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INFORMATION STUDY

Mechanism of herbal pairs with the properties of *Qi*-tonifying, blood activation, blood-stasis breaking in treating coronary heart disease

Yang Jing, Li Jian, Li Li, Zhao Ning, Niu Xuyan, He Xiaojuan, Jiang Miao, Lü Aiping, Lei Yan

Yang Jing, Experimental Research Center, and Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, Beijing 100700, China

Li Li, Zhao Ning, He Xiaojuan, Jiang Miao, Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, Beijing 100700, China

Li Jian, School of Basic Medical Sciences, Beijing University of Chinese Medicine, Beijing 100029, China

Lü Aiping, Institute for Advancing Translational Medicine in Bone & Joint Diseases, School of Chinese Medicine, Hong Kong Baptist University, Hong Kong 999077, China

Lei Yan, Experimental Research Center, China Academy of Chinese Medical Sciences, Beijing 100700, China

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Correspondence to: Prof. Lei Yan, Experimental Research Center, China Academy of Chinese Medical Sciences, Beijing 100700, China. 13651217893@163.com

Telephone: +86-10-64089526

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Abstract

OBJECTIVE: To investigating the molecular mechanism of herbal pairs in three types of Chinese medicinals: Qi-tonifying, blood activation, blood-stasis breaking in treatment of coronary heart disease (CHD).

METHODS: The components of six herbs were searched in Chinese medicine dictionary and their target proteins were found in PubChem. CHD genes were obtained from PubMed gene database. Ingenuity Pathways Analysis was used to build the pharmacological network of three herbal pairs and CHD molecular network. The canonical pathways between each herbal pair network and CHD network was compared to decipher the molecular mechanism on three herbal pairs in treating CHD.

RESULTS: The network analysis showed that there were the common signal pathways of three herbal pairs in treating CHD including hypoxia signaling in the cardiovascular system, Hypoxia-inducible factor 1-alpha signaling, glucocorticoid receptor signaling, G-Protein coupled receptor signaling and pregnane X receptor/retinoid X receptor (PXR/RXR) activation. Further to analyze cardiovascular signaling, cytokine signaling and cytokine signaling, the effective molecules for three herbal pairs in treating CHD included HIF1α and estrogen receptor 1, Qi-tonifying herbal pair included albumin and matrix metallopeptidase 2, and blood-activation herbal pair included estrogen receptor 2 and peroxisome proliferator-activated receptor-γ.

CONCLUSION: Each herbal pair can affect some respective CHD-related functions and pathways, meanwhile three herbal pairs exert some mutual effects on CHD-related functions and pathways. Mutual effects of three herbal pairs may be the key components of their total molecular mechanisms and respective effects of each herbal pair may be the characteristic components of their respective molecular mechanism.

Keywords: Coronary disease; Reinforcing *Qi* activating blood; Molecular network; Ingenuity pathways analysis

INTRODUCTION

Currently approximately 3.8 million men and 3.4 million women die each year from coronary heart disease (CHD) which is the most common type of heart disease in the worldwide.[1] It is estimated that CHD will be responsible for a total of 11.1 million deaths globally in 2020.[2] In China and even East Asia, Traditional Chinese Medicine (TCM), recognized as an interesting alternative to conventional medicine, is widely used to treat CHD. According to syndrome differentiation of TCM, appropriate TCM formula is adopted for the treatment of CHD. In TCM formula, the herb pairs that are claimed to be unique combinations of the traditionally defined TCM herbal properties have been frequently used for achieving mutual enhancement, mutual assistance, mutual restraint, mutual suppression, or mutual antagonism.[3] For improving blood circulation which is the major treatment method for blood stasis syndrome in TCM, three types of herbal pairs are often used for the treatment of CHD, including those herbal pairs with the properties of *Qi*-tonnifying, blood activation and blood-stasis breaking. However the differences in pharmacological activities among these three types of herbal pairs in treatment of CHD are not clear. Classical pharmacological tests are still unable to elucidate the pharmacological activities of the herbal pairs.

Network based analysis is a research method and can be used to further clarify the potential molecular mechanism on how to affect CHD by the three herbal pairs. Each type of herbal pairs could include some or many herbal combinations. So we first used text mining methods combined with previous studies to extract the herbal pairs. The results showed that the combination of Renshen (*Panax Ginseng*) and Huangqi (*Radix Astragali Mongolici*) was the typical herbal pair for *Qi*-tonifying, the combination of Danshen (*Radix Salviae Miltiorrhizae*) and Sanqi (*Radix Notoginseng*) was the typical herbal pair for blood-activation, and the combination of Sanleng (*Rhizoma Sparganii*) and Ezhu (*Rhizoma Curcumae Phaeocaulis*) was the typical herbal pair for blood-stasis breaking. And then, the biological target proteins of three herbal pairs were searched in PubChem databases. The disease associated genes of CHD were screened based on gene database in National Center for Biotechnology Information (NCBI). Furthermore, the protein-protein interaction PPI networks for three herbal pairs and disease network were respectively built up by Ingenuity Pathway Analysis (IPA, http://www.ingenuity.com) online. Finally, the two networks of CHD and each herbal pair treating CHD were overlaid to discover the possible targets of each type of herbal pair and decipher the differences and similarities among these herbal pairs with *Qi*-tonifying, blood-activation and blood-stasis breaking treating CHD (Figure 1).

MATERIALS AND METHODS

CHD-related genes data

Genes of CHD are searched in Gene database in National Center for NCBI database. In Gene database, gene (http://www.ncbi.nlm.nih.gov/gene) integrates information from a wide range of species. A record may include nomenclature, Reference Sequences (RefSeqs), maps, pathways, variations, phenotypes, and links to genome-, phenotype-, and locus-specific resources worldwide. We searched CHD as a key term in Gene database (until September 12, 2012) and filtered genes with variations in medical significance as reported via Variation Viewer. The homo sapiens of genes of CHD are needed.

Three herbal pairs-related target proteins

The target proteins of the six herbs are searched from PubChem (until September 12, 2012). The PubChem (http://pubchem.ncbi.nlm.nih.gov/) database is a public repository for biological activities of small molecules and small interfering RNAs (siRNAs) hosted by the US National Institutes of Health (NIH). It consists of three dynamically growing primary databases: PubChem Compound, PubChem Bioassay, and PubChem Substance. All targeted proteins related to the active compounds in the Chinese medicine can be obtained using PubChem. According to the Grand Dictionary of Chinese Medicine, we sought the active ingredients of six Chinese herbs of the three herbal pairs. Each Chinese herb was searched in PubChem. Due to the bio-information could be cross-referenced to other NCBI database,[4] the target proteins of active compounds which tested in bioassays could be collected in PubChem. Consider to the future research, we limited the category of proteins in Homo sapiens.

Networks and analysis

The related genes of CHD were uploaded to IPA and built up the molecular network of the genes (Figure 2). We uploaded the total protein targets of three herbal pairs into IPA. The Molecules we imputed to IPA were termed "focus molecules". IPA generated the focus molecules into a set of networks base on different bio-functions. Molecules were represented as nodes, and the biological relationship between two nodes is