Herbs-derived phytochemicals – a boon for combating COVID-19

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Abstract

The recent pandemic, the novel coronavirus (COVID-19), has put the whole world on alert with the threat of the virus that targets the human respiratory system. The disease has affected more than 633.6 million people globally and caused 6.5 million deaths since November 18, 2022. About 12.94 billion people are vaccinated as of November 18, 2022. Due to varied climatic conditions, SARS-CoV-2 has shown rapid mutation in recent years. Because of the lack of appropriate therapeutic drugs, inadequate diagnostic mechanisms, life-supporting medical facilities, and lack of awareness, the spread of SARS-CoV-2 has become severe. Thus, the most efficient strategy to control this disease is to follow preventive measures. However, treating SARS-CoV-2 cases in Wuhan using traditional Chinese herbs has set an example to show how traditional health can contribute to treating this novel virus. Medicinal herbs are known for their antimicrobial, antibacterial, antiviral, immunomodulatory, immunoadjuvant, and anti-inflammatory properties. These medicinal herbs are used during cooking and consumed regularly worldwide. In this view, medicinal herbs gained evident attention. These herbs can serve as a potential and economical remedy for combating the lethal effects of COVID-19. The present review highlights the phytochemicals and their mechanisms of action in preventing SARS-CoV-2.

Keywords COVID-19 · SARS-CoV-2 mode of action · Medicinal herbs · Antioxidant and functional attributes · Immunomodulator · Antiviral

Introduction

Since December 2019, the whole world has faced an outbreak of COVID-19 (novel coronavirus disease-2019), starting and reporting in Wuhan, China. The World Health Organization (WHO) declared this novel virus a pandemic on March 11, 2020, because of its high transmissibility and pathogenicity. The novel coronavirus infection is mainly due to Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and affects the respiratory system. The evidence-based treatment of COVID-19 has supported the statement that a more robust immune system helps fight against this novel virus (Rastogi et al. 2020). Our daily food habits relate to boosting our immune systems.

Coronaviruses (CoV) can be classified as Alpha-CoV, Beta-CoV, Gamma-CoV, and Delta-CoV (Li 2016). Scientists have reported six various human CoVs, which involve Alpha-CoV (HCoV-NL63 and HCoV229E) and Beta-CoV (SARS-CoV and MERS-CoV) (Tang et al. 2015). SARS-CoV-2 is a novel β-coronavirus that is different from the previously identified SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) outbreak in 2002 and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) outbreak in 2012 that was responsible for the pulmonary failure and lethal respiratory-tract infections (Zhang et al. 2020). The genomic sequence of the SARS-CoV-2 shows a 96.2% resemblance to the SARS-CoV (Astuti and Ysrafil 2020). The symptoms are fever, cough, sore throat, muscle pain,

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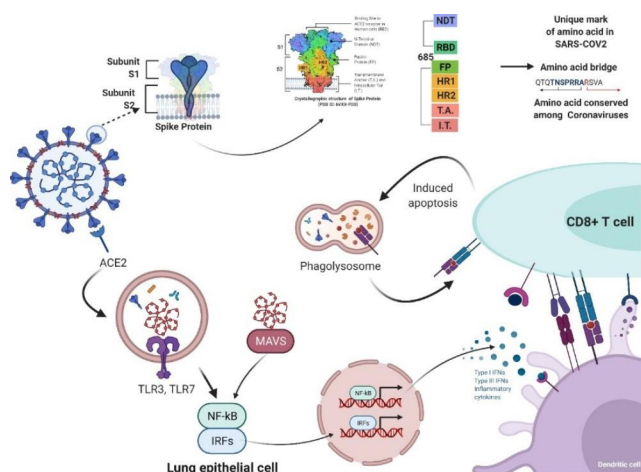
Fig. 1 Structure of novel SARS-CoV-2

chest pain, shortness of breath, and fatigue. However, the evidence has shown that the number of positive COVID-19 patients is higher among older people with underlying diseases (Chen et al. 2020a; Huang et al. 2020). An evidence-based study has shown that the recovered patient experiences certain medical conditions like acute respiratory distress syndrome (ARDS), acute renal failure (ARF), and even death (Zhang et al. 2020). Recent studies have shown the emergence of mucormycosis as post-COVID symptoms (Dyer 2021). Currently, the etiology of the coronavirus (SARS-CoV-2) is unclear, without any targeted therapies for patients. Thus, research findings have shown a link between immune function and the COVID-19 pandemic. This review discusses the potential therapeutic value of medicinal herbs and their mechanisms of action against novel coronavirus.

SARS-CoV-2 (novel coronavirus COVID-19)

The coronavirus SARS-CoV-2 enveloped a positive RNA virus ranging from 65 to 125 nm in diameter. The single RNA strand shows crown-like spikes on the surface (Fig. 1). The SARS-CoV-2 exhibits four structural proteins: spike glycoprotein, envelop glycoprotein, membrane glycoprotein, nucleocapsid protein, and accessory proteins. The spike glycoprotein is present on the virus's outer surface, having a molecular weight of 150 kDa and a size of 26,000 to 32,000 bases (Wu et al. 2020), which gives the virus a crown shape. This spike glycoprotein is responsible for infecting the respiratory system. This protein forms a homotrimer that binds the envelope viruses to host cells with ACE2 (angiotensin-converting enzyme 2) and affects the lower respiratory tract cells. The nucleocapsid protein is a structural component of coronavirus confined in the endoplasmic reticulum and Golgi bodies that binds the virus's
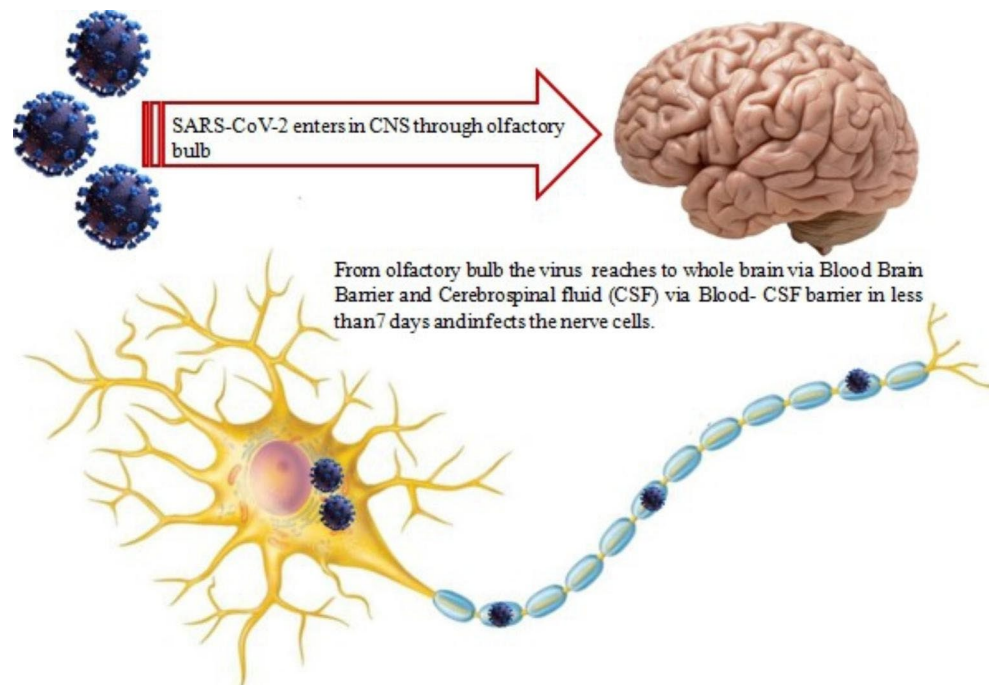
nucleic acid material. This nucleocapsid protein is further phosphorylated, leading to structural changes because of viral RNA affinity (Astuti and Ysrafil 2020). The membrane protein of the virus is responsible for determining the shape of the virus envelope and binding with other structural proteins. The envelope protein is the smallest in coronavirus and is essential for the production and maturation of the virus.

The SARS-CoV-2 spreads through saliva droplets and nose and mouth discharges of infected people via talking, coughing, and sneezing. These droplets are then aerosolized, letting the virus remain active for 3 h in the air (Van Doremalen et al. 2020). Moreover, it can also be transmitted through the stools and urine of an infected person (Omokhua-Uyi and Van Staden 2021). The Coronavirus enters the body via the nasal cavity and attacks the central nervous system (CNS) via the olfactory bulb. It passes into the cerebrospinal fluid (CSF) and infects the nerve cells (Fig. 2). When the SARS-CoV-2 enters the host cell, it binds with ACE2. It thus affects the lower respiratory tract cells, leading to ARDS, cardiac, kidney, and gastrointestinal tract disorders in COVID-19 patients (Astuti and Ysrafil 2020). Moreover, due to the virus's novel nature, the mutation occurs. Thus, the possible symptoms are not exhaustive, and research is ongoing (Omokhua-Uyi and Van Staden 2021).

Association of metabolic diseases with COVID-19

The modern lifestyle plays a vital role in our health management. Our diets and physical activities vary according to our lifestyle, leading to several metabolic diseases like obesity, hypertension, and diabetes, which may further be linked with other chronic diseases such as cardiovascular and chronic kidney diseases. These metabolic diseases are due to pro-inflammatory cytokine activity involved in SARS-CoV-2 (Matias et al. 2020). Reports of COVID-19 in China and Italy implicated that the morbidity rate of SARS-CoV-2 is higher in older adults suffering from metabolic diseases (Gasmi et al. 2020). Obesity, a central linkage of metabolic disease, is caused due to pro-inflammatory cytokines (IL-1, IL-6, IL-17, IL-23, leptin, PAI-1, TGF-β, TNF-α). These cytokines favour the hyperbolic responses of SARS-CoV-2. These responses may lead to severe respiratory failure and harm the occlusive junctions of the respiratory epithelium. The increase in the production of cytokines like IL-17 and IL-23 leads to decreased immunological responses in obese people, thus contributing to the morbidity of SARS-CoV-2 among them. It is proposed that the adipose tissue acts as a reservoir for some viruses that may favor the seriousness of novel coronavirus infection in obese people (Petrakis et

Fig. 2 Mechanism of action of SARS-CoV-2 after entering the host

SARS-CoV-2 enters in CNS through olfactory bulb

From olfactory bulb the virus reaches to whole brain via Blood Brain Barrier and Cerebrospinal fluid (CSF) via Blood- CSF barrier in less than 7 days and infects the nerve cells.

al. 2020). The expression of ACE2 in gastrointestinal tract epithelial tissue, its usage by SARS-CoV-2 as an invasion mechanism, and changes in microbiota due to obesity create a link between obesity and COVID-19. Reports suggest that around 70% of COVID-19 patients are obese. Thus, obesity damages immunological homeostasis due to SARS-CoV-2 (Matias et al. 2020).

Impact of SARS-CoV-2 on the immune system and gut microbiota

Evidence-based studies have shown that the body's immunity level plays a vital role in fighting COVID-19 (Kumar et al. 2020). The human immune system shows a cytokine-mediated response to SARS-CoV-2. SARS-CoV-2 infection, increases the CRP (C-Reactive Protein) by 86%, IL-6 by 52%, and neutrophils by 38% and reduces the total lymphocyte count by 35% (Chen et al. 2020b). The virus triggers the body's innate immune system through Antigen Presenting Cells (APC) when it enters the host cell. APC, a presenting cell of foreign antigens, comprises several Pattern Recognition Receptors (PRR), such as Toll-like, NOD-like, and RIG-I-like receptors. These PRRs induce signaling to produce immune system cell effectors for protein activation. The APC presents the SARS-CoV-2 antigen to CD4 T-helper cells that release a co-stimulatory molecule (IL-12) to stimulate the Th1 cell activation. It also starts producing pro-inflammatory cytokines by the NF-κB signaling pathway. In response to SARS-CoV-2, our body produces several antibodies, mainly IgM and IgG. This novel virus

produces a specific IgM present for a short period (12 weeks) while the IgG lasts longer. When the host is infected with SARS-CoV-2, it produces antibodies and CD4 T-cells to protect itself (Astuti and Ysrafil 2020).

Herbs-derived phytochemicals in combating COVID-19

The bioactive phytochemicals came as a ray of hope in the search for effective therapeutics against SARS-CoV-2 from medicinal herbs. These herbal phytochemicals can interact with the SARS-CoV-2 proteins to promote viral entry and replication (Omokhua-Uyi and Van Staden 2021). The replication cycle of SARS-CoV-2 and the inhibitory effect of bioactive phytochemicals in medicinal herbs are illustrated in Fig. 3. Phytochemicals such as alkaloids, aliphatics, diterpenoid lactones, glycosides, and steroids are present in medicinal herbs. These phytochemicals protect the human body against viral infections. Flavonoids have been reported to be effective against viral infections. They block the entry of viruses into cells by blocking the cellular receptors and interfering with viral replication and translation (Das et al. 2021). Alkaloids like cepharanthine, emetine, and homoharringtonine derived from herbs exhibit antiviral properties and can be potential therapeutics against SARS-CoV-2 (Wang and Yang 2020). They inhibit viral replication by blocking viral DNA polymerase function. Alkaloids with DNA intercalating properties effectively against COVID-19 (Das et al. 2021). *In silico* studies reported the effectiveness of stilbenes derived from medicinal herbs as a potent
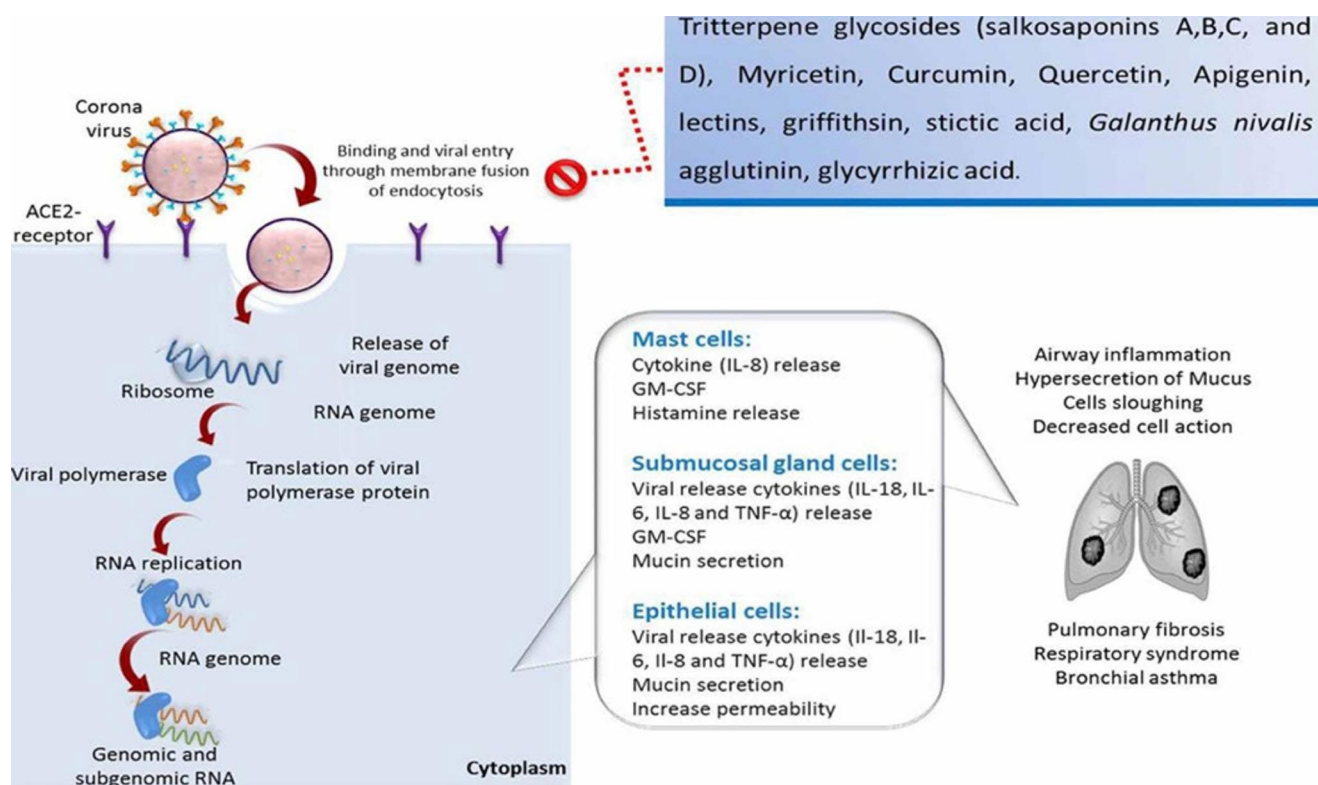
Fig. 3 Schematic illustration of the replication cycle of SARS-CoV-2, induction of respiratory syndrome and lung fibrosis, and the natural compound inhibitory effects on viral infection. IL, interleukin; TNF, tumor necrosis factor; GM-CSF, granulocyte-macrophage colony-stimulating factor. (Adapted from Attia et al. 2020)

therapeutic agent against COVID-19. They inhibit the ACE-2 and spike protein and disrupt the S-ACE-2 interface, thus blocking the host cell entry. Thus, the medicinal herbs with antiviral and immunostimulatory properties are of interest for the management of COVID-19. Turmeric (*Curcuma longa*) has many therapeutic values. The bioactive component, curcumin, is reported to possess anti-inflammatory, antiviral, antipyretic, antiflatulent, antimicrobial, and anticancer properties (Patra et al. 2018; Rattis et al. 2021). The therapeutic effect of curcumin is to suppress pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α). These can inhibit the replication of SARS-CoV at EC$_{50}$ of 10μM (Wen et al. 2007; Pawar et al. 2021) investigated the effect of curcumin/ piperine in COVID-19 patients as symptomatic adjuvant therapy. They have administered 525 mg curcumin with 2.5 mg piperine in tablet form twice daily. The patients showed early symptomatic recovery with improved oxygen saturation (more than 94%) and decreased morbidity (Pawar et al. 2021). Giloy (*Tinospora cordifolia*) is a widely used medicinal plant having immune boosting properties (Panchabhai et al. 2008). The bioactive phytochemicals in giloy are Berberine, Magnoflorine, Tinocordifoline, Tinosporin, Isocolumbin, Tinocordine, Tinosporide, and Tinsporic acid (Raju et al. 2019). Garlic (*Allium sativum*) is an essential culinary herb with medicinal properties. Garlic is known for its immune-modulating, antiviral, and antibiotic properties. Studies have shown that garlic is significant in SARS-CoV management (Keyaerts et al. 2007). Garlic contains organosulfur compounds such as allicin, which are solely accountable for the antiviral effect by suppressing the expression of pro-inflammatory cytokines like interleukin-6 and tumour necrosis factor via the extracellular-signal-regulated kinase/mitogen-activated protein kinase signalling pathway. This could further enhance the inhibition of SARS-CoV-2 viral replication in the host cell membrane by preventing the virus protein maturation, replication, and further growth (Ademiluyi et al. 2020). Quercetin, a bioactive phytochemical in *Abutilon indicum* and *Bauhinia variegate*, exhibits antiviral, anti-inflammatory, and anticancer properties. Quercetin inhibits the entry of SARS-CoV into the host cell at an EC$_{50}$ value of 83.4 μM (Yi et al. 2004). USFDA has approved quercetin as a therapeutic drug against SARS-CoV-2 (Pooladanda et al. 2020). Kalmegh (*Andrographis paniculata*) has been reported to suppress the NOD-like receptor protein-3 (NLRP3), IL-1β, and caspase-1 responsible for the pathogenesis of SARS-CoV (Liu et al. 2020).

Fig. 4 Phytochemicals regulate innate immune functions in defecting viral infection. (Adapted from Han and Hoang 2020)
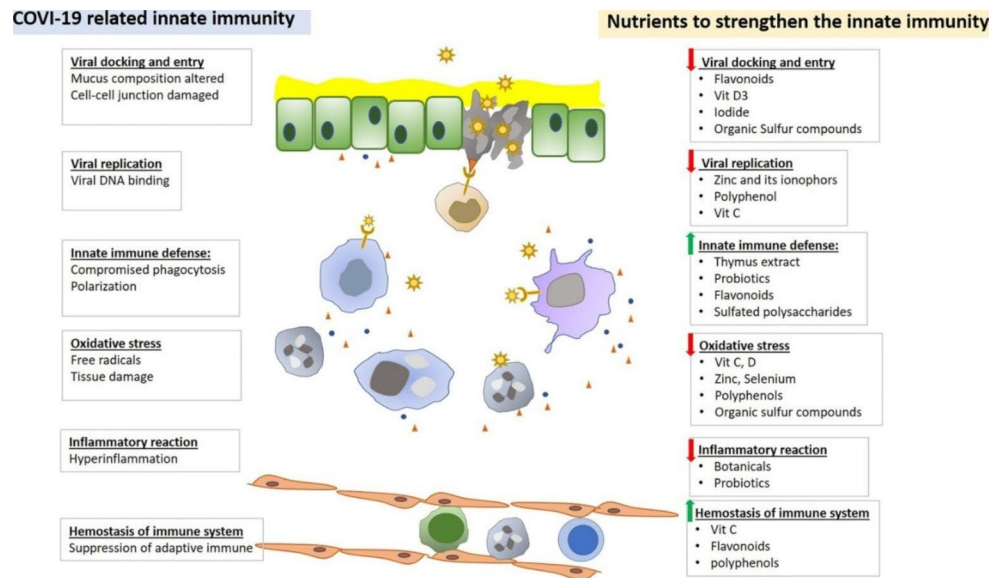
Mechanism of action of different phytochemicals

Phytochemicals show an effective mechanism against SARS-CoV-2, as depicted in Fig. 4. Alkaloids act by various mechanisms, such as inhibiting the growth of viruses and blocking the sites of virus binding. Flavonoids act by inhibiting RNA synthesis by constraining the enzyme responsible, which is reverse transcriptase. The primary mechanism of flavonoids is inhibiting the cellular receptor kinases, including MAPKs, the serine/threonine-specific protein kinase (Akt), and the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3-K) and, as a consequence, interfering with the cellular signal transduction cascade. Flavanoids, particularly luteolin, apigenin, quercetin, kaempferol, and myricitrin, interfere with the activation of NRP3 inflammasome (innate immune system receptors that regulate the activation of enzyme caspase-1 and induce inflammation in response to the infection caused by microbes and viruses) SARS beta coronavirus. Further entry into the cell includes 3-chymotrypsin-like protease, the main protease enzyme, and MPro, the chief enzyme for replicating SARS-CoV-2. Another essential protein is the S protein which is the binding protein and helps transmit the SARS-CoV-2 across the cell membrane via ACE2. 3-chymotrypsin-like protease and MPro are essential in replicating the virus by forming the virus replication complex. The ultimate targets for preventing virus replication depend on the 3-chymotrypsin-like protease, MPro, and S protein. Several investigations have been done on different plant extracts and pure compounds for potential antiviral effects on different coronavirus strains. The main targets in the virus for inhibiting activity are the proteins involved in coronaviral replication and the conductance of ion channels and proteases. The principal

mode of action remains the inhibition of virus replication. Saikosaponins compounds under triterpene glycosides have been isolated from herbal medicines such as parsley. They have been shown to suppress the SARS coronavirus's early infection, penetration, and replication. Another mechanism of the viral-dependent RNA polymerase is the inhibition and suppression of viral 3CL protease.

The molecular docking studies on the efficacy of medicinal herbs against SARS-CoV-2 have been listed in Table 1. The molecular docking study by Kar et al. (2020) suggested that the bioactive compounds adhatodine and anisotine present in *Justicia adhatoda* have been found to exhibit an inhibitory effect against the spike protein of SARS-CoV-2 at the active binding site of the receptor-binding domain (RBD) of SARS-CoV-2 with a 7.8 kcal/mol energy score. β-amyrin (*Swertia chirata*) targets the spike protein, while vasicoline, adhatodine, and anisotine from *J. adhatoda* and amaroentin from *Swertia chirata* target the Mpro protein. Graecunin E (a phytochemical of *Trigonella foenum-graecum*), Bismahanine (a phytochemical of *Murraya koeinigii*), Granatin B (a phytochemical of *Punica granatum*), cis-Miyabenol C (a phytochemical of *Foeniculum vulgare*), and Glycyrrhizic acid (a phytochemical of *Glycyrrhiza glabra*) target the SARS-CoV-2 spike protein with a binding energy score (k/cal/mol) of -8.6, -9.1, -9.1, -9.4, and −9.5, respectively in the molecular docking study (Puttaswamy et al. 2020).

Eriodictyol-7-O-rutinoside (*Citrus limon*) targets the RdRp protein of SARS-CoV-2 with a binding energy score of -9.9 kCal/mol and terflavin B (*Terminalia chebula*) -9.7 targets Mpro. Narkhede et al. (2020) reported that β-caryophyllene (*Ocimum* sp.), Crysophanic acid (*Rheum palmatum*), Hesperetin (*Citrus reticulata*), Glycyrrhizin (*Glycyrrhiza glabra*), Berberine (*Berberis aristate*), Rhein

Table 1 The molecular docking studies on the efficacy of medicinal herbs against SARS-CoV-2

Traditional Herbs	Bioactive compound	Mechanism against SARS-CoV-2	Reference
Acalypha indica	Biorobin	RdRp and hACE-2	Joshi et al. (2021)
Aloe Vera	Aloenin	Interact with protease	Srivastava et al. (2020)
Amaranthus tricolor	Amaranthin	3CL Pro inhibition	ul Qamar et al. (2020)
Azadirachta indica	Aza-diradionolide	Binds with NSP9	Parida et al. (2020)
	Nimolicinol	Protease inhibition	
	Nimbin	Interact with protease	Gurung et al. (2020)
Camellia sinensis	Epigallocatechin gallate	NF-κB, epigenetic regulation	Attia et al. (2020)
	Myricetin 3-O-beta-D-glucopyranoside	3CL Pro inhibition	ul Qamar et al. (2020)
	Theaflavin	Binds with RdRp	Mani et al. (2020)
Catharanthus roseus	Vindolinine	Binds with NSP15	Parida et al. (2020)
Cicer arietinum	Daidzein	Blocks HSPA5	Elfiky (2021)
	Formononetin		
	Genistein		
	Biochanin A		
Cinnamomum verum	Camphorating D	Blocking signalling pathway	Khanal et al. (2020)
Citrus sinensis	Naringenin	Mpro inhibitor	Khaerunnisa et al. (2020)
Curcuma longa	Demethoxy-curcumin	Mpro inhibitor	
	Curcumin	3CLpro, glycoprotein-RBD spike, ACE2 receptor	Attia et al. (2020)
Hyptis atrorubens	Methyl rosmarinate	Interacts with 3CLPro	ul Qamar et al. (2020)
Nigella sativa	Limonin	Binds with NSP16	Parida et al. (2020)
Phyllanthus emblica	(2 S)-Eriodictyol 7-O-(6″-O-galloyl)-beta-D-glucopyranoside	Protease inhibition	ul Qamar et al. (2020)
Piper nigrum	Moupinamide	PLpro	Mani et al. (2020)
Solanum nigrum	Solvanol	Binds with NSP16	Parida et al. (2020)
Tinospora cordifolia	Cordioside	Binds with main protease	Latha and Pandit (2020)
	Berberine	Interact with protease	Srivastava et al. (2020)
Withania somnifera	Quercetin	PLpro & 3CLpro	Khaerunnisa et al. (2020); Parida et al. (2020)
	Somniferine	Binds with NSP15	Parida et al. (2020)
	Anaferine	Binds with NSP10, NSP16	
	27-Deoxy-14- hydroxy withaferin A	Protease inhibition	
	27-Hydroxy withanone	Interferes with Spike protein	
	12-Deoxy witha-stramonolide	Interferes with Spike protein and binds with NSP9	
	27-Deoxy withaferin A	Interferes with Spike protein	
	2,3-Dihydro withaferin A	Interferes with Spike	
	27-Hydroxy withanolide B	Binds with NSP10, Binds with NSP9	
	Witha-stramonolide	Binds with NSP12 D2	
	Withanolide B	Binds with NSP12 D2 and binds with NSP3	
	Withanolide R	Binds with NSP12 D2	
	Withaferin A	Binds with NSP12 D2	
	27-Deoxy-14-hydroxyl withaferin A	Binds with NSP3	

(*Aloe barbadensis*), with a binding score (Kcal/mol) of -7.2, -7.3, -7.9, -8.1, -8.1, and − 8.9, respectively targets Mpro.

Conclusion

The novel coronavirus disease COVID-19 has appeared as a global pandemic with no correlation between environmental changes (like temperature and humidity) and transmission. This virus can mutate according to environmental changes, an essential point of concern while researching the potential vaccine for COVID-19. Recently, several vaccines have been approved to restrain the spread of novel coronavirus. However, its acceptance is a big challenge. The medicinal herbs demonstrate potent therapeutic and medicinal properties that can prevent and manage COVID-19. The novel coronavirus has shown unique pathogenesis, which requires specific treatment for its management. However, the consumption of unproven herbs poses a significant health risk. It is necessary that medicinal herbs used against COVID-19 is well evaluated for their mechanism of action, efficacy, and safety concerns before use. Further research is needed to develop medicinal herbs incorporated with nutraceuticals to manage COVID-19 with clinical trials to evaluate the proper doses and effectiveness. Studies promoting drug development while considering several factors, like age group and chronic diseases, for patients using these traditional herbs are promising research areas.

Declarations

Conflict of interest The authors declare no conflicts of interest.

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