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Review

# Major achievements of evidence-based traditional Chinese medicine in treating major diseases

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ABSTRACT

A long history of use and extensive documentation of the clinical practices of traditional Chinese medicine resulted in a considerable number of classical preparations, which are still widely used. This heritage of our ancestors provides a unique resource for drug discovery. Already, a number of important drugs have been developed from traditional medicines, which in fact form the core of Western pharmacotherapy. Therefore, this article discusses the differences in drug development between traditional medicine and Western medicine. Moreover, the article uses the discovery of artemisinin as an example that illustrates the "bedside–bench–bedside" approach to drug discovery to explain that the middle way for drug development is to take advantage of the best features of these two distinct systems and compensate for certain weaknesses in each. This article also summarizes evidence-based traditional medicines and discusses quality control and quality assessment, the crucial steps in botanical drug development. Herbgenomics may provide effective tools to clarify the molecular mechanism of traditional medicines in the botanical drug development. The totality-of-the-evidence approach used by the U.S. Food and Drug Administration for botanical products provides the directions on how to perform quality control from the field throughout the entire production process.



**Contents**



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## 1. Introduction

Nature is a major source of new therapeutic small molecules. About half the pharmaceuticals developed over the last three decades and approved by the U.S. Food and Drug Administration (FDA) are natural products, semisynthetic derivatives, or based on a prototype from nature [1–4]. In this period, a highly reductionist approach, based on the "single target–single compound" paradigm, or "cell-based screening" dominated the drug development in the Western pharmaceutical industry, an approach that is clearly different from those used by traditional medical systems. Thus, a more phenomenological, descriptive, and system-based (homeostasis) view is the basic concept in traditional Chinese medicine (TCM). Traditional medical doctors often apply a holistic approach in prescribing a personalized mixture of (herbal) components to a patient. In the past, the two philosophies, one adopted by Western medicine and the other adopted by TCM, did not match well. However, new insights into the complexity of human health and disease, particularly through the advent of the "omics" technologies and more systemic thinking in life sciences, have resulted in a rethinking of the importance of traditional medicine [5]. The 2015 Nobel Prize in Physiology or Medicine was recognition of the importance of traditional medicines by the Western medical world. Systemic approaches to studying health through observation-based systems biology are becoming more important now. At the same time, the need for evidence-based use of traditional medicines finds a foothold in the East. Combining traditional and Western medicine will result in important benefits for primary health care. Moreover, it opens new perspectives for drug discovery and development as the processes move from the "single target–single compound" approach to more systemic approaches to preventing and treating diseases.

This article reviews evidence-based traditional medicines for the treatment of some major diseases. In addition, we discuss differences between the development models of evidence-based traditional medicines and novel Western medicines using the discovery of artemisinin as an example. The "bedside–bench–bed side" approach to drug discovery seems to be a middle way for drug development, taking advantage of the best features of both systems and compensating for some of their weaknesses.

## 2. Comparison of drug development in traditional medicine and Western medicine

The major difference in drug development in ancient times and present days is that in the past, medicines were tested directly on humans, whereas the starting point of drug development today is screening at either the molecular or cellular level (Fig. 1A) [6–8]. In medicinal plant research, after proving the activity in bioassays at the level of molecules or cell lines, bioassay-guided fractionation is used to isolate and identify the active compound(s). Finally, the activity of the active compound(s) is further elucidated *in vivo* using whole organisms (Fig. 1A2). This illustrates the bottom-up reductionist approach practiced in Western biomedical sciences. In the past three decades, the search for novel drugs has relied on hypothesis-free and high-throughput screening (HTS) of a large number of pure compounds, combinatorial compound libraries, or extracts of various organisms, including plants, using enzyme- and receptor-binding assays related to the target disease [9]. However, this approach has not always been successful, which is best illustrated by a slowly decreasing number of novel small-molecule drugs entering the market. The problems encountered can be illustrated by the case of huperzine A, an alkaloid from *Huperzia serrata*, which showed multiple beneficial effects in preclinical models but failed in a phase 2 clinical study for Alzheimer's disease [10]. Moreover, in complex mixtures of compounds present in herbal medicines, certain combinations of compounds may be needed to attain activity. A study of *Berberis fremontii* has shown that the antimicrobial effect of the bioactive compound berberine was enhanced more than 100-fold in combination with an inactive component, 5′-methoxyhydnocarpin, isolated from the same plant [11]. This further supports the idea that the resistance of plants against microorganisms is based on synergistic effects and explains why to date no antibiotic has been developed from plants [12]. Synergy thus may play an important role, as also shown in the example of St. John's wort, in which no single active compound has been found that could explain the proven clinical activity of the plant [6]. These examples indicate the limitations of screening approaches using cell-based assays or HTS, which will not detect the synergy and prodrugs. In addition, testing of bioavailability, a major factor contributing to the effect of a medicine, requires *in vivo* studies [13,14].

Generally, treatment with traditional medicines is based on holistic characterization of the patient's syndrome. Traditional prescriptions usually comprise a group of herbs specifically tailored to the syndrome [15]. In the past, these traditional medicine mixtures must have been tested directly on humans (Fig. 1A1). After their efficacy and safety was established in humans, traditional medicines were used to cure diseases, treat symptoms, and/or maintain homeostasis. Considering the original theory of mixing certain medicinal plants, one may expect some sort of synergism to be involved, such as acting on different targets, affecting bioavailability, suppressing adverse side effects, and altering drug metabolism and excretion [16]. Consequently, the reductionist approach, i.e., testing single active components against well-defined targets, does not lead to understanding the pharmacology of a multicomponent agent as it fails to integrate the results obtained using separate reductionist approaches. Such an approach does not result in a systemic understanding of the concerted pharmacological interventions of multicomponent mixtures [17]. In contrast, traditional medical systems are aimed at a holistic understanding of the whole organism and at applying this wisdom in a top-down manner in a search for knowledge.

Therefore, instead of using a reductionist approach, evidence of the activity of a traditional medicine should come from *in vivo* tests, preferably through clinical trials or animal experiments [6]. Wang et al. pointed out the importance of metabolomics as a tool in such a systemic approach to understanding Chinese medicine [18]. The importance of such an approach is confirmed by the analysis made by Swinney and Anthony who found that more than half of the first-in-class novel antitumor compounds in the years 1999–2008 were found through phenotypic screening [19], a general trend for all the 259 novel drugs that were approved by the FDA in the period mentioned. Moffat et al. further elaborated on this and gave a vision how such an approach can even be more effective in the future [20]. Classical pharmacology, wherein a traditional preparation is taken as a starting point, holds promise for studying the synergetic nature of herbal medicine [6], while clinical trials will show if there is an activity. The various "omics" technologies, applied in a systems biology approach, offer excellent tools to get an insight into possible modes of action [6,16,18]. Animal experiments, including novel model organisms such *Caenorhabditis elegans* and zebrafish, may be used to obtain a further insight into the activity.

## 3. Drugs derived from traditional medicines for treatment of chronic diseases

Chronic disease refers to a disease that has a long period of development and lasts for a long time. Common chronic diseases