The Current Situation of Japanese Medicinal Plants Industry and its Significance on the Pharmaceutical Industry

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I. Current situation of crude drugs

I-1. Usage of crude drugs

Medicinal plants (crude drugs) have a wide array of applications in Japan including medicine, food, cosmetics, insect repellant, coloring, fragrance, bath products, etc. Since one drug may be used as medicine and/or food, statistical reports on the precise amount of medicinal plant utilization do not exist.

According to the domestic cultivation and importation data published in the "Annual Report of Pharmaceutical Production"[1] by the Japan Kampo Medicines Manufacturer Association (JKMA), 97% of the 150 most frequently used crude drugs for medicine and food in 2002 relied on importation (56,221t importation vs. 1,723t domestic cultivation). The employment of these 150 crude drugs parallels the production rate of Kampo formulations, and since the sales of these formulations and health food are rapidly increasing in the recent years, demands for crude drugs are anticipated to proliferate also. Most commonly used drugs in descending order are Ginger (23,807t), Coix seed (7,021t), Capsicum (4,000t), Turmeric (3,727t), Glycyrrhiza

(2,016t), Cinnamon bark (1,259t), Cassia seed (1,203t) and Safflower (1,055t). Glycyrrhiza is unsurpassed in its usage in medicinal products.

The 2006 statistical data[2)] from Japan Specialty Agriculture Products Association (JSAPA) of medicinal and non-medicinal crude drug importation reported that 58% were imported from China, 19% from Thailand, 13% from India, 2% from Sudan, and 1% from Taiwan. The actual proportion of importation from China is estimated to be higher if medicinal products are considered alone.

I-2. Distinction between drugs and foodstuffs

In Japan, medicinal plants are classified into two groups based on the list of characteristics in the "Distinction between drugs and foodstuffs" [3)].

(1) Medicinal plants that are used exclusively as medicine (ie., cannot be used as food):

232 plant-based species, 21 animal-based species, 58 other species, e.g., Japanese Angelica (root), Astragalus (root), Phellodendron (bark), Coptis (rhizome, fibrous root), Rhubarb (rhizome), Aconite (tuberous root), etc.

(2) Medicinal plants that are considered non-medicinal unless medicinal efficacy is clearly stated (ie., can be used as food as long as therapeutic claims are not made) :

804 plant-based species, 65 animal-based species, 147 other species, e.g., Eleutherococcus senticosus (bark, root, root bark, leaf, flower, fruit), Bitter melon (fruit, root, leaf), Astragalus (stem, leaf), Phellodendron (leaf, berry), Coptis (leaf), Rhubarb (leaf), Ginseng (fruit, root, rhizome, leaf), etc.

I-3. Standard of quality control of The Japanese Pharmacopoeia (JP)

Crude drugs must meet The Japanese Pharmacopoeia (JP)[4] criteria to qualify as medicine. In 2001, 121 crude drug species and their 52 powdered forms were listed in JP 14th edition (JP14). However, revisions and new advances from the non-JP crude drug standards (internal regulations for approval) after 2006 led to the addition of Supplement I in JP 15 in 2007 which expanded the list to 153 crude drugs and their 54 powdered forms .

The following characteristics of crude drugs are standardized in the official monographs of JP:

(1) Name, (2) Origin, (3) Medicinal part, (4) Preparation process, (5) Content of specific constituents (lower limit setting), (6) Description, (7) Identification, (8) Purity (includes heavy metals, arsenic, residual pesticides), (9) Loss of drying, (10) Total ash, (11) Acid-insoluble ash, (12) Extract content, (13) Assay.

Nonetheless, some characteristics have not been specified yet depending on the species.

Recent stringent provisions of original species have succeeded in eliminating loose nomenclatures such as “other species of the same genus” when referring to them. JP has permitted the Japanese experiential use of substituting crude drugs for Chinese species; hence, Japanese species must be differentiated from the Chinese species with identical characters. For example, the original Angelica plant that JP prescribes is *Angelica acutiloba* or *Angelica actiloba* Kitagawa var. *sugiyama* Hikino (*Umbelliferaae*). In contrast, the Phamacopoeia of the People’s Republic of China employs *Angelica sinensis*.

Some pharmaceutical companies devise their own in-house standards in addition to the legally minimal JP standards. Non-JP crude drug standards are used as a reference for drugs that are not listed in the JP, and each company must develop their own

approval standards for drugs that are not listed in the former references.

II. Current situation of crude drug products

II-1. Kampo medicines

Traditional medicine from China evolved uniquely in Japan and established itself as Kampo medicine. As with Traditional Chinese Medicine (TCM), Kampo medicine utilizes several crude drugs to prepare Kampo formulae. Nowadays, industrially manufactured dried extract formulations have outnumbered traditionally prepared decoctions, pills and powders.

Kampo formulations are available from physicians as prescriptions and as OTC formulations from regular pharmacies. Kampo formulations for prescription have fixed national drug prices and are covered by the national health insurance (NHI) which keeps patient payments fractional. Currently, 148 formulae are approved as prescriptions. In contrast, 210 OTC Kampo formulations have been authorized since 1975 by the internal regulations for approval[5]. Several more formulae that have been approved before 1975 are available also.

Official data documenting the precise market sales of Kampo medicines in Japan are not available. Instead, production values, ie., amount of production x NHI price, are construed as the proximate data on market sales. For example, the 2004 production values of the top 8 formulations in descending order are as follows: Hochuekkito (Bu-Zhong-Yi-Qi-Tang; 7% of total production values of Kampo formulations), Daikenchuto (Da-Jian-Zhong-Tang; 6%), Saireito (Chai-Ling-Tang; 5%), Kamishoyosan (Jia-Wei-Xiao-Yao-Sa; 4%), Shosaikoto (Xiao-Chai-Hu-Tan; 3%), Bakumondoto (Mai-Men-Dong-Tang,; 3%), Goshajinkigan (Niu-Che-Shen-Qi-Wan; 3%), and Rik-

kunshito (Liu-Jun-Zi-Tang; 3%)[1]. These formulations tend to have higher NHI prices also. However, formulations that are frequently administered by physicians including Kakkonto (Ge-Gen-Tang), Shakuyakukanzoto (Shao-Yao-Gan-Cao-Tang), Choreito (Zhu-Ling-Tang), Shoseiryuto (Xiao-Qing-Long-Tang) tend to have lower NHI price[6, 7].

During the early approval stage of Kampo extract formulations, lack of regulation details led to products with less content of constituents than decoctions. In 1986, the government re-established the regulations for quality control and this became known as Marukan. The revised standards[8] required extract content products to contain homogenous amount of dried extract that was equivalent to the amount generated from standard decoctions prepared via traditional methods (note that each company devised its own standard decoctions). The amount of two or more indicator ingredients of extracts had to be comparable to the standard decoction also, and the accepted range for these ingredients was defined at ±50% mid-range. In contrast to the Traditional Chinese medicinal products that incorporate whole extracts in every production, and consequently vary in amount among the batches, Kampo extract formulations contain very stable and consistent amount of ingredients across all batches.

After 2006, the JP created a regulation list for Kampo extracts based on each company's standards. The following eight formulations were added and listed in the pharmacopoeia[4]: Kakkonto (Ge-Gen-Tang), Daiokanzoto (Da-Huang-Gan-Cao-Tang), Kamishoyosan (Jia-Wei-Xiao-Yao-San), Ryokeijutsukanto (Ling-Gui-Shu-Gan-Tang), Hochuekkito (Bu-Zhong-Yi-Qi-Tang), Saireito (Chai-Ling-Tang), Hangekobokuto (Ban-Xia-Hou-Pu-Tang), Keishibukuryogan (Gui-Zhi-Fu-Ling-Wan). For each extract, the following sets of standards were defined:

(1) Contents of indicator ingredients, (2) Method of preparation, (3) Description, (4) Identification, (5) Purity (heavy metals, arsenic, etc.), (6) Loss of drying, (7) Total ash, (8) Assay, (9) Container and Storage,

Each company devised their own regulations and standards in their approval documents for formulations and crude drugs. Even though these standards were independently implemented, they all fell within the wider range of JP standards.

In addition to the official GMP for medicine, JKMA established a self-imposed standard called "GMP for Kampo products" in 1988 for the manufacturing of Kampo extract formulations. They also established a crude drug control manager who oversaw the quality assurance of crude drugs, and included additional testing of aristolochic acid and residual pesticides in the 2007 revision [9]. Regulations such as GAP, GFCP, GACP had not been established in Japan yet.

II-1-1. Kampo formulations for prescription

With the advent of national health insurance coverage of Kampo extract formulations in 1976 and concerns about adverse effects from chemical drugs, the market sales (production value) of Kampo formulations[1] for prescription soared dramatically, peaking 154 billion yen in 1992. From the end of 1991, however, newspapers and mass media reported increased mortality rate from interstitial pneumonia among patients who ingested Shosaikoto (Xiao-Chai-Hu-Tang) for chronic hepatitis. This incidence converted Kampo prescribing physicians, who regarded Kampo as safe medicines, into cautious and doubtful physicians. As a consequence, this led to a sharp decline in both Kampo formulation production and Shosaikoto prescription.

After reaching the lowest production value of 84 billion yen in 2000, however, each succeeding year demonstrated a steady recovery rate and growth of Kampo formulations for prescription. By 2004, that figure rose to 92 billion yen and now Kampo formulations compromise 1.2% of the production value of the entire Japanese pharmaceuticals.

The characteristic of Kampo medicine practice in Japan today is that physicians are capable of prescribing both the chemical drug and Kampo medicine. This is in

contrast with the Chinese system where two separate physician licensures are required to practice Western medicine and Traditional Chinese Medicine. Traditionally, very few colleges taught Kampo medicine education and the majority of physicians studied independently post graduation. In 2001, the guidelines for medical education promoted the "understanding of Wakan-yaku (Kampo medicines)" for all doctors. Since this announcement, many universities began teaching Kampo medicine and by 2004, all of the 80 medical schools integrated Kampo medicine into their curriculum.

According to the results from a physicians' survey[10], 72% of respondents answered "currently prescribing Kampo medicines", with 52.7% of physicians employing them for unidentifiable complaint and menopausal disorder, 50.8% for acute airway inflammation, and 48.4% for constipation. Many physicians reported familiarity with the following prescriptions and often used them as the first line of defense for treating diseases: Kakkonto (Ge-Gen-Tang; 51.6% of physicians prescribe this), Shakuyakukanzoto (Shao-Yao-Gan-Cao-Tang; 45.7%), Hochuekkito (Bu-Zhong-Yi-Qi-Tang; 39.0%), Shoseiryuto (Xiao-Qing-Long-Tang; 32.9%), Kamishoyosan (Jia-Wei-Xiao-Yao-San; 31.8%) .

Application for manufacturing approval of Kampo formulations for prescription are based on the 1980 regulations[8], and no other formulations have been approved since that year. This is because the current regulation mandates astringent data submission that is comparable to a new drug application with rigorous clinical trials. Unlike China, Japan does not have a separate approving system that is lenient toward empirical, traditional medicines.

II-1-2. OTC Kampo formulations

OTC Kampo formulations have a production value of approximately 1/4 to 1/5 of Kampo formulations for prescription, and they compromise 2.9% of the entire OTC sales[1]. Along with the prescriptions, the OTC production value had reached its peak

of 30 billion yen in 1992 and dropped thereafter. Sales have only recently recovered in part due to heightened awareness of lifestyle-related diseases and great hope in Bofutsushosan (Fang-Feng-Tong-Sheng-San) as an anti-obesity drug.

In 2007, the pharmaceutical affairs law was revised as part of the national attempt to promote self-medication. This allowed non-pharmacist, registered salesman to sell Kampo medicines[11]. Due to these changes, the market is expected to show an upward trend in the coming years.

In 1975, 210 formulations were selected for OTC according to the internal regulations for "Guideline for OTC Kampo formulae"[5]. These formulae had the potential for approval in the recent years if their effects and indications matched the Guideline, and if sufficient data proving equivalence in quality as standard decoctions were presented. In 2008, the outdated internal regulations were rearranged, added and/or revised to update the effects and indications of the OTC formulations.

II-1-3. Classical formulations (Decoctions)

For doctors and pharmacists who prefer a higher content of crude drugs than the pre-determined amount in extract formulations, crude drug pieces are available for sale for decoctions. Insurance will cover all prescriptions as long as they are prescribed by physicians and combine any of the 248 crude drugs that are listed in the NHI price list. Even so, some physicians opt for insurance-free practice.

II-2. Conventional crude drug products (non-Kampo crude drug products)

In Japan, crude drugs may be used in OTC products besides Kampo formulations, such as a product combining crude drugs with vitamins. Approval is granted as long as there is evidence of prior consent for using the drugs. Currently, statistical data of sales of non-Kampo crude drug products do not exist.

II-3. Health foods

Under the Japanese law, all products except drugs are traditionally considered as foods. However, many illegal sales of food and herbal products with false medicinal claims flooded the market and because of this, two new food categories were added in 2001[12)]- foods for specified health use (FOSHU) and foods with nutrient function claims (FNFC) (foods which consist of vitamins and/or minerals). FOSHU are products that can claim medicinal benefits if preliminary clinical data and scientific evidence are submitted. For example, Tochucha's (Eucommunia bark tea) health claim as the "beneficial food for people with high blood pressure" is approved by the FOSHU. As of November 7th. 2008, 806 types of FOSHU have been approved. These products contain plants such as soybean, tea, psyllium, wheat, guava, coffee, Eucommunia bark, seaweed, sesame seed, broccoli, and cabbage, etc. The FOSHU market growth is proportional to the increasing number of approved products, with 2007 sales reaching 680 billion yen (not all products contain herbs)[13)]. On the other hand, health foods that have not been approved by FOSHU and FNFC are still sold as "so-called health food" even after these regulations have been implemented. The 2007 market for these "so-called health food" have reached 1,100 billion yen[14)].

III. Theme/subjects for Japanese medicinal plants industry

III-1. Rising crude drug prices and declining product values

Crude drug prices in Japan have increased in the recent years. The main factor for this increase is due to the rising labor costs in China.

The NHI price of prescription drugs in Japan are fixed and subject for re-evaluation every two years according to the actual trading price. However, the ac-

tual trading price is lower than the NHI price because they are determined by the negotiations between the medical institutions and wholesalers. As a result, the NHI price of most prescription drugs will decrease several % every two years. Kampo formulations are not exempted from this fluctuating market either, as reflected in their considerable price reduction over the past several decades. Western pharmaceutical companies compensate for NHI price reductions of existing products with new, high-value products. Since Kampo medicine companies do not make new products, price decrement inevitably leads to lower profit.

III-2. Stable procurement of crude drugs

The market sales of Kampo formulations for prescription have steadily increased in the recent years. However, the declining NHI price and reduction in weighted average sales price from greater usage of low-priced formulations have led to crude drug demand surpassing the actual sales of Kampo formulations. With every 8% increase in crude drug exigency each year, it is estimated that the amount that will be required in nine years will double from now.

China has always been the single, greatest source of crude drugs. However, in order to protect the environment and fertile land from turning into desert, the exportation of Glycyrrhiza and Ephedra Herba from China is currently limited. This foretells the potential risk in relying on one country as the main source of procurement. Domestic cultivation of medicinal plants in Japan is trekking a downward trend also due to aging farmers, greater profit from cultivation of other crops, and defeating price competition with Chinese suppliers.

Crude drugs that are mainly domestically cultivated (2002) [1)] include bamboo grass (*Sasa veitchii* ; 20t), Zedoary (20t), Cnidium Rhizome (12t), Artemisia (10t) and Zanthoxylum Fruit (10t). The Research Center for Medicinal Plant Resources – Na-

tional Institute of Biomedical Innovation publishes "Medicinal plants – cultivation and quality evaluation" (volumes 1-11 covering 58 medicinal plants/crude drugs)[15] with the purpose of promoting cultivation techniques. The following items are described in these documents:

(1) name and origin, (2) medicinal part, (3) (aspect) properties of plant, (4) (aspect) characteristics of crude drug and production area, (5) characteristics of cultivated species, (6) cultivation method, (7) quality evaluation of crude drug, (8) classification table of characteristics, (9) cultivation almanac, (10) data.

Breedings of medicinal plant seeds are performed by a small fraction of the industry and by the Research Center for Medicinal Plant Resources – National Institute of Biomedical Innovation. Registration and application of seeds can be found on the webpage of Ministry of agriculture, forestry and fisheries[16].

A better procurement system that relies less on China for import and more on domestic cultivation of medicinal plants must be actualized in the near future.

III-3. Countermeasure for contaminations of crude drugs

Public interest in "safe food procurement" has increased after the recent quagmire with Chinese agricultural products containing high residual pesticides. Additional limits are being created for residual pesticides, heavy metals and arsenic, and microorganisms of crude drugs and their products to ensure greater safety. More investments on tests that identify potentially dangerous substances will benefit the industry in the long run, even if the immediate profit of crude drug manufacturing companies may be affected. As we proceed into the future, the traceability of crude drugs must be further established by tracking, investigating and managing transportation from agricultural farms to the factory - all this in addition to the regular downstream inspection.

III-3-1. Residual pesticides

Based on the residual pesticide investigation of crude drugs in 1997, the total BHC and DDT limit of 0.2 ppm was established for Ginseng, Powdered Ginseng, Red Ginseng, Senna Leaf, and Powdered Senna Leaf. However, crude drugs were tested again in response to public demand, and the residual pesticides limit level was delineated in the 2006 JP15 as 0.2ppm for total BHC and total DDT each for the following crude drugs (in addition to the former ones in 1997):

Astragalus Root, Polygala Root, Powdered Polygala Root, Glycyrrhiza, Powdered Glycyrrhiza, Cinnamon Bark, Powdered Cinnamon Bark, Asiasarum Root, Cornus Fruit, Perilla Herb, Jujube, Citrus Unshiu Peel, Loquat Leaf, Moutan Bark, Powdered Moutan Bark

During 2005-2006, JKMA established the following self-imposed limit for Kampo extract formulations and non-Kampo crude drug products:

Organochloric pesticides (total BHC, total DDT: below 0.2ppm)

for Kampo formulations and non-Kampo crude drug products containing Ginseng, Senna Leaf, Astragalus Root, Polygala Root, Glicyrrhiza, Cinnamon Bark, Asiasarum Root, Cornus Fruit, Perilla Herb, Jujube, Citrus Unshiu Peel, Loquat Leaf, Moutan Bark.

Organophosphorus pesticides（Parathion：0.5ppm, Methyl Parathion：0.2ppm, Methidathion：0.2ppm, Malathion：1.0ppm）

for Kampo formulations and non-Kampo crude drug products containing Polygala Root, Cornus Fruit, Perilla Herb, Citrus Unshiu Peel.

Pyrethroid pesticides（Fenvalerate：1.5ppm、Cypermethrin：1.0ppm）

for Kampo formulations and non-Kampo crude drug products containing Polygala Root, Perilla Herb, Jujube, Citrus Unshiu Peel, Loquat Leaf.

For crude drugs that are used as foods, the residual pesticide limit changed from its negative list to a positive list system in 2006, and uniform limit of 0.01ppm was

implemented for all residual pesticides of all food products that lack individual limit.

For pesticides that are not legally regulated, in-house limits are established by the company and testing is performed accordingly.

III-3-2. Heavy metals and arsenic

The 2006 JP 15 established limitations of heavy metals and arsenic for 40 varieties of crude drugs. Supplement I to JP15 (2007) added 65 more crude drugs to this list[4], and uniform standards for heavy metals (30ppm) and arsenic (3ppm) for eight Kampo extracts in JP were also implemented.

III-3-3. Microorganisms

The JP identifies acceptable limits for the following microorganisms in drugs as general information (and not as mandatory regulation): aerobic bacteria, molds and yeasts, enterobacteria and other gram-negative bacteria, Escherichia coli, Salmonella, Staphylococcus aureus. Category 1 lists established limits for crude drugs for extract formulations and decoctions which are manufactured at high temperature. Category 2 represents the more rigidly, regulating limits for powdered crude drugs, pills or powders which are manufactured without heat.

VI. Japanese association for Kampo/crude drugs

Industry organization

- Japan Kampo Medicine Manufacturers Association <http://www.nikkankyo.org/>
- Tokyo Crude Drugs Association <http://www.aa.alpha-net.ne.jp/shouyaku/index.htm>

Research institute

- Division of Pharmacognosy, Phytochemistry and Narcotics-National Institute of Health Science <http://www.nihs.go.jp/dpp/index.html>

- Research Center for Medicinal Plant Resources - National Institute of Biomedical Innovation <http://wwwts9.nibio.go.jp/>

Academic society

- The Japanese Society for Pharmacognosy <http://www.jsphcg.gr.jp/>
- Japanese Society of Breeding <http://www.nacos.com/jsb/>
- Crop Science Society of Japan <http://wwwsoc.nii.ac.jp/cssj/>
- The Japanese Society of Horticultural Science <http://www.jshs.jp/
- The Japan Society for Oriental Medicine <http://www.jsom.or.jp/html/index.htm>
- Medical and Pharmaceutical Society for WAKAN-YAKU <http://www.wakan-iyaku.gr.jp/>

Other association

- Japan Speciality Agriculture Products Association <http://www.jsapa.or.jp/index.html>

VII. References

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