

# Reconsideration of Japanese Traditional Herbal Medicine: New Field of Research and Clinical Medicine

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**Abstract:** Japanese traditional herbal medicine, which is known as “*Kampo*”, has received increasing attention as an alternative approach to the treatment of various diseases. In order to safely and effectively apply *Kampo*, it is essential to understand oriental diagnostics. Herein, an outline of such diagnostics is introduced, and current trends in *Kampo* research are reviewed.

**Keywords:** Oren-gedoku-to, Yoku-kan-san, Hange-shashin-to, Ginseng, Onji, Syakuyaku-kanzo-to, Sho-saiko-to, oriental diagnostics.

## INTRODUCTION

Asian traditional prescriptions consist of oriental herbs used in China for more than 2000 years, which has been modified in recent centuries in Japan and became to be called as “*Kampo*”. The Japanese Ministry of Health has approved more than 130 *Kampo* prescriptions for clinical use, and Japan is the only country in the world in which clinicians with a Western medical degree practice oriental herbal medicine as well as traditional medicine. In Japan, a standardized manufacturing process and the quality control of herbal prescriptions are maintained, which has led to the systematization of oriental diagnostics.

Although the main stream of medical treatment in Japan is generally based on the Western approach, *Kampo* medicine has received increasing attention as an alternative source of treatment for various diseases. One reason for this increase is that *Kampo* medicine exerts fewer adverse effects than do the Western counterparts, and *Kampo* has at times been found to be superior to Western medicine, in particular in cases involving certain hormone-related diseases such as dysmenorrhea and disorders associated with climacteric symptoms. However, *Kampo* has been considered by some to be less effective than Western medicine, and has also wrongly been viewed as harmful on certain occasions. For example, Asian ginseng, which is a main ingredient in *Kampo* medicine, is known as an effective alternative medicine with various indications even in the Western world; however, several reports have noted that the efficacy of Asian ginseng has not been established for any of these indications. Because Asian ginseng is an oriental herbal prescription based on oriental diagnostics, it is possible that it could cause harmful effects, or else be of no benefit, when not prescribed according to oriental diagnostics. It is thus essential that *Kampo* medicine be applied in a safe and effective manner, which would take into account that the

prescribing clinicians have a thorough understanding of oriental diagnostics.

Since *Kampo* medicine and Western medicine each have their own unique features, their complementary clinical application would ideally make up for defects in each respective approach. In spite of differences in these two diagnostic systems, the efficacy of *Kampo* medicine has been demonstrated in recent studies; several reports have already reviewed *Kampo*'s efficacy in the treatment of certain diseases [1-3]. However, it remains difficult to make generalizations about oriental diagnostics. In this report, we provide an outline of how to apply *Kampo* prescriptions in a manner that is based on oriental diagnostics, and we review current progress in the field of research investigating *Kampo* medicine.

## CONCEPT OF KAMPO

### Characteristics

As contrast to Western medicine, which is based on pathogen identification and the removal of the cause of a disease, the therapeutic approach in the case of *Kampo* focuses on enhancing the human body's resistance to diseases, and thereby on prevention, by improving the connections among self-controlled systems. In the absence of Western medicine, there is some danger of overlooking critical pathogens, such as viruses, and cancers; however, *Kampo* can be applied to treat any disease of unknown etiology. This difference does not imply that *Kampo* is a panacea, but it does imply that *Kampo* has the possibility to alleviate suffering in cases of incurable disease. In addition, the administration of *Kampo* treatment may avoid some of the adverse effects associated with certain synthetically derived ingredients in Western drugs.

The approach to the medical exam in those seeking *Kampo* treatment is based on a differentiation of symptoms, which is used to clarify what is wrong in a self-controlled system. Whereas Western medicine focuses on separate parts of the body, *Kampo* regards each human being as a complete and self-controlled unit, which cannot be separated into small parts. For example, *Kampo* never distinguishes between psychiatric symptoms and physical symptoms,

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because in the *Kampo* approach, every disease is considered as psychosomatic in origin, and herbs are believed to affect both the psyche and the soma equally. Therefore, *Kampo* treatment is focused on the patient, who presently finds him or herself in an unhealthy condition, rather than on the name of a disease. For example, if someone lives well no symptoms, then that person is regarded from the *Kampo* point of view as being healthy, whether or not that person has signs of illness, as defined by Western medicine, such as hypertension or hyperlipidemia.

## Theory

Two basic theories are required to practice *Kampo* medicine.

### 1. Philosophy (Yin-Yang Theory)

To account for homeostasis, *Yin-Yang* theory originated in China, and is used in *Kampo*. Originally, “*Yin*” and “*Yang*” denoted “negative” and “positive”, and the relationship between them indicated “opposites”. The ancient Chinese believed that *Yin-Yang* is defined relatively, i.e., not absolutely, and that everything in the universe can be divided into *Yin* and *Yang*, or can be seen as having two sides. This theory can be applied to many situations: dark and light, insufficient and sufficient, external and internal, cold and hot, etc. Consistent with the modern view of homeostasis, *Yin* and *Yang* are complementary, approaching such perspectives as those implied by “*Yang* declines and *Yin* rises” or “An increase in *Yang* produces a decrease in *Yin*” [4].

### 2. Components (Ki-Ketsu-Sui Theory)

In *Kampo*, human bodily functions are defined as being regulated by three essential components, “*Ki*” (originally denoting a kind of “mind” in Japanese), “*Ketsu*” (“blood” in Japanese), and “*Sui*” (“water” in Japanese). All unhealthy conditions are explained by impairments in a combination of these three components.

The first component, *Ki*, indicates the source of all energy, including physical and mental power. *Ki* circulates throughout the body and helps to smooth the flow of *Ketsu* and *Sui*. Any deficiency or congestion of *Ki* will lead not only to an unusual mental state (e.g., depression, nervousness, or irritability), but also to an abnormal physical condition (e.g., fatigue, insomnia, inflammatory response, or excessive sweating), and will often result in an imbalance in *Ketsu* and/or *Sui*. Likewise, if an unhealthy *Ketsu*- or *Sui*-based condition becomes prolonged, then *Ki* will be impaired as a consequence.

The second component, *Ketsu*, is almost equivalent to the blood and circulatory system. Disturbances in *Ketsu* are classified as either a deficiency or a congestion. A deficiency in *Ketsu* is seen in cases of anemia, and is thought to sometimes cause a sharp and subacute pain in some part of body (e.g., stomachache or headache). On the other hand, a congestion of *Ketsu* is seen in menopausal syndrome, dysmenorrhea, hemorrhoids, and similar ailments, and is regarded as occasionally causing a dull and subchronic pain in some part of the body (e.g., lumbago or headache). Symptoms caused by a “deficiency” or “congestion” often overlap with each other, because a deficiency of blood also

results in a stagnation or an imbalance. Necessarily, *Ketsu* has a close relationship with *Sui*; for example, loss of blood will lead to thirst. A perhaps unexpected example of *Ketsu* congestion would be the type of acne that tends to appear along the facial outline. Therefore, chronic recurrent acne is often cured when there is a recovery from dysmenorrhea due to an amelioration of blood congestion.

The third component, *Sui*, indicates all of the body fluids except for the blood. In other words, *Sui* includes such components as nasal mucus, gastric juices, and interstitial fluid. A typical symptom of *Sui* congestion might be identified as a splashing sound in the stomach made by shaking the abdomen upon abdominal examination. In such a case, someone with *Sui* congestion will tend to feel like something heavy is lying on the stomach. Impairments of *Sui* balance can express themselves in a number of ways, for example, as edema, diarrhea, headache, and dizziness.

The three essential components mentioned above are thought to interact with each other to maintain the homeostasis of the human body. This philosophy, which is referred to in the *Kampo* tradition as “*Ki-Ketsu-Sui*” theory, is applied to all diseases and it provides a good explanation for diseases, especially those in which psychiatric factors strongly affect the physical symptoms. As mentioned above, a major point of *Kampo* treatment is that single prescription often cures a number of different and uncomfortable symptoms, without inducing side effects, *via* the rectification of a *Ki-Ketsu-Sui* imbalance.

## Diagnosis

*Kampo* diagnosis is made by listening to a patient’s complaints and by performing a set of traditional physical examinations focusing on pulse, abdominal signs, and the appearance of the tongue, as well as by general inspection and inquiry. In particular, the examination of the abdominal signs was uniquely developed in Japan and is regarded as the most important component in understanding a patient’s condition [5]. *Kampo* prescriptions are used to correct *Yin-Yang* and *Ki-Ketsu-Sui* imbalances in the human body.

## SCIENTIFIC APPROACH TO KAMPO

The mechanism by which *Kampo* exerts its therapeutic effect has not been elucidated scientifically, as it is derived from a non-Western diagnostic system, and because all prescriptions are created by different combinations of herbs. However, an increasing number of basic studies have identified the active principle that renders these prescriptions effective.

### Sho-Saiko-To

*Sho-saiko-to* is the most well-known *Kampo* medicine and has been widely used for the treatment of various inflammatory disorders such as chronic hepatitis, bronchitis, the common cold, pneumonitis, and enterogastritis. Long-term administration of *Sho-saiko-to* has been used to treat approximately one million patients with chronic viral liver diseases, in order to reverse liver dysfunction and to prevent progression to liver fibrosis and carcinogenesis [6]. *Sho-saiko-to* is prepared from the hot water extraction of seven raw materials (Bupleurum Radix, Pinelliae Tuber, Scutellariae Radix, Zizyphi Fructus, Ginseng Radix,

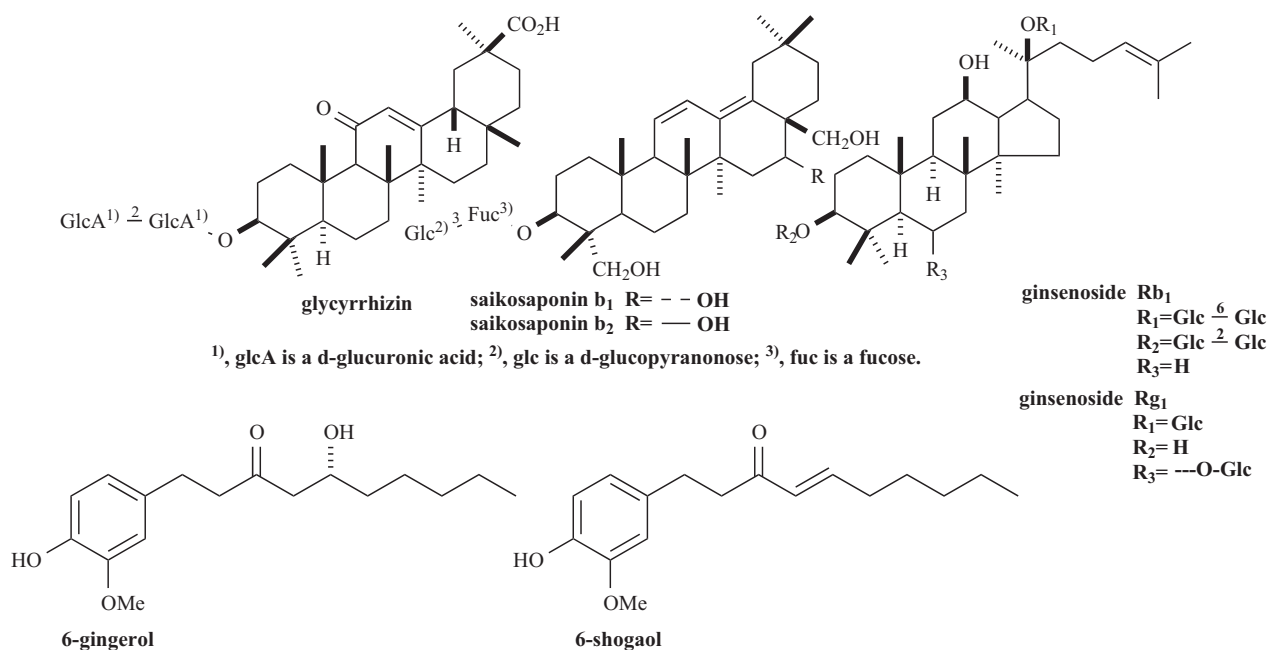


Fig. (1). Structures of the detected compounds in Sho-saiko-to.

Glycyrrhizae Radix, and Zingiberis Rhizoma). This extraction contains various classes of active compounds and 8 structures have been detected, as shown in Fig. 1 [7].

The effects of *Sho-saiko-to* on the activity of cytochrome P450 (CYP) 1A2, CYP3A, and xanthine oxidase (XO) were assessed by studying 26 healthy subjects. It was concluded that *Sho-saiko-to* reduces CYP1A2 and XO activity in humans [8]. In rats, *Sho-saiko-to* led to the decreased expression of type III procollagen 1 mRNA in the liver and to decreased proliferation of activated stellate cells, which in turn led to a reduction in fibrosis [9]. *In vitro*, *Sho-saiko-to* led to the increased production of interferon [10] and to the induction of interleukin 10 [11].

*Sho-saiko-to* has been shown to improve serum liver biochemistry levels in patients with chronic active hepatitis [12] and increase the clearance of hepatitis B envelope antigen in children with chronic hepatitis B [13]. In a prospective randomized study involving 260 patients with cirrhosis, *Sho-saiko-to* administration appeared to help prevent the development of hepatocellular carcinoma, especially in patients who were negative for hepatitis B surface antigen [14]. However, this study was not conducted in a blinded manner, and the control group did not receive treatment with placebo.

### Syakuyaku-Kanzo-To

*Syakuyaku-kanzo-to* is a basic *Kampo* prescription that is composed of only two materials (Paeoniae Radix and Glycyrrhizae Radix) and both of them are considered as active ingredients. It is widely used to relieve certain types of "traction pain" such as stomach cramps, muscle cramps [15,16,17], and colic caused by calculus. Glycyrrhizae Radix is also included in *Sho-saiko-to* and the structure of Glycyrrhizin (the active ingredient of Glycyrrhizae Radix) was already mentioned above. In *Syakuyaku-kanzo-to*, Paeoniae Radix is thought to be the main active component; Fig. 2 shows its structure [18].

In addition, it has been reported that *Syakuyaku-kanzo-to* exerts effects on gonadal hormones. *Syakuyaku-kanzo-to* decreases serum testosterone levels in androgen-sterilized rats, but causes no changes in serum testosterone, LH, or FSH levels in oophorectomized rats. These findings suggest that the mechanism of action of *Syakuyaku-kanzo-to* in terms of its ability to lower serum testosterone levels is that it directly affects the ovary, stimulating aromatase activity, resulting in a reduction in testosterone secretion [19]. *Syakuyaku-kanzo-to* treatment has been associated with a significantly low incidence of adenomyosis in an experimental animal model using an SHN strain of mice; and this approach is thus considered to be a useful tool in the treatment of uterine adenomyosis [20]. *Syakuyaku-kanzo-to* treatment is effective at treating neuroleptic-induced hyperprolactinemia [21] and risperidone-induced amenorrhea [22].

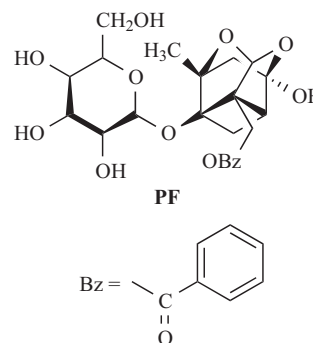


Fig. (2). Structure of Paeoniflorin (PF), active component of *Syakuyaku-kanzo-to*.

The list below describes the active ingredients isolated thus far from individual herbs.

### Onji

*Onji* (*Polygala tenuifolia*) is a component included in some prescriptions such as Kami-kihi-to, Kihi-to, and

Ninjin-Yoei-to. It is regarded to have a sedative as well as anti-inflammatory effect. As mentioned above, the impairment of *Ki* occasionally causes both mental and physical symptoms. Therefore, it is reasonable to assume that *Onji* exerts effects on both anxiety and inflammation. In clinical practice, *Onji* has been primarily reserved for treating insomnia, and palpitations accompanied by anxiety, restlessness, and disorientation [23]. The active ingredient of *Onji* is 3,4,5-trimethoxycinnamic acid (TMCA, Fig. 3) and it exerts its anti-stress effects by the suppression of norepinephrine in the locus coeruleus [24].

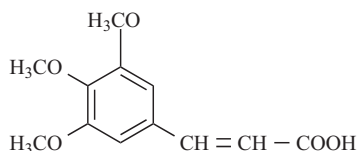


Fig. (3). Chemical Structure of TMCA.

### Ginseng (Asian Ginseng)

According to a systematic review of randomized clinical trials, it was concluded that the efficacy of *Ginseng* has not yet been established beyond reasonable doubt for any of the stated indications [25]. Nevertheless, *Ginseng* is included in the Pharmacopoeias of several countries, such as China, Germany, and the UK [26], and it remains one of the most popular herbal remedies in the U.S. The reason why *Ginseng* has been associated with such a contradictory results is most likely that it is administered regardless of a *Kampo* diagnosis. *Ginseng* should be taken by patients who are considered according to oriental diagnostics to have a “cold” intestine. From the perspective of *Yin-Yang* theory, the human body is divided into two sides (i.e., the inside and outside), and the condition of each physical part is compared to that of thermal energy i.e., either a shortage or an excess of thermal energy causes dysfunction. In *Kampo* medicine, *Ginseng* is thought to warm the internal human environment (intestine) as a therapeutic effect. According to this line of reasoning, *Ginseng* may in fact be harmful if administered to patients who have intestinal problems caused by an excess of thermal energy.

The active ingredients of *Ginseng* are the Ginsenosides. Ginsenosides are thirty carbon derivatives of the triterpenoid dammarane. They have a hydrophobic, four-ring, steroid-like structure with attached hydrophilic sugar moieties. About 30 different types of ginsenosides have been isolated and identified from the root of *Panax Ginseng*. Each of these types has at least three side chains (i.e., on carbon-3, -6, and -20) which are either free or bound to monomeric, dimeric, or trimeric sugars. The basic structures of Ginsenosides are shown in Fig. 1.

In addition to the above mentioned prescriptions, some *Kampo* prescriptions have been scientifically shown to exert therapeutic effects, although the active principles of these prescriptions remain unclear at present. Due to space limitations, only three examples are provided below.

### Hange-Shashin-To

*Hange-shashin-to* is primarily used to treat inflammatory or ulcerative gastrointestinal diseases, such as heartburn,

diarrhea, and stomatitis. It is prepared from seven herbs, *Pinelliae tuber*, *Scutellariae radix*, *Zingiberis rhizoma*, *Ginseng radix*, *Glycyrrhizae radix*, *Zizyphi fructus*, and *Coptidis rhizoma*. *Hange-shashin-to* has been shown to effectively prevent irinotecan-induced delayed diarrhea, both in animal experiments [27] and in a randomized study of patients with advanced non-small-cell lung cancer [28].

### Yoku-Kan-San

*Yoku-kan-san* is composed of seven herbs (*Angelicae Radix*, *Atractylodis Lanceae Rhizoma*, *Bupleuri Radix*, *Poria*, *Glycyrrhizae Radix*, *Cnidii Rhizoma*, and *Uncariae Uncis Cum Ramulus*) and has been used as a treatment for insomnia [29] and irritability. Especially in the case of infants, this has been found to be a useful treatment for screaming attacks, sleep terrors, and hypnic myoclonia. *Yoku-kan-san* is also effective for the treatment of tinnitus in patients with undifferentiated somatoform disorder complicated with headaches and insomnia [30].

### Oren-Gedoku-To

*Oren-gedoku-to* consists of 4 herbs including *Coptidis Rhizoma*, *Scutellariae Radix*, *Phellodendri Cortex*, and *Gardeniae Fructus*. In ancient times, this treatment was used in soldiers before battle, both to calm their minds and reduce their anger, as well as to prevent excessive bleeding. As might be expected from its history, *Oren-gedoku-to* has come to be used for the treatment of nosebleed, hypertension, irritation, and face flushing, as well as for that of inflammatory diseases such as gastritis. In an experimental rat model, *Oren-gedoku-to* has been shown to have a preventive effect against the development of stress-induced acute gastric mucosal lesions [31]. In humans, the ingestion of *Oren-gedoku-to* has been shown to significantly reduce the susceptibility of red blood cells (RBCs) to hemolysis and to exert protective effects on the RBC membrane from free-radical attack [32].

### FUTURE PROSPECTS

The *Kampo* prescriptions introduced here represent but a small part of *Kampo* medicine. In Japan, *Kampo* had been used to treat all diseases encountered thus far. Several hundred years ago, when Western medicine was introduced from Europe, *Kampo* treatment was practiced based on oriental diagnostics. Today, *Kampo* is still considered to be very useful, especially in those cases in which Western medicine has not been shown to be effective. Therefore, it is hoped that the effectiveness of each *Kampo* prescription will eventually be demonstrated by further controlled clinical and cell biological studies, and that *Kampo* will be used in combination with Western medicine in the future.

### ABBREVIATIONS

CYP	=	Cytochrome P450
XO	=	Xanthine oxidase
PF	=	Paeoniflorin
LH	=	Luteinizing hormone
FSH	=	Follicle-stimulating hormone
TMCA	=	Trimethoxycinnamic acid

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