Pharmacological characteristics of Kampo medicine as a mixture of constituents and ingredients

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ABSTRACT: Herbal medicine in Japan is termed as Kampo medicine, which is derived from traditional Chinese medicine. Shakuyakukanzoto (Shao-Yao-Gan-Cao-Tang) as a kind of Kampo formulations is composed of just two components; *Paeoniae Radix* and *Glycyrrhizae Radix*, which produced marked relaxation of intestinal tract. Mokuboito (Mu-Fang-Ji-Tang) inhibited cardiac ionic channel currents, and as a mixture also produced great vasodilatation. Sinomenine (a main ingredient of Mokuboito) as a single compound also caused the vasodilatation, but decreased it along with ageing. Gypsum containing in Mokuboito and Chotosan (Diao-Teng-San) caused more marked effects, as compared with those without Gypsum. On the other hand, Rokumigan (Liu-Wei-Wan), Hachimijigogan (Ba-Wei-Di-Huang-Wan) and Goshajinkigan (Niu-Che-Shen-Qi-Wan) increase in order the number of contained ingredients. The formulations with more herbs (ingredients) produced much more effective actions on rat aorta, presumably due to compensation of the decline of pharmacological sensitivity with ageing. Thus, there are some important differences between single chemical drugs and mixture drugs with many ingredients. The effects of Kampo medicine (mixture) are never just a sum of each effect induced by a lot of ingredients. For elder persons, furthermore, Kampo medicine exerts more effective actions.

KEYWORDS: Kampo medicine; multiple compounds; medicine, herbal; anti-ageing drugs; vasodilatation; rats

DOI: 10.3736/jintegrm2013003
Received September 11, 2012; accepted October 13, 2012.
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1 Introduction

Traditional Chinese medicine in Japan termed as Kampo medicine (herbal medicine), has been existed for centuries. Kampo medicine possesses widely effective and applicable fields. Western medicines such as digitalis, curare and morphine are also derived from herbs. Western medicine focuses on local diseased parts, whereas Kampo (or oriental) medicine treats the whole body. Since Kampo medicine is composed of a mixture with lots of herbs, it produces multiple pharmacological and pathophysiological functions, and exerts complex interactions with each ingredient. Therefore, Kampo medicine exhibits a lot of pharmacological actions mediated through the receptors and the ionic channels, and also causes complex and unknown interactions with each other[1].

In oriental medicine, a diagnostic characteristic “sho” as an assessment of clinical conditions, is quite different from a disease name based on histopathological findings in Western medicine[2]. Since Kampo treatments are made by formulation corresponding to sho, the selection of medicine is most important. Functional somatic syndrome (mibyo), clinically the disorders before diagnosing as a disease, is a traditional conception of oriental medicine. The mibyo includes many symptoms such as dry mouth, hot flush, chills and coldness of extremities. However, the pathophysiological meanings of mibyo are not clear yet. Under the mibyo, the imbalance of “qi (ki)/ketsu (xue)/sui (shui)” (neuro-immuno-endocrine) occurs. The mibyo is
most closely related with “ketsu” stagnation, called as “oketsu” (microcirculatory disorders). Kampo medicine may be expected to cure the oketsu and then, improve the symptoms.

Now we focus on the cardiovascular and intestinal pharmacology of Kampo medicine. The vascular dysfunctions are generally accompanied by menopausal disorders in women. Therefore, we debate on the usefulness for Kampo medicine as an evidenced-based herbal medicine. The comparative vasodilations related to ageing by some medicine as an evidenced-based herbal medicine. The membrane movement near the neuromuscular junction play an important role for the contraction. Paeoniflorin regulates Ca\(^{2+}\) movement near the neuromuscular junction, and relaxes due to the depolarized blockade like succinylcholine\(^1\). Glycyrrhetic acid inhibits Ca\(^{2+}\) activated K\(^+\) (I\(_{\text{KCa}}\)) channel to repolarize or hyperpolarize the membrane\(^2\). Thus, Shakuyakukanzoto has been mostly used for the relaxant effect of skeletal muscle\(^3\). The combination with Paeoniae Radix and Glycyrrhizae radix may enhance the relaxant action of skeletal muscle.

Moreover, Shakuyakukanzoto is useful to relieve pain, and exhibits an antispasmodic action on gastrointestinal smooth muscles depends on phosphodiesterase (PDE) inhibition\(^4\). Most recently, Shakuyakukanzoto has been demonstrated to play a key role in regulation of the gap junction on gastrointestinal smooth muscle\(^5\)\(^6\).\(^7\)\(^8\).\(^9\).

In our experiments using rat intestine, Shakuyakukanzoto (0.01 to 0.3 mg/mL) relaxed a carbachol (CCh, 0.3 μmol/L)-induced contraction in a concentration-dependent manner. Both components (Paeoniae Radix and Glycyrrhizae Radix) relaxed the CCh-induced contraction. Their constituents (paeoniflorin and glycyrrhetic acid) and the metabolic products (18-α- and 18-β-glycyrrhetic acids) produced almost the similar actions. Shakuyakukanzoto-induced relaxation was not modified by 1 μmol/L nicardipine, 10 μmol/L suramin (an adenosine triphosphate receptor inhibitor) and several K\(^+\) channel inhibitors, but was attenuated by 20 μmol/L 3-isobutyl-1-methylxanthine (IBMX, a phosphodiesterase inhibitor). Also, IBMX inhibited the relaxation induced by paeoniflorin and glycyrrhetic acid, but not by other ingredients. Nicardipine inhibited the relaxation of just 18-α-glycyrrhetic acid. Even in non-treatment with CCh, Shakuyakukanzoto relaxed the intestinal tract. CCh (0.3 μmol/L) often elicited spontaneous contractions in 23% of all specimens. Application of Shakuyakukanzoto completely depressed it.

Therefore, Shakuyakukanzoto exerts a remarkable relaxation due to the anticholinergic and the PDE-inhibitory actions, and may be contributed by minor contribution of Ca\(^{2+}\) channel inhibition (Table 1). Thus, Shakuyakukanzoto can exert an antispasmodic action mediated through the interaction of its ingredients.

### 3 Mokuboito (Mu-Fang-Ji-Tang)

Mokuboito (Mu-Fang-Ji-Tang) is composed of four herbal drugs: Sinomenine Acutum, Cinnamomi Cortex, Ginseng Radix, and Gypsum. Since each ingredient contains many kinds of chemical compounds, the resultant effect of Mokuboito is exhibited as a net of the complicated interactions among a lot of contained ingredients.

Mokuboito has been traditionally used as an indication for patients with the symptoms including wheezing, dark complexion and deep tight pulse. Mokuboito improved heart failure symptoms and reduced the rank of New York Heart Association classification\(^10\). The main constituent, Sinomenine Acutum (a vine plant), possesses ingredients such as sinomenine, tetrandrine and magnoflorine. Sinomenine Acutum has been applied for disturbance of body fluids and rheumatic diseases as a pain killer\(^11\). Sinomenine, a main ingredient of Sinomenine Acutum, is an alkaloid\(^12\) and exhibits pharmacological effects such as anti-inflammation\(^13\) and immunomodulation\(^14\). Thus, Mokuboito is used for clinical treatment of rheumatoid arthritis\(^15,\)\(^16\).

### Table 1 Pharmacological actions of Shakuyakukanzoto and its effective ingredients

<table>
<thead>
<tr>
<th>Formula or ingredient</th>
<th>Anticholinergic</th>
<th>Phosphodiesterase inhibition</th>
<th>Ca(^{2+}) channel inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shakuyakukanzoto</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td><em>Paeoniae Radix</em></td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td><em>Glycyrrhizae Radix</em></td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Paeoniflorin</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Glycyrrhetic acid</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>18-β-glycyrrhetic acid</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>18-α-glycyrrhetic acid</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
</tbody>
</table>

January 2013, Vol.11, No.1
In our voltage-clamp experiments using guinea pigs’ cardiomyocytes, sinomenine (1 mmol/L) and tetrandrine (100 µmol/L) inhibited the ionic currents concentration-dependently[19]. Simultaneously they also affected the action potential configurations. Sinomenine Acutum (1 mg/mL) decreased the maximum rate of depolarization \( V_{\text{max}} \). Among the ingredients in Sinomenine Acutum, tetrandrine (30 µmol/L) and sinomenine (300 µmol/L) also had the similar effects, but magnoflorine (1 mmol/L) had less or no effect. Sinomenine abolished the dysrhythmias induced by cellular Ca\(^{2+}\) overload. At even acute administrations, thus, these drugs exert the active electropharmacological actions and cardioprotections. Therefore, Mokuboito and its ingredients may improve the cardiac functions under the chronic heart failure.

On the other hand, Mokuboito and the ingredients dilated rat aorta, not only due to endothelium-dependent mechanisms (nitric oxide (NO) and prostaglandin I\(_2\)) but also due to modulation of Ca\(^{2+}\) channel and protein kinase C (PK-C) activity[20,21]. Thus, Mokuboito regulates the tone of blood vessels and adjusts the blood pressure and flow (Table 2).

Advance in ages produces various physiological and pathological deleterious changes such as plaque formation in vascular systems. Simultaneously, the age-dependent modulation of ionic channels and signal transduction pathways might be caused in the endothelium and smooth muscle cells. Chronic heart failure occurs more frequently in elderly persons. The endothelium-dependent relaxation has been reported to be attenuated in aged rat aorta[20-25]. The relaxation induced by ACh was impaired in the aortic rings obtained from old female rats[26]. From direct in situ measurement of NO in rat aorta, the NO-release diminished further in advanced aged rats. Nitro-L-arginine methyl ester (L-NAME, a NO-synthesis inhibitor) attenuated the ACh-induced vasodilatation with ageing, indicative of the age-related reduction of the NO-dependent vasodilatation[20,21].

Sinomenine at 100 µmol/L dilated norepinephrine (NE)-induced vasoconstriction by 68.8% ± 5.2% \((n = 6, P<0.01)\) in 10-week-old rats, but only by 18.6% ± 1.5% \((n = 6, P<0.01)\) in 65-week-old rats. Sinomenine Acutum (0.3 to 3 mg/mL) showed only vasodilatations in 10- and 35-week-old rats; at 3 mg/mL by 96.7% ± 4.8% \((n = 7, P<0.01)\) in 10-week-old rats. In 65-week-old rats, however, Sinomenine Acutum at low concentrations (0.03 to 0.3 mg/mL) constricted the aorta. The vasodilatation at 3 mg/mL was attenuated to 46.0% ± 5.7% \((n = 6, P<0.01)\). Mokuboito also exerted only the vasodilatation in 10-week-old rats, but at low concentrations exhibited the constriction in higher aged rats. Mokuboito at 3 mg/mL dilated aorta by 98.9% ± 2.8% \((n = 7, P<0.01)\) in 10-week-old rats and by 97.5% ± 13.5% \((n = 6, P<0.01)\) in 65-week-old rats.

From these findings, Mokuboito, Sinomenine Acutum (multiple compounds) and sinomenine (single compound) by themselves had the potent vasodilating actions. Sinomenine Acutum- and sinomenine-induced vasodilatation decreases along with ageing, but Mokuboito as a mixture has less or no effect on the age-dependent attenuation in any aged rats. The pharmacological effects of just single compound are attenuated in advance with ageing. On the other hand, Sinomenine Acutum (multiple compounds) suppresses the age-dependent attenuation of vasodilating action, and Mokuboito (as a mixture) maintains the marked action. Mokuboito contains numerous constituents, and sinomenine and the other constituents by themselves contribute to the Mokuboito-induced vasodilatation mediated through their interactions. Addition of Gypsum produces stronger vasodilatation in elder rats. The interactions among the ingredients play an important role for the pharmacological actions of herbal medicines. Therefore, the interactions may produce more effective pharmacological stability of Mokuboito against the age-dependent alterations.

4 Rokumigan (Liu-Wei-Wan), Hachimijigogan (Ba-Wei-Di-Huang-Wan) and Goshajinkigan (Niu-Che-Shen-Qi-Wan)

These Kampo formulations of Rokumigan (Liu-Wei-Wan), Hachimijigogan (Ba-Wei-Di-Huang-Wan) and Goshajinkigan (Niu-Che-Shen-Qi-Wan) are generally applied for kidney-related disorders along with ageing[23]. In oriental medicine, vital activities and functions are

<table>
<thead>
<tr>
<th>Formula or ingredients</th>
<th>NO release</th>
<th>PGL(_2) production</th>
<th>PDE inhibition</th>
<th>Ca(^{2+}) channel inhibition</th>
<th>K(^{+})/Ca(^{2+}) channel activation</th>
<th>PK-C inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mokuboito</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sinomenium Acutum</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Keisibukuryogan</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cinnamomi Cortex</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tokakujokito</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Persicae Semen</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

NO: nitric oxide; PGL\(_2\): prostaglandin I\(_2\); PDE: phosphodiesterase; PK-C: protein kinase C.
represented as five parenchymatous viscera, in which kidney means growth, development, reproductive function and ageing, as well as the functions of kidney (water metabolism). These Kampo formulations are called as the formulations with tonic effects for kidney. The formulations increase in order the number of contained ingredients in increment of two herbs. Rokumigan possesses six herbs as a base, Hachimijiogan, eight herbs (Rokumigan plus two herbs), and Goshajinkigan, ten herbs (more two herbs are added to Hachimijiogan).

All the three Kampo formulations produced a concentration-dependent vasodilatation in rat aorta\[27\]. In 10- to 15-week-old rats, prior administrations of 100 μmol/L L-NAME (a NO synthase inhibitor) and 100 μmol/L indomethacin (a cyclooxygenase inhibitor) did not affect the vasodilatation induced by three medicines. Nicardipine (a Ca\(^{2+}\) antagonist) at 2 μmol/L attenuated Rokumigan-induced vasodilatation by 51.2% ± 7.4% (n = 8, P<0.05), but failed to affect both Hachimijiogan- and Goshajinkigan-induced vasodilatations. Also, three Kampo formulations reduced high KCl-induced vasoconstriction. Furthermore, the formulations attenuated the phosphol-12,13-diburyrate (a PK-C activator)-induced vasoconstriction. Therefore, the APDs were prolonged with an increase in the percent repolarization from 50% repolarization (APD\(_{50}\)) to 90% repolarization (APD\(_{90}\)). Washout recovered to almost control value of V\(_{max}\), but failed to shorten all the APDs.

Main pharmacological action of Chotosan would be a vasodilatation, due to both endothelium-dependent and -independent actions. Recently it has been found to be involved in complicated mechanisms for the inhibitions of ion channels and PK-C activity, and also for NO release. Chotosan contains Gypsum. As compared with the effects of Chotosan and the modified Chotosan (without just Gypsum) on young and elder rats, in 10-week-old rats, Chotosan at 3 mg/mL relaxed the NE-induced vasoconstriction by 68.3% ± 7.0% (n = 6, P<0.001), and the modified Chotosan at 3 mg/mL by 54.5% ± 8.8% (n = 6, P<0.001). In 40-week-old rats, furthermore, addition of Gypsum produced stronger vasodilatation from 31.9% ± 7.6% to 69.5% ± 3.8% (n = 6, P<0.01). Therefore, increasing the number of herbal ingredients is more effective in elder rats.

6 Keisibukuryogan (Gui-Zhi-Fu-Ling-Wan) and Tokakujokito (Tao-He-Cheng-Qi-Tang)

The vascular dysfunctions accompanied by menopausal disorders are closely involved with the development of “oketsu (ketsu stagnation)”, which is primarily a sign of microcirculatory disorders\[^1^\]. The symptoms of oketsu are chills, hot flush, coldness of extremities, anemia, pale complexion, hypomenorrhea, dry mouth or skin, and loss of hair. Oketsu is developing further along with ageing, correlated with such as deterioration of erythrocyte deformability, an elevation in blood viscosity, acceleration of erythrocyte aggregation, and autonomic nervous activity changes\[^30\-\]34\]. Kinds of Kampo formulations may be expected to cure the “oketsu”. There are some anti-oketsu Kampo formulations such as Tokakujokito (Tao-He-Cheng-Qi-Tang), Keishibukuryogan (Gui-Zhi-Fu-Ling-Wan), Tokishakuyakusan (Dang-Gui-Shao-Tao-San) and Kamishoyosan (Jia-Wei-Xiao-Yao-San). The main effect of the anti-oketsu Kampo formulations would be a vasodilatation responsible for the modulation of endothelium-derived releasing factor (EDRF), endothelium-derived...
hyperpolarizing factors (EDHF), protein kinase A (PK-A), PK-C, eicosanoids, PDE and K/ Ca\(^{2+}\) channels, and further for an antioxidative action. In rat aorta, they produced the marked vasodilatation by over 80% to 90% at 1 mg/mL of each formulation.

Thus, these Kampo formulations improve the vascular dysfunctions (oketsu) along with ageing, and can prevent the functional somatic syndrome (mibyo), clinically the disorders before diagnosing as a disease.

### 7 Conclusion

The pharmacological characteristics of Kampo medicine were investigated. The comparative effects between single constituent and the formulation (as a mixture of constituents) of Kampo medicine were examined, and also the effects of increasing number of herbal ingredients contained in a formulation were examined. Shakuyakukanzoto composed with *Paeoniae Radix* and *Glycyrrhizae Radix* produced the relaxation of rat intestinal tract, but the effects induced by Shakuyakukanzoto are not equal with a sum of each effect of *Paeoniae Radix or Glycyrrhiza Radix*. In comparison between the effects of Mokubouto and sinomenine (its main ingredient), sinomenine alone declined the vasodilatation, but Mokuboito did not decrease and maintained the vasodilating action along with ageing. Moreover, addition of *Gypsum* produces stronger vasodilatation in elder rats. Rokumigan, Hachimijiogan and Goshajinkigan contain in an increment of two herbs. The larger number of the contained herbs exhibits more effective for vasodilatation in elder rats than in young rats.

The age-related alterations would be responsible for physiological and anatomical reductions such as receptors, ionic channels and cellular signal transductions. Furthermore, advanced ages produce the decline in the sensitivity to drugs. However, Kampo medicine maintains the pharmacological effects even with ageing, but not fully. From our experiments, Kampo medicine keeps the balance, and can produce either vasoconstriction or vasodilatation, according to the pathophysiological conditions (i.e., the previous tension of vessels). Increasing the number of herbal ingredients can maintain the effectiveness to some extent in elder rats, due to compensation of the decline in pharmacological sensitivity. There is an important difference between single chemical drug and mixture drugs with many ingredients. For elder persons, therefore, the mixture drugs (such as a Kampo medicine) with many herbs (ingredients) are more effective. Therefore, Kampo medicine is more effective for elder persons, but it is not clear yet whether or not Kampo medicine is more effective for women (presumably involved with estrogen hormone) as compared with men. Further extensive studies need to be conducted to elucidate in more detail mechanisms.

## 8 Competing interests

The author declares that there is no competing interests.

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