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Network analysis of primary active compounds in Danqi analogous formulas for treating cardiovascular disease

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Abstract *Objective:* Used extensively to treat cardiovascular disease, Danqi analogous formulas (DQAF) include prescriptions for Danqi (DQ), Fufang Danshen (FFDS) and Qishen Yiqi (QSYQ). Differences in prescription compatibility result in varying emphases of DQAF in clinical application.

Methods and results: Based on network analysis in this study, common and distinct mechanisms of DQAF actions on cardiovascular disease were analyzed at a systemic level. Components–targets–pathways models were developed by Cytoscape (http://www.cytoscape.org/); whereby, target information for active compounds was obtained based on the PharmMapper database (http://59.78.96.61/pharmmapper/), which was further used to search pathways using the Kyoto Encyclopedia of Genes and Genomes database (http://www.genome.jp/kegg/). Based on target and network analyses, we discovered RBP4 is a potential common target of DQAF, while mitogen-activated protein kinase 1 (MAPK1) and glutathione S-transferase P were potential targets of FFDS and QSYQ, respectively. Furthermore, the potential of DQAF to treat cardiovascular disease occurs through effects on the endocrine, immune, and digestive systems, in addition to lipid, sugar and amino acid metabolic pathways. Whereas FFDS exhibits effects on Toll-like receptor, transforming growth factor beta and MAPK signaling pathways; QSYQ exerts effects on cyclic adenosine monophosphate signaling, as well as metabolism of glutathione and arachidonic acid.

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Conclusion: This study not only reflects the formulas-effect modality of multiple compounds, targets and pathways, but also provides clues to better understand physiological mechanisms of DQAF.

Introduction

Traditional Chinese Medicine (TCM) has been recognized as a typical representative of complementary and alternative medicine.[1] Using prescriptions called "formulas", clinical applications of TCM advocate combinatory therapeutic strategies. In contrast to modern pharmacology, which often focuses upon a single chemical entity, TCM formulas can affect multiple therapeutic targets to produce a synergistic effect resulting from multiple ingredients.[2,3] In TCM theory, analogous formulas (AF) refer to series of similar prescriptions based on common herb pairs. Elucidating mechanisms of AF is significant to clarify principles for rational use, with significant emphasis on applicable indications and prevention of misuse. Network analysis has provided methodologies and opportunities to reveal mechanisms of action for TCM formulas based on complex biological systems present in the human body.[4]

Danqi analogous formulas (DQAF), a series of prescriptions primarily derived from the herb pair *Salvia miltiorrhiza* and *Panax notoginseng*, include prescriptions for Danqi (DQ), Fufang Danshen (FFDS) and Qishen Yiqi (QSYQ). The basic formula of DQAF is DQ, which consists of *S. miltiorrhiza* and *P. notoginseng*. Different emphases of DQAF in clinical applications arise from their varied composition, as shown in Table 1. DQAF are commonly prescribed to treat cardiovascular disease, the leading health problem worldwide.[5] However, many previous studies have only investigated the effects of a single DQAF composition. For example, FFDS was found to protect myocardial ischemia and reperfusion injury though the Akt-eNOS signaling pathway[6]; whereas, QSYQ was found to inhibit platelet aggregation.[7] Most of these studies have elucidated one or several pharmacological effects of a specific formula, providing the foundation for further study of common and distinct mechanisms of DQAF.

In this study, a network analysis approach was employed to analyze active mechanisms of DQAF. Based on PharmMapper (http://59.78.96.61/pharmmapper/) and Kyoto Encyclopedia of Genes and Genomes (KEGG; http://www.genome.jp/kegg/) databases, targets and pathways information for active compounds was obtained. Subsequently, components–targets–pathways network models of DQAF were constructed by Cytoscape (http://www.cytoscape.org/).[8] Potential targets and pathways that were common and distinct to DQAF were then evaluated using network model analysis. Our study aimed to provide new clues to better understand mechanisms of DQAF actions, in a concerted effort to instruct rational application of antibiotics and reflect the formulas-effect modality of multiple compounds, targets and pathways.

Table 1 DQAF composition.

Formula	Composition
DQ	*Salvia miltiorrhiza*, *Panax notoginseng*
FFDS	*Salvia miltiorrhiza*, *Panax notoginseng*, *borneolum*
QSYQ	*Salvia miltiorrhiza*, *Panax notoginseng*, *Dalbergia odorifera*, *Astragalus membranaceus*

Note: DQ stands for Danqi formula, FFDS stands for Fufang Danshen formula, QSYQ stands for Qishen Yiqi formula.

Methods and experimental section

Target-mining of DQAF's main active components

As the compositions of TCM formulas are complex, it is impossible to study all of the components and reliably separate results. Based on literature retrieval and according to principles defining the main ingredient for efficacy as having a high content and entering the blood, the main active components of DQAF were selected to clarify common and distinctive mechanisms.

Information for targets of the main active components of DQAF was extracted from PharmMapper,[9] an updated platform for potential target identification integrating pharmacophore with statistical methods. PharmMapper automatically identifies the best mapping poses of query molecules against all pharmacophore models in its PharmTargetDB, a pharmacophore database annotated from all the target information in BindingDB, TargetBank, DrugBank and potential drug target databases, including over 7000 receptor-based pharmacophore models.

Analysis of the compounds–targets–pathways network of DQAF

The pathway annotation of targets was performed based on the KEGG database, developed to facilitate understanding of high-level functions and utilities of biological systems from molecular-level information.[10]

Information regarding compounds, targets and pathways was collected to construct a compounds–targets–pathways network model using Cytoscape, a standard tool for visualization and integrated analysis of biological networks. In graphical networks, nodes represent compounds, protein targets and pathways; whereas, edges encode compound–target or target–pathway interactions. Based on such network analysis, common and distinct pathways of DQAF and the formulas-effect modality of multiple compounds, targets and pathways may be evaluated.