Journal of Evidence-Based Integrative Medicine
Volume: 27: 1-18

DOI: 10.1177/2515690X211053641
journals.sagepub.com/home/cam
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COVID-19: General Strategies for Herbal Therapies

Samaneh Soleymani, PharmD, PhD[1,*], Ayeh Naghizadeh, MD, PhD[2,*], Mehrdad Karimi, MD, PhD[2], Azadeh Zarei, MD[2], Raefeh Mardi, MD[2], Gholamreza Kordafshari, MD, PhD[2], Niusha Esmaealzadeh, PharmD[1], and Arman Zargaran, PharmD, PhD[1]

Abstract

The coronavirus disease-2019 (COVID-19) pandemic started in early 2020 with the outbreak of a highly pathogenic human coronavirus. The world is facing a challenge and there is a pressing need for efficient drugs. Plants and natural compounds are a proven rich resource for new drug discovery. Considering the potential of natural products to manage the pandemic, this article was designed to provide an inclusive map of the stages and pathogenetic mechanisms for effective natural products on COVID-19. New drug discovery for the COVID-19 pandemic can encompass both prevention and disease management strategies. Preventive mechanisms that may be considered include boosting the immune response and hand hygiene in the preexposure phase; and blocking of virus binding and entry in the postexposure phase. Potential therapeutic target mechanisms include virus-directed therapies and host-directed therapies. Several medicinal plants and natural products, such as *Withania somnifera* (L.) Dunal and propolis for prevention; *Tanacetum parthenium* (L.) for treatment; and *Ammoides verticillata* (Desf.) Briq and *Nigella sativa* L. for both prevention and treatment have been found effective and are good targets for future research. The examples of phytochemical compounds that may be effective include aloin and terpenes as anti-septics; isothymol, dithymoquinone, and glycyrrhizin as inhibitors of virus binding and entry; glycyrrhizin, and berberine as replication suppressants; ginsenoside Rg1 and parthenolide as immunomodulators; and eriocitrin, rhoifolin, hesperidin, naringin, rutin, and veronicastroside as anti-complements. Recognizing different mechanisms of fighting against this virus can lead to a more systematic approach in finding natural products and medicinal plants for COVID-19 prevention and treatment.

Keywords

coronavirus, phytotherapy, COVID-19, angiotensin-converting enzyme, plant extracts, new drug discovery

Received April 17, 2021. Received revised July 20, 2021. Accepted for publication September 27, 2021.

Introduction

New respiratory infection with clinical symptoms of fever, cough, pneumonia, rhinorrhea, dyspnea, fatigue, and myalgia was first reported in Wuhan city, China in December 2019.[1] The rapid spread of COVID-19 was identified as a pandemic and public health emergency of international concern (PHEIC) by the World Health Organization (WHO) on March 11, 2020.[2] As of January 3, 2021, around 82 356 727 COVID-19 patients and over 1 815 433 deaths worldwide have been confirmed.[3] The genetic sequence of COVID-19—classified as a beta coronavirus—has similarities to other epidemic-causing viruses of this group, with more than 80% similarity to severe acute respiratory syndrome-related coronavirus (SARS-CoV) and 50% similarity to the Middle East respiratory syndrome-related coronavirus (MERS-CoV).[4] Coronaviruses belong to the large family of Coronaviridae and their genome size ranges from 26 to 32 kb. These viruses

[1] Department of Traditional Pharmacy, School of Persian Medicine, Tehran University of Medical Sciences, Tehran, Iran
[2] Department of Traditional Medicine, School of Persian Medicine, Tehran University of Medical Sciences, Tehran, Iran

*Samaneh Soleymani and Ayeh Naghizadeh have equal role as first author in this paper.

Corresponding Author:
Arman Zargaran, Department of Traditional Pharmacy, School of Persian Medicine, Tehran University of Medical Sciences, Tehran, Iran.
Email: zargarana@sums.ac.ir

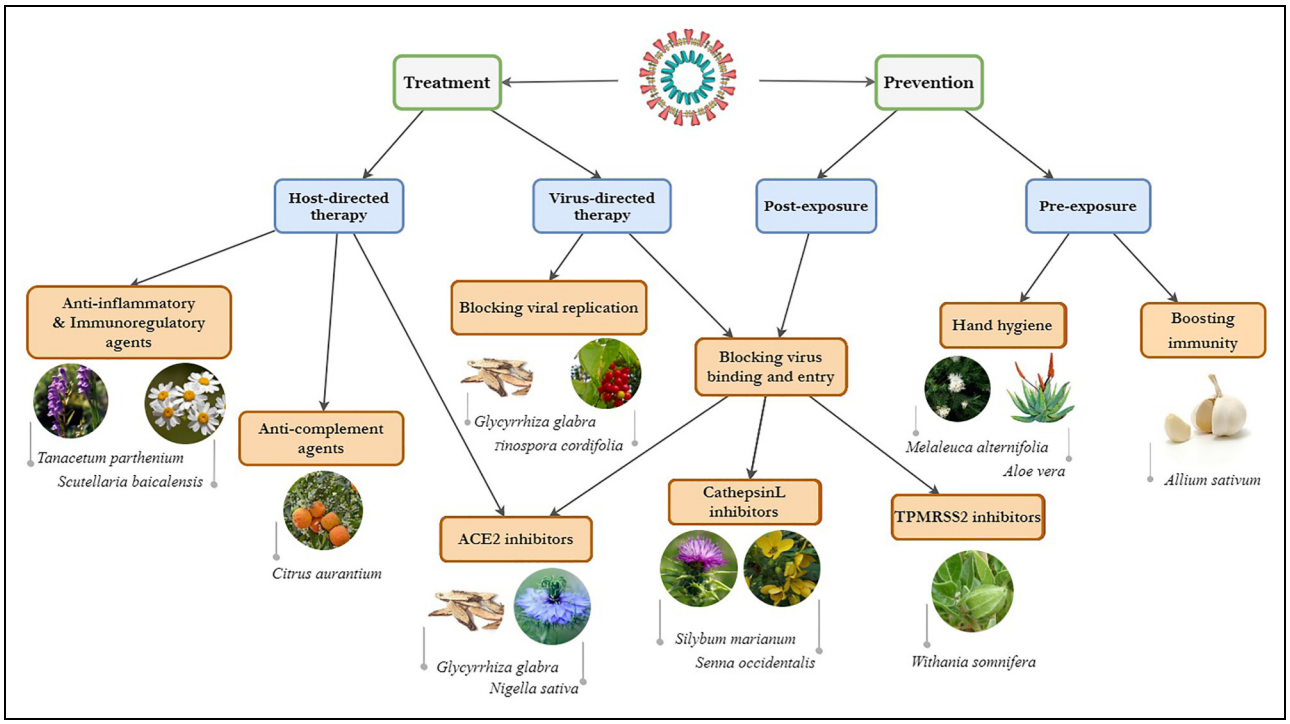


Figure 1. Strategies for prevention and treatment of coronavirus disease 2019 (COVID-19) by medicinal herbs.

possess positive-sense single-stranded RNA (+ssRNA) as their genome.[5] COVID-19 initiates by binding to angiotensin-converting enzyme 2 (ACE2) receptor on respiratory epithelial cells.[6] Following the attachment and cell invasion, heart damage, kidney damage, blood infection (RNAemia), and lung disease (acute respiratory distress syndrome [ARDS] and pneumonia) may occur (Jalali, 2020). There is a pressing demand to provide efficient drugs for this pandemic disaster to decrease the global vulnerability to a highly infectious coronavirus.[7]

The search for healing through nature has a history as old as mankind.[8] WHO has estimated about 3.5 to 4 billion people to be relying on herbal medicines in primary care.[9] Plants, their phytochemicals, and natural products are a proven rich resource for new drug discovery.[10] Considering the higher availability, accessibility, and affordability, medicinal herbs can accelerate the drug discovery process.[11] It seems that it is an opportunity for the management of COVID-19 and a rational and scientific approach to herbal therapy and traditional medicines could help to find natural products affecting COVID-19.[12] However, a scientific approach needs to be undertaken, and risks/benefits associated with natural products should be considered.

Numerous studies have been performed during the pandemic to introduce the natural products and phytochemicals effective in the management of COVID-19. Some have performed pharmacology-based reviews on medicinal plants and phytochemicals that may be effective in the management of COVID-19.[13,14] Considering the potential of natural products to manage the pandemic, this article was designed to provide an inclusive map of the stages and pathogenetic mechanisms related to the disease and strategies using effective natural products on COVID-19 (Figure 1).

Materials and Methods

This article is a narrative review to provide a map of disease-making strategies using potential natural products to prevent and manage each stage of the disease. In the first stage, queries were performed in PubMed, Scopus, and Google Scholar databases to study articles discussing the prevention, pathogenesis, and treatment targets for COVID-19. Subsequently, each stage in prevention (preexposure and postexposure) and treatment (each of the virus- and host-directed therapies) were separately searched with keywords including "herbal," "plant," "natural," and "traditional medicine" in combination with anti-viral, coronavirus, and COVID-19 to find instances of research conducted on the topic. The subject area was limited to medicine, pharmacology, toxicology, and pharmaceutics with no specific time restriction. All studies including clinical, in-vivo, in-vitro, and in-silico studies were investigated. All articles were studied to find the most robust evidences and instances of natural products on different stages. These evidences were used to find the mentioned map and strategies against COVID-19 based on the mechanism of action.

Prevention

Pre-exposure

One of the most important activities against COVID-19 is prevention. The strategy for preexposure preventive activities

could be considered as one of the main first-line attempts against this disease. The strategies to find natural solutions for pre-exposure is listed in continue:

Immunomodulatory Agents. Management of individuals in the first phase of COVID-19 can encompass improving and modulating innate (monocyte, macrophage, and natural killers [NK]) and adaptive immune responses (T-cell and B-cell) by the use of immune-boosting food and herbal supplements. Prevention of virus entry and replication is crucial.[16] The use of natural compounds may provide alternative prophylaxis by boosting the immune response in the preexposure stage. Plant-based foods enhance and help the intestinal advantageous bacteria and the overall health of the gut microbiome that makes up to 85% of the immune system of the body.[17]

Green vegetables like broccoli (*Brassica oleracea*), kale or leaf cabbage, mushrooms, and plants rich in omega-3 fatty acids like flax seeds (*Linum usitatissimum* L.) are immunity boosters that can rapidly enhance the immune system of the elderly.[17]

Curcumin, the main phytochemical of *Curcuma longa* L. has anti-SARS-CoV-2 effects, antioxidant, and potential immune-boosting properties is a potent antioxidant and stimulates the production of interferons to activate the host innate immunity.[18] Piperine is an alkaloid compound of *Piper nigrum* L. that boosts innate immunity through the phosphorylation of interferon regulatory factor 3 (IRF-3), type 1 interferon (IFN) mRNA, prevents lipopolysaccharide (LPS)-induced expression of IRF-1 and IRF-7 mRNA, and down-regulates STAT-1 activity and phosphorylation of IRF-3, type 1IFN mRNA.[16,19] In a hypothesis study, garlic (*Allium sativum* L.) was suggested as an advantageous preventive measure before infection with SARS-CoV-2, as it suppresses the production and secretion of proinflammatory cytokines and boosts immune system cells.[20] Garlic, which has also been suggested in prophylaxis, can ameliorate symptoms in infected patients. It stimulates NK cells, lymphocytes, eosinophils, and macrophages by modulation of immunoglobulin synthesis, phagocytosis, and macrophage activation, and cytokine secretion.[21] Also, garlic demonstrated immune system boosting capability by significantly increasing cluster of differentiation $(CD4)^{+}$T cells and total white blood cell count.[18,22] Target mechanisms of herbal drug discovery for COVID-19 with example studies are mentioned in Table 1.

Hand Hygiene. Hand hygiene includes hand cleaning with soap, alcohol-based hand rub and sanitizers. It is an important part of WHO, Centers for Disease Control and Prevention (CDC), and for Disease Prevention and Control (response for prevention and control of the spread of COVID-19 pathogens and infections in health care settings.[44] Personal hand hygiene plus plant and essential oil-based hand sanitizer could be efficient prevention for limiting the spread of viral and bacterial infections.[45] Leaves of tea tree oil (*Melaleuca alternifolia* [Maiden & Betche] Cheel) are a complex mixture of hydrocarbons and terpenes. Handwash formulations containing tea tree oil have been used in hospital or health care settings for many years. Several studies revealed the potent antiviral activity of this plant. Tea tree oil at a concentration of 0.02% inhibited influenza viruses from entering the host cell via disrupting the viral membrane fusion procedure and viral replication.[24]

Aloe vera (L.) Burm.f. gel and their key constituents, aloin and aloe-emodin are known as potential antiviral agents. These compounds eliminate the enveloped viruses, such as SARS-CoV-1, HIV viruses, and influenza viruses by inhibiting the viral replication or destructing the virus lipid envelope.[23,46] These properties make *Aloe* an attractive choice as a key plant in a nonalcoholic hand sanitizer.[45]

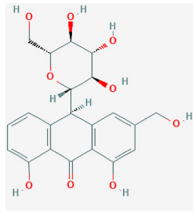
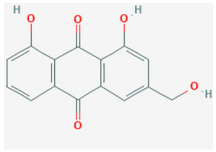
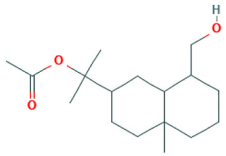
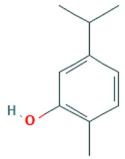
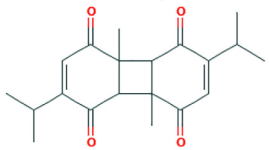
Post-exposure Prophylaxis

Blocking of Virus Binding and Entry. Viral spike protein interaction with cellular angiotensin-converting enzyme 2 (ACE2), host cell proteases including transmembrane protease serine 2 (TMPRSS2), and endosomal cathepsin L protease (CatL) or human airway trypsin-like protease (HAT) contribute to virus entry into host cells. An important strategy in drug discovery for COVID-19 would be to find compounds that can limit virus binding and entry into host cells via inhibiting these mechanisms.[31]

Angiotensin-converting enzyme 2 Inhibitors. Coronaviruses have common proteins, including nucleocapsid (N), protuberances (S), membrane (M), envelope (E), and a special type in beta-coronavirus called hemagglutinin esterase protein (HE protein).[25,47] The SARS coronavirus infection is started via the binding of spike protein-S (viral surface glycoprotein) to target membrane receptor ACE2 of a host cell.[48] Furthermore, expression of ACE2 could determine the severity of SARS-CoV-2 infection.[31,49]

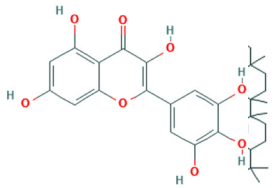
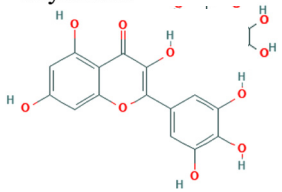
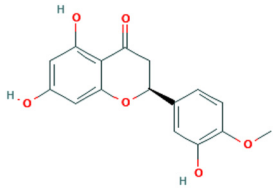
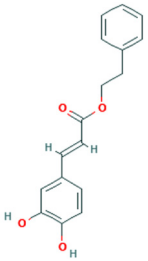
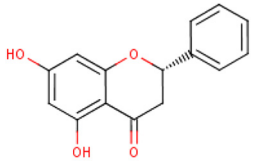
In an in-silico study on the essential oil of *Ammoides verticillata* (Desf.) Briq, its major component, isothymol, has shown good results for the isothymol-ACE2 docked complex.[48] This compound is also a constituent of Ajowan essential oil isolated from aerial parts, for which antiviral and antimicrobial properties have been identified.[49] Similarly, a combination of docking, Absorption, distribution, metabolism, elimination, and toxicity (ADMET) properties calculation, molecular dynamics, and molecular mechanics/Poisson–Boltzmann or generalized Born and surface area (MM-PBSA) approaches have revealed high potential binding to ACE2 for dithymoquinone (DTQ), an active constituent of *Nigella sativa* L.[41,50] Components of propolis, a resinous-like substance produced by bees, have also been found to have inhibitory effects on ACE2.[41] Likewise, in silico studies have proposed glycyrrhizin (the chief bioactive constituent of *Glycyrrhiza glabra* L. root), as an appropriate candidate of ACE2 inhibition due to reported safety, availability, and affordability.[51] Quercetin, a plant flavonol from the flavonoid group of polyphenols, is present in a variety of foodstuff including grapefruit, onions, apples, and black tea,[17] and herbs including *Hypericum perforatum* L. and *Sambucus nigra* L.[52] It is proposed as a

Table 1. Target Mechanisms of Drug Discovery From Natural Resources for COVID-19 With Example Studies.

	Source	Phytochemical	Structure of Phytochemicals	Study design	Mechanism	Ref
Hand hygiene	*Aloe vera* (L.) Burm.f.	Aloin and aloe- emodin	 Aloin  Aloe-emodin	*In vitro*	Inhibiting the viral replication or destructing the virus lipid envelope	26
	Melaleuca alternifolia (Maiden & Betche) Cheel.	Terpenes		*In vitro*	Disrupting the viral membrane fusion procedure and viral replication	25
Pre-exposure immunomodulation	*Allium sativum* L. (garlic)			Animal (Rat) In silico	Boosting immune system cells and suppressing production of proinflammatory cytokines	20, 22
Virus binding and entry	*Ammoides verticillata* (Desf.) Briq.	Isothymol		In silico	ACE inhibitors	30
	Nigella sativa L.	Dithymoquinone (DTQ)		In silico	ACE2 inhibitor	33
	Glycyrrhiza glabra L.	Glycyrrhizin			ACE2 inhibitor	85

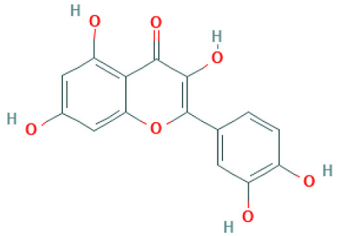
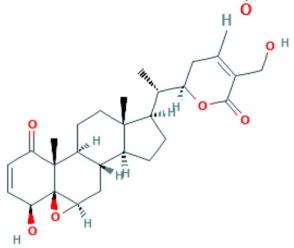
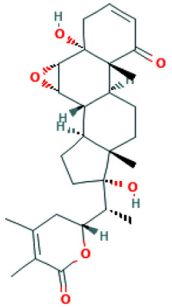
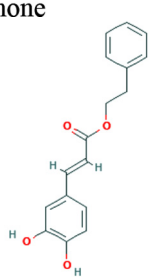
(continued)

Table 1. (continued)

Source	Phytochemical	Structure of Phytochemicals	Study design	Mechanism	Ref
Propolis	Myricetin, Caffeic acid phenethyl ester, Hesperetin, Pinocembrin	 Myricetin	In silico	Inhibitory potential with high binding energy to ACE2 (-8.97 kcal/mol)	86
	Kaempferol	 Myricetin	In silico	Inhibitory potential with high binding energy to ACE2 (-7.5 kcal/mol)	87
	Quercetin	 Hesperetin	In silico, *In vitro* (MCF7 cells)	Inhibitory potential with high binding energy to ACE2 (-10.4 kcal/mol)	88
Withania somnifera (L.) Dunal (Ashwagandha)	Withaferin-A, Withanone, Caffeic acid phenethyl ester	 Caffeic acid phenethyl ester	Computational screening	TPMRSS2 inhibition	28
Ziziphus rugosa Lam.	Rugosanine B	 Pinocembrin		Cathepsin L inhibition	2

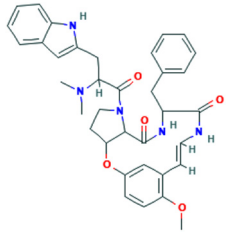
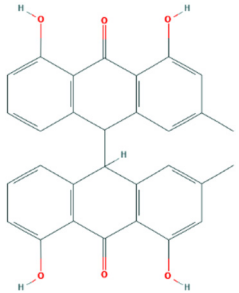
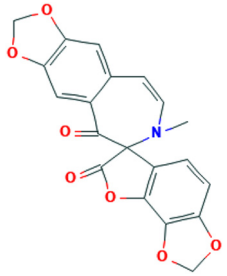
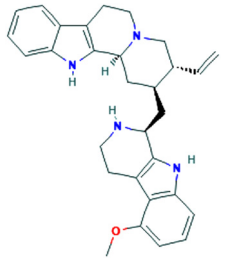
(continued)

Table 1. (continued)

Source	Phytochemical	Structure of Phytochemicals	Study design	Mechanism	Ref
Hypecoum pendulum L. *Senna occidentalis* (L.) Link	Aromoline		Computational screening	Cathepsin L inhibition	2
Cinchona calisaya Wedd.	3α,17α-cinchophylline	 Withaferin-A	Computational screening	Cathepsin L inhibition	2
Clerodendrum trichotomum Thunb.	Trichotomine	 Withanone	Computational screening	Cathepsin L inhibition	2
Tectona grandis L.f.	Tectol	 Caffeic acid phenethyl ester	Computational screening	Cathepsin L inhibition	2
Silybum marianum (L.) Gaertn.	Silymonin			Cathepsin L inhibition	2

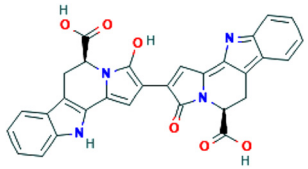
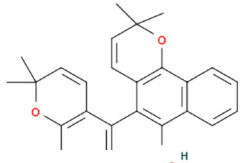
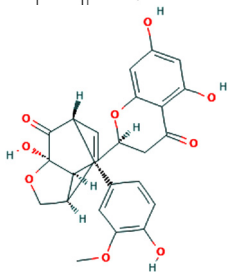
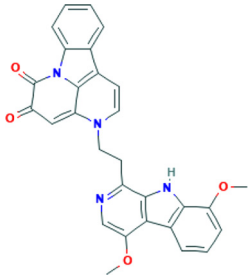
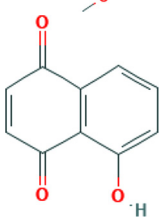
(continued)

Table 1. (continued)

	Source	Phytochemical	Structure of Phytochemicals	Study design	Mechanism	Ref
	Picrasma quassioides (D.Don) Benn.			Computational screening		
		Picrasidine M			Cathepsin L inhibition	2
				Computational screening		
	Juglans regia L.	Juglone			Cathepsin L inhibition	2
				In silico		
Viral replication	*Tinospora cordifolia* (Willd.) Miers	Berberine			Inhibition of 3CLpro function	45
	Anthemis hyalina DC.			*In vitro* (HeLa-CEACAM1a cells)	Inhibition of TRP gene expression	57
				In silico	Inhibition of N protein	48

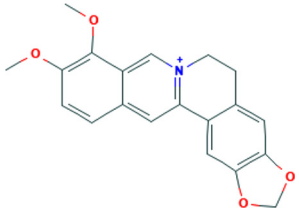
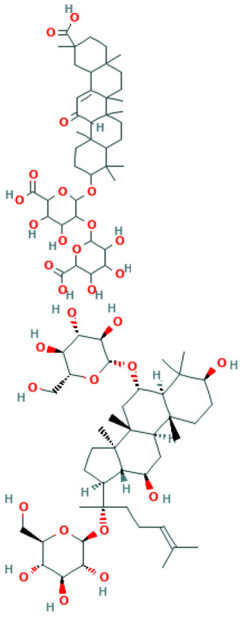
(continued)

Table 1. (continued)

	Source	Phytochemical	Structure of Phytochemicals	Study design	Mechanism	Ref
	Asparagus racemosus Willd.					
	Glycyrrhiza glabra L.	Glycyrrhizin		*In vitro*	Inhibition of viral replication	56
Immunomodulation and antiinflammation	*Lophatherum gracile* Brongn.			*In vivo*	Enhancement of CD4+/CD8+ T cell ratio, inhibition of IL-1β, TNF-α, and IFN-γ expression	74
	Panax ginseng C.A.Mey.	Ginsenoside Rg1			Enhancement of CD4+ T cell activity	72
				*In vitro, In vivo*		
	Tanacetum parthenium (L.)	Parthenolide			Inhibition of IL-1, IL-2, IL-6, IL-8, and TNF-α expression	79
						

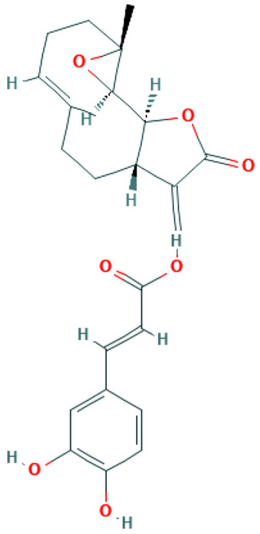
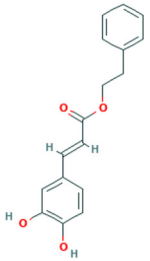
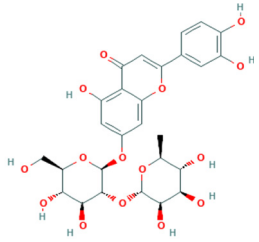
(continued)

Table 1. (continued)

	Source	Phytochemical	Structure of Phytochemicals	Study design	Mechanism	Ref
	Sch.Bip. (feverfew)					
	Viscum album L.			*In vitro*	Enhancement of CD4+ T cell migration	75
	Scutellaria baicalensis Georgi			*In vivo*	Inhibition of IL-1beta, IL- 2, IL-6, IL-12 and TNF-α expression	76
	Propolis	Caffeic acid, and Caffeic acid phenethyl ester			Downregulation and inhibition of PAK1	35
				In vitro		
	Biophytum umbraculum Welw.			*In vitro* (RAW 264.7 cell line)	Anticomplement and antiinflammatory effects	89
Anticomplement	*Citrus aurantium* L. var. *amara* Engl.	Eriocitrin/ neoeriocitrin, rhoifolin, hesperidin, naringin, rutin, veronicastroside, neohesperidin, and hesperetin			Anticomplement and antiinflammatory effects	81

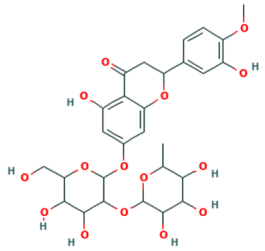
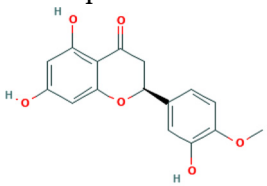
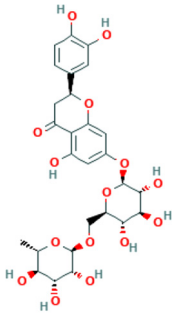
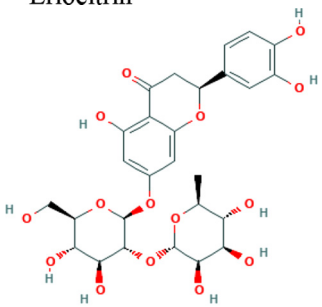
(continued)

Table 1. (continued)

Source	Phytochemical	Structure of Phytochemicals	Study design	Mechanism	Ref
		 Caffeic acid			
		 Caffeic acid phenethyl ester			
		 Veronicastroside			

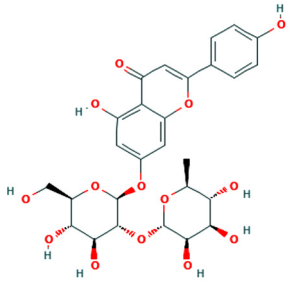
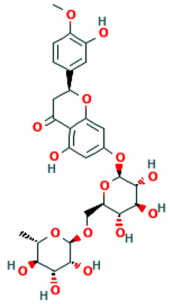
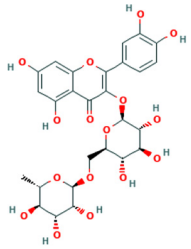
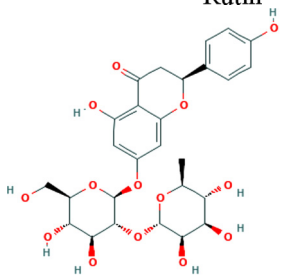
(continued)

Table 1. (continued)

Source	Phytochemical	Structure of Phytochemicals	Study design	Mechanism	Ref
		 Neohesperidin			
		 Hesperetin			
		 Eriocitrin			
		 Neoeriocitrin			

(continued)

Table 1. (continued)

	Source	Phytochemical	Structure of Phytochemicals	Study design	Mechanism	Ref
			 Rhoifolin			
			 Hesperidin			
			 Rutin			
			 Naringin			

potentially effective disruptor of virus binding. However, it should be noted that this compound is unlikely to be effective orally due to biotransformation, and is thus suggested to be used as nasal/throat spray.[53]

Transmembrane protease serine 2 Inhibitors. TMPRSS2 is a serine protease on the host cell surface with which SARS-CoV-2 interacts to replicate and induce invasion.[41] TMPRSS2 is recognized in inoculation and replication of cancer, influenza virus, and SARS-CoV-1. In one study, the flavonoids baicalein and baicalin as down-regulators of the TMPRSS-2 expression were demonstrated on in-silico studies against COVID-19.[54] Another study has revealed a potential for *Withania somnifera* (L.) Dunal (Ashwagandha) compounds—Withaferin-A, Withanone, and caffeic acid phenethyl ester, to block SARS-CoV-2 entry into the host cells, via the binding capacity to inhibit TPMRSS2.[31]

Cathepsin L Inhibitors. CatL is a lysosomal enzyme in endosomes that contributes to several physiological and pathological processes, such as extracellular matrix remodeling, antigen processing, apoptosis, invasion, inflammatory status, and viral infection. CatL is involved in degrading extracellular matrix that is a major process in binding SARS-CoV-2 spike protein and enters into host cells.[55] Therefore, plants and phytochemicals with potential CatL-inhibiting capacity could be considered a valuable therapeutic target to treat COVID-19 patients. Vivek-Ananth et al[56] have conducted a study to screen for potential CatL inhibitors and identified by computational screening 9 potential natural products such as Ararobinol (*Senna occidentalis* [L.] Link), (+)-oxoturkiyenine (*Hypecoum pendulum* L.), Rugosanine B (*Ziziphus rugosa* Lam.), Trichotomine (*Clerodendrum trichotomum* Thunb.), Tectol (*Tectona grandis* L.f.), Silymonin (*Silybum marianum* (L.) Gaertn.), Picrasidine M (*Picrasma quassioides* (D.Don) Benn.), and 3α, 17α-cinchophylline (*Cinchona calisaya* Wedd.).

Treatment

Virus-Directed Therapies

Findings from studies using herbal preparations as a complementary treatment in patients with the beta-coronavirus infections[57] have demonstrated a positive effect. However, more trials are needed to reach conclusive results. A number of in-vitro and animal studies have been conducted to identify antiviral plants,[58,59] but more research to find natural compounds that target the pathogenesis, and also clinical manifestations of COVID-19 is needed to help discover effective agents to be used as a complementary or alternative treatment.

Virus Replication. Proteins involved in the process of virus replication are an imperative target for anti-viral compounds. The most important protease enzyme in SARS-CoV is papain-like protease (PLpro) 3-chymotrypsin-like protease (3CLpro). Other nonstructural proteins (nsp) like helicase (nsp13), RdRp (nsp12/7/8), and nsp14 can also serve as drug targets.[51] A docking study has shown that the chief components of *Tinospora cordifolia* (Willd.) Miers, including berberine, can suppress 3CLpro function and thus inhibit viral replication.[32] Also, polyphenolic compounds have antiviral properties and can control infection via inhibiting these proteins.[60]

Moreover, N protein contributes to virus replication and plays a role in forming mature virions.[61] Results of an in-silico docking study have shown this protein to be inhibited by *Asparagus racemosus* Willd.[34]

Cyclophilin is required by many viruses including SARS-CoV for replication.[61] There is evidence of Cyclosporin A, a cyclophilin inhibitor, having the ability to suppress replication of coronaviruses.[62] To our knowledge, there is no study regarding cyclophilin inhibition by medicinal herbs. However, some studies have been conducted to investigate the suppression of coronavirus replication in plants.[63,64] One of the most important compounds in this regard is glycyrrhizin (the chief bioactive constituent of liquorice root), which has various antiviral activities including strong suppression of SARS-CoV replication.[35,66,67] Furthermore, *N sativa*, *Anthemis hyalina*, and *Citrus sinensis* all have significant effects on Transient receptor potential (TRP) gene expression and virus load, with *A hyalina* DC being the most potent one in this regard.[33]

Host-Directed Therapies

The first phase of COVID-19 includes infection of the upper respiratory tract, followed by subsequent involvement of the lower respiratory tract and other organs.[68] Pulmonary infection is accompanied by alveolar damage and hypoxia.[69] In many cases, COVID-19 infection is associated with inflammation in other organs. Gastrointestinal symptoms and myalgia are common manifestations of the disease.[70,71] The neurotropism of SARS-CoV-2, and the resultant inflammation, edema, and axonal damage, may lead to olfactory/gustatory dysfunction and more severe neurologic complications including acute cerebrovascular events, encephalitis, and Guillain-Barré syndrome.[72] Likewise, major mechanisms of cardiovascular complications, including acute cardiac injury, heart failure, and arrhythmias include direct myocardial injury and systemic inflammation.[73] In addition to decreasing viral load, the following targets can help ameliorate symptoms.

Angiotensin converting enzyme 2 Inhibitors. Several manifestations of COVID-19 are associated with the virus' affinity to ACE2 receptors. These receptors are widely distributed in body organs including endothelial and neuronal tissues.[74] Debatably, the main route of SARS-CoV-2 entry into neurons is via the ACE2 expressed in the heart and nervous system.[71,73] In the lungs, spike-like electron-dense projections along with SARS-CoV-2 antigen have been recognized in the ACE2-positive bronchiolar epithelium.[75] Thus, targeting this receptor can be an effective method in relieving COVID-19

symptoms. Medicinal herbs that act on ACE2 have been discussed in the previous sections.

Anti-Inflammatory and Immunoregulatory Agents. Infection of the conducting airways with SARS-CoV-2 leads to an innate cytokine response.[76] Within a week of upper respiratory tract infection, immunoglobulin M (IgM) and immunoglobulin (IgG) response is usually seen in patients.[77] COVID-19 is also associated with cell-mediated immune responses. Immune response to COVID-19 develops either in the direction of a T-cell-mediated protective immune response or an exacerbated inflammatory response.[77] In the former, CD4 and B cells produce neutralizing antibodies, which is critical for control of SARS-CoV-2 infections.[78] T cell counts are significantly reduced in COVID-19 patients, and also, decreased functionality and exhaustion of these cells exacerbate conditions.[79] Cytotoxic CD8 T-cells play an important role in clearing RNA viruses from the body while sparing damage to the host.[69,80] The exacerbated response, is associated with the inability to inhibit viral replication and remove infected cells, and may ultimately lead to a cytokine storm.[77] Profiles of several immune cells in COVID-19 have been recognized. Proinflammatory cytokines like interferon-gamma (IFN-γ), interleukin-1 (IL-1), IL-2, IL-6, tumor necrosis factor-alpha (TNF-α), leptin, and chemokines are among those exhibiting an enhancing tendency.[81] Conversely, reduced NK cells, cytotoxic and helper T cells, monocytes/macrophages, and regulatory T (Treg) cells have been mentioned.[81]

Medicinal plants can regulate the immune responses of the host. Ginsenoside Rg1, a phytochemical constituent of *Panax ginseng* C.A.Mey. can enhance the immune activity of CD4(+) T cells.[37] Also, a recent study has demonstrated that fermented ginseng extracts improve protection against influenza viruses and survival rates in conditions where adaptive immune components (CD4, CD8, B cell, Major histocompatibility complex(MHCII)) are deficient.[82]

An ethanol extract of *Lophatherum gracile* Brongn. has been found to have antiviral activity against respiratory syncytial virus (RSV) infection in rats. The proposed mechanism mediated slight enhancement of CD4 + /CD8 + T cell ratio and also, inhibition of IL-1β, TNF-α, and IFN-γ expression.[36]

Plants can also aid the migration and tissue distribution of immunocompetent cells. In this regard, *Viscum album* L. (mistletoe) can alter the migratory behavior of human peripheral $CD4^+$ T lymphocytes, and significantly enhance the mean velocity and time locomoting of these cells in collagen lattices.[39] Furthermore, the active aqueous extract of this plant has antiviral activity as shown in an in-vitro study on the human parainfluenza virus.[39]

Some medicinal herbs have been found to help alleviate the cytokine storm. For instance, *Scutellaria baicalensis* inhibits the expression of IL-1beta, IL-2, IL-6, IL-12, and TNF-α, thereby exhibiting strong anti-inflammatory activity.[40] Evidence of antiviral properties has previously been reported for this plant.[83] Although studies are limited in this regard, evidence of herbal compounds including polyphenols, triterpenoids, and flavonoids, protecting against cytokine storm during severe influenza exists.[84] Another example is parthenolide, the main biologically active constituent of *Tanacetum parthenium* (L.) Sch.Bip. This sesquiterpene lactone significantly inhibits IL-1, IL-2, IL-6, IL-8, and TNF-α expression. Considering the noticeable contribution of IL-6 in adverse clinical outcomes and fatality, parthenolide may be a potential herbal candidate for clinical evaluation.[38]

Overexpression of RAC/CDC42 (P21)-activated kinase 1 (PAK1) in response to SARS-CoV-2 infection in the lung, is a critical mediator of the cytokine storm that frequently increases mortality in hospitalized patients. Propolis-derived compounds decrease PAK1 activation, pro-inflammatory NK cells, cytokine overproduction, improve NF-KB and monocyte/macrophage immunomodulation, and enhance the production of antibodies against SARS-CoV-2.[41]

Anti-Complement Agents. Excessive cytokine release causes dysregulated complement activity, which aggravates lung damage, and ARDS in COVID-19 patients.[85] Anti-complement activity has been shown for some medicinal plants like crude polyphenols extracted from blossoms of *C aurantium* L. var. *amara* Engl.[43] Herbs with anti-complementary activity can ameliorate pulmonary edema, and improve the oxidant–antioxidant imbalance.[86] Moreover, there are growing reports of COVID-19 causing dermatological disorders, including maculopapular rashes, urticaria, vesicles, petechiae, and purpura.[87] One of the etiologies proposed for these manifestations includes complement-associated vasculitis,[88] in which case herbs acting as anti-complement agents may be helpful.

Conclusion

Natural resources and medicinal herbs are a valuable source of new drug discovery in managing COVID-19. Similar to processes of semisynthetic and synthetic drug design and production, a rational strategy should be undertaken. Natural products can provide both preventive and therapeutic aid in overcoming the pandemic. The present review attempted to highlight the potential of herbal drug discovery according to various aspects of COVID-19 prevention and treatment. Preventive mechanisms that may be considered include boosting the immune response and hand hygiene in the preexposure phase; and blocking of virus binding and entry ACE2, TMPRSS2, and CatL inhibition in the postexposure phase. Potential therapeutic target mechanisms include virus-directed therapies via inhibition of virus replication and 3C-like proteases; and host-directed therapies via ACE2 inhibition, anti-inflammation, immunoregulation, and use of anti-complement agents. Researchers can employ these strategies in the demanding conditions for drug discovery against COVID-19. This opportunity can help prevention and management of the COVID-19 pandemic. Indeed, numerous studies on natural products have been conducted during the pandemic, although many are in silico. Future studies are recommended to both verify these medicinal herbs and also explore new ones.

Author Contributions

SS and AN contributed to data gathering, analysis of data, drafting the manuscript, and approving the final version of the manuscript to be submitted; MK and AZ contributed to making the idea, supervise the project, analyze data and revise the draft and approve the final version of the manuscript to be submitted; RM, GK, and NE contributed to data gathering, revising the draft of manuscript, and approving the final version of the manuscript to be submitted.

Ethical Approval

It is a review and done according to the Committee on Publication Ethics guidelines.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Arman Zargaran https://orcid.org/0000-0003-4351-3861

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Abbreviations

ACE2	angiotensin-converting enzyme 2
ARDS	acute respiratory distress syndrome
CatL	cathepsin L protease
CDC	Centers for Disease Control and Prevention
COVID-19	coronavirus disease 2019
3CLpro	3-chymotrypsin-like protease
E protein	envelope
HAT	human airway trypsin-like protease
HE protein	hemagglutinin esterase
IFN	interferon
IL	interleukins
IRF-3	Interferon regulatory factor 3
LPS	lipopolysaccharide
M protein	membrane
MERS-CoV	Middle East respiratory syndrome-related coronavirus
MHC	major histocompatibility complex
MM-PBSA	molecular mechanics/Poisson–Boltzmann or generalized Born and surface area
N protein	nucleocapsid
NF-κB	nuclear factor kappa B
NK	natural killer
nsp	non-structural proteins
PAK1	RAC/CDC42-activated kinase 1
PHEIC	public health emergency of international concern

PLpro	papain-like protease
RSV	respiratory syncytial virus
SARS-CoV	Severe acute respiratory syndrome-related coronavirus
STAT	signal transducer and activator of transcription
TNF-α	tumor necrosis factor-alpha
TMPRSS2	transmembrane protease serine 2
WHO	World Health Organization.