

## HERBAL PLEIOTROPY–THE SCIENTIFIC INVESTIGATION MAY ADVANCE MEDICINE

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### Overlooked herb and herbal medicine around the world

Herbs of related species are sometimes used for different medicinal purposes depending on the region and medical system. Clearest difference of this is seen through the comparison between the Western (or the bio) medicine and the Eastern (or the traditional/oriental) medicine. Traditional Chinese Medicine, Traditional Japanese Medicine, or Kampo, and Traditional Korean use the same clinical classics and almost the same herbs. Therefore, here, I would like to call them "Oriental Medicine" for easier understanding.

Europe also has its own history of herbal medicine. Phytotherapy is one such example. Dr. Rudolf Fritz Weiss had taken a few branches of European traditional remedies and re-systemized into today's form [1]. I helped to add the appendix of the Japanese edition textbook of this Phytotherapy and by doing so, I had the opportunity to compare herbs of Oriental with those of Phytotherapy.

I was surprised to find that 250 herbs discussed in this textbook, which is over a half of its content, were used in the Oriental herbal treatment as well. There has been no direct medical interaction between the two systems, but it was apparent that the same herbs were used in different parts of the world.

However, its clinical use was more often for completely different purposes than similar in most cases.

### Different usages of the same or related species

Table 1 shows different usages of the same or related species [2]. Double quotation marks mean that the effects are based on the Oriental Medicine standpoints. Shoma (Shenma) is an Oriental herb, which has anti-inflammatory effect, and its related species called black cohosh is used as an estrogen receptor. Toki (Dangui), an Oriental herb, is used for blood replenishment, and the related species, European Angelica is used as a bitter stomachic.

Yakumoso (Yimucao), an Oriental herb, literally "beneficial herb for mothers" is used to induce menstruation, and its related species, motherwort is used to treat cardiac neurosis. It is interesting that both Oriental and European names include the word meaning "mother".

As Table 2 shows, Yakumoso has various related species which has been used all over the world.

*Leonurusjaponicus* and *Leonurussibiricus* is used in Japan in order to treat gynecologic disorders, but in Russia, *Leonurussibiricus* is used as sedative and anxiolytic agent. *Leonuruscadiaca* is used in Europe. As the name suggests, it is used to treat arrhythmia. It is also called "motherwort," and in England, it is used for gynecologic disorders. *Leonotisleonurus*, on the other hand, is used in South Africa to treat gynecologic disorders. In table 3, we compare active pharmacological substances among three related species. Leonurine, mildly psychoactive alkaloid, has cardiovascular, hypotensive, uterotonic, and neuroprotective effects.

Stachydrine is the main anti-arrhythmic agent here. *Leonurusjaponicus* contain 0.001-0.049 % of Leonurine, but *Leonuruscadiaca* do not. On the contrary, *Leonuruscadiaca* contain 0.6-1.5 % Stachydrine, which is more than *Leonurusjaponicus* with 0.1-1.0% [3].

These findings supported that *Leonuruscadiaca* has anti-arrhythmic effect and *Leonurusjaponicus* is effective to treat gynecologic disorder among *Leonurus* species. To understand its usage in England, we have to investigate other pharmacological substances to explain its effectiveness. However, under the theory of Oriental medicine, gynecologic disorder, arrhythmia and mental status are pathologically closely related. Therefore, we often use this herb to treat gynecologic, arrhythmic and psychiatric disorder at the same time.

### Each Herb Has a lot of Potential Effects

The result here is that even the same or related species of plants could be used differently between Phytotherapy and Oriental medicine. These findings show that each herb has potentially many effects on human other than the way it is used in Oriental medicine. Why could one herb be used differently between Phytotherapy and Oriental medicine? I think it is because these medicines are constructed on different theories and each theory focus on different aspects of herbs and that even related species contain different substances.

One herb can have various effects both in Oriental Medicine and Phytotherapy.

Similarities in usage suggest the herb's primary medicinal effect and are there for comparatively uniform in use in different regions, cultures or medical systems. However, when herbs are used for different purposes depending on the region, the culture, or the medical system, it suggests the herb's pleiotropic effect.

What is interesting is that while a certain herb is used for its specific pleiotropic effect in one medical system, other system chose - whether purposeful or by accident - not to use it. I think this is because the different medical systems perceive symptoms and physical changes based on their own theory that the effect of the herbs required are different. Scientific investigation and categorization of these pleiotropic properties of herbs should be done.

Taking the example of Yakumoso (*yimucao*), it becomes apparent that the same or related species of herb may have different medicinal properties depending on the habitat. Climate conditions such as mean temperature, humidity, amount of sunlight hours, or geographical conditions such as quality and characteristic of soil may affect each plant. There are, however, areas of the difference in usage not quite explainable by these aspects or by research findings available. We need to compile indigenous information i.e. the types of disease and individual constitution considered, and incorporate that with the scientific data to construct a comprehensive database. Such database would enable in-depth understanding of herb property mechanism and further the possibility of its medicinal use.

### Advantages of tailor-made compound medicine

Traditional medicines perceive the body as a whole and aims to extract symptoms to maintain the balance. There is a lot to learn from traditional medicines worldwide. Let us take a look at how the system is comprised in the orient.

In the orient, herbs are more commonly used in compound forms rather than in single form. What is the reason for this? A sophisticated craftsmanship is at work here. Oriental medicine is predominantly tailor-made to fit an individual's constitution. This allows for more effectiveness and less side-effects, and more importantly, such calculated selections have avoided - in most part - creating drug resistant strains.

Oriental medicine places much focus on an individual's constitution including personality. It works around the idea to promote rather than to suppress such individualities. Strength or weakness of a person's gastrointestinal system, sensitivity towards hot and cold weather, psychological vulnerabilities, grades of peripheral circulation, all of these things are considered in prescribing herbal combinations, proportion, and dosages. We all know how difficult it is to determine the amount of medication to administer as a patient develop a variety of complications as a disease progress; more and more medication are necessary in the effort to eliminate each symptom thus developing more complications. The experience of oriental medicine in its focus to individuality could open ways to solve this dilemma. Kampo also prescribe medication that works as an anti-bacterial or an anti-viral. But it rarely creates resistance. Maoto (Ma-Huang-Tang) has been used against influenza-like illness for nearly 2,000 years, and still today, it is as effective as neuraminidase inhibitors to treat influenza [4]. It has created no resistance to date.

While the above facts present clinical advantages, scientific proof has been difficult to obtain. Furthermore reason to study each herb. However, a single herb could potentially contain a variety of properties and to analyze the interactive effects of a compound in which multiple herbs are used is exponentially difficult. And yet, *in silico* analysis of a database developed of this vast information is already operational in some countries.

In Japan, after selecting the most commonly used herbal compounds, it was standardized and produced as extract pharmaceuticals. This process involves compound identification using high performance liquid chromatography (HPLC), stabilizing and standardizing the

extract, and finally reproducing it in pharmaceutical drug form. Advancement in this technology made it possible to stabilize quality and provision of herbal extract pharmaceutical drugs and prescribe it as easily as the western bio-medical drugs. At present, 149 Kampo medications are covered by national health insurance and 85% of physicians routinely prescribe them to patients. It is already an ongoing practice for Japanese physicians to comprehensively explain to patients the traditional usage and scientific benefits of present-style usage of these compounds in bio-clinical practice.

The benefit of the Kampo system's purposeful mixing of compounds is yet to be fully understood. It is anticipated that scientific advancement in the analysis and research of the interactive effects of the medicinal properties of herbs will articulate its reasoning and stand to prove the acuteness of our predecessors' herbal understanding.

### Linkage with the theory is already underway in East Asia

The Traditional medicine theory itself within the Oriental Medicine is systemized with physiology, pathology, pharmacology, diagnostics, treatment, etc, and is an effective tool in clinical settings today. And while it has been difficult to attach scientific verification to this theory, a few studies are undergoing the verification process. Here are some examples. Goreisan (Wu-Ling-San): It has properties in affect to fluid volume metabolism, and it works to increase urine volume when there is fluid overload, and decreases urine volume when dehydration is experienced. Its common usage is in correcting uneven fluid distribution so it can be safely used to treat diarrhea and dehydration. With the inhibitor effect of aquaporin (APQ), its mechanism has been clarified in part [5]. Daiken chuto (DKT, Sa-Jiang-Zhong Tang): This has been used to improve agitation caused by cold stimulus, such as hypoperistalsis and stomach pain. Verification of the correlation with the TPR channel, the temperature-difference sensory, is anticipated in the near future [6].

Yokukansan (Yigansan): This has been used to sedate hysteria-like emotional excitement, but since it is a nondopamine-dependent sedative, it has the advantage not to cause over-sedation or extrapyramidal disorder [7].

Rikkunshito (Liu-Jin-Zi-Tang): This has been used to promote appetite in patients with gastrointestinal weakness. It was commonly considered to have properties to improve absorption metabolism of digestive organs, but is now considered to be the sole medication to improve ghrelin, an appetiteregulation hormone [8].

**Table 1: Same/related species have different usages between the Eastern and the Western medicine**

Oriental medicine			Phytotherapy herb		
	Scientific name *	Oriental usage	Name	Scientific name	Phytotherapy usage
Shoma (Shenma)	<i>Cimicifuga simplex</i>	Anti-inflammatory **	Black cohosh	<i>Cimicifuga racemosa</i>	Estrogen receptor agonist
Toki (Dangui)	<i>Angelica actiloba</i> <i>Angelica var. sugiyamae</i>	Blood replenishment **	European Angelica	<i>Angelica archangelica</i>	Bitter stomachic
Yakumoso (Yimucao)	<i>Leonurus japonicus</i>	Menstruation-inducing agent **	Motherwort	<i>Leonurus cardiaca</i>	Cardiac neurosis

\*Botanical names and species as listed in Japanese Pharmacopeia, \*\*Empirical effects are empirical based on Oriental medicine

### To create a pleiotropic effect of the different medical system

The foundation of traditional medicine in the Orient; the insightful knowledge and understanding, meticulous consideration to the individual constitution in prescription, the technique in compounding herbs to avoid creating resistant strains, are in itself valuable aspects in the clinical field. But it is now time to give it scientific examination – as some are already undergoing, to provide evidence of its validity. What is more important is to verify the numerous traditional

medicines around the world in the same way, while maintaining the traditional reasoning, so that the indigenous medicines will be accredited its well deserved value and benefit from modern science.

Not only will scientific verification of reasoning and techniques of not one but numerous traditional medicine in the world give us further insight of the herbs, but will present an opportunity to further integrate our predecessors' articulation into today's science and raise modern medicine to the next level.

**Table 2: Various related species of Yakumoso used all over the world**

Japan *	Latin America	UK	Continental Europe	Russia	South Africa
<i>Leonurus sibiricus</i> <i>Leonurus japonicas</i>	<i>Leonurus japonicas</i>	<i>Leonurus cardiaca</i>		<i>Leonurus sibiricus</i>	<i>Leonotis leonurus</i>
Gynecologic disorders before and after birth	Irregular menstruation	Soothe the uterus		Valerian equivalent (sedative-hypnotic)	
Gynecologic	Gynecologic	Gynecologic	Cardiac-antiarrhythmic	Sedative anxiolytic	Gynecologic

\*Botanical names and species as listed in Japanese Pharmacopeia., Kenny Kufta, Annual Meeting of the Japanese Society of Phytotherapy, Tokyo, Japan:8<sup>th</sup>of December 2013

**Table 3: Active pharmacological substances among three related species of Yakumoso**

	Japan *	Latin America	UK	Continental Europe	Russia	South Africa
	<i>Leonurus japonicus</i>		<i>Leonurus cardiaca</i>		<i>Leonurus sibiricus</i>	<i>Leonotis leonurus</i>
Leonurine (%)	0.001-0.049		None			none
Stachydrine(%)	0.2-1.0		0.6-1.5			0.3
	Gynecologic	Gynecologic	Gynecologic	Cardiac Anti-arrhythmic	Sedative anxiolytic	Gynecologic

\*Botanical names and species as listed in Japanese Pharmacopeia., Kenny Kufta: Annual Meeting of the Japanese Society of Phytotherapy, Tokyo, Japan, 8th of December 2013

### REFERENCES

- Volker W, Stuttgart-New T. Rudolf Fritz Herbal Medicine, second edition. New York:revised and expanded;2000.
- K Ortwein HW, J Rauwald. *Leonurus japonicas*, *Leonurus cardiaca*, *Leonotis leonurus*: A novel HPLC study on the occurrence and content of the pharmacologically active guanidine derivative leonurine, Pharmzie. J Clin Psychopharmacol 2012;67.
- Kufta RB, Volk HW, K Rauwald. Stachydrine in *Leonurus cardiaca*, *Leonurus japonicas*, *Leonotis leonurus*: decoction and quantification by instrumental HPTLC and 1H-qNMR analysis, Pharmzie. J Clin Psychopharmacol 2012;68.
- Nabeshima S, Kashiwagi K, Ajisaka K, Masui S, Takeoka H, Ikematsu H, et al. A randomized, controlled trial comparing traditional herbal medicine and neuraminidase inhibitors in the treatment of seasonal influenza. J of Infection and Chemotherapy 2012;18(4):534-43.

5. Takako J, Michiko Maria Keneko. Effect of goreisan on urinary concentrating ability and expression of aquaporin-2 in 5/6 nephrectomized rats, *J Trad Med and Clin Psychopharmacol* 2013;30:145-57.
6. Tokita Y, Yamamoto M, Satoh K, Nishiyama M, Iizuka S, Imamura S, *et al.* Possible involvement of the transient receptor potential vanilloid type 1 channel in postoperative adhesive obstruction and its prevention by a kampo (traditional Japanese) medicine, daikenchuto. *J Pharmacol Sci* 2011;115(1):75-83.
7. Teranishi M, Kurita M, Nishino S, Takeyoshi K, Numata Y, Sato T, *et al.* Efficacy and tolerability of risperidone, yokukansan, and fluvoxamine for the treatment of behavioral and psychological symptoms of dementia:a blinded, randomized trial. *J Clin Psychopharmacol* 2013;33(5):600-7.
8. Mogami S, Hattori T. Beneficial effects of rikkunshito, a Japanese kampo medicine, on gastrointestinal dysfunction and anorexia in combination with Western drugs: a systematic review. *J Evidence-Based Complementary and Alternative Medicine* 2014; 2014: 519035.