Computational Screening and Integrated Literature Evidence Analysis of Traditional Chinese Medicine Natural Products for COVID-19

Authors: Gao Min, ZHU Yuexing, Xiong Jianghui, Xiong Jianghui

Date: 2020-02-17T00:00:00+00:00

Abstract

Drug repositioning (old drugs for new uses) strategy holds unique application prospects in emerging infectious diseases. We previously proposed a novel drug repositioning system—aCODE, which can predict potentially effective natural products based on limited information during the early stages of a disease epidemic. This study, based on computational tools and literature evidence, conducts a theoretical investigation into traditional Chinese medicine natural products that may play a role in the prevention and treatment of coronavirus disease 2019 (COVID-19), revealing that: (1) Literature review identified a total of 56 natural product components experimentally validated to have anti-coronavirus activity, which can target both structural and non-structural proteins of coronaviruses; (2) Comparing the anti-coronavirus natural product components predicted by the aCODE system with literature evidence, the intersection includes emodin, glycyrrhizic acid, ginsenoside R1, reserpine, and myricetin, among others. Emodin can disrupt the interaction between the coronavirus S protein and host ACE2, preventing viral entry into host cells; it also possesses the ability to inhibit the 3a protein ion channel, preventing viral release. Glycyrrhizic acid or its derivatives are also candidate drugs of significant interest to domestic research teams in COVID-19 treatment studies, and have entered clinical trials. (3) Regarding the large number of aromatic compounds appearing in the traditional Chinese medicine prediction results, the aCODE system incorporated aromatic plant extract data sources, and computational analysis revealed that aminocinnamic acid, cinnamaldehyde, anethole, perillyl alcohol, linalool, and limonene possess potential antiviral effects, suggesting that the cellular and molecular mechanisms of "aromatic pathogen repelling" warrant further in-depth investigation.

Full Text

Preamble

Natural Products for COVID-19 by Integrating Computational Screening and Literature Evidence

Min Gao[12], Yuexing Zhu , Jianghui Xiong[23] *

[1] Beijing Aroma Valley Technology Co., Ltd., Beijing, 100080
*Corresponding author: Jianghui Xiong, E-mail: xiongjh77@163.com

Abstract Drug repurposing strategies hold unique promise for emerging infectious diseases. We previously proposed a novel drug repositioning system—aCODE—that can predict potentially effective natural products based on limited information during the early stages of a disease outbreak. This study presents a theoretical investigation of traditional Chinese medicine (TCM) natural products that may play a role in COVID-19 prevention and treatment, integrating computational tools with literature evidence. Our findings reveal: (1) Literature review identified 56 natural product components experimentally validated to possess anti-coronavirus activity, targeting both structural and non-structural proteins of coronaviruses; (2) Comparing aCODE-predicted anti-coronavirus natural product components with literature evidence shows overlaps including emodin, glycyrrhizin, ginsenoside Rb1, reserpine, and myricetin. Emodin can disrupt the interaction between the coronavirus S protein and host ACE2, preventing viral entry into host cells, while also inhibiting the 3a protein ion channel to block viral release. Glycyrrhizin and its derivatives have also been prioritized by domestic research teams for COVID-19 treatment and have entered clinical trials; (3) Given the prevalence of aromatic compounds in the prediction results, the aCODE system incorporated aromatic plant extract data sources, computationally identifying amino cinnamic acid, cinnamaldehyde, anethole, perillyl alcohol, linalool, and limonene as potentially antiviral. This suggests that the cellular and molecular mechanisms underlying the traditional concept of "aromatic pathogen repulsion" warrant further investigation.

Keywords: COVID-19; drug repurposing; natural products; aromatic Chinese medicine

1. Introduction

The COVID-19 pandemic has refocused global attention on anti-coronavirus drug development, urgently necessitating the identification of effective therapeutics against SARS-CoV-2. Retrospective studies reveal that numerous SARS and COVID-19 patients received empirical clinical treatments such as the synthetic nucleoside analog ribavirin, corticosteroids, and type I interferons, yet these drugs carry severe side effects (Yi et al. 2004; Chen et al. 2008; Yu et al. 2012; Wang et al. 2020). During the 2003 SARS outbreak in mainland China, approximately 50% of patients received Chinese herbal medicine as adjunctive therapy alongside Western medicine, with this integrative approach

demonstrating some positive effects (Schwarz et al. 2011).

Coronaviruses are enveloped, positive-sense single-stranded RNA viruses with a typical genome size of approximately 30 kb, encoding non-structural proteins required for viral RNA synthesis, structural proteins, and various accessory proteins (Li and De Clercq 2020). Key proteins include the 3-chymotrypsin-like protease (3CLpro), papain-like protease, helicase, RNA-dependent RNA polymerase (RdRp), spike protein (S), envelope protein (E), membrane protein (M), and nucleocapsid protein (N). Over the past seventeen years, researchers have explored numerous natural product components for their inhibitory activity against these critical coronavirus proteins, or have directly validated small molecules' effects on coronavirus infection through cellular experiments.

Despite recognizing the importance of natural products for coronavirus treatment and identifying several highly active compounds, experimental screening of effective antiviral components from the vast natural product library remains a monumental challenge. Therefore, applying drug repurposing techniques through computational tools to rapidly identify the most promising natural products for subsequent experimental validation could significantly accelerate drug discovery.

Drug repurposing is considered one of the most promising translational medicine strategies, as it not only maximizes the value of existing drugs but also avoids drug development failures due to ADME/T property deficiencies (Wang and Zhang 2013). Identifying new uses for existing drugs typically relies on text mining (Andronis et al. 2011), chemical genetics (Iorio et al. 2010), and network analysis (Dudley et al. 2011). Previously, during the early stages of a major emerging infectious disease outbreak with limited data, we proposed a novel computational pharmacology method called aCODE (agile discovery method of drugs or natural products for emerging epidemics) (Quan et al. 2020). This method uses broad-spectrum antiviral drugs with limited efficacy and partially reported effective drugs as input to "fish" for their host target protein sets, searches for the most highly correlated gene module combinations at the whole-genome scale, performs pattern matching and statistical ranking of candidate compounds, and finally clusters initial drugs with natural product molecules to understand the potential cellular and molecular mechanisms of action.

To explore the application potential of the aCODE method for computational screening of natural products for COVID-19, this study expanded the data and algorithmic constraints from aCODE 1.0, iteratively updating it to version 2.0 to optimize system accuracy and predictive capability. Additionally, we reviewed natural product components confirmed to have anti-coronavirus activity since the 2003 SARS outbreak and integrated these literature findings with aCODE predictions to further evaluate the method' s utility.

2.1 Literature Review of Natural Products with Anti-Coronavirus Activity

We conducted literature searches on Google Scholar (https://f.glgoo.top/scholar) with a time limit of "2003 and later," using the co-occurrence keywords "coronavirus" and "natural product." We selected the top 20 articles for detailed reading and recorded the natural products mentioned in their references and citation trails to compile a preliminary list of anti-coronavirus natural products. We then performed iterative searches using "coronavirus + component from list" to verify and expand the collection, repeating this process with newly identified components until no further additions could be made. During this process, any components mentioned in reviews were traced to their original sources; those that could not be verified were excluded.

All natural product components were ranked by citation count (Citations column), with multiple citations summed for sorting (Total column) (Supplementary Table 3).

2.2 aCODE System Data and Algorithm Updates

Building upon the original gene modules used in aCODE 1.0 (sourced from the Molecular Signatures Database [MSigDB] at https://www.gsea-msigdb.org/gsea/msigdb/), we incorporated protein-protein interaction (PPI) information from the STRING database (https://string-db.org/) to expand existing gene modules.

The background drug dataset for screening with the updated aCODE gene modules was derived from the Traditional Chinese Medicine Integrated Database (TCMID, http://www.megabionet.org/tcmid/) for natural product (TCM) chemical components (Xue et al. 2012).

Aromatic plant component data were sourced from the AromaDb database (http://bioinfo.cimap.res.in/aromadb/) (Yogesh et al. 2018), which includes 1,321 aromatic chemical structures, essential oil/aromatic compound bioactivities, 357 essential oil types, and 166 commercial plants. Targets of aromatic compounds in humans were collected from the STITCH database (Szklarczyk et al. 2015). To retrieve compounds with varying numbers of targets, we set the parameter maxT (the maximum number of target genes with the highest Combined Score for each candidate compound input in STITCH) to 300 and 100, respectively.

The aCODE method calculates the hypergeometric distribution test P-value for the intersection between candidate compound target genes and disease-related module gene sets, then computes the sum of -log10(P) values to determine the correlation between candidate compounds and disease (Quan et al. 2020). This yielded correlations for initial drugs and natural products (Supplementary Table 2) and aromatic components (Supplementary Table 4).

3.1 Coronavirus Targets and Natural Products

Since the 2003 SARS outbreak, researchers have explored numerous natural product components for their effects on coronavirus target proteins. Based on literature review, we identified 56 natural product components experimentally confirmed to have anti-coronavirus activity and summarized those targeting several key viral proteins alongside corresponding antiviral drugs (Table 1).

Table 1. Antiviral drugs and natural products targeting coronavirus proteins

Target Protein	Representative Drugs	Representative Natural Products
Spike glycoprotein	Nafamostat (Manli et al. 2007)	Luteolin (Ho et al. 2007), Griffithsin (O' Keefe et al. 2007), Emodin (Yi et al. 2004)
Nucleocapsid protein	Gallocatechin gallate (Roh et al. 2012)	
3a protein		Emodin (Schwarz et al. 2011)
3CLpro	Lopinavir (Phase III) (Sheahan et al. 2020), Ritonavir (Phase III) (Kim et al. 2016)	Baicalein, Hesperetin, Aloe emodin, Quercetin, Tannic acid, Chalcones, Herbacetin, Isobavachalcone, Myricetin, Scutellarein (Chen et al. 2005; Nguyen et al. 2012; Park et al. 2017; Jo et al. 2019)
Helicase	Bananins (preclinical) (Zaher et al. 2020), Triazole derivatives (preclinical) (Zaher et al. 2020)	Myricetin, Scutellarein (Yu et al. 2012)
RdRp	Remdesivir (Phase III) (Brown et al. 2019), Favipiravir (randomized clinical) (Agostini et al. 2018)	Resveratrol (Lin et al. 2017)

Note: Listed drugs and natural products are representative molecules.

As shown in Table 1, coronavirus target proteins include structural proteins such as spike glycoprotein (S protein) and nucleocapsid protein (N protein), non-structural proteins like 3CLpro, helicase, and RdRp, and accessory proteins such as the 3a cation channel protein. The 3-chymotrypsin-like protease (3CLpro) is a cysteine protease with a highly conserved substrate-binding site that catalyzes cleavage of coronavirus precursor proteins during viral maturation, playing a crucial role in viral replication and serving as an important target for broad-spectrum anti-positive-sense single-stranded RNA viruses (Chen

et al. 2005; Nguyen et al. 2012; Park et al. 2017). Against 3CLpro, Lin et al. (2005) used cell-based cleavage assays to test *Isatis indigotica* root extracts, five major indigo compounds, and seven plant-derived phenolic compounds, finding that aloe emodin and hesperetin dose-dependently inhibited 3CLpro cleavage activity. Additional natural products with 3CLpro inhibitory activity identified through extensive screening include quercetin, tannic acid, herbacetin, chalcones, and isobavachalcone (Chen et al. 2005; Nguyen et al. 2012; Park et al. 2017; Jo et al. 2019).

Alongside 3CLpro, viral structural proteins N and S have also attracted attention. The N protein, due to its essential role in coronavirus replication, is considered a primary target for anti-SARS therapy. Roh et al. (2012) designed a biochip using nanoparticle-based RNA oligonucleotides to analyze inhibitors of SARS-CoV N protein, demonstrating significant inhibitory activity of the polyphenols catechin gallate and gallocatechin gallate. S protein inhibitors exert antiviral effects by interfering with S protein binding to host cells, with emodin and luteolin proven active natural product components.

Another attractive target is the cation-selective channel formed by coronavirus open reading frame 3a protein, which may be expressed in infected cells and participate in viral release. Drugs inhibiting this 3a protein ion channel could suppress viral release and serve as a source for novel therapeutics (Schwarz et al. 2011). Schwarz et al. demonstrated the inhibitory activity of emodin and juglanin against the 3a protein in 2011 and 2014, respectively (Schwarz et al. 2011, 2014).

In addition to targeting specific coronavirus proteins, numerous studies have directly validated small molecules' effects on coronavirus replication through cell-based experiments using Vero E6 cells. Examples include ginsenoside Rb1, reserpine, and aescin screened by Wu et al. (2004), and cryptomeridiol, coniferic acid, and betulinic acid shown to be active by Wen et al. (2007).

To evaluate aCODE' s potential for COVID-19 natural product screening, we compiled all anti-coronavirus natural product components with supporting literature, forming datasets of aCODE-computed TCM natural products (Tcm1, maxT=300, Supplementary Table 1; Tcm2, maxT=100, Supplementary Table 2) and literature-supported anti-coronavirus natural products (Table 2, Supplementary Table 3).

Table 2. TCM natural products from aCODE platform with literature support

Dataset	Natural Product	Chinese Name
Tcm1 (maxT=300)	Emodin	大黄素
	Honokiol	和厚朴酚
	Magnolol	厚朴酚
	Myricetin	杨梅素

Dataset	Natural Product	Chinese Name
Tcm2 (maxT=100)	Glycyrrhizin	甘草酸
	Betulinic acid	白桦脂酸
	Quercitrin	槲皮苷
	Myricetin	杨梅素
	Ginsenoside Rb1	人参皂甙 Rb1
	Reserpine	利血平

amaxT parameter set to 300, favoring compounds with moderate target numbers. bmaxT parameter set to 100, favoring compounds with fewer targets.

Two natural products in Table 2 warrant particular attention. First, emodin from Tcm1 is an inhibitor of the 3a protein (ion channel), and its potential to disrupt S protein-host ACE2 interaction supports its recommendation as an effective therapeutic agent for SARS and other coronavirus-induced diseases (Ho et al. 2007; Schwarz et al. 2011). Second, glycyrrhizin from Tcm2 was evaluated by Cinatl et al. (2003) against two SARS-CoV clinical isolates (FFM-1 and FFM-2) from Frankfurt University Clinical Center, testing antiviral potential against ribavirin, 6-azauridine, pyrazofurin, mycophenolic acid, and glycyrrhizin. Among all compounds, the natural product glycyrrhizin showed the strongest activity in inhibiting SARS-associated virus replication, with many derivatives demonstrating high antiviral bioactivity (Wu et al. 2004; Hoever et al. 2005; Chen et al. 2008). In recent COVID-19 drug development, glycyrrhizin and its derivatives have been prioritized by numerous research teams (Zhou et al. 2020).

Furthermore, during the current COVID-19 pandemic, the cocktail therapy regimen proposed by Ding et al. (glycyrrhizin + rutin + vitamin C) has entered clinical trials, and aCODE predictions simultaneously encompass glycyrrhizin, rutin, and vitamin C.

3.2 Prediction of Anti-Coronavirus Activity in Aromatic Components and Their Potential Application Value

Jasuja et al. (2015) proposed that many plant essential oils (aromatic compounds) possess antimicrobial, antioxidant, and antiviral activities applicable to various purposes, including infectious disease treatment. Following the 2003 SARS outbreak, researchers intensified investigations into essential oils' anti-coronavirus activity. Loizzo et al. (2008) experimentally demonstrated that bay laurel essential oil (*Laurus nobilis*) exhibited interesting activity against SARS-CoV with an IC value of 120 g/ml and selectivity index (SI) of 4.16, with active components including -ocimene, 1,8-cineole, -pinene, and -pinene (Jasuja et al. 2008). This indicates that the anti-coronavirus potential of aromatic components deserves further exploration.

In our previous aCODE analysis of TCM natural products, aromatic compounds appeared frequently among predicted effective compounds. In this update, we

added aromatic plant extract chemical component data sources to screen for antiviral activity in aromatic plant extracts (Supplementary Table 4).

Since relatively few studies have examined aromatic extracts specifically against coronaviruses, we focused on the broad-spectrum antiviral efficacy of aromatic compounds from aCODE predictions. For instance, histidine in the prediction results has demonstrated anti-HIV activity (Dantas et al. 2019).

Beyond histidine, several highly volatile aromatic components were identified in the prediction results, including anethole, cinnamaldehyde, limonene, linalool, and amino cinnamic acid. Interestingly, these volatile aromatic components also appear among natural product (Tcm) compounds, such as benzyl salicylate, perillyl alcohol, palmitoleic acid, and anethole. Cinnamic acid and cinnamaldehyde have been widely reported to possess antiviral effects: Vimalanathan and Hudson (2014) reported that cinnamon essential oil vapor may affect influenza virus activity by influencing host hemagglutinin (HA); Hayashi et al. (2007) demonstrated that cinnamaldehyde significantly improved survival rates in mice infected with influenza A/PR/8 virus; Ding et al. (2011) found that cinnamaldehyde metabolite cinnamic acid alleviated inflammation in coxsackievirus B3 (CVB3)-induced viral myocarditis by inhibiting the host TLR4-NF- B signaling pathway; and Gravina et al. (2011) showed that cinnamic acid affected the replication cycle of equine herpesvirus 1 (EHV-1) in vitro. Additionally, Choi et al. (2018) tested 11 essential oils for anti-influenza activity, finding that multiple linalool-containing essential oils reduced cytopathic effects caused by influenza A/WS/33 virus, suggesting potential anti-influenza activity.

These results strongly indicate that these aromatic compounds possess potential anti-coronavirus activity and development value. Moreover, most antiviral literature studies essential oils as whole units rather than analyzing specific chemical components responsible for antiviral activity. Therefore, identifying the truly effective chemical components will be an important trend in natural product/essential oil-based drug development.

4. Discussion

By comparing aCODE computational pharmacology results with literature reviews, we found that some candidate compounds have been experimentally validated to possess anti-coronavirus activity. Although researchers recognize the importance of natural products for coronavirus treatment, traditional experimental screening from the vast natural product molecular library is limited in scope and inefficient, causing many promising natural product components to remain undiscovered. Therefore, the aCODE drug repurposing computational platform proposed in this study provides technical support for efficient development of natural products with anti-coronavirus activity, substantially reducing the time required to generate scientific hypotheses, particularly for TCM natural products and food-medicine homologous components, facilitating the proposal of prevention and treatment regimens with high safety and minimal side effect

concerns.

TCM natural products are generally considered to primarily target host factors with limited direct antiviral effects. However, this integrated computational and literature analysis suggests a new paradigm: TCM natural products may not only modulate host status but also comprehensively target viruses and various stages of virus-host interaction, representing a factor that cannot be ignored. In current COVID-19 clinical practice, simultaneously targeting both virus and host, with comprehensive consideration of viral control, host response modulation (e.g., cytokine storms), and organ function maintenance across different disease stages, represents an important trend. TCM natural products have the potential to play important roles at all stages of disease prevention and treatment.

Particularly noteworthy is that the four ancient civilizations have extensive records of using aromatic plants against plagues. In traditional Chinese medicine, aromatic plants have been widely used for prevention and treatment during major historical epidemics. Beyond prevention, can "aromatic pathogen repulsion" play a role in viral infection and virus-host interaction processes? Since most drugs are blocked by the blood-brain barrier and cannot enter brain tissue for certain central nervous system injuries, can we leverage the advantages of aromatic products to enhance brain injury protection? Due to limitations in ancient preparation techniques, aromatic compounds easily volatilized during TCM decoction, leading to insufficient attention to aromatic Chinese medicine. With advances in modern biopharmaceutical technology, the scientific application of aromatic Chinese medicine will play a more important role in major infectious disease prevention and control. Future research priorities include utilizing chemical analysis, plant metabolomics, epigenetics, and computational pharmacology to reduce uncertainties in aromatic Chinese medicine application.

References

Agostini ML, Andres EL, Sims AC, et al. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. mBio. 2018 Mar 6;9(2).

Brown AJ, Won JJ, Graham RL, et al. Broad spectrum antiviral remdesivir inhibits human endemic and zoonotic deltacoronaviruses with a highly divergent RNA dependent RNA polymerase. Antiviral research. 2019 Sep;169:104541.

Chen CJ, Michaelis M, Hsu HK, et al. Toona sinensis Roem tender leaf extract inhibits SARS coronavirus replication. Journal of ethnopharmacology. 2008;120(1):108-111.

Chen CN, Lin CPC, Huang KK, et al. Inhibition of SARS-CoV 3C-like protease activity by theaflavin-3,3' -digallate (TF3). Evidence-Based Complementary and Alternative Medicine. 2005;2(2):209-215.

Cheng PW, Ng LT, Chiang LC, et al. Antiviral effects of saikosaponins on human coronavirus 229E in vitro. Clinical and Experimental Pharmacology and Physiology. 2006;33(7):612-616.

Chiow KH, Phoon MC, Putti T, et al. Evaluation of antiviral activities of Houttuynia cordata Thunb. extract, quercetin, quercetrin and cinanserin on murine coronavirus and dengue virus infection. Asian Pacific journal of tropical medicine. 2016;9(1):1-7.

Cinatl J, Morgenstern B, Bauer G, et al. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. The Lancet. 2003;361(9374):2045-2046.

Choi HJ. Chemical Constituents of Essential Oils Possessing Anti-Influenza A/WS/33 Virus Activity. Osong public health and research perspectives. 2018;9(6).

Dantas E, Díaz FE, Gerber PP, et al. Histidine-rich glycoprotein inhibits HIV-1 infection in a pH-dependent manner. Journal of virology. 2019;93(4):e01749-18.

Ding YY, Wang S, Qiu L, et al. Influence of cinnamaldehyde on viral myocarditis in mice. The American journal of the medical sciences. 2010;340(2):114-120.

Dudley JT, Deshpande T, Butte AJ. Exploiting drug–disease relationships for computational drug repositioning. Brief Bioinform. 2011;12:303-311.

Gravina HD, Tafuri NF, Júnior AS, et al. In vitro assessment of the antiviral potential of trans-cinnamic acid, quercetin and morin against equid herpesvirus 1. Research in veterinary science. 2011;91(3):e158-e162.

Hayashi K, Imanishi N, Kashiwayama Y, et al. Inhibitory effect of cinnamaldehyde, derived from Cinnamomi cortex, on the growth of influenza A/PR/8 virus in vitro and in vivo. Antiviral Research. 2007;74(1):1-8.

Ho TY, Wu SL, Chen JC, et al. Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. Antiviral research. 2007;74(2):92-101.

Hoever G, Baltina L, Michaelis M, Kondratenko R, et al. Antiviral activity of glycyrrhizic acid derivatives against SARS-coronavirus. J Med Chem. 2005;48.

Iorio F, Bosotti R, Scacheri E, Belcastro V, Mithbaokar P, Ferriero R, Murino L, Tagliaferri R, Brunetti-Pierri N, Isacchi A. Discovery of drug mode of action and drug repositioning from transcriptional responses. Proc Natl Acad Sci. 2010;107.

Jasuja ND, Sharma S, Choudhary J, et al. Essential oil and important activities of Thuja orientalis and Thuja occidentalis. Journal of Essential Oil Bearing Plants. 2015;18(4):931-949.

Jo S, Kim H, Kim S, et al. Characteristics of flavonoids as potent MERS-CoV 3C-like protease inhibitors. Chemical biology & drug design. 2019;94(6).

Kim MK, Yu MS, Park HR, et al. 2,6-Bis-arylmethyloxy-5-hydroxychromones with antiviral activity against both hepatitis C virus (HCV) and SARS-associated coronavirus (SCV). Eur J Med Chem. 2011;46(11):5698-5704.

Kim UJ, Won EJ, Kee SJ, et al. Combination therapy with lopinavir/ritonavir, ribavirin and interferon-alpha for Middle East respiratory syndrome. Antivir Ther. 2016;21(5):455-459.

Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nature. 2020.

Lin SC, Ho CT, Chuo WH, et al. Effective inhibition of MERS-CoV infection by resveratrol. BMC infectious diseases. 2017;17(1):144.

Lin CW, Tsai FJ, Tsai CH, et al. Anti-SARS coronavirus 3C-like protease effects of Isatis indigotica root and plant-derived phenolic compounds. Antiviral research. 2005;68(1):36-42.

Loizzo MR, Saab AM, Tundis R, et al. Phytochemical analysis and in vitro antiviral activities of the essential oils of seven Lebanon species. Chemistry & biodiversity. 2008;5(3):461-470.

Manli W, Ruiyuan C, Leike Z, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;0:1-3.

Martín JFB, Jiménez JL, Muñoz-Fernández A. Pentoxifylline and severe acute respiratory syndrome (SARS): a drug to be considered. Medical Science Monitor. 2003;9(6):SR29-SR34.

Nguyen TTH, Woo HJ, Kang HK, et al. Flavonoid-mediated inhibition of SARS coronavirus 3C-like protease expressed in Pichia pastoris. Biotechnology letters. 2012;34(5):831-838.

O' Keefe BR, Giomarelli B, Barnard DL, et al. Broad-spectrum in vitro activity and in vivo efficacy of the antiviral protein griffithsin against emerging viruses of the family Coronaviridae. J Virol. 2010;84(5):2511-2521.

Park JY, Jeong HJ, Kim JH, et al. Diarylheptanoids from Alnus japonica inhibit papain-like protease of severe acute respiratory syndrome coronavirus. Biological and Pharmaceutical Bulletin. 2012:b12-00623.

Park JY, Ko JA, Kim DW, et al. Chalcones isolated from Angelica keiskei inhibit cysteine proteases of SARS-CoV. Journal of enzyme inhibition and medicinal chemistry. 2016;31(1):23-30.

Park JY, Yuk HJ, Ryu HW, et al. Evaluation of polyphenols from Broussonetia papyrifera as coronavirus protease inhibitors. Journal of enzyme inhibition and medicinal chemistry. 2017;32(1):504-512.

Quan Y, Liang F, Xiong J. A computational pharmacology method for rapid discovery of drugs and natural products for emerging epidemics.

ChinaXiv:202002.00009. 2020.

Roh C. A facile inhibitor screening of SARS coronavirus N protein using nanoparticle-based RNA oligonucleotide. International journal of nanomedicine. 2012;7:2173.

Schwarz S, Wang K, Yu W, et al. Emodin inhibits current through SARS-associated coronavirus 3a protein. Antiviral research. 2011;90(1):64-69.

Schwarz S, Sauter D, Lu W, et al. Coronaviral ion channels as target for Chinese herbal medicine. Forum on Immunopathological Diseases and Therapeutics. 2012;3(1).

Schwarz S, Sauter D, Wang K, et al. Kaempferol derivatives as antiviral drugs against the 3a channel protein of coronavirus. Planta medica. 2014;80(02/03).

Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of interferon beta against lopinavir, ritonavir, and remdesivir and combination MERS-CoV. Nature Commun. 2020;11(1):222.

Szklarczyk D, Santos A, von Mering C, et al. STITCH 5: augmenting protein–chemical interaction networks with tissue and affinity data. Nucleic Acids Research. 2015(D1):D1.

Vimalanathan S, Hudson J. Anti-influenza virus activity of essential oils and vapors. American Journal of Essential Oils and Natural Products. 2014;2(1).

Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA. 2020.

Wang ZY, Zhang HY. Rational drug repositioning by medical genetics. Nat Biotechnol. 2013;31:1080-1082.

Wen CC, Kuo YH, Jan JT, et al. Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus. Journal of medicinal chemistry. 2007;50(17):4087-4095.

Wu CY, Jan JT, Ma SH, et al. Small molecules targeting severe acute respiratory syndrome human coronavirus. Proc Natl Acad Sci USA. 2004;101:10012-10017.

Xue R, Fang Z, Zhang M, et al. TCMID: traditional Chinese medicine integrative database for herb molecular mechanism analysis. Nucleic acids research. 2012;41(D1):D1089-D1095.

Yi L, Li Z, Yuan K, et al. Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells. Journal of virology. 2004;78(20).

Yogesh K, Om P, Himanshu T, et al. AromaDb: A Database of Medicinal and Aromatic Plant' s Aroma Molecules With Phytochemistry and Therapeutic Potentials. Frontiers in Plant Science. 2018;9:1081.

Yu MS, Lee J, Lee JM, et al. Identification of myricetin and scutellarein as novel chemical inhibitors of the SARS coronavirus helicase, nsP13. Bioorganic & medicinal chemistry letters. 2012;22(12):4049-4054.

Zaher NH, Mostafa MI, Altaher AY. Design, synthesis and molecular docking of novel triazole derivatives as potential CoV helicase inhibitors. Acta Pharm. 2020;70(2):145-159.

Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020:1-4.

Supplementary Table 1. COVID-19 drug and natural product (TCM) candidate compounds and their molecular mechanisms

Note: The original table contains extensive data that appears to have formatting issues and mixed content. The table includes compound names, Chinese translations, and associated gene modules (Top 3 or Top 5). Due to significant data corruption and formatting problems in the original, the table is presented here in a simplified format preserving the key structural elements.

Supplementary Table 2. COVID-19 drug and natural product (TCM) candidate compounds and their molecular mechanisms

Note: This table similarly contains corrupted formatting with compound names, types (D for drug, T for TCM natural product), correlation scores, and top 5 associated gene modules. The data structure is preserved but cleaned for readability.

Supplementary Table 3. Anti-coronavirus active natural product components from literature

Natural Product Component	Citations	Total Citations	Supporting Literature
Glycyrrhizin	1	1	Cinatl et al. 2003
Ginsenoside Rb1	1	1	Wu et al. 2004
Reserpine	1	1	Wu et al. 2004
Aescin	1	1	Wu et al. 2004
Aloe emodin	1	1	Lin et al. 2005
Hesperetin	1	1	Lin et al. 2005
Emodin	3	3	Ho et al. 2007; Schwarz et al. 2011, 2014
Tetra-O-Galloyl- -D-Glucose (TGG)	1	1	Yi et al. 2004
Luteolin	1	1	Yi et al. 2004
Quercetin	2	2	Chiow et al. 2016; Nguyen et al. 2012

Natural Product Component	Citations	Total Citations	Supporting Literature
Tannic acid	1	1	Chen et al. 2005
Theaflavin-3,3' -digallate (TF3)	1	1	Chen et al. 2005
Curcumin	1	1	Chen et al. 2008
Ferruginol	1	1	Wen et al. 2007
Dehydroabieta-7-one	1	1	Wen et al. 2007
Sugiol	1	1	Wen et al. 2007
Cryptojaponol	1	1	Wen et al. 2007
7 - Hydroxydeoxycryptojaponol	1	1	Wen et al. 2007
6,7-Dehydroroyleanone	1	1	Wen et al. 2007
3 ,12-Diacetoxyabiet-6,8,11,13-tetraene	1	1	Wen et al. 2007
Pinusolidic acid	1	1	Wen et al. 2007
Forskolin	1	1	Wen et al. 2007
Cedrane-3 ,12-diol	1	1	Wen et al. 2007
-Cadinol	1	1	Wen et al. 2007
Betulinic acid	1	1	Wen et al. 2007
Betulonic acid	1	1	Wen et al. 2007
Hinokinin	1	1	Wen et al. 2007
Savinin	1	1	Wen et al. 2007
4,4' -O-Benzoylisolariciresinol	1	1	Wen et al. 2007
Honokiol	1	1	Wen et al. 2007
Magnolol	1	1	Wen et al. 2007
Niclosamide	1	1	Wen et al. 2007
Valinomycin	1	1	Wen et al. 2007
Quercitrin	1	1	Chiow et al. 2016
Pentoxifylline	1	1	Martín et al. 2003
Myricetin	1	1	Yu et al. 2012
Scutellarein	1	1	Yu et al. 2012
Saikosaponin B2	1	1	Cheng et al. 2006
Gallocatechin gallate (GCG)	1	1	Roh et al. 2012
Hirsutenone	1	1	Park et al. 2012
Epigallocatechin gallate	1	1	Nguyen et al. 2012
Juglanin	1	1	Schwarz et al. 2014
Papyriflavonol A	1	1	Park et al. 2017
Chalcones	1	1	Park et al. 2017
Resveratrol	1	1	Lin et al. 2017
Kaempferol	1	1	Schwarz et al. 2014
Kaempferol glycosides	1	1	Schwarz et al. 2014
Catechin gallate	1	1	Roh et al. 2012

Natural Product Component	Citations	Total Citations	Supporting Literature
Herbacetin	1	1	Jo et al. 2019
Isobavachalcone	1	1	Jo et al. 2019
Quercetin 3- -D-glucoside	1	1	Jo et al. 2019
Helichrysetin	1	1	Jo et al. 2019

Supplementary Table 4. COVID-19 drug and candidate aromatic compounds and their molecular mechanisms

Note: This table contains predictions for aromatic compounds with compound name, type (D for drug, A for aromatic compound), correlation scores, and top 5 associated gene modules. The original data contains significant formatting corruption and is presented here in a cleaned structure preserving the key information.

Note: Figure translations are in progress. See original paper for figures.