



## REVIEW ARTICLE

## Network Pharmacology and Traditional Chinese Medicine: Development of Anti-Diabetic Therapies

Zhongxia Lu<sup>1</sup>, Wenjun Xu<sup>1</sup>, Xi Chen<sup>2</sup>, Changyu Li<sup>3\*</sup> and Yitao Chen<sup>1\*</sup>

<sup>1</sup>College of Life Sciences, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China

<sup>2</sup>College of Traditional Chinese Medicine, Beijing University of Chinese Medicine, China

<sup>3</sup>College of Pharmacy, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China

\*Corresponding author: Yitao Chen, MD, College of Life Sciences, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, 310053, China, E-mail: [cytworld@163.com](mailto:cytworld@163.com);

Changyu Li, MD, College of Pharmacy, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, 310053, China, E-mail: [lcyzcmu@sina.com](mailto:lcyzcmu@sina.com)



### Abstract

Partly due to the failure of single-target drugs, diabetes mellitus, a chronic metabolic disease with complex pathogenesis and long-term medication requirements, is increasing in prevalence worldwide and urgently needs multi-component and multi-target treatments. Traditional Chinese herbs are the principal drug of Chinese medicine, which is effective against diabetes. However, Chinese herbs' mechanism of action is difficult to elucidate due to its multiple components and multi-target effects. Based on the theories of systems biology and biological network equilibrium, network pharmacology could be applied to study disease mechanism and drug efficacy. This review postulates that network pharmacology may play a key role in revealing the anti-diabetic mechanism of Traditional Chinese Medicine (TCM) and will have potential effects on the modernization of TCM.

### Keywords

Diabetes mellitus, Network pharmacology, Multi-targets, Traditional Chinese Medicine

Diabetes mellitus, “xiao-ke” in TCM, is a chronic metabolic disease affecting more than 400 million people worldwide [1]. The onset of diabetes is attributed to a deficiency in insulin secretion or impaired biological activity of insulin. Due to the explosive increase in diabetes prevalence rates, diabetes has become a serious social problem in China. In 2017, China accounted for more than 100 million people with diabetes, nearly a quarter of world's diabetic population [2,3].

### Research and Development Dilemma for Anti-Diabetes Drugs

Type 2 Diabetes Mellitus (T2DM), generally agreed to be caused by insulin resistance and/or insulin deficiency, constitutes almost 95 percent of all diabetes cases [4]. Because of the pathogenesis, the mainstream anti-diabetic drugs are insulin secretagogues (sulphonylureas and meglitinide analogues), insulin sensitizers (metformin) and drugs developed for new targets that regulate metabolism (GLP-4 agonists, DPP-4 receptor inhibitors, SGLT2 inhibitors and GPR119 agonists) [5-9].

However, the chronic and progressive nature of diabetes increases the probability that single-agent treatment will eventually fail. To continue effective management of blood sugar, physicians resort to increased drug doses or multi-drug therapy for patients with T2DM. UK Prospective Diabetes Study (UKPDS) records that approximately 50% of patients with T2DM needed combination therapy after 3 years to delay deterioration of health; and by 9 years, this number increased to 75% [10].

Drug Research and Development (R&D) has continually been guided by the principle of “one target, one drug, one disease”, likely due to regulations requiring clear and documented mechanism of drug action. Short-

tcomings in this R&D approached are gradually emerging through failure to therapeutically treat multi-factorial diseases such as T2DM. In both USA and Europe, the average success rate for all therapeutic areas is approximately 11%, highlighted by the failure of more than 70% of oncology compounds in phase II trials [11]. The low success rate of new drug R&D demonstrates that the “single-target and high-selectivity” approach is meeting a theoretical “bottleneck” and introduces enormous challenges.

### The Development of Network Pharmacology

The validity of the traditional R&D approach of “one target, one drug, one disease” is questioned by the fact that multiple drugs act on one target and one drug may act on multiple targets. Yildirim, et al. investigated 4,252 drug entries, including 1,178 FDA-approved drugs (1,065 small molecules and 113 proteins/peptides). The results showed that most drugs target only a few proteins, but some have numerous targets, with the average number of target proteins per-drug being 1.8. Conversely, many proteins are targeted by more than one drug [12].

As shown in Figure 1, in 2007, Hopkins from the University of Dundee postulated “the main reason for failures in R&D may not be technological, environmental or even scientific but philosophical” [13,14]. This postulation led him to publish the concept of network pharmacology [13]. Network pharmacology is an approach to drug design that encompasses systems biology, network analysis, connectivity, redundancy, and pleiotropy, and offers an approach to drug discovery that simultaneously embraces efforts to improve clinical efficacy and minimize side effects and toxicity [14]. Network pharmacology highlights the philosophic shift from the “one target, one drug, one disease” strategy to a novel R&D strategy of considering the “network target and multi-components”.

### Network Pharmacology and TCM

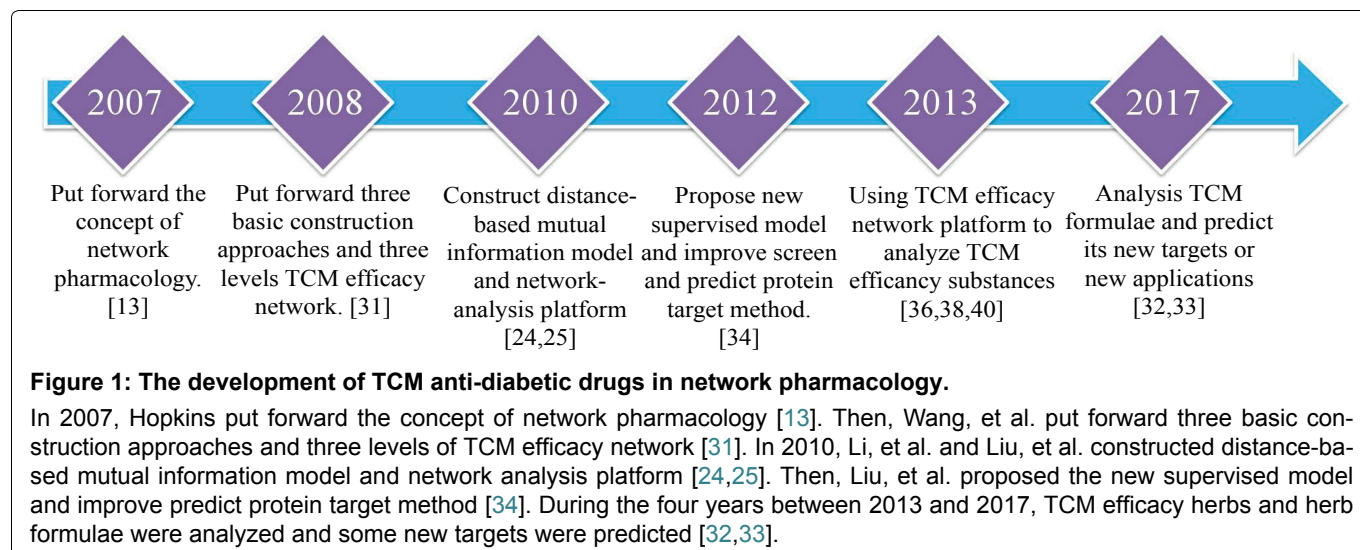
Traditional Chinese Medicine (TCM), characterized by a holistic view and treatment based on syndrome differentiation, has a history of thousands of years [15]. In its long history of treating disease, TCM has accumulated rich clinical experience, forming a comprehensive and unique medical system [16]. Herbal formulae, which are capable of systematically treating diseases by interactions between different herbs, are widely used in TCM [17]. Thus, it is difficult to completely elucidate its therapeutic mechanisms. As the efficacy of TCM to cure complex disease became more apparent, increased numbers of people gradually began to pay attention to TCM and eventually initiated a boom in TCM research [18].

### Network Pharmacology is Similar to the Holistic Viewpoints in TCM

The holistic concept is one of the most important guiding ideologies in TCM. From a TCM perspective, various components of the human body such as organs and tissues can be harmonious and unified because a communication network system exists [19]. Therefore, TCM doctors often integrate their treatment to restore the original state of equilibrium of the human body, rather than treat one ailment. As network pharmacology progresses and is becoming generally accepted, the concept of understanding the human body as a communication network closely resembles the holistic viewpoints in TCM.

In harmony with a holistic viewpoint, compound compatibility is essential to TCM prescriptions, whose principle is “monarch, minister, assistant, and guide” [20]. The theory of compound compatibility guides prescription construction by dividing the prescription into principal agents and lesser agents. Modes of administration are identified in a dialectical method depending on the condition of the patients. From a network pharmacology perspective, chronic diseases, especially T2DM, are a multi-mechanism, multi-gene disease, involving numerous metabolic pathways, can apply the concepts of compound compatibility in TCM [21]. For example, a drug intervention target network is often a subset of the network of biomolecules involved in the disease [22]. For various reasons, some molecules of the disease network could not be targeted directly. However, effective interventions can be achieved by designing drugs which target bio-molecules at neighboring nodes of the network. For instance, elevated Asymmetric Dimethylarginine (ADMA), an endogenous Nitric Oxide (NO) synthase inhibitor, decreases NO bioavailability and increases hydrogen peroxide production. Theoretically, this mechanism would impair pancreatic  $\beta$ -cells and worsen T2DM [23]. Although associations such as that among ADMA, NO, and diabetes require validation through further research, it would be possible to manipulate ADMA to affect NO levels since it is not possible to directly target NO. Network pharmacology advocates combining direct and indirect targets, such as ADMA, to develop a drug delivery model that is dynamic, multi-channel, and multi-target, an approach which resembles the principle of compound compatibility in TCM.

Li, et al. [24] established a Distance-Based Mutual Information Model (DMIM) to extract the herb relationships from 3865 collaterals-related herbal formulae. From this “herb network”, and follow up *in vitro* experiments, the angiogenic effects and synergistic properties of connected herbs and herb pairs were evaluated, which is mentioned in Figure 1. Liu, et al. [25] developed a network-analysis platform based on numerous credible TCM herbal formulae. Applying this platform to the data mining field of TCM will significantly improve its research level (as shown in Figure 1). Based on modern pharmacological experimental data, Zhang, et al. [26] con-



structured the five-flavor Bayesian Belief Network (BBN) and obtained a bayesian topological network graph and conditional probability table, from which they could reliably predict the flavors of TCM or TCM effective components.

### Network Pharmacology is Similar to Multi-Component Multi-Target Theory in TCM

Chinese medicine effective components are a group of chemical substances from a single herb or herbal formulae which produce the desired effects and are regarded as the basis for quality control and the core of modernization of TCM [27]. Therefore, it is clear that the promising efficacy of TCM should be attributed to the result of multi-component effects on multiple targets rather than the result of one specific active compound that manipulates a single-target [28]. In summary, the compatibility and constraints dictated by links between components and targets exist in TCM herbal formulae networks just as they do in network pharmacology.

Under the guidance of network pharmacology, drug networks could be constructed based on the chemical structure, efficacy, and other aspects of similarity [22]. By applying network pharmacology to TCM research, several modern Chinese medicine scholars successfully predicted the effective components of TCM chemical formulae. Zhang, et al. [29] presented a-self-developed TCM network pharmacology platform to decipher the network regulation mechanism of qing-luo-yin and to identify active ingredients as well as to guide further experiments. Yang, et al. [30] used 1743 Differentially Expressed Genes (DEGs), identified after treating a T2DM mice model with Xiao-Ke-An (XKA), to establish a T2D-specific compound-target-pathway network. Based on the network, they deciphered XKA therapeutic mechanisms mainly by improving carbohydrate and lipid metabolism. As shown in Figure 1, Wang, et al. [31] published three types of TCM efficacy networks, namely molecular network, module network and concept network, along with three basic construction approaches.

These approaches identify the targets of TCM, confirming the relevant pharmacological indexes and combining the TCM theory with basic known information (as shown in Figure 1) [31]. After investigating potential anti-diabetic herbs from a large amount of data in ancient TCM formulas, Wang, et al. [32] identified 10 TCM herbs had favorable anti-diabetic effects, demonstrating their  $\alpha$ -glucosidase inhibitory, glucose-stimulated insulin secretion and intestinal glucose transport inhibitory effects (as shown in Figure 1). As shown in Figure 1, Hu, et al. [33] used network pharmacology method to design new herbal formulae for treatment of type 2 diabetes. Liu, et al. [34] proposed a new bipartite graph supervised model to predict drug-target protein interactions and new targets (as shown in Figure 1). Gu, et al. [35] studied the interaction among 1729 compounds in qishen yiqi diwan and 26 drug targets by molecular docking computational pharmacological methods and used the discovered interactions to predict treatment efficacy for cardiovascular disease. By using molecular docking and an arachidonic acid metabolic network, Gu, et al. [36] analyzed 28 TCM herbs for their anti-inflammatory functions and predicted new herbal combinations (as shown in Figure 1). This analysis may further elucidate the combinatorial effects of herbal compounds on disease networks. The above-mentioned studies illuminate the efficacy of Chinese medicine material and the ability of network pharmacology to inspire the in-depth study of the efficacy of TCM and eventually modernize it.

### Advantages of Network Pharmacology for Diabetes and TCM Research

In TCM, herbal formulae are a traditional way to treat diseases [37]. However, the effective components and their mechanisms of action are not very clear. Nonetheless, these approaches are effective and TCM multi-compound, multi-target properties can be related to human complex physiological regulation networks. Therefore, we can develop novel anti-diabetic medicines based on effective TCM substances networks and human regulation networks.

As shown in Figure 1, Yang, et al. [38] established a knowledge database (T2D@ZJU) with varying levels of data reliability and information coverage due to three sources of data, namely Curated Directed Connections (CDC) data set, Protein-Protein Interaction (PPI) data set and Text-Mining-Based Relationships (TMR) data set, this platform would provide users with detailed information that would aid in future research. Vinay, et al. [39] constructed a protein-protein interaction network associated with T2DM. Analysis of this network identified *MAPK1*, *EP300*, and *SMAD2* as the proteins of most potential therapeutic value as a target of phloridin in TCM medicine. As shown in Figure 1, Kim, et al. [40] investigated the effects of anti-diabetic drugs on gene expression in Zucker diabetic fatty rats and built gene expression networks. By analyzing the networks, they found alterations in Oxidative Phosphorylation (OXPHOS) gene expression in white adipose tissue. It is likely these genes may play a role in the pathogenesis and drug-mediated recovery of T2DM.

Recently, scientists have also found new applications for both new and old compounds. Yu, et al. [41] constructed the "components-targets-diabetes" network and predicted that corydalis yanhusuo alkaloids would have beneficial effects on diabetes and diabetic complications. These predictions were confirmed by experiments. The experimental results demonstrated that corydalis yanhusuo alkaloids can ameliorate 21 different diabetes complications as well as modulate *MAPK/ERK*, *VEGF*, and *NOS3* signaling proteins. This body of work validated TCM knowledge that corydalis yanhusuo alkaloids may have profound significance for the treatment of T2DM.

## Perspectives for the Future

Diabetes mellitus is an extremely complex chronic disease related to many metabolic pathways; and TCM, characterized by multiple components and targets, holds much promise for effective treatment. However, the multi-parameter mechanism of diabetes on the one hand; and the multiple components and targets of herbal formulae on the other hand, are too complex to be clearly understood by traditional pharmacology approaches. However, the development of network pharmacology provides a bridge for this gap in knowledge. Owing to network pharmacology, the field of TCM can advance and solve outstanding complex issues with one method. Although much progress has been made in network pharmacology, there is still need for improvement. The advancements in bioinformatics and the increasing pace of discovering diabetes drug targets, provide confidence that network pharmacology will advance research in TCM and diabetes, and eventually provide cures.

## Compliance with Ethical Standards

This study was funded by Project of National Great New Drug Research and Development (No. 2012ZX09503001-

001) and grants from the National Natural Science Foundation Project (81374023). The work was also supported by Traditional Chinese Medicine Open funds of Zhejiang Chinese Medical University (No. 752223A00201/005/019).

## Conflict of Interest

Yitao Chen declares that he has no conflict of interest. Wenjun Xu declares that he has no conflict of interest. Xi Chen declares that he has no conflict of interest. Zhongxia Lu declares that he has no conflict of interest. Changyu Li declares that he has no conflict of interest.

## Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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