China's Medicine Progress Series/中国医药进展丛书

Heart Disease (TCM)

心脏疾病 (中医卷)

Editor-in-Chief/主编

LIU Jianxun/刘建勋

China Academic Journals (CD Edition) Electronic Publishing House Co., Ltd.

《中国学术期刊（光盘版）》电子杂志社有限公司

Title:	China's Medicine Progress Series	**书　　名：**	心脏疾病（中医卷）
Editor-in-Chief:	LIU Jianxun	**主　　编：**	刘建勋
Editing Unit:	China Academic Journals (CD Edition) Electronic Publishing House Co., Ltd.	**编辑单位：**	《中国学术期刊（光盘版）》电子杂志社有限公司
Executive Editor:	LI Jie	**责任编辑：**	李杰
Cover Designer:	HOU Shanlin	**封面设计：**	侯姗琳
Publisher:	China Academic Journals (CD Edition) Electronic Publishing House Co., Ltd.	**出　　版：**	《中国学术期刊（光盘版）》电子杂志社有限公司
Address:	Building A2, No. 66 Xixiaokou Ave., Haidian District, Beijing 100192, China	**地　　址：**	中国北京市海淀区西小口路 66 号东升科技园北领地 A2 楼，100192
Publication Date:	October 2020	**出版时间：**	2020 年 10 月
Distributor:	Tongfang Knowledge Network Technology Co., Ltd. (Beijing)	**发　　行：**	同方知网（北京）技术有限公司
Producer:	China Academic Journals (CD Edition) Electronic Publishing House Co., Ltd.	**制 作 者：**	《中国学术期刊（光盘版）》电子杂志社有限公司
Website:	http://jtp.cnki.net/bilingual	**网　　址：**	http://jtp.cnki.net/bilingual
Language:	English	**语　　种：**	英语
File size:	82M	**容　　量：**	82M
ISBN xxx-x-xxx-xxxxx-x pdf		ISBN xxx-x-xxx-xxxxx-x pdf	

Foreword by Editor-in-Chief

主 编 卷 首 语

Angina pectoris, myocardial infarction, and heart failure are common heart diseases. According to the report of World Health Organization, heart diseases, which are mainly caused by smoking, lack of exercise, and unhealthy diets, represent the leading cause of mortality worldwide. With social and economic development, the incidence of heart diseases is increasing due to the life stress accumulation and unhealthy diet and exercise habits. The current therapies for heart diseases in western medicine include slowing the progression of coronary atherosclerosis, alleviating symptoms, and improving life quality, thereby delaying the progression of complications and minimizing the incidence of cardiovascular events. However, the adverse effects of medication and the high cost of long-term nursing care prompt many patients to seek treatment by traditional Chinese medicine (TCM). It is well known that TCM focuses on regulating yin and yang as well as deficiency and excess of the human body as a whole. According to the TCM theory, the primary causes of heart diseases are phlegm accumulation, blood stasis, and qi blockage in the chest due to the deficiency of healthy qi. Based on patients' conditions, the treatment should target symptoms in acute cases and root cause in non-acute cases. TCM has inherent advantages in the treatment of heart diseases, with unique efficacy and slight side effect. With the gradual recognition and acceptance worldwide, TCM has gradually become a new effective means for treating heart diseases.

Since 2014, *Chinese Acupuncture & Moxibustion*, *Acupuncture Research*, *China Journal of Chinese Materia Medica*, *Chinese Journal of Integrated Traditional and Western Medicine*, *Liaoning Journal of Traditional Chinese Medicine*, *World Chinese Medicine*, *Natural Product Research and Development*, and *The Chinese Journal of Clinical Pharmacology* have joined the Journal

心绞痛、心肌梗死和心力衰竭是常见的心脏疾病。据世界卫生组织报告，心脏疾病是全球范围造成死亡的最主要原因，与其它原因相比，心脏疾病每年造成的死亡最多，其主要病因是吸烟、缺乏运动和不健康的饮食。随着社会经济的发展和生活压力的增加，以及人们饮食、运动习惯的原因，全世界心脏疾病的发病率在逐年增加。目前西医治疗该病的目的包括降低冠状动脉粥样硬化的发病进程，改善症状，提高生活质量，从而延缓并发症进展，减少心血管事件的发生。然而，药物治疗的不良影响及持续昂贵的护理费用，使较多病人开始选择中医药治疗。众所周知，中医以调节人体整体的阴阳虚实为着眼点，认为此病多由于正气不足而引起痰、瘀、气等病理性产物阻滞于胸中所导致，治疗则根据病人病情，急则治其标，缓则治其本，在心脏疾病的治疗中具有得天独厚的优势，疗效独到且具有较低或没有副作用。伴随着中医药被世界逐步认识与认可，她逐步成为被世界广泛接受的治疗心脏疾病的新的有效手段。

《中国针灸》《针刺研究》《中国中药杂志》《中国中西医结合杂志》《辽宁中医杂志》《世界中医药》《天然产物研究与开发》《中国临床药理学杂志》等期刊自2014年先后加入“中文精品学术期刊外文版数字出版工程”（Journal Translation

Translation Project (JTP, http://jtp.cnki.net/bilingual). As of 2020, 1 719 articles from these journals have been included in JTP and published in both Chinese and English, which has enhanced the international influence of these journals. To further promote the international dissemination of TCM culture and journals, and to inform more readers about the research progress of heart disease treatment with TCM, China National Knowledge Infrastructure collaborated with the editorial offices of these journals to constitute a panel of experts to select 26 excellent articles on heart disease research with TCM. These articles are recommended by the editorial boards of the journals in which they were originally published, covering theoretical, mechanism, and clinical studies. They are compiled into the book *Heart Disease* (*TCM*) as a part of *China's Medicine Progress Series* (English edition). These articles fully demonstrate the unique therapies and good efficacy of TCM in treating heart diseases, with scientific methodological support and objective conclusions. The original articles were published in Chinese, and this book is a compilation of English versions of the selected articles.

As the editor-in-chief, I believe this book will provide useful experience and methods from the Chinese community of Chinese medicine for the heart disease treatment worldwide. This book provides scientific, practical, and up-to-date literature for those who engage in TCM research worldwide, which help to enhance the international influence of TCM journals and contribute to the dissemination of TCM culture.

Editor-in-chief: LIU Jianxun

Project，JTP，http://jtp.cnki.net/bilingual）。截至 2020 年，来自这些期刊的 1719 篇文章先后入选 JTP，经过中英双语出版，提升了这些期刊的国际影响力。为了进一步加强中医药文化以及期刊的国际性传播，使更多读者了解中医药治疗心脏疾病的研究进展，中国知网联合期刊编辑部组织专家，遴选出 26 篇使用中医药方法的心脏疾病研究论文，汇编为《心脏疾病（中医卷）》（英文版）。本书属于《中国医药进展》（英文版）系列丛书，所收录的论文均由其一次发表的期刊编委会推荐，论文内容包含理论研究、机理机制研究、临床研究等板块，充分展示了中医药方法治疗心脏疾病的独特疗法和良好疗效，有科学的方法学支持和客观结论。原始论文以中文发表，本书以英译文的形式进行精选汇编。

作为本书的主编，我认为该书的出版能够对全球的心脏疾病治疗提供来自中国中医药学界的有效经验和方法，并为从事中医药工作的各国人士提供有科学性、实用性的最新文献资料，进一步提升中医药期刊的国际影响力，为传播中医药文化做出贡献。

主编：刘建勋

Contents

Mechanism of Salvianolate Injection Combined with Aspirin in Treatment of Stable Angina Pectoris based on Biomolecules Network

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Abstract: Biomolecular network analysis was used to predict the mechanism of Salvianolate injection combined with aspirin for the treatment of stable angina pectoris (SAP). Related genes of Salvianolate injection, aspirin and SAP were obtained from Genecards, STITCH and DisGeNET databases. Agilent literature search software was used to construct biomolecular network; modules were identified by AP, MCODE and MCL methods. DAVID software was used for identification of related KEGG pathways. Results showed that Salvianolate injection and aspirin had a coverage rate of 45.92%, and 62.56% respectively for SAP molecular network, and the coverage rate was 71.64% in combined use. The top 10 important nodes of SAP overlapped with Salvianolate injection and aspirin included MAPK14, MAPK8, IL-6 and IL-8. The important SAP nodes overlapped with Salvianolate injection alone included AKT1 and IFNG, and the important SAP nodes overlapped with aspirin included EPHB2 and TP53. Related SAP signaling pathways with combined Salvianolate injection and aspirin included Jak-STAT signaling pathway and MAPK signaling pathway. Related SAP signaling pathways with Salvianolate injection alone included VEGF signaling pathway and type 1 diabetes signaling pathway. Related SAP signaling pathways with aspirin alone included AA metabolism, linoleic acid metabolism signaling pathway, etc. The results showed that Salvianolate injection and aspirin combination had an enhancement effect in treatment of SAP through anti-inflammatory reaction and inhibition of atherosclerosis development; in addition, the combination use may have an additive effect through the antiplatelet aggregation, protecting endothelial cells, regulating blood lipid and regulating glucose metabolism.

Keywords: Salvianolate injection; aspirin; stable angina pectoris (SAP); drug combination; biomolecular network analysis; molecular mechanism

Stable angina pectoris (SAP) is a clinical syndrome of sharp and temporal ischemia/anoxia cardiac muscle due to cardiac muscle load increase based on severe, fixed coronary artery stenosis, and it is one of the most common types of angina pectoris in clinic [1]. Aspirin as the most widely used antiplatelet drug at present is mainly used for the treatment of angina pectoris, myocardial infarction and so on [2]. Meanwhile, there also exists aspirin resistance [3]. In recent years, the combination of Chinese and Western medicine in the treatment of complex diseases has achieved a preferable efficacy in clinic. In previous research, we found in hospital information system (HIS) of 18 grade 3 class A hospitals nationwide that most of 14,191 patients were treated with Salvianolate Injection combined with aspirin for the treatment of coronary heart disease [4–5]. Besides, a large number of literature studies [6–9] have proved that the curative effect of Salvianolate Injection combined with aspirin is superior to that of simple western medicine therapy for the treatment of SAP and that there is no obvious adverse reaction. Salvianolate Injection was prepared by extracting water-soluble effective constituents from Radix Salviae Miltiorrhizae that has the effects of promoting blood circulation and resolving blood stasis. It is applied to patients with SAP or blood stasis syndrome through syndrome differentiation in traditional Chinese medicine (TCM) [10]. The injection has the effects of promoting blood circulation, dispersing blood stasis, and dredging meridians. Magnesium lithospermate B (MLB)/salvianolic acid B) accounts for 80% and the remaining 20% include sodium rosmarinic acid (RA), magnesium lithospermic acid (LA), potassium Danshensu, dipotassium lithospermic acid, and salvia dipotassium acetate [10–11].

Biomolecular network emphasizes that the network is used for expressing the complex relation among drug, target and diseases. Most complex diseases are caused not by single virulence gene but several genes or product dysfunction inducing regulatory network imbalance [12]. TCM shows a good efficacy in treatment of complex diseases. Biomolecular network analysis can be used for systematical and comprehensive observation of intervention and effect of drugs on disease network and for analyzing "disease-gene-drug" multilevel network, providing an effective research method for revealing the mechanism of drug combination and polymolecular drugs synergism on human

Received: 2016-06-08
Supported by: Science and Technology Development Project of Traditional Chinese Medicine of Beijing, China (JJ2014-53)
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body [12–13]. Therefore, the mechanism of Salvianolate Injection combined with aspirin in treatment of SAP was explored on the basis of biomolecular network analysis, and the effects of the two drugs on SPA related important nodes and signaling pathways were analyzed in molecular level. This research provided reference for the research on clinical drug combination.

1 Materials and methods

1.1 Gene acquisition

"Aspirin" and the main constituents ("MLB/salvianolic acid B", "RA", and "LA") [10] of Salvianolate Injection were set as the key words, and drug-related target genes were retrieved from Genecards (http://www.genecards.org/) database and STITCH (http://stitch.embl.e/) database. By taking "Homo sapiens" as the background, all related genes from Genecard database and those with high reliability (> 4.0 scores) from STITCH database were obtained. Then, the overlapped genes were removed, and their names were unified. "Angina, stable" was set as the key word, and SAP related genes were obtained through DisGeNET (http://www.disgene.org/web/DisGeNET/menu) database under the background of human genes.

1.2 Establishment of molecular network

Related genes of Salvianolate Injection, aspirin and SAP obtained from database were submitted to Agilent Literature Search 3.1.1 (http://www.chem.agilent.com/scripts /Literature-Search. asp); human genes were set as premise and interaction vocabulary was limited; literature search through full text was selected. Target genes related genes from references were found and the biomolecular network was established. The visual processing and topological structure analysis were conducted on the platform of Cytoscape_v3.2.

1.3 Module identification of molecular network

Modules from molecular network of Salvianolate Injection, aspirin and SAP were identified by affinity propagation clustering (AP) [14], Markov clustering (MCL) [15] and MCODE [16] methods on the basis of gene clustering in the network. The identification results by the three methods, i.e., entropy values, were compared. The entropy value is a standard to judge the dispersion degree of modules. The smaller the entropy value is, the slighter the dispersion degree of modules is, and the higher the stability is [17–18]. The divided modules were ranked according to scores in a descending order. Each module was composed of relevant genes. The higher score meant higher significance of a module.

1.4 Biological function annotation of modules

In this research, GO function enrichment analysis was conducted for the main modules of molecular network of Salvianolate Injection, aspirin and SAP by using Functional Annotation Clustering tool of DAVID Bioinformatics Resources 6.7 (https://david.ncifcrf.gov/). In the background of human genes, GO biological process and KEGG pathways of remarkable enrichment in modules were identified. In order to detect whether there is significant difference in GO terms and KEGG pathways of remarkable enrichment in modules, P (EASE score) was calculated by Fisheris Exact Test on DAVID, and then Benjamini multiple testing and correction was conducted for P. Finally, GO terms and KEGG pathways ($P < 0.05$) after correction were regarded as prominent biological function and signaling pathways of modules.

2 Results

2.1 Establishment of molecular network

Through retrieval in Stitch and Genecards databases (October 3, 2015), it was found that there were 79 genes related to the main components (MLB, RA, and LA) of Salvianolate Injection and 498 aspirin related genes. Seventy-five SAP related genes were obtained through retrieval in DisGeNET database (October 4, 2015).

The molecular network of Salvianolate Injection consisted of 715 nodes and 2,310 sides; the molecular network of aspirin was composed of 2,120 nodes and 9,064 sides; SAP molecular network was constituted by 630 nodes and 2,385 sides (Fig. 1). The topological structure analysis showed that node degree distributions of molecular network of 2 drugs and SAP were scale free network (Fig. 1) following the characteristics of power-law distribution. For molecular networks of Salvianolate Injection, aspirin and SAP, the clustering coefficient was 0.615, 0.586, and 0.671, respectively, the radius was all 1, and the diameter was 10, 9 and 11, respectively (Table 1)

2.2 Module division

The identification results of modules by AP, MCODE and MCL methods indicated that the entropy value of network modules by MCODE was the smallest, which was 5.607,8, 6.629,6 and 5.707,99 respectively (Table 2). The identification result by MCODE method: there were 61 modules in Salvianolate Injection molecular network, and the biggest and the smallest modules were composed of 37 nodes and 3 nodes, respectively (Fig. 2A); 122 modules were identified from molecular network of aspirin, and the biggest and the smallest modules consisted of 112 nodes and 3 nodes, respectively (Fig. 2B); 40 modules were identified from SAP molecular network, and the biggest and the smallest modules were composed of 57 nodes and 3 nodes, respectively (Fig. 2C).

Ginseng Prescription Rules and Molecular Mechanism in Treating Coronary Heart Disease Based on Data Mining and Integrative Pharmacology

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Abstract: In *Shen Nong's Classic of the Materia Medica*, *The Grand Compendium of Materia Medica* and other works, ginseng has been recorded as top grade with the effect of tonifying primordial qi. It is reported that the main active ingredient of ginseng is ginsenoside according to the literatures. Modern studies have found that ginseng mono saponins are effective for cardiovascular related diseases. This paper preliminary clarified the traditional efficacy of ginseng—nourishing qi and cardiovascular disease through the traditional Chinese medicine (TCM) inheritance auxiliary platform and integrative pharmacology platform. With the help of integrative pharmacology platform—"Chinese medicine database", the rule of Chinese patent drugs containing Ginseng treating current diseases was discussed, so the traditional effect was associated with modern medicine and pharmacology. Drug target, gene function and metabolic pathway enrichment were analyzed based on integration platform, to further explore the molecular mechanism of ginseng in the treatment of coronary heart disease, aiming at mining the molecular mechanism of ginseng in the treatment of coronary heart disease. *National Standard for Chinese Patent Drugs* contains 307 ginseng prescriptions, 87 kinds of disease indications, coronary heart disease—disease of Western medicine which is treated by Chinese patent drugs containing Ginseng. Through the analysis of molecular mechanism of integrative pharmacology platform for the treatment of coronary heart disease, 1 556 potential targets were found which were related with the mitochondrial respiratory. Ginsenosides (Ra_1, Ra_2, Rb_1, Rb_2, Rg_1, Ro) bind the targets (PRKAA1, PRKAA2, NDUFA4, COX5B, UQCRC1) to affect chemokines, non-alcoholic fatty liver, gonadotropin, carbon metabolism, glucose metabolism and other pathways, treating coronary heart disease indirectly. The molecular mechanism of Panax ginseng's multi-component, multi-target and synergistic action is preliminarily elucidated in this paper. **DOI:** 10.19540/j.cnki.cjcmm.20180115.006-en

Keywords: ginseng; integrative pharmacology; molecular mechanism; coronary heart disease

Panax ginseng C. A. Mey is the perennial herb of Araliaceae family with the history of about 60 million years. Every part of ginseng presents high medicinal value, especially the root, which is a traditional Chinese medicine and precious nutrition in China and even Southeast Asia. Early in *Shen Nong's Classic of the Materia Medica*, it has been recorded as top grade with the description as "It can nourish the body without toxicity; it will not harm the body no matter for how long it is taken. It can strong the body, tonify qi, and prolong life" [1]. *Treatise on Cold Damage and Miscellaneous Diseases* of ZHANG Zhongjing, *The Grand Compendium of Materia Medica* of LI Shizhen and many herbal records in the Qing dynasty have specific depiction on the effects of ginseng. Ginseng is sweet in favour and tolerates cold. It is warm in property after processing, without toxicity, with the traditional effects including tonifying primordial qi, invigorating spleen, benefiting lung, nourishing blood, producing fluid and calming the heart and tranquilizing the mind. Current studies have shown that ginseng has the pharmacologic actions including DNA protection, antioxidation and anti-inflammation [2–4]. More than 300 chemical contents have been separated and identified from every part of ginseng, including saponins, saccharides, organic acids and proteins [5]. Among them, ginsenosides are the primary active substances [6]. Currently, the studies on ginseng mainly concentrate on the pharmacological actions and molecular mechanisms of ginseng mono saponins, which show that the saponin and non-saponin of ginseng also present pharmacological activities [7]. When studying panaxadiol saponin and panaxatriol saponin, the author has found that, connecting saccharide at C3– and C20– or different saccharides will produce different ginseng mono saponins in

Received: 2017-11-14
Supported by: Program with Significant Increase or Decrease at the Central Governmental Level
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panaxdiol saponin, which all show pharmacological actions. It shows the same rule at C6– and C20– in panaxatriol saponin. Based on the mentioned principle, it is hard to determine the material basis of ginseng. As a result, only the least part of the mechanism can be revealed by the traditional methods in the complex Chinese medical system. To meet the needs of the times, integrative pharmacology are produced.

The integrative pharmacology stresses the combination of the integration and local, macroscopy and microscopy, in vitro ADME process and active evaluation [8]. Such strategies integrate several disciplines of computer science, Chinese medicine, chemistry, pharmacokinetics and pharmacology, which absorb the virtual computer, in vitro experiments and integral animal experiments to systematically and comprehensively reveal the pharmacodynamic material basis and mechanism of Chinese Medical Formulae so as to provide evidences for the clinical application, quality evaluation, pharmacodynamic material basis, mechanism principle of recipes and new drug study in Chines medicine. The Computation Platform for Integrative Pharmacology (IP) of Traditional Chinese Medicine (TCM) (TCMIP, www.tcmip.cn),based on the big data of Chinese medicine, is supported by the methods and skills of artificial intelligence, data modeling and mining, and network science to realize the self-service model and construct the integrative pharmacology platform [9]. The platform is V1.0 version, and the main function is to investigate the mechanisms of Chinese medical recipe based on the virtual blocks of computer. In later stage, the platform will be improved from the in vitro metabolism and pharmacodynamics evaluations to completely transfer the integrative pharmacology strategies so as to help the modernization of Chinese medicine.

This article has explained the molecular mechanism of ginseng in treating coronary heart diseases based on the integrative pharmacology platform V1.0 from "Chinese medicine-chemical component-disease-target-pathway", which has provided theoretical basis for the basic research and clinical application of ginseng.

1 Materials and methods

1.1 Origins of prescriptions

The recipes including ginseng in the *National Standard for Chinese Patent Drugs* were collected and arranged. Taking "ginseng" as search keyword, ("ginseng powder", "sugar ginseng", "fresh ginseng", "ginseng juice" and "suncured ginseng" were included into the search results as medical ginseng), a total of 307 prescriptions were included.

1.2 Analysis of medication rule of ginseng in Chinese patent medicine

First, the data in the traditional TCM inheritance auxiliary platform 2.5 were changed into the Chinese patent prescription database. Then, the TCM inheritance auxiliary platform 2.5 software was used, and the data analysis block was opened. Taking "ginseng" as keyword, we searched and calculated the disease frequencies of ginseng treating Traditional Chinese medicine disease and diseases of Western medicine (WM) to obtain the disease indications treated by ginseng.

1.3 Construction of compound database of ginseng

Based on the Chinese medical database of integrative pharmacology platform V1.0 (http://www.tcmip.cn/), the components in the ginseng medicine were collected as the compound database of ginseng.

1.4 Construction of target library confined by coronary heart disease

The keyword "coronary" should be input in the integrative pharmacology platform/syndrome target database, then we should search for the drug treating coronary heart disease, and finally the target of treating coronary heart disease can be determined.

1.5 Prediction of ginseng target

The platform used the two dimensional structure (.mol) of chemical components of ginseng and compared the chemical fingerprint characteristics with the approved drugs in DrugBank. The Tanimoto coefficient was used for the similarity grading. Drugs with score larger than 0.6 were considered as similar drugs and the targets were regarded as the candidate targets of ginseng.

1.6 Construction of protein-protein interaction (PPI) network

The PPI data in the HAPPI, Reactome, OPHID, InAct, HPRD, MINT, DIP, and PDZBase were embedded in the platform. Based on the five database, the network of ginseng medical targets and coronary heart disease targets was constructed and the visualized work was done. Visualized report was primarily composed of nodes and sides, among which, the first one represented drug targets, or disease targets or the common targets, and the side represented the target pairs. The importance of node in network was topological parameters including degree, between and closen, etc. Degree and between could determine the importance of topological structure in the node of network. The higher the value was, the more importance the structure was.

1.7 Genetic function analysis and metabolic pathway analysis

Integrative pharmacology platform had the genetic function and pathways enrichment function, and the relative information came from GO database (http://www.geneontology.org)