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# Natural products as a source of novel drugs for treating SARS-CoV2 infection

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A B S T R A C T

COVID-19, the infectious disease caused by the beta-corona virus SARS-CoV2, has posed a global health threat causing more than five million of deaths in the last two years in the world. Although the disease often presents with mild cold-like symptoms, it may have lethal consequences following thromboembolisms, hyperinflammation and cytokine storm eventually leading to pulmonary fibrosis and multiple organ failure.

Despite the progress made in the understanding of the SARS-CoV2 pathology and the clinical management of COVID-19, the viral illness is still a health concern since outbreaks continue to resurge due to the emergence of mutant variants of the virus that resist the vaccines.

Therefore, there is an urgent need for therapeutics that can block SARS-CoV2 viral transmission and the progression from infection to severe symptomatic illness.

Natural products could be a valuable source of drugs for the management of COVID-19 disease, particularly because they can act on multitargets and through different mechanisms including inhibition of biochemical pathways, epigenetic regulation of gene expression, modulation of immune response, regulation of pathophysiological stress response.

Here we present an overview of the natural products that possess SARS-CoV2 antiviral activity and the potential to benefit the management of COVID-19.



## 1. Introduction

In late winter 2019, cases of atypical pneumonia associated with a novel beta-corona virus were reported in the city of Wuhan in China.[1] The virus was named SARS-CoV2, given the high homology of the genome with that of SARS-CoV, responsible of the Severe Acute Respiratory Syndrome (SARS) described in 2003.[2] SARS-CoV2 genome is made of a single-strand positive-sense RNA of approx. 30 kb coding for four structural proteins (S, E, M, and N) and sixteen non-structural proteins (nsp 1–16). One important feature of this virus is the avidity of the amino acid sequence RBD (receptor binding domain) of the Spike protein for human angiotensin-converting enzyme 2 (ACE2), used as a receptor for epithelial and endothelial cell attachment.[3] The high infectivity for human cells is also facilitated by the presence in the Spike sequence of a cleavage site processed by furin (a protease abundant in human tissues), which leads to the open conformation of the Spike protein required for binding to ACE2 and subsequent membrane fusion and viral entry into the host cell.[3]

The infectious disease has been named COVID-19, for COrona VIrus Disease 2019, and it has been declared a pandemic by the World Health Organization on March 11, 2020.

Clinically, COVID-19 presents with variable symptoms that range from headache, cough, muscle pain, sore throat, fever, loss of smell and taste, diarrhoea, up to dyspnoea and severe respiratory distress that may require intensive care. Especially elders and patients with co-morbidities are at risk of multiple organ failure, as consequence of the hyper-inflammatory response and so-called cytokine storm causing disseminated intravascular coagulation and thromboembolism.[4,5]

As of now (January 28th, 2022), there have been reported globally 366, 508, 042 cases, and up to 5,638,667 fatalities have been attributed to the infection.

Vaccination is considered the most promising strategy for curbing the pandemic.[6] The vaccines with the largest diffusion across the world are those based on the transfer, via liposomes or adenovectors, of the genetic information (cDNA or mRNA) driving the synthesis of the Spike protein, with the aim of triggering the production of neutralizing antibodies IgG.[7]

Although vaccines provide protection and have proved to reduce the burden of hospitalization, several limitations render the vaccination not a sufficient prophylaxis measure for halting the pandemic. First, the plasma titer of neutralizing antibodies

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*Abbreviations:* COVID-19, Corona Virus Disease 2019; SARS-CoV2, Severe Acute Respiratory Syndrome Corona Virus 2.

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starts waning from the third month.[8]; second, vaccinated people can still be infected and spread the virus.[9]; third, the virus shows a high propensity to mutate in the Spike protein targeted by the vaccines.[10]; fourth, vaccines may not be efficacious in immunocompromised patients.[11]

As a matter of fact, the latest variant Omicron brings more than 30 changes to the Spike protein, shows a 13-fold increase in viral infectivity, and is likely to evade not only vaccine immunization but also monoclonal anti-Spike antibodies.[12]

Overall, it seems that an integrated approach in the management of COVID-19 that also includes adjuvant therapeutics for limiting viral reproduction and spreading as well as the onset of severe illness could be the winning strategy. In this regard, clinical studies provide evidence for the advantages of combining standard of care with pharmacologic interventions, according to western medicine protocols, together with dietary supplements and herbal medicines that could boost the antiviral immune response, prevent from systemic inflammation-related damages, and relief from symptoms.[13]

## 2. Natural products as a source of *anti*-covid-19 drugs

Natural products may provide a rich source for new drugs encompassing both prevention and management of symptoms of COVID-19.[14] A variety of flavonoids, polyphenols, alkaloids and polysaccharides from plants and mushrooms traditionally used to treat infectious diseases for their immune-booster, antimicrobic, and anti-inflammatory properties have been repurposed for treating COVID-19.[15–17] These natural products have shown the ability to interfere with the viral entry and replication and to regulate the immune-inflammatory response.[15,18]

A variety of herbal medicines have proved to be efficacious toward respiratory viral infections and likely can benefit the treatment of COVID-19. A short list of herbal-derived bioactive molecules that were shown able to inhibit viral entry, viral replication and progression of COVID-19 disease include thymoquinone, α-hederin, and nigellidine from *Nigella sativa*[19] quercetin found in Ginko biloba, green tea, and other food stuff,[20] Ellagic acid from Moringa oliefera,[21] and rosmarinic acid from *Plectranthus amboinicus* .[22] To this list we can add *Panax ginseng*, for its therapeutic effects against COVID-19 mediated thrombosis and platelet aggregation[23] and curcumin, luteolin, piperine, quercetin, epigallocatechin-3-gallate, resveratrol and herbs of *Polygonum cuspidatum* for their ability to dampen the COVID-19 cytokine storm and thus preventing pulmonary fibrosis.[24,25] As for medicinal fungi, extracts of Ganoderma lucidum were shown capable of preventing SARS-CoV2 infection in animal models.[26]

## 3. Herbal medicinal formulas for adjuvant therapy of COVID-19

Clinical studies have shown that Traditional Chinese Medicine (TCM) is a formidable add—on therapy that can effectively delay the progression of disease and reduce the mortality of COVID-19 patients.[27–29]

Formulas of TCM that incorporate a mix of natural products have been successfully used in the management of COVID-19. For instance, Lian-Hua-Qing-Wen (LHQW), a combination of thirteen herbs, was shown to limit SARS-CoV-2 replication and to dampen the production of pro-inflammatory cytokines.[30] A recent review and meta-analysis of eighteen clinical trials (ten randomized and eight retrospective) evaluated the efficacy and safety of three Chinese patented formulas, namely Lian-Hua-Qing-Wen (LHQW), Jin-Hua-Qing-Gan (JHQG), and Xue-Bi-Jing (XBJ), and three Chinese medicine prescriptions, namely Qing-Fei-Pai-Du (QFPD), Xuan-Fei-Bai-Du (XFBD), and Hua-Shi-Bai-Du (HSBD), and it was found that adding these formulas (particularly LHQW) to pharmacological treatments improved the clinical outcome of COVID-19 patients compared to only-chemical drug treated patients.[31] Another revision of registered TCM trials (94 randomized controlled trials and 114 trials for assessment of therapeutic effects) found that Qingfei Paidu decoction, Huashi Baidu decoction (HSBD), Lian-Hua-Qing-Wen (LHQW) capsules, and Toujie Quwen granules could efficaciously relief symptoms in COVID-19 patients.[32]

## 4. The topic collection and the special issue

In April 2020, eJTCM launched the Special Issue “SARS-CoV-2 and Coronavirus Disease 19 (COVID-19)” guest edited by the Editor in Chief Dr Ciro Isidoro.

By the end of December 2021, we had received and processed altogether eighty articles, of which fifteen had been finally accepted for publication in this topic collection (overall rejection rate was >80%).

Of the 80 submissions, 37 (46%) were desk rejected; of the remaining 43 manuscripts that were sent out for external review, 28 (35%) did not pass the peer-review scrutiny, and finally only fifteen were accepted after one or more rounds of revision. Taken together, the peer review process yielded an overall acceptance rate of approx. 20%, which is in line with the acceptance rate of regular articles.

To make the research soon available to the scientific community, the first six articles were published right away as soon as accepted, while the other nine articles are published within the present Special Issue.

A synopsis of the topic collection that includes all the fifteen articles is reported in Table 1.

## 5. Limitations and perspectives

The pandemic COVID-19 has been ravaging the global health systems and threatening human lives for almost two years. The lack of effective medicines, especially in the first year, has led to an increased use of herbal medicines traditionally employed for the treatment of infectious diseases.

In parallel, this stimulated the search for medical treatments of COVID-19 based on natural products.

A comprehensive collection of natural compounds that resulted effective against human coronaviruses is freely accessible at https://bigdatainhealth.org/letsbe/anti-HCoV.php.[17]

Here we have briefly discussed the relevance of an integrated approach that includes the tools and methodology of traditional and complementary medicine for the management of COVID-19. Meanwhile, we have introduced the articles collected in a dedicated Special Issue by the e-Journal of Traditional and Complementary Medicine (Table 1 and Fig. 1).

We wish to stress the importance of the quality of evidence for supporting the employment of herbal medicine as source of new drugs and for adjuvant therapies, as anecdotal and empirical data cannot be taken as a proof of efficacy.[48]

Overall, the evidence-based clinical efficacy of the natural compounds repurposed for the treatment of SARS-CoV2 infection is presently still poor.

*In silico* and in vitro studies provide insightful indications for the development of new drugs from natural products, yet it should be emphasized that the antiviral potency of these drugs must be tested in *in vivo* model of SARS-CoV2 infection, and thereafter their therapeutic effects must be assessed in clinical settings.

Data from clinical trials and meta-analysis support the contention that herbal medicine can provide adjuvant benefits, especially

**Table 1**
The Topic collection.

| AUTHORS | TITLE | Methodology | Findings/take home message | Ref |
|---|---|---|---|---|
| A-D Fuzimoto, C. Isidoro | The antiviral and coronavirus-host protein pathways inhibiting properties of herbs and natural compounds - Additional weapons in the fight against the COVID-19 pandemic? | Literature review | Over 450 herbs and natural compounds were reported to possess antiviral properties specifically targeting $3CL^{PRO}$, $PL^{PRO}$, RdRp, helicase protein, S protein, N protein, 3a protein, Cathepsin L, Nsp1, Nsp3c, and ORF7a, and the S protein/ACE-2 interaction. | 33 |
| S. Panyod, C-T Ho, L-Y Sheen | Dietary therapy and herbal medicine for COVID-19 prevention: A review and perspective | Literature review | A variety of food products and herbs could be used as dietary or complementary therapy to prevent infection and strengthen immunity, as well as for sanitary purposes. | 34 |
| A. Prasansuklab, A. Theerasri, P. Rangsinth, C. Sillapachaiyaporn,S. Chuchawankul, T. Tencomnao | *Anti*-COVID-19 drug candidates: A review on potential biological activities of natural products in the management of new coronavirus infection | Literature review | A total of 150 natural compounds were identified as potential candidates for development of new *anti*-COVID-19 drugs, among which quercetin is proposed as a lead candidate. | 35 |
| P. Rangsinth, C. Sillapachaiyaporn, S. Nilkhet, T. Tencomnao, A-T Ung, S. Chuchawankul | Mushroom-derived bioactive compounds potentially serve as the inhibitors of SARS-CoV-2 main protease: an *in silico* approach | Molecular docking and *in silico* ADMET analysis. | 25 mushroom-derived compounds showed the potential to inhibit the main viral protease; based on ADMET analysis, 6 out of 25 are proposed as the best drug-like property candidates. | 36 |
| F. Rahman, S. Tabrez, R. Ali, A-S Alqahtani, M-Z Ahmed, A. Rub | Molecular docking analysis of rutin reveals possible inhibition of SARS-CoV-2 vital proteins | Molecular docking, inhibition constant, hydrogen bond calculations, and ADMET analysis. | Rutin showed significant docking ability to Mpro, RdRp, PLpro, and S proteins of SARS-CoV-2. | 37 |
| Y–W Zhu, X–F Yan, T-J Ye, J. Hu, X-L Wang, F-J Qiu, C–H Liu, X-D Hu | Analyzing the potential therapeutic mechanism of Huashi Baidu Decoction on severe COVID-19 through integrating network pharmacological methods | Protein-protein interaction network through STRING database; GO and KEGG enrichment analysis for signal pathways. | 45 potential genes related to inflammation and immune regulatory pathways could be targeted by Huashi Baidu Decoction. | 38 |
| S. Vardhan, S–K Sahoo | Virtual screening by targeting proteolytic sites of furin and TMPRSS2 to propose potential compounds obstructing the entry of SARS-CoV-2 virus into human host cells | *In silico* molecular docking screening to identify potential phytochemicals inhibiting the proteolytic cleavage activity of furin and TMPRSS2. | Limonin, gedunin, eribulin, pedunculagin, limonin glycoside and betunilic acid bind at the active site of both furin and TMPRSS2. | 39 |
| A-A. Zaki, A. Ashour, S–S. Elhady, K-M. Darwish, AA-Al. Karmalawy | Calendula glycoside A showing potential activity against SARS-CoV-2 main protease: Molecular docking, molecular dynamics, and SAR studies | Molecular docking studies to investigate the ability of phytochemicals from *Calendula officinalis* to target SARS-CoV-2 Mpro. | Calendula glycoside A (SAP5) showed a superior binding affinity towards the Mpro of SARS-CoV-2 than the co-crystallized inhibitor. | 40 |
| R. Singh, V–K Bhardwaj, J. Sharma, R. Purohit, S. Kumar | In-silico evaluation of bioactive compounds from tea as potential SARS-CoV-2 nonstructural protein 16 inhibitors | Molecular docking and structural dynamic studies to test the ability of 65 Tea bioactive compounds to inhibit NSP16 of SARS-CoV-2. | Teaflavin from *Camellia sinensis* can bind to and inhibit NSP16 of SARS-CoV2. | 41 |
| S. Vardhan, S–K Sahoo | Exploring the therapeutic nature of limonoids and triterpenoids against SARS-CoV-2 by targeting nsp 13, nsp14, and nsp15 through molecular docking and dynamics simulations | *In silico* molecular docking screening of 369 phytochemicals. | Limonoids and Triterpenoids can target nsp 13 and nsp15 of SARS-CoV2. | 42 |
| C. Vidoni, A. Fuzimoto, A. Ferraresi,C. Isidoro | Targeting autophagy with natural products to prevent SARS-CoV-2 infection | Literature review | Natural products can inhibit viral replication through modulation of autophagy. | 43 |
| T. Tanikawa, T. Hayashi, R. Suzuki, M. Kitamura, Y. Inoue | Inhibitory effect of honokiol on furin-like activity and SARS-CoV-2 infection | *In vitro* and in cell studies to assess the inhibition of furin by honokiol and magnolol. | Honokiol partially inhibited furin-like enzymatic activity (in vitro) and SARS-CoV-2 infection in VeroE6 cells stably expressing TMPRSS2. | 44 |
| G-Y Chen, Y–C Pan, T-Y Wu, T-Y Yao, W-J Wang, W-Jou Shen, A. Ahmed, S-T Chan, C–H Tang, W –C Huang, M – C Hung, J-C Yang, Y–C Wu | Potential natural products that target the SARS-CoV-2 spike protein identified by structure-based virtual screening, isothermal titration calorimetry and lentivirus particles pseudotyped (Vpp) infection assay | 39 natural products tested for binding to RBD of Spike protein using AutoDock Vina program and isothermal titration calorimetry. | Dioscin, celastrol, saikosaponin C, epimedin C, torvoside K, and amentoflavone showed the ability to bind the Spike protein and prevent SARS-CoV-2 from entering cells. | 45 |
| P. Singh, S–S Chauhan, S. Pandit, M. Sinha, S. Gupta, A. Gupta, R. Parthasarathi | The dual role of phytochemicals on SARS-CoV-2 inhibition by targeting host and viral proteins | Structure-based activity, density-Functional Theory based quantum chemical methods, molecular dynamics simulations. | Phytochemicals from *Andrographis paniculata, Aconitum heterophyllum, Costus speciosus* and *Inula racemose* may target SARS-CoV2 viral proteins (Spike glycoprotein, Papain-like protease, and Main protease) and host proteins (ACE2, Importin-subunit $\alpha$-5, and $\beta$-1). | 46 |
| A.Kumar, A. Rai, M – S Khan, A Kumar, Z-U Haque, M. Fazil, G. Rabbani | Role of herbal medicines in the management of patients with COVID-19: A systematic review and meta-analysis of randomized controlled trials. | Systematic review and meta-analysis of RCTs to assess the effect and safety of herbal intervention. | Herbal intervention, as an adjuvant with standard treatment, improved the treatment outcomes in COVID-19 patients without significant adverse effects. | 47 |

in combination with standard of care, for the treatment of COVID-19 patients.[27,28,30,32] However, for herbal medicine being incorporated in standard management of COVID-19 more high-quality clinical studies are needed. Particularly, it is important to test the effectiveness of formulas containing a mix of supplements and natural products in RCTs with clear endpoints. Most importantly,

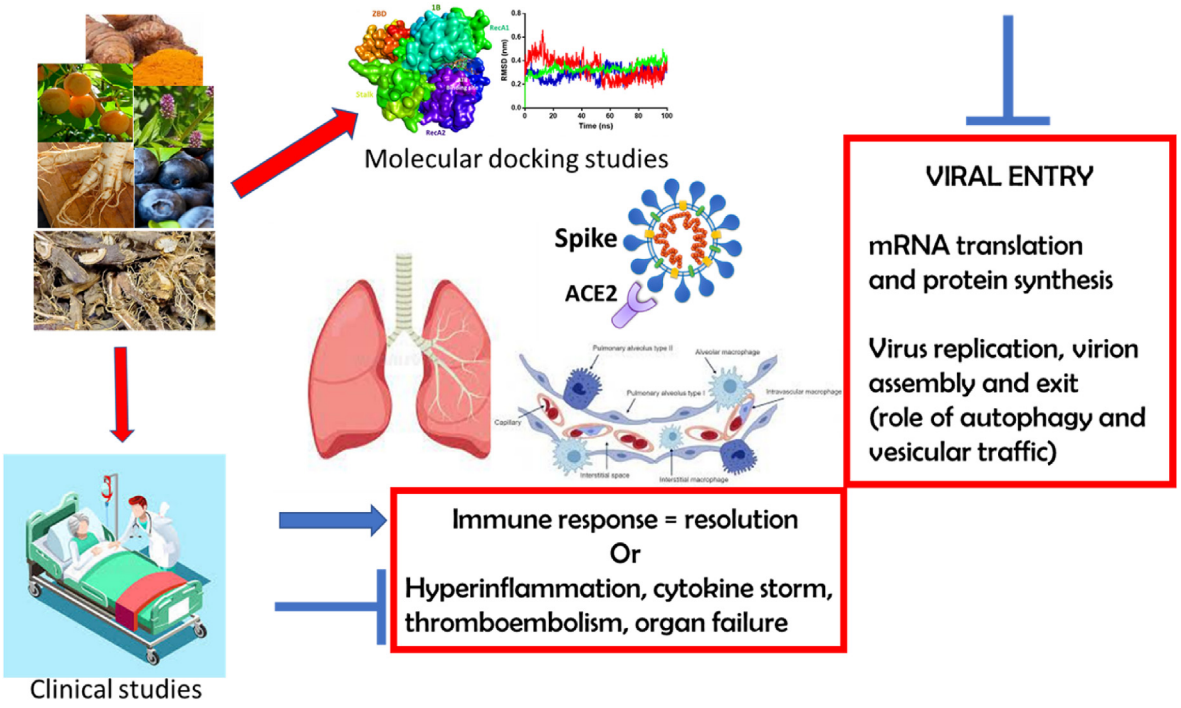


**Fig. 1.** The potential effects of natural products in COVID-19 management: biological targets and clinical outcome.

understanding the mechanism of action of the natural product is mandatory to define at which stage of the disease it can be effective and whether and how it might interact with other drugs.

Finally, it is to be stressed that managing COVID-19 requires a strict monitoring of the patients, since the clinical conditions could rapidly deteriorate, especially in patients aged over 70 and with co-morbidities such as diabetes or cardiovascular diseases. The studies on natural products surely are inspiring for designing new drugs and treatments for COVID-19. However, given the low absorption of phytochemicals, it is important to carefully consider the dosage and the time needed for the bioactive molecule to reach the effective concentration in the plasma and organs of the patient. Therefore, it should be clear that the use of phytochemicals and dietary supplements for therapeutic purposes while helpful in the early stage of the disease to prevent worsening of the disease, it may not be sufficient for treating COVID-19 at advanced clinical stage.

## Conflicts of interest

Authors declare no conflict of interest.

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