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Review

Methodology of network pharmacology for research on Chinese herbal medicine against COVID-19: A review

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ABSTRACT

Traditional Chinese medicine, as a complementary and alternative medicine, has been practiced for thousands of years in China and possesses remarkable clinical efficacy. Thus, systematic analysis and examination of the mechanistic links between Chinese herbal medicine (CHM) and the complex human body can benefit contemporary understandings by carrying out qualitative and quantitative analysis. With increasing attention, the approach of network pharmacology has begun to unveil the mystery of CHM by constructing the heterogeneous network relationship of "herb-compound-target-pathway," which corresponds to the holistic mechanisms of CHM. By integrating computational techniques into network pharmacology, the efficiency and accuracy of active compound screening and target fishing have been improved at an unprecedented pace. This review dissects the core innovations to the network pharmacology approach that were developed in the years since 2015 and highlights how this tool has been applied to understanding the coronavirus disease 2019 and refining the clinical use of CHM to combat it.

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1. Introduction

Traditional Chinese medicine (TCM), as a treasure of the Chinese nation and a critical component of China's medical and health care system, plays an essential role in the field of healthcare for the Chinese people [1]. Characterized by holistic, personalized, and rich experience-based therapy, TCM, including modalities such as Chinese herbal medicine (CHM) and acupuncture, has broad applications for the systematic control of complex diseases [2]. Due to the complexity of CHM which comprises a crucial part of TCM, traditional reductionism method remains difficult to simplify the interplay between the multiple compounds present in an herbal formula and the multiple targets on which they act; this has become a major obstacle to TCM's modernization and its incorporation into modern healthcare [3].

Systems biology is a new frontier in biological research which provides a framework for assembling models of biological systems from systematic measurements. Further, bioinformatics is conceptualizing biology from a molecular perspective and applying "informatics techniques," including applied mathematics, computer science and statistics, to extract knowledge from biological data for large-scale analysis, prediction, imaging and visualization [4]. Cheminformatics is an emerging frontier in the field of information technology, focusing on the collection, storage, analysis and operation of chemical data [5]. Hence, with the development and integration of fields such as systems biology, bioinformatics, cheminformatics, artificial intelligence, and "big data," research on the mechanisms of CHM has shifted from investigating single, isolated compounds to a new multi-faceted and systematic research approach [6]. One of these breakthroughs is network pharmacology, which is used to explore the molecular mechanisms of CHM from the perspective of a complex biomolecular network. Utilizing this network approach generates an unprecedented opportunity for systematic research into CHM. In the last five years, network pharmacology studies of CHM have increased rapidly [7], and it is evolving as a systematic paradigm and the leading edge in research and development of CHM [8]. At the same time, computational methodologies and high-quality databases play an essential role in satisfying the data-driven aspects of network pharmacology. Therefore, a concise overview of the use of network pharmacology in CHM research is urgent.

This review is structured into two main sections. In the first section, the cutting-edge CHM network pharmacology studies published between 2015 and 2021 that established strategies for active compound screening, target prediction, and network analysis are reviewed and summarized alongside the specialized databases on which these techniques depend. In the second section, the application of network pharmacology in mechanistic investigation and repositioning of CHM against coronavirus disease 2019 (COVID-19) is highlighted.

2. Network pharmacology for CHM research

2.1. Strategies for compound screening

Lack of certainty in the bioactive compounds responsible for the actions of CHM is one of the key issues that makes CHM research difficult. It is extremely time-consuming and labor-intensive to obtain the chemical profiles of CHM formulas following traditional chemical methods (i.e., isolation, identification and evaluation). Many natural product databases are open-source, although it can be difficult to extract and screen the active compounds present in CHM from these databases, as they contain vast amounts of data. In the modern drug discovery procedure, there is a high failure rate for converting candidate active compounds into effective drugs; this is primarily caused by undesirable absorption, distribution, metabolism, elimination and toxicity (ADMET) profiles of the target compound. Thus, it is practical to include ADMET data in parallel with information on CHM that can be gathered from natural product databases. Insufficiency of data is, however, often a problem in this approach. To fill in some of these information gaps, some researchers prefer to use their own experiments to profile compounds that are present in CHM, combined with ADMET filtering. For instance, ultra-performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UPLC-Q-TOF-MS) was used for the chemical profiling of *Isatis indigotica* roots and leaves, and the active constituents present in *I. indigotica* were then screened using the prediction of gastrointestinal absorption and drug-likeness (DL) analysis in SwissADME (https://www.swissadme.ch) [9]. The active components in ginsenoside H dripping pills were identified by UPLC-Q-TOF-MS and then filtered based on oral bioavailability (OB) and DL [10]. To detect the volatile compounds from *Scutellaria baicalensis*, gas chromatography-MS (GC-MS) was performed. The active compounds were further screened by OB, druggability and blood brain barrier (BBB) screening [11]. Likewise, the bioactive constituents in *Morus alba* L. leaves were detected using GC–MS and then screened for DL and their topological polar surface area [12]. Further, GC–MS was used to detect chemical constituents from *Hibiscus cannabinus* L. leaves and *Ganoderma lucidum*, and then they were filtered according to Lipinski's rule through the SwissADME to identify their DL [13,14]. Liu et al. [15] used OB, DL, human colonic adenocarcinoma cells, and BBB criteria to screen the potential active compounds of Guanxinshutong Capsule that had been identified through LC-MS and GC-MS profiling.

Experimental errors in the datasets, poor-quality models and the idea of applicability domain are major concerns related to the reliability of ADMET predictions. Compared to the compounds isolated from herbs, considering the CHM constituents that are absorbed *in vivo* could reduce the rate of false-positive results from ADMET prediction [16]. For example, based on the serum/plasma pharmacochemical evaluation, the compounds from formulas (Shentong Zhuyu Decoction, Xiaokewan, and Shenzhi Jiannao Formula) or single herbs (Viticis fructus, *Poria cocos* [Schw.] Wolf, and *Cyclocarya paliurus* [Batal.] Iljinskaja leaves) that could enter the serum were considered to be potential active compounds for network pharmacology analysis [17–22]. The compounds present in other biological samples, such as urine and tissues, could be also used for network pharmacology analysis [23,24]. If metabolites have potential biological activities, they should be included with prototype compounds in the network pharmacology analysis. Zhang et al. [25] used phellodendrine and its main *in vivo* metabolites to explore the potential pharmacological network to address diabetes mellitus. Arctiin and prim-*O*-glucosylcimifugin and their *in vivo* metabolites were used for network pharmacology analysis [26,27]. The *in vivo* metabolites of *Achyranthes bidentata* Blume

saponins and their targets associated with rheumatic arthritis were used to construct a multi-layer network [28]. The prototype constituents plus metabolites of *Schisandra chinensis* (Turcz.) Baill. fruits and *Paeonia lactiflora* Pall. roots that were retrieved from rat plasma were considered to be bioactive ingredients used for network pharmacology analysis [29,30].

It is also useful to identify suitable pharmacokinetic marker(s) of CHM as bioactive compounds. For instance, network pharmacology was conducted by selecting the pharmacokinetic markers from *Phlomis brevidentata* H.W.Li extract [31]. Further, an everted gut sac model, coupled with UPLC-Q-TOF-MS, was used to screen and identify the active compounds of Xijiao Dihuang Decoction combined with Yinqiao Powder [32]. Considering the pivotal role of gut microbial transformation, three phenylethanoid glycosides from *Cistanche deserticola* Y.C.Ma stems and their *in vitro* metabolites transformed by intestinal bacteria were forwarded to network pharmacology analysis [33].

Overall, integrating computational and analytical methods serves as a credible method for identifying preliminary bioactive compounds present in CHM.

2.2. Strategies for target prediction

Compound-target interaction (CTI) is the core part of network pharmacology to understand comprehensive mechanisms of CHM [34]. The traditional way to identify CTIs is to quantitatively determine the inhibitory or activation values between compounds and targets by *in vitro* or *in vivo* assays [35]. However, it is not feasible to determine all possible CTIs present in the thousands of CHMs [36]. The development of various computational methods, such as molecular docking-based [37], pharmacophore-based [38], chemical similarity-based [39], machine learning-based [40], and network-based [41] methods, has provided valuable strategies for the systematic prediction of potential CTIs. Several data sources for screening and prediction of CTIs are introduced in Table 1 [42–51].

Multi-omics technologies (e.g., transcriptomics and metabolomics) could pave the discovery of potential CTIs. For example,

Dai et al. [52] combined the target information collected from publicly available databases and their own transcriptomics data of celastrol treatment for osteoarthritis. Liu et al. [53] screened the potential targets of Danggui Buxue Decoction against anemia by integrating the data-mined upstream proteins of the differential metabolites from metabonomics and the anemia-associated targets obtained from GeneCards database (https://www.genecards.org/). Similarly, metabolic proteins related to potential biomarkers from metabolomics and predicted proteins of cantharidin were all introduced into String database (https://string-db.org/) to conduct a protein–protein interaction analysis. The hub targets were then filtered by mean degree value and selected for network pharmacology analysis [54]. Thus, it is feasible to unveil the potential CTIs of CHM via computational methods integrated with multi-omics strategy.

2.3. Strategies for network analysis

Network thinking has contributed a number of important unanticipated insights on the complex mechanisms underlying CHM, so how to extract key information from the heterogeneous networks is the main goal. Many network-based computational approaches have been conducted to excavate effective components and hub targets (Fig. 1).

2.3.1. Scoring active compounds

As a demonstrative example, we proposed a contribution index (CI) to estimate each active compound's contribution to the efficacy of CHM based on network topology property (NE) and efficacy weight. The CI was proposed and calculated by equations (1) and (2):

$$NE(j) = \sum_{i=1}^{n} d_i \tag{1}$$

$$CI(j) = \frac{c_j \times NE(j)}{\sum_{i=1}^{m} c_i \times NE(i)} \times 100\% \tag{2}$$

where n is the target number of compound j in the compound-target network; d_i is the target i's degree of compound j in the

Table 1
Several representative databases and web servers for screening and prediction of CTI data.

Database and web server	Website	Contents and main features	Quantitative activity values	Reference
Binding MOAD	https://www.bindingmoad.org	Including 23,269 complexes and 8156 binding affinities.	Yes	[42]
DrugCentral	https://drugcentral.org/	Integrating structure, bioactivity, regulatory and pharmacologic actions, and indications for active pharmaceutical compounds.	Yes	[43]
IUPHAR/BPS Guide to PHARMACOLOGY	https://www.guidetopharmacology.org/	Including approximately 9000 ligands, 15,000 binding constants, 6000 papers and 1700 human proteins.	Yes	[44]
PubChem BioAssay	https://www.ncbi.nlm.nih.gov/pcassay/	Covering 5000 protein targets and 30,000 gene targets, and providing over 130 million bioactivity outcomes.	Yes	[45]
Therapeutic Target Database	https://bidd.nus.edu.sg/group/ttd/ttd.asp	Providing the known and explored therapeutic protein and nucleic acid targets, the targeted diseases, pathway information and corresponding drugs directed at each of these targets.	No	[46]
SIDER	https://sideeffects.embl.de/	Containing marketed medicines and their recorded side effects, as well as drug-target associations.	No	[47]
SwissTargetPrediction	https://www.swisstargetprediction.ch/	Inferring the targets of small molecules based on the combination of 2D and 3D similarity values with known ligands.	No	[48]
DGIdb 3.0	https://dgidb.org/	Containing > 40,000 genes and > 10,000 drugs involved in > 100,000 drug-gene interactions.	No	[49]
TargetNet	https://targetnet.scbdd.com/	Netting or predicting the binding of multiple targets for any given molecule.	No	[50]
HIT 2.0	https://hit2.badd-cao.net/	A comprehensive searching and curation platform for CTI information based on literature evidence.	No	[51]

2D: two dimensions; 3D: three dimensions; CTI: compound-target interaction.
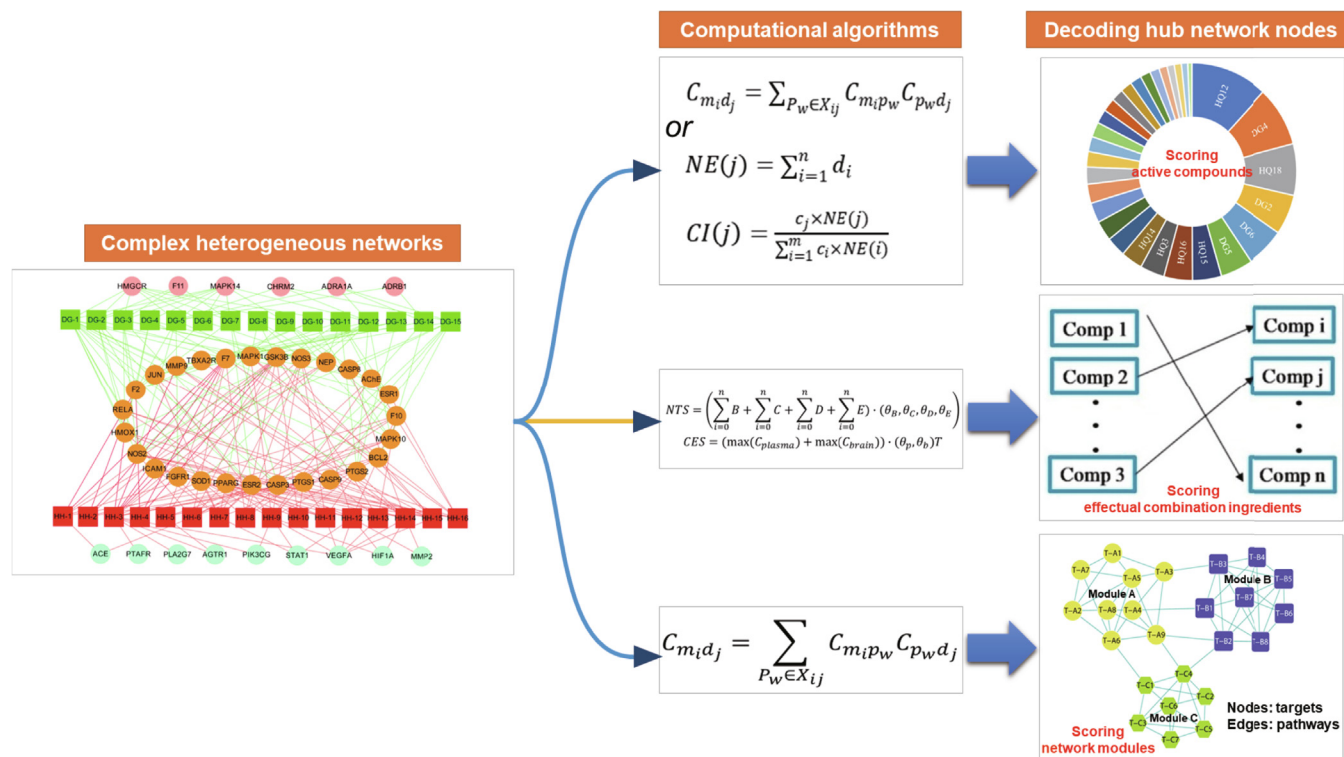
Fig. 1. Network-based computational algorithms to excavate effective components and underlying mechanisms of Chinese herbal medicine.

target-pathway network; c_i is the number of disease-related literature of compound i; m is the number of compounds; $NE(j)$ is the NE of compound j; $CI(j)$ is the CI of compound j [55,56].

Likewise, Wang et al. [57] proposed a contribution score (CS) to evaluate the effectiveness of each compound of two herbs in a Chinese patent medicine. C_{Ai} and C_{Bi} represent the degree of each compound only in compound-target network of herb A and herb B, respectively; C_{edge} and T_{edge} represent the edge of compounds and targets in compound-target network, respectively; P represents the degree of each protein; A_{ij} is the index of affinity determined from the ω_{ei} value as shown in equations (3)–(5).

$$A_{ij} = \omega_{ei} + \left| \frac{C_{Ai} + C_{Bi}}{C_{Ai} - C_{Bi}} \right| \tag{3}$$

$$\omega_{ei} = \frac{C_{edge}}{T_{edge}} \tag{4}$$

$$CS(\text{i}) = \sum_{ij}^{n} C_i \times \left[A_{ij} \times P_j \right] \tag{5}$$

Gao et al. [58] let m denote compounds, n denote the specific disease genes, X_{ij} ($i = 1,\ldots, m$; $j = 1,\ldots, n$) represent a compound-target interacting score (X_{ij} ranged from 0 to 1), and C_j represent the correlation coefficient (specifically, $C_j = 0.1$ [degree < 5], $C_j = 0.2$ [$5 \leq$ degree < 10], $C_j = 0.3$ [$10 \leq$ degree < 20], and $C_j = 0.4$ [degree $\geq$ 20]). The anti-aging score of compound i (AA_i) was calculated by the following formula, i.e., equation (6):

$$AA_i = \sum_{1}^{j} C_j X_{ij} \tag{6}$$

Wang et al. [59] performed a computational algorithm with Fisher's exact test method (equation [7]) to investigate and rank the active compounds of a prescription in treating specific disease: specifically, if compounds have no known targets, $n = 20$ and k was the number of disease-related genes in n; if compounds have s

known targets, $n = 20 + s$, and k was s plus the number of disease-related genes in n. N was the number of protein-coding genes in the constructed network and K was the number of all disease-related genes in the network. P value was calculated and adjusted by Benjamini-Hochberg method, for ranking all compounds.

$$P(\text{X} = k) = \frac{\binom{K}{k}\binom{N-K}{n-k}}{\binom{N}{n}} \tag{7}$$

Zhang et al. [60] developed an index of effective rate, indicating the possibility of a compound affecting a specified function (see equation [8]). The outdegree and sub-outdegree mean the number of putative targets for each compound and the number of putative targets for a specific function, respectively. This algorithm has also been successfully applied in our previous network pharmacology study of Danggui Buxue Decoction [61].

$$Effective\ rate = \frac{Sub - outdegree}{Total\ outdegree} \tag{8}$$

Suo et al. [62] assumed that if one unit of information comes to a node of degree k_j, it flows downstream through $k_j - 1$ branch, each of which transfers $1/k_j - 1$ unit of the original information. Then, the scoring scheme for the active ingredients can be evaluated as equations (9)–(11),

$$I_i(m \rightarrow n) = \frac{1}{k_m} \prod_{j \in V(i)} \frac{1}{k_j - 1} \tag{9}$$

$$I(m \rightarrow n) = \sum_{i} I_i(m \rightarrow n) \tag{10}$$

$$I(m) = \sum_{n} I(m \rightarrow n) \tag{11}$$

where $V(i)$ is the protein nodes between n and m in path i; $I_i(m \rightarrow n)$ is the effectiveness of ingredient m on target n; $I(m \rightarrow n)$ gives the specificity of ingredient m to target n;

and $I(m)$ shows the overall effectiveness of ingredient m on the disorder under investigation.

Considering that CHM compounds vary dramatically in content, we proposed another CI based on both the intrinsic properties (active components' content and OB) of CHM and the rank-sum ratio (RSR) of integrated network topology parameters (including degree, closeness, betweenness, eccentricity, neighborhood connectivity and average shortest path length) of active compounds in the heterogeneous network [63], as equation (12):

$$CI_{i,j} = \frac{m_i}{\sum_i^n m_i} \times \frac{C_{i,j}}{M_j} \times OB_j \times RSR_j \times 10^7 \qquad (12)$$

where $CI_{i,j}$ is the CI of component j in herb i, m_i is the weight of herb i in a formula, n is the total count of herbs in a formula, $C_{i,j}$ is the content of component j in herb i, and M_j is the molecular weight of component j; OB_j represents the OB value of compound j retrieved from the TCMSP database (https://old.tcmsp-e.com/tcmsp.php); and RSR_j is the RSR of component j in the compound-target-pathway network.

2.3.2. Scoring effectual-combination ingredients

With the attempt to find the effectual-combination ingredients (ECIs) from CHM, a strategy was proposed by Liu et al. [64]; it was defined as metabolic exposure-oriented network regulation for identification of ECIs, including network topology score (NTS) and component exposure score (CES) (see equations [13] and [14]). NTS represents the topological importance of a compound's targets in CHM-regulated network, by calculating "Betweenness" (B), "Closeness" (C), "Degree" (D), and "Eigenvector centrality" (E) of all regulated genes through principal component analysis (PCA). CES represents the metabolic exposure of each compound by PCA integrating the C_{max} of plasma and brain of each compound. Finally, the combinatory compounds of which the NTS or CES was above 2, 1 and 0 were selected as candidate ECIs.

$$NTS = \left(\sum_{i=0}^n B + \sum_{i=0}^n C + \sum_{i=0}^n D + \sum_{i=0}^n E\right) \times (\theta_B, \theta_C, \theta_D, \theta_E) \qquad (13)$$

$$CES = \left(\max\left(C_{plasma}\right) + \max\left(C_{brain}\right)\right) \times (\theta_p, \theta_b)T \qquad (14)$$

Similarly, Luo et al. [65] screened ECIs of a formula by combination of NTS and variable importance in projection (VIP) value. The VIP values of differential absorbed components in plasma were revealed by metabolomics-driven strategy coupled with the orthogonal-partial-least-squares-discrimination analysis. The combinatory compounds of which the VIP was above 1.5, 1.25 and 1.0 or NTS was above 2, 1 and 0 were selected as candidate ECIs.

2.3.3. Scoring network modules

To estimate the intensity of associating a specific network module with a specific disease, Zuo et al. [66] used an algorithm in the "targets-(pathways)-targets" network, as equation (15):

$$C_{m_i d_j} = \sum_{P_w \in X_{ij}} C_{m_i p_w} C_{p_w d_j} \qquad (15)$$

where X_{ij} is a subset of P and refers to the pathways that are relevant to m_i and d_j simultaneously; C_{midj} refers to the CS of m_i to d_j, which is the sum of the contribution of m_i to d_j through all its relevant p_w in X_{ij}. The value of C_{midj} varies from 0 to 1: the higher the value, the greater the contribution m_i might make to d_j; and all the modules contribute 1 to a particular disease.

Recently, in order to integrate the target score information of the TCM prescription as well as the disease, Xiong et al. [67] used two iterations of PageRank algorithm to obtain the PageRank value of targets in prescription-disease system shown in equations (16)–(18).

$$V_p = M_2 M_1 V_h \ / \ \max\left(M_2 M_1 V_h\right);$$
$$V_0 = V_p; V_1 = \alpha M V_0 + (1 - \alpha)1 / N;$$
$$V_2 = \alpha M V_1 + (1 - \alpha)1 / N; V_{rank1} = V_2 \qquad (16)$$

$$V_0 = V_d; V_1 = \alpha M V_0 + (1 - \alpha)1 / N;$$
$$V_2 = \alpha M V_1 + (1 - \alpha)1 / N; V_{rank2} = V_2 \qquad (17)$$

$$V_{avg} = (V_{rank1} + V_{rank2}) / 2 \qquad (18)$$

where V_0 is a target score vector of a prescription or a disease; V_1 and V_2 are the target score vectors after the first and second iterations; N denotes the total number of targets; M is a symmetric adjacency stochastic matrix which denotes target interaction network; $\alpha \in (0, 1)$ is a constant representing the importance of the network while ranking targets. With target score vector V_p of a TCM prescription and target interaction matrix M, PageRank score vector V_{rank1} was achieved; with target score vector V_d of a disease and matrix M, PageRank score vector V_{rank2} was achieved; finally the average PageRank score vector V_{avg} was achieved.

2.3.4. Network cluster/subgroup analysis

Generally, a network can be analyzed from three different levels: individual, subgroup and whole network. Clusters/subgroups refer to highly interconnected regions distilled from different, complex objects with similar underlying properties. It is of great significance to divide the biological regulatory network into subgroups/clusters to analyze and identify key node groups. Currently, various methods have been reported to dissect the cluster/subcluster structure of networks. Some of these methods are graph theory-based (spectral dichotomy and Kernighan-Lin algorithm), such as sociological-based methods (-plexes, -cores, and maximal clique algorithms) and cluster-based methods (optimization correlation algorithms and similarity correlation methods) [68]. For example, Song et al. [69] conducted a cluster analysis on the network of Maxing Shigan Decoction in treating asthma, and found that it involved 5 functional clusters such as gene expression, silencing and replication, DNA/RNA damage repair and transcriptional regulation, and inflammatory immune response. Therefore, the cluster/subgroup analysis of CHM network pharmacology will help to identify active ingredient and key target groups for disease prevention and treatment.

Overall, the development of network analysis methodology is critically important for finding effective components in the discovery pipelines and generating systematic insights into the mechanism of action of CHM in the treatment of diseases.

2.4. Databases and web servers

2.4.1. Web servers for Gene Ontology enrichment and pathway analysis

Since TCM involves using multi-compound, multi-target agents, annotating their targets in the context of networks can help reveal its mechanisms of action. Gene Ontology resource (GO, https://geneontology.org) is the most comprehensive knowledge base concerning the functions of genes/targets. It provides three major categories of controlled terms for describing gene products: molecular function (activity of gene products at the molecular level), cellular component (location of gene product activity relative to biological structures), and biological process (larger biological programs that exploit gene molecular function) [70]. Identifying GO terms within a given gene list can provide a better understanding of the genes involved in these functions and further elucidate the

role of CHM in regulating genes involved in improving disease processes. Furthermore, pathway analysis has become the preferred choice for gaining insights into the underlying biology of differentially expressed genes and proteins. The action of drugs is not only related to target proteins, but also affected by the biological pathways of the target proteins, especially for multi-target CHM. Table 2 lists several web sources for GO enrichment and pathway analysis [71–76]. Among them, the Reactome knowledgebase provides molecular details of signal transduction, transport, DNA replication, metabolism and other cellular processes as an ordered network of molecular transformations in a single consistent data model [71]; and the STRING database aims to integrate all known and predicted associations between proteins, including both physical interactions and functional associations, which relies on the annotated proteomes maintained by Swiss-Prot (https://www.expasy.org/sprot/ and https://www.ebi.ac.uk/swissprot/) [72].

2.4.2. Databases for CHM network pharmacology

Network pharmacology is a new frontier that is becoming a paradigm for investigating the therapeutic mechanism of CHM from a systemic and molecular perspective. During the past five years, with the aid of cheminformatics and big data science, many high-quality databases have been curated to support CHM network pharmacology research and CHM repositioning. Some of the important databases are introduced in Table 3 [77–93]. From the citation metrics in Fig. 2, four specialized databases in network pharmacology were cited over 100 times. More importantly, the majority of them were built via curating TCMSP, a well-known database for CHM network pharmacology with 1346 citations as of the time of this writing. TCMSP includes 29,384 ingredients, 3311 targets and 837 associated diseases, as well as 12 ADME-related properties involving DB, DL, intestinal epithelial permeability and BBB, etc. [94]. The majority of them, however, suffer from common limitations, such as lack of experimental evidence in the cited literature, as well as lack of ingredient composition of CHM from high-performance liquid chromatography or mass spectrographic analysis. In addition, it is worth paying attention to how to reasonably analyze the large number of targets predicted from the databases. On the one hand, a goal of CHM network pharmacology is to predict the potential efficacy or disease spectrum of CHM, so further analysis of the whole genome predicted by CHM is appropriate; on the other hand, it is to explore the active ingredients and mechanism of action of CHM in the treatment of specific diseases, so focusing on drug targets is also needed. More importantly, these databases are slow to update, thereby lagging behind

the latest development of CHM research. Therefore, a more comprehensive and complete database with powerful web services is necessary and will more effectively promote the network pharmacology research of CHM.

3. Network pharmacology for mechanism elucidation of CHM against COVID-19

COVID-19 was initially reported at the end of 2019 and spread rapidly around the world. Hundreds of millions of lives have been affected during this pandemic [95], and the overwhelmed healthcare systems greatly impacted the global economy. As of January 16, 2022, there have been reported over 323 million confirmed cases and over 5.5 million deaths worldwide [96].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belongs to the same family of coronaviruses responsible for the severe acute respiratory syndrome in 2003 and Middle East respiratory syndrome in 2012 [97]. The emergence of SARS-CoV-2 variants is continuing to surge, causing a large number of virus replications. Since the outbreak, researchers are developing vaccines and targeted antiviral drugs. At the moment, vaccines are still one of the most important means to alleviate the COVID-19 pandemic. However, for some underdeveloped countries and regions, it remains difficult to achieve vaccination for the whole population. Thus, people are struggling to seek alternative ways to protect themselves from this virus or to reduce its severity.

The World Health Organization reported that > 80% of the world's population rely on herbal medicines (involving TCM, Persian medicine, and traditional Indian medicine) for a particular aspect of their primary health care needs. TCM has a long history and plays a unique role in the prevention and treatment of major infectious diseases. During the SARS epidemic in 2003, TCM was shown to provide remarkable therapeutic effects [98]. TCM was included in the Chinese guideline on diagnosis and treatment of COVID-19 since the beginning, and abundant clinical usage demonstrated that CHM exerted positive effects against COVID-19 through increasing the cure rate of Western medications, and decreasing severity and concomitant symptoms [99]. The national percentage of treating confirmed cases of COVID-19 patients with CHM-integrated therapy exceeds 90% with the support from over 4900 TCM practitioners all over China [100]. And modern pharmacological studies have shown that CHM was effective in clearing heat and toxicity, as well as in dispelling dampness, thereby inhibiting the virus [101]. In most cases, CHM inhibits the virus-mediated inflammatory response by regulating the immune func-

Table 2
Several web sources for GO enrichment and pathway analysis.

Web server	Website	Contents and main features	Reference
Reactome	https://reactome.org	Including molecular details of signal transduction, transport, DNA replication, metabolism, and other cellular processes as an ordered network of molecular transformations—an extended version of a classic metabolic map, in a single consistent data model.	[71]
STRING	https://string-db.org/	Aims to integrate all known and predicted associations between proteins, including both physical interactions and functional associations.	[2]
Gene Ontology Annotation Database	https://www.ebi.ac.uk/GOA	Including evidence-based GO annotations to proteins in the UniProt knowledgebase; supplies 368 million GO annotations to almost 54 million proteins in more than 480,000 taxonomic groups.	[73]
GOATOOLS	https://github.com/tanghaibao/goatools	A Python-based library, making it more efficient to stay current with the latest ontologies and annotations; performs gene ontology enrichment analyses to determine over- and under-represented terms, and organizes results for greater clarity and easier interpretation using a novel GOATOOLS GO grouping method.	[4]
PANTHER	https://pantherdb.org	A multifaceted data resource for classification of protein sequences by evolutionary history, and by function.	[75]
Metascape	https://metascape.org/	A web-based portal designed to provide a comprehensive gene list annotation and analysis resource for experimental biologists, including functional enrichment, interactome analysis, gene annotation, and membership search.	[76]

GO: Gene Ontology.

Table 3
Several representative databases for CHM network pharmacology research.

Database and web server	Website	Contents and main features	Reference
BATMAN-TCM	https://bionet.ncpsb.org/batman-tcm/	Including (1) ingredients' target prediction; (2) functional enrichment analyses of targets; (3) the visualization of ingredient-target-pathway/disease association network and KEGG pathway; (4) comparison analysis of multiple CHMs.	[77]
TCMIP (including ETCM)	https://www.tcmip.cn/TCMIP/index.php; https://www.nrc.ac.cn:9090/ETCM/	Including 403 herbs, 3962 formulae, 7274 herbal ingredients, 2266 validated or predicted drug targets, and 3027 related diseases.	[78]
TCMID	https://47.100.169.139:8000/tcmid/	Containing approximately 47,000 prescriptions, 8159 herbs, 25,210 compounds, 6828 drugs, 17,521 targets and 3791 diseases.	[79]
SymMap	https://www.symmap.org/	Focusing on TCM symptoms and their relationships to herbs and diseases.	[80]
NPASS	https://bidd2.nus.edu.sg/NPASS/	Providing 35,032 natural products, 25,041 species, 5863 targets; containing 222,092 natural product-target pairs and 288,002 natural product-species pairs.	[81]
TCM-Mesh	https://mesh.tcm.microbioinformatics.org/	Containing 6235 herbs, 383,840 compounds, 14,298 genes, 6204 diseases, 144,723 gene-disease associations, and a web-based software to construct a network between herbs and treated diseases.	[82]
CancerHSP	https://lsp.nwsuaf.edu.cn/CancerHSP.php	Including 2439 anticancer herbs, 2439 active compounds, and activity data based on 492 cancer cell lines.	[83]
TM-MC	https://informatics.kiom.re.kr/compound/	Including 536 medicinal materials, 14,492 compounds, and 24,154 links between them.	[84]
CMAUP	https://bidd2.nus.edu.sg/CMAUP/	Including 47,645 active ingredients against 646 targets in 234 KEGG pathways associated with 2473 gene ontologies and 656 diseases.	[85]
YaTCM	https://cadd.pharmacy.nankai.edu.cn/yatcm/home	Containing 6220 herbs, 47,696 herbal compounds, 18,697 targets, 1907 predicted targets, 390 pathways and 1813 prescriptions.	[86]
HERB	https://herb.ac.cn/	Linking 7263 herbs and 49,258 ingredients to 12,933 targets and 28,212 diseases, and providing six pairwise relationships among them.	[87]
TCMAnalyzer	https://www.rcdd.org.cn/tcmanalyzer	Allowing to (1) identify the potential compounds that are responsible for the bioactivities for a CHM through scaffold-activity relation search techniques, (2) investigate the molecular mechanism for a CHM at the systemic level, and (3) explore the potentially targeted bioactive herbs.	[88]
PharmDB-K	https://pharmdb-k.org	Containing 262 traditional medicines, 7815 drugs, 32,373 proteins, 3721 diseases, and 1887 side effects.	[89]
KampoDB	https://wakanmoview.inm.u-toyama.ac.jp/kampo/	Containing 42 traditional medicines, 54 drugs, 1230 compounds, 460 known targets, and 1369 potential targets, together with biological pathways and molecular function annotations.	[90]
TCMIO	https://tcmio.xielab.net/	Including the data of TCM on immuno-oncology.	[91]
DCABM-TCM	https://bionet.ncpsb.org.cn/dcabm-tcm/#/Home	Including 4206 blood constituents, 194 herbs and 192 prescriptions.	[92]
SuperTCM	https://tcm.charite.de/supertcm	Providing the information about 6516 CHMs with 5372 botanical species, 55,772 active ingredients against 543 targets in 254 KEGG pathways associated with 8634 diseases.	[93]

CHM: Chinese herbal medicine; KEGG: Kyoto encyclopedia of genes and genomes; TCM: traditional Chinese medicine.
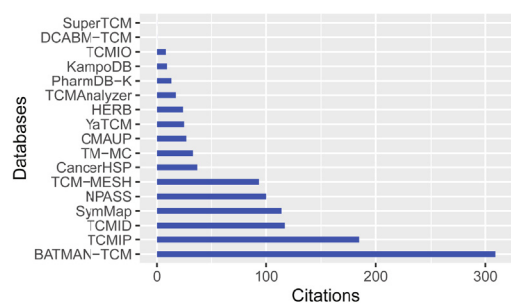

Fig. 2. The citation metrics of databases for Chinese herbal medicine (CHM) network pharmacology research and CHM repositioning. The citations were curated from Google Scholar on November 15, 2021.

tion of the body, which corresponds to the multi-target role of CHM in the overall regulation of the body's systems [102]. Despite the widespread use and promising results of CHM in clinical practice, proving its effectiveness via scientific trials and dissecting the molecular mechanisms are still big challenges.

There is increasing evidence indicating the reliability and effectiveness of network pharmacology in expanding the rationale and mechanism for the clinical efficacy of CHM against COVID-19 [103]. In this pandemic, three herbal formulas have been key players used during different COVID-19 stages. Yang et al. [104] performed network pharmacology combined with experimental study on Qingfei Paidu Decoction and Maxing Shigan Decoction

in treating COVID-19, revealing that the therapeutic effects against COVID-19 may be attributed to their anti-inflammatory effects via the thrombin and Toll-like receptor signaling pathway. Zhao et al. [105] also conducted a network pharmacological study to illustrate the immune regulation, anti-infection, anti-inflammation, and multi-organ protection mechanisms of Qingfei Paidu Decoction against COVID-19, and results showed that 88 high-confidence targets affected by SARS-CoV-2 infection of 12 active compounds in Qingfei Paidu Decoction were identified and involved in biological processes related with COVID-19 development, such as pattern recognition receptor signaling, interleukin signaling, cell growth and death, hemostasis, and injuries of the nervous, sensory, circulatory, and digestive systems. Zheng et al. [106] employed a network pharmacology approach and found that Lianhua Qingwen formula has the most relationship to the respiratory system, indicating specific effects in lung diseases, and modulates the inflammatory process, exerts antiviral effects and repairs lung injury. Moreover, it also relieves the "cytokine storm" and improves angiotensin-converting enzyme 2 (ACE2)-expression-disorder-caused symptoms. Ai et al. [107] performed network pharmacology on "Fei Yan No. 1," a specific formula against COVID-19 recommended by the Health Commission of Hubei Province, and revealed that it may exert antiviral and immune response-regulatory effects through multiple pathways, also affecting influenza A, hepatitis B, hepatitis C, Kaposi sarcoma-associated herpesvirus infection, human cytomegalovirus infection, viral carcinogenesis and human immunodeficiency virus 1 infection.

Notably, network pharmacology shows an immense advantage in the feasibility analysis of drug repositioning, especially in the analysis of CHM ingredients. Wang et al. [108] applied network pharmacology (integrated network proximity and network diffusion) to quantify the relationship between CHM ingredients' targets and COVID-19 disease targets in the protein–protein-interaction network, thereby predicting new anti-COVID-19 ingredients. Quercetin, luteolin, acacetin and kaempferol were screened as anti-COVID-19 candidates. Other CHM ingredients such as berberine [109], emodin [110], astragaloside IV [111], matrine [112], puerarin [113], glycyrrhizic acid [114], hesperidin, isorhaponti-genin and gallocatechin-7-gallate [115] were also repurposed as therapeutic candidates against COVID-19 based on network pharmacology analysis (Fig. 3), and some typical compounds (berberine, emodin and glycyrrhizic acid, etc.) have been validated by molecular docking and dynamics simulation as potential inhibitors for different proteins of SARS-CoV-2 or a drug in treating COVID-19 cytokine storm [116–118]. In preclinical explorations on cell or animal models, luteolin, quercetin, emodin, glycyrrhizic acid, hesperidin, isorhapontigenin and gallocatechin-7-gallate have been successfully validated to block the SARS-CoV-2 replication or the spike protein and ACE2 interaction [115,119].

Although network pharmacology research on CHM against COVID-19 is expanding, there are still many limitations that need to be discussed and resolved [99]. For example, the CTIs obtained by database-based strategy should be experimentally validated. TCM as adjunctive therapy to Western medication remains the mainstream treatment of COVID-19 in China, so a systematic network-based model should be built to better understand how integrated Chinese and Western medicine works together. Last but not least, it is necessary to combine network pharmacology-based identification, experimental validation and clinical data.

4. Concluding remarks

Network pharmacology presents an immense scope for exploring traditional knowledge to find solutions for the modernization of TCM. In this review, we mainly introduced many pioneering explorations on active compound identification, CTI prediction and network topology analysis embedded in the workflow of network pharmacology as well as specialized databases, thereby providing reference for deciphering the exact mechanisms of CHM against diseases. The spotlight of network pharmacology in the mechanistic investigation and repositioning of CHMs against COVID-19 was also discussed.

Recently, the first international standard for evaluating network pharmacology—"Network Pharmacology Evaluation Method Guidance" (2021) was released by the World Federation of Chinese Medicine Societies, to promote more standardized implementation of network pharmacology by result verification from the perspective of computer models, experimental models, and clinical data [120]. From this, we conclude that (1) the best future direction for network pharmacology is to integrate the post-network analysis (e.g., molecular docking and simulation) and the experimental and clinical data, such as analytic and multi-omics data; (2) the reliability and repeatability of the network pharmacology results should be improved; (3) more robust computing algorithms/softwares should be developed for the systematic screening, integration, and processing of data on various compounds, genes, and proteins; (4) the specialized database development with high data quality and quantity along with constant updating and regulation is very necessary. Collectively, by integrating reductionist and systems approaches as well as computational and experimental methods, network pharmacology will accelerate the modernization process of TCM in the future.
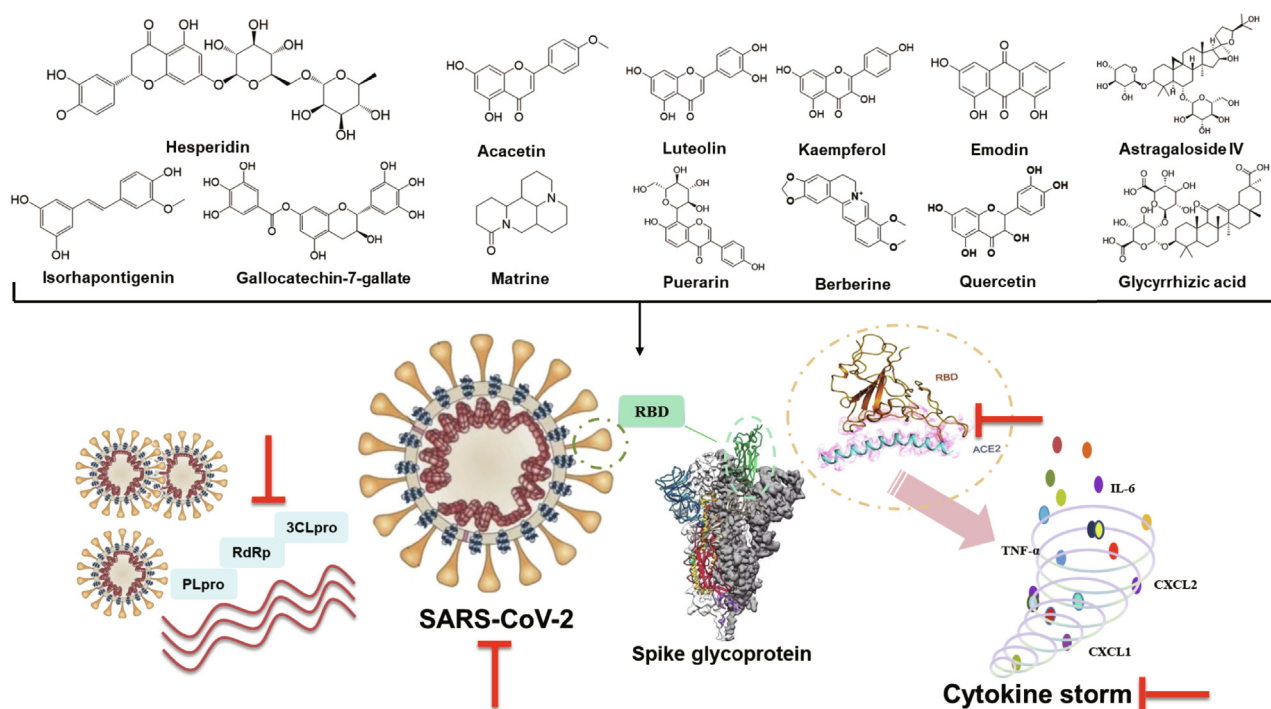

Fig. 3. Rich resources of Chinese herbal medicine ingredient repositioning via network pharmacology for coronavirus disease 2019 treatment mainly targeting SARS-CoV-2 replication, ACE2 receptor and/or cytokine storm. ACE2: angiotensin-converting enzyme 2; 3CLpro: 3-chymotrypsin-like protease; CXCL: chemokine (CXC motif) ligand 1; IL-6: interleukin-6; PLpro: P-like protease; RBD: receptor-binding domain; RdRp: RNA-dependent RNA polymerase; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; TNF-α: tumor necrosis factor-α.

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Authors' contributions

SJY and YPT conceived of and proposed the idea. SJY and YXW designed the study. YXW, ZY and WXW reviewed the literature. SJY, YXH, QZ, JJL and YPT contributed to writing, revising and proof-reading the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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