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An efficacy-driven approach to the research and development of traditional Chinese medicine

試論以「療效為主導」的中醫藥研究策略

Research activities in traditional Chinese medicine have, to date, focused on the search for relevant active substances and mechanisms of action. This research approach is shaped partly by the conventional drug development model, which commences with determining the mechanism of disease, followed by the design and synthesis of therapeutically active compounds or molecules, animal and in vitro studies, and finally clinical trials in humans. Demonstration of clinical efficacy in humans using randomised controlled trials may be a better starting point for research into traditional Chinese medicine, given that these therapies are already in common use. An efficacy-driven approach could avoid basic research into therapies that are clinically ineffective, thus sparing precious research resources.

迄今為止，中醫藥研究的重心集中在尋找相關的活性物質和作用機理。這種以機理為中心的研究策略主要受西藥研究開發模式的影響。目前西藥開發多由機理研究開始，然後設計和合成相關的化學物質或生物分子，再到離體及動物實驗，最後才能進行臨床試驗檢驗其療效。由於中醫藥已經在人類廣泛使用，用隨機對照試驗展示中醫藥療效可能是中醫藥研究開發的一個更好的起點。採用以「療效為主導」的研究策略可避免大量不必要的基礎研究，因此節省寶貴的醫療衛生的資源。

Key words:
Clinical trials;
Evidence-based medicine;
Medicine, Chinese traditional;
Randomized controlled trials;
Research

關鍵詞：
臨床試驗；
實證醫學；
醫學，中國傳統；
隨機對照試驗；
研究

HKMJ 2001;7:375-80

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Introduction

A recent editorial in the Lancet[1] conveyed a clear message to the growth enterprise of traditional medicine: first, the evidence. The evidence refers to knowledge on efficacy and safety obtained from clinical trials rather than intermediate mechanisms. Over the past 50 years, the mechanism-centred approach has dominated research and development in traditional Chinese medicine (TCM). In this mechanism-centred paradigm, scientists are primarily preoccupied with the search for the molecular, cellular, and pharmacological basis of TCM, with identification of relevant active substances, and investigation into the mechanism of individual therapies. The question of efficacy has been largely neglected.

This obsession with mechanisms is extremely costly. Tens of thousands of scientists and billions of dollars may have been committed to this quest since the founding of the People's Republic of China. Almost every theory, every concept, and every technique in modern biomedical science has been employed. Successes are occasionally claimed, such as with respect to acupuncture.[2,3] However, many basic questions have not been satisfactorily answered, such as the nature of Shenxu syndromes (腎虛,

insufficiency of the 'kidney') and the material basis for Jingluo (經絡), a 'network' of conduits that guide and channel the circulation of nutrients (血) and energy (氣) through the body.[4] In the words of Liang[4]: "The search for the nature of disease in TCM has descended into a downward spiral. All the breakthroughs that were once cheerily foreseen and awaited seem to have become a sad illusion. The whole field of TCM research is currently in a state of disarray. Basic research has come to a standstill. What has gone wrong? Where should we go from here?"

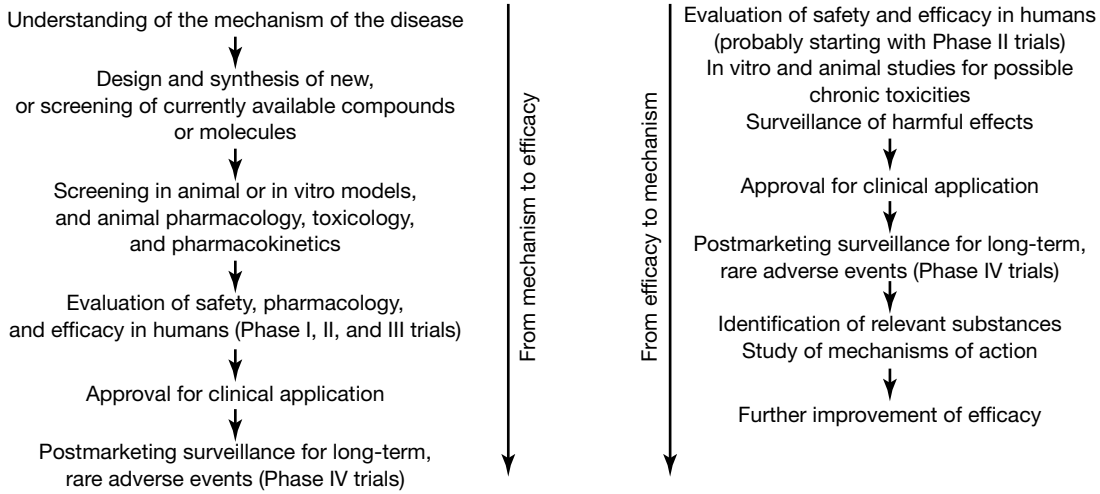
Why should research and development in traditional Chinese medicine adopt an efficacy-driven approach?

The mechanism-centred approach to TCM research is shaped partly by the belief that every TCM therapy works and therefore further demonstration of its clinical efficacy is unnecessary.[5] As many current research activities in TCM aim to develop new drugs, the model by which new drugs are designed and developed in modern scientific medicine is relevant.[6] The development of new drug therapies for cancer provides a good example of this model.[7] The model has three important conventions (Box: left). Firstly, the potential drug must be a single, chemically known compound or molecule, or a combination of known substances. Secondly, for ethical reasons, evaluation of the drug's safety and efficacy must begin in vitro and then in animals. Thirdly, the drug's pharmacology and mechanism of action must be well understood before it is subjected to evaluation in humans. This model is very successful in modern conventional (western or scientific) medicine and is readily available for application to TCM.

For TCM, however, it may be best to conduct research in the reverse order, commencing with demonstration of the clinical efficacy in humans using randomised controlled clinical trials (Box: right). Clinical efficacy refers to the capacity of a drug to bring about more good than harm in treated patients and is what matters most for any medical intervention.[1,8,9] In the efficacy-driven approach, investigation into the mechanisms and the search for active substances is also important, but should be undertaken after clinical efficacy is firmly demonstrated.[10] If a therapy does not work clinically, then it should be discarded and not subjected to further investigation. Demonstration of clinical efficacy first will thus save resources by avoiding unnecessary basic research into ineffective therapies.

Even if a therapy is deemed efficacious, it may not be possible to immediately determine the relevant underlying mechanisms and active substances, particularly when dealing with the complexity of many compounds contained in a herbal therapy. In the realm of scientific discovery, successes are often hard to predict.[11] However, we need not wait for such discoveries. Lack of knowledge about the mechanisms and active substances involved does not have to prevent the use of clinically efficacious therapies. Many powerful medical interventions, such as penicillin and smallpox vaccinations, were accepted and widely used before their mechanisms were understood.[12] Interventions lacking efficacy will eventually be

Comparison of the mechanism-based research approach to drug development in conventional medicine and the proposed efficacy-driven approach advocated for the advancement of traditional Chinese medicine



discarded whether we understand the underlying mechanisms or not. Bloodletting is a classic example, and beta-carotene for the prevention of heart disease and cancer provides a modern equivalent.[13-16]

Furthermore, investigations into mechanisms of action provide tentative and hypothetical explanations. Theories change over time and as new knowledge becomes available. How does cowpox prevent smallpox? The answer to this question today differs from the explanation given 200 years ago. Similarly, understanding of the value of treating fever has changed greatly over time. Some would even argue against the search for 'deep [explanatory] models'. Any good empiricist can attest the fact that sound evidence is hard won. "The human mind can concoct a theory to support any set of notions and observations."[9]

Studies that evaluate the clinical efficacy of interventions will have immediate clinical or public health applications regardless of whether they demonstrate positive or negative results. If a therapy is proven to be efficacious, further promotion of its use will benefit many more. On the other hand, if the therapy is lacking in efficacy, termination of its use will save resources.

Finally, the value of medical theories lies in successfully guiding medical practice and generating efficacious therapies. Thus, demonstration of clinical efficacy is the best empirical test of the validity of TCM theories. Based on therapies with confirmed clinical efficacy, new and improved TCM theories will be on more solid ground.

Evidence for efficacy: convention or randomised trials?

To many supporters of TCM, the long history of use, tradition, faith, popularity, and anecdotal reports are still the best evidence for the efficacy of TCM interventions. Undoubtedly, convention and popularity provide useful indications of possible efficacy but should not be taken as equivalent to scientific evidence derived from organised research. Case series and concurrent but non-randomised controlled studies are of value, particularly when the intervention is exceptionally efficacious, such as the Polio trivalent vaccine, bone setting, and penicillin for lobar pneumonia.

In conventional medicine, the most rigorous method for the evaluation of any medical intervention is the randomised controlled clinical trial.[17,18] As randomised trials are conducted in human subjects, their results are directly applicable to human patients. More importantly, randomisation, blinding, intention-to-treat analysis, and other bias-prevention techniques in trials help to reduce possible biases to a minimum. The ascendancy of randomised controlled trials in conventional medicine heralded the arrival of evidence-based medicine.[19] Clinical experience and pathophysiological reasoning are crucial and necessary, but not sufficient to provide reliable knowledge and safeguard against ineffective therapies being introduced into medical practice. It is now accepted that a drug should not enter clinical practice without a demonstration of its efficacy in clinical trials.[19] Almost half a million clinical trials have been conducted on medical interventions in various disciplines of medicine.[20] Organised efforts, such as The Cochrane Collaboration,[21] have also been made to systematically review and disseminate the best available evidence from organised research. More importantly, physicians, health workers, and policy makers have widely recognised the importance of randomised trial evidence in clinical and health care decision making. Due to their scientific rigour, randomised trials can evaluate therapies with effects of only moderate magnitude and should be particularly applicable to TCM. It is time for TCM to be tested against this higher standard.[22,23]

Useful interventions should do more good than harm

Irrespective of potential beneficial effects, we have a legal as well as a moral duty towards our patients to avoid or minimise possible harmful effects of interventions used.[24,25] Excessive emphasis on adverse effects, however, could stifle the development of TCM and lead to the rejection of efficacious therapies. Every efficacious treatment that alters body function has side-effects. If we were to discard all therapies associated with adverse events, many routinely used, beneficial medical interventions would be excluded.

Toxicology should also be evidence-based.[26] An observation of adverse effects of a drug in a single patient or a group of patients provides valuable information but should not be used as the sole evidence supporting discarding the treatment.[27] It should be no great surprise that of the millions of users of Viagra (a drug for treating erectile dysfunction), a few die of myocardial infarction.[28,29] Some deaths due to myocardial infarction would be expected in the population taking Viagra, irrespective of Viagra use.[30]

Nonetheless, it would not be correct to overemphasise benefits of a treatment over safety issues.

For the advancement of traditional medicine as well as conventional medicine, there should be a balance (or more appropriately an imbalance) between benefits and harm—useful treatments should be able to bring about more good than harm.[8,31] The best way to demonstrate this balance is through a clinical trial, though trials may not always be feasible or provide information within a desired time-frame, particularly when the harmful effect is with long-term use and rare.[32] The efficacy-driven approach would also argue for surveillance of the long-term toxicity of widely used TCM therapies.

Ethical paradox of clinical research in traditional Chinese medicine

Is it ethically acceptable to evaluate the efficacy of TCM in humans first? Traditional Chinese medicine has been used in humans for thousands of years. Whether we put it to the test or not, TCM will continue to be used in countries and regions where it is officially recognised. New therapeutic methods and herbal recipes will continue to be 'invented' according to the principles of TCM, and given to human patients by individual physicians without any systematic evaluation. Given this situation, randomised controlled trials of TCM therapies would be nothing more than a systematic application of the medicine with explicit research objectives.

Currently, TCM practitioners can prescribe a therapy to patients for which the potential benefits and harm have not been studied systematically. A TCM researcher, however, is required to demonstrate the pharmacology and safety of a herbal therapy in animals before it can be considered for research in humans.[33] Should there be one standard for the ethics of therapeutic trials and another for routine medical care?[34,35] Is it ethical not to carry out randomised controlled trials of therapies that are widely used but have uncertain efficacy? Discussion and debate on ethical issues in relation to TCM are also relevant to its advancement, and are needed urgently.

Randomised clinical trials available in traditional Chinese medicine

There have been very few randomised clinical trials of TCM reported in western medical literature.[36-38] In 1997, research was undertaken to estimate the number and assess the methodological quality of randomised controlled trials on TCM that were published in China.[39-40] Of the approximately 100 TCM journals in China, 28 were randomly selected for study. A total of 2938 randomised controlled trials were published in these journals in the 16 years prior to 1997, with the number of reports doubling every 2 to 3 years since the early 1980s. It was estimated on this basis that approximately 10 000 randomised trials would have been published in China prior to 1997.

The majority of the trials examined by the researchers were of poor methodological quality. Major problems included lack of blinding, use of short-term outcomes, lack of data on adverse effects, lack of use of the intention-to-treat analysis, and selective publication of positive trials. These methodological problems complicated the interpretation of trial results.

Can clinical trials be used to evaluate traditional Chinese medicine for the treatment of diseases defined by conventional medicine?

Traditional Chinese medicine and conventional medicine originated from different world views: the former from ancient Chinese philosophy and the latter from ancient Greek and Roman medicine.[41,42] Consider the ancient Buddhist tale, where a few blind men try to find out what an elephant is like. The man who touched a leg concluded that the elephant was like a post, while the one who grabbed the tail believed that the elephant was like a rope. Using this analogy, conventional medicine may see only the 'leg', while TCM identifies the 'tail'. The same disease can be different problems in the two different paradigms of medicine. This difference in view means that for TCM to be evaluated appropriately, it cannot be evaluated by the standards of conventional medicine. It must be evaluated within its own paradigm.

Continuing with the analogy of the blind men and the elephant, if the elephant were gone, the blind men would draw the same conclusion. The very existence of the elephant is essential to any deduction from the evidence. If the two approaches to medicine see and deal with the same underlying disease in different ways, and the disease is 'cured' by either form of medicine, it will be 'gone' regardless of methods. This suggests two ways of designing valid trials, using the prognostic outcomes of conventional medicine to assess the efficacy of TCM. Firstly, patients with the same syndrome according to TCM are recruited from those with a particular conventional medicine disease. In such a trial, the same TCM therapy can be evaluated and generalisation about the therapy is valid though the number of eligible patients may be relatively small and difficult to recruit. Secondly, patients with the same

disease according to conventional medicine are recruited regardless of their diagnosis in TCM. Finding and selecting eligible patients would be much easier but patients then must be treated with different TCM therapies. Many TCM trials thus far are of the latter type, and may demonstrate that TCM is efficacious, but generalisation about each therapy has been difficult unless the trial is sufficiently large to allow subgroup analyses.

Can clinical trials be used to evaluate individualised treatments in traditional Chinese medicine?

It has been argued that since TCM treatments are tailored individually to the patient's need, randomised controlled trials cannot be applied to TCM as such trials require similar patients requiring similar treatments. This critique of randomised trials is not new.[43,44] Sir Austin Bradford Hill, noted 40 years ago: "The most frequent and the most foolish criticism of the statistical approach in medicine is that human beings are too variable to allow of the contrasts inherent in a controlled trial of a remedy..." He challenged his critics: "If each patient is unique, how can a basis for treatment be found in the past observations of other patients?"[45]

One can always find ways in which a patient differs from others. What matters is whether or not this dissimilarity is relevant to the efficacy of the treatment. As in conventional medicine, there are a limited number of identified 'syndromes' in TCM (that is, Zheng or 症), and there are probably only a few hundred which are common. This implies that patients do have similar TCM syndromes requiring similar treatments. In TCM, a syndrome is the state of a disease at a certain time point. The same disease may manifest different syndromes at different times and different 'diseases' may demonstrate the same syndrome.

Syndromes rather than diseases normally determine the choice of treatment. Classic herbal formulas, such as Liu Wei Di Huang Wan (六味地黃丸) for deficiency in the Yin of 'kidney' (腎陰虛) and Si Wu Tang (四物湯) for deficiency in 'blood' (血虛), were developed for specific syndromes. Evidence is often lacking for further tailoring of a treatment beyond these somewhat standardised formulas.[38] The same TCM therapy is also often prescribed to patients with the same disease, regardless of syndrome.[4] Given these arguments, it would be foolish to deny the value of randomised trials in TCM since that would be a denial of the greater tenets of science—induction and causation.

Creating the context for the efficacy-driven approach

"One of the greatest methodological fallacies of the last century in social research is the belief that science is a particular set of techniques; it is, rather, a state of mind, or attitude, and the organisational conditions which allow that attitude to be expressed."[46] Is this also true of TCM? It is the authors' view that the sceptical attitude towards the need for evaluation, rather than methodological difficulties, has hindered the evaluation of TCM. For many advocates of TCM, every therapy works, so evaluation is unnecessary. For sceptics, TCM is a quack science, so evaluation is pointless. The truth most likely lies somewhere in between these opposing viewpoints: some TCM therapies may be effective and some are probably not effective. Methodological difficulties can be resolved and new methods can be developed only when it is accepted that evaluation is necessary.

Conclusions

Clinical efficacy is crucial for any medical intervention. In TCM, however, the need to demonstrate clinical efficacy has not been widely recognised. Tradition, faith, popularity, adherents' enthusiasm, and anecdotal accounts are still commonly used as evidence for clinical efficacy rather than the results from organised research. For the past 50 years in China, resources have been focused on the search for the scientific basis of TCM, for the active substances used in therapies, and for the mechanisms of action. Experience shows that this mechanism-centred approach has been costly and largely unsuccessful. The advancement of TCM now requires that the demonstration of clinical efficacy is placed high on the research agenda, with basic research taking place only after efficacy has been clearly demonstrated in clinical trials. Irrationally held truths may, after all, be more harmful than reasoned errors.[47] It is hoped that this paper will stimulate new ideas and vigorous debate on the future advancement of TCM.

Acknowledgements

We would like to thank Prof T Chan, Prof J Dickinson, Prof TW Wong, Prof J Woo, and Mr J Liu for their valuable comments and suggestions on early versions of the manuscript, and to Prof C Silagy and Dr M Clark for providing some of the examples used in the paper.

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