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Review

Network Pharmacology-based Approaches Capture Essence of Chinese Herbal Medicines

Yan-qiong Zhang[1], Xia Mao[1], Qiu-yan Guo[1], Na Lin[1], Shao Li[2*]

1. Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing 100700, China

2. MOE Key Laboratory of Bioinformatics and Bioinformatics Division, TNLIST, Department of Automation, Tsinghua University, Beijing 100084, China

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ABSTRACT

Traditional Chinese Medicine (TCM), a crucial component of the current medical system, has been extensively used in clinical practice due to its valuable therapeutic efficacy, and its potentials as an important source of new pharmacophores. TCM is characterized by holistic theory, which emphasizes maintaining the balance of the patient's whole body using herbal formulae (fangji in Chinese) composed of mixtures of herbs with multiple bioactive ingredients. Because of the complex nature of these formulae, it is necessary to develop systematic methods to identify their bioactive ingredients and to clarify their mechanisms of action. With the rapid progress in bioinformatics, systems biology, and polypharmacology, "network pharmacology", which shifts the "one target, one drug" paradigm to the "network target, multi-component" strategy, has attracted the attention because it can not only reveal the underlying complex interactions between a herbal formula and cellular proteins but detect the influence of their interactions on the function and behavior of the system. Growing evidence shows that the network pharmacology strategy can be a powerful approach to modern research on TCM. The present paper focuses on the basis of network pharmacology and the recent progress in its methodology, illustrates its utility in screening bioactive ingredients and elucidating the mechanisms of action of TCM herbal formulae, analyzes its limitations and problems, and discusses its development direction and application prospects.

Key words

bioactive ingredient; Chinese herbal medicine; molecular mechanism; network pharmacology; network target

1. Introduction

Traditional Chinese Medicine (TCM), which is based on empirical applications and experience distillation over thousands of years, has become a crucial component of the current medical system and has been extensively used as complementary and alternative health care in clinical practice. TCM is characterized by holistic theory and emphasizes maintaining the balance of the patient's whole body using herbal formulae (Fangji in Chinese), which are complex mixtures of herbs consisting of multiple bioactive ingredients. There are a number of synergistic and antagonistic interactions among the various bioactive ingredients of TCM. Moreover, these compounds bind to the corresponding target proteins transiently, simultaneously, or weakly, which in combination enables to treat the complex diseases in a

***Corresponding author: Li S** Tel: +86-11-6401 4411-2869 Fax: +86-11-6401 3996 E-mail: shaoli@mail.tsinghua.edu.cn

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systematic manner. Due to their complex nature, the ingredient profiling and molecular mechanisms of TCM herbal formulae remain elusive due to the limitations of reductionism approach, which has hindered the application of Chinese herbal formulae in mainstream medicine and the modernization of TCM.

With the rapid progress in bioinformatics, systems biology and polypharmacology, "network pharmacology" (Hopkins, 2007; 2008), shifting the "one target, one drug" paradigm to the "network target, multi-component" strategy (Li, 2011), have attracted the attention because they can not only reveal the underlying complex interactions between a herbal formula and cellular proteins, but detect the influence of their interactions on the function and behavior of the human system, of which the key idea is in line with the holistic theory of TCM. Actually, network-based TCM studies (Li et al, 2007; Li, 2007) were earlier than the term "network pharmacology". Li's lab has established a series of network-based TCM research strategies since 2007 (Li and Zhang, 2013), and proposed the new concept of "network target" (Li, 2011). TCM network pharmacology integrates TCM theory with molecular networks and utilizes "network target" as a key concept that focuses on the systematic effects of drug targets on the biological network (Li, 2011). This framework aims to decipher the mechanisms of the therapeutic effects of drugs, or TCM herbal formulae, and to understand their possible toxicity and unknown pharmacological activities. Various network topological and dynamic features, such as degree, closeness, betweenness, modularity, feedback, connectivity, and propagation, have been used to investigate the combinatorial rules and holistic regulation effects of herbal formulae (Yang et al, 2015). Thus, the network pharmacology strategy can provide a powerful means for modern research on TCM.

The present paper focuses on the basis of network pharmacology and the recent progress on its methodology, illustrates its utility in screening bioactive ingredients and elucidating the mechanisms of action of TCM herbal formulae, analyzes its limitations and problems, and discusses its development direction and application prospects.

2. Methods and tools of TCM network pharmacology

2.1 "Network target" theory

Network target, a key concept in network pharmacology that firstly proposed by Li (Li, 2011; Li et al, 2011), is an attempt to define a disease-specific molecular network as a therapeutic target for the designation of appropriate treatments. Because many complex human diseases stem from the disruption of molecular networks functions, it is not surprising that the underlying mechanism of a herbal formula acting on a disease process is to reverse the imbalance of a disease-specific network rather than to regulate single molecules. When creating a TCM herbal formula which is a complicated chemical system involving a mixture of many types of chemical compounds, TCM clinicians combine herbs under the guidance of a unique and vital "Emperor-Minister-Assistant-Messenger" (Jun-Chen-Zuo-Shi in Chinese) rule. The "Jun" (emperor) herb is the principal herb in the formula and is responsible for treating the main disease or principal syndrome; The "Chen" (minister) herb assists the "Jun" herb in promoting a curative effect; The "Zuo" (assistant) herb is applied to modulating the effects of the "Jun" and "Chen" herbs, including alleviating toxicity and generally improving drug efficacy; Finally, the "Shi" (messenger) herb plays an indispensable supporting role in harmonizing the actions and enhancing the functions of the other herbs. This combinatorial principle has been demonstrated to act on the "network target" of a disease-specific network, which can be constructed using the interactions of disease-related genes or gene products, signaling pathways and the co-functions of biological processes. Network targets can be defined as the key components with topological importance in a disease-specific molecular network according to the calculation of various topological features. Network target theory provides the means to comprehensively identify all possibly affected targets and their interactions for deciphering the mechanisms of the therapeutic effects of drug treatments, including TCM herbal formulae, and clarifying their possible toxicity and unknown pharmacological activities (Li et al, 2007).

2.2 Features of disease/drug specific molecular network

In TCM network pharmacology, a "network" is often constructed to illustrate the associations between herbal formulae and specific diseases using the links between various herbs/herb ingredients containing a herbal formula and the corresponding targets or the links between drug targets and disease-related genes. The major features of biological network include topological, functional, and dynamic features. Following the network construction, the evaluation of these features can provide a quantifiable description of the complex biological system and its response to various drug/herbal treatments. Here, we briefly describe these features that pertain to biological networks.

Topological features: For each node i in an interaction network, the following features can be calculated to assess its topological property, for example: (1) "Degree" is defined as the number of links to node i. (2) "Node betweenness" is viewed as a measure of how many shortest paths between pairs of nodes that run through node i. (3) "Closeness" is defined as the inverse of the farness, which is the sum of node is distance to all other nodes. The closeness centrality can be used to evaluate the distance from node i to all other nodes in the network. As a node's degree/node betweenness/closeness centrality becomes larger, the importance of the node in the interaction network increases (Wang et al, 2012). (4) K-core analysis is an iterative process in which the nodes are removed from the networks in the order of least connected to most connected (Wuchty and Almaas, 2005). The core of maximum order is viewed as the main core or the highest k-core of the network. A k-core sub-network of the original network can be generated by recursively deleting vertices