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Design of new traditional Chinese medicine herbal formulae for treatment of type 2 diabetes mellitus based on network pharmacology

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[ABSTRACT] In the present study, 28 Chinese medicinal herbs belonging to traditional Chinese medicine (TCM) for the treatment of type 2 diabetes were selected to explore the application of network pharmacology in developing new Chinese herbal medicine formulae for the treatment of type 2 diabetes mellitus (T2DM). These herbs have the highest appearance rate in the literature, and their compounds are listed. The human protein–protein interaction network and the T2DM disease protein interaction network were constructed. Then, the related algorithm for network topology was used to perform interventions on the interaction network of disease proteins and normal human proteins to test different Chinese herbal medicine compound combinations, according to the information on the interaction of compounds–targets in two databases, namely TarNet and the Medicinal Plants Database. Results of the intervention scores indicate that the method proposed in this study can provide new effective combinations of Chinese herbal medicines for T2DM. Network pharmacology can effectively promote the modernization and development of TCM.

[KEY WORDS] Network pharmacology; TCM formulae; Protein–protein interaction network; Type 2 diabetes mellitus; Nework intervention

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Introduction

The philosophy of modern drug development is "single compound, single target", *i.e.,* the development of a drug with only one compound that targets the exact protein to treat a particular symptom. As society develops, however, lifestyles are constantly changing, and an increasing number of complex diseases are constantly introduced. A "single target" drug exhibits a weakness in treating such diseases. Network pharmacology provides a novel approach to developing or discovering new drugs from the current "single compound, single target" mode to the new "multi-components, network targets" mode [1–5].

Traditional Chinese medicine (TCM) has a long history and accumulated a considerable amount of clinical experiences that form a comprehensive and unique medical and cultural system. The use of TCM herbal formula (*FuFang* in Chinese) is the fundamental of TCM and includes several medicinal herbs [6–8]. The typical nature of TCM treatments is "multi-component, multichannel," which shares the majority of the key ideas of emerging network pharmacology and network biology, and satisfies the requirements for treating complex diseases [3, 4, 9–11].

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder characterized by insulin resistance. Individuals with T2DM experience difficulty in controlling their blood sugar level, which leads to high blood sugar level, sugar in the urine, and high blood insulin level. Increased thirst, frequent urination, and unexplained weight loss are common symptoms of

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T2DM. If not treated properly, T2DM can cause kidney damage, poor circulation, numbness in the feet, and heart diseases.

To explore the application of network pharmacology in developing and discovering new Chinese herbal medicines (*i.e*., TCM herbal formulae), we established a computational method for developing formulae to treat T2DM in a high-throughput manner. The sample calculation presented in this article demonstrated the accuracy and efficiency of the proposed method.

Methods

Retrieval of TCM formulae for treating T2DM

TCM herbal formulae are the fundamental components of the TCM system. A herbal formula is a complicated chemical system that involves a mixture of many types of chemical compounds that follows the combinatorial principle of Sovereign–Minister–Assistant–Envoy (*Jun–Chen–Zuo–Shi* in Chinese) [12]. On the basis of the aforementioned concerns and related studies, herbal formulae are proposed to act on the "network target" of specific diseases. This concept attempts to comprehensively describe all possible vulnerable targets to determine the efficiency and toxicity of drug treatments, such as herbal formulae [13–15]. It represents an evolutionary approach to design and optimization of network-based multi-component therapeutics [16-17].

Diabetes is a typical complex disease with a variety of complications that can lead to multiple organ damage and consequently brings considerable suffering and burden to patients. Diabetes mellitus has many types; the most common types are type 1 (T1DM) and T2DM [18]. In both types, a "relative surplus" of blood glucose exists. Hypoglycemic agents play a major role in the drug treatment of diabetes; they include oral hypoglycemic agents as well as insulin and insulin analogues, such as sulfonylureas, glinides, metformin, thiazolidine diketones, and alpha glucosidase inhibitors.

Diabetes, including its symptoms, causes, and treatment methods, has been recorded in the Chinese ancient medical treatise *Huang Di Nei Jing* during the periods of the Qin and Han Dynasties in China. In our study, we collected over 1200 articles from 14 traditional Chinese medicine core journals and 10 traditional Chinese medical college journals that involved T2DM treatment using TCM herbal formulae from 1980 to 2015 [19]. From the statistics of these TCM herbal formulae used for the treatment of T2DM, 28 kinds of effective traditional Chinese medicinal herbs, which were the most common herbs used in these formulae, were listed. All the chemicals contained in these herbs as well as their targets were retrieved from the Medicinal Plants Database (MPDB) and TarNet, a visualization analysis platform for diseases associated networks and network pharmacology.

Data collection of human protein–protein interaction (PPI) network and T2DM-associated PPI network

Synergistic action is one of the typical characters of TCM. A single formula that contains many compounds may target numerous proteins. A huge PPI network exists in the human body [20]. The actions of compounds that target several proteins will produce a torrent of reactions. We collected human PPI data from seven major public PPI databases, namely, BioGRID, BIND, DIP, HPRD, iRefWeb, IntAct, and MINT. Entries with the Entrez Gene ID column for "None" and self-interaction entries were removed, and all the data were merged by removing redundant entries.

T2DM-related proteins were collected from T2D-Db (http://t2ddb.ibab.ac.in/home.shtml), a database of all the molecular factors reported to be involved in the pathogenesis of T2DM in humans, mice, and rats; T-HOD (http://bws.iis.sinica.edu.tw/THOD/), a literature-based candidate gene database for hypertension, obesity, and diabetes; and T2D@ZJU (http://pharminfo.zju.edu.cn/t2d), a knowledge database that integrates three levels of connections associated with T2DM. The proteins that appeared in at least two of these databases were kept. The most reliable ones from the literature were also manually curated and extracted.

Robustness of the networks and design of TCM herbal formulae

The robustness of a system is used to represent its capability in resisting disturbance and keeping its function or natural circumstances. When subjected to outside interference or damage, structural robustness should not only reflect the network structure itself to maintain the capability to resist destruction, but should also reflect the recovery capability for structural destruction [21]. After being attacked in the network, the remaining nodes can still continue to maintain the communication capability of the network, which is referred to as the connectivity robustness of a network [22].

We aimed to add reasonable interventional measures to the PPI network to destroy the robustness of the disease network but maintain the functionality of normal networks to achieve a "cure for the disease with no (or few) side effect(s)." We analyzed the topological properties of the PPI network and found that the biological processes in the human body would be frequently involved in "a variety of biochemical cascades/paths," rather than a single gene or protein. Therefore, the robustness of the connection network is defined as

$$M = \max([\text{length(g.node)for g in netword. connected\_component\_subgraphs(G)}])$$

$$N = \text{length(G.node)},$$

$$R = \frac{M}{(N - N_r)},$$

where N represents the size of the initial network (number of nodes), N_r represents the number of nodes that are removed from the network, and M represents the number of nodes in the maximal connected subgraphs of the network system after the N_r nodes are removed.

On the basis of the compound–target relationship data, nodes (targets) were removed from the network that the compounds were targeting. Finally, we obtained a quantitative indicator for the network structural changes affected by the formulae of the com-