Journal of Food and Drug Analysis

Volume 5 | Issue 4 Article 6

1997

Modernization of Chinese herbal medicine through scientific and clinical validations

Journal of Food and Drug Analysis
1997. 5(4) : 235-240

藥物食品分析
第五卷 第四期

Modernization of Chinese Herbal Medicine through Scientific and Clinical Validations

YUAN LIN*

Marco Polo Technologies, Bethesda, Maryland, U.S.A.

ABSTRACT

Traditional herbal products are heterogeneous in nature. They impose a number of challenges to quality control, quality assurance and the regulatory process. Most herbal products on the market today have not been subjected to drug approval process to demonstrated their safety and effectiveness. To gain public trust and to bring these products into the mainstream of today's health care system, the researchers, the manufacturers and the regulatory agency must apply rigorous scientific methodologies and clinical trials to ensure the quality and lot-to-lot consistency of the traditional herbal products.

Since the identities of the final products are not well defined and there are essentially no purification steps involved in the production of herbal products, the quality and lot-to-lot consistency of the products rely mostly on the quality control of source materials and their manufacturing into final products. Using modern technologies, the quality and consistency of heterogeneous herbal products can be monitored. A well designed clinical trial is the method of choice to prove the safety and effectiveness of a therapeutical products. Manufacturers of the herbal products must adhere to the requirements of Good Manufacturing Practices (GMPs) and pre-clinical testing before these products can be tested on humans. The basic principle and design of the clinical trials for herbal products are the same as those for single component chemical products. A number of randomized, double blinded controlled studies have been carried out using herbal formulations. These studies have proven the effectiveness of the herbal products tested and shown little side effects. Thousands of years of traditional use can provide us with valuable guides to the selection, preparation and application of herbal formulations. To be accepted as viable alternatives to Western medicine, the same rigorous methods of scientific and clinical validations must be applied.

Key words: **Chinese herbal medicine, regulation, clinical trial, quality control.**

INTRODUCTION

The recent increase in popularity of traditional herbal medicines has prompted researchers, regulators and manufacturers around the world to focus their attention on the following issues:

- how to improve the quality of the herbal products;
- how to regulate this group of products;
- how to bring these products into the main-

Correspondence to: Yuan Lin

Accepted for Publication: Oct. 27, 1997

stream of the health care system.

Traditional herbal products are heterogeneous in nature. They impose a number of challenges to quality control, quality assurance and other facets of the regulatory process. Since the final product cannot be easily characterized, the quality of the product relies heavily upon the process monitoring in which source material identification and testing are key to a consistently high quality product.

A well designed clinical trial is the method of choice to establish the safety and effectiveness of a therapeutical product. Manufacturers of herbal products must adhere to the requirements of Good Manufacturing Practices (GMPs) and pre-clinical testing before these products can be tested on humans. Using modern technologies, the quality and consistency of heterogeneous herbal products can be monitored. Thousands of years of traditional use can provide us with valuable guidelines for the selection, preparation and application of herbal formulations. To be accepted as viable alternatives to Western medicine however, the same rigorous methods of scientific and clinical validations must be applied.

In this report, traditional Chinese medicine (TCM) is used interchangeably with traditional herbal medicine although the former includes other treatment modalities.

PRE-CLINICAL HERBAL PRODUCT CHARACTERIZATION

Herbal products are used in Asia and in most European countries as drugs. While in the U.S., they are mostly sold as dietary supplements and are not subject to the drug regulations imposed by the Food and Drug Administration (FDA). The aim of such a policy is to give the public easy access to herbal products. There are numerous herbal products on the U.S. market today that are misrepresented, misbranded and misused. There is a booming market for herbal products in the U.S. today but there is very little quality control. Most herbal products are poorly labeled because manufacturers are not allowed to make specific disease treatment claims in the absence of human clinical trials. To gain public trust and to bring these products into the mainstream of today's health care system, the researchers, the manufacturers and the regulatory agency must apply rigorous scientific methodologies and clinical trials to ensure the quality and lot-to-lot consistency of the traditional herbal products.

I. *Product Characterization*

Many biologics, such as vaccines and allergenic extracts used in humans are complex mixtures of heterogeneous components. Since the identities of the final products are not well defined, the quality and safety of the products rely largely on process monitoring in the collection and processing of source material and manufacturing. The same principles can be applied to botanical products.

(I) *Source Materials*

There are essentially no purification steps involved in the production of many herbal products, the quality of the final products therefore depends on the quality of the plant source materials. Each batch of source material must be properly identified by trained personnel, first by its morphology, and then by microscopic examination. Electron microscopic examination of tissue sections has also been used for plant identification. If the source material is acquired from a supplier, each batch must be accompanied by a certificate of analysis. On site inspections of the suppliers are necessary to assure they comply with GMP Guidelines.

In addition to identification of plant source, it is also important that the source material adheres to the limits of the level of contamination both for foreign materials and other plant parts. When the whole herb is used as a source material, the plant part contamination is not an issue. However, on many occasions, different plant parts are used for different purposes. One of the very commonly used plants in TCM is Mulberry (*Morus alba* L.). Different parts of the plant (i.e. the bark, the fruit, the leaf, and the root) are used for different indications. In such a case, contamination by other plant

parts may present a problem, and should be kept to a minimum.

Plant source material collected at different locations, in different seasons, with different rain falls and with variations in the micro-environment can alter its quality. Reliable quantitative methods must be developed with defined parameters and limits for each plant source to ensure it meets the specifications. High performance liquid chromatography (HPLC), thin layer chromatography (TLC) and more recently capillary electrophoresis (CE) are effective technologies for quality controls.

(II) *Manufacturing Control*

In most of the botanical products, the manufacturing process is relatively simple. However, each manufacturing step must be performed based on a specified protocol. When a product is in the form of a concentrated extract, the extraction ratio, the length and temperature of extraction must be carefully controlled. A Standard Operational Procedure (SOP) must be developed for each step in the process. If more than one extract is prepared at the same time, care must taken to insure that there is no cross-contamination between one extract and another.

On February 6, 1997, the U.S. FDA published the proposed regulations for GMPs for dietary supplements and put out a request for comments (Current Good Manufacturing Practice in Manufacturing, Packing or Holding Dietary Supplements, *Federal Register*, vol. 62, No. 25, Feb. 6, 1997). The proposed regulations were based primarily on a document submitted by the industry to the agency. The addition of a quality control unit, the increase in record-keeping requirements, and the expiration dating to be based on real-time stability studies are among many new requirements which exceed the current GMPs for foods.

(III) *Final Products*

Traditional herbal products are mixtures of many components, most of which are not identified and may or may not have any effect on the activities of the final products. However, it is not a requirement to define and characterize each and every one of the constituents in the botanical product. It is recommended that the contents of active or key components as well as a finger print profile be used as indicators of product quality and consistency. A reference standard can thus be very useful for comparison both in composition and in activity. The same techniques used in quality control of source materials (HPLC, TLC or CE) can be applied to final products. In addition, it is desirable to demonstrate that the biological activities of the final products are consistent from batch to batch.

II. *Demonstration of Safety*

TCM has a long history of safe use which is well documented. Historical data of previous human use may be used to support the safety of the product without the conventional pre-clinical testing required of synthetic drugs. However, the formulation must not contain any controlled plant product and should not be adulterated with any synthetic drug substances.

Ma Huang (*Ephedra sinica* Stapf. Ephedraceae) is one of the most commonly used Chinese herbs. It contains 6 naturally occurring alkaloids, most important ones being ephedrine and pseudoephedrine. Ephedrine has been shown to be a vasoconstrictor which provides relief of congestion in bronchial asthma. However it is also a stimulant of the central nervous system. This herb was heavily misused in the U.S. as a "street drug" to get high or to boost energy levels. In recent years, more than 15 deaths were reported in the U.S. linked to overdose of Ma Huang. A committee of scientists and regulators decided that a restriction on the daily dose and warning labels were needed. The U.S. FDA recently published the following recommendations:

The maximum allowable dosage for total ephedrine alkaloids is proposed to be 8 mg per unit dose with a maximum daily dose of 24 mg. The maximum allowable duration of use will be 7 days. These restrictions, especially the maximum duration (7 days) will cause problems when Ma

Huang is used for the treatment of chronic conditions.

This was an unfortunate incidence in which the misuse of an unregulated herbal product prompted the regulators to over-react to the situation and resulted in diminishing the effectiveness of one of the most useful herbs when properly used.

III. *Stability/Expiration Dating*

The GMPs for the nutritional supplements also recommended that the expiration date be supported by data and rationale to assure that the product meets established specifications at the expiration date. Accelerated stability studies or data may be used for an initial determination of shelf life. Product shelf life shall be confirmed and may be extended on the basis of real time studies on product stored under labeled storage conditions.

The reduced pre-clinical requirements in product characterization, in safety and pharmacokinetic studies used by the U.S. FDA were intended to encourage the submission of exploratory clinical trials (phase 1 and 2) with botanical products. A number of companies and research institutes have taken advantage of this new approach and submitted the Investigational New Drug applications for clinical trials.

CLINICAL TRIALS ON HETEROGENEOUS HERBAL PRODUCTS

I. *Some Fundamental Differences in the Practice of TCM and Western Medicine*

With few exceptions, Western medicines are based on the one drug one disease model i.e. the same medication is prescribed to all patients diagnosed with the same illness. In TCM, each patient is prescribed with an individual formulation, based on the evaluation the patient's health conditions and the environment. Using the Western paradigm in the design of clinical trial basically goes against the grain of TCM. However, a number of double blinded placebo control studies have been conducted using heterogeneous herbal mixtures. Such studies are important in the sense that they led the way in breaking into the medical establishment by demonstrating the efficacy and safety of the herbal products using Western clinical trial protocols. Many of these studies were carried out outside of the U.S. but they can be performed in the U.S. after the FDA has reviewed the protocol and gives permission to proceed with them.

The basic principle and design of the clinical trials for botanicals are the same as those for single component pharmaceutical products. The current gold standards are those with randomized, blinded and controlled studies. The population size must be large enough to allow unambiguous interpretation of results.

II. *Points to Consider*

There is no single protocol which can be applied to all clinical studies, a number of points should be considered before embarking on a costly and time consuming effort.

- Design of the clinical trial: Carefully choose a well defined end point(s) and consider the ethical issues of denying the patient of an existing treatment. The need to have enough statistical power in order to analyze the results of the clinical trial cannot be over emphasized.
- Intended market: Herbal products are regulated differently from country to country. A number of countries have published guidelines on the regulation of botanicals. Marketing of such products requires the careful study of such regulations.
- Selection of products: Products of choice are those for diseases with no effective treatment by conventional western medicine and/or current treatments with severe side effects.

III. *Examples of Double Blinded Control Studies on Herbal Mixtures*

There are two well known clinical trials carried out by a team of clinicians in Great Britain using TCM formulations on atopic eczema, one for adults [(1)], one for children [(2)]. Forty patients, equally divided into a test group and a control group, were used in each study. The herbal formulation and the placebo were carefully chosen to

match each other in taste and appearance. The herbal mixture used consisted of 10 Chinese herbs with oral infusion for a period of 20 weeks. Significant statistical improvements in those receiving active treatment over those given placebo were seen in both adults and children. A one year follow up of children [3] who were enrolled in the original study was performed by the same group of physicians. Of the 23 children remaining in the study throughout the follow-up year, all continued to enjoy substantial improvement. Considering the high recurring frequency of this disease, the fact that at the end of one year most children were able to discontinue or reduce the amount of medicine required to maintain control of their eczema is an impressive result.

Bupleurum combination (minor) is a formulation of 7 herbs used in a double blind placebo trial conducted at 21 university hospitals and medical facilities in Japan [4]. Over an 8-months period from June 1994 through January 1995, 220 patients with allergic rhinitis were enrolled, divided into two groups and treated either with this herbal formulation or with a placebo for two weeks. The results showed that the testing drug produced a consistently higher degree of symptomatic relief in comparison with the placebo for each of the symptoms of allergic rhinitis:

--For sneezing, a 59.5% improvement rate (versus 30.4% with placebo);

--For runny nose, 50.0% (versus 30.1% for placebo);

--For stuffy nose, 62.3% (versus 36.5%).

One remarkable feature of this formulation is that, unlike common antihistamine medications, it does not cause drowsiness as a side effect, making it less disruptive of a patient's daily life.

The ephedrine and scute combination was used in a multicenter clinical trial in patients with steroid-dependent bronchial asthma [5]. One hundred and twelve patients were randomly assigned into group A, the treatment group and group B, the placebo group. Patients were allowed to take prednisolone, the standard Western drug for asthma, as needed. After twelve weeks of treatment, the following results were obtained:

--Global improvement of more than moderate degree: 32.8% for A and 10.4% for B

-- Global improvement of more than slight degree: 60.9% for A and 18.8% for B

--Reduction or total withdrawal of steroid intake was much higher for A than for B.

There were no side effects attributable to the herbal preparation with the exception of one patient in group A with minor stomach pain and gastric discomfort.

This study is particularly important since most patients who were dependent on steroid drugs became less dependent on the steroids following treatment with the herbal preparation for 12 weeks. Steroids such as prednisolone have been shown to ellicit many undesirable side effects such as hypertension, depression, muscle weakness and peptic ulcer, especially after long term use.

CONCLUSION

The reason for the increase in popularity in herbal medicine is due in part to the fact that many conventional chemical drugs are not very effective in treating chronic illness and have the possibility of side effects after long term use. This is not to advocate that herbal medicines are superior to Western medicines. On the contrary, conventional Western medicines do certain things very well. Each medicinal approach has its limitations and strengths.

Western medicine is best equipped in dealing with acute conditions and in emergency situations. The action is fast and predictable. We have all benefited from the use of antibiotics for the eradication of infectious agents. Side effects are not a major problem for short term users but can become serious for chronic users. TCM , on the other hand, tends to focus on the daily function of the body in a holistic manner. It strives to maintain and restore functional balance of the body taking a gentler and less invasive measure and is most suitable for treating chronic illness. However, its action is often slow and the effectiveness is more difficult to measure. No system

of medicine has all the answers. Today, we are fortunate in having multiple choices from both Western medicine and alternative treatments. Both patients and health care professionals must be well informed about the available different treatments and make the best choice for the patients.

However, entry into the main stream of the health care system requires that the same rigorous scientific and clinical validations used for the Western drugs must be applied to herbal medicines. Technologies available today for the research and development of single component drugs can be used directly or with modifications to herbal medicine. A well designed and well executed clinical trial is the best vehicle to introduce TCM to the modern society.

REFERENCES

1. Sheehan, M.P., Rustin,M. H.A. and Atherton, D. A. et al. 1992. Efficacy of traditional Chinese herbal therapy in adult atopic dermatitis. Lancet 340: 13-17.
2. Sheehan, M. P. and Atherton, D. J. 1992. A controlled trial of traditional Chinese medicinal plants in widespread non-exudative atopic eczema. Brit. J. of Dermatology 126: 179-184.
3. Sheehan, M. P. and Atherton D. J. 1994. One-year follow up of children treated with Chinese medicinal herbs for atopic eczema. Brit. J. of Dermatology 130: 488-493.
4. 1997. Japan's Health Ministry confirms efficacy of another Tsumura's kampo drug. Kampo Today. Vol. 2, Feb.
5. Egashira, Y. and Nagano, H. 1993. A multicenter clinical trial of TJ-96 in patients with steroid-dependent bronchial asthma. Ann N.Y. Acad Sci. 685: 580-583.

經由科學方法及臨床確效以達到傳統中藥之現代化

林　遠

Marco Polo Technologies, Bethesda, Maryland, U. S. A.

摘　要

傳統中藥產品本質上由不同藥材組成。因此在品質管制、品質保證及法規管理具諸多挑戰。現今市場上大部份中藥尚無法透過藥品審核程序證明其安全性與有效性。然爲能得到大衆的信賴以及將其導入目前的醫療保健體系主流，研究人員、製造廠及管理部門等必須應用嚴謹的科學方法及臨床試驗以確保傳統中藥品質及批次間品質的均一性。

因爲最終產品的均一性難以界定，更甚的是中藥產程均不經純化步驟，故對產品品質及批次間之均一性端賴原料品質管制及其製程管制。應用現代科技係可監控中藥之品質及其均一性。亦即須設計一良好的臨床試驗方法以證明其安全性及有效性，且中藥製造者必須遵循優良藥品製造標準以及這些產品在執行人體臨床試驗前必須進行非臨床試驗。中藥臨床試驗之基本原則及設計亦應與單一化學成分之西藥相同。目前已有中藥方劑進行隨機、雙盲控制臨床試驗，而這些試驗已證實受試中藥之有效性及顯示無副作用。數千年來傳統的使用經驗能提供我們有關中藥方劑之選用、製備及應用的寶貴指南。因此必須應用如同西方醫學一樣的嚴謹之科學方法及臨床確效，方能被大衆接受。

關鍵詞：中藥，管理，臨床試驗，品質管理。