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Review

The Wakan-yaku Universe: A useful authorized traditional concept for developing novel therapeutic categories and medicinal drugs

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Abstract

This review article mentions about the following points, and proposes its importance and positive thinking. 1) Wakan-yaku (Japanese oriental medicines) is covered by the national health insurance system in Japan as therapeutic drugs to be actively used in medical practice to treat illness. 2) Applications of Wakan-yaku is accomplished based on the reliable own theories which are established with long histories. 3) Promotion of studies based on these theories will be highly expected to find novel view points which breaks conventional concepts and to novel standards for developing new medicinal drugs. Although studies based on the reliable Wakan-yaku theories are not advancing satisfactorily till now, the possibilities to obtain the advanced resources for drugs and novel viewpoints for experiments by studies about Wakan-yaku theories are discussed in this review.

Key Words; Wakan-yaku (Japanese oriental medicines), drug development,
challenging exploratory research, Wakan-yaku theories,
ultra low dose
Introduction: Historical background

Traditional medicine in Japan (Kampo medicine) was independently developed based on the traditional medicine in China with around 2,000-year history. ‘Kampo medicine’ was systematized in the middle of the 18th century. In addition, it had been also systematized Kampo prescriptions as treatment drug for the Kampo medicine. The medical crude drugs constituting the Kampo prescriptions are Wakan-yaku. Wakan-yaku includes both the traditional crude drugs originally used in Japan and the transported crude drugs from China with the intrinsic theories. They are put together based on Japanese intrinsic theories to make the systematized Kampo prescriptions and contribute to traditional Japanese medicine, Kampo medicine.

Its development was stopped at the end of the 19th century because the Japanese government changed the main direction of medical administration to Western medicine style. The development restarted after the world War II, for examples in 1963 the founding of the Research Institute for Wakan-yaku at Toyama University. Currently, over 150 extracts of Kampo prescriptions are released from pharmaceutical companies. And crude drug, Wakan-yaku, compositions of each are mostly standardized. Kampo prescriptions are covered by the national health insurance system as therapeutic drugs to be used in medical practice to treat illness. And most of Kampo prescriptions are also available as OTC at community pharmacies.

The high safety and efficacy of Kampo prescriptions and Wakan-yaku have been assured by standardization in Japan [1], as described above; however, scientific evidence for their efficacy is still lacking even though it has been investigated using advanced modern science and bioinformatics approaches recently [2]. Studies on Wakan-yaku have been performed based on analytical methods with great achievements, and new therapeutic drugs and leading compounds have been discovered through these studies [3], but there is still a need to
evaluate Wakan-yaku from the specific viewpoints to make Kampo prescriptions, and further studies may produce new innovative findings.

In this report, distinctive viewpoints for Wakan-yaku, and the specific theories and scientific principles forming the basis of Wakan-yaku are introduced. Moreover, its significance and potential will be briefly discussed.

**Uniqueness of Kampo medicine**

Kampo medicine which comprises Wakan-yaku complexes has unique natures when compared with pure drugs, as shown in Fig. 1: 1) The timing of drug administration is between meals, 2) the effects are through supporting biological reactions, and 3) rather than treating disease, it treats humans (personalized medicine). Although there may be exceptions, Wakan-yaku has each of these characteristics explained below.

1) Drug ingestion between meals: The optimum timing of ingestion is approximately 30 minutes after meals for many oral pure drugs in general because direct damage to the stomach can be easily prevented by taking drugs while content is present in the digestive system, especially in the stomach, and drug absorption rate is expected based on the bile acid secretion time. In contrast, Wakan-yaku may be considered food because the active ingredient often contains sugars. Accordingly, Wakan-yaku is ingested in a fasting state.

2) Agonistic mode of action: Many pure drugs are considered to act as an inhibitor of biological reactions. In contrast, many Wakan-yaku drugs act through a mechanism assisting the biological reaction such as activation of the immune system. For example, ‘Kakkonto’, which is frequently used in the early stage of colds, promotes heat production inside of the body with inducing sweating on the body surface, through which fever is released by a radiator effect, resulting in continuous heat production. On the other hand, general antipyretic analgesics decrease fever to normal levels. In other words, antipyretic analgesics regard fever
as unfavorable and decrease it, whereas Wakan-yaku favors fever and acts to support it. ‘Kakkonto’ is considered a typical body-warming prescript and is very frequently used in Kampo medicine. There is a Japanese traditional story (in Rakugo) of a physician who frequently used ‘Kakkonto’, named ‘Dr. Kakkonto’, in which the physician recommends Kakkonto to an attendant in the waiting room as a prescription for boredom, lacking of concentration.

3) Established personalized medicine: In Western medicine, diseases are specified based on objective diagnostic indices, which automatically leads to selection of therapeutic drugs. In present Kampo medicine, specialized physicians judge the state of the body and prescribe a therapeutic drug corresponding to the state of each individual patient (the details are explained below).

**Difference between pharmacognosy and Wakan-yaku science**

Most previous studies investigated the effective crude drug contained in Wakan-yaku prescriptions for the disease and found the active ingredient in the crude drug, and the efficacy of the formulation was described with the active ingredient. This method produces clear results. Many effective drugs have been discovered by this method and the efficacy of Wakan-yaku has been demonstrated. However, with this method, once the study subject switches from the formulation to individual crude drugs, the Wakan-yaku universe is no longer related and the study becomes pharmacognosy’s field. Thus, what is the difference between pharmacognosy and Wakan-yaku science? As shown in Fig. 2, the difference is that pharmacognosy starts from a single crude drug, whereas Wakan-yaku science starts with a combination of 2 crude drugs. The combination is termed ‘herb pairs’ just like parents for the effective action [4].

When a crude drug effective for a certain condition is discovered, it is scientifically
analyzed to identify the active ingredient from which the effect is derived in pharmacognosy. The isolated ingredient may be used as a new drug or serve as a leading compound. In contrast, in Wakan-yaku science, an increase in the efficacy, inhibition of adverse reactions, or isolation of the action itself depending on the case is attempted by investigating combinations with the discovered effective crude drug. This is the fundamental way of thinking in Wakan-yaku science, and many prescriptions have resulted from complex combinations based on the original theories (described below).

An example is shown in Table 1. ‘Maoto’, which has been attracting attention as a therapeutic drug for early-stage influenza, is composed of 4 crude drugs. ‘Makyokansekito’, with a high antitussive effect, is also composed of 4 crude drugs. Only one crude drug is different between these 2 Kampo prescriptions, but their effects on sweating are completely opposite: the former promotes sweating but the latter stops sweating. This is considered to be due to the difference in the herb paired with the ephedra herb (Mao) as a mechanism in Wakan-yaku theory. Ephedra herb/cinnamon bark promotes sweating but ephedra herb/gypsum stops sweating, and this may be due to control of ephedrine activity by the ephedra herb. This cannot be explained by the action of a single crude drug and pharmacognosy analysis alone cannot provide a conclusion.

**Historical and traditional theories supporting Wakan-yaku: Wakan-yaku pharmacology and Kampo physiology**

As fundamental theories promote new drug development and analysis of biological functions, firm theories supported by a long history also underlie the way of thinking for Wakan-yaku, although it appears to be empirical intuitive medicine. Studies about crude drug extracts without close composition analysis are often not accepted by top class of the scientific journals, but many important findings may be overlooked by this selection because
there is a possibility that ‘the main ingredient and main components’ are not necessarily consistent with the ‘main active ingredient’. Acceptance of studies based on the unique theories of Wakan-yaku, as described below, is likely to create a completely new research concept.

Each of the 8 items shown in Fig. 3 includes specific details and it is not possible to explain the detail of these individually. Therefore, only an overall introduction is described. For simplification, the items are divided into pharmacological ‘Wakan-yaku pharmacology’ and medical ‘Kampo physiology’.

1) Wakan-yaku pharmacology:

Kampo prescriptions are composed of combinations of plural Wakan-yaku, as described above. Each Wakan-yaku is considered to have a ‘static property’, which is expressed with 5 concepts: cold, cool, normal, warm, or hot (①). Each crude drug is also considered to have a ‘dynamic property’ of how it acts on the body (②): warming or cooling the body, adding or removing something, moistening or drying, collecting or dispersing something, and lifting or lowering something. This ‘something’ corresponds to ‘qi (ki: mood), blood, or fluid’, as explained in Kampo physiology below. The performance of each crude drug may be changed by processing (③, alteration). This is termed ‘shuhchi (specific processing)’ in Japanese. For example, detoxification of aconite by heating, or the steaming and drying of ginger to oxidize components to induce warming deep side in the body. In addition, the combination of 2 crude drugs (③, herb pairs) can also form the basic structure of prescriptions as described above, referred to as family [4]. Furthermore, the effective direction of the original fundamental prescriptions, which has the basal effect of the family, is emphasized or changed by adding a new crude drug (④). For example, ‘Keishito’ combined with pueraria root (kakkon) and ephedra herb becomes Kakkonto, and its body-warming activity is strengthened.
Pharmaceutical modification by simple addition of ‘koi’ to Keishikashakuyakuto, which has the same constitution of Keishito in crude drugs with different amount, changes the formulation to ‘Shoukenchuto’ which acts on the digestive system.

2) Kampo physiology

In Oriental medicine/Kampo Medicine, greater importance is attached to the condition of individual patients, and treatment aims at returning the condition to normal using Wakan-yaku. The most fundamental concepts in Kampo physiology are ‘qi (ki: mood), blood, and fluid’ (⑤), considered to be the ‘3 basic constituents’ circulating in the body required for human life. Health is maintained by the circulation of these 3 elements, and excess, insufficiency, or stagnation of these impair the physical condition. In Oriental medicine, ‘qi (ki: mood)’ is considered an important concept, as it is said that ‘sickness starts with the mind’, but its actual state is difficult to identify by modern medicine. It is not organic, but it represents something functional. Modern medicine is not good at defining ‘something functional/dynamic action’, which may be where Wakan-yaku science can play the most active role. ‘Blood’ and ‘fluid’, in Kampo medicine’s concept representing body fluids including lymph, are not necessarily consistent with blood and body fluid in modern medicine.

Although ‘qi (ki), blood, and fluid’ represent dynamic elements circulating in the body, the five-element theory forms a concept indicating the place in which the source of biological activity is present and interacts with these elements (⑥). The five-element theory is originally a conceptualization of the origin of the universe. It may be similar as the concept of horoscope in Western countries. Oriental medicine incorporated the concept into medical care and assigned anger, joy, worry, sorrow, and fear to the liver, heart, spleen (digestive system), lung, and kidney, respectively, and associated them with wood, fire, earth, metal, and water, respectively (Fig. 4). A review article is available on this five-element theory [5]. Applying
these theories about the Wakan-yaku treatment to ‘functional mental disorders’, especially ‘depression’, may provide us interesting viewpoints. And new studies on depression based on this are also expected. It’s briefly described below.

The ‘eight-direction theory’ is a diagnostic method in Kampo Medicine (⑦). This is a method to express the physical condition of patients with 2 directions of 4 elements: yin/yang, deficiency/excess, cold/heat, and exterior/interior. Based on each diagnosis, crude drugs and the formulation for Wakan-yaku pharmacology-based treatment are determined. For example, when the condition is ‘cold’, a formulation to warm is selected. The elements are not necessarily direct opposites, giving slight complexity. For example, in yin/yang, ‘yin’ is considered an element forming basic physical strength, and ‘yang’ is considered its accumulation. The use of a formulation may be decided depending on the adequacy of ‘yin’. ‘Yang’ does not necessarily indicate a favorable condition, and sometimes it may be the target to remove by treatment. It is not possible to fully describe the complexities here.

Regarding diagnostic methods in Kampo Medicine, tongue inspection, pulse examination, abdominal examination, and other original methods are used (⑧), but the details are omitted here.

**New treatment strategy based on the Wakan-yaku theory: Depression as an example**

The monoamine theory has been the major basis of antidepressant development for more than a half century. Based on recent imaging diagnostic studies, different findings, such as focusing on the glutamate system, have been frequently reported. For treatment of depression as a sickness of ‘qi (ki)’ based on the 5-element theory, the Kampo perscriptions shown in Table 2 may be useful, i.e., different therapeutic drugs are used depending on the cause and background of depression in individuals [6]. Applying this way of thinking to studies on the causative factor of depression and on basis of new therapeutic drug development, acquisition
of novel drugs and ideas which overturn the former common sense may be born.

Conclusion

As described in the introduction, Wakan-yaku has unique characteristics different from those of pure drugs. The vector direction for treatment seems to be completely opposite. The main treatment strategy in Western modern medicine is to discover and remove impaired sites by an analytical viewpoint. For example, fever is treated with antipyretics as undesirable fact. Thus the Western modern medicine thinking is an unreplaceable advantage for cancer treatment, early discover and remove treatment. In contrast, in Kampo medicine, treatment is performed to support the biological reactions of repairing from disease, such as activation of the immune system. It is suitable to complement regions with reduced function, and may exhibit characteristics for disease in which organic changes are unclear such as functional mental disease. Furthermore, ultra low doses may be efficient. Western analytical medicine and Oriental integrated medicine seems to have the opposite directions, but the fundamental theories, pharmacology and physiology, are basically the same as this review article proposed. It should not be difficult for researchers with a Western analytical viewpoint to understand Oriental medicine because the fundamental way of thinking is similar. In this context, utilization of Wakan-yaku, which has been highly systemized medical care for long time in Japan, and the integration of Oriental and Western medicine depending on the both fundamental basic philosophies have the potential to become a new method of medical care expected to improve the human’s welfare and of studies on obstinacy disease, especially for functional mental disease.

Conflict of Interest

The authors declare no conflict of interest.
References


Legends for figures

Fig. 1  Specific Personalities of Wakan-yaku

Fig. 2  Difference between pharmacognosy and Wakan-yaku science

If an effective crude drug in a certain condition is discovered, scientifically analyzing to identify the active ingredient will derive in pharmacognosy. In contrast, in Wakan-yaku science, an increase in the efficacy, inhibition of adverse reactions, or isolation of the action itself is attempted by investigating combinations with the discovered effective crude drug.

Fig. 3 Historical and traditional theories supporting Wakan-yaku: Wakan-yaku pharmacology and Kampo physiology

Fig. 4 The concept of the 5-element theory in Wakan-yaku

The five-element theory forms a concept indicating the place in which the source of biological activity is present and interacts with these elements (This figure is cited from the author’s previous review [6]).
1) Timing of administration is between meals
2) Agonistic effects is preferential
   Treatment using vital reaction
   (not restraintal)
3) Treatment for human (not for disease)
   Highly established tailor-made medicine

Is “the personalities” reflected in the study?
effective Crude drug

Study of the evidence
  Molecular mechanisms (=Reported findings)
  Isolation of the active compounds
  Development of the novel medicines

Individualization of the Efficacy
  Attenuation of the side effects

Which crude drug can combine with?

Modern science  Wakan-yaku theories

Herb Pairs

Fig.2
Wakan-Pharmacology

① galenical natures of five stages
cold/cool/normal/warm/hot
② galenical natures of five factors
warming/colding, adding/removing
moistening or drying,
collecting/dispersion,
lifting or lowering
③ herb pairs, specific processing
④ basic formula

Kampo-Physiology

⑤ qi (ki)·blood·fluid
⑥ five elements theory
liver , heart, spleen, lung, kidney
⑦ eight direction theory
yin/yang (in/yoh),
deficiency/excess
cold/heat, exterior/interior
⑧ Kampo-diagnostics
tongue inspection
pulse examination
abdominal examination
and others
Fig. 4

- Gallbladder
- Liver (Wood)
- Bladder
- Kidney (Water)
- Lung (Metal)
- Spleen (Earth)
- Stomach (Fire)
- Small intestines

→: stimulation
→→: inhibition

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## Table 1

Table 1 The composition of crude drugs in ‘Maoto’ and ‘Makyokansekito’

<table>
<thead>
<tr>
<th></th>
<th>Maoto</th>
<th>Makyokansekito</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ephedra Herb</td>
<td>5.0 g</td>
<td>4.0 g</td>
</tr>
<tr>
<td>Apricot Kernrl</td>
<td>5.0 g</td>
<td>4.0 g</td>
</tr>
<tr>
<td>Cinnamon Bark</td>
<td>4.0 g</td>
<td>—</td>
</tr>
<tr>
<td>Glycyrriza</td>
<td>1.5 g</td>
<td>2.0 g</td>
</tr>
<tr>
<td>Gypsum</td>
<td>—</td>
<td>10.0 g</td>
</tr>
<tr>
<td><strong>Sweating</strong></td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>

Both ‘Maoto’ and ‘Makyokansekito’ are composed of 4 crude drugs. Only one crude drug is different between, but their effects on sweating are completely opposite. This is considered to be due to the difference in the herb paired with the ephedra herb (Mao) as a mechanism in Wakan-yaku theory. Ephedra herb/cinnamon promotes sweating but ephedra herb/gypsum stops sweating, and this may be due to control of ephedrine activity by the ephedra herb. This cannot be explained by the action of a single crude drug and pharmacognosy analysis alone cannot provide a conclusion.
### Table 2

Table 2 Possible classification of depression types and the effective Wakan-yaku prescriptions by the “5-element thory”

<table>
<thead>
<tr>
<th>Category</th>
<th>Element</th>
<th>Organ</th>
<th>Emotion</th>
<th>5-Elements Theory of Wakan-yaku (Symptom (background))</th>
<th>Prescription for depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category-1</td>
<td>Wood</td>
<td>Liver</td>
<td>Anger</td>
<td>Stress (Scial-Relationship)</td>
<td>Shigyakusan</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sleeplessness (Pessimistic Nature)</td>
<td>Keishikaryukotsuboreito</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Inappetence (Confidential Thinking (Love?))</td>
<td>Hochuekkito</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Autonomic-inbalance (Enviromental Disagreement)</td>
<td>Juzendaihoto</td>
</tr>
<tr>
<td>Category-2</td>
<td>Fire</td>
<td>Heart</td>
<td>Joy</td>
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<td></td>
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<tr>
<td>Category-3</td>
<td>Earth</td>
<td>Spleen</td>
<td>Pensive</td>
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<tr>
<td>Category-4</td>
<td>Metal</td>
<td>Lung</td>
<td>Grief</td>
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</tr>
<tr>
<td>Category-5</td>
<td>Water</td>
<td>Kidney</td>
<td>Fear</td>
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</tbody>
</table>

(This table is modified and cited from the author’s previous review [6]).