

Abstract: Inflammation is a common condition in the human body that significantly impairs immune function. Network pharmacology, with its strengths in bioinformatics and biomedical fields, offers a powerful tool for exploring the complex interactions involved in inflammation. By using traditional Chinese medicine (TCM) as a carrier, network pharmacology helps elucidate specific molecular mechanisms and biological processes, and identifies effective TCM components for targeting and treating inflammation. This review summarizes recent advancements in the application of network pharmacology for the treatment of inflammation using TCM. It highlights the progress and mechanisms by which TCM addresses inflammation, providing valuable insights for future research in this area.

Keywords: Inflammation; Network pharmacology; Traditional Chinese medicine;

Introduction

Inflammation is a fundamental pathological process occurring in living tissues with a vascular system in response to various injury stimuli, primarily through defense reactions. It is a non-specific immune response produced by the body to stimuli such as infection and tissue damage. Conceptually, inflammation is a physiological process that systematically responds to specific states. However, long-term and severe recurrent inflammation can cause significant harm, leading to the destruction of the immune system and other pathological damage. Severe inflammation is associated with allergic diseases, cardiovascular and cerebrovascular diseases, liver and kidney diseases, arthritis, and other conditions, posing a substantial threat to human health.

Currently, experimental techniques for studying inflammation, such as network pharmacology, utilize traditional Chinese medicine (TCM) or its components as carriers. These techniques leverage the advantages of bioinformatics and biomedical science to elucidate the biological mechanisms of action. Network pharmacology aligns well with the holistic and systematic principles of TCM, which emphasize "multi-level, multi-component, and multi-target" approaches. By combining bioinformatics and biomedicine, network pharmacology establishes correlations between TCM components and regulatory targets, improves the accuracy of predictive results, and promotes the rapid modernization of TCM.

1 Concepts of Network Pharmacology

Network pharmacology is an emerging discipline that uses network construction and bioinformatics to explore the "correlation, wholeness, and systematicity" between drugs and diseases, emphasizing the interaction between drugs and targets. This approach aligns with the holistic concepts of TCM, including syndrome differentiation and treatment. Network pharmacology systematically reveals the regulatory roles of TCM on the body's networks.

Network pharmacology involves computer simulation and database queries to screen for drug (TCM) component targets related to diseases, predict signaling pathways, and summarize mechanisms of action. Relevant software is used to visualize the "compound-target-pathway" network, and key nodes (drug targets) are selected through topological parameter analysis. The widespread application of this method has saved costs in drug development, clarified the specific biological mechanisms and pharmacological effects of TCM in treating diseases, and addressed the current lack of direct evidence for TCM.

In practice, network pharmacology is often used as an auxiliary experimental method in TCM pharmacology research. It reduces the reliance on empirical research and emphasizes scientific, systematic, and logical approaches. Network pharmacology plays an indispensable role in elucidating the specific biological mechanisms of drug action, thus enhancing our understanding of TCM's efficacy in treating inflammation.

2 The Application of Network Pharmacology in the Research Field of Compound Chinese Medicine for Treating Inflammation

Traditional Chinese medicine (TCM) is widely utilized in the treatment of inflammation, known for its broad availability and stable efficacy. Despite its extensive use, the specific biological mechanisms and physiological pharmacological reactions underlying TCM's effects are not fully understood.

Network pharmacology addresses this gap by constructing a complex network of "drugs-genes-targets-diseases." This interdisciplinary approach leverages the data advantages of bioinformatics and biomedical science to intuitively predict or reveal the mechanisms of drug action on the body through network relationships. By doing so, network pharmacology facilitates the targeted development and innovative application of TCM.

2.1 Single Traditional Chinese Medicine

In the practical application of network pharmacology, single traditional Chinese medicine has a good therapeutic effect on inflammation.

Pan Feng et al. [7] used network pharmacology to study the mechanism of action of Bai Ji on ulcerative colitis (UC). They identified 9 target genes of Bai Ji and 68 target genes related to the treatment of UC. Analysis of Gene Ontology (GO) function and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways revealed that these common targets are mainly involved in signal transduction, peptide tyrosine phosphorylation, protein phosphorylation, and other processes. It was found that the target genes for treating UC in white blood cells are primarily enriched in pathways such as phosphatidylinositol 3-kinase protein kinase B, proteoglycans in cancer, prostate tumors, Rap1, and MAPK. The binding energy between the active ingredients of Bai Ji and the core target protein of UC is generally less than -5 kcal/mol, with 20 components having a binding energy of less than -7 kcal/mol, indicating a strong correlation between Bai Ji's potential active ingredients and UC's key targets. These components and targets are likely the material basis and key targets for Bai Ji's treatment of UC.

Yang Jingxing et al. [8] used network pharmacology to study the mechanism of action of *Scutellaria baicalensis* in the treatment of chronic sinusitis (CRS). They identified 35 main active parts and 438 target genes of *Scutellaria baicalensis*, along with 1743 related target genes for CRS, resulting in a total of 121 targets. GO functional analysis revealed that common targets significantly impact biological processes such as lipopolysaccharide response, bacterial-derived molecule response, and peptide tyrosine phosphorylation. At the molecular level, the functions are related to protein tyrosine kinase activity, transmembrane receptor protein tyrosine kinase activity, and phosphatase binding. In cellular components, these targets are associated with membrane rafts, membrane microregions, and membrane regions. KEGG enrichment analysis showed that *Scutellaria baicalensis* impacts CRS mainly through pathways like phosphatidylinositol 3-kinase protein kinase B, advanced glycation end products receptor signaling, Ras signaling, and chemokine signaling. Molecular docking results indicated that berberine, an active ingredient, showed stable binding with AKT1, PIK3R1, PIK3CD, and STAT3.

Qian Rui et al. [9] used network pharmacology to study the mechanism of action of the alcohol extract of white meat *Ganoderma lucidum* in treating silicosis-induced inflammation. They identified 36 main active parts and 868 target genes of *Scutellaria baicalensis* and white meat *Ganoderma lucidum*, along with 313 related target genes for CRS, totaling 67 targets. KEGG pathway analysis revealed that common targets mainly involve inflammation-related pathways such as IL signaling, cytokine signaling of immune cells, and TNF signaling, as well as fibrosis-related pathways like TGF- β signaling and pulmonary fibrosis. GO functional analysis indicated that the biological processes include positive and negative regulation of apoptosis and smooth muscle/vascular smooth muscle cell proliferation and differentiation. The cellular components involved mainly include the cytoplasm, extracellular space, and caspase complex, while molecular functions are related to protein binding, enzyme activation, and peptidase activation.

Xie Liangshan et al. [10] used network pharmacology to study the mechanism of action of pineapple in treating rheumatoid arthritis (RA). They identified 11 main active parts and 308 target genes of pineapple, with 513 related target genes for RA, totaling 49 targets. GO function analysis revealed that common targets involved biological processes such as extracellular matrix breakdown, collagen metabolism, protein phosphorylation, protein hydrolysis, and extracellular matrix tissue. KEGG enrichment analysis showed that pathways such as TNF signaling, IL-17 signaling, cancer signaling, Relaxin signaling, AGE-RAGE signaling, and chemokine signaling are related to the treatment of RA, with the TNF signaling pathway being the most relevant.

Sun Jinmeng [11] used network pharmacology to study the mechanism of action of ginseng in treating periodontitis. Through screening, 22 active ingredients of ginseng and 591 related targets were identified, with 2249 corresponding targets and 145 intersecting targets for periodontitis. GO analysis indicated that key targets are involved in biological processes such as inflammatory response, protein hydrolysis, protein phosphorylation, cell proliferation, and gene expression regulation. KEGG analysis showed that ginseng's core targets for periodontitis treatment involve pathways like hypoxia-inducible factor-1 signaling, TNF signaling, cancer pathways, and apoptosis. Molecular docking results demonstrated that the active ingredients of ginseng, kaempferol, and β -sitosterol, have strong binding affinities with core targets such as VEGFA, CASP3, AKT1, EGFR, HSP90AA1, and TNF, with binding energies of less than -5.0 kcal/mol, confirming good docking results.

2.2 Compatibility of drugs

The application of a medicine pair, a commonly used minimal formula unit in traditional Chinese medicine, involves the paired use of two medicinal substances. This approach, while simpler than compound formulas, enhances therapeutic effects and reduces toxicity and side effects.

Zhang Yanyan [12] employed network pharmacology to explore the mechanism of honeysuckle and large blood vine in treating rheumatoid

arthritis (RA). The study identified 165 effective ingredients and 323 related targets of the two herbs, with 5093 corresponding targets and 213 intersecting targets for RA. GO functional analysis revealed that the key targets are involved in responses to inorganic substances, nitrogen compounds, and drugs; cellular components such as membrane rafts, cyclin-dependent protein kinase enzyme complexes, and axons; and molecular functions including protein homodimerization, protein domain-specific binding, and nuclear receptor activity. KEGG pathway analysis showed that common targets were mainly related to cancer pathways, the AGE-RAGE signaling pathway in diabetic complications, hepatitis C, apoptosis, and the HIF-1 signaling pathway. Molecular docking results indicated that the binding energy between core targets (PTGS1, PTGS2) and core components was less than -5 kcal/mol, suggesting stable binding.

Liu Hui [13] utilized network pharmacology to investigate the mechanism of Ma Huang Gui Zhi Yao in treating allergic rhinitis (AR). The study identified 27 effective ingredients and 199 related targets of Ma Huang Gui Zhi Yao, with 1282 corresponding targets and 109 intersecting targets. GO functional analysis indicated that key targets are involved in responses to lipopolysaccharides, bacterial molecules, toxins, oxidative stress, and apoptosis signaling pathways. Cellular components included membrane rafts, receptor complexes, and mitochondrial membranes, while molecular functions encompassed cytokine activity, receptor binding, transcription factor binding, and oxidoreductase activity. KEGG pathway analysis revealed involvement in cancer signaling, atherosclerosis, PI3K-Akt signaling, TNF signaling, and IL-17 signaling pathways. Molecular docking showed that quercetin, kaempferol, IL-6, and AKT1 had good binding affinities.

Tao Yu et al. used network pharmacology to study the mechanism of *Atractylodes macrocephala* Guizhi medicine in treating non-alcoholic steatohepatitis (NASH). They identified 16 active ingredients and 383 related targets, with 656 corresponding targets of NASH and 77 intersecting targets. GO functional analysis showed that main targets involved inflammatory response, cholesterol homeostasis, cellular response to lipopolysaccharides, cholesterol metabolism, insulin secretion regulation, and positive regulation of inflammatory response. KEGG analysis indicated pathways related to lipid and atherosclerosis, endocrine resistance, hepatitis C, and non-alcoholic fatty liver disease. Molecular docking showed strong binding of baicalin from *Atractylodes macrocephala* with PTGS2, suggesting therapeutic effects on NASH.

Feng Mingqing et al. [15] studied the mechanism of turmeric and *Angelica sinensis* in treating knee osteoarthritis (KOA) using network pharmacology. They identified 59 effective ingredients and 591 related targets, with 707 corresponding targets of KOA and 28 intersecting targets. GO functional analysis revealed BP enrichment in positive regulation of smooth muscle cell proliferation, apoptosis, angiogenesis, protein hydrolysis, and inflammatory response. KEGG analysis highlighted pathways such as TNF signaling, osteoclast differentiation, IL-17 signaling, relaxin signaling, and MAPK signaling. Molecular docking showed good binding between key targets and components, consistent with network pharmacology predictions.

Zou Xiujuan et al. [16] used network pharmacology to study *Chuanxiong Danguai* medicine in treating rheumatoid arthritis. They identified 9 effective components and 27 intersecting targets. GO function analysis indicated involvement in TNF signaling, IL-17 signaling, estrogen signaling, and disease pathways such as breast cancer, non-small cell lung cancer, colon cancer, measles, hepatitis B, and tuberculosis.

2.3 Compound Chinese medicine

In the realm of inflammation treatment, traditional Chinese medicine (TCM) formulations exhibit notable therapeutic efficacy and are extensively applied in clinical settings.

Jiang Xiaoqian et al. [17] employed network pharmacology to explore the mechanism underlying the efficacy of the salt compress formula in treating knee osteoarthritis (KOA). Their study revealed 94 effective ingredients and 255 related targets, with 415 KOA corresponding targets and 51 intersecting targets. GO functional analysis highlighted enrichment in inflammatory response, regulation of inflammatory response, and cell response to lipids, among others. KEGG pathway analysis emphasized pathways such as IL-17, tumor necrosis factor, rheumatoid arthritis, and NF- κ B signaling.

Gong Yuanxun et al. investigated the mechanism of Xinyi powder in treating allergic rhinitis (AR) using network pharmacology methods. They identified 184 active ingredients and 224 related targets, with 2116 AR corresponding targets and 104 intersecting targets. Their findings revealed enrichment in pathways like IL-17, HIF-1, NF- κ B, PPAR, and Wnt signaling. Molecular docking validated the binding affinity of key components like kaempferol and viscidin with core protein targets.

Xu Jun et al. explored the mechanism of Jiawei Huangqi Guizhi Wuwu Tang in treating rheumatoid arthritis (RA) through network pharmacology. They identified 141 effective ingredients and 303 related targets, with 4937 corresponding targets of RA and 127 intersecting targets. GO and KEGG analyses revealed involvement in processes like response to lipopolysaccharides and signaling pathways such as PI3K/AKT and TNF.

Zhang Ye et al. utilized network pharmacology to investigate the efficacy of Ma Xing Hua Yu Tang in treating *Mycoplasma pneumoniae* pneumonia (MMP) in children. They identified 126 effective ingredients and 189 related targets, with 3126 corresponding targets for RA and 78 intersecting targets. Their analysis revealed enrichment in processes like positive regulation of gene expression and pathways such as the intracellular PI3K/AKT signaling pathway.

Xiong Shilin et al. studied the mechanism of Ginger Xiexin Tang in treating ulcerative colitis (UC) using network pharmacology methods. They identified 215 effective ingredients and 247 related targets, with 5186 corresponding targets for UC and 171 intersecting targets. Molecular docking analysis demonstrated stable binding of active ingredients like gingerol A and quercetin with proteins such as AKT1 and IL-1 β , underscoring their therapeutic potential.

3 Summary and conclusion

In recent years, significant investments in traditional Chinese medicine (TCM) research at the national level have spurred accelerated progress in natural drug exploration rooted in TCM principles. One prominent research methodology gaining traction in TCM innovation is network pharmacology, which seamlessly integrates bioinformatics and biomedical advantages [22].

The credibility of experimental outcomes in network pharmacology hinges on the precision and reliability of TCM ingredients and their potential disease targets. Currently, network pharmacology methods draw upon multiple databases, typically utilizing resources like TCMSp and TCMIp for predicting TCM component targets, and platforms such as GeneCards and DisGeNET for identifying disease targets. However, variations in target information across different databases pose a challenge. The solution lies not in indiscriminately expanding the number of databases but in elucidating the correlation between TCM ingredients and authentic regulatory targets. Leveraging advancements in molecular docking and artificial intelligence, the construction of prediction models that amalgamate distinct chemical structures with disease targets through extensive big data analysis and deep learning holds promise for significantly enhancing the accuracy of network pharmacology predictions, thereby advancing targeted pharmacology research [23].

The widespread application of network pharmacology in forecasting the efficacy of TCM in inflammation treatment has spurred the development and utilization of key active ingredients, encompassing individual TCM herbs, combination therapies, and compound formulations. This trend has propelled the modernization and innovative utilization of TCM. With the dissemination of a plethora of research findings, an increasing number of researchers are recognizing the potential of employing network pharmacology methodologies to explore the innovative medicinal properties of TCM.

References

- [1] Jing Ling, Zhang Xin. A study on the correlation between post stroke hemorrhage transformation and inflammatory response [J]. Journal of Beihua University (Natural Science Edition), 2024,25 (01): 82-86
- [2] Yue Dongya, Zhu Jingbo, Liu Yulong. Inflammatory factors PCT and IL-1 β A study on the correlation between multiple injuries and traumatic complications in adults [J]. Journal of Medical Forum, 2022, 43 (17): 54-57
- [3] Sun Xiaojie, Wei Kaihui. Network pharmacology analysis and research on the treatment of COVID-19 infection with effective components of traditional Chinese medicine [J]. Chinese Journal of Pathogenic Biology, 2024,19 (03): 371-373
- [4] Xie Chengzhi, Ren Jianxun. Network pharmacology research and reflection on the efficacy of traditional Chinese medicine and compound formulas [J]. Chinese Journal of Experimental Formulas, 2024,30 (01): 198-207
- [5] Song Yucheng, Ou Guoyi, Yang Yongqiang, et al. Network pharmacology study on the mechanism of tonifying kidney and unblocking collaterals in the treatment of knee osteoarthritis [J]. China Pharmaceutical, 2023,32 (24): 61-64
- [6] Zhang Yijia, Yu Qinghua, Wang Yu, et al. Research progress on the mechanism of network pharmacology in the treatment of constipation with traditional Chinese medicine [J]. Journal of Practical Traditional Chinese Medicine, 2022, 36 (10): 52-54
- [7] Pan Feng. Exploring the mechanism of action of Bai Ji in the treatment of ulcerative colitis based on network pharmacology and molecular docking [J]. Zhejiang Journal of Integrated Traditional Chinese and Western Medicine, 2024,34 (04): 362-368
- [8] Yang Jingxing, Zhao Yan, Chen Luquan, et al. Exploring the potential mechanism of Huangqin in the treatment of chronic sinusitis based on network pharmacology [J]. Journal of Capital Medical University, 2024,45 (02): 252-261
- [9] Qian Rui, Zhang Luoning, Xu Yunyi, et al. Exploring the improvement effect and mechanism of white meat *Ganoderma lucidum* alcohol extract on silicosis inflammatory response based on network pharmacology [J]. Chinese Journal of Occupational Medicine, 2024,51 (01): 6-15

- [10] Xie Liangshan, Anyang, Xu Hui, et al. Exploring the mechanism of action of Pineapple in the treatment of rheumatoid arthritis based on network pharmacology and experimental verification [J]. Shenzhen Journal of Integrated Traditional Chinese and Western Medicine, 2024,34 (01): 1-6+137
- [11] Sun Jinmeng, Zhang Ying, Zheng Zejun, et al. Exploring the potential therapeutic mechanism of ginseng on periodontitis based on network pharmacology and molecular docking technology [J]. West China Journal of Stomatology, 2024,42 (02): 181-191
- [12] Zhang Yanyan, Xu Ziqi, Kao Xiliang. Network pharmacology analysis of the mechanism of action of honeysuckle and large blood vine in the treatment of rheumatoid arthritis [J]. Shandong Medical Journal, 2024,64 (08): 15-18
- [13] Liu Hui, Shen Qi. Study on the mechanism of action of ephedra Guizhi medicine in the treatment of allergic rhinitis based on network pharmacology and molecular docking [J]. Western Traditional Chinese Medicine, 2024,37 (04): 77-86
- [14] Tao Yu, Liu Wenjuan, Ma Qianqian, et al. Analysis of the mechanism of action of Atractylodes macrocephala Guizhi in the treatment of non-alcoholic steatohepatitis based on network pharmacology [J]. Pharmaceutical Research, 2023,42 (10): 759-764
- [15] Feng Mingqing, Liao Taiyang, Yang Nan, etc LC-MS combined with network pharmacology to explore the mechanism of action of volatile oil from turmeric and Angelica sinensis in the prevention and treatment of knee osteoarthritis [J]. Chinese Journal of Modern Applied Pharmacy, 2023,40 (17): 2403-2413
- [16] Zou Xiujuan, Guo Yuqin, Luan Zhengli, et al. Network pharmacology analysis of the mechanism of action of Chuanxiong Danggui medicine in the treatment of rheumatoid arthritis [J]. Clinical Research of Traditional Chinese Medicine, 2023,15 (19): 31-36
- [17] Jiang Xiaoqian, Zhang Yuqin, Teng Haiying. Exploring the mechanism of action of salt application in the treatment of knee osteoarthritis based on network pharmacology [J]. Medical Theory and Practice, 2024,37 (07): 1093-1096+1108
- [18] Gong Yuanxun, Zhao Jingjie, Luo Miao, et al. Exploring the potential mechanism of action of the classic formula Xinyi San in the treatment of allergic rhinitis based on network pharmacology and molecular docking technology [J/OL]. Youjiang Medical Journal, 1-10 [2024-04-30]
- [19] Xu Jun, Zhang Yanhong, Chen Jiaojiao, et al. Exploring the mechanism of action of modified Huangqi Guizhi Wuwu Tang in the treatment of rheumatoid arthritis based on network pharmacology and cell experiments [J]. Henan Traditional Chinese Medicine, 2024,44 (04): 542-548
- [20] Zhang Ye, Ren Yaoquan, Li Jingcheng. Exploring the mechanism of action of Ma Xing Hua Yu Tang in the treatment of Mycoplasma pneumoniae pneumonia in children based on network pharmacology [J]. Journal of Traditional Chinese Medicine Pediatrics, 2024,20 (02): 40-47
- [21] Xiong Shilin, Lin Xiaohe, Huang Song, et al. Potential effects of ginger Xiexin decoction in the treatment of ulcerative colitis based on network pharmacology and in vitro cell experiments [J]. New Traditional Chinese Medicine, 2024,56 (05): 36-43
- [22] Wang Chunli, Li Ziyang. Current Status and Trends of Innovative Development of Traditional Chinese Medicine in China [J]. Chinese Journal of New Drugs, 2023,32 (20): 2013-2021
- [23] Li Shao, Wang Boyang, Cao Liang, et al. Research and Development Practice of Traditional Chinese Medicine Based on Network Target Theory and Technology [J]. Chinese Journal of Traditional Chinese Medicine, 2023,48 (22): 5965-5976