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# Introductory Chapter: Future Prospect of Licorice, Popular Crude Drug and Food Sweetener

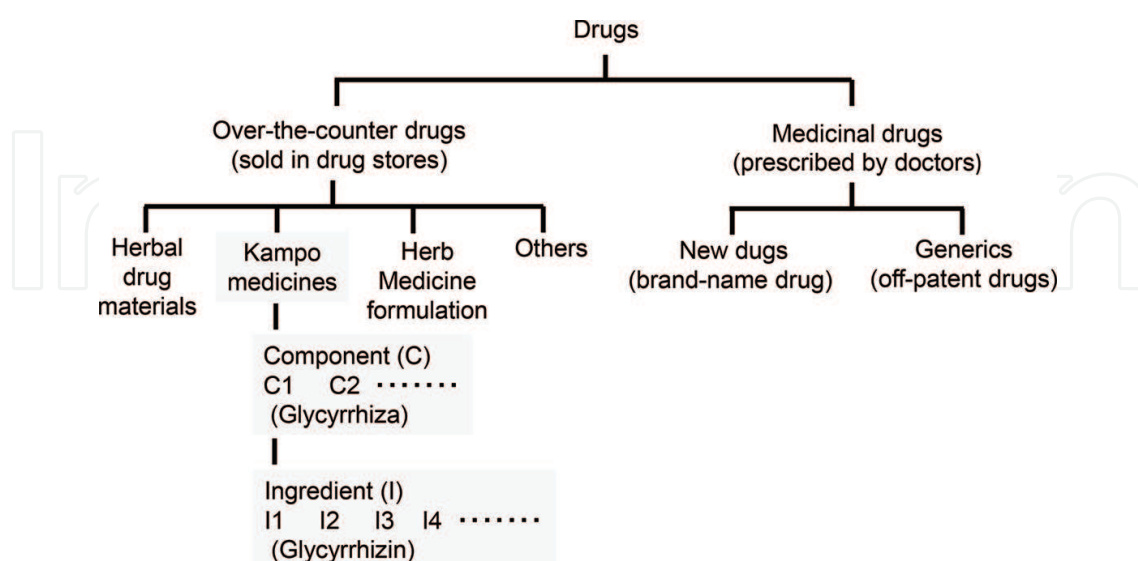
Hiroshi Sakagami

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## 1. Classification of drugs

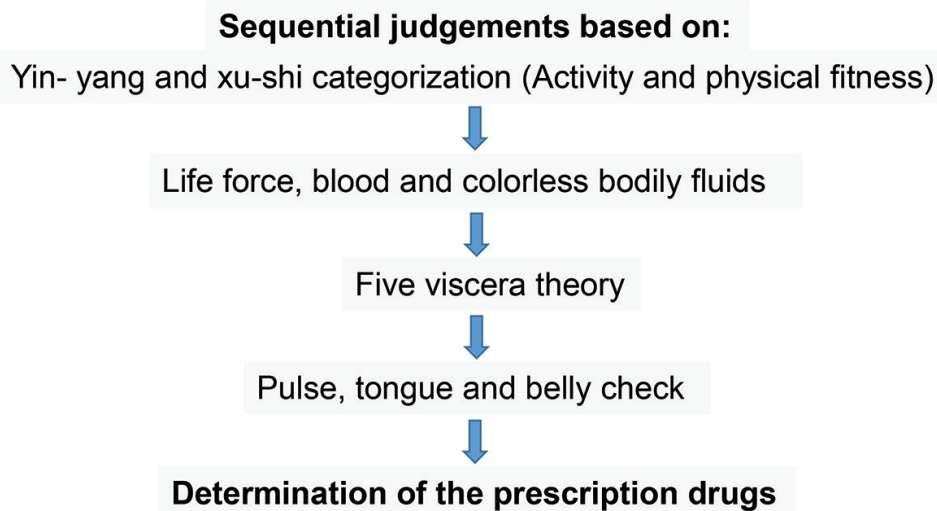
Drugs are classified into “over-the-counter (OTC) drugs” that are sold in drug stores and “medicinal (or ethical) drugs” that are prescribed by doctors [1] (**Figure 1**). “Herbal drug materials” and “Kampo (Japanese Traditional Medicines)” belong to OTC drugs, whereas new drugs and generics belong to the medicinal drugs. In contrast to Western medicines that recognize the drug as single compounds, Kampo medicines are a mixture of more than two components of herbal extracts. Pharmacopeia 17th edition accommodates a total of 323 herbal medicines (33 Kampo medicine + 290 herbal drug materials/formulations). Licorice is a crude drug prescribed in various herbal formulas in traditional Japanese and Chinese medicines and also used worldwide as a food natural sweetener. The origin of licorice was the root or stolon of *Glycyrrhiza uralensis* or *G. glabra* (Legminosae) [1]. Licorice contains three orders higher amounts of glycyrrhizin, as compared with other components [2].



**Figure 1.** Classification of drugs.

## 2. Difference of Kampo medicine and Western medicine

To select the best Kampo medicine, the patient's condition will be first checked by the criteria of yin-yang and xu-shi categorization (activity and physical fitness) and then narrowed down by the life force, blood and colorless bodily fluids, (if necessary) followed by the five viscera theory and the pulse, tongue and belly (Figure 2). As compared with Western medicine, Kampo medicine is more empirical (rather than scientific), comprehensive (rather than analytical), global (rather than local) and personal (rather than general) and normalizes the patient's condition (rather than removing the cause of disease).



**Figure 2.** Process of grasping the patient's condition prior to the prescriptions of drugs.

During the business sorting work in 2009, the then Japanese regime proposed the exemption of insurance against Kampo medicines, fomentations and mouth washes, claiming that Kampo medicine is evidence less and it can be obtained very easily by anybody. However, the patients, herbalists and medical personnel moved against this proposal by means of collecting approximately one million signatures and made the proposal withdrawn. Now, in Japan, approximately 150 Kampo medicines and 200 herbal drugs used as decoctions are covered by health insurance. Among the 900 physicians who worked in the core cancer treatment hospitals, 92.4% reported having prescribed Kampo medications [3]. Nationwide, random-sampled and population-weighted telephone survey demonstrated that respondents who had used at least one complementary and alternative medicine (CAM) therapy (76.0%) were greater than those who had used orthodox Western medicine (65.6%) and that the expenditure for CAM was nearly half that of orthodox Western medicine [4]. The most common CAM practice was Kampo, which corresponded to 96.1% of CAM-practicing doctors [5]. However, it still remains to be clarified why the Kampo medicines exert beneficial effects on our body.

### 3. Application of Kampo medicines

Kampo medicines have been used to improve the symptoms of various diseases (**Table 1**). Bakumondoto, Hochuekkito and Kiyoshihaiyu, which contains licorice, have been reported to improve the symptoms of chronic obstructive pulmonary disease (COPD) [6, 7]. Daikenchuto (that contains hydroxy- $\alpha$ -sanshool and 6-shogaol as major ingredients) improved the intestinal motor paralysis and Crohn's disease, by increasing the RAMP (receptor activity-modifying membrane protein) 1, 2, 3, mobilizing the CGRP (calcitonin gene-related peptide) and AMD (adrenomedullin) and inhibiting the expression of pro-inflammatory cytokines (TNF- $\alpha$ , IFN- $\gamma$ ) [8]. Rikkunshito recovered the meal uptake by increasing the plasma des-acyl ghrelin level, suggesting its possible application to dyspepsia [9].

Old people experience the decline of body strength and vital function, the continuous languor, the loss of appetite and the fatigability. This kind of aging-associated characteristics cannot be remedied by Western medicines, but more easily alleviated by treating with co-agents such as Hochuekkito and Juzentaihoto. However, licorice present therein may induce hypokalemia

	Used to treat or improve the symptom of:	Presence of Licorice
<b>Bakumondoto</b>	Chronic obstructive pulmonary disease (COPD)	■
<b>Bofutsushosan</b>	Insulin resistance, obesity	
<b>Daikenchuto</b>	Increase in intestinal blood flow, Crohn's disease	
<b>Goreisan</b>	Migraine	■
<b>Hachimijiogan</b>	Arteriosclerosis, dysuria, prostatomegaly	
<b>Hangekobokuto</b>	Depression	
<b>Hochuekkito</b>	COPD, depression	
<b>Juzentaihoto</b>	Hepatic fibrosis, carcinogenesis	
<b>Kakkonto</b>	Migraine	
<b>Keishibukuryogan</b>	Oxidant stress, vascular endothelial damage in patient arthritis, acne	
<b>Kiyoshihaiyu</b>	COPD	
<b>Maoto</b>	Inhibition of neuraminidase	
<b>Rikkunshito</b>	Functional-dyspepsia, gastroesophageal reflux disease, depression	
<b>Saikokaryukotsuboreito</b>	Depression	■
<b>Shosaikoto</b>	Hepatic fibrosis, carcinogenesis	
<b>Shoseiryuto</b>	Allergic rhinitis	
<b>Tokishigyakukashokyoto</b>	Sensitivity to cold, numbness	
<b>Yokukansan</b>	Dementia	

**Table 1.** Application of Kampo medicines to various diseases.



	Stomatitis	Xerostomia	Taste disturbance	Halitosis	Glossodynia	TMJ	Tooth extraction	Periodontal disease	Presence of Licorice
Juzentaihoto	●	●	●		●				●
Kakkonto	●					●			
Kamishoyosan	●	●		●	●	●			
Kanbakutaisoto						●			
Keishikajutsubuto	●	●			●	●			
Keishibukuryogan						●			
Kikyoto							●		●
Kososan	●								
Orengedokuto	●		●	●				●	●
<b>Orento</b>	●			●				●	
<b>Rikkosan</b>	●				●		●		●
Rikkunshito	●	●	●	●	●				
Saibokuto			●		●	●			●
Saikokaryukotsuboreito		●	●		●				
Saikokeishikankyoto			●						●
Saikokeishito							●		
Saireito	●	●							●
Seishinrenshiin		●							
Shakuyakukanzoto						●			●
<b>Shosaikoto</b>	●		●		●		●		
Sokeikakketsuto						●			●
Tokishakuyakusan					●	●			
Unseiin	●							●	

**Table 2.** Application of Kampo medicines to oral diseases.

Hangeshashashinto showed anti-inflammatory [17], oral ulcer-induced pain-releasing [18], antimicrobial [19], antimucositis [20] and antioxidative activities [21]. Orento prevented the inflammatory responses in lipopolysaccharide-treated human gingival fibroblasts [22]. Rikkosan also induced anti-inflammatory activity [17]. Shosaikoto showed anti-inflammatory [23] and anti-hyperlipidemic and anti-atherosclerotic activities [24]. It should be noted that all these four Kampo medicines contain licorice (**Table 2**).

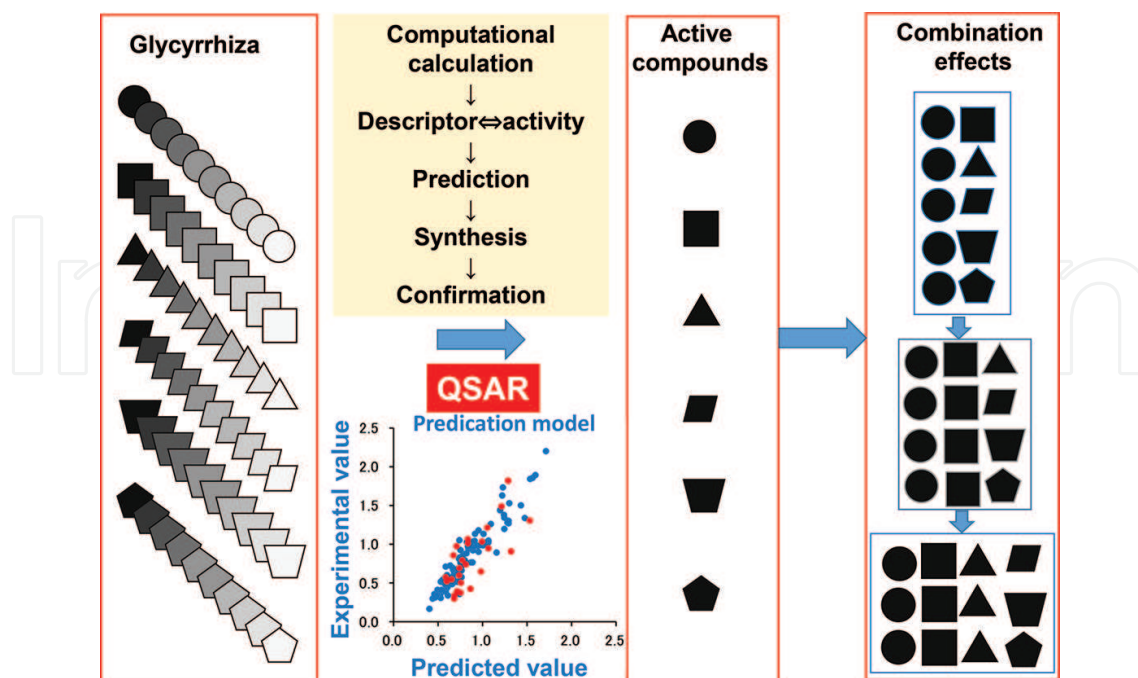
Kampo medicines are also effective to alleviate the glossodynia [25] and cancer thermotherapy-induced side effects [26–28].

## 5. Future direction

We sometimes experience that purification of active ingredients leads to significant loss of the biological activity. Furthermore, the amount of ingredients is different from one batch to another depending on where they are harvested. Therefore, it is essential to reconstruct the best sets of active ingredients for the standardization of the contents. First step to accomplish this is to investigate the relationship between the biological activity of structurally related compounds and chemical descriptors, using quantitative structure-activity relationship (QSAR) analysis. Once the best 3D structure is predicted, such compounds should be quickly synthesized to confirm its biological activity. This process is repeated until the satisfactory results are obtained. The next step is to determine the best combination of ingredients (**Figure 3**).

The relative potency of ingredients may depend on the type of target cells. For example, licorice flavonoids showed potent anti-HSV activity, while they were inactive against HIV infection [29]. During isolation of active ingredients, some aggregations between ingredients may happen [30]. Accumulation and analysis of such data are crucial to manufacture the best Kampo medicine.

Using QASR analysis, we recently found that anti-HSV activity of 19 flavonoids including 10 licorice flavonoids correlated well with six chemical descriptors that represent polarizability



**Figure 3.** Chart flow to select the best combination of licorice ingredients. Each symbol is any compound. The same shapes indicated the compounds with similar structure.

(MATS5p, GATS5p), ionization potential (GATS5i), number of ring systems (NRS), atomic number (J\_Dz(Z)) and mass (J\_Dz(m) ( $p < 0.0001$ )). This result suggests that the physico-chemical properties, rather than the category of compound, are important factors in determining the anti-HSV activity [29]. The possibility that their target site may be common is under investigation.

It is expected that in the future, alternative therapy with Kampo medicines will be versioned up, in synchronization with the improvement in the personalized medicine based on the gene information.

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