Why and How to Globalize Traditional Chinese Medicine

Yung-Chi Cheng*

Henry Bronson Professor of Pharmacology, Yale University School of Medicine; Professor of Pharmacology and Internal Medicine, Yale University School of Medicine; Chairman, Consortium for the Globalization of Chinese Medicine (CGCM)

New Concept of Medicines

Nowadays, medicine is no longer for clinical diseases only. The paradigm of medicine has changed from disease to healthcare. The scope of medicine includes uses for disease treatment (therapeutic medicine), disease prevention (preventative medicine), life quality enhancement of patients and healthy individuals (functional medicine), and for improving the use of other medicines (accessory medicine).

The current paradigm of mainstream pharmaceutical discovery uses a reductionist approach to identify a target associated with disease or a single compound that can regulate a given target associated with a disease. Such compounds are expected to have potency and selectivity for the treatment of the disease targeted.

There are several challenges to the current mainstream drug discovery approach. A given disease can be caused by multiple reasons; therefore, it will be difficult to find one chemical with a defined target related to a specific disease, because the overall medicine helped treat a majority of the patients and prevented a majority from contracting the disease. Many potent drugs for the treatment or prevention of chronic diseases may require long-term use, and delayed toxicity may occur.

A new pharmaceutical industry, polychemical in nature, based on historical information from each geographical area, and with clinical evidence-based and consistent preparation, could be a focal point of economic development in each geographical area. Therefore, a new paradigm for future medicine is a multiple-target and polychemical medicine instead of a one-chemical medicine with a system-biology approach in mind. There are two approaches to polychemical medicine: conventional “step by step”, and revisiting history as the basis of reinventing medicine.

Figure 1 indicates the FDA pathway for botanical drugs. Botanical products with a history of safe use may start efficacy studies at Phase 2 clinical trials without preclinical requirements. Actual new drug application (NDA) requirements are identical to those of new chemical entities (NCEs), except that the combination product rule is waived; therefore, it is not necessary to study the individual active ingredients. The FDA has defined special policies for meeting chemistry, manufacturing, and control requirements; and as you might expect, this is technically quite challenging. The drug sponsor has considerable flexibility over when the required toxicology and human safety studies are conducted; therefore, development programs may be compressed with a parallel execution of toxicity, safety, and efficacy studies, or reversed as compared to NCEs with safety and toxicity studies following efficacy

*Correspondence to:
Dr. Yung-Chi Cheng, Department of Pharmacology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06520, USA. E-mail: yycheng@yale.edu
studies. In PhytoCeutica’s view, the pathway has opened up a large pool of previously untapped drug candidates, many of which have both clinical and market validation, enabling accelerated development with a lower risk of attrition. PhytoCeutica’s focus is on acute disease markets where existing therapies do not meet patients’ needs (Jiang et al., 2011).

The Unique Features of Traditional Chinese Medicine

Many traditional medicines took a “holistic approach,” which is just becoming an important area of medical research today. Some of these traditional medicines have claimed to meet those unmet clinical needs. Chinese herbal medicine takes a holistic approach, and is an early form of “system biology”-based “integrated medicine.” Chinese medicine is prescribed on an individual basis to optimize its usage (Lu et al., 2011). It is “individualized medicine.” Chinese herbal medicine has multiple medical claims for the treatment of complicated diseases, multiple symptoms, disease prevention, and life quality improvement. Chinese herbal medicine also has many chemicals that could target multiple sites, or act on a single site additively or synergistically through direct or indirect interaction (Konkimalla and Efferth, 2008). Chinese herbal medicine could meet some of the current unmet medical needs. It has its own concept, and can serve as the basis for developing future medicine.

The Approaches for Advancing Traditional Chinese Medicine

The approaches for advancing traditional Chinese medicine are described in Figure 2.

![Figure 2. Approaches for advancing traditional Chinese medicine](image-url)

The basic regulatory requirements for modern drugs enforce consistency of preparation, evidence-based clinical efficacy, safety, certain knowledge of a drug’s action, sites of actions, active ingredients, and interactions with other drugs.

As mentioned above, the approval of Chinese herbal medicine must ensure that a consistent preparation of clinical trial material should work. Therefore, the manner in which consistent preparations of herbal medicine can be made is important. We have to identify herbs using microscopic/morphological analysis, gene sequence analysis, and chemical analysis in vitro (solution state) and in situ (solid state). We also can use Good Agricultural Practices (GAP) and Good Manufacturing Practices (GMP) to guarantee the quality of herb. Botanical/herbal medicine quality control in GAP is consistent with the use of raw herbal ingredients. GAP monitors botanical identification, collection, post-harvest processing, and agriculture contaminants, including heavy metals, pesticides, fungicides, herbicides, bacteria, plant, and fungal contaminants.

Chinese herbal medicines are mixture medicines; therefore, the quality control for complex mixtures is very important. A novel approach is required; we can use multiple parameters and inclusive Comprehensive Quality Control Measures. Moreover, there are two tiered approaches to botanical quality control (QC). Tier 1 is the fingerprint analysis, which includes global and relative quantitation by chemical fingerprint, bioresponse fingerprint, and informatics/data mining technologies. Tier 2 is the simplified analysis, which includes the specific and absolute quantitation, such as chemicals relevant to the pharmacological activity, genomic pathways, and a biological analysis relevant to the pharmacological activity, including the impact on the targeted enzyme/receptor.

Clinical trials of traditional Chinese medicine must ensure that a consistent preparation of clinical trial material is possible to produce. Double blind and placebo design is preferable in clinical trials. Other alternative designs could be taken into consideration, such as a clear clinical endpoint that is acceptable worldwide and regulations for carefully monitoring efficacy and toxicity. Statistical consideration is also critical in the drug design.

The basic study of herbal medicine includes rigorous preclinical and clinical studies, multiplex analysis, and a systems biology approach, which is driven by information and data mining.
Discoveries using the approaches outlined above for herbal medicine could facilitate the single-targeted orientation approach in Western Medicine.

**Collaboration is Highly Required**

The evolution of medicine is not only a responsibility for scientists but also for the botanical drug industry. The botanical drug industry should heed the following responsibilities: evidence-based therapeutic claims, high-level Quality Control, full documentation of agricultural sourcing, full use of standard operating procedures, attention to drug-botanical drug interactions, and research focuses on the mechanism of action and the identification of active phytochemicals.

The outcome of developing such a polychemical and herb-based industry will provide high-quality products based on traditional healthcare uses, decrease the cost of healthcare, provide new scientific information to advance future medicine, stimulate value-added agricultural development, and provide economic development with a regional flavor.

To globalize Chinese herbal medicine, collaboration is critical (Figure 3). Close collaboration among academia, industry, and government is important. Given the limitation of resources (human, technological, and financial), international collaboration is critical for this advancement.

Therefore, the global, non-profit, non-discriminatory, and non-political organization Consortium for Globalization of Chinese Medicine (CGCM) was established in December 2003. The mission of CGCM is to advance the field of Chinese Herbal Medicine to benefit humankind through joint efforts with academics, industries, and regulatory agencies worldwide in the spirit of contributions and sharing.

**Globalizing Chinese Medicine**

In order to globalize Chinese herbal medicine, we need more scientific evidence. Figure 4 describes the evolution of medicines.

Chinese herbal medicine is a historical medicine with many experience-based claims; however, its defects are not very evidence-based. Therefore, the first step is to convert experience-based claims to evidence-based claims. The use of Chinese herbal medicine is based on the experiences of the doctor; and the doctor can adjust the components of the prescription through her or his own experience. Therefore, Chinese herbal medicine should add more objective quality control to prescriptions. Further, the preparation of Chinese herbal medicine involves many procedures. Some Chinese herbs require complicated processing procedures to become Chinese herbal medicine. All these requirements indicate that Chinese herbal medicine is not a friendly system for general use. Because Chinese herbal medicine formulas usually contain more than one component and the components are modulated by doctors’ experiences, the practice differs from Western medicine. Chinese herbal medicine is based on a holistic approach; there is not enough scientific evidence to demonstrate safe dosage of Chinese herbs. Hence, Chinese medicines need more short-term and long-term clinical trials to understand the dosage safety of Chinese herbal medicine. If Chinese herbal medicine can overcome the defects mentioned above, it could become a mainstream medicine or a strong support for mainstream medicine. Chinese herbal medicine’s interactions with mainstream medicine also need to be estimated, such as whether it collaborates in a good way.
or bad way. Moreover, Chinese herbal medicine could use modern scientific technology to deduce its quality control, informatics, clinical uses, herbal resources, molecular mechanisms and active compounds, intellectual properties, education benefits, and industrial liaisons. We should encourage Chinese herbal medicine to become evidence-base medicine. If we could identify the resources, molecular mechanisms, etc. of Chinese herbal medicine, it could be a resource for new medicine. Overall, collaboration is a crucial point for Chinese herbal medicine; it could instigate a further evolution of medicine.

References
Jiang, Z., Mark, Y., Zhao, Y., Stroncek D. F., White, J., Marincola, F. M., Cheng Y.C., 2011. Interaction of a traditional Chinese Medicine (PHY906) and CPT-11 on the inflammatory process in the tumor microenvironment. BMC Medical Genomics 11,4:38-50.
Konkimalla, V. B., Efferth, T., 2008. Evidence-based Chinese medicine for cancer therapy. Journal of Ethnopharmacology 116, 207–210.
Lu, A., Jiang, M., Zhang C., Chan, K., 2011. An integrative approach of linking traditional Chinese medicine pattern classification and biomedicine diagnosis. Journal of Ethnopharmacology [in press. doi:10.1016/j.jep.2011.08.045].