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Oriental Medicine

Application of network pharmacology in the prevention and treatment of COVID-19 by traditional Chinese medicine

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Author contributions
Zhan Li and Zhan-Dong Li conceived the idea. Zhan Li and Zhan-Dong Li drafted the manuscript. Yue Liu and Wang Li searched relevant data and arranged references. Zhan-Dong Li, Hao Li and Xiu-Hua Wu revised and proofed the manuscript.

Competing interests
The authors declare no conflicts of interest.

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Abbreviations
COVID-19, coronavirus disease 2019; 2019-nCoV, 2019 novel coronavirus; SARS, severe acute respiratory syndrome; SARS-CoV, severe acute respiratory syndrome coronavirus; TCM, traditional Chinese medicine; TCMs, traditional Chinese medicines; RBD, receptor-binding domain; nCoV-SP, S protein of 2019 novel coronavirus; ACE2, angiotensin converting enzyme II; M^{pro}, main protease; $3CL^{pro}$, 3C-like protease; IL6, interleukin 6; JAK3, Janus kinase 3; NOX5, NADPH oxidase 5.

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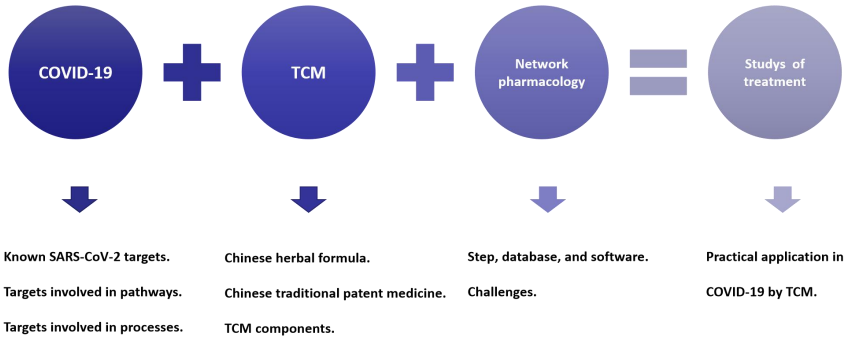
Abstract
Network pharmacology is an emerging technology based on systems biology and computer information technology, with the help of databases and related auxiliary software, to carry out new drug development and the screening analysis of drug active ingredients and targets. At present, the network pharmacology has been used widely in the research of prevention and treatment drugs for coronavirus disease 2019 (COVID-19). This paper reviews the research methods of network pharmacology in the field of prevention and treatment of COVID-19 by traditional Chinese medicine (TCM) and the development of its specific drugs and further explores the concrete application ideas of this technology. The necessary databases and tools of necessary for screening the active components and targets to molecular docking are summarized. In addition, the practical application of network pharmacology in the study of several potential TCM and active components against COVID-19 is reviewed, mainly including the screening of active components, the discovery of target, and the elucidation of action mechanism. The diversification of research ideas of network pharmacology in the field of TCM was realized, in particular, with two specific ideas in the study of active ingredients of TCM. Finally, the difference of control effect among several TCM and Western medicines on COVID-19 and the limitation and challenge of network pharmacology in TCM, i.e., the insufficient integrity and accuracy of the database, the uncertain complexity of components analysis, the unclear mechanism of component-target action, and some new challenges due to the characteristics of TCM, are discussed. In view of the importance of TCM in the field of control of COVID-19, the combination of TCM and network pharmacology will continue to play an important role in the development of specific drugs of COVID-19 in the future, in particular, to save time and reduce the workload of drug developers, which is also a direction of TCM development. This study provides theoretical reference and methodological basis for the prevention and treatment of COVID-19 by TCM.

Keywords: network pharmacology; COVID-19; traditional Chinese medicine; molecular docking



Highlights

1. Systematically summarized the common steps, databases and software of network pharmacology in preventive treatment of coronavirus disease 2019 (COVID-19) by traditional Chinese medicine (TCM).
2. The application status of network pharmacology in the prevention and treatment of COVID-19 in Chinese herbal formula, Chinese traditional patent medicine, and TCM compounds was described.
3. Compare the differences between some Chinese and Western medicines in the prevention and treatment of COVID-19.

Medical History of Objective

As a treasure in the field of traditional medicine, TCM is now widely used in the prevention and treatment of COVID-19. The earliest records of pneumonia diseases described by TCM can be traced back to the ancient Chinese medical classics *Inner Canon of Huangdi · Plain Questions* (written in the 2nd century B.C.E., author unknown). The earliest treatment for pneumonia was recorded in *Synopsis of Golden Chamber*, which is a classic clinical book of TCM authored by Zhong-Jing Zhang (150 C.E.–219 C.E.). According to the ancient records, classic ancient prescription of Chinese medicine Xiaoqinglong decoction plus Shigao decoction is mainly used to treat symptoms such as lung distension, cough, and asthma. Classic ancient prescription of Chinese medicine Shegan Mahuang decoction can also be used to treat cough and asthma. Classic ancient prescription of Chinese medicine Shen Zhu powder was first recorded in *Yang's Hereditary Medical Formulary* written by Tan Yang in 1178 C.E., and included in the *Prescriptions of the Bureau of Taiping People's Welfare Pharmacy* written by Shi-Wen Chen in 1151 C.E., showing effectiveness in treating respiratory diseases. Classic ancient prescription of Chinese medicine Yinqiao powder was first recorded in Tang Wu's *Detailed Analysis of Epidemic Warm Diseases* (written by Tang Wu in 1798 C.E.), with the anti-inflamatory functions of. With the continuous development of generations of doctors and the rapid development of modern medicine, it has been shown that the main components of Shen Zhu powder (e.g., luteolin) contain a combination with 3C-like protease and angiotensin converting enzyme II and may intervene with COVID-19.

Background

In late 2019, an epidemic of pneumonia (i.e., coronavirus disease 2019 (COVID-19)) caused by the β-coronavirus, a 2019 novel coronavirus (2019-nCoV), was outbroken in Wuhan, China. As a novel coronavirus with high infectivity and disease risk [1, 2], the 2019-nCoV is similar to severe acute respiratory syndrome coronavirus (SARS-CoV) in clinical lineage, epidemiology, and pathogenicity. Infected persons may be affected to varying degrees in their respiratory system, digestive system, mental health, and other indicators, in addition to common influenza symptoms such as fever, fatigue, and dry cough [3–7]. According to relevant studies, with the continuous expansion of the range of 2019-nCoV infection, different adaptive responses may be generated [8]. While climate factors can play a role in response to some endemic infections, the impact of climate is slightly smaller during the pandemic phase of 2019-nCoV. Without the relatively effective control measures, a second wave of infection is likely to occur [9, 10]. Therefore, it is particularly important to control the spread of the epidemic effectively and carry out the research on the prevention and treatment of COVID-19.

As a treasure in the field of traditional medicine, the traditional Chinese medicine (TCM) is widely used in the prevention and treatment of COVID-19 [11–14]. In fact, the earliest records of pneumonia diseases in TCM can be traced back to the ancient Chinese medical classics *Inner Canon of Huangdi · Plain Questions* (written in the 2nd century B.C.E., author unknown). The earliest treatment for pneumonia was recorded in *Synopsis of Golden Chamber*, which is a classic clinical book of TCM written by Zhong-Jing Zhang (150 C.E.–219 C.E.). Classic ancient prescription of Chinese medicine Xiaoqinglong decoction plus Shigao decoction (mainly composed of Mahuang (*Ephedrae Herba*), Xixin (*Asari Radix et Rhizoma*), Gancao (*Glycyrrhizae Radix et Rhizoma*), Wuweizi (*Schisandrae Chinensis Fructus*), and Shigao (*Gypsum Fibrosum*), etc.) and classic ancient prescription of Chinese medicine Shegan Mahuang decoction (mainly composed of Shegan (*Belamcandae Rhizoma*), *Ephedrae Herba*, *Asari Radix et Rhizoma*, *Schisandrae Chinensis Fructus*, and Dazao (*Jujubae Fructus*), etc.) listed in this book can play a certain role in the treatment of pneumonia. Xiaoqinglong decoction plus Shigao decoction is mainly used to treat symptoms such as lung distension, cough, and asthma. Shegan Mahuang decoction can also be used to treat cough and asthma. Meanwhile, modern clinical examples and pharmacological research have also proved the effectiveness of these two prescriptions in the treatment of pneumonia and related symptoms, verified the reliability of TCM prescriptions, and laid a foundation for the application of TCM in the field of pneumonia treatment, including COVID-19 [15–21]. Classic ancient prescription of Chinese medicine Shen Zhu powder and Yinqiao powder were also originated from the ancient prescriptions of TCM. Shen Zhu powder (mainly composed of Cangzhu (*Atractylodis Rhizoma*), *Asari Radix et Rhizoma*, Baizhi (*Angelicae Dahuricae Radix*), Qianghuo (*Notopterygii Rhizoma et Radix)*, and Chuanxiong (*Chuanxiong Rhizoma*), etc.) was first recorded in *Yang's Hereditary Medical Formulary* written by Tan Yang in 1178 C.E. and included in the *Prescriptions of the Bureau of Taiping People's Welfare Pharmacy* written by Shi-Wen Chen in 1151 C.E.. It is effective in treating respiratory diseases [18, 22]. Yinqiao powder (mainly composed of Jinyinhua (*Lonicerae Japonicae Flos*), Lianqiao (*Forsythiae Fructus*), Bohe (*Menthae Haplocalycis Herba*), Jingjie (*Schizonepetae Herba*), and *Glycyrrhizae Radix et Rhizoma*, etc.) is first recorded in Tang Wu's *Detailed Analysis of Epidemic Warm Diseases* (written by Tang Wu in 1798 C.E.), with the anti-inflammatory functions [18, 23, 24]. Since the 21st century, with the continuous development of many generations of doctors and the rapid development of modern medicine, the treatment of pneumonia by TCM have entered the fast lane, and the means of treatment have become more and more abundant, including the traditional prescription treatment, injection, combined internal and external treatment, and other ways, showing the remarkable curative effect [25].

As a hot topic of drug research in recent years, network pharmacology can break the limitation of "single target" thinking, and is more suitable for the treatment of lung diseases. In particular, in the field of control of COVID-19, it has been confirmed that some traditional Chinese medicines (TCMs) contain effective compounds possessing the potential of directly inhibiting 2019-nCoV and its inflammation [26]. If it is combined with network pharmacology, the molecular target networks of both target medicine and COVID-19 can be constructed to study the effective components and its mechanism of action, ultimately providing guidance for the prevention and treatment of COVID-19 by TCM [27, 28]. Wang et al. [29] investigated the Shen Zhu powder by using network pharmacology and molecular docking technology, showing that the main components of Shen Zhu powder (e.g. luteolin) contained the combination of 3C-like protease ($3CL^{pro}$) and angiotensin converting enzyme II (ACE2) and may intervene with COVID-19. Furthermore, Tao et al. [30] screened out 121 kinds of active ingredients in Yinqiao powder, and explored its mechanism of action, providing a reference for treating COVID-19 with Yinqiao powder. In this paper, the application of network pharmacology in the prevention and treatment of COVID-19 by TCM was systematically summarized and analyzed.

Network pharmacology

Network pharmacology is an interdisciplinary subject combining traditional pharmacology with modern network analysis techniques of biomolecules. It is one of the important branches of pharmacology. It is widely used in the fields of new drug design and development, mechanism of action, drug relocation, and target analysis [11, 31–35]. At the theoretical level, it is supported by the theories of systems biology, multidimensional pharmacology, and network [31]. At the practical level, network pharmacology can be divided into three parts, i.e., network construction, network analysis, and network verification [32]. Among these parts, the network construction focuses on discovering the relationships among network components, while network analysis focuses on searching and clarifying the relationships in the network [33]. Network pharmacology has completely abandoned the traditional "single target" thinking in the traditional field of drug development, and turned to analyze the relationship among drugs, targets, and diseases in the biological network with innovative ideas. The combination rule and network regulation effect of TCM formulations are explained in a high-throughput way, supporting the effectiveness of the study of active ingredients in Chinese medicine and their related mechanism of action based on the network method [34].

With the development and progress of computer virtual screening technology, more and more active ingredients of Chinese medicine and their mechanism of action have been discovered by scientists [36, 37]. In the research of drug active ingredients and their mechanism of action, network pharmacology is often combined with molecular docking technology. As a computer technology based on structural design, molecular docking technology is combined with the powerful database of network pharmacology, showing great advantages. At the same time, the combination of emerging network science and ancient oriental Chinese medicine will also promote the development of modern Chinese medicine system and provide a solid theoretical basis and technical support for the application of TCM [33, 35].

Application of network pharmacology in prevention and treatment of COVID-19

The COVID-19 caused by a new type of virus, i.e., 2019-nCoV, is highly harmful to the public, and there is no specific drug for the treatment of this new type of pneumonia [38, 39]. As a unique medical system in China, the TCM has shown a miraculous effect on the prevention and treatment of COVID-19 [11]. Meanwhile, with the development of information technology, the study of network pharmacology combined with TCM gradually leads the trend in the area of treatment of COVID-19 [40].

Selection of application ideas, database, and tools

In the actual study of the active ingredients and its mechanism that can prevent and treat COVID-19, the researchers have applied the basic operation principle of network pharmacology and combined molecular docking technology, with the help of the appropriate database and related graphics and visualization software, to support related targets screening, build the network system, and carry out molecular docking simulation and system analysis [41]. A summary of the specific steps and some commonly used databases and software for the prevention and treatment of COVID-19 with network pharmacology in TCM is provided in Table 1 [42–55].

Table 1 Common steps, databases, and software of network pharmacology in preventive treatment of COVID-19

Category	Name	Website	Reference
Ingredients collection and targets fishing	TCMSP	http://tcmspw.ccitcmsp.php/	[42, 43]
	PubChem	https://pubchem.ncbi.nlm.nih.gov/	[44]
	STP	http://www.swisstargetprediction.ch/	[44, 45]
	SuperPred	http://prediction.charite.de/	[45]
	STITCH	http://stitch.embl.de/	[45]
	TCMID	http://www.megabionet.org/tcmid/	[46]
	BATMAN-TCM	http://bionet.ncpsb.org/batman-tcm/	[46]
	Drug Bank	https://www.drugbank.ca/	[47]
	HIT	http://bigd.big.ac.cn/databasecommons/database/id/690/	[47]
Target gene name conversion	bioDBnet	https://biodbnet-abcc.ncifcrf.gov/db/db2db.php/	[47]
	UniprotKB	https://www.uniprot.org/	[48]
Collection of COVID-19 related targets	DisGeNET	http://www.disgenet.org/	[47]
	TTD	https://db.idrblab.org/ttd/	[48]
	GeneCards	https://www.genecards.org/	[48, 49]
	OMIM	https://www.omim.org/	[50]
	CTD	http://ctdbase.org/	[44, 51]
Selection of drug-disease common targets	Venny	https://bioinfogp.cnb.csic.es/tools/venny/	[50]
Network construction and key target screening	Cytoscape	http://cytoscape.org/	[52, 53]
	STRING	https://string-db.org/	[48, 54]
Enrichment analysis	DAVID	https://david.ncifcrf.gov/	[54, 55]
	KEGG BRITE	https://www.genome.jp/kegg/brite.html	[45]
	R	https://www.r-project.org/	[45, 51]
Molecular docking	RCSB PDB	https://www.rcsb.org/	[48, 51]
	PyMOL	http://www.PyMOL.org/	[45, 46]
	AutoDock	http://autodock.scripps.edu/	[45]

COVID-19, coronavirus disease 2019; TCMSP, Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform; STP, SwissTargetPrediction; STITCH, Search Tool for Interacting Chemicals; TCMID, Traditional Chinese Medicine Integrated Database; BATMAN-TCM, a Bioinformatics Analysis Tool for Molecular mechANism of Traditional Chinese Medicine; HIT, Herbal Ingredients' Targets Database; bioDBnet, Biological Database Network; UniprotKB, Universal Protein Resource Knowledgebase; TTD, Therapeutic Target Database; OMIM, Online Mendelian Inheritance in Man; CTD, Comparative Toxicogenomics Database; STRING, Search Tool for the Retrieval of Interacting Genes/Proteins; DAVID, Database for Annotation, Visualization, and Integrated Discovery; KEGG BRITE, Kyoto Encyclopedia of Genes and Genomes BRITE; RCSB PDB, RCSB Protein Data Bank.

Application of network pharmacology in TCM

When using network pharmacology to conduct a systematic and detailed analysis of prevention and treatment effect of COVID-19 by TCM, researchers have different ideas in the selection of subjects, such as Chinese herbal formula, Chinese traditional patent medicine, and some TCM compounds. Table 2 provides a review of the specific application of network pharmacology in the prevention and treatment of COVID-19 by TCM [18, 22, 23, 29, 56–84].

Table 2 Related information of several Chinese herbal formulas and Chinese traditional patent medicine

Name	Main herbs*	Character	Approved serial number by FDA in China	Reference
Shen Zhu powder (classic ancient prescription of Chinese medicine)	Cangzhu (*Atractylodis Rhizoma*); Xixin (*Asari Radix et Rhizoma*); Baizhi (*Angelicae Dahuricae Radix*); Qianghuo (*Notopterygii Rhizoma et Radix*); Chuanxiong (*Chuanxiong Rhizoma*); Gancao (*Glycyrrhizae Radix et Rhizoma*).	Traditional Chinese herbal formula. This prescription can effectively improve symptoms such as fever, cough, and headache. These are similar to the symptoms of COVID-19. Network pharmacology has also demonstrated the possibility of dealing with COVID-19 by Shen Zhu powder.	-	[18, 22, 29, 56]
Yinqiao powder (classic ancient prescription of Chinese medicine)	Jinyinhua (*Lonicerae Japonicae Flos*); Lianqiao (*Forsythiae Fructus*); Bohe (*Menthae Haplocalycis Herba*); Jingjie (*Schizonepetae Herba*); Gancao (*Glycyrrhizae Radix et Rhizoma*); Niubangzi (*Fructus Arctii*).	Traditional Chinese herbal formula. This prescription has heat-clearing, detoxifying, anti-inflammatory, and anti-bacterial effects, and is mainly used for treating viral infectious diseases such as upper respiratory tract infection and pneumonia. It can be used with other Chinese medicines or Western medicines to effectively deal with the symptoms of cough and dyspnea of patients, reduce adverse reactions, increase the negative conversion rate of nucleic acid detection of 2019-nCoV.	-	[18, 23, 57–62]
Jiawei Buhuanjin Zhengqi powder (classic ancient prescription of Chinese medicine)	Cangzhu (*Atractylodis Rhizoma*); Chenpi (*Citri Reticulatae Pericarpium*); Houpo (*Magnoliae Officinalis Cortex*); Gancao (*Glycyrrhizae Radix et Rhizoma*); Huoxiang (*Agastache rugosa*); Banxia (*Pinelliae Rhizoma*).	Traditional Chinese herbal formula. It is effective in treating diarrhea and ulcerative colitis. During the period of COVID-19, some patients developed digestive symptoms, such as vomits and diarrhea, and these symptoms correspond to the efficacy of Jiawei Buhuanjin Zhengqi powder.	-	[18, 63–66]
Pudilan preparation (Chinese patent medicines, including Pudilan Xiaoyan tablet, Pudilan Xiaoyan capsule, and Pudilan Xiaoyan liquid)	Pugongying (*Taraxaci Herba*); Kudiding (*Corydalis Bungeanae Herba*); Banlangen (*Isatidis Radix*); Huangqin (*Scutellariae Radix*).	Chinese traditional patent medicine. This prescription has the functions of eliminating inflammation, detumescence, and detoxifying. In particular, the Pudilan Xiaoyan oral liquid is widely used in the treatment of mycoplasma pneumonia and viral pneumonia, and is widely used in the fever clinic of hospitals during the period of COVID-19.	Z20003294; Z20050027; Z20030095.	[18, 67–70]

*If the number of herbs in a prescription or medicine is greater than six, then the top six herbs are listed.
FDA, Food and Drug Administration; COVID-19, coronavirus disease 2019; SARS, severe acute respiratory syndrome.

Table 2 Related information of several Chinese herbal formulas and Chinese traditional patent medicine (*Continued*)

Name	Main herbs*	Character	Approved serial number by FDA in China	Reference
Shufeng Jiedu capsule (Chinese patent medicine)	Huzhang (*Polygoni Cuspidati Rhizoma et Radix*); Lianqiao (*Forsythiae Fructus*); Banlangen (*Isatidis Radix*); Chaihu (*Bupleuri Radix*); Lugen (*Phragmitis Rhizoma*); Gancao (*Glycyrrhizae Radix et Rhizoma*).	Chinese traditional patent medicine. This medicine has the functions of antiviral and enhancing immunity. It has a remarkable curative effect on various infectious diseases, such as influenza, pneumonia, and bronchitis. Meanwhile, it is combined with other Western medicine to treat COVID-19 to effectively reduce the clinical symptoms (e.g., cough, weakness, and chest tightness) to promote the absorption of lung inflammatory lesions.	Z20090047.	[18, 71–73]
Jingyin granule (Chinese patent medicine)	Jingjie (*Schizonepetae Herba*); Jinyinhua (*Lonicerae Japonicae Flos*); Yuxingcao (*Houttuyniae Herba*); Pugongying (*Taraxaci Herba*); Niubangzi (*Fructus Arctii*); Gancao (*Glycyrrhizae Radix et Rhizoma*).	Chinese traditional patent medicine. This medicine has antiviral, anti-inflammatory, analgesic, and other effects. It is effective in the treatment of acute pneumonia and respiratory diseases and has been proved to be an effective medicine against SARS and H1N1. Meanwhile, it is also suitable for the characteristics of a long period of mild illness of COVID-19, and plays a role in the prevention and treatment of COVID-19.	Z20090039.	[18, 74–76]
Liushen capsule (Chinese patent medicine)	Rengongniuhuang (*Bovis Calculus Artifactus*); Shexiang (*Moschus*); Zhenzhu (*Margarita*); Bingpian (*Borneolum*); Chansu (*Bufonis Venenum*); Xionghuang (*Realgar*).	Chinese traditional patent medicine. This medicine has the functions of detumescence, analgesia, and antiviral. It has a good effect on influenza diseases and induced inflammatory reactions. Meanwhile, some studies showed that it could clearly reduce the content of interleukin-6 and tumor necrosis factor-α in the serum of pneumonia mice infected with influenza A virus, alleviate the lesions of lung, and play a role in intervening COVID-19.	Z20060207.	[18, 77–81]
Zukamu granule (Chinese patent medicine)	Shannai (*Kaempferiae Rhizoma*); Bohe (*Menthae Haplocalycis Herba*); Dazao (*Jujubae Fructus*); Gancao (*Glycyrrhizae Radix et Rhizoma*); Dahuang (*Rhei Radix et Rhizoma*); Yingsuqiao (*Papaveris Pericarpium*).	Chinese traditional patent medicine. This medicine is a Uygur medicine, with antiviral and anti-inflammatory effects. It is often used in the treatment of upper respiratory tract infections and other diseases. This medicine contains a variety of active ingredients, playing a role in the prevention and treatment of COVID-19.	Z65020179.	[18, 82–84]

*If the number of herbs in a prescription or medicine is greater than six, then the top six herbs are listed.
FDA, Food and Drug Administration; COVID-19, coronavirus disease 2019; SARS, severe acute respiratory syndrome.

Chinese herbal formula and Chinese patent medicine are a class of drugs with efficacy in treating COVID-19 that have been proved in clinical practice, and are of great significance in the field of COVID-19 prevention and treatment [85–88]. To date, there have been hundreds of Chinese herbal formulas and Chinese patent medicine are applied in prevention and treatment of COVID-19 [89, 90]. In the study of Wang et al. [22] applying network pharmacology to analyze the potential mechanism of Shen Zhu powder against COVID-19, there were a total of 627 targets of 116 active ingredients were screened, and most of these targets were detected in immune cells or tissues. Lai et al. [65] used Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform and correlation analysis software to carry out network pharmacological analysis of classic ancient prescription of Chinese medicine Jiawei Buhuanjin Zhengqi powder with a total of 187 active ingredients and 12,921 targets screened. They found that Jiawei Buhuanjin Zhengqi powder may regulate immune function or glycosylation by responding to specific biological processes such as oxidative stress, apoptosis, cytokine receptor binding, and cytokine activity. These results provide a basis for the application of TCM in the prevention and treatment of COVID-19. In addition to traditional Chinese herbal formula Shen Zhu powder and Jiawei Buhuanjin Zhengqi power, the Chinese patent medicines Shufeng Jiedu capsule, Jingyin granule, and Pudilan preparation (including Pudilan Xiaoyan tablet, Pudilan Xiaoyan capsule, and Pudilan Xiaoyan liquid) also showed possibilities in the prevention and treatment of COVID-19. Shufeng Jiedu capsule has a significant therapeutic effect on acute upper respiratory tract infection [91]. Zhang et al. [92] used network pharmacology and molecular docking technology to conduct an explorative study on the common mechanism of Shufeng Jiedu capsule in the treatment of severe acute respiratory syndrome (SARS), middle east respiratory syndrome, and COVID-19, with a total of 110 active ingredients and 47 core targets screened. Meanwhile, molecular docking results showed that luteolin and rhein showed sound docking effects with related core targets with strong antiviral effects as well. It proves the possibility of Shufeng Jiedu capsule in the COVID-19 treatment. Jingyin granule contains a variety of active components and can resist the infection of 2019-nCoV [76, 93]. Wang et al. [76] used network pharmacological methods to study the active components in Jingyin granules and the therapeutic mechanism of COVID-19. They found that Jingyin granule can directly target major genes, regulate the immune system, and exert therapeutic effects. Pudilan preparation is a type of TCM with the function of clearing away heat and detoxification. It is effective in treating upper respiratory tract infections in children [94, 95]. It has been clinically applied to resist 2019-nCoV [96]. Kong et al. [67] used network pharmacological analysis to screen 68 common targeted genes/proteins of Pudilan preparation and COVID-19. They also found that Pudilan preparation may block the entry of 2019-nCoV into cells by blocking ACE2 to regulate the immune system and eventually delay the development of COVID-19.

In terms of the selection of research objects, in addition to Chinese herbal compounds and Chinese traditional patent medicine, many scholars also choose to directly study the active ingredients in some Chinese herbal medicines, instead of screening the Chinese herbal compounds. For example, quercetin, glabridin, and gallic acid can control the development of COVID-19 by changing the expression of ACE2 [28]. However, acacetin and other compounds can regulate the apoptosis pathway and tumor necrosis factor pathway by acting on relevant targets to positively guide the disease [27]. Furthermore, in the practical study of the prevention and treatment of COVID-19 by TCM, no matter whether the object of study is Chinese herbal formula, Chinese traditional patent medicine, or TCM compounds, researchers almost always go through the process of studying the active components of TCM (i.e., the screening of active components and the analysis of common targets of active components and diseases), which is also a part of the research thinking of the network pharmacology of TCM. Although some scholars also choose to directly study some components, generally they can be classified into the analysis of active components of TCM. In the practical research on the target screening of TCM active ingredients for the treatment of COVID-19, researchers often present two different ideas. One is the study of known SARS-CoV-2 targets, such as the ACE2 and the main protease (M^{pro})/$3CL^{pro}$. The other is the study of targets involved in inflammatory and oxidative stress and other processes, such as interleukin 6 (IL6) and Janus kinase 3 (JAK3). The relevant information of some active components illustrated with examples according to different research ideas are presented here (Tables 3 and 4, Figures 1 and 2) [27, 28, 84, 97–113].

In fact, no matter what kind of research ideas, the ultimate research direction is to analyze the relationship between active components and disease targets. Here are some details of the applications of the above-mentioned active components in the study of network pharmacology of TCM, component screening, and molecular docking. The review will be carried out according to the types of compounds.

Saponin is widespread in Chinese herbal medicine, and some saponins have been proved to be effective in preventing and treating COVID-19 [114], including astragaloside IV, saikosaponins, polyphyllin, and timosaponin [99, 106, 110, 111]. Ge et al. [111] systematically analyzed astragaloside IV by using network pharmacology with many shared genes screened. Saikosaponins is a kind of bioactive substance which widespread in TCM and has certain antiviral and immunomodulatory effects [115–117]. Chikhale et al. [110] studied the potential mechanism of saikosaponins in the adjuvant treatment of COVID-19 by molecular docking of 23 saikosaponins with the crystal structures of the extracellular domains of IL6, JAK3, and NADPH oxidase 5 (NOX5) respectively. The protein-ligand complexes were simulated by molecular dynamics. The results showed that IL6, JAK3, and NOX5 had good docking and molecular dynamics characteristics with certain kinds of saikosaponins. The interaction between JAK3 and saikosaponins showed the highest docking ability. Meanwhile, saikosaponins can interact with enzymes that regulate the cellular homeostasis and DNA damage, suggesting the possibility of improving COVID-19 immune response. Huangjing (*Rhizoma Polygonati*) is a type of Chinese herbal medicine with a variety of effective active components, such as polysaccharide [118] and saponin [119]. Sapogenins are the part of saponins, *Rhizoma Polygonati* also contains diosgenin, the relevant contents of diosgenin are expounded in this paragraph. Mu et al. [101] found that diosgenin had a high protein binding affinity with some targets of 2019-nCoV in the network pharmacological analysis of COVID-19, providing a way for the prevention and treatment of COVID-19.

Flavonoids are a class of botanical compounds that have been proven to be effective against SARS, middle east respiratory syndrome, and COVID-19, and possess a high content in some selected TCM [102, 120, 121]. Bhowmik et al. [104] selected more than 100 types of flavonoids with antioxidant, anti-inflammatory, and antiviral activities as ligand or inhibitor, to interact with the target protein receptor-binding domain (RBD) of S protein of 2019 novel coronavirus (nCoV-SP) and ACE2. The results revealed that hesperidin, naringin, epigallocatechin gallate, and quercetin showed sound pharmacokinetic properties with advantages in absorption, solubility, permeability, toxicity, and bioavailability. Meanwhile, the selected compounds show a strong binding affinity for RBD of nCoV-SP and ACE2, and the structure of the protein ligand complexes is stable. Patil et al. [102] found that 15 plant-derived flavonoids are involved in the regulation of p53, FoxO, MAPK, and other signaling pathways, and play important roles in immune regulation, reduction of oxidative stress, and inflammation. Meanwhile, molecular docking and molecular dynamics simulations also showed the potential of these compounds (e.g., glycyrrhizic acid) in inhibiting the activities of key proteins of 2019-nCoV. Furthermore, related experiments also showed that glycyrrhizic acid may act on COVID-19 through some targets (e.g., intercellular adhesion molecule 1, matrix metallopeptidase 9, toll-like receptor 2, and suppressor of cytokine signaling 3) [113]. Simayi et al. [84] analyzed the effective active ingredients of 10 types of TCM in the Chinese patent medicine Zukamu granules based on network pharmacology and molecular docking technology. They found that

luteolin, kaempferol, and quercetin combined well with the 2019-nCoV-M^{pro} and ACE2.

In the actual research on the prevention and treatment of COVID-19 in TCM ingredients, in addition to saponins and flavonoids, many other bioactive compounds have been discovered by scientists. They are also proved to be effective in the prevention and treatment of COVID-19 [121–123]. Liu et al. [112] explored the potential therapeutic mechanism of matrin on COVID-19 combined with liver injury by using network pharmacology and molecular docking combined with real-time polymerase chain reaction detection. The results suggested that the potential therapeutic mechanism of matrine for the treatment of target diseases is related to several processes, e.g., regulation of inflammatory cytokines and improvement of immune system. Meanwhile, the matrine and receptor protein also showed strong binding force. Chikale et al. [109] studied 66 active components in Yuganzi (*Phyllanthus Emblica*) and found that chlorogenic acid had higher binding energy to 2019-nCoV protein target. Furthermore, the network pharmacological analysis also confirmed the possibility of the compound against COVID-19.

Comparative analysis of TCM and Western medicine

At present, more and more TCMs have been proved by relevant experiments or clinical trials to show effects on the treatment of COVID-19 [28, 124–130]. In addition to TCM, other clinical drugs, including Western medicine and Indian herbal medicine, are also under constant study [131]. Meo et al. [132] compared the efficacy of chloroquine and hydroxychloroquine, convalescent plasma, and remdesivir in COVID-19 treatment, and found that each method had its own advantages and disadvantages. Apart from the possibility that convalescent plasma presents a clinical advantage, there is currently no clear evidence to support which method is more favorable for the early treatment or prevention of COVID-19. Cao et al. [133] found that in molecular docking analysis of Yinqiao powder, the molecular docking binding energy of the core active components with SARS-CoV-2 and the key proteins (ACE2 and transmembrane serine protease 2) was less than 0 kJ/mol. These results indicate that the core active ingredients have better binding activities with SARS-CoV-2, ACE2, and transmembrane serine protease 2. Compared with the Western medicine reported to treat COVID-19, the binding energy of the active ingredients in Yinqiao powder are lower and the therapeutic effect is more possible. Ma et al. [78] compare the molecular docking result that three core compounds (ergotamine, ursolic acid, and chenodeoxycholic acid) and five chemical drugs (remdesivir, chloroquine, favipiravir, ritonavir, and ribavirin) combined separately with SARS-CoV-2 RdRp in related studies of the treatment of COVID-19 by the Chinese patent medicine Liushen capsule. The results showed that the binding energy of ergotamine, ursolic acid, and chenodeoxycholic acid are −15.9 kJ/mol, −14.6 kJ/mol, and −11.9 kJ/mol, respectively. Compared with remdesivir (−10.4 kJ/mol), chloroquine (−7.4 kJ/mol), favipiravir (−6.7 kJ/mol), ritonavir (−9.5 kJ/mol), and ribavirin (−8.1 kJ/mol), the binding energy of the core components of Liushen capsule was lower, suggesting that Liushen capsule may have a better effect on COVID-19. At present, because of the limitations of the individual use of TCM or Western medicine, researchers are also trying to combine TCM and Western medicine to build a new treatment system of COVID-19, which integrates both Chinese and Western medicines. This treatment system has already achieved results and provided a new direction for the clinical treatment of COVID-19 [134–137].

Challenges of network pharmacology

With the continuous progress of network pharmacology and molecular docking technology, drug design, drug development, and other related fields have brought unprecedented opportunities. The method of drug research is no longer limited to a single target, but through the establishment of three levels of drug–target–disease networks to carry out computer simulations. This technology has great potential for development in drug active components and mechanisms of action [137–140]. But with the need for social development and the enhancement of scientific research requirements, network pharmacology and molecular docking technology have gradually exposed their own shortcomings and deficiencies [141, 142]. These disadvantages of network pharmacology include the insufficient integrity and accuracy of database, uncertain complexity of components analysis, and unclear mechanism of component-target action [31, 143]. In the future, it will be a major challenge for all scholars to perfect and improve the existing databases, carry out a detailed analysis of drug ingredients by combining relevant disciplines, realize the organic combination of computer technology with biology and pharmacy, and establish a more modern and networked drug screening system [144].

In addition to the general shortcomings of the above network pharmacology technology, due to the complexity of the mechanism of action of TCM itself, the diversity of drug collocation types and the difference of TCM processing methods as well as the combination of the TCM and network pharmacology also brings new challenges to the practical application of network pharmacology. Here, the actual research of Chinese herbal formula and Chinese traditional patent medicine is selected as examples to elaborate the problems. First of all, the step of screening the active ingredients of TCM in network pharmacology separates each TCM from the Chinese herbal formula and Chinese traditional patent medicine, and uses some databases to screen the active ingredients of each herb separately to take a union, ultimately, the active components in the whole formulas/medicines are obtained. However, this step ignores the impact on the curative effect of the disease, caused by the differences in the characteristics of "Jun-Chen-Zuo-Shi" (monarch-minister-assistant-guide, a combination principle of TCM prescriptions, which four different professions in ancient society to analogize the priority, subordinate and their mutual relations of various herbs) of the TCM and the difference of the processing methods, and instead simply regards the mechanism of Chinese herbal formula and Chinese traditional patent medicine as the superposition of several single herbs, which leads to the lack of accuracy of the drug mechanism described [145, 146]. Although some scholars have studied the function of compatibility of several TCM by network pharmacology, e.g., the compatibility of Chishao (*Paeoniae Radix Rubra*) and Mudanpi (*Moutan Cortex*) in the treatment of cerebral hemorrhage [147], the method is almost consistent with the analysis of Chinese herbal formula and Chinese traditional patent medicine, without breaking away from the limitations of composition superposition. Secondly, as an extraneous virtual computer experiment method, the network pharmacology belongs to the category of theoretical research.

Table 3 Examples of active components of TCM related to known targets of COVID-19

Name	Origin	Molecular weight	Molecular formula	PubChem CID	Potential targets of COVID-19	Reference
Acacetin	Banlangen (*Isatidis Radix*)	284.26	$C_{16}H_{12}O_5$	5280442	ACE2	[27]
Syrigin	Banlangen (*Isatidis Radix*)	372.40	$C_{17}H_{24}O_9$	5316860	ACE2	[27]
Glabridin	Guangguogancao (*Glycyrrhiza Glabra*)	324.40	$C_{20}H_{20}O_4$	124052	ACE2	[28, 97]
Gallic acid	Wubeizi (*Galla Chinensis*)	170.12	$C_7H_6O_5$	370	ACE2	[28, 98]
Luteolin	Bohe (*Menthae Haplocalycis Herba*)	286.24	$C_{15}H_{10}O_6$	5280445	M^{pro}/$3CL^{pro}$, ACE2	[84]

TCM, traditional Chinese medicine; COVID-19, coronavirus disease 2019; ACE2, angiotensin converting enzyme II; M^{pro}, main protease; $3CL^{pro}$, 3C-like protease.

Table 3 Examples of active components of TCM related to known targets of COVID-19 (*Continued*)

Name	Origin	Molecular weight	Molecular formula	PubChem CID	Potential targets of COVID-19	Reference
Kaempferol	Shannai (*Kaempferiae Rhizoma*)	286.24	$C_{15}H_{10}O_6$	5280863	M^{pro}/$3CL^{pro}$, ACE2	[84]
Polyphyllin I	Chonglou (*Paris Polyphylla*)	855.00	$C_{44}H_{70}O_{16}$	71571451	ACE2	[99]
Polyphyllin VI	Chonglou (*Paris Polyphylla*)	738.90	$C_{39}H_{62}O_{13}$	10417550	ACE2	[99]
Polyphyllin VII	Chonglou (*Paris Polyphylla*)	1049.20	$C_{51}H_{84}O_{22}$	46200822	ACE2	[99]
Anemarsaponin E	Zhimu (*Anemarrhenae Rhizoma*)	935.10	$C_{46}H_{78}O_{19}$	71307556	SARS-CoV-2-S-RBD-ACE2	[100]
Anemarsaponin B	Zhimu (*Anemarrhenae Rhizoma*)	903.10	$C_{45}H_{74}O_{18}$	53462233	SARS-CoV-2-S-RBD-ACE2	[100]
Diosgenin	Huangjing (*Rhizoma Polygonati*)	414.60	$C_{27}H_{42}O_3$	99474	ACE-2, Spike protein S1, Rd Rp, M^{pro}/$3CL^{pro}$	[101]
Glycyrrhizic acid	Gancao (*Glycyrrhizae Radix et Rhizoma*)	822.90	$C_{42}H_{62}O_{16}$	14982	NSP15	[102, 103]
Hesperidin	Chenpi (*Citri Reticulatae Pericarpium*)	610.60	$C_{28}H_{34}O_{15}$	10621	RBD of nCoV-SP, ACE2	[104, 105]
Naringin	Huajuhong (*Citri Grandis Exocarpium*)	580.50	$C_{27}H_{32}O_{14}$	442428	RBD of nCoV-SP, ACE2	[104, 106]
Epigallocatechin gallate	Tea (*Camellia Sinensis* (L.) *O. Kuntze*)	458.40	$C_{22}H_{18}O_{11}$	65064	RBD of nCoV-SP, ACE2	[104, 107]
Quercetin	Dasuan (*Allii Sativi Bulbus*)	302.23	$C_{15}H_{10}O_7$	5280343	RBD of nCoV-SP, ACE2	[104, 108]
Chlorogenic acid	Yuganzi (*Phyllanthus Emblica*)	354.31	$C_{16}H_{18}O_9$	1794427	NSP15, M^{pro}/$3CL^{pro}$, RBD of nCoV-SP	[109]

TCM, traditional Chinese medicine; COVID-19, coronavirus disease 2019; RBD, receptor-binding domain; nCoV-SP, S protein of 2019 novel coronavirus; ACE2, angiotensin converting enzyme II; NSP15, non-structural protein-15 endoribonuclease; M^{pro}, main protease; $3CL^{pro}$, 3C-like protease; SARS-CoV-2-S-RBD-ACE2, complex of RBD of nCoV-SP and ACE2 protease domain; Rd Rp, RNA-dependent RNA polymerase.

Table 4 Examples of active components of TCM related to inflammatory, oxidative stress and other processes of COVID-19

Name	Origin	Molecular weight	Molecular formula	PubChem CID	Potential targets of COVID-19	Reference
Acacetin	Banlangen (*Isatidis Radix*)	284.26	$C_{16}H_{12}O_5$	5280442	CASP3, CASP8, FASLG	[27]
Saikosaponin U	Chaihu (*Bupleuri Radix*)	1269.40	$C_{59}H_{96}O_{29}$	100958092	IL6	[110]
Saikosaponin V	Chaihu (*Bupleuri Radix*)	1107.20	$C_{53}H_{86}O_{24}$	100958093	IL6	[110]
Saikosaponin B4	Chaihu (*Bupleuri Radix*)	813.00	$C_{43}H_{72}O_{14}$	21637636	JAK3	[110]
Saikosaponin I	Chaihu (*Bupleuri Radix*)	927.10	$C_{48}H_{78}O_{17}$	73817573	JAK3	[110]
Saikosaponin BK1	Chaihu (*Bupleuri Radix*)	927.10	$C_{48}H_{78}O_{17}$	441945	NOX5	[110]
Saikosaponin C	Chaihu (*Bupleuri Radix*)	943.10	$C_{48}H_{78}O_{18}$	131801344	NOX5	[110]
Astragaloside IV	Huangqi (*Radix Astragali Mongolici*)	785.00	$C_{41}H_{68}O_{14}$	13943297	IL6, MMP13, GBP1, NLRP3, IL1B, TNF, ADORA2A, MLNR, NFKBIA, PTAFR, ADRB2	[111]
Matrine	Kushen (*Sophora Flavescens Ait*)	248.36	$C_{15}H_{24}N_2O$	91466	AKT1, TP53, TNF, IL6, BCL2L1, ATM	[112]
Glycyrrhizic acid	Gancao (*Glycyrrhizae Radix et Rhizoma*)	822.90	$C_{42}H_{62}O_{16}$	14982	ICAM1, SOCS3, MMP9, TLR2	[103, 113]

TCM, traditional Chinese medicine; COVID-19, coronavirus disease 2019; CASP3, caspase 3; CASP8, caspase 8; FASLG, Fas ligand; IL6, interleukin 6; JAK3, Janus kinase 3; NOX5, NADPH oxidase 5; MMP13, matrix metallopeptidase 13; GBP1, guanylate binding protein 1; NLRP3, NLR family pyrin domain containing 3; IL1B, interleukin 1 beta; TNF, tumor necrosis factor; ADORA2A, adenosine A2a receptor; MLNR, motilin receptor; NFKBIA, NFKB inhibitor alpha; PTAFR, platelet activating factor receptor; ADRB2, adrenoceptor beta 2; AKT1, AKT serine/threonine kinase 1; TP53, tumor protein p53; BCL2L1, BCL2 like 1; ATM, ATM serine/threonine kinase; ICAM1, intercellular adhesion molecule 1; SOCS3, suppressor of cytokine signaling 3; MMP9, matrix metallopeptidase 9; TLR2, toll-like receptor 2.

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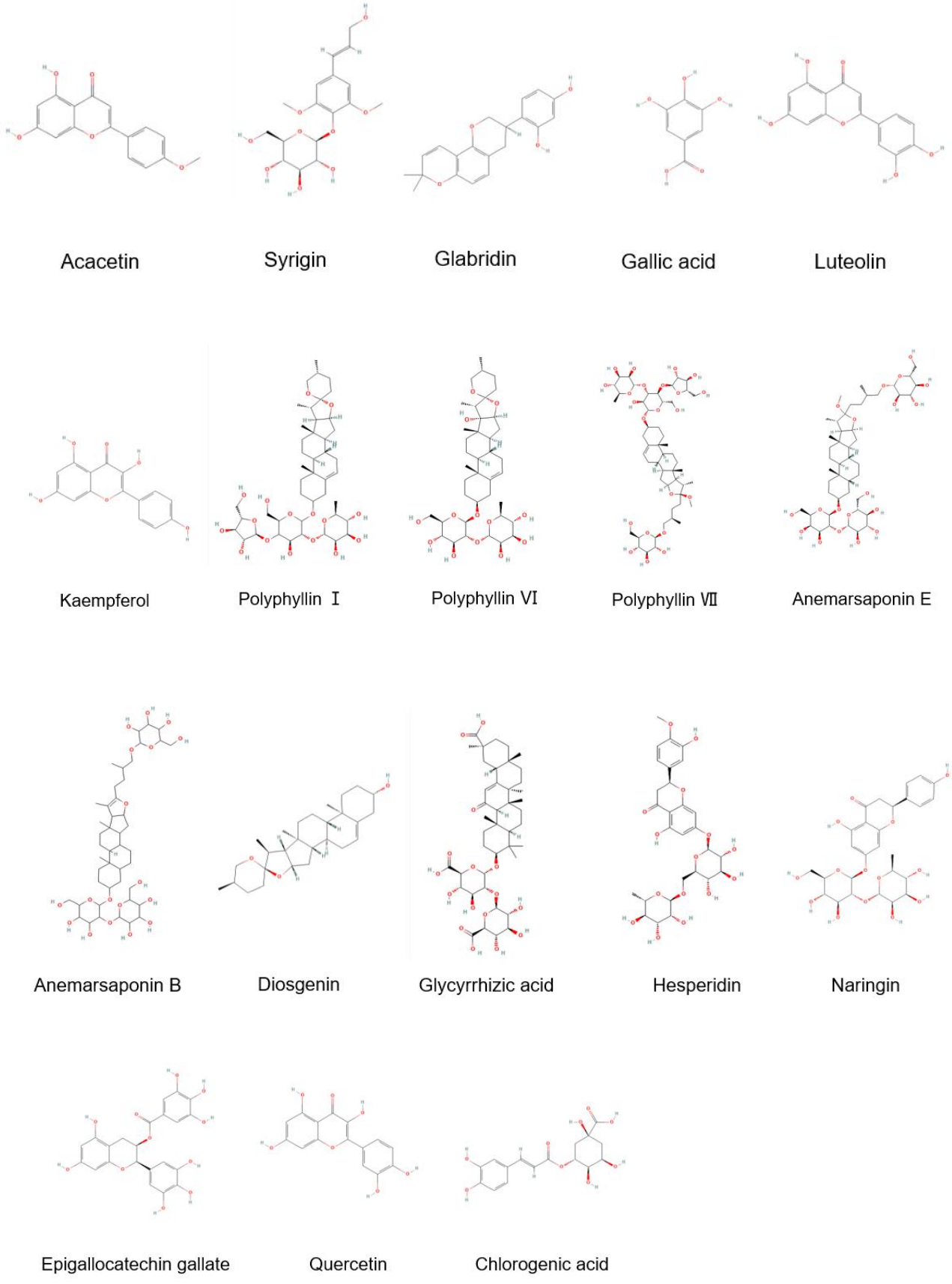

Figure 1 The chemical structure of several active components of TCM related to known targets of COVID-19. TCM, traditional Chinese medicine; COVID-19, coronavirus disease 2019.

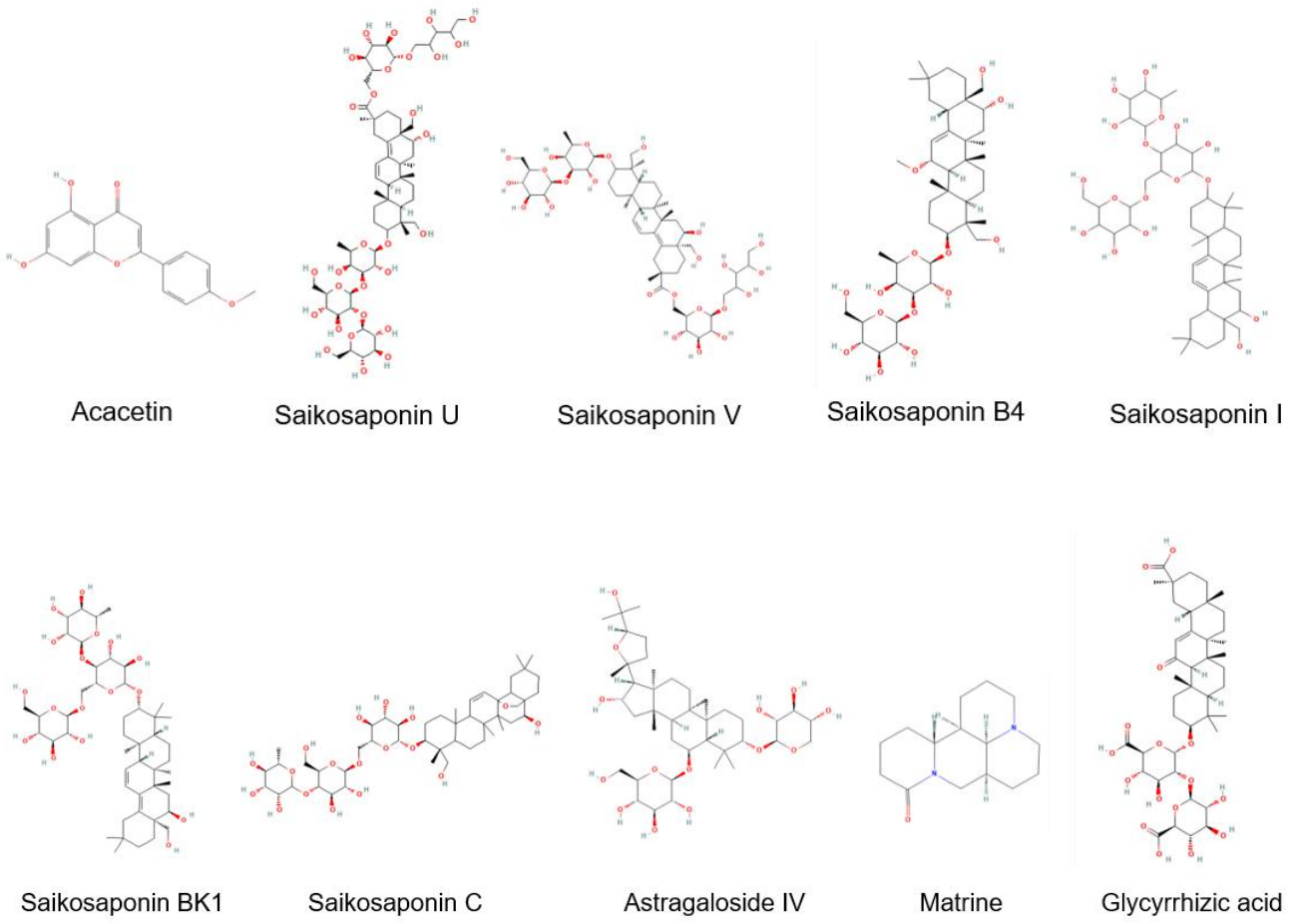

Figure 2 The chemical structure of several active components related to inflammatory, oxidative stress and other processes of COVID-19. TCM, traditional Chinese medicine; COVID-19, coronavirus disease 2019.

Although it can omit the time used for components screening in the general study of drugs and reduce the workload of experimental personnel, it ignores the complexity of the mechanism of drug action in living organisms, such as the organs of actual distribution of active ingredients, the interaction of various organs in the body, and the synergistic effect of multiple signaling pathways. The simple superposition of functions or pathways cannot guarantee the accuracy of the mechanism of action and the consistency of the effect of drugs in vivo and in vitro [148–150]. Furthermore, although a compound was shown with a strong binding affinity in network pharmacology and molecular docking experiments, it failed to show any activity in vivo. It is premature to claim significance from in network pharmacology and molecular docking findings without confirmation by biological data. For example, both arctiin and arctigenin are two quality markers in *Fructus Arctii*, which are closely related to the changes in efficacy before and after processing [148]. Sun et al. [149] studied the differences in the distribution of the two chemical components in organs in vivo and in vitro, and it was found that the distribution of the two components in the lungs was optimal both in vivo and in vitro, but the differences in other organs were large. In addition, due to the limitation of the database in network pharmacology, the targets that can be retrieved incompletely in the main compounds of *Fructus Arctii* and the changes in some component indexes caused by the compatibility of TCM cannot be predicted [150]. This shows that there are certain differences in the results obtained by the four experimental methods (i.e., in vivo, in vitro, in theory, and in practice) used by the researchers in carrying out the actual research on the components of target TCM. The results of simple extraneous theoretical experiments can only be used as a reference to guide practice.

Conclusion

In conclusion, in the field of COVID-19 prevention and treatment, network pharmacology and molecular docking technology possess great advantages, but still have some disadvantages and deficiencies. To make this technology more systematic and accurate in the analysis of drug active ingredients and mechanism of action will be a key content for future scientists to study. At present, the pneumonia epidemic with novel coronavirus as the source of infection has not been completely suppressed, and the entire world is still facing the severe outcome of the epidemic. To date, scientific research and medical workers, including Chinese scholars, are actively carrying out prevention and treatment of COVID-19 and new drug development based on the global prevention and treatment status of novel coronavirus and existing reported therapeutic drugs, striving to obtain the effective ingredients and mechanism of action for the treatment of this new pneumonia. These efforts set up a foundation for the development of specific drugs and vaccines [151–154]. We believe that under the international cooperation and the support of World Health Organization, with the deepening of the research on existing possible drugs and the continuous optimization of network pharmacology and molecular docking technology, the experimental data and relevant database will become increasingly perfect. The weaknesses of novel coronavirus will be inevitably exposed. Humanity will certainly score a full victory against the epidemic.

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