J. Phytomol. Pharmacol., 3(1), 08-19, 2024
https://doi.org/10.56717/jpp.2024.v03i01.023
ISSN(Print): 2957-5818, ISSN(Online): 2958-6224

Journal of
Phytomolecules & Pharmacology

Review Article

An arsenal of naturopathic compounds for the treatment of COVID-19: A comprehensive review

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Abstract

Despite the tremendous efforts to find a reasonable potent and efficacious drug candidate for the treatment of COVID-19, there is not a magic drug to cure the symptoms of this deadly disease. This study aims to give some information about natural compounds against SARS-CoV-2 and their ethnopharmacology, and the possible antiviral mechanism of especially plant secondary metabolites. Nowadays, although several NCEs were approved for the treatment of COVID-19 or to ease the symptoms, most of these new medicines seem to eventually be less effective in large populations. Moreover, it is imperative to use prophylactic agents and natural remedies to prevent infections as well as boost the immune system. When we look at the epidemiological and geographical movement of viral infections, it is obvious that the countries that follow naturopathic/homeopathic treatment options seem to recover faster than the other countries. Thus, it is extremely important to identify what natural treatment recipe works for certain households. For methodology, Web of Science, Sci-Finder, Google Scholar, Science Direct, Scopus, TUBIVES, CITES, and other databases were used as initial origins to look for related articles and apply search terms. In this review, many medicinal and aromatic plants, natural products, and commercial compounds were screened against SARS-CoV-2. Furthermore, it gives details about these compounds and related medicinal and aromatic plants. Also, this comprehensive review sheds light on current natural treatment options reported in the literature and the future projections to halt this deadly disease via natural medicines.

Article Information
Received: 02 February 2024
Revised: 08 April 2024
Accepted: 08 April 2024
Published: 12 April 2024

Academic Editor
Prof. Dr. Marcello Iriti

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Keywords
Natural products, COVID-19 treatment, SARS-CoV-2 activity, antiviral phytoche-micals, phytotherapy agents, homeo-pathic medicine.

1. Introduction

COVID-19 was seen for the first time in the Hubei Province of the People's Republic of China on 30 January 2019, World Health Organization Emergency Committee declared a global health emergency, briefly some studies determined that viral particles can enter the human body by respiratory tract [1] and the patients with COVID-19 have symptoms such as fever, shortness of breath, dry cough [2], dysgeusia and anosmia [3]. Also, this virus can penetrate the ACE-2 receptor found in some organs such as lungs and kidneys [4], it affects not only the respiratory system but also the gastrointestinal, nervous, and hepatic systems [5]. After this virus isolated and identified, some antiviral commercial drug as remdesivir [6], favipiravir [7], chloroquine [8], and natural products (Xiu Powder, An Gong Niu Huang Pill, Hou Po Xia Ling Decoction) utilized in treatment of COVID-19 [9]. Natural active compounds have significant properties for lung health, such as reducing lung damage, preventing the development of pneumonia, suppressing the emission of proteins on the alveolar surface, and minimizing lung damage [10]. Almost one million metabolites are estimated to be produced throughout the plant kingdom, and most of them have not been discovered, yet [11]. Nowadays, natural compounds were used in the treatment of some diseases in the 20 plant families such as Arecaceae, Aristolochiaceae, Cucurbitaceae, Piperaceae, Rubiaceae, Ranunculaceae, Zingiberaceae in a totally 450 families [12]. Especially for COVID-19, many natural compounds and their antiviral mechanisms were reported. One study reported that bioflavonoids from *Torreya nucifera* negatively affected SARS-CoV 3CLpro's replication [13]. Moreover, the combination of 13 herbs (such as Forsythia suspense (Thunb.), *Ephedra sinica* Stapf Cao, and *Gypsum fibrosum*) not only suppressed the replication of SARS-CoV-2 but also led to a change in the structure of virus cells [14]. For using these active compounds in the treatment of many diseases, these plant- based compounds have many advantages as safe for human consumption, not environmental pollution, and more acceptable to pharmaceuticals and local farmers [15, 16]. In view of the fact that these recent studies, this study aims to give some information about natural compounds against SARS-CoV-2 and their ethnopharmacology.

2. Materials and methods

This review consists of many parts such as ethnopharmacology of natural products for COVID-19 treatment, important natural products for COVID-19 treatment, plant primary and secondary metabolites and mainly antiviral mechanisms. All the databases were collected by electronic libraries which are Web of Science, SciFinder, Google Scholar, Science Direct and Scopus. Also, most of the details were given about plants from many book chapters and published books. The scientific names of medicinal and aromatic plants were checked by using Natural Agriculture Library in the U.S. Department of Agriculture (USDA), Medicinal Plant Services in Royal Botanic Garden, Türkiye's Plants Data Service (TÜBİVES), the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES). All the primary and secondary metabolites found in Dr. Duke's Phytochemical and Ethnobotanical Databases in USDA and their chemical structures were checked by PubChem.

3. Results and discussion

3.1. Ethnopharmacology of natural products for COVID-19 treatment

Plants used ethnobotanically in the treatment of flu and colds were used in the symptomatic treatment of coronavirus disease during the pandemic period. It is noteworthy that the plants selected for the studies against the coronavirus were selected from those with antiviral effect potential and used in the treatment of influenza [17, 18]. For this reason, many plants are used ethnobotanically in the treatment of flu and colds listed in this study. Looking at different ethnobotanical studies, *R. canina* stands out as the most used plant against flu and colds. According to one study's results, volunteers and patients with flu took medication with 2 g of liquid rosehip and placebo for six months during the winter, respectively. After six months, the incidence of symptoms of the flu and cold (coughing, headache, muscle stiffness, and fatigue) decreased statistically in patients compared to volunteers [19].

Following rosehip, *A. sativum, U. dioica, S. nigra, R. officinalis, O. vulgare, M. spicata* and *M. longifolia, Eucalyptus* species are among other frequently used plants. Each of them draws attention to the plants whose effects are discussed during the COVID-19 pandemic. It can be considered as having the potential to act of most plants against coronavirus. The fact that

https://doi.org/10.56717/jpp.2024.v03i01.023

these plants, briefly summarized in Table 1 and some of them given in Fig. 1 (drawn by Biorender), were compiled from ethnobotanical information is an indication that there is also reliable human use.

Figure 1. Some medicinal and aromatic plants

3.2. Important natural products for COVID-19 treatment

The COVID-19 pandemic, still being present since 2019, created awareness about human immunology health. The scientific community has made significant progress in mitigating the threat of COVID-19 through the discovery and development of vaccines which can be classified as Inactivated and Protein subunit, Viral vector, and mRNA vaccines. On the contrary to common belief about most of plant-based vaccine leading to allergenic conditions [20], The Novavax, saponin-based Matrix M adjuvant, showed great efficacy against COVID-19 of 89% [21]. One of plant-based vaccine is the NVX-CoV2373 (Novavax) vaccine, developed by using the bark of the *Quillaja saponaria* (Soapbark) tree, and was efficacious in preventing Sars-CoV-2- B.1.351 variant. A total of 4387 participants (2199 with NVX-CoV2373 and 2188 with placebo) were randomized and dosed at least once. The vaccine efficacy was 49.4% and 60.1% in 2684 baseline seronegative participants and HIV-negative symptomatic of COVID-19, respectively. Noticeably, in the post-hoc analysis, the vaccine efficacy was 51.0% in HIV-negative participants and 43.0% in the combined HIV-negative and PLWH population [22]. Another example is the CoVLP+AS03 vaccine, which showed anti-viral activity against SARS-CoV-2 by efficacy ranging from 69.5% against symptomatic infection to 78.8% against moderate-to severe disease. (Funded by Medicago; ClinicalTrials.gov number, NCT04636697.) [23].

Not only vaccines but merely monoclonal antibodies utilized in treatment of the disease. Naturally immune serum and panels of monoclonal antibodies used against the Omicron variants known as COVID-19 sublineages. The virus had reduced neutralization by serum from a person vaccinated with 3 doses of Pfizer or AstraZeneca vaccine rather than BA 1 and BA 2 variants [24]. However, promising drugs do not exist. Thus, scientists reported that the secret to a healthy life is to use functional nutrients for a powerful immune system, sleep quality and exercise. On the other hand, some of these lines for protecting against this disease are isolation, using vitamins, and avoiding contact with another person. Particularly, the separate property of COVID-19 from other viral diseases is an asymptomatic course of the disease, and using some antiviral products based on medicinal and aromatic compounds can prevent this problem. However, there was no evidence found any of these products using clinical. Although it suggests that using aromatherapeutic products decreases stress in human life during the pandemic, it is exactly known that these products can be harmful such as lung irritation by using unconscious, so we must know some documents for using right these products. "Pharmacopoeia" is used as a document for making medicine in Ancient Greek, and these documents defined as involving physicochemical properties, some qualitative and quantitative methods of inactive and active compounds in pharmaceutical production, and rules to follow at both national and international levels [25]. On the other hand, monographs are described as active and inactive compounds of one pharmacophore like chemical/ biological, plant-derived medicines, comments, and properties (physical, soluble, boiling, and melting temperatures). Thanks to these analyses for achieving character analysis of completed product's dosage, keeping storage conditions and impurity. Furthermore, the quality control analyses of these products contain some analytical methods such as stability, microbiological purity, and solubility [26]. Shed light on these traditional medicines [27], and small molecule agents [28, 29], this scenario, bioactivenatural products [30, 31] playing an irreplaceable role in the treatment of SARS-CoV-2 infection.

https://doi.org/10.56717/jpp.2024.v03i01.023

Table 1. Plants used ethnobotanically for flu and common cold

Plant name	Usage	Reference
Achillea vermicularis Trin.	Int. Dec.	[60]
Aconitum heterophyllum Wall. ex Royle.	Int. Dec.	[61]
Acorus calamus L.	Int. Inf.	[62]
Adhatoda vasica Nees.	Int. Inf.	[63]
Allium sativum L.	Int.	[64]
Arbutus unedo L.	Int. Dec.	[65]
Artemisia afra Jacq.ex Willd.	Int. Inf.	[66]
Artemisia macrocephala Jacquem. ex Besser	Int. Inf.	[61]
Artemisia scoparia Waldst. et Kit	Int. Dec.	[67]
Capsicum annuum L.	Int. Dec.	[61]
Conium sphaerocarpum Hilliard & B.L.	Ext. Inf.	[66]
Conyza scabrida DC	Int. Inf.	[66]
Crocus sativus	Int. Inf.	[68]
Cydonia oblonga Mill.	Int. Dec.	[69]
Cymbopogon citratus	Ext. Inf.	[70]
Dactylorhiza osmanica (Klinge) P.F. Hunt & Summerh.	Int. Dec.	[65]
Ephedra gerardiana Wall. exStapf ex Decne.	Int. Inf.	[61]
Eucalyptus camaldulensis Dehnhardt.	Int. Dec.	[61]
Eucalyptus globulus L.	Int. Dec.	[64]
Hedera helix L.	Int. Dec.	[71]
Juniperus drupacea Labill.	Int. Dec.	[65]
Lavandula dentata	Inf.Dec.	[72]
Table 1. *Continued*	Fum.	
Leonotis nepetifolia	Int. Inf.	[70]
Lepidium sativum L.	Int. Inf.	[71]
Mentha pulegium	Int. Dec.	[64]
Mentha spicata L.	Int. Inf.	[73]
Nepeta cataria	Int. Inf.	[66]
Nigella sativa L.	Int.	[74]
Orchis anatolica Boiss.	Int. Dec.	[65]
Pistacia terebinthus L.	Int. Dec.	[74]
Plantago ovata Forssk.	Int. Dec.	[61]
Punica granatum L.	Int. Dec.	[61]
Rosa canina L.	Int. Dec.	[74]
Rosmarinus officinalis L.	Int. Inf.	[64]
Salvia moorcroftiana Wall. ex Benth	Int. Powder	[61]
Thymus kotschyanus Boiss. & Hohen.	Int. Inf.	[73]

3.2.1. Whole natural plants products

Recently, it is known that medicinal and aromatic plants are used for the development of some nutrients against many diseases [32-35]. Especially, COVID-19 [36, 37]. In one of the studies, we emphasize Artemisia annua may be better candidate to prophylactically control SARS-COV-2 infection [38]. In addition, in Swiss, the clinical experiments of artemi C oral spray product, curcumin and artemisinin, are still ongoing for treatment in SARS-COV-2 infection [39].

3.2.2. Isolated/elucidated natural products

These plant natural compounds are classified as primary and secondary metabolites according to their role and biosynthetic pathway [40], in addition, the secondary metabolites are produced by only one species or related groups, whereas primary metabolites are produced from all plant kingdoms [41].

3.2.2.1. Plant primary metabolites for the treatment of COVID-19

https://doi.org/10.56717/jpp.2024.v03i01.023

The plant primary metabolism used for surviving, growing, enveloping, and communicating with nature [42], and they produced by the shikimate pathway, TCA cycle, glucose pathway [43] which their precursor molecules are CO2, H20, and NH3 in these pathways [44]. One of the primary metabolites is hesperidin obtained from *Citrus* sp. [45] prevents virus replication via binding main protein receptors of SARS-CoV-2 such as spike glycoprotein and protease domain. By virtue of it binds to ACE-2 receptors, virus cannot hold on, this molecule can be utilized for the treatment of COVID-19 [46].

3.2.2.2. Plant secondary metabolites of natural products for the treatment of COVID-19

Under some abiotic (drought, salty, elevated temperature, UV radiation) and biotic conditions (some microorganisms, insects, and nematodes in the soil), plants produce some secondary metabolites for defense and adapting the nature. These secondary metabolites are utilized by Mevalonic acid, Methyl-erythritol and shikimate pathways and shikimic acid, the amino acids phenylalanine/tyrosine, tryptophan, ornithine, and lysine are precursor molecules in these pathways [47,48]. These metabolites consist of the main groups such as phenolics, terpenes, and nitrogen-containing compounds [48]. Focus on the COVID-19, some secondary metabolites such as emodin, palmatine are suggested as potential drug candidates against SARS-CoV-2 [49, 50] (Table 2), [51-54]. Quercetine increased caspase activity [55], kaemferol inhibited TNF-α, IL-6, IL-1β cytokinins and increase SOD [56], resveratrol inhibited MAPK, PI3K, AKT [57], and also cannabidiol inhibited expression of TNF-α and IL-6 cytokines [58], (Fig. 2, drawn by Biorender).

Particularly, these natural compounds have some roles in antiviral disease which has cancellation to penetration to the host cell (lectin), adhesion to lungs and reproduction (alkaloids) of coronavirus, as well as inhibition of binding to the surface of host cells by changing proteins in the surface of virus cells (polyphenols), prevent to replication of virus by inhibition reverse transcriptase enzyme (flavonoids and terpenes), block translation proteins and recognize viral proteins for replication, repress active caspase 1 for preventing cytokine storm [59].

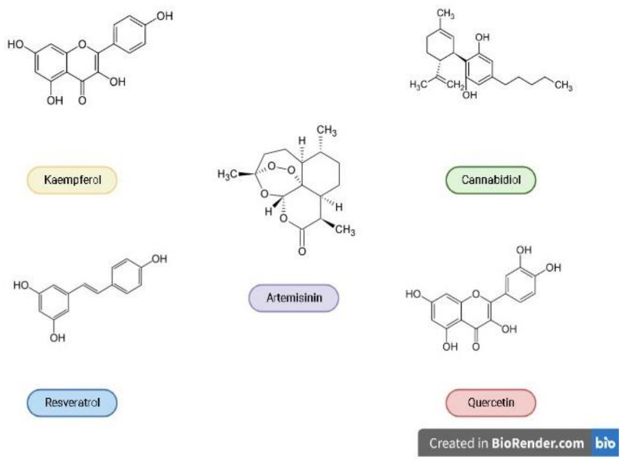

Figure 2. The structures of plant secondary metabolite

4. Conclusion and future perspectives

Natural treatment will always be center of the attention since the regulations and applications as well as availability are easier than the drugs. The main advantage of the use of natural medicines are cost-effectiveness since the new COVID-19 medicines will be expensive and non-affordable for some countries. Thus, naturopathic treatment options will always be a popular alternative. Because of the exponentially growing food supplement market in the last decades, effective and less costly natural medicines as well as research and development around this concept will be one the most attractive areas for researchers who study natural products. Additionally, in the future more medicines will be translated from natural compounds to potentially treat certain therapeutic areas including infectious diseases. In conclusion, several natural products and commercial compounds were screened against SARS CoV-2. Among those screened compounds decent antiviral activity has been observed. Some of these natural compounds and their analogs demonstrated reasonable antiviral activity against SARS CoV-2. In future, some of these compounds are worth investigating their anti-viral activity in vivo models. Natural medicines will always be the center of attention for the treatment of viral and bacterial infections because of the availability and cost-effectiveness of these supplements compared to expensive and not easily accessible drugs.

Abbreviations

3CLpro: 3-chymotrypsin like protease; ACE: Mitogen-activated protein kinase; AKT: Activation protein

https://doi.org/10.56717/jpp.2024.v03i01.023

Table 2. The Possible Antiviral Mechanism of Plant Secondary Metabolites

Secondary metabolite	Biological activity mechanism	References
Alkaloids		
Cepharantine	Inhibit MPro	[75]
Emetine	Inhibit RdRp	[76]
Hyoscyamine	Inhibit S protein	[77]
Incanumine	Inhibit 3C-like protease	[78]
Magnoflorine	Inhibit S protein	[52]
Neoechinulin A	Inhibit MPro	[79]
Nigellidine	Inhibit ACE-1 receptor	[80]
Flavonoids		
Afzelin	Inhibit MPro, hACE-2 and RdRp	
Amentoflavone	Inhibit ACE-2 receptor	[82]
Baicalein	Inhibit RdRp	[83]
Biflavone	Inhibit PLpro	[84]
Chrysin	Inhibit S protein and ACE-2 receptor	[85]
Hesperidin	Inhibit to bind ACE-2 receptor	[86]
Luteolin	Inhibit ACE-2 receptor	[87]
Quercetin 3-glucuronide-7-glucoside	Inhibit MPro and ACE-2 receptor	[53]
Phenolic compounds		
Deoxyshikonin	Inhibit MPro	[88]
Corilagin	Exhibit SARS-CoV-2-RBD and hACE2 protein	[89]
Coumarine	Inhibit 3CLpro	[90]
ellagic acid	Inhibit RBD-ACE-2 receptor	[91]
Epicatechin	Inhibit ACE-2 receptor	[92]
Kazinol J	Inhibit PLpro	[93]
Resveratrol	Inhibit MAPK, PI3K, AKT	[54]
Shikonin	Inhibit MPro	[94]
Theaflavin	Inhibit RdRp	[95]
Terpenes		
Abietane	Inhibit PLpro	[96]
Cannabidiol	Inhibit expression of TNF-α and IL-6 cytokines	[97]
Carvacrol	Inhibit ACE-2 receptor	[52]
Nimocin	Inhibit M and E proteins	[98]
Parthenolide	Reduce IL-1, IL-2, IL-6, IL-8, and TNF-α production pathways	[99]
Rosmariquinone	Inhibit PLpro	[100]
Saikosaponin C	Inhibit NSP15 endoribonuclease	[101]

activated protein kinase; AKT: Activation protein kinase B; CAT: Catalase; CITES: Convention on International Trade in Endangered Species of Wild Fauna and Flora; COVID-19: Coronavirus disease-19; COX-2 Cyclooxygenase-2; Dec: Decoction; Ext: External; IFN-γ: Interferon gamma; IL: Interleukin; Inf Infusion; Int: Internal; MAPK: Mitogen-activated protein kinase; MPro: Main protease; NF- κB: Nuclear factor-kappa B; Nsp15: Non-structural protein 15; P13K: Phosphoinositide 3-kinase; PLpro: papain-like protease; RBD: Receptor binding domain; RdRp: RNA-dependent; RNA: polymerase; S: Spike; SARS-CoV: Anti-severe acute respiratory syndrome coronavirus; SOD: Superoxide dismutase; TNF-α: Tumor necrosis factor-α; TUBIVES: Türkiye's Plants Data Service; TNF-α: Tumor necrosis factor-α; USDA: U.S. Department of Agriculture; WHO : World Health Organization.

Authors' contributions

Designed this study, M.G.; Extracted all necessary data for this review, A.E.K., M.T., K.F.E., Drawn all figures, M.T.; Revised this study, M.G., M.T.

https://doi.org/10.56717/jpp.2024.v03i01.023

Acknowledgements

Not applicable.

Funding

This research received no specific grant from any funding agency (the public, commercial, or not-for-profit sectors).

Availability of data and materials

All data will be made available on request according to the journal policy.

Conflicts of interest

The authors declare no conflict of interest.

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