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Standardization of traditional Chinese medicine and evaluation of evidence from its clinical practice

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ABSTRACT: Traditional Chinese medicine (TCM) is a typical traditional medicine (TM) with a long-standing history of preventing and curing diseases in China and other countries in East Asia. Standardization of TCM has been a topic of discussion over the past few decades in China with the goal of promoting advances in TCM in China and elsewhere around the world. Many quality and safety control standards for TCMs have been implemented in China, but systematic standards of efficacy have not been established for TCMs until now because of the absence of evidence from clinical practice. Evidence-based medicine (EBM) is the best way to provide evidence from clinical practice, but the quality of current EBM studies of TCM, and especially randomized controlled trials (RCTs) of TCM, needs to be improved. International registration of clinical trials (CTs) of TCM is a good way to provide quality evidence from clinical practice of TCM because it can improve research transparency and ultimately enhance the validity and value of scientific evidence. This evidence will provide the springboard for efforts to standardize TCM.

Keywords: Traditional medicine, Chinese medicine, evidence, standards system

1. Introduction

In recent decades, a serious situation has developed with the constant appearance of drug side effects and drug tolerance; this situation is compounded by the relatively high cost and length of time needed to develop new drugs. In contrast, the traditional Chinese medicine (TCM), one of the typical traditional medicines (TMs), is low-cost and contains natural products of therapeutic value (*1,2*). Several systematic reviews of rigorous clinical trials (CTs) have shown that many TCM, such as Andrographis, Ginkgo, and Nettle, have therapeutic value in treating certain conditions (*3*). As a result, TM and the TCM in particular have played an increasingly important role in modern health care, with the potential for new or improved clinical protocols and reduced treatment costs (*4*).

The World Health Organization (WHO) stresses that TM can play an important role in achieving the goal of "Health for All" and is dedicated to facilitating the integration of TM and Western medicine worldwide (*5*). TMs have been, and continue to be, used in every country around the world in some capacity. In much of the developing world, 70-95% of the population relies on these TMs for primary care, and the global market for TM was estimated to be US$ 83 billion annually in 2008, with a rate of increase that has been exponential (*6*). In 2000, the WHO proposed that all TMs should be evidence-based (*7*). In order to provide evidence, many countries have promoted CTs of TM in recent years. According to the CTs registry and results database affiliated with U.S. Food and Drug Administration (FDA) and National Institutes of Health (NIH), 739 CTs of TM and 228 CTs of TCM have been registered thus far worldwide (*8*).

2. Standardization of TCM in China

With a long tradition and over 2500 years of continuous practice and refinement through observation, testing, and critical thinking, TCM has played a key role in preventing and curing diseases in China and other countries in East Asia (*9,10*). In order to encourage advances in TCM, the Chinese Government has devised several national standards for TCM over the past few decades (Table 1).

The Chinese Pharmacopoeia is the cornerstone of national standards for TCM. The first edition was compiled by the Ministry of Health of the People's

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Table 1. The National Standards on TCM in China

Years	A series of standards
1953	Chinese Pharmacopoeia
1989	Drug Standards of the Ministry of Health (Finished Herbal Products Volume)
1992	Drug Standards of the Ministry of Health (Herbs Volume)
1999	Regulations for New Drug Approval
1999	Good Clinical Practices
1999	Good Laboratory Practices
2000	Good Supply Practices
2001	Good Manufacturing Practices
2002	Good Agriculture Practices
2005	Clinical Medicine Guidelines (Traditional Chinese Medicines Volume)
2010	Clinical Medicine Guidelines (Herbal Materials Volume)

Republic of China in 1953 and was then updated in 1963, 1977, 1985, 1990, 1995, 2000, 2005, and 2010 with additional records incorporated (*11*). The latest edition (the 2010 edition) describes aspects of 2,136 TCMs in terms of properties, processing, function, *etc*. (*12*). The Drug Standards of the Ministry of Health provides quality control standards for herbs and finished herbal products (*13-15*). In order to guide medical personnel in the scientific use of the Chinese Pharmacopoeia, the Clinical Medicine Guidelines have been published as support of the Chinese Pharmacopoeia since 1990. The Traditional Chinese Medicines Volume was first compiled in the 2005 edition of the Clinical Medicine Guidelines (*16*), which stress the theory and clinical practice of TCM as well as the integration of TCM with modern pharmacology and clinical medicine. The Traditional Chinese Medicines Volume records 1,460 finished herbal products, including all of those in the Chinese Pharmacopoeia, National Essential Drugs List, and Catalog of Drugs for Basic National Medical Insurance. The Herbal Materials Volume was first compiled in the 2010 edition of the Clinical Medicine Guidelines (*17*) and describes aspects of 656 herbal materials in terms of properties, processing, function, *etc*. The Herbal Materials Volume plays an important role in guiding the clinical practice of TCM. The Chinese Government has also devised and implemented several standards to regulate the pharmaceutical industry, such as Regulations for New Drug Approval, Good Laboratory Practices (GLP), Good Clinical Practices (GCP), Good Manufacturing Practices (GMP), Good Supply Practices (GSP), and Good Agricultural Practices (GAP) (*18,19*). The Chinese Government has also promoted the internationalization of TCM in recent years. Announced in 2006, the Development Plan on Standardization of TCM (2006-2010) intends to draft or revise 500 standards (including 50 national standards) implemented in China, sponsor 3-4 international standards, and participate in drafting at least 20 international standards (*20*).

However, the current reality is that the current national standards on TCM focus mainly on identification, processing, and manufacture to control the quality and safety of TCMs. Few standards for the efficacy of TCM have been implemented. The Clinical Medicine Guidelines describe the function of TCMs, the adverse reactions they cause, precautions regarding their use, *etc.*, but evidence regarding usage, dosage, efficacy, and properties of TCMs is mainly based on traditional theories of TCM rather than data from modern scientific research in accordance with evidence-based medicine (EBM). Moreover, there are many limitations in promoting the standards for TCM in Western countries (*21*). This is mainly because a TCM prescription is usually complex and involves a mixture of various bioactive compounds that have diverse mechanisms of action and synergistic/combinational effects. And the prescription emphasizes the overall condition of the individual patient and adopts a holistic approach rather than a particular course of disease or allopathic approach (*19*). Thus, some professionals are skeptical and critical of TCM because they think it is based on inaccurate and mysterious interpretations and experientialism rather than scientific evidence such as definite pharmacokinetic analysis, toxicity testing, and double-blinded clinical trials (*22*).

Given this situation, many measures have been taken in China to further promote the standardization of TCM. In the Chinese Pharmacopoeia (2010 edition) (*12*), the names of Chinese herbal medicine and their Latin names have been corrected in accordance with international standards. Many advanced techniques and methods, such as liquid chromatography/mass spectrometry (LC/MS), DNA molecular identification, have been used to identify components to enhance the sensitivity and specificity of analysis. Measures to control impurities and sterility tests are also required in accordance with pharmacopoeias from Europe and the U.S. With regard to safety standards, inductively coupled plasma mass spectrometry (ICP-MS) is required to test for arsenic, mercury, lead, cadmium and copper in medicines in the Chinese Pharmacopoeia (2010 edition) in order to further control heavy metals, hazardous materials, impurities, residual solvents, and other components. Many Chinese experts are exploring the standardization of TCM, such as standardized verfication (*23*), standardized processing (*24*), and standardized good usage practices (*25*), with using advanced science and technology . Recently, experts built a combination system to predict the properties of medicines in herbals based on their chemical components (*26*). The system had an accuracy of 83.3% for a training set of medicines and 81.0% for a test set. Experts believe that this system will characterize medicines in herbals with TCM properties to help design new prescription for better therapies.

3. Evidence of TCM from clinical practice

Many national standards on TCM have been established in China over the past few decades, and many advanced techniques and methods have also been implemented in recent years to regulate the identification, processing, and manufacture of TCMs, but the established standards focus mainly on quality and safety control of TCMs. Systematic standards for the efficacy of TCMs have not been established until now. The absence of evidence from clinical practice precludes the drafting of standards of efficacy for TCMs. EBM is the best way to provide evidence from clinical practice of TCM and includes evidence from prospective randomized controlled trials (RCTs) of TCMs and evidence from systematic reviews or meta-analysis of RCTs on TCMs.

EBM was introduced in China in 1996. Experts systematically reviewed 3,312 RCTs on TCMs published in 13 journals from mainland China from 1980 to1998 and found that few were RCTs (RCTs accounted for 10.06% of 32,939 clinical research papers in total) and that many were of poor quality (*27,28*). With the development of EBM, experts systematically evaluated 7,422 RCTs on TCM from 26,263 clinical research papers published in mainland China from 1999 to 2004 according to the Cochrane Handbook, Consolidated Standards of Reporting Trials (CONSORT) checklist, Jadad scale, and similar information. They found that the proportion of published RCTs in relation to all types of published CTs increased from 18.6% in 1999 to 35.9% in 2004 ($p < 0.001$) (Figure 1), representing a significant increase. The quality of reported RCTs on TCM also improved, but remains poor overall. Out of a total of 7,422 RCTs, only 587 (7.9%) were randomized or used sequentially generated patient identifiers, 55 (0.7%) were adequately double-blinded, and 823 (11.1%) mentioned drop-outs (*29,30*). A number of other studies have also evaluated the quality of published RCTs on TCM (*31-35*) and found that the poor methodological quality limited the quality of the trial. Flaws included a small sample size, no double-blind testing, lack of long-term outcomes, lack of compliance data, incomplete follow- up data, failure to quantitatively express efficacy, and failure to include data on baseline characteristics or side effects. Experts also assessed the quality of systematic reviews and meta-analysis of TCM published in mainland China from 1994 to 2006 according to the 18 items of the Quality of Reporting of Meta-analyses (QUOROM) Statement and related information. They found that few systematic reviews or reports of meta-analysis met international standards due to insufficiently described methodology or lack of reproducibility (*36*).

Internationally, the trend is to promote multi-center, double-blind CTs with a large sample in order to provide the best evidence from clinical practice. The Declaration of Helsinki states that "Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject." The WHO stresses that international CTs registration will improve research transparency and ultimately enhance the validity and value of scientific evidence. International CTs registration means the publication of an internationally-agreed set of information about the design, conduct and administration of CTs (*37*). Many authoritative international CTs registry platforms have been established worldwide, such as the International Clinical Trials Registry Platform (ICTRP) administrated by the WHO, the Clinical Trials.gov (*www.clinicaltrials.gov*) affiliated with the U.S. FDA and NIH, and the National Research Register (*www.nrr.nhs.uk*) administrated by the U.K. National Health Service (NHS). All of these platforms allow free registration of CTs by investigators from all over the world and numerous aspects, such as study type, study design (allocation, intervention model, masking, *etc.*), the inclusion/exclusion criteria for eligibility, implementation site, are required to register a CT. According to Clinical Trials.gov, 228 studies on CTs of TCM have been registered thus far; of 132 studies sponsored by China (*38*), 83 are from mainland China, 27 are from Hong Kong, and 22 are from Taiwan. Of a total of 132 studies, 50 have been completed, 35 are recruiting, and 47 are not recruiting or have an unknown status. Moreover, 112 studies are randomized and 73 studies are double-blind, respectively accounting for 84.8% and 55.3% of the 132 studies in total.

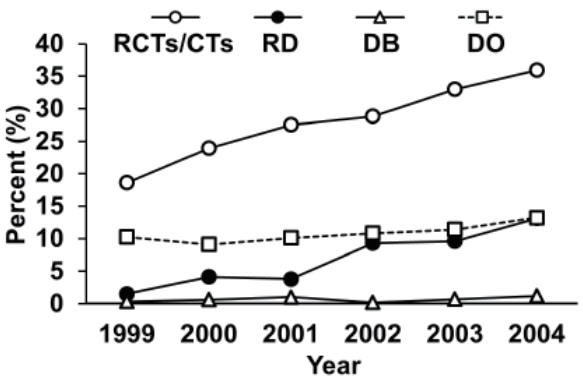

Figure 1. Distribution of RCTs on TCM published in 13 journals from mainland China from 1980 to 2004 and their Jadad scores. RCTs: randomized controlled trials; TCM: traditional Chinese medicine; CTs: clinical trials; RD: randomization; DB: double-blind; DO: dropouts.

In conclusion, the quality of evidence from clinical practice of TCM must be improved and multi-center, double-blind RCTs of TCM with a large sample should be conducted. International registration of CTs on TCM is a good way to provide quality evidence from clinical practice of TCM because it can improve research transparency and ultimately enhance the validity and value of scientific evidence. This evidence will provide the springboard for efforts to standardize TCM.

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