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Inflammation

炎症

Editor-in-Chief/主编

LIU Changxiao/刘昌孝

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Foreword by Editor-in-Chief

主 编 卷 首 语

Inflammation refers to the defensive response of living tissue with vascular system to pro-inflammation cytokines and local injury, which is centered in vascular response. Inflammation is manifested as physiological responses initiated by stimuli such as trauma, bleeding, and pathogenic infection. These responses include redness, swelling, fever, and pain. Inflammation is a protective measure of the innate immune system to remove harmful irritants or pathogens or to promote repair, which is different from the acquired immune system that targets specific pathogens. Inflammation can be induced by burn, chemical stimulus, frostbite, toxin, pathogen infection, and necrocytosis. Studies have confirmed that persistent inflammation caused by infection or autoimmunity can progress to tumors. The available therapies for treating inflammation in western medicine mainly include non-steroidal anti-inflammatory drugs, steroids, and physiotherapy. With the gradual recognition and acceptance worldwide, traditional Chinese medicine (TCM) has attracted extensive attention in anti-inflammation attributed to the excellent performance and a growing number of clinicians and researchers have devoted to the study of anti-inflammation with TCM. The discovery of a variety of anti-inflammatory Chinese medicinal materials and the study of effective therapies such as acupuncture and moxibustion provide powerful tools to fight inflammation. Despite the rapid advancement of modern technology and medical care, the mechanisms of many anti-inflammatory drugs remain unclear, and new drugs are yet to be developed. Researchers in China have actively developed new Chinese and western anti-inflammatory drugs, optimized chemical drug structures, elucidated drug action mechanisms, explored the potential of acupuncture and moxibustion in treating inflammation, and improved the nursing of patients with inflammation, making great contribution to the treatment of inflammation.

炎症反应、炎性反应，俗称发炎，是指具有血管系统的活体组织对致炎因子及局部损伤所发生的防御性为主的反应，中心环节是血管反应，是生物组织受到外伤、出血或病原感染等刺激所激发的生理反应。其中包括了红肿、发热、疼痛等症状。炎性反应是先天免疫系统为移除有害刺激或病原体及促进修复的保护措施，并非如后天免疫系统般针对特定病原体。烧伤、化学刺激、冻伤、毒素、病原菌感染、细胞坏死等均可以诱发炎症。很多研究已经证实持续的炎症可以使病变从感染或者自身免疫性的炎症进展为肿瘤。目前西医抗炎治疗的手段主要包括非类固醇抗炎剂、类固醇、物理治疗等。伴随着中医药被世界逐步认识与认可，她在抗炎领域的优秀表现令世界广为关注，全球越来越多的临床医师和研究者都投入到中医药抗炎的研究中来。多种具有抗炎活性的中药的发现以及针刺、艾灸等中医药特有有效治疗措施的研究为人类对抗炎症提供了有利的武器。尽管现代科技水平和医疗水平的进步突飞猛进，然而许多抗炎药物的机理并不明确，许多具有抗炎活性的新药有待挖掘。在这些方面，中国的研究者积极开发抗炎中西新药物，改进和优化药物化学结构，积极阐明抗炎药物的机理机制，积极发掘针灸对抗炎症的潜力，同时积极推动炎症患者护理水平的提升，为炎症患者的治疗和康复做出了不少的贡献。

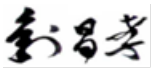
Since 2014, *Chinese Acupuncture & Moxibustion*, *Acupuncture Research*, *China Journal of Chinese Materia Medica*, *Acta Pharmaceutica Sinica*, *Chinese Pharmacological Bulletin*, *Chinese Journal of Integrated Traditional and Western Medicine*, *Chinese Pharmaceutical Journal*, *The Chinese Journal of Clinical Pharmacology*, *Journal of Chinese Medicinal Materials*, *Chinese Archives of Traditional Chinese Medicine*, *Liaoning Journal of Traditional Chinese Medicine*, *Chinese Traditional and Herbal Drugs*, *Disease Surveillance*, and *Chinese Journal of Nursing* have joined the Journal Translation Project (JTP, http://jtp.cnki.net/bilingual). As of 2020, 5 049 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 medical and pharmaceutical journals published in China and to inform more readers about the latest progress of inflammation treatment in the medical and academic sectors in China, China National Knowledge Infrastructure collaborated with the editorial offices of these journals to constitute a panel of experts to select 76 excellent articles on inflammation research, which have been compiled into the book *Inflammation* (English edition) as part of *China's Medicine Progress Series* (English edition). These articles included were recommended by the editorial boards of the journals in which they were originally published, covering theoretical, drug, mechanism, clinical, and nursing research and fully demonstrating the cutting-edge advances in inflammation treatment in China, with methodological support and objective conclusions. The original articles are published in Chinese, and this book is a compilation of English versions of selected articles.

As the editor-in-chief, I believe this book will provide useful experience and methods from the Chinese medical community for inflammation treatment worldwide. This book provides scientific, practical, and up-to-date literature for global medical professionals and further enhances the international influence of medical and pharmaceutical journals published in China.

Editor-in-chief: LIU Changxiao

《中国针灸》《针刺研究》《中国中药杂志》《药学学报》《中国药理学通报》《中国中西医结合杂志》《中国药学杂志》《中国临床药理学杂志》《中药材》《中华中医药学刊》《辽宁中医杂志》《中草药》《疾病监测》《中华护理杂志》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 Project，JTP，http://jtp.cnki.net/bilingual）。截至 2020 年，来自这些期刊的 5 049 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。为了进一步加强国内医药期刊的国际性传播，使更多读者了解中国医学界及学术界治疗炎症的最新研究进展，中国知网联合期刊编辑部组织专家，遴选出 76 篇炎症研究论文，汇编为《炎症》（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，论文内容包含理论分析、药物研究、机理研究、临床研究、护理研究等板块，充分展示了中国炎症治疗领域的前沿进展，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炎症治疗提供来自中国医药学界的有效经验和方法，并为从事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，进一步提升中国医药期刊的国际影响力。

主编： 

Editor-in-Chief/主编:

LIU Changxiao/刘昌孝

Introduction/简介:

LIU Changxiao is the honorary president, tenured principal scientist and academic committee director of Tianjin Institute of Pharmaceutical Research, and the director of the State Key Laboratory of Drug Delivery Technology and Pharmacokinetics, the Center for TCM Academicians and Experts of the Healthy China Promotion Network of the Development Research Center of the State Council, the Committee of Experts of the Center for Regulatory Science Research of Chinese Medicinals, the National Medical Products Administration, as well as the China Office for International Society for the Study of Xenobiotics (ISSX). Besides, he is also the president of both Tianjin Pharmaceutical Society and Tianjin Society Research Institution, as well as the professor and doctoral supervisor of Tianjin University and Xi'an Jiaotong University.

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Part 1

Theoretical Analysis

Network Pharmacology-based Study on Mechanisms of Huanglian Jiedu Decoction Impact on Macrophage Inflammation Response

HENG Xia[1,2], ZHU Bao-jie[1,2], SUN Li-min[1,2], PAN Lin-mei[1,2], DUAN Jin-ao[1,2], ZHANG Qi-chun[1,2], ZHU Hua-xu[1,2]

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Abstract: This study was designed to explore the impact of Huanglian Jiedu Decoction (HLJDT) on macrophage inflammation reaction using the network pharmacology method. Glycolysis, sphingolipid metabolism and glutamine metabolism were also investigated for "multi-component, multi-target and multi-pathway", which supports a foundation for drug innovative research. The TCMSP database was used to screen the active components of HLJDT, the target protein predicted by Pharm Mapper database and the DAVID database for pathways annotation and analysis. The Cytoscape 3.2.1 software was used to construct the active component target–pathway network map and GENEMANIA database for protein interaction analysis. System Dock Database Site is used in verification of molecular docking. The results showed that 84 active ingredients were screened in HLJDT with a total of 111 target targets. Fourteen pathways are affected according to 13 macrophage-related inflammatory proteins, and 8 pathways including 34 target proteins from glycolysis, sphingolipid metabolism and glutamine metabolism. Inflammation-related proteins and metabolism-related proteins can interact with each other through physical correlation, protein co-expression, etc. Berberine, baicalin and geniposide combined well with 5 important targets. Huanglian Jiedu Decoction may act on the glycolysis and sphingolipid pathways to regulate macrophage inflammatory responses. **DOI:** 10.16438/j.0513-4870.2018-0276-en

Keywords: network pharmacology; Huanglian Jiedu Decoction; inflammation; metabolism

Based on the theories of holistic view and syndrome differentiation for treatment, traditional Chinese medicine compound prescription has the characteristics of multi-component, multi-target and multi-pathway synergistic effect, with complex mechanism of action. It is relatively difficult to elaborate its mechanism by adopting the model of "one drug for one target" [1]. However, with the rapid development of public biomedical science, the network pharmacology method has emerged, providing a new approach to elucidate the mechanism of action of compound prescription of traditional Chinese medicine [2]. Network pharmacology is a new subject based on systematic biology, multi-direction pharmacology and molecular network analysis. The application of network pharmacology technology plays an important role in understanding the integrity, complementarity and synergy of traditional Chinese medicine compound prescription.

Huanglian Jiedu Decoction is a traditional famous prescription for clearing heat and toxic materials. It is composed of four Chinese medicines: Rhizoma Coptidis, Radix Scutellariae, Cortex Phellodendri and Fructus Gardeniae. A large number of studies have shown that Huanglian Jiedu Decoction plays an important role in a variety of diseases such as tumor, diabetes, arthritis, ischemic stroke and liver diseases, while the activation of immune cells and inflammatory responses initiated by metabolic reprogramming are involved in the occurrence and development of the above diseases [3−6]. Based on metabolic regulation network, regulation of immune cell function might be the biochemical mechanism of anti-inflammatory effect of Huanglian Jiedu Decoction. This study used the analysis technology of network pharmacology to explore the multi-component, multi-target and multi-pathway interaction rules and regulation network of Huanglian Jiedu Decoction on regulating macrophage inflammation reaction, glycolysis, sphingomyelin metabolism and glutamine metabolism, in order to lay a foundation for in-depth research on the mechanism of Huanglian Jiedu Decoction regulating inflammation and the development of new and valuable drugs.

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Materials and methods

Software and databases

The following software and databases were used in this study: TCMSP database (http://lsp.nwsuaf.edu.cn/tcmsp.php), Pubchem database (https://pubchem.ncbi.nlm.nih.gov/), PharmMapper database (http://lilab.ecust.edu.cn/pharmmapper/ index.php), OMIM database (http://www.omim.org/), DAVID database (https://david.ncifcrf.gov/), Kyoko Encyclopedia of Genes and Genomes (KEGG) access database (http://www.Genome.jp/kegg/), GENEMANIA database (http://genemania.org/), System Dock Database Site (http://systemsdock.unit.oist.jp), and Cytoscape 3.2.1 software.

Screening for active ingredients of Huanglian Jiedu Decoction

Huanglian Jiedu Decoction contains four Chinese medicines: Rhizoma Coptidis, Radix Scutellariae, Cortex Phellodendri and Fructus Gardeniae. The Chinese names of these four Chinese medicines were entered into the TCMSP database as keywords for retrieval. The results were screened based on oral bioavailability (OB) > 30%, drug-likeness (DL) > 0.18, and the ingredients obtained after screening were used as active ingredients of Huanglian Jiedu Decoction.

Potential targets prediction of active ingredients in Huanglian Jiedu Decoction

The active ingredients screened in Huanglian Jiedu Decoction were entered into the Pubchem database by using the name of the medicine as keywords, and the 3D structural formula of each active ingredient was searched and stored in the SDF (.sdf) format. Then the 3D structural formula of each active ingredient was submitted in the PharmMapper database for target prediction. The parameters were selected sequentially as follows [7]: Generate Conformers—Yes; Maximum Generated Conformations—100; Select Targets Set—Human Protein Targets Only (2 241); Number of Reserved Matched Targets (Max 1 000)—100. Results such as target name, gene, Uniprot ID, and fit score associated with each compound were obtained. The top 10 targets were screened based on fit score as important target proteins for the compound.

Target prediction of inflammatory macrophages and metabolism

The words “inflammation” and “macrophages” as keywords were entered into the OMIM database to search for target proteins related to inflammation and macrophages, and “glycolysis”, “sphingolipid metabolism” and “glutamine metabolism” as keywords were entered into the OMIM database to search target proteins related to glycolysis, sphingolipid metabolism, and glutamine metabolism. These target proteins were sorted and matched with the selected target proteins of the active ingredients to obtain targets related to inflammatory macrophages and metabolism in Huanglian Jiedu Decoction.

Annotation and analysis of related pathways

In the form of standard gene name, the relevant target gene list of the active ingredients were entered into the DAVID database; OFFICIAL_GENE_SYMBOL (official gene marker), Gene list, and Submit list were marked; the gene function classification tool was chosen; the background was modified to human; Pathway was chosen to get “KEGG–Pathway” data; the data was saved; the pathway of $P < 0.01$ was selected as a reliable path; the KEGG database was combined for pathway annotation and analysis.

Establishment of “active ingredient–target–pathway” network map for the anti-inflammatory and metabolic effects of Huanglian Jiedu Decoction

The active ingredients, corresponding predicted targets and pathway analysis results in Huanglian Jiedu Decoction were used to construct the relationships of “active ingredient–target” and “target–pathway” in Excel table respectively, which were imported into Cytoscape software to establish the network maps of “active ingredient–target” and “target–pathway”. The Merge function in the software was used to combine the two network maps to obtain the “active component–target–pathway” network. In the map, the active component, target protein, and pathway are three types of nodes, and the interactions between them were represented by edges. The network was analyzed by the network analysis function in the software, and the degree and edge betweenness reflected the size of nodes and thickness of edges.

Protein interaction analysis

The screened inflammatory macrophage target proteins and metabolic target proteins were uploaded to the GENEMANIA database as standard gene names, and the interaction between proteins was analyzed to obtain a protein interaction network map. The network layout was arranged and the images were saved.

Main active ingredient–target molecular docking

With the Systems Dock Web Site database, five common targets obtained by the interaction analysis of berberine, baicalin and geniposide with proteins in Huanglian Jiedu Decoction were subjected to molecular docking verification. The target name/PDB ID, 3D structures of berberine, geniposide, and baicalin SDF in (.sdf) format were uploaded after logging into the Systems Dock Web Site database. Subsequently, the docking would be performed, and the Docking Score in the docking results were sorted and analyzed.

Mechanisms of Anti-inflammation of Taurochenodeoxycholic Acid Based on Network Pharmacology

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Abstract: To investigate the anti-inflammatory mechanisms of taurochenodeoxycholic acid (TCDCA), the molecule structure file of TCDCA was downloaded from PubChem database, PharmMapper and GeneCards were used to predict and screen the targets of TCDCA. STRING database and Cytoscape software were used to construct protein interactions network. GO and KEGG analysis was preformed through STRING database. The key targets were validated by molecular docking and the targets type was attributed by DisGeNET database. The network showed that 89 targets were involved in 68 biological processes including response to stimulus, multicellular organismal process, single-multicellular organism process, response to chemical, response to organic substance, by adjusting 51 signaling pathways, such as pathways in cancer, progesterone-mediated oocyte maturation, MAPK signaling pathway, proteoglycans in cancer. These findings provide an overview of anti-inflammation of TCDCA, which reflects the characteristic of multi-targets and multi-pathways of TCDCA. It pointed out the direction for further research on anti-inflammatory mechanism of TCDCA. **DOI:** 10.16438/j.0513-4870.2018-0600-en

Keywords: taurochenodeoxycholic acid; inflammation; network pharmacology; pharmacological mechanism; molecular docking

Bile, which is bitter in flavor and cold in nature, has the effects of clearing away heat and toxic materials, clearing liver and improving vision, clearing lung heat and relieving cough, nourishing yin and moistening lung. Derived from animals, it is a traditional Chinese medicinal material in China with a long history of application. It has received much attention because of its extensive source and definite therapeutic effect[1]. Cow bile was recorded as early as in *Shen Nong's Classic of the Materia Medica*, and in *Tang Materia Medica*, the application of bear bile was also recorded. A total of 31 and 44 kinds of animal bile were recorded in *Grand Compendium of Materia Medica* and *Chinese Materia Medica* respectively [2], and the definite therapeutic effect of bile was proved by thousands of years of medication history.

Modern pharmacological studies have found that animal bile has significant effects on the treatment of respiratory diseases (such as acute and chronic tracheitis, cough, etc.), hepatic and gall diseases (such as cholesterol calculus), digestive system diseases (such as infantile dyspepsia) and other diseases [3, 4]. In addition, animal bile also has pharmacological effects on antipyretic analgesia [5], bacteriostasis, anti-inflammation [6, 7], immune regulation [8], etc. The composition of bile in different animals is slightly different, but it mainly contains bile acids, bile pigments, lipids, proteins and trace elements, among which bile acids are considered as the material basis for bile to exert its functions. According to the source, bile acids can be divided into primary and secondary bile acids. The former is synthesized by cholesterol through many enzymatic reactions in the liver, while the latter is mainly produced by the former through 7-site dehydroxylation after intestinal bacteria hydrolysis. According to the chemical structure, bile acids can be divided into free bile acids and conjugated bile acids.

Among all kinds of bile acids, taurochenodeoxycholic acid (TCDCA, Fig. 1) mainly exists in the bile of various animals (such as chicken, duck, goose, snake, etc.) as a conjugated bile acid. There is a certain difference in TCDCA content in the bile of different animals, and the bite content in the poultry such as chicken, duck, and goose is relatively high, all exceeding 38%[9]. The research group has found in the previous study that TCDCA has a good inhibitory effect on acute and chronic inflammatory reactions caused by various reasons [10], but its exact mechanism of action has not yet been clarified. In this study, we analyzed the anti-inflammatory mechanism of TCDCA through network

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pharmacology in order to provide the support for further revealing the pharmacological effects of TCDCA.

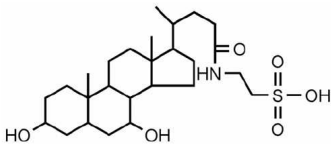

Fig. 1 The chemical structure of taurochenodeoxycholic acid (TCDCA)

Materials and methods

Acquisition of the targets of TCDCA The 3D molecule structure file of TCDCA was downloaded from PubChem database and stored in SDFile (*.sdf) format. Then the TCDCA.sdf file was input into the PharmMapper server [11] to obtain the targets of TCDCA. Using the Retrieve/ID Mapping function [12] of the UniProt database, the UniProt ID of the target was converted to Gene Symbol.

Screening of inflammation-related targets Inflammation and anti-inflammation were input into the GeneCards server to search for the reported inflammation-related genes [13]. After the repetitive genes were removed, the genes were matched with TCDCA targets returned by PharmMapper to obtain TCDCA anti-inflammatory targets.

Construction and analysis of protein interaction network The TCDCA anti-inflammatory targets were introduced into STRING database (https://string-db.org/, Version 10.5) [14], and the species was set as human to obtain target protein interaction relationship. The relevant information such as node1, node2 and combine score extracted from the results was imported into the Cytoscape to construct the target protein network [15], and the network was analyzed. The analysis results were saved; the color and size of the nodes were set to reflect the size of degree; the thickness of the edge was set to reflect the size of combine score; the target protein interaction network was established.

Biological function and pathway analysis The TCDCA targets information was input into STRING database for GO enrichment analysis and KEGG pathway annotation analysis. The results were saved and the threshold value was set as $P < 0.05$ to screen biological processes or pathways.

Molecular docking verification The enriched targets in the KEGG pathway were selected and their PDB IDs were searched, which were input into the System Dock Web Site (http://systemsdoc.unit.oist.jp, Version 2.0) to perform molecular docking with TCDCA [16]. The docking results were saved and the docking scores were analyzed to evaluate the binding activity between TCDCA and each target.

Target type attribution The targets which could dock with TCDCA were input into DisGeNET database [17] to obtain the information related to target types.

Results

1 Target predication

The first 100 potential targets returned by TCDCA in the PharmMapper server were sorted according to the fit score. The UniProt ID was converted into Gene Symbol through UniProt database, and then compared with the genes related to inflammation in GeneCards to screen out 89 potential anti-inflammatory targets for TCDCA, as shown in Table 1.

2 Construction and analysis of protein interaction network

The target protein information was input into STRING database to obtain the target protein interaction relationship, and the target protein interaction network was visualized by Cytoscape program (Fig. 2). The nodes represent the target protein molecules, and the edges represent the relations between the targets, with a total of 85 nodes and 356 edges (HRSP12, RORA, CRAT and ISG20 did not interact with other target proteins, so they were not reflected in the network). The color and size of the nodes reflect the degree values of the target proteins. The color changing from green to red and the larger node indicate larger degree value of the target protein, and vice versa. The thickness of the edge indicates the combine score between target proteins, and the thicker edge suggests the greater score.

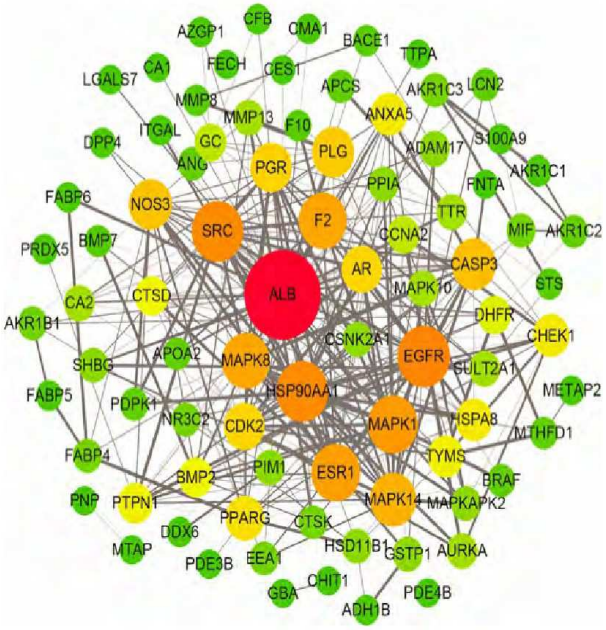

Fig. 2 Target protein interaction network of TCDCA