Network Pharmacology Study of Action Mechanism of Traditional Chinese Medicine in The Treatment Of COVID-19

Xiaohan Ji *

Animal Science and Technology College, Beijing University of Agriculture, Beijing, China

* Corresponding Author Email: 202020322082@bua.edu.cn

Abstract. Background: Big data was utilized to analyze the network of biological systems and multi-target drug signal nodes, and despite traditional Chinese medicine proving effective against COVID-19 since the 2019 outbreak, the complexity and challenging actions of network pharmacology are essential for in-depth analysis. **Objective:** To present an overview of the literature on the mechanism of traditional Chinese medicine (TCM) in the treatment of COVID-19 based on network pharmacology. **Methods:** A succinct explanation of the data sources: Twenty items in all were found after browsing the English and Chinese data websites. Following screening, data synthesis techniques and the remaining eight publications were located. **Results:** This study contained eight publications, including network pharmacology investigations on the mechanisms of action of eight prescription TCM medications. Many prescription drugs and specialty treatments from traditional Chinese medicine, including astragalus membranaceus-atractylodes rhizoma, LHQW, TJQWG, ephedra and glycyrrhiza, Yinqiao powder, rhizoma polygonati, MXSGD, and HSBDF, have been utilized in the clinical treatment of COVID-19. Their primary modes of action entail several components working on many targets and pathways related to immune modulation, organ protection, antiviral, and anti-inflammatory properties. **Conclusion:** This study reviewed eight Chinese herbal formulas used for treating COVID-19 and found they all contain quercetin, a compound that may reduce lung damage, and target at least one of TNF, IL-2, or IL-6, potentially decreasing inflammation and boosting immunity. All these traditional Chinese medicine (TCM) treatments were effective against COVID-19, offering valuable insights and inspiration for future drug research.

Keywords: COVID-19; SARS-CoV-2; traditional Chinese medicine; network pharmacology.

1. Introduction

1.1. COVID-19

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of the coronavirus disease 2019 (COVID-19), an infectious illness that has spread around the world. It is very infectious and rapidly spreads. Respiratory symptoms, which resemble pneumonia, the flu, or a cold, are the most prevalent signs of COVID-19. It's not just patients' lungs and respiratory system that COVID-19 can target. It's possible that the illness will also affect other body parts. Most people with COVID-19 have mild symptoms, but some develop severe disease. After being discovered for the first time in China in December 2019, the novel coronavirus, or nCoV, has quickly spread to neighboring nations. As a result, the WHO on 30 January 2020 declared the outbreak to be a Public Health Emergency of International Concern and on 11 March 2020 to be a pandemic [1].

So far, the virus has caused 774,834,251 infections and 7,037,007 deaths worldwide. Although on May 2023, more than three years after the onset of the pandemic, WHO declared that given the now established and persistent nature of the disease, it no longer fits the definition of the international public health emergency (PHEIC). That doesn't mean the pandemic itself is over, but the global emergency caused by the pandemic is still ongoing. Globally, there are still around 60,000 new cases per week [2].

As of right now, a significant portion of the population- roughly 67% has received the whole primary series of the COVID-19 vaccination [2]. COVID-19 vaccine does not completely remove the possibility of Ncov infection, even while it greatly lowers the risk of COVID-associated morbidity and mortality, especially in those who are most at risk of developing a serious illness.

1.2. TCM treatment in COVID-19

Since ancient times, many Chinese medicine prescriptions against viral diseases have been recorded in ancient books, widely used, and handed down to the present. Numerous traditional Chinese medicines and treatments have been discovered via extensive study; these medications not only have the ability to withstand viruses such as the herpes simplex, influenza, hepatitis B, and C viruses, but also effectively prevent and control these infections. Since the COVID-19 epidemic, a never-ending series of studies on the virus's therapy has surfaced, with traditional Chinese medicine among them [3]. According to studies, individuals with COVID-19 have lowered white blood cell and lymphocyte counts as well as compromised immune system performance. Research on SARSCov-2 has also demonstrated that patients will exhibit aberrant blood biochemical markers, such as C-reactive protein (CRP) and cytokines, as the disease progresses [4]. It has been observed that some cytokines are directly linked to lung damage and viral load. In the concept of traditional Chinese medicine (TCM), immune function is called "Zhengqi", which can improve the body's immunity by enhancing lung function [5]. Therefore, many traditional Chinese medicines with related functions have been applied to the treatment of COVID-19, such as Lianhua Qingwen, Maxingganshi Decoction, etc.

1.3. Network pharmacology

Network pharmacology is a new discipline. It is a science that attempts to explain the microscopic principle of action of drugs in the body and the interactions between drugs and multiple targets in the body [6]. Make use of the database's computational capability to uncover the mechanisms behind drug molecules in organisms, as well as to methodically catalog the intermolecular interactions of drug molecules in biological cells and identify their active components, targets, and other details. Research on the mechanism of action of multi-target traditional Chinese herbal medicine benefits greatly from the use of NP, which is a crucial tool for comprehending the intricate link between plant prescriptions and the entire body [7, 8].

1.4. Network pharmacology and TCM

A comprehensive medical system known as Traditional Chinese Medicine (TCM) was developed over thousands of years of clinical application [8]. Unlike synthetic medications, numerous substances, several targets, and various paths are features of traditional Chinese medicine. Therefore, in order to elucidate the principle of traditional Chinese medicine, it is necessary to comprehensively explore the complex network of natural drug ingredients-targets-pathways-disease-metabolites-intestinal bacterial groups [9]. By using network pharmacology techniques, we can not only analyze the efficacy of some proven Chinese herbs, but also explore their suitability for treating other types of diseases and provide reference for the discovery of more accurate prescriptions. Clarifying the effectiveness of traditional Chinese herbal medicine in treating the novel corona-virus pneumonia is the aim of this study.

Although network pharmacology has brought many beneficial effects to the research and development of TCM, it still has many challenges and deficiencies. NP is a pilot prediction that requires a large number of hypotheses to be confirmed, so possible false positive result is inevitable [10]. Thus, NP prediction methods are too simple to fully assess the efficacy and toxicity of TCM. Traditional Chinese medicine is a combination of multiple herbs, not a single drug, and there is no guarantee that the final efficacy is the result of the addition of a single compound. In the process of processing, the components of TCM interact with each other, and the results are inevitably biased, which cannot be measured by NP.

Research on the pharmacological basis of traditional Chinese medicine and the viability of using traditional Chinese herbal medicine to treat new coronavirus pneumonia is now underway in the field of network pharmacology, and various research papers are being published one after another. However, there is no comprehensive paper.

Based on network pharmacology, this article summarizes the mechanism research on the clinical application of 8 traditional Chinese medicines, finds out their similarities and differences, and summarizes their characteristics.

2. Methods

A thorough literature search on China's National Knowledge Infrastructure was done for this research. (Chinese database) and PubMed (English database) for articles published between 2020 and 2024. The search employed keywords related to “novel coronavirus” (including synonyms such as “coronavirus” and “SARS-CoV-2”), “traditional Chinese medicine” (including synonyms such as “Chinese medicine” and “herbal medicine”), and “network pharmacology”. In the first screening phase, reading abstracts and titles to identify articles relevant to our themes and methods. Subsequent detailed full-text reviews helped eliminate articles lacking valid data or relevancy.

To ensure that this review is accurate and comprehensive, the articles included had the following screening criteria. The inclusion criteria are: (1) Articles must be published within the timeframe from 2020 to 2024. (2) Articles focusing specifically on the treatment of COVID-19 using traditional Chinese herbal medicine. (3) Articles that includes analysis using network pharmacology to investigate the action mechanisms of TCM in the context of COVID-19. The exclusion criteria are: (1) Articles that contain redundant information or previously published data. (2) Articles where statistical analysis does not directly relate to the evaluation of the drugs under investigation.

This review contained data from eight different investigations. Each article has carried out research on different drugs or prescriptions, such as Astragalus - Atractylodes, Lianhua Qingwen capsule, toujiequwen Granules, Ephedra - Glycyrrhiza, Yinqiao powder, rhizoma polygonati, Maxing Shigan decoction and Huashi Baidu Formula. Analyzing each study's contribution to our understanding of TCM's function in controlling COVID-19 required synthesis, with a particular emphasis on the data given in terms of clinical relevance and network pharmacology discoveries.

3. Results

3.1. Study Selection and Characteristics

There were 20 articles in all, including 2 articles in CNKI and 18 articles in PubMed. After screening by whether to provide full text, 16 articles were obtained. 11 papers in all were found by going through the titles and abstracts once more and eliminating any that had nothing to do with the subject. After intensive reading of the articles, the articles with undetailed data and contents that did not meet the theme were removed, and 8 articles were finally obtained (Figure 1).

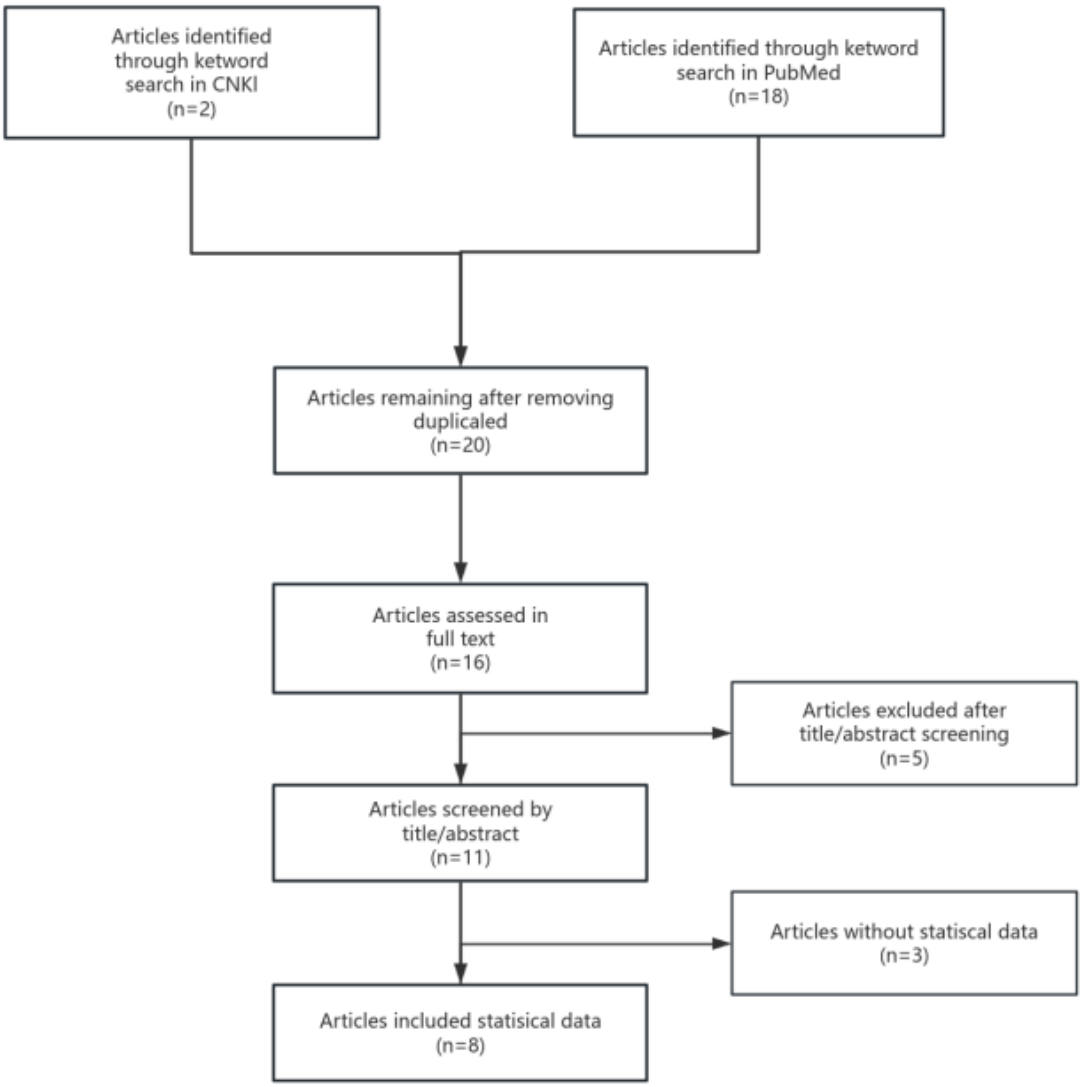


Fig. 1 Study selection

Each of these articles analyzed and studied different TCM prescriptions. Through network pharmacology, multiple component and multiple target analysis of traditional Chinese medicine in clinical use was carried out. Including: Astragalus - Atractylodes, Lianhua Qingwen capsule, toujiequwen Granules, Ephedra - Glycyrrhiza, Yinqiao powder, rhizoma polygonati, Maxing Shigan decoction and Huashi Baidu Formula.

3.2. Results of Individual Studies

Because of the variety of traditional Chinese medicine, the effects of treating diseases also converge. Therefore, it is important to distinguish the difference between each prescription. Astragalus membranaceus and Atractylodes atractylodes had 19 active ingredients, and 41 common targets with covid-19, of which 22 were the core targets, which shown anti-inflammatory, anti-SARS-CoV-2, and immune-regulating properties. (TU et al., 2021) [5] Lianhua-qingwen had 158 active ingredients, and 49 targets, played the role of intervening inflammatory response and immunity. (Zhang et al., 2021) [11] Toujiequwen Granules had 57 active ingredients, includes the 15 main COVID-19 objectives. 53 different chemicals have the potential to impact DPP4, which suggests that DPP4 will likely become a critical new target for COVID-19 management. For COVID-19-positive individuals, multi-target intervention for many signaling pathways implicated in the virus's growth is helpful in reducing the symptoms of underlying conditions. (Yang et al., 2021) [12] Ephedra and Glycyrrhiza had 112 active ingredients, 5 core targets, might play immune regulation, organ

protection and antiviral effects. (Li et al., 2021) [13] Yinqiao powder had 43 targets, 19 core targets and 30 ingredients. It inhibits inflammation factor, antioxidant, the role of immune intervention. (Lin et al., 2021) [14] Rhizoma polygonati had 10 ingredients and 23 targets. They could be involved in controlling apoptosis, redox, repair of DNA damage, metabolism of cells, and inflammatory response. (Mu et al., 2021) [15] With 105 active components, the Maxing Shigan decoction was used to illustrate the pharmacodynamic elements and mechanism of the antiviral and anti-inflammatory properties. Moreover, 83 targets linked to COVID-19 and MXSGD were discovered. (Li et al., 2021) [16] 46 signaling pathways, 223 active components, and 84 common targets of the Huashi Baidu Formula were discovered. The high binding affinity of severe acute respiratory syndrome is mostly caused by coronavirus-related characteristics such as metabolism, protein binding, cellular response to stimuli, and receptor function. (Cai et al., 2021) [17]

Table 1. Study characteristics

Author	TCM prescription	Ingredients	Ingredients number	Core targets	Core targets number	Pharmacologic actions
TU et al., 2021 [5]	Astragalus membranaceus-Atractylodes rhizoma	Mairin, Jaranol, etc.	19	IL-6, MAPK8, DPP4, etc.	22	anti-SARS-CoV-2, improving immune
Zhang et al., 2021 [11]	Lianhua-qingwen	Quercetin, luteolin, etc.	158	TNF, IL-1, IL-6, IL-2, etc.	49	anti-SARS-CoV-2, anti-inflammatory
Yang et al., 2021 [12]	toujiequwen Granules	quercetin, isoquercitrin, astragaloside IV, etc.	57	DPP4, TNF, IL-6, etc.	15	anti-inflammatory, antiSARS-CoV-2, improving immune
Li et al., 2021 [13]	Ephedra and Glycyrrhiza	dehydroglyasperins C, phaseol, etc.	112	TNF-α, IL-2, etc.	5	anti-SARS-CoV-2, improving immune
Lin et al., 2021 [14]	Yinqiao powder	Hesperetin, eriodictyol, luteolin, etc.	30	TNF, IL-6, MAPK3, etc.	19	anti-SARS-CoV-2, anti-inflammatory
Mu et al., 2021 [15]	rhizoma polygonati	Diosgenin, Sitosterol, etc.	10	MAPK14, etc.	23	anti-SARS-CoV-2, anti-inflammatory
Li et al., 2021 [16]	Maxing Shigan decoction	quercetin, kaempferol, isorhamnetin, naringenin, wogonin, etc.	105	MAPK3, IL-6, TNF, etc.	83	inhibiting SARS-CoV-2 replication, reducing cytokine storm
Cai et al., 2021 [17]	Huashi Baidu Formula	quercetin, luteolin, kaempferol, baicalein, etc.	223	IL-6, MAPK8, MAPK1, etc.	84	anti-inflammatory, inhibiting SARS-CoV-2 replication

IL: interleukin; MAPK: mitogen-activated protein kinase; DPP: Dipeptidyl peptidase; TNF: tumor necrosis factor

3.3. Synthesis of Results

Each study performed an integrated network pharmacology approach for each TCM or prescription, including pharmacokinetic screening, target prediction, network analysis, virtual docking, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis, and Gene Ontology (GO) enrichment analysis (Table 1). Finally, the targets of action and active components were examined. Relatively similar results were also obtained. Nearly all TCM targets are connected to the inflammatory response, the oxidative stress response, and other biological processes, according to GO functional analysis. The TNF signaling pathway, T cell signaling pathway, B cell signaling pathway, and other immune response and inflammation-related pathways are essentially where these TCM targets are found, according to KEGG enrichment study. The main targets of most traditional Chinese medicines include TNF and IL-2, which are related to improving the activity of immune cells and participating in the immune process. The active ingredients also almost all have anti-inflammatory, immune intervention and symptom relief effects. This indicates that, when choosing traditional Chinese herbal medicine to treat novel corona-virus pneumonia, all forms of the drug including prescription forms have comparable, if not identical, active components and targets, and they all serve comparable purposes. They all treat COVID-19 by anti-inflammation, intervention in immune regulation, and delay the disease.

4. Discussion

Following the 2019 corona-virus epidemic (COVID-19), research on drugs to treat it has emerged one after another. As one of the main treatment options, its mechanism has also been widely discussed. Due to the flexible use and different methods of traditional Chinese medicine, Drugs of many kinds are used to treat COVID-19 illness, and it is important to summarize the research on several traditional Chinese treatments.

According to clinical studies, in individuals infected with COVID-19, interleukin-6 (IL-6), IL-10, IL-2, and tumor necrosis factor-α (TNF-α) surge during illness and decrease during recovery [3, 18]. Among the Chinese medicine prescriptions studied in the eight articles included in our study, each Chinese medicine contains at least one of the above primary action targets.

TNF-αand IL-6 are two common inflammatory mediators in the inflammatory response. The TNF-α pathway is a two-edged sword that regulates cell growth and death. When there is an acute tissue damage, a cytokine storm brought on by defective TNF-α signaling leads to significant cell death. Acute liver failure (ALF) and acute lung injury (ALI) are conditions where the TNF-α pathway is frequently elevated. In the acute phase of tissue injury, its prolonged rise or excessive production might set off a cytokine storm that results in cell death [19]. Despite the fact that IL-6 helps the body resist infection and tissue damage. On the other hand, a "cytokine storm" and an abrupt, severe systemic inflammatory response might result from elevated IL-6 production in response to environmental stress [20]. It has also been proposed that 2019-ncov infection stimulates the activation of pathogenic T cells to produce IL-6 and another cytokine called granulocyte colony-stimulating factor (GM-CSF) [21]. IL-6 and other inflammatory factors are produced in larger quantities by CD14+ and CD16+ monocytes when they are further activated by GM-CSF. This could set off a cytokine storm and cause the lungs to become severely inflamed [22]. As a result, the treatment approach of inhibiting the inflammatory response, preventing cytokine storm, and stopping the course of pneumonia involves blocking the action route by acting on TNF, IL-6, and other targets. Among the eight traditional Chinese medicine prescriptions we studied, almost everyone contains relevant action targets and can treat COVID-19 through relevant mechanisms. In addition, it is worth mentioning that most of the traditional Chinese medicine also contains DPP4 as a core target, and the correlation is very high. DPP4 is another possible important target for COVID-19 therapy.

The alveolar epithelial cells were destroyed, a hyaline membrane developed in the alveolar space, and monocytes and macrophages were infiltrated, according to both the autopsy results and lung pathology. Severe type 2 alveolar epithelial cell hyperplasia was also seen, along with some cell

sloughing. The fundamental component of the lung and the primary site of gas exchange are the alveoli. For effective gas exchange in the lung, the alveolar-capillary barrier must remain intact. Alveolar-capillary barrier changes as a result of extravascular edematous fluid buildup, inflammatory cell infiltration, and increased permeability caused by disruption of the alveolar endothelium and epithelial barriers [23, 24]. In all the included studies, each TCM contained active ingredients that could alleviate lung diseases. Each of them contains quercetin. Typical flavonoid quercetin is the primary active component of all TCM formulas that are presented, has been shown to inhibit inflammatory responses by inhibiting TNF-α, IL-6, IL-1β and IL-2 [25, 26]. There are also other components of traditional Chinese medicine that can reduce lung injury by regulating cytokines that affect lung function. For example, naringenin in Yinqiao Powder can inhibit autophagy and pulmonary fibrosis cytokines to reduce lung injury [27].

4.1. limitations

Firstly, none of the studies included in this article mentioned the concept of side effects, and it is uncertain whether the eight prescriptions of TCM discussed in this article have no side effects or have unclear side effects. This point should be observed with caution in future studies and in the clinical use of these prescriptions. In addition, since network pharmacology is analyzed based on databases, the incompleteness of Chinese herbal medicine databases is inevitable, so there is no guarantee that the accuracy of the results is 100 percent. Secondly, Chinese herbal medicine has many intricate components, and these complex chemical substances and proteins interact with each other, which may lead to false positive or false negative results using existing instrumental analysis and computer analysis [10].

4.2. Conclusions

Network pharmacology research shows that many traditional Chinese medicines have the effect of inhibiting inflammatory responses, suppressing immune processes, and alleviating clinical symptoms when treating COVID-19. This article synthesizes 8 network pathology studies on the principle of traditional Chinese medicine to treat COVID-19 and concludes that these traditional Chinese medicines share common pharmacological effects. Almost all traditional Chinese medicines use TNF, IL-2 or IL-6 as core targets, and they are all related to suppressing inflammation and suppressing immunity. Traditional Chinese medicine contains quercetin as an active ingredient, which has been linked to alleviating lung disease. This article uses network pharmacology to conduct a comprehensive study on the potential effect of traditional Chinese herbal medicine in treating COVID-19 and analyzes relevant knowledge in order to inspire future research.

References

[1] Coronavirus disease (covid-19) pandemic. (n.d.). Retrieved from https://www.who.int/europe/emergencies/situations/covid-19

[2] World Health Organization 2023 data.who.int, WHO Coronavirus (COVID-19) dashboard > Data [Dashboard]. https://data.who.int/dashboards/covid19/data

[3] C. Huang et al.. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet, 2020, 395(10223).

[4] X. Sun and K. Wei. Network pharmacological analysis of effective components of traditional Chinese medicine in treatment of Novel coronavirus infection. Chinese Journal of Pathogen Biology(Chinese), 2024, 19(3): 371-373.

[5] W. Tu, J. Zhu, M. Li, M. Chen, C. Yang and H. Gan. Based on the network pharmacological research on the mechanism of Huangqi and Baizhu in the treatment of COVID-19. Fujian Traditional Chinese Medicine(Chinese), 2021, 52(2): 1-5.

[6] A. L. Hopkins. Network pharmacology. Nat Biotechnol, 2007, 25(10): 1110-1111.

[7] S. I. Berger and R. Iyengar. Network analyses in systems pharmacology. Bioinformatics, 2009, 25(19): 2466-2472.

[8] B. Zhang, X. Wang, and S. Li. An Integrative Platform of TCM Network Pharmacology and Its Application on a Herbal Formula, Qing-Luo-Yin. Evid Based Complement Alternat Med, 2013, 2013: 456747.

[9] W. U. Jiashuo, Z. Fangqing, L. I. Zhuangzhuang, J. Weiyi, and S. Yue. Integration strategy of network pharmacology in Traditional Chinese Medicine: a narrative review. J Tradit Chin Med, 2022, 42(3): 479-486.

[10] S. Li and B. Zhang. Traditional Chinese medicine network pharmacology: theory, methodology and application. Chin J Nat Med, 2013, 11(2): 110-120.

[11] X. Zhang et al.. A network pharmacology based approach for predicting active ingredients and potential mechanism of Lianhuaqingwen capsule in treating COVID-19. Int J Med Sci, 2021, 18(8): 1866-1876.

[12] B.-Y. Yang et al.. A Network Pharmacology Study to Uncover the Multiple Molecular Mechanism of the Chinese Patent Medicine Toujiequwen Granules in the Treatment of Corona Virus Disease 2019 (COVID-19). Curr Med Sci, 2021, 41(2): 297-305.

[13] X. Li et al.. Chemical composition and pharmacological mechanism of ephedra-glycyrrhiza drug pair against coronavirus disease 2019 (COVID-19). Aging (Albany NY), 2021, 13(4): 4811-4830.

[14] H. Lin et al.. Exploring the treatment of COVID-19 with Yinqiao powder based on network pharmacology. Phytother Res, 2021, 35(5): 2651-2664.

[15] C. Mu, Y. Sheng, Q. Wang, A. Amin, X. Li, and Y. Xie. Potential compound from herbal food of Rhizoma Polygonati for treatment of COVID-19 analyzed by network pharmacology: Viral and cancer signaling mechanisms. J Funct Foods, 2021, 77:104149.

[16] Y. Li et al.. Potential effect of Maxing Shigan decoction against coronavirus disease 2019 (COVID-19) revealed by network pharmacology and experimental verification. J Ethnopharmacol, 2021, 271: 113854.

[17] Y. Cai, M. Zeng, and Y.-Z. Chen. The pharmacological mechanism of Huashi Baidu Formula for the treatment of COVID-19 by combined network pharmacology and molecular docking. Ann Palliat Med, 2021, 10(4): 3864-3895.

[18] S. F. Pedersen and Y.-C. Ho. SARS-CoV-2: a storm is raging. J Clin Invest, 2020, 130(5): 2202-2205.

[19] W.-Y. Lai, J.-W. Wang, B.-T. Huang, E. P.-Y. Lin, and P.-C. Yang. A Novel TNF-α-Targeting Aptamer for TNF-α-Mediated Acute Lung Injury and Acute Liver Failure. Theranostics, 2019, 9(6):1741-1751.

[20] T. Tanaka, M. Narazaki, and T. Kishimoto. Immunotherapeutic implications of IL-6 blockade for cytokine storm. Immunotherapy, 2016, 8(8): 959-970.

[21] B. Fu, X. Xu, and H. Wei. Why tocilizumab could be an effective treatment for severe COVID-19? J Transl Med, 2020, 18(1): 164.

[22] Y. Zhou et al.. Pathogenic T-cells and inflammatory monocytes incite inflammatory storms in severe COVID-19 patients. Natl Sci Rev, 2020, 7(6): 998-1002.

[23] Z. Xu et al.. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med, 2020, 8(4): 420-422.

[24] S. Tian, W. Hu, L. Niu, H. Liu, H. Xu, and S.-Y. Xiao. Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lung Cancer. J Thorac Oncol, 2020, 15(5): 700-704.

[25] S.-C. Cheng, W.-C. Huang, J.-H. S Pang, Y.-H. Wu, and C.-Y. Cheng. Quercetin Inhibits the Production of IL-1β-Induced Inflammatory Cytokines and Chemokines in ARPE-19 Cells via the MAPK and NF-κB Signaling Pathways. Int J Mol Sci, 2019, 20(2):2957.

[26] A. B. Granado-Serrano, M. Á. Martín, L. Bravo, L. Goya, and S. Ramos. Quercetin attenuates TNF-induced inflammation in hepatic cells by inhibiting the NF-κB pathway. Nutr Cancer, 2012, 64(4): 588-598.

[27] W. Ngwa et al.. Potential of Flavonoid-Inspired Phytomedicines against COVID-19. Molecules, 2020, 25(11): 2707.