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LETTER TO THE EDITOR

Filling the gap between traditional Chinese medicine and modern medicine, are we heading to the right direction?

KEYWORDS

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 Gap;
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 Intelligent mixture

Summary Traditional Chinese medicine (TCM), the ancient medicine popular in China and surrounding areas, has been recognized as a typical representative of complementary and alternative medicine. Over long period in clinical practice, especially the progress in basic research, data on the effectiveness and beneficial contribution of TCM herbs to public health and disease control have been accumulated while the quality of the evidence is generally poor. The most common clinical practice of TCM herbs is herb combination called formula which consists of several types of medicinal herbs or minerals, which is quite different from modern medicine. Definitely, tens of hundreds of compounds could be identified in even a small formula. With the regained enthusiasm on natural products based new drug R&D, the proposed multi-target drug discovery strategy, the booming of -omics technologies, and the implementation of ambitious plan of TCM modernization in China, attempts have been made to fill the gap between TCM herbs and modern drugs. However, are we heading to the right direction?

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A series of ethnomedicines have been appeared and disappeared in the long course of human history. Among which, only few of them has been handed down and preserved to present. Even less shows vitality and vigor in health care and disease control under the impact of modern medicine, an international medicine mainly derived from experiments. Traditional Chinese medicine (TCM), a typical ethnomedicine derived from the practice of ancient Chinese, is a summary of thousands years of clinical experiences. During its formation and development, it has been greatly impacted by traditional Chinese culture and exhibits significant cultural imprint. In contrast, modern medicine has abandoned the cultural impact and is entirely based on the experimental natural sciences. It is clear that dramatic differences have existed between TCM and modern medicine in the theoretical development, the cognitive approach, and the way of thinking, *etc.*, which forms the huge gap between them. This gap is affecting the potential of jointed use of TCM and modern medicine to treat diseases.

The most common practice in TCM therapy is through TCM herbs which remain as popular therapeutic remedy and dietary food not only in China but also in Japan, Korea, Singapore, Hong Kong, and Macau SAR of China, where it was considered as contributing a lot to public health and disease control. For East Asians, particularly the Chinese,

TCM herbs are not so ‘‘hard to swallow,’’ as described in Nature.¹ However, internationally, TCM herbs are often criticized as being without proven effectiveness and safety and is merely approved as functional food or food additive even though significant progress has been made in recent years, such as the therapeutic effect of arsenic trioxide for acute promyelocytic leukemia,² and artemisinin for malaria.³

The flourishing of modern biomedical technologies provides a good opportunity for TCM development. With the rise of the Chinese economy in the past 10 years, the Chinese government has formulated ambitious plans for the modernization and internationalization of TCM herbs,⁴ such as the launch of the ‘‘Chinese Medicine Modernization Program’’ (2002–2010) and the herbalomics project,⁵ among others. In the meantime, the fact that no significant increase in the number of FDA approved new molecular entities (NCE) in last decade promote us to reevaluate the drug discovery strategies.⁶ In addition, the failure of combinatorial chemistry and high-throughput screening (HTS) to increase new drug productivity promotes the regained enthusiasm for natural products based drug discovery as natural products provide crucial and unmatched chemical diversity to modern drug discovery programs.⁷ Many large international pharmaceutical companies showed great enthusiasm to TCM herbs, particularly after the approval of the Guidance for Industry Botanical Drug Products by the FDA in 2004. From drug

discovery point of view, filling the gap between them are urgently needed.

In fact, shortly after the introduction of modern medicine to China about 170 years ago, attempts have been made by some farsighted TCM experts to fill the gap. As a result, an academic school called converged traditional and western medicine school was formed. However, nearly all the pioneers in the school are clinical doctors with views and perspectives mainly from TCM theories and clinical practices. The integration of TCM and modern medicine from herb/drug, the common carrier for both, point of view has not been well performed. The integration of TCM herbs with modern drugs might be a feasible and effective way to fill the gap between the two systems.

However, microscopic dissection of the action and mechanisms of Chinese herbs has been largely neglected. K.K. Chen might be the first expert to use modern technologies to study Chinese herbs. In last 20s, he isolated ephedrine from a Chinese herb called Mahuang and found that it showed adrenergic effect.⁸ This strategy is guided by reductionism and expected to find powerful and effective pure compounds from Chinese herbs by isolation, purification and pharmacological evaluation and among others. The application of advance technologies, thus, has been considered as the critical step to success. However, the fact that no key breakthrough has been made in the modernization and internationalization of TCM herbs despite the applications of HTS,⁹ high content screening,¹⁰ nanotechnology,¹¹ -omics,^{12–14} systems biology,¹⁵ network pharmacology,¹⁶ is embarrassing. Although the discovery of artemisinin is worthy of the Lasker Clinical Research Award,¹⁷ such successful stories are few and far from becoming a common drug discovery model for TCM herbs. Furthermore, such pure-compound based research model has been frequently questioned and criticized due to its negligence of TCM theory. Thus, new research strategies are necessary.

The essence of TCM herbs in clinical practice is compatibility, that is, several different herbs are prescribed simultaneously according to the patient's condition. This combination of different herbs is called TCM formula. A typical formula contains at least four herbs which are addressed as the Emperor, the Minister, the Assistant, and the Envoy according to their different contributions in the formula. Generally, the Emperor contributes the main therapeutic effect for the formula and the Minister enhances the Emperor's effect. The primarily role of the Assistant is to enhance the therapeutic effect of the Emperor and the Minister and/or eliminate or restrict their undesired side effects or potential toxicity. The Envoy is considered to guide all the other herbs to reach the treatment sites and to reconcile them. Modern phytochemical studies have shown that each herb contains dozens or even hundreds of pure compounds. Obviously, reductionism-based strategy varies greatly from the both the theory and the clinical practice of TCM. Recently, the HTS has been widely applied in TCM screening and evaluation. With thousands and millions of samples, the selection of "hit" is prudent and stringent. Accumulated data indicated that, as natural products, the pure compounds isolated from TCM herbs show relatively lower pharmacological potency and selectivity. For example, the cytotoxicity of curcumin, berberine, and oridonin to many cancer line cells expressed as IC₅₀ are approximately

5–100 μM , 40–100 μM , 3–80 μM , respectively.¹⁸ However, while performing screening for anti-cancer drugs, candidates with more potencies are welcomed.¹⁹ Therefore, the current single-compound-based screening strategy of TCM herbs, which works through a variety of low-potency ingredients, together with the high-selectivity and potency-based evaluation system, is an undoubtedly impassable test for TCM herb derived pure compounds. Thus, some potential candidates or lead compounds have been overpassed. On the other hand, the unidentified components, unconfirmed effects and potential toxicities and among others have formed formidable barriers for quality control of TCM herbs. Thus, to maintain "the original taste and flavor" of TCM formula is extremely difficult. That's the dilemma. Some Chinese scholars have aware of this issue and proposed several alternative strategies in recent years. For example, the multi-component Chinese medicine research strategy has been raised,^{20,21} which attempts to use the active constituents or effective parts of Chinese herbs to replace the original formula. Though this strategy exhibits some advantages by simplifying the complicated components of Chinese herbs to certain active parts and applies fingerprinting technologies to fulfill the quality control, the consistency of the combined active parts in pharmacology, toxicology, phytochemistry, etc., still remains to be resolved.

TCM formula is an ancient empirical-based form of drug combination which requires rigorous experimental design, system evaluation and analysis. Pure compounds combined investigations is a new trend in recent years for exploring the actions and potential mechanisms of TCM formula. Realgar-Indigo naturalis is a formula designed by TCM doctors in the 1980s entirely based on TCM theories which contains realgar, *Indigo naturalis*, *Salvia miltiorrhiza*, and *Radix psudostellariae*. Multicenter clinical trials showed that this formula is very effective in acute promyelocytic leukemia (APL) patients. In this formula, realgar, is considered as the principal element (the Emperor), whereas *I. naturalis*, *S. miltiorrhiza*, and *R. psudostellariae* are adjuvant components to assist the effects of realgar. Tetraarsenic tetrasulfide, indirubin, and tanshinone IIA are the major active ingredients of realgar, *I. naturalis*, and *S. miltiorrhiza*, respectively. Combination of tetraarsenic tetrasulfide, indirubin, and tanshinone IIA showed synergistic effect in APL models both *in vitro* and *in vivo*. Tetraarsenic tetrasulfide is confirmed as the principal component of the formula, whereas tanshinone IIA and indirubin serve as adjuvant ingredients.²² This study sheds a good strategy in exploring the value of traditional medicine.

From pharmacological point of view, the effect of a TCM formula is the combined effects of all the compounds in the formula. In view of the basic theory of concentration-effect relationship and the dose-limitation of each Chinese herb in a formula (Generally, the common dosage for each herb in a formula is about 6–9 g.), it is reasonable to assume that even though there are hundreds of compounds in each herb the number of compound in a certain formula that real work is very limited. We called these compounds intelligent mixture. Therefore, we speculated that if a formula is real effective, there will be no difference in the therapeutic effect between the formula and the intelligent mixture. Each compound in the mixture might interact with others in form of synergistic,

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