quercus stenophylla* (Urajiro-gashi in Japanese) is used for urinary tract calculi.

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Historical books, such as Koji-ki (Records of Ancient Matters) (712), include descriptions of the use of reed mace (*Typha* spp., Fig. 2) for injury. Koji-ki records historical matters or folklores of the prehistoric ages in Japan.

Cultural exchanges, including those involving envoys to the Tang Dynasty (7th–9th centuries), and trade with China brought various crude drugs to Japan. Some of these drugs are the "Shosoin drugs" of today.TJM was practiced by Buddhism priests during those eras.



Figure 1. Examples of plants used as Japanese folk medicines. (a) *Geranium thunbergii* Sieb. et Zucc. (family Geraniaceae), and (b) *Mallotus japonicas* Muell.-Arg. (family Euphorbiaceae)

Chinese medicine changed based on historical changes in the dynasties, and the Chinese medicine of each era, until the present one, has influenced Japanese medicine. Chinese medicine was introduced during the Yuan dynasty in Japan and was practiced by Sanki Tashiro (1465–1537) and his successors, including Dosan Manase (1507–1594), who developed the medicines. They were known as the Gosei-ho-ha (the Latter-day Medicine School). The medicine taught by this school was based on two principles [Yin (active/positive) and Yang (inactive/negative)] combined with five elements (wood, fire, earth, metal, and water). The pharmacological characteristics of the herbal/crude drugs were separated into five tastes (pungent, sweet, sour, bitter, and salty) based on the five-element theory. Other characteristics, such as emotions, which may affect illnesses, are also attributed to the five elements (Table 1) [2, 3].

A trend toward a return to the fundamentalism of Confucianism appeared in China during the Ming Dynasty (14th–17th centuries), and an analogous fundamentalism was also seen in Chinese medicine. Some leaders in this field advocated reliance on the ideas or spiritual content related to medicine in the Shokan-zatsubyo-ron (*Shang-Han-Za-Bing-Lun* in Chinese, "Treatise on Cold Damage Disorders and Accompanied Various Diseases") edited by Zhong-Jing Zhang during the Han Dynasty (BC200–AD200).



Figure 2. *Typha latifolia* L. (Typhaceae)

Element	*Mu (Wood)*	*Huo (Fire)*	*Tu (Earth)*	*Jin (Metal)*	*Shui (Water)*
Viscera	Heart	Liver	Spleen	Lung	Kidney
Bowel	Gallbladder	Small intestine	Stomach	Large intestine	Urinary bladder
Taste	Sour	Bitter	Sweet	Pungent	Salty
Emotion	Joy	Anger	Anxiety	Sorrow	Fear

Table 1. Five-element theory based on traditional Chinese medicine (TCM) and Gosei-ho-ha medicine in traditional Japanese medicine (TJM)

These ideas affected the leading physicians in Japan, who stressed that medicine in Japan should be based on Shokan-zatsubyo-ron, which was established in the Han Dynasty. Gonzan Goto (1659–1733) was such a physician, and he insisted on considering diseases to be based on ki (*qi* in Chinese) stagnation. Goto mentored many younger physicians, who were known as Koho-ha (fundamentalists). Toyo Yamawaki, one such physician, guided dissections and prepared a book entitled Zo-shi ("Records of Human Organs"), in which he clarified the differences between the actual structure of the human body and the structure depicted by TCM. Followers of this school insisted on practical evidence or actual results from medical trials. Todo Yoshimasu established a new approach to medicine based on this foundation.

4. Yoshimasu's TJM

Todo Yoshimasu established a new approach to medicine based on the notions described above. He was regarded as a highly skilled physician and contributed to new developments in the area of medical diagnosis. He stressed the importance of the abdomen, in addition to that of the radial artery pulse, in diagnosis. He actually simplified the causes of various diseases based on his unique "one-poison theory" and thereby eliminated conceptual confusion [1, 3-5].

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However, Yoshimasu's most important contribution concerned the use of herbal prescriptions. During the Edo era, Honzo-komoku (*Ban-Cao-Gang-Mu* in Chinese, "Compendium of Materia Medica") (1590, Ming Dynasty), written by Shi-Zhen Li (1518–1593), was the most authoritative book in Asia, including Japan, to describe the efficacy of herbal drugs. However, Yoshimasu decided to revise sections on the effects of herbal drugs as he thought that the descriptions in the book were useless in terms of practical clinical applications. Yoshimasu thought that the descriptions were written under the influence of delusions/superstitions based on ethnic religion.

Thus, he first addressed cases in which major prescriptions are used for Shokan-zatsubyo-ron. Shokan-zatsubyo-ron is composed of two parts, which were identified separately. Shokan-ron (*Shang-Han-Lun* in Chinese, "Treatise of Cold Damage Disorders"), which addresses acute feverish diseases and Kinki-yoryaku (*Jin-Gui-Yao-Lue* in Chinese, "Essential Prescriptions as A Treasure Box"), which addresses sub-acute and chronic diseases.

He also added discussion based on his clinical experience concerning the uses of each prescription. These were gathered in Ruiju-ho ("a classified collection of prescriptions"). In Shokan-zatsubyo-ron, the author indicated the uses of each prescription during the course of an illness. However, the author did not explain the reasons for using each prescription, but instead stated that the physician should "just use it in exemplar cases." In this way, Todo Yoshimasu clarified the actions of the prescriptions by analyzing the kind of case in which it should be used.

Yoshimasu then began to collect the herbal drugs to be used in prescriptions. He gathered descriptions of the prescriptions containing each herbal drug from Shokan-zatsubyo-ron and discussed the effects of each herbal drug based on commonalities in the properties of prescriptions containing the drug. In other words, common symptoms referenced in the descriptions of the prescriptions were regarded as related to the herbal drug that was common to the prescriptions. He learned about the efficacy of each of the herbal drugs from Shokan-zatsubyo-ron by comparing it with his clinical experience. Such knowledge was collected in Yaku-cho ("Properties of Herbal Drugs").

For example, the action of the herbal drug licorice is discussed as follows: Although licorice (root with stolon of *Glycyrrhiza uralensis* Fisch. or *G. glabra* L.) is included in many prescriptions, prescriptions containing a particularly large quantity of licorice are shakuyaku-kanzo-to ("peony and licorice combination"), kanzo-kankyo-to ("licorice and ginger combination"), kanzo-shashin-to ("pinellia and licorice combination"), and kan-baku-taiso-to ("licorice and jujube combination"). Based on the cases described in the literature that involved use of these prescriptions and on comparisons with his own clinical experience, he concluded that licorice suppressed various otherwise imminent symptoms.

He next listed the effects of each prescription based on the actions of the constituent crude drugs he had examined. These findings are summarized in the book Ho-kyoku ("The Ultimate Properties of the Prescriptions").

For example, the keishi-to ("cinnamon combination") prescription, which is composed of cinnamon (bark of *Cinnamomum cassia* Blume), peony (root of *Paeonia lactiflora* Pall.), licorice,

jujube (fruit of *Zizyphus jujuba* Mill. var. *inermis* Rehd.), and ginger (rhizome of *Zingiber officinalis* Rosc.), is used for patients with some upward streams such as hot flashes, headaches, fevers, sweats, and dislike of wind (feeling sick when exposed to wind). According to Yoshimasu, keishi-ka-kakkon-to ("cinnamon and pueraria combination"), formed by adding pueraria (root of *Pueraria lobata* Ohwi), should be used for patients with keishi-to symptoms in combination with "tension from the nape to the back," which indicated that pueraria should be added.

Another example is seen in the addition of peony (i.e., an increase in the amount of peony in keishi-to) to form keishi-ka-shakuyaku-to ("cinnamon and peony combination"). If the patient exhibited intense convulsions of the rectus abdominis in addition to the symptoms of keishi-to, a prescription with an excess amount of peony was used, as per Ho-kyoku.

In summary, Yoshimasu reorganized descriptions of the efficacy of prescriptions using the following analytical procedures:

1. Collecting information on the uses of prescriptions from Shokan-zatsubyo-ron.
2. Clarifying the efficacy of the respective herbal drugs based on the uses of the prescriptions containing those herbal drugs.
3. Identifying the effectiveness of prescriptions based on the efficacy of the constituent herbal drugs.

This simplification by Yoshimasu was quite useful for understanding the uses of herbal prescriptions in TJM today and also for clarifying the pharmacological properties of the herbal drugs constituting the prescriptions. Based on this simplification, herbal drugs can be linked to modern analyses of Oriental medicine to understand drug actions in ways that are analogous to those that enable understanding of Western medicine.

However, such a simplification ignores the notion that an illness should be understood in terms of sequential stages or states of the patient. Considering that, physicians of the Secchu (compromising) School, including Sohaku Asada (1815–1894), avoided extreme simplification and proposed that the good points of the theories underpinning both the Koho and the Gosei-ho should be used. The current major trend in TJM is based on his efforts.

5. Differences in herbal drugs used in TJM and TCM

The two forms of herbal medicine differ with respect to prescriptions and crude drugs. Many herbal drugs used in TCM are also used in TJM. However, it had been difficult to import herbal products from China to Japan during the Edo era because of the Japanese national policy of isolation. During this era, Japanese herbalists searched for plant materials that could act as alternatives to Chinese materials. Thus, the following are examples of differences between the plant materials used in TCM and TJM [6].

1. (Fig. 3a and b) Nin-jin: Japanese ginseng (chiku-setsu-nin-jin in Japanese, rhizome of *Panax japonicus* C. A. Meyer, family Araliaceae) used in TJM is much more effective

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than is Korean ginseng (ninjin in Japanese, root of *P. ginseng* C. A. Meyer, *ren-shen* in Chinese) for stomach diseases accompanied by an epigastric obstruction (shin-ka-hi, *Xin-xia-pi* in Chinese). Thus, TJM and TCM both use *P. ginseng* root as a nourishing tonic.

2. (Fig. 3c) To-ki: Root of *Angelica acutiloba* Kitagawa (or *A. acutiloba* Kitagawa var. *sugiyamae*, family Umbelliferae) is used as To-ki (for soothing pain, corresponding to dong-gui in Chinese) in TJM, whereas the root of *A. sinensis* Diels is used in TCM.

3. (Fig. 3d) Sen-kyu (Kyu-kyu): Rhizome of *Cnidium officinale* Makino (family Umbelliferae) is used as sen-kyu (Cnidium rhizome) in Japan (corresponding to *chuan-xiong* in Chinese) for soothing pain and is often used in combination with to-ki. The use of *Ligusticum chuangxiong* (family Umbelliferae) originated in TCM.



Figure 3. Examples of herbal drugs used in traditional Japanese medicine (TJM). (a) chiku-setu-nin-jin (rhizome of *Panax japonicus* C. A. Meyer), (b) nin-jin (root of *P. ginseng* C. A. Meyer), (c) to-ki (root of *Angelica acutiloba* Kitagawa), and (d) sen-kyu (rhizome of *Cnidium officinale* Makino)

4. Sai-ko: Root of *Bupleurum falcatum* L. (family Umbelliferae) is used as sai-ko (Bupleurum root), an antifebrile agent and to regulate liver functions in TJM, whereas *chai-hu*, the root of *B. chinense* DC (and *B. scorzonerifolium* Willd.) is considered a diaphoretic in TCM.

5. Ko-boku: Magnolia bark is used in both TJM and TCM for distension from the chest to the stomach that is due to a digestive organ disorder, which is often accompanied by

pain, and also for relief of bronchitis. The bark of *Magnolia obovata* Thunb. (family Magnoliaceae), regarded as wa-ko-boku (Japanese Magonolia bark), is different from the Chinese preparation (*hou-po* in Chinese) from *M. officinalis* Rehd. et Wils. and *M. officinalis* var. *biloba* Rehd. et Wills. In this case, Yoshimasu preferred the Chinese version.

6. Byaku-jutsu: Rhizomes from the following *Atractylodes* species are used for dyspepsia. That derived from *Atractylodes japonica* Koidz. ex Kitam. (family Compositae) is regarded as wa-byaku-jutsu (Japanese Atractylodes rhizome). In contrast, kara-byaku-jutsu (Chinese Atractylodes rhizome, *bai-zhu* in Chinese) is derived from *A. macrocephala* Koidz. (=*A. ovata* DC.). The latter is used in both China and Japan.

7. O-ren: Rhizome derived from the following *Coptis* species is used to eliminate fever of the upper body, particularly in the heart. *Coptis japonica* Makino (family Ranunculaceae) is cultivated in Japan, and its rhizome, particularly that from Ishikawa Prefecture has been used since the Edo era. In contrast, Chinese products, used in both in China (*huang-lian* in Cinese) and Japan, are derived from *C. chinensis* Franchet, *C. deltoidea* C. Y. Cheng, and *C. teeta* Wallich.

8. San-sho: Fruit of *Zanthoxylum piperitum* DC. (family Rutaceae) is known as "Japanese pepper," and its peel is used for dyspepsia in TJM. *Z. bugeanum* Maxim. or *Z. simulans* Hance are the source plants of Sichuan pepper (*hua-jiao* or *chuan-jiao* in Chinese), and they are used in analogous ways in TCM. However, they are not used for medicinal purpose in Japan.

9. Bo-fu: Root (including rhizome) of *Saposhnikovia divaricata* Schischk. (family Umbelliferae) is used for fever, pain, and spasms in TJM and TCM (*fang-feng* in Chinese). The root (with rhizome) of *Glehnia littoralis* Fr. Scmidt ex Miq. (family Umbelliferae) was developed as a subsitute for bo-fu in Japan and is called hama-bo-fu in Japanese. In contrast, *G. littoralis* is regarded as *bei-sha-shen* in China, and the root is used for coughs.

10. In-chin-ko: Spike composed of many minor flowers of *Artemisia capillaris* Thunb. (family Compositae) is used for thirst and jaundice in TJM, whereas young shoots of this plant are used for the same purpose under the name of *yin-chen* in China.

These differences should be understood when these herbal drugs are used clinically and studied in research settings.

6. Constituents of herbal drugs used in TJM

This section discusses studies on the constituents of the herbal drugs that are used in TJM and in our laboratory. Yoshimasu's work on the practical aspects of herbal drugs is quite useful for researchers attempting to understand the uses of herbal drugs in TJM, and the researchers in our laboratory are searching for new constituents based on such materials rather than considering the implications of the complex theories underlying TCM.

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6.1. Tannins and related compounds: Major constituents of Japanese folk medicines or TJM

6.1.1. Hydrolyzable tannins of Geranium thunbergii

Hydrolyzable tannins are esters of galloyl and related polyphenolic acyl groups with glucose or some other sugars/polyalcohols. Although various types of hydrolyzable tannins have been found in plants, geraniin (**1**) is a representative one among them [7]. One of the most important herbal drugs in Japan is the geranium herb, the overground parts of *G. thunbergii*. The main constituent is crystalline tannin geraniin (**1**), and the structure containing a dehydrohexahydroxydiphenoyl group (**1'**) was reported in 1977 [8]. Although this compound equilibrates in a mixture, the structural factor forming the mixture was not clarified at that time. Detailed analysis with ^{1}H and ^{13}C nuclear magnetic resonance spectra revealed that it forms a mixture of six-membered (**1a**) and five-membered hemi-ketal structures (**1b**) (Fig. 4) [9]. An X-ray analysis of crystalline geraniin revealed the **1a** form with seven molecules of water [10].

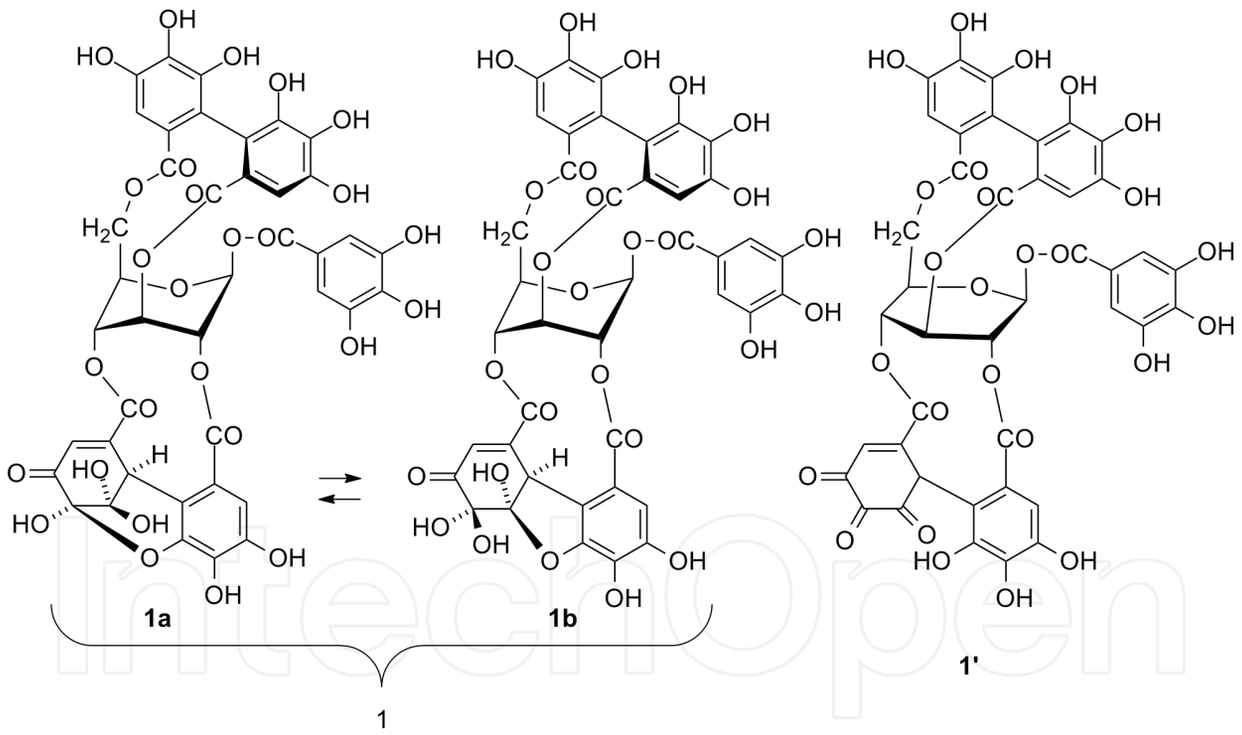


Figure 4. Structure of geraniin (**1**) forming an equilibrium mixture of six-membered hemi-ketal (**1a**) and five-membered hemi-ketal (**1b**) forms. Structure **1** was assigned to geraniin, firstly.

Further examination of this source plant revealed the presence of the co-existing hydrolyzable tannins furosin; didehydrogeraniin; furosinin [11]; geraniinic acids B and C; phyllunthusiins B, C, E, and F [12]; and acalyphidin M1 [13]. However, several compounds are formed after linking with ascorbic acid in the plant; these include ascorgeraniin (= elaeocarpusin) (**2**) [14,15] and furosonin (**3**) [13] (Fig. 5). We also found that geraniin is

easily converted to corilagin (**4**) and repandusinic acid A (**5**) (Fig. 5) under near physiological conditions (pH 7.4) [13].

Because some hydrolyzable tannins show noticeable effects on β-lactam resistance of methicillin-resistant *Staphylococcus aureus* (MRSA) [16-18], we examined the effects of several available tannins, and repandusinic acid A and corilagin showed a noticeable suppressive effect on oxacillin resistance of MRSA [13].

The presence of tannins with analogous structures including mallotusinic acid (**6**) in *Mallotus japonicus* is shown in Fig. 5 [8,19].

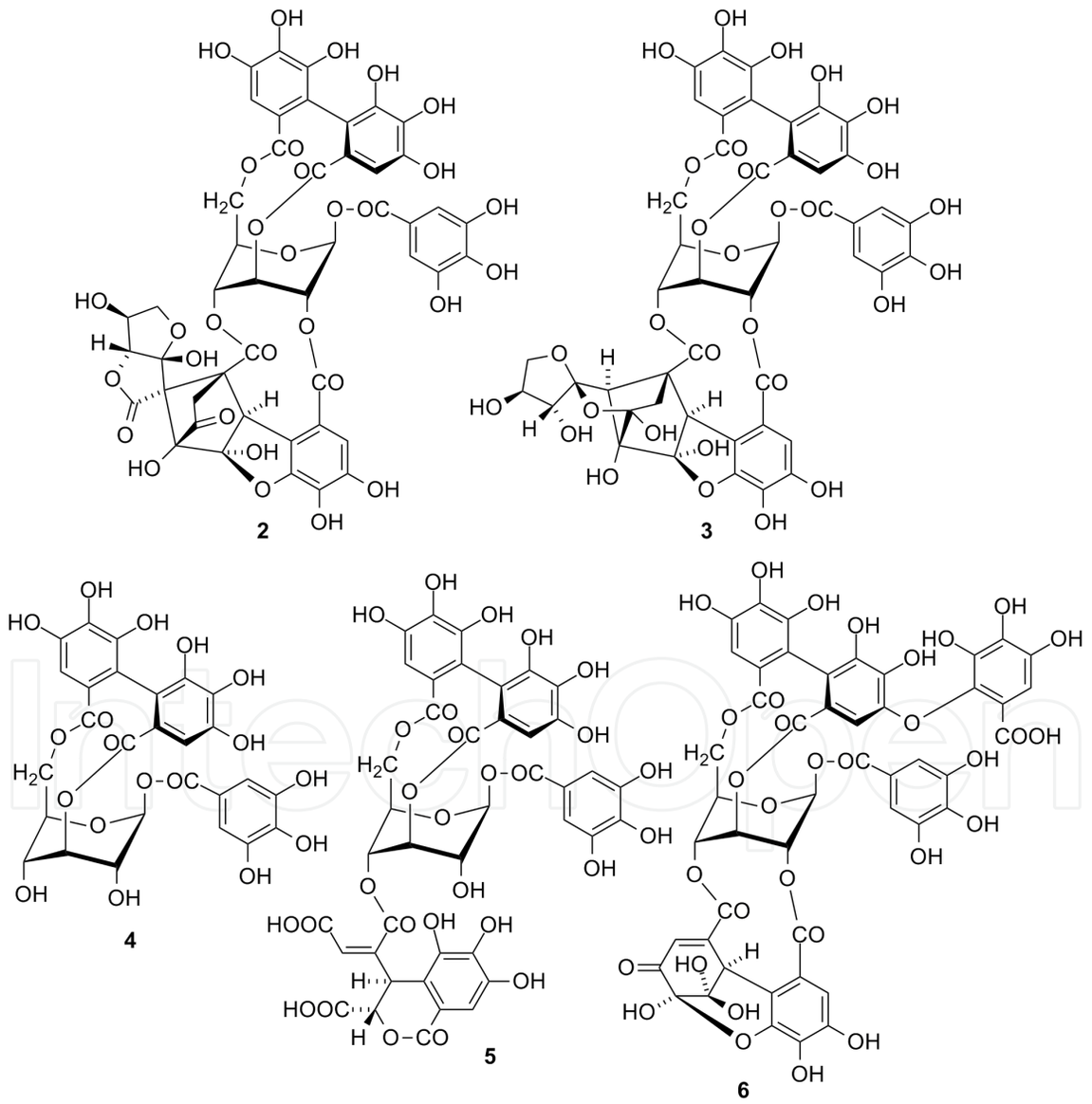


Figure 5. Tannins structurally related to geraniin. Compound 6 was isolated from *M. japonicus*.

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6.1.2. Proanthocyanidins of Saxifraga stolonifera

Saxifraga stolonifera Curtis (family Saxifragaceae) is used as an ethnic medicine in Japan and China. A study of the constituents of this plant revealed that the major polyphenolic constituents of the overground part are proanthocyanidins, which are highly galloylated at O-3 of the respective flavan [(-)-epicatechin unit] in addition to 11-*O*-galloylbergenin (7) [20,21]. An oligomeric proanthocyanidin fraction, Ss-tannin-1 (8), with a molecular weight of 2300 shows potent antioxidant effects on lipid peroxidation in rat mitochondria induced by adenosine diphosphate (ADP) and ascorbic acid, and on that in rat microsomes induced by ADP and nicotinamide adenine dinucleotide phosphate [21]. Among the isolated constituents from this plant (Fig. 6), the administration of 3-*O*-galloylepicatechin-(4β→8)- 3-*O*-galloylepicatechin (**9**) and 3-*O*-galloylepicatechin-(4β→6)-3-*O*-galloylepicatechin (**10**) results in a noticeable increase in the life span of mice after inoculation of Sarcoma-180 [22].

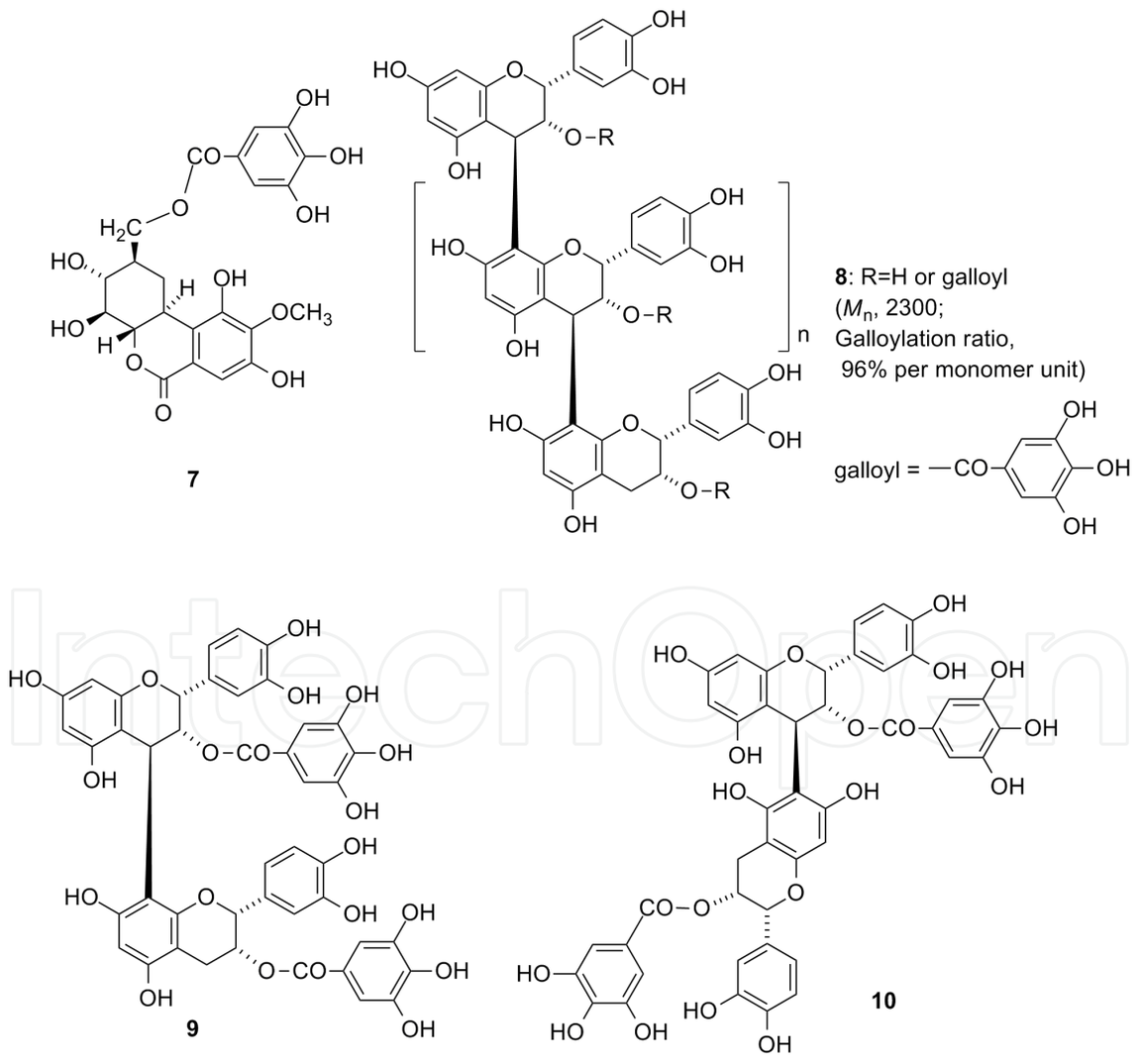
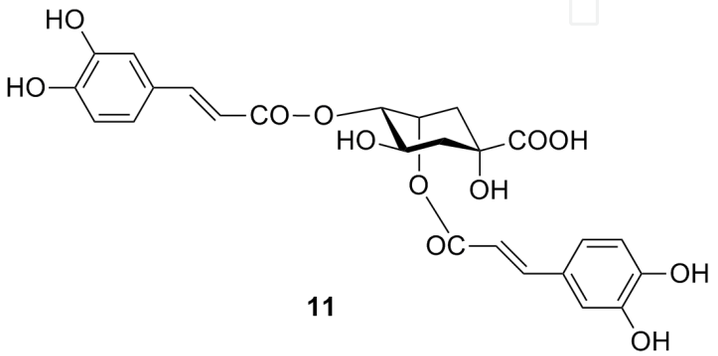


Figure 6. Structures of proanthocyanidins obtained from *Saxifraga stolonifera*.

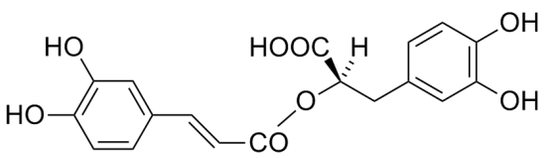
6.2. Polyphenolics in herbal drugs used in TCM and TJM

6.2.1. Caffeic acid derivatives of Artemisia leaf and Perilla herb

The leaves of *Artemisia princeps* Pamp. or *A. montana* Pamp. (family Compositae) are used as gai-yo to stop bleeding and blood circulation difficulties in Japan, and the corresponding *A. argyi* Levl. et Vant. is used as *ai-ye* in China. Investigations of the constituents of the leaf revealed that dicaffeoylquinic acids [particularly 3,5-di-*O*-caffeoylquinic acid (**11**)] are the major constituents of *A. princeps* and *A. montana* [23] (Fig. 7).



11



12

Figure 7. Structures of caffeic acid derivatives found in Artemisia leaf and Perilla herb

The aboveground part of *Perilla frutescens* Brit. var. *acuta* Kudo (or *P. frutescens* Brit. var. *crispa* Decne., family Labiatae) is used as so-yo or shi-so-yo for regulating energy flow or treating bronchial asthma and bronchitis in TJM and is used in analogous ways in TCM under the name *zi-su-ye*. Our study on the leaf constituents revealed that rosmarinic acid (an ester of caffeic acid with 3,4-dihydroxyphenyllactic acid, **12**) is a major constituent and showed that instability during the drying process of the leaves should be considered when using this herbal drug [24] (Fig. 7).

Caffeoylquinic acids show inhibitory effects on histamine release from rat peritoneal mast cells [25,26] and also on the formation of leukotriene B4 (LTB4) in human polymorphonuclear leukocytes (PMN-L). Rosmarinic acid shows a strong inhibitory effect on the formation of 5-hydroxy-6,8,11,14-eicosatetraenoic acid and LTB4 in PMN-L [25]. Because arachidonate metabolism is related to allergic inflammation and asthma, these results suggest that the effects of these constituents may participate in the actions of the herbal drugs containing them.

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6.2.2. Flavonoids and 3-arylcoumarins from licorice

Licorice, the root (with stolon) of *Glycyrrhiza uralensis* and *G. glabra*, is widely applied in various TCM and TJM prescriptions. Although glychyrrhizin and related triterpene glycosides are regarded as the major constituents, Japanese researchers have reported on the importance of flavonoids and related phenolics [27].

Our investigation of licorice constituents revealed the inhibitory effects of flavonoids, including new ones, on xanthine oxidase [28] and monoamine oxidase [29]. Several also effective against the cytopathic effects of human immunodeficiency virus (HIV). The inhibitory effects of those constituents on giant cell formation induced by HIV were constituents are examined using a cell line sensitive to the cytopathic activity of HIV. Licochalcone A (**13**), isolicoflavonol (**14**), glycycoumarin (**15**), glycyrrhisoflavone (**16**), and licopyranocoumarin (**17**) inhibited at a 1:25 concentration (20 μg/ml) relative to that of glychyrrhiziin showed an analogous effect (500 μg/ml) (Fig. 8) [30]. Further investigation revealed that the HIV promoter activity induced by 12-O-tetradecanoylphorbol-13-*O*-acetate is suppressed by licorice phenolics. Those including glycycoumarin, and tetrahydroxymethocychalcone showed a specific suppressive effect on the HIV promoter; this effect was in contrast to its effects on the cytomegalovirus promoter [31].

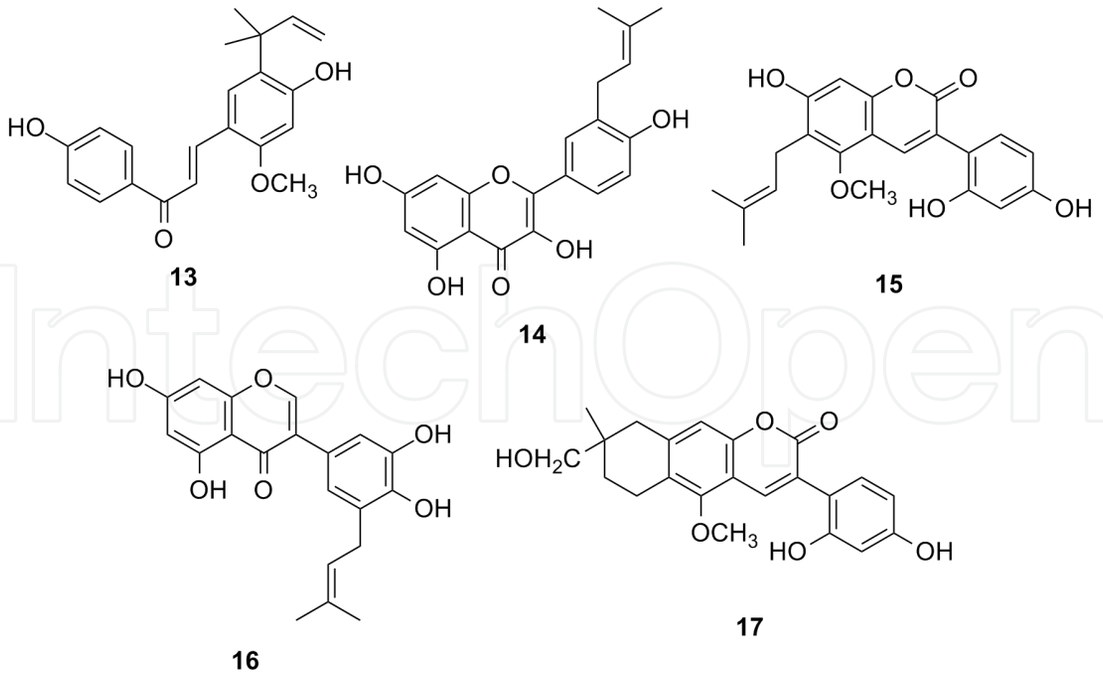


Figure 8. Structures of licorice phenolics that suppress human immunodeficiency virus (HIV) cytopathic effects.

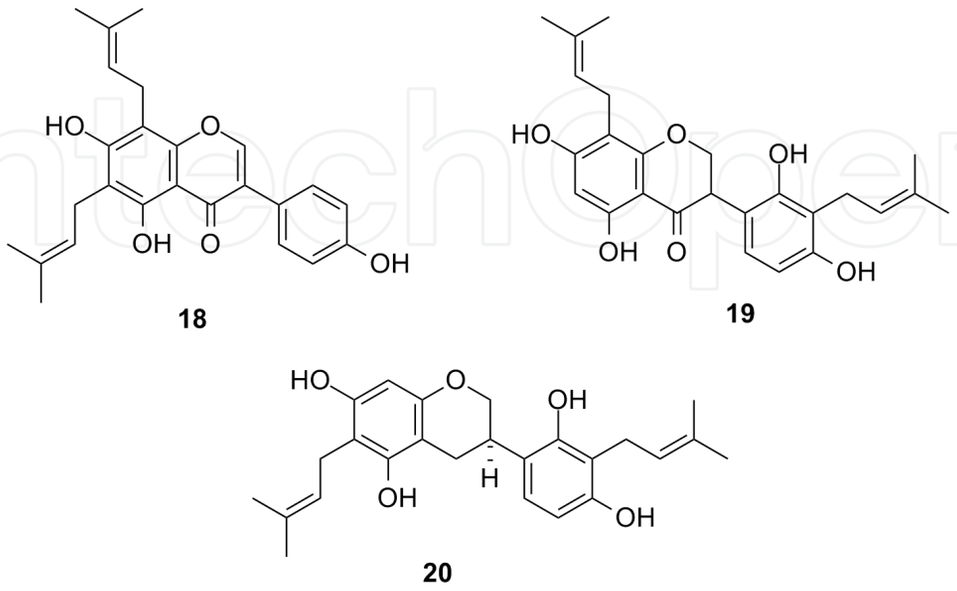


Figure 9. Licorice phenolics that show the most potent antibacterial effects on methicillin-resistant *Staphylococcus aureus* (MRSA) (compounds **18** and **19**) and noticeable suppressive effects on oxacillin resistance of MRSA.

Minimum inhibitory concentration (MIC) of oxacillin (μg/ml)					
Licoricidin	MRSA strains				MSSA
concentration	OM481	OM505	OM584	OM623	209P
None	512	64	256	512	<0.5
8 μg/ml	<0.5	<0.5	<0.5	<0.5	<0.5
4 μg/ml	16	8	16	16	<0.5

Table 2. Effect of licoricidin on the antibacterial activity of oxacillin.

The effects of licorice phenolics on MRSA were also investigated. Two flavonoids, 8-(γ,γ-dimethyally)-wighteone (**18**) and 3′-(γ,γ-dimethylallyl)-kievitone (**19**) showed their most potent antibacterial effects at a minimum inhibitory concentration (MIC) of 8 μg/ml. Furthermore, licoricidin (**20**) induced an effective decrease in oxacillin MIC (Fig. 9, Table 2) [32].

These findings suggest that licorice is a useful herbal source for the development of the primary constituents of the compounds used in modern medicine.

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6.3. Ameliorating effect of extracts from Polygala root and Uncaria hook on scopolamine-induced impairment of spatial cognition

It is very important to develop new drugs for the treatment of patients with dementia as the number of individuals with this condition is now rapidly increasing due to the increase in the elderly population. The root of *Polygala enuifolia* Willd. (on-ji in Japanese and *yuan-zhi* in Chinese; family Polygalaceae) is used in TJM and TCM prescriptions for forgetfulness, neurasthenia, and insomnia. An investigation to identify the constituents of this herbal drug that are effective for impaired spatial cognition was conducted in rats using an eight-arm radial maze task. This task is useful for discriminating shshort-term memory from long-term one. The results showed that sinapic acid had the most potent effect among the cinnamic acid derivatives examined. Sinapoyl derivatives such as 3,6'di-*O*-sinapoylsucrose (21) are contained in this plant [33]. Analogous results have been obtained for phenolic constituents, including (+)-catechin of Uncaria hook (stem with hooks of *Uncaria rhynchophylla* Miq., *U. sinensis* Havil., and *U. macrophylla* Wall.; cho-to-ko in Japanese, *gou-teng* in Chinese; family Rubiaceae) [34]. Further studies of the adsorption/metabolism process and the mechanisms are required.

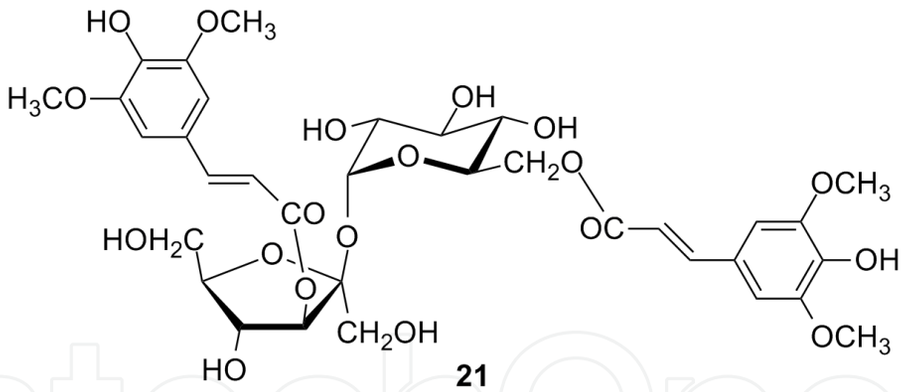


Figure 10. Structure of 3',6-di-O-sinapoyl-sucrose contained in *Polygala tenuifolia* root.

7. Conclusion

Explanations of the pharmacological properties of herbal drugs based on TJM concepts have been useful for identifying new compounds with various structures. These explanations are also useful for understanding the roles of herbal prescriptions and applications in modern medicine. Modern medicine should consider some of the basic concepts of traditional medicine as they may contain wisdom.

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