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Quality Control of Chinese Medicine

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Published Date: September 14, 2015

INTRODUCTION

It is always challenging to define what belongs to Chinese Medicine, and later on, you will find that it is even more difficult to say which is not. Generally, most of the Chinese Medicine originated from China. Certainly, there are a few exceptions, such as Cordyceps, *Panax quinquefolius* (American Ginseng), *Crocus sativus* (Saffron), etc. And we should not omit that the border of China keeps changing along the 2,000 – 3,000 years history of Chinese Medicine. Meanwhile, new species and other herbal or non-herbal resources became available through tributes and trading, such as Korean Ginseng and Edible Bird's Nest imported in Ming dynasty (1368–1644) [1]. On the other hands, it is obvious that a large portion of Chinese Medicine composed of herbal materials. However, some of the Chinese Medicine are originated from animal parts, such as Calculus bovis which is the dried gallstones of cattle. Surprisingly, even highly toxic minerals, such as Cinnabar, are also regarded as Chinese Medicine.

Another knotty issue is the differentiation between common food and Chinese Medicine. Chinese Medicine has been consumed by Chinese population and the surrounding countries for several thousand years. It has been incorporated into their daily life long time ago and consuming Chinese Medicine became part of the Chinese culture. Obviously, there are a lot of differences in the fundamental medicinal concept between modern medicine and Chinese Medicine. For example, you will never see a healthy person taking "medicine" in western countries.

But in China, people consume Chinese Medicine even they seemed nothing wrong. We called it preventive treatment of disease. In this case, the role of Chinese Medicine is similar to health food supplements or in another term: nutraceuticals. The medicinal functions of Chinese Medicine are not necessarily taken effect after getting inside our bodies through digestive system. Most of the raw materials for aromatherapy products came from the essential oils extracted from Chinese Medicine, such as *Nardostachys chinensis* and *Aquilaria agallocha*. Moreover, some of the famous cosmetics brand name also applied the extracts from Chinese Medicine such as Gin seng, Edible Bird's Nest or Cordyceps into their products [2-6].

To reflect these unique multi-disciplinal features of Chinese Medicine, I have made the following definition of Chinese Medicine:

"Chinese Medicine is anything able to enhance the quality of life, which medicinal functions can be explained by Chinese medicinal theory."

"Efficacy-Safety-Cost effectiveness" is the rule number one for the assessment on quality control in pharmacology. However, as Chinese Medicine shared a lot of common features with food or health supplement, "Safety" always goes first. Sometimes, the population concerns about the cost effectiveness even higher than the efficacy.

SAFETY CONCERNS ON CHINESE MEDICINE

Adulteration

Owing to the high market value and limited supply, rampant adulteration in Chinese medicine, especial precious herbs, is frequently found. Materials with similar texture and appearance are added into the herbs. Other adulteration methods include staining, bleaching, and incorporating low grade herbs into the more expensive one.

For example, the price of wild ginseng positively depends on the size and head of ginseng. Some counterfeiters reprocess small wild ginseng with scissors and glue to make a bigger wild ginseng with a larger body and longer fibrous root. Others simply use planted ginseng to re-shape as wild ginseng with glue and chemical adhesives. The price of wild ginseng normally is ten to hundred folds compare with planted ginseng [7]. Because of the very limited supply, the price of wild *Cordyceps sinensis* has dramatically increased by 900% within a decade; and the price ranged from 3000 to over 18,000 USD per kg in 2008. To rapidly increase the weight of cordyceps, unscrupulous businessmen inserted a tiny lead wire or trace amount of lead powder into the body of cordyceps or soaked it with chemicals. It is not easy for consumers to identify all kinds of Chinese medicine since there are species with similar appearance and textures. Some actually sold *Cordyceps militaris, Cordyceps hawkesii Gray* or *Nepal caterpillar* fungus instead of *Cordyceps sinensis*. They may induce different and unpredicted therapeutic outcome although they belong to the same genus. Some of them cannot be used as medicine; and intake of them could cause nausea and dizziness [7-9].

Recently, there was a notably increased reporting of Chinese herbal products adulterated with undeclared non-prescription or even prescription western drugs such as paracetamol, indomethacin, aminopyrine, caffeine and hydrocortisone [10]. In Hong Kong, drugs associated with serious adverse effects like corticosteroids has been found in Chinese medicines that claimed for treatment of skin conditions in 2011 [11]. Another report from Taiwan proposed that 24% of Chinese medicine samples were contaminated with at least one ordinary pharmacological compound among all testing samples. The adulteration of Chinese medicine with western drugs is a potentially severe problem which has to be urgently addressed and regulated [10,12].

Contamination

Most of Chinese medicines are herbal and grow on the farm, they may highly subject to the contamination of pesticides, heavy metals, aflatoxins or other foreign matters. Controlling the level of contaminants is critical for ensuring the quality of Chinese medicine and safeguarding the health of consumers.

With the increase in industrial pollution and external contamination, heavy metals are more easily absorbed and accumulated in Chinese Medicine. Those heavy metals with relatively high toxicity to human beings, including Arsenic **(As),** cadmium **(Cd),** lead **(Pb)** and mercury **(Hg)** are strictly regulated by Chinese medicine standards and analyzed by Inductively Coupled Plasma Mass Spectrometry **(ICP-MS)** [13-15]. Pesticides are chemicals that aim to prevent, terminate, control of diseases, pets or grass. However, they are often hazardous to agriculture, forestry as well as human.

Pesticides are commonly used in agriculture, such aschlordane, endrin and hexachlorobenzene are analyzed and evaluated in Chinese medicine by Gas Chromatography–Mass Spectrometry **(GC-MS)** [13-15]. Owing to the concern over the contamination of aflatoxins, which is the toxic metabolites generated by molds or fungi, a harmonized method was developed to monitor the content of aflatoxin B1, B2, G1 and G2 in Chinese Medicine. Aflatoxins are toxic and among the most carcinogenic substances known, therefore the amount of total aflatoxins must be less than 10ppb levels in Chinese medicine [13-14]. Foreign matters such as stones, sand and lumps of soil could increase the weight of Chinese medicine, the allowance of foreign matters in Chinese medicine is specified in the individual monograph [13-14].

Some contaminants may be specific to certain Chinese Medicine due to their natural cultivation environments and methods. In 2011, a report of high nitrite content was found in Edible Bird's Nest, which caused a heavy economic loss in the industry of many Asian countries. The source of nitrite was eventually proven which coming from the conversion of nitrate by the enzyme of nitrogen fixing bacteria. And both the nitrate and bacteria were most possibly contaminants from the food source of the swiftlet [16-17]. On the other hand, high content of zinc is also found in those Cordyceps originated from Tibet. It was found that the soil of the cultivation site also got high content of zinc (unpublished data).

To protect the interest of consumers from adulteration and contamination, it is crucial to have a reliable quality assurance methods as well as strong enforcement of the regulations.

MODERN TECHNOLOGY ON QUALITY CONTROL OF CHINESE MEDICINE

DNA Barcoding

Chinese Medicine has been used for centuries and is still widely used today. However, substitutes and adulterants of medicinal materials are often introduced either intentionally or accidentally, which can seriously affect the therapeutic effects, or even lead to life-threatening poisoning. Because of the increasing demand for herbal remedies and for authentication of the source material, it is necessary to provide a database containing information about authentic plant materials and their potential adulterants. In order to obtain such barcodes, several molecular methods have been applied to develop markers that aid with the authentication and identification of medicinal plant materials. With the advance in molecular technology, herb authentication based on Deoxyribonucleic Acid **(DNA)**-based markers has become an objective and accurate approach.

The traditional system of medicine utilizes medicinal plants to cure various ailments but the herbal industry suffers from substitution and adulteration of medicinal herbs with closely related species. The efficacy of the drug decreases if it is adulterated, and in some cases, can be lethal if it is substituted with toxic adulterants. Hence, the correct formulation is important for the medicinal herb to be effective. The traditional methods of medicinal plant identification include organoleptic methods (identification by the senses: taste, sight, smell, touch), macroscopic and microscopic methods (identification by shape, colour, texture) and chemical profiling (e.g. TLC, HPLC-UV, HPLC-MS). However, neither method can identify the related species easily in processed products because the former method requires trained personal for macroscopic and microscopic examinations. In the latter method, chemical profiles or markers may be affected by physiological and storage conditions. Authentication at the DNA level provides more reliability because, in contrast to RNA, DNA is a stable macromolecule that is not affected by external factors and is found in all tissues. Therefore, development of DNA-based markers is important for authentication of medicinal plants.

DNA is a double-stranded macromolecule composed of two complementary chains of nucleotides. Each nucleotide bears one of the purine or pyrimidine bases: Adenine **(A),** Guanine **(G),** Thymine **(T)** and Cytosine **(C).**The sequence of the nucleotides on the DNA serves as genetic codes. Different species would have different DNA sequences. Two approaches are commonly used for molecular authentication of traditional Chinese medicine, both involve the use of Polymerase Chain Reaction **(PCR)** to obtain DNA. DNA fingerprints, the first approach, are used to obtain several regions in the genome and compare fingerprints of different samples.

Another approach, DNA sequences are used to obtain DNA sequences of a particular region and they are aligned and compared using bioinformatics tools. Barcoding uses a very short genetic sequence from either nuclear or organelle genomes to identify biological specimens. In 2003, Paul Hebert of University of Guelph proposed "DNA barcoding" as a way to identify species. He prescribed that the 50 end of cytochrome C Oxidase 1 **(CO1)** from the mitochondrial genome was adequate to create DNA standardized identifications for the recognizable proof of animal [18-20]. CO1 was recommended as the locus that could give acknowledgment labels to all living beings. However, the mitochondrial qualities in plants are gradually advancing, with low substitution rates and were not suitable for barcoding. Hence, chloroplast and nuclear genomes with high substitution rates was used instead of mitochondrial genome. The Consortium for the Barcode of Life Plant Working Group **(CBOL)** evaluated several chloroplast genomic regions across the plant kingdom and proposed a combination of matK and rbcL as plant barcodes [21]. A combination of rbcL and matK can help achieving maximum species discrimination. All things considered, in firmly related species, the segregating capacity of these two markers is low. Accordingly, the China Plant BOL Group proposed the expansion of nuclear ITS (Internal Transcribed Spacer) to the matK + rbcL as plant DNA barcode with a specific goal to accomplish most extreme recognizable proof rates even in closely related species [22].

A total of 17 barcode regions (matK, rbcL, ITS, ITS2, psbA-trnH, atpF-atpH, ycf5, psbK-I, psbM trnD, rps16, coxI, nad1, trnL-F, rpoB, rpoC1, atpF-atpH, rps16) in the authentication and identification of medicinal plant materials were reported. Other than utilizing known genomic areas, other PCR-base methods: RAPD, RFLP, microsatellites, ISSRs, SNPs, and ARMS have been applied to create markers for authentication and identification of medicinal plant material. SCAR markers have been developed from RAPD, ISSR and a variety of genomic regions [23-27].

Using DNA barcoding to identify Chinese herbal medicine has several advantages when compared with other molecular markers:

- Directly based on the DNA sequence for species identification, it is an accurate, unique and repeatable method.
- Universal DNA barcode sequences between species are comparable. Establishing a unified global standard for species identification is better for studying the evolution of plants and animals, and other DNA molecular identification techniques will not have this advantage.
- Technical principle is simple, easy to operate, for most animals, only one pair design universal primers is enough, but for the other DNA molecular identification techniques, a dozen or even dozens of pairs of primers is required.
- A unified platform for barcode identification database shows the trend of the future of species identification technology.
- Suitable for families, genera, species, populations of all taxa, a stable identification result could be obtained as the individual's genetic information does not change.

DNA molecules offer a conclusive method for validation with favorable circumstances, for example, uniqueness for every taxon, and indistinguishable crosswise over distinctive organs. Different points of interest are that DNA molecules are not influenced by age, growth conditions and physiological states, and that just a little amount of sample is needed. The cost of DNA work continues decreasing while steps can be automated. With this comprehensive molecular technology, quick recognizable proof of diverse normally utilized, harmful, profitable and rare traditional Chinese medicine can be directed to maintain a strategic distance from abuse of herbal materials as well as to ensure public safety.

LC-MS/MS Fingerprint

The quality control has always been the key issue in the development of Traditional Chinese Medicines **(TCMs).** Fingerprint analysis is considered as an effective strategy for the quality assessment of multi-component TCMs. In contrast to other methods, it presents the entire composition information and fulfills the TCMs characteristics, such as systematic and comprehensive nature, and has been widely accepted as a useful means for the evaluation and quality control of TCMs and their finished products [28]. Therefore, fingerprint analysis has been internationally accepted for the quality control of herbal medicines. There has been a number of reports regarding the use of HPLC, CE, TLC, NIR, IR fingerprints on the quality assessment of some TCMs and their raw materials. Among the fingerprint technique for TCMs, HPLC is still the most popular one, due to its easy operation, wide suitability and high accuracy for the qualitative and quantitative analyses of TCMs.

Furthermore, many traditional preparations are compose of multiple TCMs, so that only highly selective, sensitive and versatile analytical techniques will be suitable for quality control purposes. HPLC-MS is a powerful technique for the analysis of complex chemical mixtures, and is particularly suitable for minor compounds in herbal extracts. Following efficient separation of constituents by HPLC, MS provides abundant information for structural elucidation by using MS/MS. Therefore the use of HPLC-MS and its fingerprint for the qualitative and quantitative analysis of constituents in medicinal plants and preparations steadily increased over the last few years [29]. For instance, the quality control method by LC-MS/MS fingerprint of *Solanum xanthocarpum* [30], *Cimicifuga Species* [31], *Niuhuang Shangqing pill* [32] and *Shenmai injection* [33] have been well reported.

C-MS/MS Fingerprint

Volatile oils are one of the major bioactive natural products of TCMs, and generally consist of terpenoid, fatty group and aromatic series. GC and GC-MS are commonly used for the analysis and quality control of volatile constituents of TCMs, and GC–MS has been an effective analytical technique for characterization and identification of volatile organic compounds in complex mixtures due to the powerful separation efficiency and the sensitive detection, especially in establishing the chromatographic fingerprint for the quantity control of traditional Chinese medicine.

WithIn recent years, many new sample extraction and pretreatment methods for GC-MS have been developed, making the application of GC-MS more simple and rapid, such as Solid-Phase Microextraction **(SPME),** Headspace Single-Drop Microextraction **(HSDME),** Headspace Solid-Phase Microextraction **(HS-SPME),** and Microextraction Coupled with Pressurized Hot Water Extraction **(PHWE)** or Microwave-Assisted Extraction **(MAE)** [34]. The GC-MS fingerprint has been demonstrated to be a powerful tool for the quality control of TCMs, such as Curcumae longae [35], Caulophyllum robustum [36] and Portulaca oleracea [37].

Metabolomics Analysis

Metabolomics is a relatively new field of 'omics' technology that is primarily concerned with the global or system-wide characterization of small molecule metabolites. A variety of analytical metabolic profiling tools are used routinely, including proton Nuclear Magnetic Resonance **(NMR)** Spectroscopy and Mass Spectrometry with a Prior Online Separation Step, such as High-Performance Liquid Chromatography **(HPLC),** Ultra-Performance Liquid Chromatography **(UPLC),** or Gas Chromatography **(GC).** In recent years, metabolomics has played an increasingly important roles in TCMs research and development, especially for the pharmacological studies, drug discovery and development of TCMs, and for the discovery of biomarkers and perturbed pathways which can clarify the action mechanism of TCMs [38-39]. By employing multivariate statistical tools, such as Principal Components Analysis **(PCA)** and partial least squares discriminant analysis **(PLS-DA),** metabolomics can be commonly used for the classification or discrimination of TCMs [40-41].

Multi-origin Chinese herbal medicines, with herbs originating from more than one species of plants, are a common phenomenon but an important issue in TCMs. According to the statistics, more than 2000 plant-based products have been included in the Pharmacopoeia of People's Republic of China (2010 Edition), including 134 herbal medicines with multiple botanical origins [42]. The herbal medicines with multiple botanical origins may have similar morphological and microscopic characteristics, however the differences of chemical profiling and pharmacological activity among multiple botanical origins has been observed [43-45]. Recently, metabolomics by combining LC-MS/NMR with multivariate statistical analysis has been a powerful tool for the discrimination of Multi-origin TCMs, the marker compounds responsible for samples classification or discrimination can be discovered, it would be an effective approach for authentication and quality control of TCMs with multiple botanical origins.

Herbochips Analysis

In the Tradition Medicine Strategy published by WHO, traditional medicine, despite of the vast variation among countries and cultures, is increasingly important in both healthcare system and economic importance. A decade ago, Traditional Chinese Medicine **(TCM)** accounts for about 40% healthcare needs of Chinese people, and the demand continue to grow. However, among all herbal medicine studied and used globally, very few biological targets have been identified. Traditionally, drug targets discovery of herbal medicines results after functional identification and clinical trials.

Such passive screening method of targets is inefficient and time-consuming. In 2003, Chang et al. published Herbochip®, a microarray-based drug screening technology which allows functional characterization of herbal compounds fractionated by HPLC using a defined protein drug target. The technology reverses the traditional screening method. Such that, researchers are able to proactively screen the interaction between drug target and massive amount of herbal extracts within a short period of time. In addition, the microarray nature of Herbochip technology makes large scale screening affordable by reducing the drug target demand considerably.

The unambiguous signals obtained by Herbochip hybridization analysis indicate chemical interaction of herbal extract and target protein. To prove the efficacy of Herbochip technology, in vitro cell-based assays should be employed. Huang et al evaluated the effectiveness of Herbochip by validating the anti-inflammatory effects of *Geranium Wilfordii* Ethanolic Extract **(GWE)** using Tumor Necrosis Factor-Alpha (TNF-α) as a drug target. Using TNF-α as a molecular probe, fractions of 82 selected herbal extracts, including GWE, were then screened to identify plant extracts containing TNF-α-binding agents. Cytotoxicity of GWE and modulatory effects of GWE on TNF-α expression were evaluated by cell-based assays using TNF-α sensitive murine fibrosarcoma L929 cells as an *in vitro* model. The hybridization data obtained by Herbochip® analysis showed unambiguous signals which confirmed TNF-α binding activity in 46 herbal extracts including GWE. In L929 cells GWE showed significant inhibitory effect on TNF-α expression with negligible cytotoxicity. The unanimous results have thus proven the efficacy of the Herbochip® drug screening platform using TNF-α as a molecular target. Although the above example is just a sneak peak of the Herbochip efficacy, such examples are piling up as Herbochip are more widely used. Therefore, we could conclude that the Herbochip drug screening platform does have a very promising future [46-47].

QUALITY CONTROL OF PROPRIETARY CHINESE MEDICINE

The pCM is composed solely of the raw materials of herbs, processed into various forms including various forms of pills, powder or ointment. The platform will be tailored for standardization of the herbal mixtures of pCM. The initial research of this platform will study several selected ancient CM herbal decoctions (at least 10 pCM), e.g. Danggui Buxue Tang, Ganmai Dazao decoction, Guizhi decoction, and Qizhiweitong particles. These selection are based on the exisiting strength of HKUST and the exisiting products from China Resources. Besides, these herbal formulations are derived from ancient record having excellent clinical application. During the first 3 years, we are targeting to provide standardized chemical profiles (metabolomics) of about 50 pCM deriving from ancient herbal decoction. Few attempts will be done here. The sources of CM will be analyzed by its chemical components. Those functional components could be selected as the indicator (chemical marker), and the selection of indicators should be based on the following rules: (i) the indicators can represent the pharmacological activity of the pCM; (ii) sufficient amounts of the indicators; and (iii) the indicators will be the

representative chemicals in the multi-component profiling, such as “multi-measure assessment”, “semi-quantitative approach” and “multi-dimensional chromatography”. These methods will be suitable in revealing multiple indicators to evaluate the quality of pCM. The developed method in quality control of pCM chemically could be opened for all industries, as to upgrade our current technology in quality control of CM.

Characterized the Overall Function by Systems Biology

The pCM contains numbers of active ingredients. To identify and characterize the active ingredients in pCM, we have to employ the omics biology, including genome-wide association analysis (genomics), SELDI protein chip, 2D protein electrophoresis, immunohistochemistry techniques (proteomics), the alternated metabolism (metabolomics) and animal studies, in evaluating the possible biological functions and its signaling mechanism. According to the theory of systems biology, the bioinformatics-based technology will be developed to explore the activities of the pCM. In addition, “omics” studies will be performed to search and characterize the targets for active ingredients. Furthermore, the interaction between targets will be studied for their possible synergistic effects. These methods have been well developed within our team members.

Characterize the Synergistic Effects of Multiple Components of pCM

In general, pCM contains many active ingredients, which might interact with different targets producing the synergistic effects. The center at HKUST has established several effective multi-disciplinary research techniques for the mechanistic analyses, such as multi-dimensional chromatography and high-throughput screening technology. Using these techniques, the synergistic effects and underlying mechanisms between single targets can be characterized. A major problem in combinatorial therapies lies in the number of possible combinations, which becomes more challenging in optimizing the herbal mixtures in pCM. Besides, the combined effect of numerous constituents within an herbal composite prescription is hard to validate. Among different classes of strategy in discovering combinatorial therapies, our group at HKUST has developed a feedback system control (FSC) scheme to implement an iterative stochastic search. At HKUST, we have employed FSC efficiently to discover potent combinations for anti-hypoxia function from different flavonoids deriving from CM. Having this system in-house, we aim to optimize an herbal mixture for therapeutic goals by using the FSC scheme, and therefore we are able to quickly pinpoint the optimal CM combinations in pCM for maximizing the pharmacological activity. The targets of the ingredients in regulating the interaction between single cells, organs and biological systems will also be studied, as to illustrate the action mechanisms of multi-functions provided by the pCM mixtures. Furthermore, based on the achievements, the novel pCM products will be obtained by pairing the different active ingredients from different CM. Thus, new pCM could be generated, and which will be patented for the commercialization of pCM product. Here, animal study on toxicity and efficiency could be performed, provided the new pCM is targeting for product development.

Identified The Function Of Active Ingredients Of pCM And Target Validation

Using the genome-wide association analysis, protein chips, protein-flight mass spectrometry and affinity chromatography, single or groups of molecular targets of the active ingredients in pCM will be identified. According to the theory of biological systems, the network pharmacological analysis will be applied to screen and characterize the molecular targets for those active ingredients. Molecular reverse docking, pharmacophore model, and similarity analysis of mode of action will also be used for characterizing and identifying the molecular targets, which might be regulated by the active ingredients. Furthermore, RNAi and animal models will be used to validate the molecular targets for active ingredients from the pCM. These methods have been well-developed in the laboratories of the PI or Co-I here in the proposed center for pCM. In addition, the team has developed a platform of herbal-chip in high-throughput screening of active ingredients from CM. As of today, our collaborators have collected over 5,000 chips from CM in China. This system has been shown successfully in identifying new chemicals from CM that have novel bio-functions. Animal models, such as knock-out mice and pathogenic model will be applied for study if needed. More information of the efficacy of our pCM to animal model helps elucidating and verifying the underlying action mechanism. Hence, increase the successful rate of the clinical trial in the later phases.

REGULATIONS ON QUALITY CONTROL ON CHINESE MEDICINE

In general, quality control of Chinese medicine is based on three important pharmacopoeial definitions, identity, purity, content or assay. Compared to Western medicine, Chinese medicine is mainly derived from herbs. Pharmacopoeias and monographs are primary quality standard for Chinese medicine all over the world.

Chinese Medicine Policy in Hong Kong

In Hong Kong, the Department of Health **(DH)** is responsible for overseeing the safety, efficacy and quality of all medicines marketed in Hong Kong. Chinese medicines are regulated under Chinese Medicine Ordinance (Cap.549) [48]. The Chinese Medicine Division of the DH regulates both Chinese herbal medicines and proprietary Chinese medicines.

To regulate the quality of TCM in Hong Kong, the Chinese Medicine Division set up the Hong Kong Chinese Materia Medica Standards **(HKCMMS)** office, which aims to formulate Hong Kong Chinese Materia Medica Standards. The HKCMMS project was first launched in 2002 to develop standards for commonly used CMM in phase to ensure the safe use and the quality of CMM. One of the principles that the work of HKCMMS is guided by is to ensure the safety and quality of CMM in protection of public health [51]. Seven editions of the HKCMMS converting standards for a total of 236 CMM have been published so far to control the quality of TCM in Hong Kong.

Chinese Medicine Policy in Mainland China

In China, the supervision on TCM is as strict as that of chemical drugs and biological products. Safety data are compulsory although TCM that demonstrate historical use may have partial application data exempted. Chinese herbal products are governed by the State Food and Drug Administration **(SFDA),** and Chinese herbal drugs are controlled by the Division of TCMs & Ethno-Medicines under the Department of Drug Registration.

The SFDA works on conjunction with these national and regional TCM laws to create national legislation regulating the development, production of pharmaceuticals, specifically including TCM drugs [52-53]. The Drug Administration Law of the People's Republic of China (Drug Administration Law), enacted in 2001, is the fundamental law governing drug administration in China to ensure drug quality and safety for human beings, to protect the health of people and their legitimate rights and interests in the use of drugs. It offers the regulation for the protection of TCM products, which provide administrative protections for TCM products, manufactured within China [52].

TCM must follow the national drug standards and provincial standards. The former standard is defined by the Pharmacopoeia of PRC **(ChP)** and specifications approved by SFDA. In the ChP, there are standards for Chinese prepared sliced crude drugs and TCM products. The standards for the herbal granules, being extracts for single herbs or combination classical formulae, will be available in the 2015 edition. Provincial standards are monographs of Chinese material medical and processing of TCM herbal slices approved by individual provinces [53].

The quality control and standards on TCM in the 2010 ChP were rational and strict continuously. It improved and perfected the quality standards of TCM comprehensively. Furthermore, it established a quality control system, which was adapted to the characters of TCM, gradually changed from single ingredient test to combination test of active ingredient and bioassay, and to macro quality control mode including multi-components, fingerprint and character chromatogram. It also added and perfected the safety test methods of TCM, enhanced the specificity of test methods, and established scientific and reasonable control indexes.

Chinese Medicine Policy in United States

U.S Pharmacopoeia **(USP)**/National Formulary **(NF)** and American Herbal Pharmacopoeia are documents including the quality standard of herbal medicine. In the year 2001, population in US spent $17.8 billion on dietary supplements, $4.2 billion of this amount on herbs [56]. Within the U.S., preparations of Chinese medicine generally come within the legal classification of ''dietary supplements'' rather than conventional medical ''drugs.'' Concerning about vast consumer usage of dietary supplements, the U.S. Congress in 1994 passed the Dietary Supplement Health and Education Act **(DSHEA)** [57].

In U.S Pharmacopoeia/National Formulary (2007 Edition), 65 species of medicinal plant are included as dietary supplements [56]. In June 2003, FDA's Center for Food Safety and Applied Nutrition **(CFSAN)** put in place the CFSAN Adverse Event Reporting System **(CAERS)** to monitor adverse event reports for foods, cosmetics, and dietary supplements [57]. In recent years, the United States Pharmacopoeial Convention establishes and improves regulation system globally at increasing speed.

According to U.S Pharmacopoeia/National Formulary, the scientific name, medicinal part and index component quantity of the medicinal plants should be elucidated. These records mainly include information of packaging, storage and label, U.S Pharmacopoeia reference standards (medicinal plant powder, extract powder, chemical mixture and pure compound), botanical characteristics (property and microscopic property), identification, microbial enumeration, loss on drying, exogenous organic impurity, total ash content, acid-insoluble ash content, extractum, pesticide residue, heavy metal content, major or effective constituent content assay. The assays for microbial enumeration, pesticide residue and heavy metal content are clearly defined in U.S Pharmacopoeia/National Formulary, which is obviously different from the other pharmacopoeias.

Chinese Medicine Policy in Europe

Due to its union property, Europe has lots of documents related to quality control on Chinese medicine from different countries. European Pharmacopoeia defines qualitative and quantitative composition of medicines including herbal medicines. In 2007, European Pharmacopoeia (6th Edition) recorded 211 species herbal medicine monographs containing information, such as definition, identification, content assay, etc [58].

Countries in Europe have different regulations on Chinese medicine quality control. In UK, British Pharmacopoeia (2007 Edition) has more comprehensive information on Traditional Chinese Medicine (TCM), which is more developed than European Pharmacopoeia. It added content related to herbal medicine in TCM as individual sector, which made great contribution to internationalizing the quality control on Chinese medicine [59]. British Pharmacopoeia includes the action and uses, definition, identification, assay, storage information of herbal medicine.

German Commission E Monograph **(GCEM)** defines that herbal medicine sold in Germany must meet the requirements in monograph. GCEM has 380 monographs and 360 species herbal medicine consisting of approved 186 single herbs, 66 fixed combinations, 2 component characteristics and unapproved 110 single herbs, 6 fixed combinations, 10 component characteristics [60]. The monographs record the name, components, pharmacological activity, pharmacokinetics, pharmacological toxicology, use purpose, contraindication, adverse effect, interaction between drugs, dosage and administration, combination partner in herb combination [61].

CONCLUSIONS

Indeed, the knowledge of Chinese Medicine is extensive and profound. It is a masterpiece gathering the knowledge of historical, cultural and medicinal science. Modernization of Chinese Medicine not only revitalize the old folk traditions, but also provide us another angle to understand the mystery of biological sciences.

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