Network Pharmacology: An Approach to the Analysis of Complex Systems Underlying Traditional Chinese Medicine

As one of the most important complementary and alternative therapies in clinical practice, traditional Chinese medicine (TCM) holds great potential in treating various complex diseases, especially in the area of chronic and non-communicable diseases. However, in terms of the complexity of chemical and biological profiles in TCM, a traditional reductionist cannot adequately explain the scientific nature of TCM.

TCM is typically a complex system, with multi-component, multitarget, and multieffect features. Over the past two decades, network pharmacology has widely been explored and accepted as a promising approach for understanding the scientific basis of TCM, especially in terms of its distinct advantage in the analysis of the complex system.

TCM network pharmacology stems from several pioneering works. First, the original hypothesis concerning the potential associations between TCM syndromes (ZHENG in mandarin), herbal formula and molecular networks was proposed in 1999[1] and 2002.[2] Subsequently, relevant biomolecular networks were established and demonstrated experimentally,[3,4] and then the term "network pharmacology" was introduced in a "news and views" article in Nature Biotechnology.[5] On the basis of these initial works, network pharmacology was then further applied to the extensive exploration of various issues in TCM, such as the biological basis of syndromes, active compounds, the action mechanisms of formulas, and even the development of new indications and innovative drugs.

In this context, it is reassuring to hear that WJTCM continues this trend by issuing a special issue on TCM and network pharmacology. Based on rigorous selection and peer review, we are delighted to recommend five selected articles for publishing in this special issue. These consist of one bibliometric study, three studies on TCM formulae, and one on TCM clinical research.

First, Shen Xiao *et al*.[6] performed bibliometric research by visualizing the research status of network pharmacology through CiteSpace software, (Drexel University, USA) in order to understand the development of network pharmacology and, further, to grasp the knowledge systems, research hotspots, and dynamic frontiers. A visualized knowledge map (2001–2017) was used to analyze the knowledge system in the field in order to identify the research hotspots and dynamic frontiers. In addition, with the comparison of the research status of network pharmacology and its development both nationally and worldwide, both the problems and advantages in network pharmacology research were clearly identified. This study is of great significance for understanding of the current situation of network pharmacology and facilitating its future development.

Furthermore, the next three works reveal the frontier in applying the approach of network pharmacology for the analysis of TCM formulae. In these studies, the network model mainly contains the visualization and analysis of multilayer interaction, including "component/compound/drug–target," "target–pathway," and "target–disease." These network pharmacology-based studies all aim to identify the active ingredients and targets, as well as the underlying therapeutic mechanisms. First, the Bu-Shen-Jian-Pi formula (BSJPF), a combined decoction of Si-Jun-Zi decoction (SJZD) and Liu-Wei-Di-Huang decoction (LWDHD), is regarded as a useful herbal clinical formula with the main function of nourishing kidney yin and replenishing spleen qi. Xiao-Yan Li *et al*.[7] employed network pharmacology to explore the chemical composition, relevant targets, and pharmacological mechanism of BSJPF. The results showed that 143 compounds could be screened out as potential effective ingredients of BSJPF and 275 targets and 334 diseases were predicted to be associated with the formula. The compatibility of LWDHD and SJZD generates a synergistic effect between formulated herbs.

Shexiang Baoxin Pill (SBP) is a widely used formula in clinical practice for treating cardiovascular diseases, especially coronary heart disease. Shou-De Zhang *et al*.[8] carried out research based on the whole components, in order to explore the pharmacological actions of SBP comprehensively through the network pharmacology approach. In this study, a total of 330 targets were identified for 26 blood constituents of SBP. Moreover, a pathway enrichment analysis found that these targets mapped onto 171 KEGG pathways, 31 of which were more enriched. Among these identified pathways, three were selected for an analysis of the mechanisms of SBP for treating coronary heart disease.

Depression is one of the most prevalent and prominent complex psychiatric diseases. Xiaoyaosan, a famous herbal formula, is widely used for treating depression, with satisfactory effects. Using this formula as an example, Jun-Sheng Tian *et al*.[9] applied network pharmacology to illustrate the antidepression mechanisms of Xiaoyaosan. They also employed bioinformatic methods and approaches to the active compounds and the identification of potential targets.

Xue-Ling Ma *et al*.[10] applied GenCLip online platform to retrieve the up-to-date literature referred to essential hypertension from PubMed database, clustering the abnormal expression of essential hypertension-related genes and analyzing their function. Their purpose is to construct gene co-occurrence network of hypertension and liver-fire hyperactivity syndrome, to investigate the biological basis of hypertension

and liver-fire hyperactivity syndrome and the characteristics of the molecular network from gene level. Finally, the top 1000 genes of essential hypertension were retrieved from GenCLip 2.0 online platform, which mainly clustered in the regulation of ambulatory blood pressure, regulation of renin-angiotensin-aldosterone system (RAAS), and sympathetic nervous system activity, as well as endothelial dysfunction.

Despite the abundant achievements in the study of TCM network pharmacology, we still need to undertake a deeper analysis of the challenges within the field. For example, the lack of sufficient reliable data on TCM compounds remains an obvious obstacle for the construction of a sufficiently predictable TCM network, despite an abundance of data collected from existing databases and literature or produced by high-throughput experimentation and computational modeling. Another significant challenge lies in scientific and robust validation based on the chemical and biological experiments and the predicted results of network analysis. Repeatability, reliability, and consistency are indispensable elements in scientific research.

Although TCM network pharmacology faces serious challenges in its infancy, its prospects are nevertheless promising, especially with the development of big data and artificial intelligence. This approach is therefore expected to bridge the gap between traditional and modern medicine, enable the investigation of the scientific principles of TCM, and accelerate its modernization.

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Conflicts of interest

There are no conflicts of interest.

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