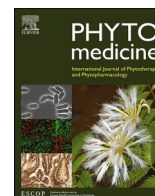




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Review

A review on computational approaches that support the researches on traditional Chinese medicines (TCM) against COVID-19

Chattarin Ruchawapol^{a,b}, Wen-Wei Fu^{a,b,*}, Hong-Xi Xu^{a,b,*}

^a School of Pharmacy, Shanghai University of Traditional Chinese Medicine, Cai Lun Lu 1200, Shanghai 201203, China

^b Engineering Research Centre of Shanghai Colleges for TCM New Drug Discovery, Cai Lun Lu 1200, Shanghai 201203, China



ARTICLE INFO

Keywords:

Computational approaches
Traditional Chinese Medicine (TCM)
Structure-based approach
Knowledge-mining
Network-based approach

ABSTRACT

Background: COVID-19 highly caused contagious infections and massive deaths worldwide as well as unprecedentedly disrupting global economies and societies, and the urgent development of new antiviral medications are required. Medicinal herbs are promising resources for the discovery of prophylactic candidate against COVID-19. Considerable amounts of experimental efforts have been made on vaccines and direct-acting antiviral agents (DAAs), but neither of them was fast and fully developed.

Purpose: This study examined the computational approaches that have played a significant role in drug discovery and development against COVID-19, and these computational methods and tools will be helpful for the discovery of lead compounds from phytochemicals and understanding the molecular mechanism of action of TCM in the prevention and control of the other diseases.

Methods: A search conducting in scientific databases (PubMed, Science Direct, ResearchGate, Google Scholar, and Web of Science) found a total of 2172 articles, which were retrieved via web interface of the following websites. After applying some inclusion and exclusion criteria and full-text screening, only 292 articles were collected as eligible articles.

Results: In this review, we highlight three main categories of computational approaches including structure-based, knowledge-mining (artificial intelligence) and network-based approaches. The most commonly used database, molecular docking tool, and MD simulation software include TCMSP, AutoDock Vina, and GROMACS, respectively. Network-based approaches were mainly provided to help readers understanding the complex mechanisms of multiple TCM ingredients, targets, diseases, and networks.

Conclusion: Computational approaches have been broadly applied to the research of phytochemicals and TCM against COVID-19, and played a significant role in drug discovery and development in terms of the financial and time saving.

Introduction

COVID-19, the disease caused by the novel coronavirus SARS-CoV-2, caused a global emergency shortly since the late December 2019 (Chitsike and Duerksen-Hughes, 2021; Hu et al., 2021a). As vaccines for COVID-19 have been developed and tested for their efficacy and long-term adverse effects, the latest emerging COVID-19 variant named

Omicron may cause the existing vaccines to be less effective due to its heavily mutated species. Moreover, there is no guaranteed for all vaccinated people to be totally protected, so both direct-acting antiviral agents (DAAs) and vaccines are developed to restrain the spreading of COVID-19. The provided outcomes have not reached satisfaction, and the urgent development of new antiviral medications are required.

Computational approaches are effective strategies in the process of

Abbreviations: TCM, Traditional Chinese medicine; CADD, Computer-aided drug design; AI, Artificial Intelligence; MD, Molecular dynamics; MOA, Mechanism of action; ADMET, Absorption, distribution, metabolism, excretion, and toxicity; QSAR, Quantitative structure–activity relationship; HTVS, High-Throughput virtual screening; SBDD, Structure-based drug discovery; MM/PBSA, Molecular Mechanics Poisson-Boltzmann Surface area; MM/GBSA, Molecular Mechanics Generalized Born Surface area; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; PPI, Protein-protein interaction; MXSGD, Maxing Shigan Decoction; LHQWC, Lianhua Qingwen Capsule; QFPDT, Qingfei Paidu Tang; SPR, Surface plasmon resonance; GTM, Generative Topographic Mapping; DL, Deep learning; KG, Knowledge graph; ML, Machine Learning; OB, Oral bioavailability; CNN, Convolutional neural network; NCEs, New chemical entities.

* Corresponding authors at: School of Pharmacy, Shanghai University of Traditional Chinese Medicine, Cai Lun Lu 1200, Shanghai 201203, China.

E-mail addresses: fuwenwei@shutcm.edu.cn (W.-W. Fu), hxxu@shutcm.edu.cn (H.-X. Xu).

<https://doi.org/10.1016/j.phymed.2022.154324>

Received 21 February 2022; Received in revised form 23 June 2022; Accepted 5 July 2022

Available online 6 July 2022

0944-7113/© 2022 Elsevier GmbH. All rights reserved.

drug discovery and development, and computational methods and tools have grown exponentially in recent decades with the dramatic increase in the availability of computational resources (Tiwari and Singh, 2022). Much of the research effort has focused on the drug discovery against COVID-19 by exclusively computational or computer-aided experimental method, and a commercially available drug named PF-07321332 has been designed and optimized as an orally bioavailable SARS-CoV-2 main protease inhibitor (Owen Dafydd et al., 2021). Medicinal herbs are promising resources for drug discovery because of its favorable efficacy and acceptable toxicity, which can become prophylactic candidate against COVID-19 (Huang et al., 2020; Li et al., 2022a). Recent studies showed that some phytochemicals have been developed as the potential anti-COVID-19 drugs by the computer-aided experimental method (Bharadwaj et al., 2021; Gopinath et al., 2020; Huang et al., 2020; Pamuru et al., 2020; Verma et al., 2020).

Traditional Chinese medicine (TCM) has a long history for over thousands of years of accumulated clinical evidence and pharmacological studies (Gao et al., 2019), and exerts an important role in the prevention and treatment of the COVID-19 caused by SARS-CoV-2 (Lyu et al., 2021; Yang et al., 2020; Zhao et al., 2021d). TCM preparations include extracts from a single source of plants, animals, minerals and their preparations and preparation of TCM formulas. Multicomponent therapeutic formulae are the most important and are most commonly used in TCM for clinical applications. However, the formulae sometimes are very complex which makes it mandatory to use systematic research supported by computational methods to elucidate their mechanism of action.

In the manuscript, the computational approaches employed in the research of TCM against COVID-19 have been reviewed, and scientific literature with valid experiment and comprehensive studies combining computational investigation will be included in this review until 31st January 2022. The general procedure of computational approaches had been summarized in the Fig. 1.

Materials and methods

A systematic review has been prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and followed the inclusion of relevant studies. The literature search was conducted in the databases: PubMed, Science Direct, ResearchGate, Google Scholar, and Web of Science for published articles. The keyword ‘COVID-19’ was paired with ‘Traditional Chinese medicine’, ‘traditional herb’, ‘natural products’, ‘active components’, ‘in

silico, ‘computational approaches’, ‘ADMET’, ‘structure-based’, ‘molecular docking’, ‘molecular dynamics simulation’, ‘ligand-based’, ‘QSAR’, ‘pharmacophore’, ‘generative neural network model’, ‘chemical cartography’, ‘chemography approaches’, ‘knowledge mining’, ‘artificial intelligence’, ‘machine learning methods’, ‘deep learning approaches’, ‘computer-aided drug design’, ‘system pharmacology’, and ‘network pharmacology’ to obtain published records until 31st January 2022. Boolean search strategies were used on these keywords without any language restrictions. Data inclusion criteria included (a) the focus of this study is on COVID-19 pandemic disease, and (b) the articles about natural products and/or TCM derivatives conducting *in silico* with experimental validation were included. Exclusion criteria included (a) any data duplication, titles, or content that did not meet the inclusion criteria, (b) reports on antiviral activities of natural products or their derivatives against other diseases, and (c) studies that involved synthetically conventional chemicals, which were not originated from natural sources.

A search conducted in scientific databases (PubMed, Science Direct, ResearchGate, Google Scholar, and Web of Science) found a total of 2172 articles, which were retrieved via web interface of the following websites. After applying some inclusion and exclusion criteria and full-text screening, only 292 articles were collected as eligible articles and displayed in pie charts. All of the extracted information was thoroughly checked by all authors to reach an agreement.

Databases and research resources that support research on TCM against COVID-19

Over the past decades, TCM has promoted its system biology and various data integration in order to modernize and internationalize its concept (Xu et al., 2021a). Several databases have been developed, such as TCMSP (<https://tcmsp-e.com/>), TCMIP (www.tcmip.cn), BATMAN-TCM (<http://bionet.ncpsb.org.cn/batman-tcm/>), ETCM (www.tcmip.cn/ETCM), SymMap (www.symmap.org), TCMID (<http://bidd.group/TCMID/>), TCMATCOV (<http://tcmatcov.bbtml.com/>), and TCM database@Taiwan (tcm.cmu.edu.tw), etc. Keywords “Traditional Chinese Medicine” and “COVID-19” were paired with each database and found a total of 105 cited databases. These data were screened, and pie chart in Fig. 2 was illustrated. The most popular database is TCMSP, which constitutes 44% among all that support research on TCM against COVID-19. TCMIP (11%), BATMAN-TCM (9%), ETCM (9%), SymMap (7%), TCMID (6%), TCMATCOV (5%), TCM database@Taiwan (5%), and other databases (4%) are also applied in the research of TCM

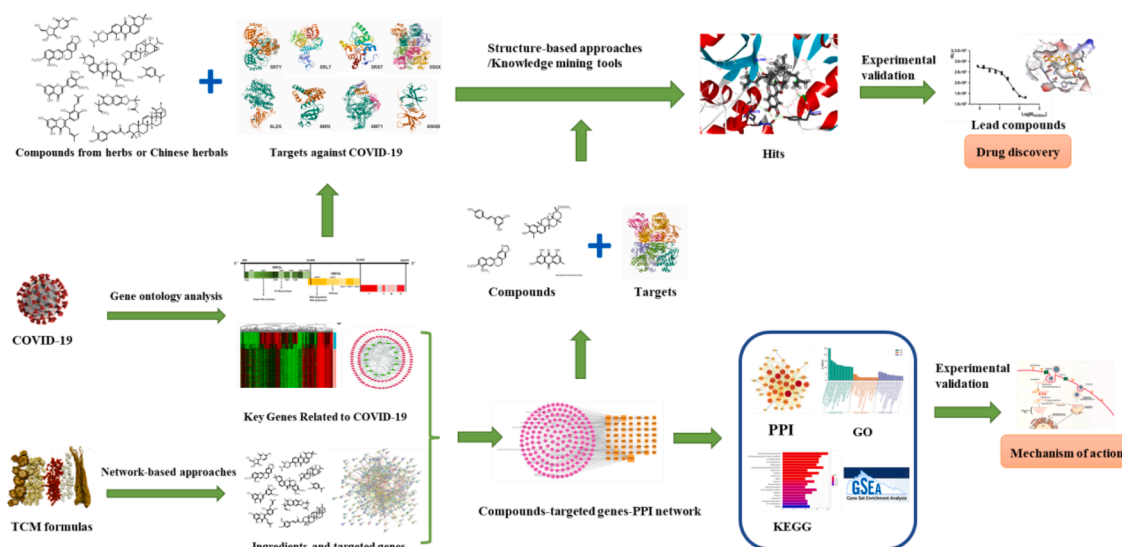


Fig. 1. General Procedure of Computational Approaches.

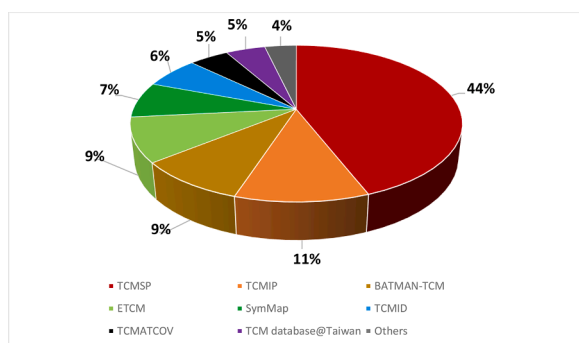


Fig. 2. Databases Supporting TCM Research against COVID-19.

against COVID-19.

The results shows that TCMSp (System pharmacology-based traditional Chinese medicine) is the most popular database, which includes chemicals, targets and drug-target networks, and associated drug-target-disease networks, as well as pharmacokinetic properties for natural compounds to understand the relationships between drugs, targets and diseases (Ru et al., 2014).

Structure-based approaches

Structure-based drug discovery (SBDD) methods have been used in numerous pharmaceutical industries and by medicinal chemists to assess binding energy between protein and ligand interactions as well as conformational changes of the receptor during in complex with a ligand (Kalyaanamoorthy and Chen, 2011). Structure-based approaches usually includes the target structure-based approach and ligand structure-based approach, which will be discussed in the next section of this review.

Target structure-based approach

Target structure-based approach involves target protein structure analysis, molecular docking, and molecular dynamics (MD) simulations. These help researchers to understand disease at a molecular level, specifically identify lead molecules and their optimization in a fast pace (Lionta et al., 2014). Essential steps of SARS-CoV-2 replication cycle have been investigated mainly on S protein, ACE2, TMPRSS2, Mpro, PLpro, RdRp, and other non-structural proteins as described in the previous viral targeted discovery section. The majority of virtual docking programs and databases are used to repurpose potential approved, preclinical, experimental drugs, and natural products. The commonly used docking tools are AutoDock, AutoDock Vina, GOLD, CDOCKER, FlexX, Surflex, G, DOCK6, and SwissDock (Gurung et al., 2021). Following the results of molecular docking, free energy perturbations and binding models are intensively determined using MD software packages including GROMACS, AMBER, CHARM, NAMD, Desmond, Tinker, LAMMPS, and DL_POLY (Gurung et al., 2021). The main objectives of using these tools are to find effective therapeutics for those who are seriously infected by SARS-CoV-2. Target structure-based approach will be further discussed.

Potential targets against COVID-19

SARS-CoV-2 genome consists of nearly 30,000 RNA bases and 29 encoded proteins functioning as host invasion and vital replication. Therefore, successfully inhibiting these target proteins can result in therapeutic actions. The genetic variability of 58 coronaviruses have been assessed in order to determine broad spectrum antivirals (Yazdani et al., 2021). A public web portal named SARS-CoV-2 pocketome was established for displaying 3D structures of 15 SARS-CoV-2 proteins, and

19 putative drug binding sites were mapped on these structures. Scientists can analyze their binding sites of interest for future SBDD efforts. CADD targeting key coronaviral proteins will be summarized with tools using computational modeling.

Three main functional categories of viral proteins include attachment and penetration into host cells, viral replication and transcription, and suppression of the host immune response. To better understand the replicative and host invasive mechanisms of SARS-CoV-2, structure-based drug discovery plays a significant role in rapid determination of many viral protein structures. Several highlighted *in silico* studies covers major targets against COVID-19, which was illustrated in Fig. 3.

Docking tools

Molecular docking is popular for identification of potential drug candidates or ingredients in TCM prescriptions. Keywords “Traditional Chinese Medicine” and “COVID-19” were paired and found a total number of 107 cited docking tools listed in Table 1. These data were screened, and pie chart in Fig. 4 was illustrated. The most popular docking tool is AutoDock Vina, which constitutes 42% among all that support research on TCM against COVID-19. GLIDE (19%), AutoDock (17%), MOE (11%), SwissDock (5%), GOLD (3%), and COVID-19 Docking Server (3%) are also applied in the research of TCM against COVID-19 Table 2.

The results shows that AutoDock Vina is the most popular docking tool in the target structure-based approach. AutoDock Vina is an open-source molecular docking program, which can virtually pre-calculate grid maps without any requirements on choosing atom types because it calculates the grids internally and instantly for the atom types that are needed (Trott and Olson, 2010).

Molecular dynamics simulations

MD simulations can obtain comprehensive information about drug target dynamics and potential ligand interactions. These are several most commonly used softwares for MD calculations: AMBER (Case et al., 2005; Song et al., 2019), YASARA (Land and Humble, 2018), GROMACS (Groningen Machine for Chemical Simulation) (Selvaraj et al., 2021b), VMD (Visual Molecular Dynamics) (Umesh et al., 2021), CHARMM (Chemistry at Harvard molecular mechanics) (Brooks et al., 2009), NAMD (Gyebi et al., 2020; Lee et al., 2016), Desmond (Patel et al., 2021), and Tinker (Sawant et al., 2021). Keywords “Traditional Chinese Medicine” and “COVID-19” were paired and found a total number of 80 cited MD simulation software. These data were screened, and pie chart in Fig. 5 was illustrated. The most popular MD simulation software is GROMACS, which constitutes 22% among all that support research on TCM against COVID-19. Desmond (20%), AMBER (17%), CHARMM (15%), YASARA (10%), VMD (8%), NAMD (5%), and Tinker (3%) are also applied in the research of TCM against COVID-19.

The results shows that GROMACS is the most popular MD software in supporting with the research of TCM against COVID-19 facilitate the potential drug discovery and target identification

Examples of active compounds derived from TCM by structure-based approaches

We briefly review some hit natural products that have been further investigated for experimental validation using structure-based approaches. Several natural compounds have been evaluated for their activity against SARS-CoV-2 S protein, 3CL^{pro} and PL^{pro} in virus-infected cells as shown in Tables 3–5.

ACE2 (S protein) inhibitors

Viral attachment and entry are of particular interest therapeutic targets in the life cycle of viruses. SARS-CoV-2 use the receptor-binding

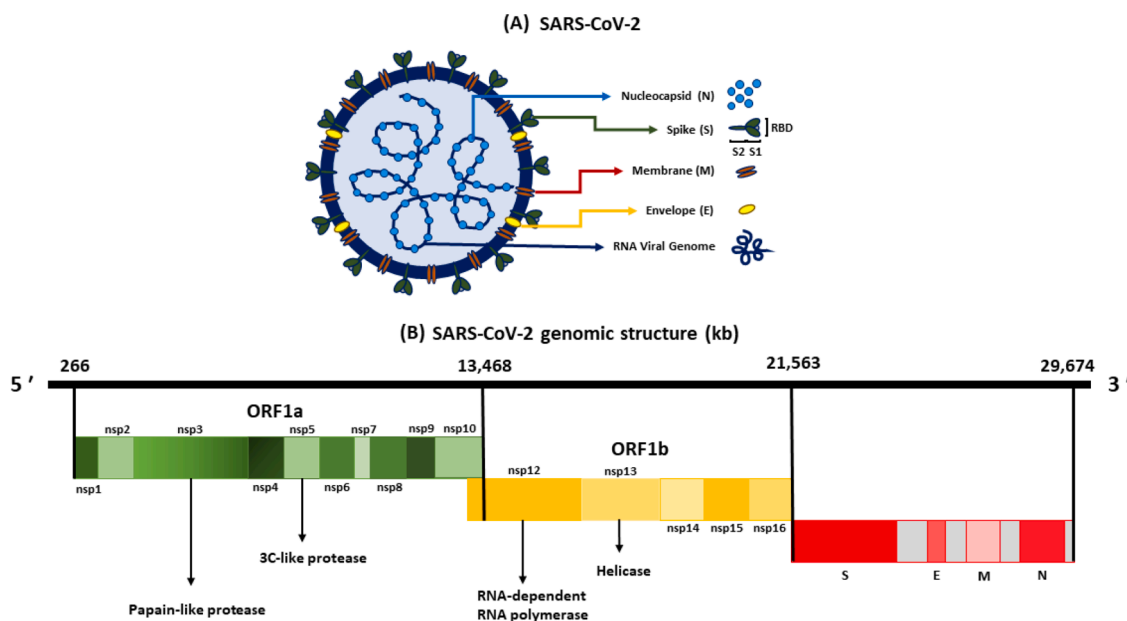


Fig. 3. Structure of SARS-CoV-2. (A) Schematic representation of the structure of SARS-CoV-2. It has four structural proteins, S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins; the N protein holds the single strand, positive-sense RNA genome, and the S, E, and M proteins together create the viral envelope. (B) SARS-CoV-2 genomic structure.

domain (RBD) of its glycosylated S protein to bind to human angiotensin converting enzyme 2 (hACE2) and initiate membrane fusion and virus entry. Hence, the inhibitor of the RBD–hACE2 protein–protein interaction (PPI) can disrupt infection efficiency (Bojadzic et al., 2021). Some natural compounds isolated from natural extracts are listed in Table 3 as the ACE2 (S protein) protein inhibitors.

Here is a detailed example by structure-based approaches: Elebeedy et al. reported four major active compounds against SARS-CoV-2 S protein, which are tanshinone IIA and salvianolic acid B from TCM herb *Salvia miltiorrhiza* and carnosic acid and rosmarinic acid from *Rosmarinus officinalis* (Elebeedy et al., 2021). Molecular docking and MD simulation studies have been performed on all four compounds and showed promising anti-SARS-CoV-2 binding affinities. Therefore, to validate the computational model, the activity of these compounds was further conducted *in vitro* using plaque reduction assay and MTT assay on Vero E6 cells for IC_{50} and CC_{50} values, respectively. The promising activity of Tanshinone IIA, carnosic acid, rosmarinic acid, and salvianolic acid B ranged as following from lowest to highest with IC_{50} of 4.08, 15.37, 25.47, and 58.29 ng/ μ l. All compounds demonstrated no significant cytotoxic effects on Vero E6 cells.

Chymotrypsin-like (3CL^{pro}) inhibitors

SARS-CoV-2 3CL^{pro} (M^{pro}) is well known to be ideal target for treating COVID-19, and several natural products from different sources including TCM herbs and formulas have potential antiviral activities on the main protease. Some natural compounds isolated from natural extracts are listed in Table 4 as the M^{pro} inhibitors.

One study has screened 1920 natural products and identified two anti-SARS-CoV-2 compounds, namely ginkgolic acid and anacardic acid (Chen et al., 2021c). Both demonstrated similar IC_{50} values of 1.79 and 2.07 μ M, respectively. No significant cytotoxicity effects were observed at 20 μ M for ginkgolic acid and anacardic acid. Simultaneously, these two hits can block SARS-CoV-2 replication at nontoxic concentration of 15 μ M in a viral plaque reduction assay. Epigallocatechin gallate (EGCG), an active ingredient in TCM commonly known as green tea was a promising inhibitor of SARS-CoV-2 M^{pro} (Du et al., 2021).

Papain-like protease (PL^{pro}) inhibitors

Papain-like protease (the phosphatase domain of nsp3) is believed to interfere with the immune response by acting as a ADP-ribose phosphatase to remove ADP-ribose from host proteins and RNAs, and then is the therapeutic target against COVID-19 (Freitas et al., 2020; Klemm et al., 2020; Shin et al., 2020). Some natural compounds isolated from natural extracts are listed in Table 5 as the PL^{pro} inhibitors.

One study further investigated numerous natural PL^{pro} inhibitors from the phytochemical library named national compound library of traditional Chinese medicines (NCLTCMs), which contained more than 9000 TCM compound derivatives and proved with valid experiment of fluorogenic enzymatic and Pro-ISG15 cleavage assays (Li et al., 2022b). The total of nine natural hits, namely amentoflavone, ginkgetin, isoginkgetin, sciadopitysin, morelloflavone, podocarpusglavone, hinokiflavone, cryptomerin B, and 4'-O-methylchnaflavone demonstrated effective PL^{pro} inhibitors with anti-proteolytic activity and IC_{50} ranging from 9.5 to 43.2 μ M in the enzymatic assay. Moreover, this study was reported for the first time that 4'-O-methylchnaflavone exhibited promising inhibitory effects on both proteolytic and deISGylation activities of SARS-CoV-2 PL^{pro}. This natural product remarkably suppressed PL^{pro}-induced deISGylation at decreased concentration of 2.5 μ M with 60.7% inhibition rates. Pitsillou et al. performed enzymatic inhibition assay of natural hits namely hypericin, rutin and cyanidin-3-O-glucoside, which are small molecules SARS-CoV-2 PL^{pro} inhibitors at 100 micromolar range (Pitsillou et al., 2021). These natural compounds were screened from OliveNet™ library, subjected to molecular docking using the selective PL^{pro} inhibitor, GRL-0617, as control, and further implemented MD simulation at 100 μ s prior to *in vitro* evaluation. In another study, cryptotanshinone and tanshinone I, two active components in TCM herb named *Salvia miltiorrhiza*, were identified as top PL^{pro} inhibitors with IC_{50} = 5.63 and 2.21 μ mol/L, respectively (Zhao et al., 2021b). Both compounds were performed using qRT-PCR analysis, immunofluorescence microscopy, plaque-reduction, and cytotoxicity assays using a clinical isolate of SARS-CoV-2 (nCoV-2019BetaCoV/Wuhan/WIV04/2019) infected Vero E6 cells. EC_{50} was of 0.70 and 2.26 μ mol/L for cryptotanshinone and tanshinone I, respectively, for a plaque-reduction assay. This means that the penetration of viral cellular membrane by these two hits created access to the

Table 1
Docking tools that support research of TCM against COVID-19.

Docking tools	Website	Description	License	Refs.
AutoDock	https://autodock.scripps.edu/	Automated docking tools for predicting the binding between substrates (ligand) and a known 3D structural receptor (protein)	Free	Abd El-Mageed et al. (2021), Gentile et al. (2020), Huang et al. (2021), Li et al. (2021a), Mazzini et al. (2020), Morris et al. (2008), Mu et al. (2021), Niu et al. (2021), Prasanth et al. (2021), Saidijam et al. (2021), Sivaraman and Pradeep, 2020), Vardhan and Sahoo, 2022), Wang et al. (2021b), Xia et al. (2020), Xiong et al. (2020), Yu et al. (2020), Zhang et al. (2020), Zhao et al. (2020b)
AutoDock Vina	https://vina.scripps.edu/	An open-source program with more accurate binding mode of predictions compared to AutoDock	Free	Alhadrami et al. (2021), Arora et al. (2020), Beirami et al. (2020), Bharadwaj et al. (2020), Bung et al. (2021), Gao et al. (2020), Gentile et al. (2020), Gu et al. (2021), Guo et al. (2020), Hasan et al. (2022), Huynh et al. (2020), Khuntia et al. (2021), Li et al. (2021a), Liao et al. (2021), Liu et al. (2021a), Mazzini et al. (2020), Mu et al. (2021), Murugan et al. (2021), Peng et al. (2020), Prasanth et al. (2021), Rajpoot et al. (2021), Ram et al. (2021), Ruan et al. (2020), Shree et al. (2022), Simayi et al. (2022), Singh et al. (2022), Sinha et al. (2021a), 2020), Trott and Olson, 2010), Vardhan and Sahoo, 2022), Wang et al.

Table 1 (continued)

Docking tools	Website	Description	License	Refs.
				(2021b), Wei et al. (2020), Wu et al. (2021a, 2021b), Xia et al. (2020), Xie et al. (2021b), Xu et al. (2021b), Ye et al. (2020), Ye et al. (2021), Yu and Li, 2022), Zackria et al. (2022), Zhang et al. (2020), Zhao et al. (2020b,), 2021c), Zheng et al. (2020)
COVID-19 Docking Server	https://ncov.schanglab.org.cn/	A web server for predicting the interaction between small molecules, peptides and antibodies and COVID-19 protein targets	Free	Cai et al. (2021), Chen et al. (2020), Kong et al. (2020b)
GLIDE	https://www.schrodinger.com/products/glide	A ligand-receptor docking program from HTVS to SP to XP at high accuracy levels	Commercial	Chen et al. (2021b), Chikhale et al. (2021a,2021b), Dutta et al. (2021), Emirik, 2022), Fathy et al. (2020), Kumar et al. (2022), Li et al. (2021b), Liao et al. (2021), Liu et al. (2021b), Mahmud et al. (2021), Mei et al. (2021), Rakib et al. (2020), Selvaraj et al. (2021a, 2021b), Shah et al. (2021), Shawky et al. (2020), Shree et al. (2022), Sinha et al. (2021b), Zhao et al. (2021a)
GOLD	https://www.ccdc.cam.ac.uk/solutions/cs-d-discoverly/Components/Gold/	A protein-ligand docking software with optimized scoring functions for drug discovery	Commercial	Nawrot-Hadzik et al. (2021), Tejera et al. (2022), Verdonk et al. (2003)
MOE	https://www.chemcomp.com/Products.htm	A comprehensive package for visualizing, modeling, and simulating computer aided molecular design of small molecules,	Commercial	Chikhale et al. (2021a), Elebeedy et al. (2021), Han et al. (2020), Liao et al. (2021), Rauf et al. (2021), Saidijam et al. (2021), Tahir UI Qamar et al.

(continued on next page)

Table 1 (continued)

Docking tools	Website	Description	License	Refs.
		peptides, and biologics		(2020), Vilar et al. (2008), Wang et al. (2020), Wei et al. (2020), Yu et al. (2021), Zaki et al. (2021)
SwissDock	http://www.swissdock.ch/	A web server for predicting the interaction between a target protein and small molecule	Free	Arora et al. (2020), Chen et al. (2021a), Grosdidier et al. (2011), Kong et al. (2020a), Rajpoot et al. (2021), Zhang et al. (2021b)

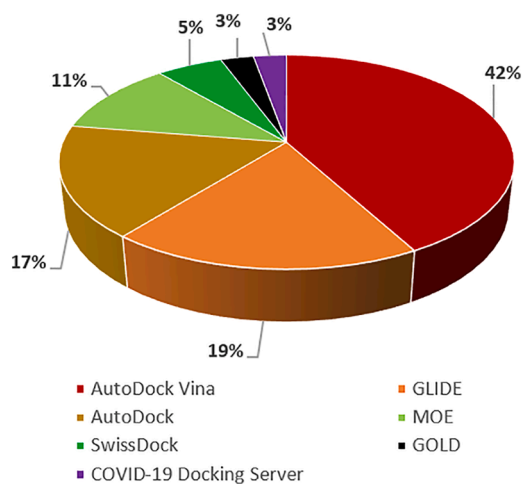


Fig. 4. Docking Tools Supporting TCM Research against COVID-19.

PLpro target.

Ligand structure-based approaches

In this section, the application of traditional ligand-based methods and knowledge mining approaches will be discussed. This can exploit and lead to the experimental drug discovery for COVID-19. We highlight the utility of some recent innovative techniques such as Generative Topographic Mapping (GTM) and deep learning (DL) for the discovery of novel DAA agents.

Chemical cartography or chemography approaches

Chemical cartography or chemography approaches, allows visual analysis of an ensemble of chemical structures encoding vectors of molecular descriptors, which can project extremely complex data onto a 2D chemical space map (Gaspar et al., 2015). This method utilizes the neighborhood behavior principle, which suggests that close-proximity compounds have similar chemical properties, so chemical space maps can relate to structural-activity relationship (SAR) studies. Joshi et al. conceptualized the key druggable parameters of chemical space and analyzed molecular similarity on already identified phytochemicals in COVID-19 (Joshi et al., 2021). Chemical space exploration using key parameters including MW, TPSA, number of rotational bonds (nROTB), hydrogen bond donors (nHBDdon) and acceptors (nHBAcc), and partition coefficient (AlogP) using Platform for Unified Molecular Analysis (PUMA) online server (Gonzalez-Medina and Medina-Franco, 2017).

Table 2

MD simulation software that support research of TCM against COVID-19.

Docking tools	Website	Description	License	Refs.
AMBER	https://ambermd.org/	A package of biomolecular simulation software including MM force fields and MD simulations	Free	Case et al. (2005), Chikhale et al. (2021a, 2021b), Dutta et al. (2021), Gentile et al. (2020), Gopinath et al. (2020), Liao et al. (2021), Liu et al. (2021a), Murugan et al. (2021), Shree et al. (2022), Wang et al. (2020, 2021b), Wang et al. (2020), Wei et al. (2020), Ye et al. (2020)
YASARA	http://yasara.org/	A molecular-graphics, modeling, and simulation program for visualizing bioinformatics	Proprietary	Dutta et al. (2021), Gentile et al. (2020), Land and Humble, 2018), Mahmud et al. (2021), Patel et al. (2021), Shree et al. (2022), Swargiary et al. (2020), Xinqiang et al. (2020)
GROMACS	http://www.gromacs.org/	An MD package for complex bonded interactions including proteins, lipids, and nucleic acids, as well as polymers	Free	Abraham et al. (2015), Chen et al. (2021a), Elekofehinti et al. (2021), Khuntia et al. (2021), Mazzini et al. (2020), Prasanth et al. (2021), Rajpoot et al. (2021), Selvaraj et al. (2021b), Sinha et al. (2020), ul Qamar et al. (2020), Vardhan and Sahoo, 2022), Wu et al. (2021b), Xie et al. (2021a, 2021b), Ye et al. (2020), Zackria et al. (2022), Zaki et al. (2021), Zhao et al. (2021c)
VMD	http://www.ks.uiuc.edu/	A molecular visualization program	Proprietary and free	Abd El-Mageed et al. (2021),

(continued on next page)

Table 2 (continued)

Docking tools	Website	Description	License	Refs.
	Research/vmd/	supporting large biomolecular systems using 3-D graphics and built-in scripting		Alhadrami et al. (2021), Humphrey et al. (1996), Khuntia et al. (2021), Vardhan and Sahoo, 2022, Zaki et al. (2021)
NAMD	http://www.ks.uiuc.edu/Research/namd/	A parallel MD code designed for high-performance simulation of large biomolecular systems using the setup and trajectory analysis of VMD program	Proprietary and free	Abd El-Mageed et al. (2021), Alhadrami et al. (2021), Huynh et al. (2020), Phillips et al. (2005)
CHARMM	http://www.charmm.org/	A biomolecular simulation program with comprehensive set of energy functions, various enhanced sampling approaches as well as multi-scale techniques	Proprietary and commercial	Abd El-Mageed et al. (2021), Alhadrami et al. (2021), Arora et al. (2020), Brooks et al. (2009), Chen et al. (2021a), Huynh et al. (2020), Khuntia et al. (2021), Mazzini et al. (2020), Ram et al. (2021), Sinha et al. (2020), Zaki et al. (2021), Zhao et al. (2021c)
Desmond	https://www.deshawresearch.com/resources.html	A high-speed MD software suite on biological system with high performance and accuracy on NVIDIA GPU	Proprietary and commercial	(Abel et al. (2020), Alhadrami et al. (2021), Badraoui et al. (2022), Bharadwaj et al. (2020), Emirik, 2022), Gopinath et al. (2020), Hasan et al. (2022), Kumar et al. (2022), Li et al. (2021b), Patel et al. (2021), Ram et al. (2021), Shah et al. (2021), Shree et al. (2022), Şimşek et al. (2021), Singh et al. (2022), Vetrivel et al. (2021)
Tinker	https://dasher.wustl.edu/tinker/	A molecular modeling program for MM and MD	Proprietary	Mazzini et al. (2020), Rackers et al. (2018)

Table 2 (continued)

Docking tools	Website	Description	License	Refs.
		including several commonly used parameters for molecular design		

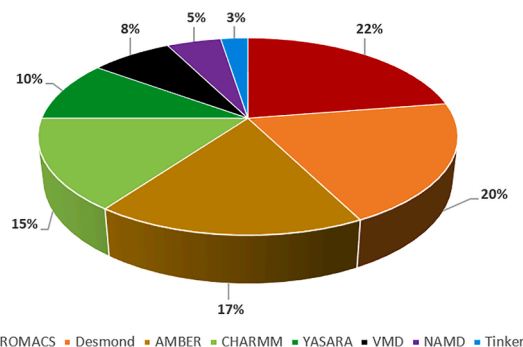


Fig. 5. MD Simulation Software Supporting TCM Research against COVID-19.

These parameters were used to compare potential hit compounds from *in silico*-based studies from natural sources against COVID-19, FDA approved drugs from natural products, and with FDA approved anti-infectives. A strong correlation of identified phytochemicals was observed and was further subjected to molecular docking and MD simulation.

Generative Topographic Mapping (GTM) is one of the most commonly used chemical space mapping (chemography) methods. It is a non-linear grid-based method, which can be used for visualizing data, modeling structural activity, and evaluating database comparison. The GTM algorithm has 2D smooth surface called manifold fitted into a high-dimensional descriptor space and subsequently projected molecules on 2D latent space superposed with a square grid of nodes (Lin et al., 2020a). The results of biological tests can be involved with a map through activity or classification landscapes, which can visualize the specific sites surrounded by molecules with a provided activity along with proximity-based classification of untested compounds (Bocci et al., 2020). In the past, there was no available experimental data for drug discovery against SARS-CoV-2, so information was mainly associated with related pathogens. Moreover, GTM was implemented for visualizing the interactive chemical space of natural product databases including ChemGPS-NP, COCONUT, D-Peptide Builder, and an intuitive online tool NP Navigator (Medina-Franco et al., 2021; Sorokina et al., 2021; Zabolotna et al., 2021). These are open-source and easily accessible tools and websites to calculate molecular descriptors and interpret chemical space notion of small molecules derived from natural product. Zabolotna et al. introduced the Natural Product Universal map (NP-U-map) and obtained density landscape of natural products from COCONUT to support the investigation of natural product chemical space (Zabolotna et al., 2021). The ISIDA descriptors have also been used to explore the chemical space of natural product. MinHashed Atom Pair fingerprint with diameter of four bonds (MAP4) was reported as a molecular fingerprint with good performance in similarity searching and chemical space visualization for different molecular sizes, which were analyzed in Natural Products Atlas (NPAtlas) containing microbial origins (Capecchi et al., 2020; Capecchi and Reymond, 2020). These could be great ideas for conducting experimental research using natural product databases, molecular descriptors and fingerprints, chemical space navigation of natural product against COVID-19.

Table 3

Examples of active compounds isolated from natural extracts with ACE2 (S protein) inhibitory activity.

Source	Family	Hits	Class of compounds	Bioactivities	Ref.
<i>Camellia sinensis</i> (Linnaeus) Kuntze	Theaceae	Epigallocatechin gallate (EGCG)	Catechin	IC ₅₀ = 2.47 µg/ml	Henss et al. (2021)
<i>Caragana sinica</i> (Buc'hoz) Rehder	Fabaceae	Kobophenol A	Stilbenoid	IC ₅₀ = 1.81 µM EC ₅₀ = 71.6 µM	Gangadevi et al. (2021)
<i>Glycyrrhiza glabra</i> Linnaeus	Fabaceae	Glycyrrhizic acid	Triterpenes	IC ₅₀ = 22 µM	Yu et al. (2021)
<i>Polygonum cuspidatum</i> (Houttuyn) Ronse Decraene	Polygonaceae	Emodin 8-O-β-D-glucoside	Hydroxyanthraquinone glycoside	IC ₅₀ = 22.50 µmol/l	Chen et al. (2021b)
<i>Rheum palmatum</i> Linnaeus	Polygonaceae	Rhein	Anthraquinone	IC ₅₀ = 18.33 µmol/l	
<i>Salvia miltiorrhiza</i> Bunge	Lamiaceae	Tanshinone IIA, Carnosic acid Rosmarinic acid Salvianolic acid B	Diterpene quinone Phenolic acids Diterpene Polyphenols	IC ₅₀ = 4.08 µM IC ₅₀ = 15.37 µM IC ₅₀ = 25.47 µM IC ₅₀ = 58.29 µM EC ₅₀ = 6.22 µM EC ₅₀ = 10.14 µM EC ₅₀ = 11.31 µM	Elebeedy et al. (2021) Elebeedy et al. (2021) Hu et al. (2021b) Hu et al. (2021b)

Table 4Examples of active compounds isolated from natural extracts with 3CL^{pro} (M^{pro}) inhibitory activity.

Source	Family	Hits	Class of compounds	Bioactivities	Ref.
Actinomycetes QFPDT	Actinomycetaceae	Leupeptin	Tripeptide	IC ₅₀ = 127.2 µM EC ₅₀ = 42.34 µM	Fu et al. (2021)
<i>Aloe vera</i> (Linnaeus) Burman	Asphodelaceae	Kaempferol	Flavonoid	93% inhibition at 62.5 µM 88% inhibition at 125 µM	Khan et al. (2021)
<i>Ampelopsis japonica</i> (Thunberg) Makino	Vitaceae	Myricetin	Flavonoid	IC ₅₀ = 2.86 µM IC ₅₀ = 3.684 µM	Xiao et al. (2021)
<i>Anacardium occidentale</i> Linnaeus	Anacardiaceae	Anacardic acid	Phenolic acid	IC ₅₀ = 2.07 µM	Chen et al. (2021c)
<i>Camellia sinensis</i> (Linnaeus) Kuntze	Theaceae	Epigallocatechin gallate (EGCG)	Catechin	IC ₅₀ = 0.874 µM	Du et al. (2021)
<i>Cannabis sativa</i> Linnaeus	Cannabaceae	Cannabidiol Δ ⁹ -tetrahydrocannabinol	Cannabinoid	IC ₅₀ = 7.91 µM IC ₅₀ = 10.25 µM	Raj et al. (2021)
<i>Cirsium japonicum</i> de Candolle	Asteraceae	Pectolinarin	Flavonoid	IC ₅₀ = 37.78 µM	Jo et al. (2020)
<i>Ginkgo biloba</i> Linnaeus	Ginkgoaceae	Ginkgolic acid	Phenolic acid	IC ₅₀ = 1.79 µM	Chen et al. (2021c)
<i>Linum usitatissimum</i> Linnaeus	Linaceae	Herbacetin	Flavonoid	IC ₅₀ = 33.17 µM	Liu et al. (2021b)
<i>Poria cocos</i> (F.A. Wolf) Ryvarden & Gilbertson	Polyporaceae	Pachymic acid	Triterpenoid	IC ₅₀ = 18,607 µmol/l	Wu et al. (2021b)
<i>Rhus succedanea</i> (Linnaeus) Kuntze	Anacardiaceae	Rhoifolin	Flavonoid	IC ₅₀ = 27.45 µM	Liu et al. (2021b)
<i>Scutellaria baicalensis</i> Georgi	Lamiaceae	Baicalin Baicalein	Flavone glycoside Flavone	IC ₅₀ = 6.41 µM IC ₅₀ = 0.94 µM IC ₅₀ = 0.39 µM EC ₅₀ = 2.9 µM	Su et al. (2020) Liu et al. (2021b)
		Scutellarein	Flavonoid	IC ₅₀ = 5.8 µM	

Table 5Examples of active compounds isolated from natural extracts with PL^{pro} inhibitory activity.

Source	Family	Hits	Class of compounds	Bioactivities	Ref.
<i>Carpobrotus edulis</i> (Linnaeus) Brown	Aizoaceae	Rutin	Flavonol glycoside	38% inhibition at 100 µM	Pitsillou et al. (2021)
<i>Garcinia lateriflora</i> Blume	Clusiaceae	Morelloflavone		IC ₅₀ = 36.4 µM	Li et al. (2022b)
<i>Ginkgo biloba</i> Linnaeus	Ginkgoaceae	Amentoflavone Ginkgetin Isoginkgetin Sciadopitysin	Biflavones	IC ₅₀ = 13.0 µM IC ₅₀ = 29.8 µM IC ₅₀ = 31.2 µM IC ₅₀ = 34.8 µM	
<i>Hibiscus sabdariffa</i> Linnaeus	Malvaceae	Cyanidin-3-O-glucoside	Anthocyanin	20% inhibition at 100 µM	Pitsillou et al. (2021)
<i>Hypericum perforatum</i> Linnaeus	Hypericaceae	Hypericin	Naphthodianthrone	97% inhibition at 100 µM	
<i>Lonicera japonica</i> Thunberg	Caprifoliaceae	4'-O-Methylchnaflavone		IC ₅₀ = 22.8 µM	Li et al. (2022b)
<i>Platycladus orientalis</i> (Linnaeus) Franco	Cupressaceae	Hinokiflavone Cryptomerin B		IC ₅₀ = 9.5 µM IC ₅₀ = 26.3 µM	
<i>Podocarpus nakaii</i> Hayata	Podocarpaceae	Podocarpusglavone		IC ₅₀ = 43.2 µM	
<i>Salvia miltiorrhiza</i> Bunge	Lamiaceae	Cryptotanshinone Tanshinone I	Diterpenoid	IC ₅₀ = 5.63 µmol/L IC ₅₀ = 2.21 µmol/L	Zhao et al. (2021b)

Generative neural network models

Different from virtual screening of available chemical libraries, constructing *de novo* molecule provides access to a virtually infinite chemical space and offers innovative molecular architecture with desired properties (Yang et al., 2019). Recently, the use of generative artificial intelligence to develop drug-like chemical compounds with desirable pharmacological effects supports drug discovery of DAAs

(Schneider and Clark, 2019). Recent generative approaches usually construct on deep neural networks (DNNs), which aims to model the underlying distribution of a given set of molecules and by sampling from the modelled distribution to construct novel chemical entities (Foster, 2019). The application of recurrent neural networks (RNNs) with long short-term memory (LSTM), variational autoencoders, generative adversarial networks (GANs), graph neural networks (GNNs), and other network architectures have been studied (Grisoni and Schneider, 2019;

Lin et al., 2020b; Pogány et al., 2019; Sattarov et al., 2019). These approaches are trained using ML algorithms to understand the meaning of text and language analytics. For the purpose of molecular design, the training molecules are represented in form of string notations as simplified molecular-input line-entry systems (SMILES strings). This generative DL model is important because internal representations of SMILES are automatically derived without relying on human-engineered molecular descriptors that require one's prediction of physicochemical properties. The generative model captures the syntax corresponding to valid training molecules and renders new SMILES-encoded molecules of interest, which can also lead to discovery of novel compounds with desired bioactivities (Merk et al., 2018). Bung et al. employed deep neural network-based generative and predictive models for *de novo* design of small molecules with SARS-CoV-2 3CL^{pro} inhibitory effects (Bung et al., 2021). Transfer learning followed by reinforcement learning aided the design of protease-specific inhibitors with optimized new chemical entities (NCEs) properties. The SymMap database of TCM was used to compare the potent NCEs by generative model that potentially targeted 3CL^{pro} (Wu et al., 2019). 33 NCEs were selected for the identification of pharmacokinetic and toxicity properties using SwissADME, ToxTree, and pkCSM (Bung et al., 2021). Two NCEs shared similar results of Tanimoto coefficient of 0.80 to the natural product named aurantiamide. This phytochemical was extracted from *Baphicacanthus cusia*, the TCM herb treating cold, fever, and influenza, and possessed anti-viral properties. The generalized approach was used to rapidly accelerate drug discovery process and tested against SARS-CoV-2 3CL^{pro}.

Another study has developed deep learning model using convolutional neural network (CNN) framework for predicting compounds with 3CL^{pro} inhibitory activity (Kumari and Subbarao, 2021). 423 unique chemical structures including 80 active and 343 inactive compounds as chemical descriptors were trained into the CNN model. Classification ML approaches including Random Forest, naïve Bayes, decision tree, and support vector machine were also implemented to compare with the CNN model. The results of the test set exhibited an accuracy, sensitivity, specificity, precision, recall, F-measure, and ROC of 0.86, 0.45, 0.96, 0.73, 0.45, 0.55, and 0.71, respectively. The CNN architecture screened 10 hit molecules from phytochemical compounds, 59 hits from NCI divest IV and 14,025 ZINC natural product database as anti-COVID-19 agents.

Examples of active compounds derived from TCM by ligand-based approaches

The examples of active compounds from TCM by structure-based approaches have been previously discussed. Only few studies have been investigated on main TCM components acting against COVID-19 using ligand-based approaches, which will be reviewed in this section. Rahman et al. reported a ligand-based pharmacophore approach using the Molecular Operating Environment (MOE) software (Rahman et al., 2020). Approximately 30,927 compounds from NPASS were screened for the pharmacophore features of standard serine protease inhibitor camostate mesylate, which is a trypsin-like protease inhibitor. Subsequently, 2140 compounds were identified from the ligand-based compound screening approach and further subjected to molecular docking against TMPRSS2 to determine potent inhibitors of this target. The authors selected 10 pharmacophoric features including anionic and cationic atoms, H-Bond donor and acceptor, aromatic center, Pi ring center, and a hydrophobic center. Following physicochemical and ADMET prediction, NPC306344 was the hit compound for TMPRSS2. Further investigation on experimental and animal studies is required to develop this anti-COVID-19 drug. Gaudêncio & Pereira proposed five marine natural products, such as Reaxys ID: 7450892, 19384758, 26845562, 10714788, and 10720065 as most promising SARS-CoV-2 M^{pro} inhibitors using quantitative structure-activity relationship (QSAR) classification modeling (Gaudêncio and Pereira, 2020). This

CADD ligand-based study consists of two extensive sets of descriptors including six different types of fingerprints with different sizes and 1D&2D descriptors. These molecular descriptors and fingerprints were calculated using PaDEL-Descriptor version 2.21, available on <http://www.yapcwsoft.com/dd/padeldescriptor/>. Random Forest (RF) machine learning technique was used for constructing classification modeling to evaluate performance of SARS-CoV-2 activity. The authors highlighted three selected models, which are MACCS model, ExtCDK model, and 1D&2D descriptors. The best MACCS model built with sets of fragment fingerprints include MACCS, Sub, Sub C, and PubChem, and the best ExtCDK model built with sets of circular fingerprints include CDK and CDKExt. For 1D&2D descriptors, Q and MCC parameters were selected. The best model for each training set of ExtCDK fingerprints and 1D&2D descriptors were obtained by using the RF algorithm of the selected 150 fingerprints and descriptors, respectively. MACCS model was excluded because descriptors comprise only 166 fingerprints. Probability of being class A (Prob_A) can be used as an additional parameter assigned by the RF algorithm and a predicting criterion (≥ 0.5). JChem Standardizer tool version 5.7.13.0 was then used to standardize the molecular structures of all data sets by normalizing tautomeric and mesomeric groups and removing small disconnected fragments. The pkCSM software was used to predict fifteen selected marine natural products by QSAR model, molecular docking, and ADMET properties. Finally, the top five aforementioned marine natural products were achieved and could be further investigated experimentally. Ghosh et al. reported the development of multiple classification QSAR models including several Monte Carlo optimized-based and structural and physicochemical interpretation (SPCI) analysis with a diverse dataset of 88 compounds with SARS-CoV-2 M^{pro} inhibitory properties (Ghosh et al., 2021). In SPCI analysis study, four machine learning approaches including Gradient boosting classification (GBC), Random Forest (RF), Support Vector Machine (SVM), and *k*-nearest neighbor (*k*NN) are used to perform diverse classification-based QSAR models for identifying and predicting different fragments that contribute for M^{pro} inhibition. These models were further assessed for balanced accuracy, sensitivity, and specificity (Polishchuk et al., 2016). The results of SPCI analysis suggested heterocyclic scaffolds including diazole, furan, and pyridine have a positive contribution, while thiophen, thiazole, and pyrimidine seem to have negative contribution to M^{pro} inhibition (Ghosh et al., 2021). Furthermore, Monte Carlo optimization-based QSAR was implemented to screen some natural product hits from recent publications. SMILES-based descriptors, Graph-based descriptors, and Hybrid descriptors are employed in this study. The statistical characteristics of twenty-one different models from three different splits were obtained from Monte Carlo optimization method, and the model M21 (SMILES and HSG with ¹EC_k) from split-3 was applied for the best model screening. Subsequently, 13 active molecules from natural sources were found as the most potent coronavirus M^{pro} inhibitors. These compounds consist of one lignan, eleven flavonoids, and one pentacyclic triterpenoid. This approach plays a significant role on fragment investigation and QSAR based active compound screening against SARS-CoV-2 M^{pro} enzyme.

Knowledge mining tools

The COVID-19 pandemic results in urgent establishments of open science and FAIR (Findable, Accessible, Interpretable, Reusable) data initiatives to help researchers, institutions, publishers, companies and regulators better understanding the disease and search for effective treatment as soon as possible (Wilkinson et al., 2016). For instance, the Natural Products Atlas, a microbial natural product database with over 20,000 compounds containing structural data references, compound names, source organisms, isolation references, total syntheses, and structural reassignment, has been developed using FAIR principles as a community-supported resource for known structural characterizations of microorganisms from natural product (Van Santen et al., 2019).

Various structured and unstructured COVID-19 data sources have been made publicly available. This highlights the use of accelerated tools for COVID-19 drug discovery from knowledge graph approaches and AI, which will be discussed with examples in the following section (Bullock et al., 2020).

Knowledge graph (KG) is a collection of integrated knowledge resources or correlation between library and data descriptions in a form of mapping graph (LiuQiao and DuanHong, 2016). KG implemented visualization AI technology to illustrate, construct, connect knowledge resources, and display relationships between these carriers. In TCM field, the use of KG analysis could explain complex relationships between therapeutics and prevention of diseases as well as other research fields, which could be an alternative for studying the information on TCM. Several studies have applied KG to the TCM diagnostic and medical treatment (Wang, 2020; Yu et al., 2017; Zhao et al., 2020a). However, in this review, the TCM prescription using COVID-19 KG will be summarized in detail.

FP-Growth algorithm, a modified version of Apriori algorithm, has been developed for analyzing TCM data correlation between natural active constituents in 41 TCM prescriptions with 8 characteristics of medical properties, 10 kinds of medical tastes, and 10 kinds of meridian tropism (Yan et al., 2020). In this study, Neo4j, a high-performance NoSQL graph database, as well as various programming languages, for instances Python, Java, GO, R, etc. were also provided in order to construct COVID-19 KG. Three populations including medical observation, mild general, and COVID-19 infected patients were included in the study with equally distributed number ratio of 1:1:1 to enhance reliable association analysis results. To be more specific, TCM prescriptions for COVID-19 infected patients will be summarized in our review. There are two major modules, which comprises of FP-tree construction by FP-Growth algorithm and the use of Cypher language analysis on the algorithm to map the graph of COVID-19 prescription. The initial step was to establish relationships between tastes, properties, and population and make correlation analysis to produce the graph of “applicable population – properties, tastes, and meridian tropism of Chinese medicinal herbs” (Yan et al., 2020). The results demonstrated that TCM herbs with neutral property, acrid taste, and spleen-invigorating meridians were commonly used in the prescriptions to treat COVID-19 infected patients. The highest proportions of each TCM characteristics type of herbs in COVID-19 prescriptions statistically contributed 39% of warm-natured properties, 41% of acrid tastes, and 24% of stomach meridian tropism. Subsequently, the use of operation instructions, such as MATCH and WHERE in Cypher suggested that core TCM herbs including Radix Glycyrrhizae (Gan Cao), Herba Asari (Xi Xin), Rhizoma Atractylodis (Cang Zhu), and etc. were recommended as well as TCM prescriptions including phlegm-resolving, wind-dispelling, cough/pain/exterior syndrome-relieving, spleen-invigorating, and digestion-aiding medicines for the COVID-19 infected patients. Further investigations on improving KG efficacy are required. For examples, the KG of COVID-19 prescriptions reported here only supported a small number of data, so FP_G algorithm should be applied to enhance FP_tree construction in FP-Growth algorithm for a larger volume of prescription data expansion. The use of KG approaches for COVID-19 TCM prescriptions could be applied in relevant research scholars and increased the reliability of TCM research content.

Network-based approaches

Network-based approaches is very important for network pharmacology, system pharmacology and integrated pharmacology research on TCM against COVID-19.

Network pharmacology

Network pharmacology comprehensively integrates multitarget drugs and compound-disease pathways in order to comprehend complex

biological systems, drugs, and diseases in a network point of view. This results in shifting drug discovery concepts of network theory and systems biology from the concept of one gene, target, and disease to the novel paradigm of multitargeted mechanisms in treatment of complicated diseases, especially COVID-19.

Zhang et al. conducted a network pharmacological methodology to explore significant biological mechanisms of Lianhua Qingwen Capsule (LHQWC), which is another TCM formula used for treating respiratory diseases as well as COVID-19 (Zhang et al., 2021a). 263 ingredients of 13 herbs, including *Fructus Forsythiae*, *Flos Lonicerae Japonicae*, *Herba Ephedrae*, Almond, *Radix Isatidis*, *Fortunes Boss fern Rhizome*, *Herba Houttuyniae*, *Herba Pogostemonis*, *Rheum palmatum*, and *Glycyrrhiza uralensis Fisch*, were retrieved from TCMSP database while *Rhodiola rosea*, *Mentha haplocalyx Briq* and *Gypsum Fibrosum* were retrieved from BATMAN-TCM and TCMID databases (Liu et al., 2016; Xue et al., 2012). 226 compounds excluding duplicated portions from these herbs were selected for further study. To standardize the protein name, UniProtKB was utilized to acquire the official symbols (Consortium, 2015). The gene intersection between active ingredients and COVID-19 was illustrated and visualized using a Venn diagram (Heberle et al., 2015). GeneCards database was used to obtain COVID-19 human related genes (Rebhan et al., 1997), and the STRING database was employed to predict PPI interaction data (Mering et al., 2003). 643 therapeutic genes were collected from GeneCards for COVID-19 and 49 intersected genes were generated. These ingredient-disease co-target genes were further imported into STRING to construct PPI. GO and KEGG pathway enrichment were further carried out using R package to determine biological processes and molecular interactions associated with top 20 selected common genes (Kanehisa and Goto, 2000). Ingredient–target network and ingredient–disease PPI networks were analyzed and constructed using Cytoscape software (Shannon et al., 2003). The ingredient-target network contains 153 nodes (49 targets and 104 compounds) and 299 edges, which represent a biological relationship between two nodes. LHQW-C may exert synergistic pharmacological effects on COVID-19 as suggested by the degree (number of links to nodes) of compounds. For instance, quercetin (degree 38), luteolin (degree 17), wogonin (degree 12), and kaempferol (degree 11) exhibited multiple targets in network regulation. On the other hand, the result revealed PPI network consisted of 46 nodes and 331 edges. Nodes with an average value of degree ≥ 27 , node betweenness ≥ 0.0009993 , and closeness ≥ 0.618 suggested that the target network of LHQW-C plays significant roles on IL-6, TNF, MAPK1, which were associated with inflammatory responses, oxidative stress reactions, and other biological processes. Finally, the potential mechanism of LHQW-C using an integrating network pharmacology method suggested that some anti-inflammatory ingredients may inhibit viral replication, suppress cytokine storm, and protect the pulmonary alveolar-capillary barrier in patients with serious COVID-19 illness.

Similarly, Li et al. reported the antiviral and anti-inflammatory effects of Maxing Shigan decoction (MXSGD), the key formula for treating pulmonary diseases, using multiple open-source TCM databases, network pharmacology, PPI construction, as well as biological enrichment analysis (Li et al., 2021c). Four TCM herbs in MXSGD formula consist of *E. sinica*, *S. armeniaca amarum*, *G. Fibrosum*, and *G. uralensis* have proved to be effective against COVID-19, and Lianhua Qingwen Capsule, Qingfei Paidu decoction, Huashi Baidu formula, and Xuanfei Baidu granule, were all formulated based on MXSGD. Ye et al. reported the ingredients of Toujie Quwen Granules were proved to have therapeutic effects on COVID-19 via regulating viral infection, immune and inflammatory related targets and pathways using network pharmacology, molecular docking, and surface plasmon resonance (SPR) technology (Ye et al., 2021). The results of SPR experiments revealed the combination of quercetin and isoquercitrin preferably bound to SARS-CoV-2 S protein while astragaloside IV and rutin selectively bound to ACE-2. He et al. identified the therapeutic effect of Xuebijing injection on COVID-19-induced cardiac dysfunction using bioinformatics analysis (He et al., 2021). Xuebijing injection indicated oxidative stress

inhibition, atherosclerotic plaque prevention, inflammatory repression and apoptosis by targeting 7 central hub genes including CCL2, CXCL8, FOS, IFN β , IL-1A, IL-1B, SERPINE1 that have protective mechanism on COVID-19-induced cardiac dysfunction. Lin et al. systematically and comprehensively analyzed the active ingredients, targets, and possible mechanisms of Yinqiao powder for treating COVID-19 using drug-ingredient-gene and PPI network construction as well as GO and KEGG pathway analysis (Lin et al., 2021). The active ingredients of Yinqiao powder, such as hesperetin, eriodictyol, luteolin, quercetin, and naringenin have antagonistic effect on the inflammatory storm caused by COVID-19 and may be associated with the regulation of IL-6, MAPK3, TNF, and TP53 targets using network pharmacology. Tao et al. proposed the therapeutic mechanism of Shufeng Jiedu Capsule (SFJDC) against SARS-CoV-2 pneumonia using an integrated systemic study of ADME assessment, target fishing, network construction, and functional bioinformatics analyses to understand potential immunomodulatory and anti-inflammatory mechanisms (Tao et al., 2020). Many TCM prescriptions have been investigated using network pharmacology methods due to complicated multiple TCM ingredients, targets, diseases, and mechanisms. Next, discussion part will be mentioned.

System pharmacology

The combination of herbal medicine formula contains over thousands of chemical compounds, and only some parts of them show favorable pharmacokinetics along with potential biological effects (Li et al., 2012). Moreover, possible therapeutic effects of herbal products might result from cooperate actions of the herbal ingredients. This concept screens out the conventional analytical chemistry and pharmacology technologies which attempt to isolate and identify possible pharmacological effects of chemical constituents. Also, the chemical components in multiple TCM herbs or even in one herb are too complex to identify because they produce various biological targets involving in various pathogenesis. Due to these addressed issues, systems pharmacology has been applied in a biological complex system for screening drug safety, active compounds, predicting the targets, and analyzing the potential ingredient target-disease networks.

A unique system pharmacology platform of Chinese herbal medicines named Traditional Chinese medicine systems pharmacology (TCMSP) was developed for accelerating drug discovery from herbal medicines (Ru et al., 2014). This database covers a large-scale structural data integration with experimentally validated information for all registered herbs in Chinese pharmacopoeia, active compound screening with key ADME-related properties from diverse sources, compound-target and target-disease network construction with applied TCM theory, as well as mechanisms of action and discovery of new drugs. Wang et al. systematically reported the pharmacological effects and mechanisms of Jingyin granule containing multiple herbs for treating respiratory system diseases using computational approaches (Wang et al., 2021a). Firstly, the ingredients in Jingyin granule were assessed using TCMSP and Traditional Chinese medicine integrated database (TCMID). These databases were used to search for the identified herbal ingredients with ADME properties, oral bioavailability (OB), and drug likeness (DL). A total of 168 selected druggable ingredients identified in Jingyin granule were screened in TCMSP database with the criteria of OB \geq 30% and DL \geq 0.18. Subsequently, 865 potential therapeutic targets of ingredients were identified using SwissTargetPrediction database, and for possible targets of COVID-19, Online Mendelian Inheritance in Man (OMIM), DisGeNET, and GeneCards databases were implemented and identified 88 interacting genes as potential therapeutic targets of Jingyin granule to COVID-19. As a result of using these computational approaches, Jingyin granule could directly target the ACE gene, and ACE protein shared similar domain with ACE2, which had been identified as one of the most important targets for SARS-CoV-2 entry (Wang et al., 2021a). Gene Ontology (GO) enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway

analysis were further investigated for these relevant target genes with similar functions using an R package clusterProfiler (Yu et al., 2012). The results of GO and KEGG analysis suggested Jingyin granule could regulate immunoreaction as Flos Ionicera and Licorice demonstrated anti-inflammatory activities (Wang et al., 2021a).

Another example of system pharmacology was included in the study of TCM Shenfuhuang Formula (SFHF) in treatment for septic syndrome of COVID-19 (Liu et al., 2020). Data mining was performed and collected 231 ingredients from SFHF, including 92 ingredients of *Rheum palmatum* L. (Da Huang), 74 compounds of *Panax ginseng* C.A.Mey (Hong Shen), and 65 compounds of *Aconitum carmichaeli* Debeaux (Fu Zi) from TCM pharmacology analysis databases, TCMSP and ETCM. Suitable drug candidates were selected when they fulfilled active screening criteria including oral bioavailability (OB) \geq 30%, Caco-2 permeability (Caco-2) $>$ -0.4, drug-likeness (DL) \geq 0.18, and half-life (HL) \geq 4. Only 49 potential SFHF compounds were selected. Weighted ensemble similarity (WES) approach was also utilized to obtain comprehensive drug target information of SFHF. The results of 64 identified targets were predicted for the 49 potential drug compounds. In compound-target analysis network, compounds with most targets (sitosterol, emodin, chrysophanol, and deltoin) as well as proteins (GSK3 β , ESR1, PPAR γ , PTGS2, AKR1B10, and MAPK14) were determined (Liu et al., 2020). SFHF was further analyzed in PharmGKB, Drugbank, and TTD databases for a target-disease network, and the results suggesting 46 targets were directly involved with immune system as well as nine potential targets on inflammatory disease. KEGG and DAVID databases were subsequently connected potential targets and related signaling pathways. These signaling pathways, such as Toll-like receptor, MAPK, JAK/STAT, PPAR, VEGF, NOD-like receptor and NF-kappa B have a strong relationship with sepsis, infection immunity, inflammatory response, coagulation function, organ damage, immune disorders and other diseases. Furthermore, synergistic effects of three herbal compounds in SFHF were constructed, and the targets of this TCM formula were related with the calcium, MAPK, T cell receptor, and PI3K-AKT signaling pathways. These are main pathological pathways for sepsis. There are more upcoming studies on TCM formulas with system pharmacology approaches and MOA analysis for COVID-19 in the future.

Discussion

COVID-19 pandemic has globally brought researchers to conduct extensive studies in order to comprehend pathological diseases, viral components of protein structure, and viral-host interactome. The current search for potential antiviral inhibitors, such as vaccines seems to be massively time-consuming as well as conventional drugs with undesirable effects in a long term. Hence, the search for accelerated methods, safe, and effective antiviral drugs is required. Computer-aided drug discovery (CADD) approaches play a significant role in simulating drug-target interactions, analyzing potential drug targets, and accurately predicting hit compounds by using bioinformatics databases, docking tools, software, and other computational methods for the optimization of drug design. In the early stage of drug discovery, CADD can save time, financial investment, and economical resources spending on wet lab, and prove chemical safety profile of natural ingredients in TCM. An effective CADD approach was previously utilized to study modern sciences of complex multi-target diseases and mechanisms using TCM formula and/or natural products derived from TCM (Yang, 2013). Moreover, a recent study on CADD, publication resources, and other computational approaches was implemented to discover novel drug candidates against COVID-19 (Muratov et al., 2021). We truly inspired by the concept of these two studies, so we focus on small molecule drugs derived from natural products and Traditional Chinese medicine (TCM) in treatment of COVID-19 using CADD approaches.

In this review, there are more studies mentioning on databases and research resources, docking tools, and MD simulation software that aid TCM drug discovery against COVID-19. For instances, the identification

of natural hit compounds named Gracillin and Proanthocyanidins from traditional medicinal plants were virtually screened using AutoDock Vina and visualized by Discovery Studio Visualizer, and both exhibited the highest binding affinity of 9.2 kcal/mol to 3CL^{PRO} (PDB ID: 6WNP) (Khanh and Hoa, 2021). Elekofehinti et al. reported post-docking analysis by MM/GBSA of the natural hit compound named STOCK1N-98687 from natural products library and confirmed binding stability of the ligand and 3CL^{PRO} complex (Elekofehinti et al., 2021). STOCK1N-98687 has high GLIDE docking score against SARS-CoV-2 3CL^{PRO}, induced-fit docking score, and satisfactory calculated binding free energy score with good predicted inhibitory prowess (pIC₅₀) compared to the experimental drug lopinavir. 50 ns MD simulation was performed using GROMACS software and revealed high stability with low fluctuation of the complex suggesting STOCK1N-98687 as the potential 3CL^{PRO} inhibitor. Pie charts are illustrated in Figs. 2, 4, 5, and the most popular database, docking tool, and MD simulation software on TCM research articles against COVID-19 are TCMSp, AutoDock Vina, and GROMACS, respectively. However, this can be further indicated that databases, tools or MD software conducting on TCM research articles against COVID-19 are low in number of publications. Many readers could take this opportunity to exploit and develop their own TCM-related research field against COVID-19 from our review.

We have found more *in vitro* examples of active ingredients on TCM using structure-based approaches while ligand-based approaches will be summarized using *in silico* methods. QSAR classification modeling was constructed using RF machine learning techniques in order to propose five marine natural products (Reaxys ID: 7450892, 19384758, 26845562, 10714788, and 10720065) as top SARS-CoV-2 M^{PRO} inhibitors (Gaudêncio and Pereira, 2020). Deep neural networks were employed for generating *de novo* design of small molecules and compared 33 NCEs with TCM phytochemicals in order to determine which compounds are able to inhibit SARS-CoV-2 3CL^{PRO} (Bung et al., 2021). In this study, aurantiamide from TCM herb *Baphicacanthus cusia* possessed antiviral properties, and this method can accelerate drug discovery process. For knowledge mining tools, the use of COVID-19 knowledge graph can be applied in TCM prescriptions for diagnostic and medical treatment (Yan et al., 2020). The applications of systems pharmacology focus mainly on a biological system including active ADME screening model, target prediction, and compound target-disease network analysis. For network pharmacology, the integration across multiple drug-target and ingredient-disease pathways totally shifts the paradigm of drug discovery from one gene, target, and pathway to complex network theory, biological systems, and multiple target mechanisms. Many TCM formula have included both systems pharmacology and network pharmacology in their research articles for better understanding of their multiple mechanisms and targets. Different CADD approaches that support TCM research on COVID-19 have been reviewed in this paper. After determining hit selection, every study requires further experimental validations in order to be readily tested in animal and clinical studies.

Conclusion

Overall, different approaches supporting TCM research on COVID-19 including research databases, docking tools, and MD simulation software have been totally summarized. The application of databases and research resources on TCM ingredients for COVID-19 listed in this paper facilitates a wide range of audience to employ CADD tools to datasets and biological targets regarding to SARS-CoV-2 drug discovery. Computational investigation including databases, molecular docking tools and MD simulation software on natural compounds and TCM herbs have been applied and predicted as potential targets for COVID-19. The most commonly used database, molecular docking tool, and MD simulation software include TCMSp, AutoDock Vina, and GROMACS, respectively. These are subsequently illustrated in Figs. 2, 4, and 5 as pie charts. MD simulation software is implemented for MM/PBSA and MM/

GBSA methods for binding free energy calculation. Several examples of active components derived from TCM by structure-based and ligand-based approaches were also mentioned, which were conducted *in vitro* and *in silico*, respectively. Active components derived from natural products or TCM for structure-based approaches are summarized against key COVID-19 targets including ACE2, 3CL^{PRO}, and PL^{PRO}. Only few studies were found in active ingredients of natural products derived from TCM for ligand-based approaches. COVID-19 knowledge graph, an example of knowledge mining tool, is used to analyze complex TCM relationships between TCM herbal properties and therapeutics on COVID-19 infected patients. System/network pharmacology databases were used to identify the multitarget mechanisms of COVID-19 due to the complex of chemical ingredients, targets, and pathological mechanisms in multiple TCM herbs. In the future, computational approaches, tools, and resources are necessary for the upcoming unknown diseases. We recommend readers to exploit our information for the development of future drug discovery in TCM.

Funding

This research was funded by NSFC-Joint Foundation of Yunnan Province (Grant No. U1902213), and Key-Area Research and Development Program of Guangdong Province (Grant No. 2020B1111110003).

CRedit authorship contribution statement

Chattarin Ruchawapol: Investigation, Writing – original draft, Writing – review & editing. **Wen-Wei Fu:** Writing – review & editing. **Hong-Xi Xu:** Supervision.

Declaration of Competing Interest

The authors declare no conflict of interest.

References

- Abd El-Mageed, H., Abdelrheem, D.A., Rafi, M., Sarker, M., Al-Khafaji, K., Hossain, M., Capasso, R., Emran, T.B., 2021. *In silico* evaluation of different flavonoids from medicinal plants for their potency against SARS-CoV-2. *Biologics* 1, 416–434.
- Abel, R., Paredes Ramos, M., Chen, Q., Pérez-Sánchez, H., Coluzzi, F., Rocco, M., Marchetti, P., Mura, C., Simmaco, M., Bourne, P.E., 2020. Computational prediction of potential inhibitors of the main protease of SARS-CoV-2. *Front. Chem.* 8, 1162.
- Abraham, M.J., Murtola, T., Schulz, R., Páll, S., Smith, J.C., Hess, B., Lindahl, E., 2015. GROMACS: high performance molecular simulations through multi-level parallelism from laptops to supercomputers. *SoftwareX* 1, 19–25.
- Alhadrami, H.A., Sayed, A.M., Hassan, H.M., Youssif, K.A., Gaber, Y., Moatasim, Y., Kutkat, O., Mostafa, A., Ali, M.A., Rateb, M.E., 2021. Cnicin as an anti-SARS-CoV-2: an integrated *in silico* and *in vitro* approach for the rapid identification of potential COVID-19 therapeutics. *Antibiotics* 10, 542.
- Arora, S., Lohiya, G., Moharir, K., Shah, S., Yende, S., 2020. Identification of potential flavonoid inhibitors of the SARS-CoV-2 main protease 6YNQ: a molecular docking study. *Digital Chinese Medicine* 3, 239–248.
- Badraoui, R., Saoudi, M., Hamadou, W.S., Elkahoui, S., Siddiqui, A.J., Alam, J.M., Jamal, A., Adnan, M., Suliemen, A.M., Alreshidi, M.M., 2022. Antiviral effects of artemisinin and its derivatives against SARS-CoV-2 main protease: computational evidences and interactions with ACE2 allelic variants. *Pharmaceuticals* 15, 129.
- Beirami, A.D., Hatamabadi, D., Iranpanah, S., Rezaei, M., Ziai, S.A., 2020. *In silico* identification of potentially effective herbal inhibitors of SARS-CoV-2 main protease by virtual screening method. *Sch. Med. Stud. J.* 2, 2–6.
- Bharadwaj, S., Azhar, E.I., Kamal, M.A., Bajrai, L.H., Dubey, A., Jha, K., Yadava, U., Kang, S.G., Dwivedi, V.D., 2020. SARS-CoV-2 Mpro inhibitors: identification of anti-SARS-CoV-2 Mpro compounds from FDA approved drugs. *J. Biomol. Struct. Dyn.* 40, 1–16.
- Bharadwaj, S., Dubey, A., Yadava, U., Mishra, S.K., Kang, S.G., Dwivedi, V.D., 2021. Exploration of natural compounds with anti-SARS-CoV-2 activity via inhibition of SARS-CoV-2 Mpro. *Brief Bioinform* 22, 1361–1377.
- Bocci, G., Bradfute, S.B., Ye, C., Garcia, M.J., Parvathareddy, J., Reichard, W., Surendranathan, S., Bansal, S., Bologa, C.G., Perkins, D.J., 2020. Virtual and *in vitro* antiviral screening revive therapeutic drugs for COVID-19. *ACS Pharmacol. Transl. Sci.* 3, 1278–1292.
- Bojadzic, D., Alcazar, O., Chen, J., Chuang, S.T., Condor Capcha, J.M., Shehadeh, L.A., Buchwald, P., 2021. Small-molecule inhibitors of the coronavirus Spike: ACE2 protein–protein interaction as blockers of viral attachment and entry for SARS-CoV-2. *ACS Infect. Dis.* 7, 1519–1534.

- Brooks, B.R., Brooks, C.L., Mackerell, A.D., Nilsson, L., Petrella, R.J., Roux, B., Won, Y., Archontis, G., Bartels, C., Boresch, S., 2009. CHARMM: the biomolecular simulation program. *J. Comput. Chem.* 30, 1545–1614.
- Bullock, J., Luccioni, A., Pham, K.H., Lam, C.S.N., Luengo-Oroz, M., 2020. Mapping the landscape of artificial intelligence applications against COVID-19. *J. Artif. Intell. Res.* 69, 807–845.
- Bung, N., Krishnan, S.R., Bulusu, G., Roy, A., 2021. De novo design of new chemical entities for SARS-CoV-2 using artificial intelligence. *Future Med. Chem.* 13, 575–585.
- Cai, Y., Zeng, M., Chen, Y.Z., 2021. The pharmacological mechanism of Huashi Baidu Formula for the treatment of COVID-19 by combined network pharmacology and molecular docking. *Ann. Palliat. Med.* 10, 3864–3895.
- Capecchi, A., Probst, D., Reymond, J.L., 2020. One molecular fingerprint to rule them all: drugs, biomolecules, and the metabolome. *J. Cheminform.* 12, 1–15.
- Capecchi, A., Reymond, J.L., 2020. Assigning the origin of microbial natural products by chemical space map and machine learning. *Biomolecules* 10, 1385.
- Case, D.A., Cheatham, T.E., Darden, T., Gohlke, H., Luo, R., Merz, K.M., Onufriev, A., Simmerling, C., Wang, B., Woods, R.J., 2005. The Amber biomolecular simulation programs. *J. Comput. Chem.* 26, 1668–1688.
- Chen, J., Wang, Y.K., Gao, Y., Hu, L.S., Yang, J.W., Wang, J.R., Sun, W.J., Liang, Z.Q., Cao, Y.M., Cao, Y.B., 2020. Protection against COVID-19 injury by qingfei paidu decoction via anti-viral, anti-inflammatory activity and metabolic programming. *Biomed. Pharmacother.* 129, 110281.
- Chen, R.H., Yang, L.J., Hamdoun, S., Chung, S.K., Lam, C.W.K., Zhang, K.X., Guo, X., Xia, C., Law, B.Y.K., Wong, V.K.W., 2021a. 1, 2, 3, 4, 6-pentagalloyl glucose, a RBD-ACE2 binding inhibitor to prevent SARS-CoV-2 infection. *Front. Pharmacol.* 12, 150.
- Chen, X., Wu, Y., Chen, C., Gu, Y., Zhu, C., Wang, S., Chen, J., Zhang, L., Lv, L., Zhang, G., 2021b. Identifying potential anti-COVID-19 pharmacological components of traditional Chinese medicine Lianhuaqingwen capsule based on human exposure and ACE2 biochromatography screening. *Acta Pharm. Sin. B* 11, 222–236.
- Chen, Z., Cui, Q., Cooper, L., Zhang, P., Lee, H., Chen, Z., Wang, Y., Liu, X., Rong, L., Du, R., 2021c. Ginkgolic acid and anaradic acid are specific covalent inhibitors of SARS-CoV-2 cysteine proteases. *CELL Biosci.* 11, 1–8.
- Chikhale, R.V., Gupta, V.K., Eldesoky, G.E., Wabaidur, S.M., Patil, S.A., Islam, M.A., 2021a. Identification of potential anti-TMPRSS2 natural products through homology modelling, virtual screening and molecular dynamics simulation studies. *J. Biomol. Struct. Dyn.* 39, 6660–6675.
- Chikhale, R.V., Sinha, S.K., Patil, R.B., Prasad, S.K., Shakya, A., Gurav, N., Prasad, R., Dhaswadikar, S.R., Wanjari, M., Gurav, S.S., 2021b. In-silico investigation of phytochemicals from *Asparagus racemosus* as plausible antiviral agent in COVID-19. *J. Biomol. Struct. Dyn.* 39, 5033–5047.
- Chitsike, L., Duerksen-Hughes, P., 2021. Keep out! SARS-CoV-2 entry inhibitors: their role and utility as COVID-19 therapeutics. *Virology* 18, 154.
- Consortium, U., 2015. UniProt: a hub for protein information. *Nucleic Acids Res.* 43, D204–D212.
- Du, A., Zheng, R., Disoma, C., Li, S., Chen, Z., Li, S., Liu, P., Zhou, Y., Shen, Y., Liu, S., 2021. Epigallocatechin-3-gallate, an active ingredient of traditional Chinese medicines, inhibits the 3CLpro activity of SARS-CoV-2. *Int. J. Biol. Macromol.* 176, 1–12.
- Dutta, M., Tareq, A.M., Rakib, A., Mahmud, S., Sami, S.A., Mallick, J., Islam, M.N., Majumder, M., Uddin, M., Alsubaie, A., 2021. Phytochemicals from *Lucas zeylanica* targeting main protease of SARS-CoV-2: chemical profiles, molecular docking, and molecular dynamics simulations. *Biology* 10, 789 (Basil).
- Elebeedy, D., Elkhatib, W.F., Kandeil, A., Ghanem, A., Kutkat, O., Alnajjar, R., Saleh, M. A., Abd El Maksoud, A.I., Badawy, I., Al-Karmalawy, A.A., 2021. Anti-SARS-CoV-2 activities of tanshinone IIA, carnosic acid, rosmarinic acid, salvianolic acid, baicalein, and glycyrrhethinic acid between computational and *in vitro* insights. *RSC Adv.* 11, 29267–29286.
- Elekofehinti, O.O., Iwalaye, O., Molehin, O.R., Famusiwa, C.D., 2021. Identification of lead compounds from large natural product library targeting 3C-like protease of SARS-CoV-2 using E-pharmacophore modelling, QSAR and molecular dynamics simulation. *In Silico Pharmacol.* 9, 1–19.
- Emirik, M., 2022. Potential therapeutic effect of turmeric contents against SARS-CoV-2 compared with experimental COVID-19 therapies: *in silico* study. *J. Biomol. Struct. Dyn.* 40, 2024–2037.
- Fathy, H., Abdelhady, W., Ibrahim, R.S., 2020. *In-silico* recognition of liquorice phytoconstituents specially glabranin b as a potential cathepsin I inhibitor to hinder 2019-ncov host cell entry. *Int. J. Pharm. Sci. Rev. Res.* 64, 197–202.
- Foster, D., 2019. Generative Deep learning: Teaching Machines to paint, write, compose, and Play. O'Reilly Media.
- Freitas, B.T., Durie, I.A., Murray, J., Longo, J.E., Miller, H.C., Crich, D., Hogan, R.J., Tripp, R.A., Pegan, S.D., 2020. Characterization and noncovalent inhibition of the deubiquitinase and deISGylase activity of SARS-CoV-2 papain-like protease. *ACS Infect. Dis.* 6, 2099–2109.
- Fu, L., Shao, S., Feng, Y., Ye, F., Sun, X., Wang, Q., Yu, F., Wang, Q., Huang, B., Niu, P., 2021. Mechanism of microbial metabolite leupeptin in the treatment of COVID-19 by traditional Chinese medicine herbs. *Mbio* 12, e02220–e02221.
- Gangadevi, S., Badavath, V.N., Thakur, A., Yin, N., De Jonghe, S., Acevedo, O., Jochmans, D., Leyssen, P., Wang, K., Neyts, J., 2021. Kobophenol a inhibits binding of host ace2 receptor with spike rbd domain of sars-cov-2, a lead compound for blocking covid-19. *J. Phys. Chem. Lett.* 12, 1793–1802.
- Gao, K., Song, Y.P., Song, A., 2020. Exploring active ingredients and function mechanisms of Ephedra-bitter almond for prevention and treatment of Corona virus disease 2019 (COVID-19) based on network pharmacology. *BioData Min.* 13, 19.
- Gao, Y., Liang, A., Fan, X., Hu, L., Hao, F., Li, Y., 2019. Safety research in traditional Chinese medicine: methods, applications, and outlook. *Engineering* 5, 76–82.
- Gaspar, H.A., Baskin, I.L., Marcou, G., Horvath, D., Varnek, A., 2015. Chemical data visualization and analysis with incremental generative topographic mapping: big data challenge. *J. Chem. Inf. Model.* 55, 84–94.
- Gaudêncio, S.P., Pereira, F., 2020. A computer-aided drug design approach to predict marine drug-like leads for SARS-CoV-2 main protease inhibition. *Mar. Drugs* 18, 633.
- Gentile, D., Patamia, V., Scala, A., Sciortino, M.T., Piperno, A., Rescifina, A., 2020. Putative inhibitors of SARS-CoV-2 main protease from a library of marine natural products: a virtual screening and molecular modeling study. *Mar. Drugs* 18, 225.
- Ghosh, K., Amin, S.A., Gayen, S., Jha, T., 2021. Chemical-informatics approach to COVID-19 drug discovery: exploration of important fragments and data mining based prediction of some hits from natural origins as main protease (Mpro) inhibitors. *J. Mol. Struct.* 1224, 129026.
- Gonzalez-Medina, M., Medina-Franco, J.L., 2017. Platform for unified molecular analysis: PUMA. *J. Chem. Inf. Model.* 57, 1735–1740.
- Gopinath, K., Jokinen, E.M., Kurkinen, S.T., Penttinen, O.T., 2020. screening of natural products targeting SARS-CoV-2-ACE2 receptor interface—a MixMD based htvs pipeline. *Front. Chem.* 8, 1084.
- Grisoni, F., Schneider, G., 2019. De novo molecular design with generative long short-term memory. *Chimia* 73, 1006–1011 (Aarau).
- Grosdick, A., Zoete, V., Michielin, O., 2011. SwissDock, a protein-small molecule docking web service based on EADock DSS. *Nucleic Acids Res.* 39, W270–W277.
- Gu, S., Xue, Y., Xue, S., Tang, Y., Hu, Z., Wu, H., Cai, G., Dou, D., 2021. Mechanism of E Lian granule reversing chronic atrophic gastritis with intestinal metaplasia based on integrated pharmacology and GEO gene chip. *Res Sq.* <https://doi.org/10.21203/rs.3.rs-174231/v1>.
- Guo, S., Wu, W.X., Xie, H., Li, Q., Wang, H.B., Duan, J.A., 2020. Molecular mechanism of Bufeif Huoxue capsule on COVID-2019 based on network pharmacology and molecular docking. *Chin. Tradit. Herb. Drugs* 9, 2307–2316.
- Gurung, A.B., Ali, M.A., Lee, J., Farah, M.A., Al-Anazi, K.M., 2021. An updated review of computer-aided drug design and its application to COVID-19. *Biomed. Res. Int.* 2021, 8853056.
- Gyebi, G.A., Adegunloye, A.P., Ibrahim, I.M., Ogunyemi, O.M., Afolabi, S.O., Ogunro, O. B., 2020. Prevention of SARS-CoV-2 cell entry: insight from *in silico* interaction of drug-like alkaloids with spike glycoprotein, human ACE2, and TMPRSS2. *J. Biomol. Struct. Dyn.* 40, 2121–2145.
- Han, L., Wei, X.X., Zheng, Y.J., Zhang, L.L., Wang, X.M., Yang, H.Y., Ma, X., Zhao, L.H., Tong, X.L., 2020. Potential mechanism prediction of cold-damp plague formula against COVID-19 via network pharmacology analysis and molecular docking. *Chin. Med.* 15, 78.
- Hasan, A., Biswas, P., Bondhon, T.A., Jannat, K., Paul, T.K., Paul, A.K., Jahan, R., Nissapatorn, V., Mahboob, T., Wilairatana, P., 2022. Can artemisia herba-alba be useful for managing COVID-19 and comorbidities? *Molecules* 27, 492.
- He, D.D., Zhang, X.K., Zhu, X.Y., Huang, F.F., Wang, Z., Tu, J.C., 2021. Network pharmacology and RNA-sequencing reveal the molecular mechanism of Xuebijing injection on COVID-19-induced cardiac dysfunction. *Comput. Biol. Med.* 131, 104293.
- Heberle, H., Meirelles, G.V., da Silva, F.R., Telles, G.P., Minghim, R., 2015. InteractiVenn: a web-based tool for the analysis of sets through Venn diagrams. *BMC Bioinform.* 16, 1–7.
- Henss, L., Auste, A., Schürmann, C., Schmidt, C., von Rhein, C., Mühlebach, M.D., Schnierle, B.S., 2021. The green tea catechin epigallocatechin gallate inhibits SARS-CoV-2 infection. *J. Gen. Virol.* 102, 001574.
- Hu, B., Guo, H., Zhou, P., Shi, Z.L., 2021a. Characteristics of SARS-CoV-2 and COVID-19. *Nat. Rev. Microbiol.* 19, 141–154.
- Hu, S., Wang, J., Zhang, Y., Bai, H., Wang, C., Wang, N., He, L., 2021b. Three salvianolic acids inhibit 2019-nCoV spike pseudovirus viropexis by binding to both its RBD and receptor ACE2. *J. Med. Virol.* 93, 3143–3151.
- Huang, J., Tao, G., Liu, J., Cai, J., Huang, Z., Chen, J.X., 2020. Current prevention of COVID-19: natural products and herbal medicine. *Front. Pharmacol.* 11, 588508.
- Huang, K., Zhang, P., Zhang, Z., Youn, J.Y., Zhang, H., Cai, H.L., 2021. Traditional Chinese medicine (TCM) in the treatment of viral infections: efficacies and mechanisms. *Pharmacol. Ther.* 225, 107843.
- Humphrey, W., Dalke, A., Schulten, K., 1996. VMD: visual molecular dynamics. *J. Mol. Graph.* 33–38.
- Huynh, T., Wang, H., Cornell, W., Luan, B., 2020. *In Silico* exploration of repurposing and optimizing traditional Chinese medicine rutin for possibly inhibiting SARS-CoV-2's main protease. *ChemRxiv*. <https://doi.org/10.26434/chemrxiv.12281078.v1>.
- Jo, S., Kim, S., Shin, D.H., Kim, M.S., 2020. Inhibition of SARS-CoV 3CL protease by flavonoids. *J. Enzyme Inhib. Med. Chem.* 35, 145–151.
- Joshi, G., Sindhu, J., Thakur, S., Rana, A., Sharma, G., Poduri, R., 2021. Recent efforts for drug identification from phytochemicals against SARS-CoV-2: exploration of the chemical space to identify druggable leads. *Food Chem. Toxicol.* 152, 112160.
- Kalyaanamoorthy, S., Chen, Y.P.P., 2011. Structure-based drug design to augment hit discovery. *Drug Discov. Today* 16, 831–839.
- Kanehisa, M., Goto, S., 2000. KEGG: kyoto encyclopedia of genes and genomes. *Nucleic Acids Res.* 28, 27–30.
- Khan, A., Heng, W., Wang, Y., Qiu, J., Wei, X., Peng, S., Saleem, S., Khan, M., Ali, S.S., Wei, D.Q., 2021. *In silico* and *in vitro* evaluation of kaempferol as a potential inhibitor of the SARS-CoV-2 main protease (3CLpro). *Phytother. Res.* 35, 2841–2845.
- Khanh, N.T., Hoa, T.T., 2021. *In silico* studies of natural products from medicinal plants to identify potential inhibitors for SARS-CoV-2 3C-like protease. *Vietnam J. Chem.* 59, 557–562.
- Khuntia, B.K., Sharma, V., Qazi, S., Das, S., Sharma, S., Raza, K., Sharma, G., 2021. ayurvedic medicinal plants against COVID-19: an *in silico* analysis. *Nat. Prod. Commun.* 16, 1–9, 1934578X211056753.

- Klemm, T., Ebert, G., Calleja, D.J., Allison, C.C., Richardson, L.W., Bernardini, J.P., Lu, B. G.C., Kuchel, N.W., Grohmann, C., Shibata, Y., Gan, Z.Y., Cooney, J.P., Doerflinger, M., Au, A.E., Blackmore, T.R., Heden van Noort, G.J., Geurink, P.P., Ovaia, H., Newman, J., Riboldi-Tunnicliffe, A., Czabotar, P.E., Mitchell, J.P., Feltham, R., Lechtenberg, B.C., Lowes, K.N., Dewson, G., Pellegrini, M., Lessene, G., Komander, D., 2020. Mechanism and inhibition of the papain-like protease, PLpro, of SARS-CoV-2. *EMBO J.* 39, e106275.
- Kong, Q., Wu, Y., Gu, Y., Lv, Q., Qi, F., Gong, S., Chen, X., 2020a. Analysis of the molecular mechanism of Pudinil (PDL) treatment for COVID-19 by network pharmacology tools. *Biomed. Pharmacother.* 128, 110316.
- Kong, R., Yang, G., Xue, R., Liu, M., Wang, F., Hu, J., Guo, X., Chang, S., 2020b. COVID-19 docking server: a meta server for docking small molecules, peptides and antibodies against potential targets of COVID-19. *Bioinformatics* 36, 5109–5111.
- Kumar, B.K., Faheem, Sekhar, K.V.G.C., Ojha, R., Prajapati, V.K., Pai, A., Murugesan, S., 2022. Pharmacophore based virtual screening, molecular docking, molecular dynamics and MM-GBSA approach for identification of prospective SARS-CoV-2 inhibitor from natural product databases. *J. Biomol. Struct. Dyn.* 40, 1363–1386.
- Kumari, M., Subbarao, N., 2021. Deep learning model for virtual screening of novel 3C-like protease enzyme inhibitors against SARS coronavirus diseases. *Comput. Biol. Med.* 132, 104317.
- Land, H., Humble, M.S., 2018. YASARA: a Tool to Obtain Structural Guidance in Biocatalytic Investigations, Protein Engineering. Springer, pp. 43–67.
- Lee, J., Cheng, X., Swails, J.M., Yeom, M.S., Eastman, P.K., Lemkul, J.A., Wei, S., Buckner, J., Jeong, J.C., Qi, Y., 2016. CHARMM-GUI input generator for NAMD, GROMACS, AMBER, OpenMM, and CHARMM/OpenMM simulations using the CHARMM36 additive force field. *J. Chem. Theory Comput.* 12, 405–413.
- Li, H., Wei, W., Xu, H., 2022a. Drug discovery is an eternal challenge for the biomedical sciences. *Acta Mater Medica* 1, 1–3.
- Li, J., Huang, Z., Lu, S., Luo, H., Tan, Y., Ye, P., Liu, X., Wu, Z., Wu, C., Stalin, A., Wang, H., Liu, Y., Shen, L., Fan, X., Zhang, B., Yi, J., Yao, L., Xu, Y., Wu, J., Duan, X., 2021a. Exploring potential mechanisms of Suhexiang Pill against COVID-19 based on network pharmacology and molecular docking. *Medicine* 100, e27112 (Baltimore).
- Li, J., McKay, K.T., Remington, J.M., Schneebeli, S.T., 2021b. A computational study of cooperative binding to multiple SARS-CoV-2 proteins. *Sci. Rep.* 11, 1–9.
- Li, L., Ma, L., Hu, Y., Li, X., Yu, M., Shang, H., Zou, Z., 2022b. Natural biflavones are potent inhibitors against SARS-CoV-2 papain-like protease. *Phytochem* 193, 112984.
- Li, X., Xu, X., Wang, J., Yu, H., Wang, X., Yang, H., Xu, H., Tang, S., Li, Y., Yang, L., 2012. A system-level investigation into the mechanisms of Chinese traditional medicine: compound Danshen formula for cardiovascular disease treatment. *PLoS ONE* 7, e43918.
- Li, Y., Chu, F., Li, P., Johnson, N., Li, T., Wang, Y., An, R., Wu, D., Chen, J., Su, Z., 2021c. Potential effect of Maxing Shigan decoction against coronavirus disease 2019 (COVID-19) revealed by network pharmacology and experimental verification. *J. Ethnopharmacol.* 271, 113854.
- Liao, Q., Chen, Z., Tao, Y., Zhang, B., Wu, X., Yang, L., Wang, Q., Wang, Z., 2021. An integrated method for optimized identification of effective natural inhibitors against SARS-CoV-2 3CLpro. *Sci. Rep.* 11, 1–12.
- Lin, A., Baskin, I.I., Marcou, G., Horvath, D., Beck, B., Varnek, A., 2020a. Parallel generative topographic mapping: an efficient approach for big data handling. *Mol. Inform.* 39, 2000009.
- Lin, E., Lin, C.H., Lane, H.Y., 2020b. Relevant applications of generative adversarial networks in drug design and discovery: molecular de novo design, dimensionality reduction, and de novo peptide and protein design. *Molecules* 25, 3250.
- Lin, H., Wang, X., Liu, M., Huang, M., Shen, Z., Feng, J., Yang, H., Li, Z., Gao, J., Ye, X., 2021. Exploring the treatment of COVID-19 with Yinqiao powder based on network pharmacology. *Phytother. Res.* 35, 2651–2664.
- Lionta, E., Spyrou, G., K Vassiliatis, D., Cournia, Z., 2014. Structure-based virtual screening for drug discovery: principles, applications and recent advances. *Curr. Top. Med. Chem.* 14, 1923–1938.
- Liu, C., Zhu, X., Lu, Y., Zhang, X., Jia, X., Yang, T., 2021a. Potential treatment with Chinese and Western medicine targeting NSP14 of SARS-CoV-2. *J. Pharm. Anal.* 11, 272–277.
- Liu, H., Ye, F., Sun, Q., Liang, H., Li, C., Li, S., Lu, R., Huang, B., Tan, W., Lai, L., 2021b. Scutellaria baicalensis extract and baicalein inhibit replication of SARS-CoV-2 and its 3C-like protease *in vitro*. *J. Enzyme Inhib. Med. Chem.* 36, 497–503.
- Liu, T., Guo, Y., Zhao, J., He, S., Bai, Y., Wang, N., Lin, Y., Liu, Q., Xu, X., 2020. Systems pharmacology and verification of ShenFuHuang formula in zebrafish model reveal multi-scale treatment strategy for septic syndrome in COVID-19. *Front. Pharmacol.* 11, 1464.
- Liu, Z., Guo, F., Wang, Y., Li, C., Zhang, X., Li, H., Diao, L., Gu, J., Wang, W., Li, D., 2016. BATMAN-TCM: a bioinformatics analysis tool for molecular mechanism of traditional Chinese medicine. *Sci. Rep.* 6, 1–11.
- Lyu, M., Fan, G., Xiao, G., Wang, T., Xu, D., Gao, J., Ge, S., Li, Q., Ma, Y., Zhang, H., Wang, J., Cui, Y., Zhang, J., Zhu, Y., Zhang, B., 2021. Traditional Chinese medicine in COVID-19. *Acta Pharm. Sin. B* 11, 3337–3363.
- Mahmud, S., Uddin, M.A.R., Paul, G.K., Shimu, M.S.S., Islam, S., Rahman, E., Islam, A., Islam, M.S., Promi, M.M., Emran, T.B., 2021. Virtual screening and molecular dynamics simulation study of plant-derived compounds to identify potential inhibitors of main protease from SARS-CoV-2. *Brief. Bioinform.* 22, 1402–1414.
- Mazzini, S., Musso, L., Dallavalle, S., Artali, R., 2020. Putative SARS-CoV-2 Mpro inhibitors from an in-house library of natural and nature-inspired products: a virtual screening and molecular docking study. *Molecules* 25, 3745.
- Medina-Franco, J.L., Sánchez-Cruz, N., López-López, E., Díaz-Eufracio, B.I., 2021. Progress on open chemoinformatic tools for expanding and exploring the chemical space. *J. Comput. Aided Mol. Des.* 1–14. <https://doi.org/10.1007/s10822-021-00399-1>.
- Mei, J., Zhou, Y., Yang, X., Zhang, F., Liu, X., Yu, B., 2021. Active components in Ephedra sinica Stapf disrupt the interaction between ACE2 and SARS-CoV-2 RBD: potent COVID-19 therapeutic agents. *J. Ethnopharmacol.* 278, 114303.
- Mering, C.v., Hutyne, M., Jaeggi, D., Schmidt, S., Bork, P., Snel, B., 2003. STRING: a database of predicted functional associations between proteins. *Nucleic Acids Res.* 31, 258–261.
- Merk, D., Friedrich, L., Grisoni, F., Schneider, G., 2018. De novo design of bioactive small molecules by artificial intelligence. *Mol. Inform.* 37, 1700153.
- Morris, G.M., Huey, R., Olson, A.J., 2008. Using AutoDock for ligand-receptor docking. *Curr. Protoc. Bioinformatics.* <https://doi.org/10.1002/0471250953.bi0814s24>.
- Mu, C., Sheng, Y., Wang, Q., Amin, A., Li, X., Xie, Y., 2021. Potential compound from herbal food of *Rhizoma polygonati* for treatment of COVID-19 analyzed by network pharmacology: viral and cancer signaling mechanisms. *J. Funct. Foods* 77, 104149.
- Muratov, E.N., Amaro, R., Andrade, C.H., Brown, N., Ekins, S., Fourches, D., Isayev, O., Kozakov, D., Medina-Franco, J.L., Merz, K.M., 2021. A critical overview of computational approaches employed for COVID-19 drug discovery. *Chem. Soc. Rev.* 50, 9121–9151.
- Murugan, N.A., Pandian, C.J., Jeyakanthan, J., 2021. Computational investigation on *Andrographis paniculata* phytochemicals to evaluate their potency against SARS-CoV-2 in comparison to known antiviral compounds in drug trials. *J. Biomol. Struct. Dyn.* 39, 4415–4426.
- Nawrot-Hadzik, I., Zmudzinski, M., Matkowski, A., Preissner, R., Kesik-Brodacka, M., Hadzik, J., Drag, M., Abel, R., 2021. Reynoutria rhizomes as a natural source of SARS-CoV-2 Mpro inhibitors-molecular docking and *in vitro* study. *Pharmaceuticals* 14, 742 (Basel).
- Niu, W.H., Wu, F., Cao, W.Y., Wu, Z.G., Chao, Y.C., Peng, F., Liang, C., 2021. Network pharmacology for the identification of phytochemicals in traditional Chinese medicine for COVID-19 that may regulate interleukin-6. *Biosci. Rep.* 41, BSR20202583.
- Owen Dafydd, R., Allerton Charlotte, M.N., Anderson Annaliesia, S., Aschenbrenner, L., Avery, M., Berritt, S., Boras, B., Cardin Rhonda, D., Carlo, A., Coffman Karen, J., Dantonio, A., Di, L., Eng, H., Ferre, R., Gajiwala Ketan, S., Gibson Scott, A., Greasley Samantha, E., Hurst Brett, L., Kadar Eugene, P., Kalgutkar Amit, S., Lee Jack, C., Lee, J., Liu, W., Mason Stephen, W., Noell, S., Novak Jonathan, J., Obach, R.S., Ogilvie, K., Patel Nandini, C., Pettersson, M., Rai Devendra, K., Reese Matthew, R., Sammons Matthew, F., Sathish Jean, G., Singh Ravi Shankar, P., Stepan Claire, M., Stewart Al, E., Tuttle Jamison, B., Updyke, L., Verhoest Patrick, R., Wei, L., Yang, Q., Zhu, Y., 2021. An oral SARS-CoV-2 Mpro inhibitor clinical candidate for the treatment of COVID-19. *Science* 374, 1586–1593.
- Pamuru, R.R., Ponneri, N., Damu, G.A., Vadde, R., 2020. Targeting natural products for the treatment of COVID-19 – an updated review. *Curr. Pharm. Des.* 26, 5278–5285.
- Patel, C.N., Jani, S.P., Jaiswal, D.G., Kumar, S.P., Mangukia, N., Parmar, R.M., Rawal, R. M., Pandya, H.A., 2021. Identification of antiviral phytochemicals as a potential SARS-CoV-2 main protease (Mpro) inhibitor using docking and molecular dynamics simulations. *Sci. Rep.* 11, 1–13.
- Peng, W., Xu, Y., Han, D., Feng, F., Wang, Z., Gu, C., Zhou, X., Wu, Q., 2020. Potential mechanism underlying the effect of matrine on COVID-19 patients revealed through network pharmacological approaches and molecular docking analysis. *Arch. Physiol. Biochem.* 1–8.
- Phillips, J.C., Braun, R., Wang, W., Gumbart, J., Tajkhorshid, E., Villa, E., Chipot, C., Skeel, R.D., Kale, L., Schulten, K., 2005. Scalable molecular dynamics with NAMD. *J. Comput. Chem.* 26, 1781–1802.
- Pitsillou, E., Liang, J., Ververis, K., Hung, A., Karagiannis, T.C., 2021. Interaction of small molecules with the SARS-CoV-2 papain-like protease: *in silico* studies and *in vitro* validation of protease activity inhibition using an enzymatic inhibition assay. *J. Mol. Graph. Model.* 104, 107851.
- Pogány, P., Arad, N., Genway, S., Pickett, S.D., 2019. De novo molecule design by translating from reduced graphs to SMILES. *J. Chem. Inf. Model.* 59, 1136–1146.
- Polishchuk, P., Tinkov, O., Khristova, T., Ognichenko, L., Kosinskaya, A., Varnek, A., Kuz'min, V., 2016. Structural and physico-chemical interpretation (SPCI) of QSAR models and its comparison with matched molecular pair analysis. *J. Chem. Inf. Model.* 56, 1455–1469.
- Prasanth, D., Murahari, M., Chandramohan, V., Bhavya, G., Lakshmana Rao, A., Panda, S.P., Rao, G.K., Chakravarthi, G., Teja, N., Suguna Rani, P., 2021. *In-silico* strategies of some selected phytoconstituents from *Melissa officinalis* as SARS CoV-2 main protease and spike protein (COVID-19) inhibitors. *Mol. Simul.* 1–14. <https://doi.org/10.1080/08927022.2021.1880576>.
- Rackers, J.A., Wang, Z., Lu, C., Laury, M.L., Lagardère, L., Schnieders, M.J., Piquemal, J. P., Ren, P., Ponder, J.W., 2018. Tinker 8: software tools for molecular design. *J. Chem. Theory Comput.* 14, 5273–5289.
- Rahman, N., Basharat, Z., Yousuf, M., Castaldo, G., Rastrelli, L., Khan, H., 2020. Virtual screening of natural products against type II transmembrane serine protease (TMPRSS2), the priming agent of coronavirus 2 (SARS-CoV-2). *Molecules* 25, 2271.
- Raj, V., Park, J.G., Cho, K.H., Choi, P., Kim, T., Ham, J., Lee, J., 2021. Assessment of antiviral potencies of cannabinoids against SARS-CoV-2 using computational and *in vitro* approaches. *Int. J. Biol. Macromol.* 168, 474–485.
- Rajpoot, S., Alagumuthu, M., Baig, M.S., 2021. Dual targeting of 3clpro and Plpro of Sars-Cov-2: a novel structure-based design approach to treat COVID-19. *Curr. Res. Struct. Biol.* 3, 9–18.
- Rakib, A., Paul, A., Chy, M., Uddin, N., Sami, S.A., Baral, S.K., Majumder, M., Tareq, A. M., Amin, M.N., Shahriar, A., 2020. Biochemical and computational approach of selected phytochemicals from *Tinospora crispa* in the management of COVID-19. *Molecules* 25, 3936.

- Ram, T.S., Munikumar, M., Raju, V.N., Devaraj, P., Boiroju, N.K., Hemalatha, R., Prasad, P., Gundeti, M., Sisodia, B.S., Pawar, S., 2021. *In silico* evaluation of the compounds of the ayurvedic drug, AYUSH-64, for the action against the SARS-CoV-2 main protease. *J. Ayurveda Integr. Med.* 13, 100413.
- Rauf, A., Rashid, U., Khalil, A.A., Khan, S.A., Anwar, S., Alafnan, A., Alamri, A., Rengasamy, K.R., 2021. Docking-based virtual screening and identification of potential COVID-19 main protease inhibitors from brown algae. *S. Afr. J. Bot.* 143, 428–434.
- Rebhan, M., Chalifa-Caspi, V., Prilusky, J., Lancet, D., 1997. GeneCards: integrating information about genes, proteins and diseases. *Trends Genet.* 13, 163–163.
- Ru, J., Li, P., Wang, J., Zhou, W., Li, B., Huang, C., Li, P., Guo, Z., Tao, W., Yang, Y., 2014. TCMSP: a database of systems pharmacology for drug discovery from herbal medicines. *J. Cheminform.* 6, 1–6.
- Ruan, X., Du, P., Zhao, K., Huang, J., Xia, H., Dai, D., Huang, S., Cui, X., Liu, L., Zhang, J., 2020. Mechanism of Dayuanyin in the treatment of coronavirus disease 2019 based on network pharmacology and molecular docking. *Chin. Med.* 15, 62.
- Saidijam, M., Khaksarimehr, N., Rezaei-Tavirani, M., Taherkhani, A., 2021. Bioinformatics prediction of potential inhibitors for the SARS-CoV-2 NTPase/Helicase using molecular docking and dynamics simulation from organic phenolic compounds. *J. Cell. Mol. Anesth.* 6, 222–239.
- Sattarov, B., Baskin, I.I., Horvath, D., Marcou, G., Bjerrum, E.J., Varnek, A., 2019. De novo molecular design by combining deep autoencoder recurrent neural networks with generative topographic mapping. *J. Chem. Inf. Model.* 59, 1182–1196.
- Sawant, S., Patil, R., Khawate, M., Zambre, V., Shilimkar, V., Jagtap, S., 2021. Computational assessment of select antiviral phytochemicals as potential SARS-CoV-2 main protease inhibitors: molecular dynamics guided ensemble docking and extended molecular dynamics. *In Silico Pharmacol.* 9, 1–17.
- Schneider, G., Clark, D.E., 2019. Automated de novo drug design: are we nearly there yet? *Angew. Chem. Int. Ed.* 58, 10792–10803. Engl.
- Selvaraj, C., Dinesh, D.C., Panwar, U., Abhirami, R., Boura, E., Singh, S.K., 2021a. Structure-based virtual screening and molecular dynamics simulation of SARS-CoV-2 Guanine-N7 methyltransferase (nsp14) for identifying antiviral inhibitors against COVID-19. *J. Biomol. Struct. Dyn.* 39, 4582–4593.
- Selvaraj, C., Panwar, U., Dinesh, D.C., Boura, E., Singh, P., Dubey, V.K., Singh, S.K., 2021b. Microsecond MD simulation and multiple-conformation virtual screening to identify potential anti-COVID-19 inhibitors against SARS-CoV-2 main protease. *Front. Chem.* 8, 595273.
- Shah, S., Chaple, D., Arora, S., Yende, S., Mehta, C., Nayak, U., 2021. Prospecting for *Cressa cretica* to treat COVID-19 via *in silico* molecular docking models of the SARS-CoV-2. *J. Biomol. Struct. Dyn.* 1–10. <https://doi.org/10.1080/07391102.2021.1872419>.
- Shannon, P., Markiel, A., Ozier, O., Baliga, N.S., Wang, J.T., Ramage, D., Amin, N., Schwikowski, B., Ideker, T., 2003. Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome Res.* 13, 2498–2504.
- Shawky, E., Nada, A.A., Ibrahim, R.S., 2020. Potential role of medicinal plants and their constituents in the mitigation of SARS-CoV-2: identifying related therapeutic targets using network pharmacology and molecular docking analyses. *RSC Adv.* 10, 27961–27983.
- Shin, D., Mukherjee, R., Grewe, D., Bojkova, D., Baek, K., Bhattacharya, A., Schulz, L., Widera, M., Mehdipour, A.R., Tascher, G., 2020. Papain-like protease regulates SARS-CoV-2 viral spread and innate immunity. *Nature* 587, 657–662.
- Shree, P., Mishra, P., Selvaraj, C., Singh, S.K., Chauhan, R., Garg, N., Tripathi, Y.B., 2022. Targeting COVID-19 (SARS-CoV-2) main protease through active phytochemicals of ayurvedic medicinal plants—*Withania somnifera* (Ashwagandha), *Tinospora cordifolia* (Giloy) and *Ocimum sanctum* (Tulsi)—a molecular docking study. *J. Biomol. Struct. Dyn.* 40, 190–203.
- Simayi, J., Nuermaimaiti, M., Wuaimaier, A., Khan, N., Yusufu, M., Nuer, M., Maihemuti, N., Bayinsang, Adurusul, K., Zhou, W., 2022. Analysis of the active components and mechanism of Shufeng Jiedu capsule against COVID-19 based on network pharmacology and molecular docking. *Medicine* 101, e28286 (Baltimore).
- Şimşek, Y., Baran, S.S., Aslim, B., 2021. *In silico* identification of SARS-CoV-2 cell entry inhibitors from selected natural antivirals. *J. Mol. Graph. Model.* 109, 108038.
- Singh, J., Malik, D., Raina, A., 2022. Computational investigation for identification of potential phytochemicals and antiviral drugs as potential inhibitors for RNA-dependent RNA polymerase of COVID-19. *J. Biomol. Struct. Dyn.* 40, 3492–3507.
- Sinha, S.K., Prasad, S.K., Islam, M.A., Chaudhary, S.K., Singh, S., Shakya, A., 2021a. Potential leads from liquorice against SARS-CoV-2 main protease using molecular docking simulation studies. *Comb. Chem. High Throughput Screen.* 24, 591–597.
- Sinha, S.K., Prasad, S.K., Islam, M.A., Gurav, S.S., Patil, R.B., AlFaris, N.A., Aldayel, T.S., AlKehayez, N.M., Wabaidur, S.M., Shakya, A., 2020. Identification of bioactive compounds from *Glycyrrhiza glabra* as possible inhibitor of SARS-CoV-2 spike glycoprotein and non-structural protein-15: a pharmacoinformatics study. *J. Biomol. Struct. Dyn.* 1–15.
- Sinha, S.K., Shakya, A., Prasad, S.K., Singh, S., Gurav, N.S., Prasad, R.S., Gurav, S.S., 2021b. An *in-silico* evaluation of different Saikosaponins for their potency against SARS-CoV-2 using NSP15 and fusion spike glycoprotein as targets. *J. Biomol. Struct. Dyn.* 39, 3244–3255.
- Sivaraman, D., Pradeep, P.S., 2020. Revealing anti-viral potential of bio-active therapeutics targeting SARS-CoV2-polymerase (RdRp) in combating COVID-19: Molecular investigation on Indian traditional medicines. Preprints. <https://doi.org/10.20944/preprints202003.0450.v1>.
- Song, L.F., Lee, T.S., Zhu, C., York, D.M., Merz, K.M., 2019. Using AMBER18 for relative free energy calculations. *J. Chem. Inf. Model.* 59, 3128–3135.
- Sorokina, M., Merseburger, P., Rajan, K., Yirik, M.A., Steinbeck, C., 2021. COCONUT online: collection of open natural products database. *J. Cheminform.* 13, 1–13.
- Su, H.X., Yao, S., Zhao, W.F., Li, M.J., Liu, J., Shang, W.J., Xie, H., Ke, C.Q., Hu, H.C., Gao, M.N., 2020. Anti-SARS-CoV-2 activities *in vitro* of Shuanghuanglian preparations and bioactive ingredients. *Acta Pharm. Sin.* 41, 1167–1177.
- Swargiary, A., Mahmud, S., Saleh, M.A., 2020. Screening of phytochemicals as potent inhibitor of 3-chymotrypsin and papain-like proteases of SARS-CoV2: an *in silico* approach to combat COVID-19. *J. Biomol. Struct. Dyn.* 1–15.
- Tahir Ul Qamar, M., Alqahtani, S.M., Alamri, M.A., Chen, L.L., 2020. Structural basis of SARS-CoV-2 3CL(pro) and anti-COVID-19 drug discovery from medicinal plants. *J. Pharm. Anal.* 10, 313–319.
- Tao, Z., Zhang, L., Friedemann, T., Yang, G., Li, J., Wen, Y., Wang, J., Shen, A., 2020. Systematic analyses on the potential immune and anti-inflammatory mechanisms of Shufeng Jiedu capsule against severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2)-caused pneumonia. *J. Funct. Foods* 75, 104243.
- Tejera, E., Perez-Castillo, Y., Toscano, G., Noboa, A.L., Ochoa-Herrera, V., Giampieri, F., Alvarez-Suarez, J.M., 2022. Computational modeling predicts potential effects of the herbal infusion "horchata" against COVID-19. *Food Chem.* 366, 130589.
- Tiwari, A., Singh, S., 2022. Computational approaches in drug designing. *Bioinformatics* 207–217.
- Trott, O., Olson, A.J., 2010. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *J. Comput. Chem.* 31, 455–461.
- ul Qamar, M.T., Alqahtani, S.M., Alamri, M.A., Chen, L.L., 2020. Structural basis of SARS-CoV-2 3CLpro and anti-COVID-19 drug discovery from medicinal plants. *J. Pharm. Anal.* 10, 313–319.
- Umesh, Kundu, D., Selvaraj, C., Singh, S.K., Dubey, V.K., 2021. Identification of new anti-nCoV drug chemical compounds from Indian spices exploiting SARS-CoV-2 main protease as target. *J. Biomol. Struct. Dyn.* 39, 3428–3434.
- Van Santen, J.A., Jacob, G., Singh, A.L., Aniebok, V., Balunas, M.J., Bunsko, D., Neto, F. C., Castaño-Espriu, L., Chang, C., Clark, T.N., 2019. The natural products atlas: an open access knowledge base for microbial natural products discovery. *ACS Cent. Sci.* 5, 1824–1833.
- Vardhan, S., Sahoo, S.K., 2022. Exploring the therapeutic nature of limonoids and triterpenoids against SARS-CoV-2 by targeting nsp13, nsp14, and nsp15 through molecular docking and dynamics simulations. *J. Tradit. Complement Med.* 12, 44–54.
- Verdonk, M.L., Cole, J.C., Hartshorn, M.J., Murray, C.W., Taylor, R.D., 2003. Improved protein–ligand docking using GOLD. *Proteins* 52, 609–623.
- Verma, S., Twilley, D., Esmear, T., Oosthuizen, C.B., Reid, A.M., Nel, M., Lall, N., 2020. Anti-SARS-CoV natural products with the potential to inhibit SARS-CoV-2 (COVID-19). *Front. Pharmacol.* 11, 561334.
- Vetrivel, U., Deshpande, S., Hegde, H.V., Singh, I., Chattopadhyay, D., 2021. Phytochemical moieties from Indian traditional medicine for targeting dual hotspots on SARS-CoV-2 spike protein: an integrative *in-silico* approach. *Front. Med.* 8, 672629 (Lausanne).
- Vilar, S., Cozza, G., Moro, S., 2008. Medicinal chemistry and the molecular operating environment (MOE): application of QSAR and molecular docking to drug discovery. *Curr. Top. Med. Chem.* 8, 1555–1572.
- Wang, B., Sun, X., Kong, X., Gao, Y., 2021a. Systematic elucidation of the mechanism of Jingyin granule in the treatment of Novel Coronavirus (COVID-19) pneumonia via network pharmacology. *Int. J. Med. Sci.* 18, 1648.
- Wang, Y., 2020. A novel Chinese traditional medicine prescription recommendation system based on knowledge graph. *J. Phys. Conf. Ser.* 1487, 012019. IOP Publishing.
- Wang, Y., Gu, W., Kui, F., Gao, F., Niu, Y., Li, W., Zhang, Y., Guo, Z., Du, G., 2021b. The mechanism and active compounds of semen armeniacae amarum treating coronavirus disease 2019 based on network pharmacology and molecular docking. *Food Nutr. Res.* 65 <https://doi.org/10.29219/fnr.v65.5623>.
- Wei, T.Z., Zhang, H., Wu, X.Q., Lu, Y., Guan, S.H., Dong, F.Q., Dong, C.L., Zhu, G.L., Bao, Y.Z., Wang, J., Wang, G.Y., Li, H.Y., 2020. *In silico* screening of potential spike glycoprotein inhibitors of SARS-CoV-2 with drug repurposing strategy. *Chin. J. Integr. Med.* 26, 663–669.
- Wilkinson, M.D., Dumontier, M., Aalbersberg, I.J., Appleton, G., Axton, M., Baak, A., Blomberg, N., Boiten, J.W., da Silva Santos, L.B., Bourne, P.E., 2016. The FAIR guiding principles for scientific data management and stewardship. *Sci. Data* 3, 1–9.
- Wu, H., Gong, K., Qin, Y., Yuan, Z., Xia, S., Zhang, S., Yang, J., Yang, P., Li, L., Xie, M., 2021a. *In silico* analysis of the potential mechanism of a preventive Chinese medicine formula on coronavirus disease 2019. *J. Ethnopharmacol.* 275, 114098.
- Wu, Y., Zhang, F., Yang, K., Fang, S., Bu, D., Li, H., Sun, L., Hu, H., Gao, K., Wang, W., 2019. SymMap: an integrative database of traditional Chinese medicine enhanced by symptom mapping. *Nucleic Acids Res.* 47, D1110–D1117.
- Wu, Z., Chen, X., Ni, W., Zhou, D., Chai, S., Ye, W., Zhang, Z., Guo, Y., Ren, L., Zeng, Y., 2021b. The inhibition of Mpro, the primary protease of COVID-19, by *Poria cocos* and its active compounds: a network pharmacology and molecular docking study. *RSC Adv.* 11, 11821–11843.
- Xia, Q.D., Xun, Y., Lu, J.L., Lu, Y.C., Yang, Y.Y., Zhou, P., Hu, J., Li, C., Wang, S.G., 2020. Network pharmacology and molecular docking analyses on Lianhua Qingwen capsule indicate Akt1 is a potential target to treat and prevent COVID-19. *Cell Prolif.* 53, e12949.
- Xiao, T., Cui, M., Zheng, C., Wang, M., Sun, R., Gao, D., Bao, J., Ren, S., Yang, B., Lin, J., 2021. Myricetin inhibits SARS-CoV-2 viral replication by targeting mpro and ameliorates pulmonary inflammation. *Front. Pharmacol.* 12, 1012.
- Xie, P., Jin, X., Lai, Y., 2021a. The active ingredients of Huanglian Jiedu decoction in treatment of COVID-19 based on network pharmacology, molecular docking and molecular dynamics simulation. *TMR Modern Herb. Med.* 4, 3.
- Xie, R., Lin, Z., Zhong, C., Li, S., Chen, B., Wu, Y., Huang, L., Yao, H., Shi, P., Huang, J., 2021b. Deciphering the potential anti-COVID-19 active ingredients in *Andrographis*

- paniculata (Burm. F.) Nees by combination of network pharmacology, molecular docking, and molecular dynamics. *Rsc Adv.* 11, 36511–36517.
- Xinqiang, S., Yu, Z., Erqin, D., Yajun, Y., Lei, W., Hongtao, D., 2020. Screening of active ingredients from traditional Chinese medicine against the Novel Coronavirus based on molecular docking. *J. Xinyang Norm. Univ.* 33, 210–219 (Natural Science Edition).
- Xiong, H., Dong, Z., Lou, G., Gan, Q., Wang, J., Huang, Q., 2020. Analysis of the mechanism of Shufeng Jiedu capsule prevention and treatment for COVID-19 by network pharmacology tools. *Eur. J. Integr. Med.* 40, 101241.
- Xu, H., Zhang, Y., Wang, P., Zhang, J., Chen, H., Zhang, L., Du, X., Zhao, C., Wu, D., Liu, F., 2021a. A comprehensive review of integrative pharmacology-based investigation: a paradigm shift in traditional Chinese medicine. *Acta Pharm. Sin. B* 11, 1379–1399.
- Xu, J., Gao, L., Liang, H., Chen, S.D., 2021b. *In silico* screening of potential anti-COVID-19 bioactive natural constituents from food sources by molecular docking. *Nutrition* 82, 111049.
- Xue, R., Fang, Z., Zhang, M., Yi, Z., Wen, C., Shi, T., 2012. TCMID: traditional Chinese medicine integrative database for herb molecular mechanism analysis. *Nucleic Acids Res.* 41, D1089–D1095.
- Yang, X., Wang, Y., Byrne, R., Schneider, G., Yang, S., 2019. Concepts of artificial intelligence for computer-assisted drug discovery. *Chem. Rev.* 119, 10520–10594.
- Yan, C., Qingyue, G., Jingjing, Q., Chenlin, L., Xing, Z., Haoyu, W., Rixin, W., Meilin, Z., Junkang, S., Kongfa, H., 2020. Design of knowledge graph of traditional Chinese medicine prescription and knowledge analysis of implicit relationship. *ISAIMS 2020* 56–63.
- Yang, J., 2013. Application of computer-aided drug design to traditional Chinese medicine. *Int J Org Chem* 3, 1–16.
- Yang, Y., Islam, M.S., Wang, J., Li, Y., Chen, X., 2020. Traditional Chinese medicine in the treatment of patients infected with 2019-new coronavirus (SARS-CoV-2): a review and perspective. *Int. J. Biol. Sci.* 16, 1708.
- Yazdani, S., De Maio, N., Ding, Y., Shahani, V., Goldman, N., Schapira, M., 2021. Genetic variability of the SARS-CoV-2 pocketome. *J. Proteome Res.* 20, 4212–4215.
- Ye, C., Gao, M., Lin, W., Yu, K., Li, P., Chen, G., 2020. Theoretical study of the anti-NCP molecular mechanism of traditional Chinese medicine Lianhua-Qingwen Formula (LQF). *ChemRxiv*. <https://doi.org/10.26434/chemrxiv.12016236.v1>.
- Ye, M., Luo, G., Ye, D., She, M., Sun, N., Lu, Y.J., Zheng, J., 2021. Network pharmacology, molecular docking integrated surface plasmon resonance technology reveals the mechanism of Toujie Quwen Granules against coronavirus disease 2019 pneumonia. *Phytomedicine* 85, 153401.
- Yu, G., Wang, L.G., Han, Y., He, Q.Y., 2012. clusterProfiler: an R package for comparing biological themes among gene clusters. *Omics J. Integr. Biol.* 16, 284–287.
- Yu, J.W., Wang, L., Bao, L.D., 2020. Exploring the active compounds of traditional Mongolian medicine in intervention of novel coronavirus (COVID-19) based on molecular docking method. *J. Funct. Foods* 71, 104016.
- Yu, R., Li, P., 2022. Screening of potential spike glycoprotein/ACE2 dual antagonists against COVID-19 *in silico* molecular docking. *J. Virol. Methods.* 301, 114424.
- Yu, S., Zhu, Y., Xu, J., Yao, G., Zhang, P., Wang, M., Zhao, Y., Lin, G., Chen, H., Chen, L., 2021. Glycyrrhizic acid exerts inhibitory activity against the spike protein of SARS-CoV-2. *Phytomedicine* 85, 153364.
- Yu, T., Li, J., Yu, Q., Tian, Y., Shun, X., Xu, L., Zhu, L., Gao, H., 2017. Knowledge graph for TCM health preservation: design, construction, and applications. *Artif. Intell. Med.* 77, 48–52.
- Zabolotna, Y., Ertl, P., Horvath, D., Bonachera, F., Marcou, G., Varnek, A., 2021. NP Navigator: a new look at the natural product chemical space. *Mol. Inform.* 40, e2100068.
- Zackria, A.A., Pattabiraman, R., Murthy, T., Kumar, S.B., Mathew, B.B., Biju, V.G., 2022. Computational screening of natural compounds from *Salvia plebeia* R. Br. for inhibition of SARS-CoV-2 main protease. *Vegetos* 35, 345–359.
- Zaki, A.A., Ashour, A., Elhady, S.S., Darwish, K.M., Al-Karmalawy, A.A., 2021. Calendulaglycoside A showing potential activity against SARS-CoV-2 main protease: molecular docking, molecular dynamics, and SAR studies. *J. Tradit. Complement Med.* 12, 16–34.
- Zhang, X., Gao, R., Zhou, Z., Tang, X., Lin, J., Wang, L., Zhou, X., Shen, T., 2021a. A network pharmacology based approach for predicting active ingredients and potential mechanism of Lianhuaqingwen capsule in treating COVID-19. *Int. J. Med. Sci.* 18, 1866.
- Zhang, Y., Lu, L., Liu, Y., Yang, A., Yang, Y., 2021b. Predicting the molecular mechanism of Shenling Baizhu San in treating convalescent patients with COVID-19 based on network pharmacology and molecular docking. *Nat. Prod. Commun.* 16, 1–17.
- Zhang, Z.J., Wu, W.Y., Hou, J.J., Zhang, L.L., Li, F.F., Gao, L., Wu, X.D., Shi, J.Y., Zhang, R., Long, H.L., 2020. Active constituents and mechanisms of Respiratory Detox Shot, a traditional Chinese medicine prescription, for COVID-19 control and prevention: network-molecular docking-LC-MSE analysis. *J. Integr. Med.* 18, 229–241.
- Zhao, J., Tian, S., Lu, D., Yang, J., Zeng, H., Zhang, F., Tu, D., Ge, G., Zheng, Y., Shi, T., Xu, X., Zhao, S., Yang, Y., Zhang, W., 2021a. Systems pharmacological study illustrates the immune regulation, anti-infection, anti-inflammation, and multi-organ protection mechanism of Qing-Fei-Pai-Du decoction in the treatment of COVID-19. *Phytomedicine* 85, 153315.
- Zhao, K., Shi, N., Sa, Z., Wang, H.X., Lu, C.H., Xu, X.Y., 2020a. Text mining and analysis of treatise on febrile diseases based on natural language processing. *World J. Tradit. Chin. Med.* 6, 67.
- Zhao, Y., Du, X., Duan, Y., Pan, X., Sun, Y., You, T., Han, L., Jin, Z., Shang, W., Yu, J., 2021b. High-throughput screening identifies established drugs as SARS-CoV-2 PLpro inhibitors. *Protein Cell* 12, 877–888.
- Zhao, Y., Hu, J., Song, J., Zhao, X., Shi, Y., Jiang, Y., 2020b. Exploration on Shufeng Jiedu capsule for treatment of COVID-19 based on network pharmacology and molecular docking. *Chin. Med.* 11, 9.
- Zhao, Y., Tian, Y., Pan, C., Liang, A., Zhang, W., Sheng, Y., 2021c. Target-based *in silico* screening for phytoactive compounds targeting SARS-CoV-2. *Interdiscip. Sci.* 14, 64–79.
- Zhao, Z., Li, Y., Zhou, L., Zhou, X., Xie, B., Zhang, W., Sun, J., 2021d. Prevention and treatment of COVID-19 using traditional Chinese medicine: a review. *Phytomedicine* 85, 153308.
- Zheng, W.J., Yan, Q., Ni, Y.S., Zhan, S.F., Yang, L.L., Zhuang, H.F., Liu, X.H., Jiang, Y., 2020. Examining the effector mechanisms of Xuebijing injection on COVID-19 based on network pharmacology. *BioData Min* 13, 17.