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Evaluation of botanicals as potential COVID-19 symptoms terminator

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Abstract

Information about the coronavirus disease 2019 (COVID-19) pandemic is still evolving since its appearance in December 2019 and has affected the whole world. Particularly, a search for an effective and safe treatment for COVID-19 continues. Botanical mixtures contain secondary metabolites (such as flavonoids, phenolics, alkaloids, essential oils *etc.*) with many therapeutic effects. In this study, the use of herbal treatments against COVID-19 was evaluated. Medical synthetic drugs focus mainly on respiratory symptoms, however herbal therapy with plant extracts may be useful to relieve overall symptoms of COVID-19 due to the variety of bioactive ingredients. Since COVID-19 is a virus that affects the respiratory tract, the antiviral effects of botanicals/plants against respiratory viruses have been examined through clinical studies. Data about COVID-19 patients revealed that the virus not only affects the respiratory system but different organs including the gastrointestinal (GI) system. As GI symptoms seriously affect quality of life, herbal options that might eliminate these problems were also evaluated. Finally, computer modeling studies of plants and their active compounds on COVID-19 were included. In summary, herbal therapies were identified as potential options for both antiviral effects and control of COVID-19 symptoms. Further data will be needed to enlighten all aspects of COVID-19 pathogenesis, before determining the effects of plants on severe acute respiratory syndrome coronavirus 2.

Key Words: COVID-19; Herbal therapies; Plant; SARS-CoV-2; Antiviral; Symptom

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Core Tip: To stop the coronavirus disease 2019 (COVID-19) pandemic, extensive search is ongoing to develop effective and safe drugs against severe acute respiratory syndrome coronavirus 2. COVID-19 in a major way affects the respiratory system, but many patients also have gastrointestinal (GI) symptoms. Plants have beneficial effects

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on various systems with their varied array of metabolites. In our study, the potential effects of herbal treatments against COVID-19 were examined. Their antiviral effects, their effects on the respiratory system, GI system, and other COVID-19 symptoms were investigated.

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INTRODUCTION

New coronavirus disease 2019 (COVID-19), which emerged in Wuhan in December 2019, spread rapidly and affected the whole world. The emergence, epidemiology, origin and evolution of COVID-19 has been extensively studied by Sun *et al*[1].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been shown to carry out viral replication in the human host mainly through three main proteins and enzymes: 3-chymotrypsin-like protease (3CLpro), angiotensin-converting enzyme-2 (ACE2) and spike protein (TMPRSS2)[2,3]. ACE2 receptors are found in the body not only in the lungs but also in tissues such as the endothelium, heart, kidney and intestine[2]. This distribution makes many organs a target of COVID-19. The significance of ACE2, which is found in intestinal tissues, especially for amino acid uptake from foods, has been emphasized and it has been suggested that the intestine may be an important entry site for SARS-CoV-2[2-4]. Azithromycin, chloroquine, lopinavir, remdesivir, ritonavir are options used in treatment and whose effects are evaluated[5]. Effective and safe drugs and vaccines are sought all over the world to prevent novel coronavirus. Minerals, herbs, herbal products, probiotics and vitamins are the main natural resources, whose effectiveness and also the usability of herbal medicines in COVID-19 were investigated and benefit, risk assessments were evaluated[6-8]. Truly, since the beginning of the COVID-19, herbal medicines have been used in China. A study has shown that 90% of the 214 patients were treated with the traditional herbal medicine, moreover, it is reported that some of them prevented COVID-19 infection in healthy individuals and enhanced the health state of patients with mild or severe symptoms[9,10]. Health scientists from the Zhongnan Hospital of Wuhan University included the use of traditional medicines in the guidelines for the treatment and prevention of COVID-19. The experts recommended using medicinal plants for the prevention of COVID-19, additionally, the use of different herbal mixtures were recommended according to the disease-stage[11].

Herbs and herbal products provide generous sources of primary and mostly secondary metabolites, which are valuable compounds (phenolics, flavonoids, tannins, alkaloids, essential oils, *etc.*) for prophylactic and chronic therapeutic purposes. Some of these metabolites in herbs and herbal mixtures have high chemical variety than the synthetics in stopping viral proliferations, and having antiviral activities[12]. Thus, botanicals can both show antiviral effects and relieve the symptoms of COVID-19 thanks to the different substance groups, which demonstrate different biological effects that will not be possible to achieve with a single synthetic drug. Based on this understanding, in this review, we offer all the potential interventions for COVID-19 infection according to previous and recently found antiviral effects of herbals. Considering the major transmission routes of COVID-19, where mostly ACE2 receptors found and the symptoms, the plants have been handled especially with their effects on the mostly respiratory and also gastrointestinal (GI) systems. Although ACE2, is typically expressed in epithelial cells of the airways, various GI symptoms in COVID-19 might be explained by the high expression of ACE2 in the digestive tract. Additionally, liver tests abnormalities, active viral replication in GI tract and patients' manifestations with GI symptoms (abdominal pain, diarrhea, nausea, vomiting) and possible fecal-oral transmission reveal the GI involvement in COVID-19[13].

Recent findings demonstrated that early blocking of COVID-19 with ACE2 inhibitors was one of the mechanisms used by novel drugs[14], on the other hand diabetes mellitus and hypertension enhanced the risk of COVID-19 infection, in spite of using ACE2 inhibitors[15-17]. Furthermore, unpredicted ACE2 upregulation by

ACE2 inhibitors, ibuprofen and angiotensin II type-I receptor blockers lead to need of identifying/using alternative ACE2 blockers[18]. Consequently, botanicals or natural products might be alternatively and selectively might block the ACE2 receptors without inhibiting the enzyme activity in order to treat and/or prevent COVID-19 spread in humans without increasing ACE2 expression in patients and therefore increased risk for COVID-19[19].

Clinical human studies showing the effect of plants on respiratory infections are presented as a table. Based on the pharmacological properties of plants, their practicality on COVID-19 symptoms have been evaluated. In the last part of the article, plants that inhibit ACE receptors, the research studies and their active compounds on COVID-19 also included and it is aimed to examine the plants from a broad perspective.

ANTIVIRAL EFFECTS OF HERBAL THERAPIES

Most of the respiratory diseases (approximately 80%) are caused by viral agents[20]. Viral respiratory diseases are responsible for high mortality and morbidity, especially in disadvantaged and sensitive elderlies and immunocompromised individuals[21, 22]. The main respiratory viruses are adenovirus, coronavirus, influenza virus, respiratory syncytial virus and rhinovirus[20]. Plants with antiviral effects and studies showing the effects of these on respiratory viruses are given in Table 1. Human clinical studies showing the effects of plants on respiratory tract infections are presented in Table 2.

EFFECTS OF HERBAL TREATMENT ON COVID-19 SYMPTOMS

Cough and fever are common symptoms in patients with COVID-19, including fatigue, shortness of breath, headache, muscle pain, sore throat, sputum, hemoptysis, diarrhea, dyspnea, rhinorrhea, chest pain, nausea, and vomiting[23]. COVID-19 symptoms in children are similar to those in adults and are relatively mild[24].

Although, the current synthetic drugs focus on mainly respiratory symptoms, herbal therapy can be used to relieve overall symptoms of COVID-19 with their bioactive ingredients[25]. The meta-analysis study, which included randomized controlled trial studies, found significant effects of the combination of western medicine and herbal therapies. Combined treatment has been effective in cough, fever, dry and sore throat, fatigue and overall GI symptoms. The combined therapy significantly improved the disappearance rate of cough and sputum production[26]. In another meta-analysis, it was found that the addition of Chinese herbal medicine for standard care improved the symptoms and signs of COVID-19 as well as decreased levels of C-reactive protein[27]. The effects of plants that can alleviate the symptoms of COVID-19 are summarized in Table 3. In addition, plants regarded as ACE inhibitors are shown in Table 4.

THE EFFECTS OF HERBS AND THEIR ACTIVE COMPOUNDS ON COVID-19

In recent years, artificial intelligence has often been used to discover natural products as medicine[28,29]. After the outbreak of COVID-19, computer models were used to investigate the effect of many plants and their components on SARS-CoV-2. Khaerunnisa *et al*[30], determined the COVID-19 Main Protease (Mpro) inhibitor effects of medicinal plant components in a molecular docking study. They suggested apigenin-7-glucoside, curcumin, catechin, demethoxycurcumin, epicatechin-gallate, luteolin-7-glucoside, and oleuropein, as potential inhibitors of COVID-19 Mpro. In a similar molecular docking study using sixty-seven molecules of natural origin, crocin, digitoxigenin and b-eudesmol were proposed as inhibitors against coronavirus[31]. Another study was carried out using one hundred seventy-one essential oil components. The study determined the best docking ligands for the SARS-CoV target proteins were (E)--farnesene, (E,E)--farnesene and (E,E)-farnesol, thereby suggesting essential oil components may act synergistically with other antiviral agents, or they may provide some relief of COVID-19 symptoms[32]. Computer modeling studies and clinical studies against SARS-CoV-2 in some prominent plants/products and their

Table 1 Antiviral effects of plants on respiratory viruses

Plant name	Preparation	Susceptible viruses	Ref.
<i>Allium sativum</i> (Garlic)	Aqueous extracts	Influenza A (H9N2)	Rasool <i>et al</i> [53], 2017
	Extract	Infectious bronchitis virus	Mohajer Shojai <i>et al</i> [54], 2016
	Ethanol extract	Influenza A (H1N1)	Chavan <i>et al</i> [55], 2016
	Garlic oil	Influenza A (H1N1)	Choi[56], 2018
	Fresh extract	Influenza A (H1N1)	Mehrbod <i>et al</i> [57], 2013
	Aqueous extract	Adenovirus (ADV3 and ADV41)	Chen <i>et al</i> [58], 2011
<i>Aloe vera</i> (Aloe)	Aloe anthraquinones and several derivatives (3-O-tetraacetoglycosylated)	Influenza A	Borges-Arg��ez <i>et al</i> [59], 2019
	Aloe-emodin	Influenza A	Li <i>et al</i> [60], 2014
<i>Astragalus mongholicus</i> (Astragalus)	<i>Astragalus</i> polysaccharides	Avian infectious bronchitis virus	Zhang <i>et al</i> [61], 2018
	<i>Astragalus</i> polysaccharide	Influenza A (H9N2)	Kallon <i>et al</i> [62], 2013
<i>Camellia sinensis</i> (Green tea)	Catechins -EGCG	Adenovirus	Weber <i>et al</i> [63], 2003
	Catechin	Influenza A	Kuzuhara <i>et al</i> [64], 2009
	Catechins	Influenza A (H5N1)	Liu <i>et al</i> [65], 2012
	Polyphenols	Influenza A; Influenza B	Yang <i>et al</i> [66], 2014
<i>Curcuma longa</i> (Turmeric)	Curcumin	Influenza A virus	Chen <i>et al</i> [67], 2013
			Dai <i>et al</i> [68], 2018
	Curcumin	Influenza A (H1N1, H6N1)	Chen <i>et al</i> [69], 2010
	Curcumin	RSV	Obata <i>et al</i> [70], 2013
<i>Echinacea purpurea</i> (Purple coneflower)	<i>E. purpurea</i> fresh herb and root tinctures	Influenza	Vimalanathan <i>et al</i> [71], 2013
	Standardized <i>E. purpurea</i> extract	Influenza A (H5N1, H7N7, H1N1)	Pleschka <i>et al</i> [72], 2009
	Standardized <i>E. purpurea</i> extract	Rhinoviruses, RSV	Hudson <i>et al</i> [73], 2011
<i>Eucalyptus globulus</i> (Eucalyptus)	Essential oil- vapor phase	Influenza	Vimalanathan <i>et al</i> [74], 2014
<i>Ginkgo biloba</i> (Ginkgo)	Leaf extract	Influenza A (H1N1, H3N2)	Haruyama <i>et al</i> [75], 2013
<i>Glycyrrhiza</i> sp. (Licorice)	Water extract of licorice (<i>Glycyrrhiza uralensis</i>)	RSV	Feng Yeh <i>et al</i> [76], 2013
	Glycyrrhizic acid derivatives	SARS-CoV	Hoever <i>et al</i> [77], 2005
	Extract of <i>Glycyrrhiza inflata</i>	Influenza A (H1N1)	Dao <i>et al</i> [78], 2011
	Glycyrrhizin	Influenza A	Wolkerstorfer <i>et al</i> [79], 2009
	Glycyrrhizin	Influenza A (H5N1)	Michaelis <i>et al</i> [80], 2010
<i>Lepidium meyenii</i> (Maca)	Extracted with methanol	Influenza A; Influenza B	Del Valle Mendoza <i>et al</i> [81], 2014
<i>Melaleuca alternifolia</i> (Tea tree)	Tea tree oil	Influenza A (H1N1)	Garozzo <i>et al</i> [82], 2011
	Aerosol and vapor of tea tree oil	Influenza A (H11N9)	Usachev <i>et al</i> [83], 2013
	Tea tree oil	Influenza A (H11N9)	Pyankov <i>et al</i> [84], 2012
<i>Melissa officinalis</i> (Lemon balm)	Essential oil	Influenza A (H9N2)	Pourghanbari <i>et al</i> [85], 2016
	Extract	Avian infectious bronchitis	Lele��sius <i>et al</i> [86], 2019
<i>Mentha piperita</i> (Peppermint)	Ethanol extract	RSV	Li <i>et al</i> [87], 2017
	Extract	Avian infectious bronchitis	Lele��sius <i>et al</i> [86], 2019

<i>Nigella sativa</i> (Black cumin)	Ethanol extracts of	Influenza A (H5N1)	Dorra <i>et al</i> [88], 2019
	Ethanol extracts of	Influenza A (H9N2)	Umar <i>et al</i> [89], 2016
	Extract	Coronavirus	Ulasli <i>et al</i> [90], 2014
<i>Panax ginseng</i> (Ginseng)	Root of plant <i>Panax ginseng</i>	RSV	Lee <i>et al</i> [91], 2014
	Panax Korean red ginseng extract	RSV	Lee <i>et al</i> [92], 2014
	Red ginseng extract and polysaccharide and saponin fractions	Influenza A (H1N1)	Yin <i>et al</i> [93], 2013
	Korean red ginseng extract	Influenza A (H1N1, H3N2)	Yoo <i>et al</i> [94], 2012
<i>Pelargonium sidoides</i> (Pelargonium)	<i>Pelargonium sidoides</i> radix extract EPs® 7630	Rhinovirus	Roth <i>et al</i> [95], 2019
	EPs® 7630	Respiratory viruses	Michaelis <i>et al</i> [96], 2011
	EPs® 7630	Influenza A (H1N1, H3N2)	Theisen <i>et al</i> [97], 2012
<i>Sambucus nigra</i> (Black elder)	Extract	Infectious bronchitis virus	Chen <i>et al</i> [98], 2014
	Standardized elderberry liquid extract	Influenza A; Influenza B	Krawitz <i>et al</i> [99], 2011
	Concentrated juice of elderberry	Influenza A	Kinoshita <i>et al</i> [100], 2012
	Elderberry flavonoids	Influenza A (H1N1)	Roschek <i>et al</i> [101], 2009
<i>Scutellaria baicalensis</i> (Chinese skullcap)	Chemical constituents	Influenza A (H1N1)	Ji <i>et al</i> [102], 2015
	Baicalin	SARS-CoV	Chen <i>et al</i> [103], 2004
<i>Torreya nucifera</i> (Japanese nutmeg yew)	Ethanol extract	SARS-CoV	Ryu <i>et al</i> [104], 2010
<i>Thymus vulgaris</i> (Thyme)	Essential oil- liquid phase	Influenza	Vimalanathan <i>et al</i> [74], 2014
	Extract	Avian infectious bronchitis	Lelešius <i>et al</i> [86], 2019
<i>Withania somnifera</i> (Ashwagandha)	Withaferin A	Influenza A (H1N1)	Cai <i>et al</i> [105], 2015
<i>Zingiber officinalis</i> (Ginger)	Aqueous extracts	Influenza A (H9N2)	Rasool <i>et al</i> [53], 2017
	Ethanol extracts	Influenza A- (H5N1)	Dorra <i>et al</i> [88], 2019
	Fresh ginger	RSV	Chang <i>et al</i> [106], 2013

Influenza A strains: H1N1, H3N2, H5N1, H6N1, H7N7, H9N2, H11N9; RSV: Respiratory syncytial virus; H1N1: Influenza A; SARS-CoV: Severe acute respiratory syndrome coronavirus.

metabolites are given below.

Curcuma longa

Utomo and Meiyanto[33] revealed the potential of several compounds of *Curcuma longa* against SARS-CoV-2 by binding to three protein receptors (*RBD-S*, *PD-ACE2*, *SARS-CoV-2 protease*). They showed that *Curcuma* sp. compounds can bind to target receptors, thus, have potential inhibitory effects on SARS-CoV-2 infectivity. Rajagopal *et al*[34] showed in their *in silico* docking study that *Curcuma longa* components could be effective against COVID-19 by inhibiting the SARS-CoV-2 Mpro enzyme. Moreover, cyclocurcumin and curcumin possess significant binding at the active site of SARS-CoV-2 Mpro when compared to hydroxychloroquine and nelfinavir. When compared to remdesivir, cyclocurcumin is significantly more active [Glide score: Cyclocurcumin (−6.77); remdesivir (−6.38); curcumin (−6.13); nelfinavir (−5.93); hydroxychloroquine (−5.47)]. In a similar study, diacetylcurcuminin was more effective on COVID-19 (Mpro) than nelfinavir[35]. Another study suggested the use of curcumin with hydroxychloroquine to destabilize the SARS-CoV2 receptor proteins[36]. Gonzalez-Paz *et al*[37] showed that curcumin strongly binds to 3CL-protease of COVID-19 Curcumin caused enzyme folding and structural changes in viral protease. Moreover, curcumin bound more strongly to the enzyme than chloroquine.

Eucalyptus globulus

Sharma[38] suggested that eucalyptus essential oil active compounds are potential inhibitors of COVID-19 Mpro. They conducted a molecular docking study to evaluate

Table 2 Human clinical studies showing the effect of plants on respiratory infections

Plant	Disease state	Participant	Dosage	Study design	Results
Aged garlic extract[107]	Cold and flu illness	120 healthy subjects, 2 groups (21-50 yr)	4 capsules/d (2.56 g); 90 d	Double-blind, randomized, placebo-controlled parallel intervention	Increase in $\gamma\delta$ -T cell and NK cell. Reduction in cold and flu severity; decrease in symptom days
<i>E. purpurea</i> and <i>E. angustifolia</i> root[108]	New-onset common cold	719 patients, 4 parallel groups (12-80 yr)	First 24 h: Equivalent of 10.2 g of root. Next 4 d: 5.1 g	Randomized, controlled trial	Disease duration and severity are not statistically significantly changed
<i>Echinacea purpurea</i> alcohol extract (Echinaforce®)[109]	Common cold	755 healthy subjects, 2 groups ($\geq$ 18 yr)	Illness prevention: 3 $\times$ 0.9 mL. Acute stages of colds: 5 $\times$ 0.9 mL	Randomized, double-blind, placebo-controlled trial	Reduction of the total number of cold episodes, cumulated episode days, and pain-killer medicated episodes. Inhibited virally confirmed colds and especially prevented enveloped virus infections. Maximal effects on recurrent infections. Prophylactic intake of <i>E. purpurea</i> over a period of 4 mo to provide a positive risk/benefit ratio
<i>Echinacea</i> root extract[110]	Respiratory symptoms	175 adults, 2 groups (18–65 yr)	Tablets: 112.5 mg <i>E. purpurea</i> 6:1 extract (equivalent to 675 mg dry root) and 150 mg <i>E. angustifolia</i> 4:1 extract (equivalent to 600 mg dry root) 3 $\times$ 1 tablet, if required: 3 $\times$ 2 tablets	Randomized, double blind, placebo-controlled trial	Lower respiratory symptom scores. Preventive effect against the development of respiratory symptoms during travel, including long-haul flights
Green tea catechins and theanine[111]	Influenza	200 healthcare workers, 2 groups	Capsules: Green tea catechins (378 mg/d) and theanine (210 mg/d). 5 m	Randomized, double-blind, placebo-controlled trial	Lower incidence of influenza infection in the catechin/theanine group
Ivy leaf extract[112]	Acute or chronic bronchial inflammatory disease	9657 patients (5181 children)	Ivy leaves extract [drug-to-extract ratio: 5-7.5:1; extraction solvent: ethanol 30% (w/w)]. 0–5 yr: 3 $\times$ 2.5 mL; 6–12 yr: 3 $\times$ 5 mL; 12 yr and adults: 3 $\times$ 5–7.5 mL. 7 d	Prospective, open, multicenter post marketing study	Healing or improvement in 95% of symptoms. Effective and well tolerated
Ivy extract (Hedelix®)[113]	Acute respiratory catarrh and/or chronic recidivating inflammatory bronchial disease	268 children, 2 groups (syrup and drops groups) (0-12 yr)	0-1 yr: 1 $\times$ 2.5 mL syrup or 3 $\times$ 5 drops, 1-4 yr: 3 $\times$ 2.5 mL syrup or 3 $\times$ 16 drops, 4-10 yr: 4 $\times$ 2.5 mL syrup or 3 $\times$ 21 drops, 10-12 yr: 3 $\times$ 5 mL syrup or 3 $\times$ 31 drops. 14 d	Independent open, non-interventional studies	Effective and safe treatment of cough. Reduction in symptoms (especially rhinitis, cough and viscous mucus)
Ivy leaves dry extract (Prospan®)[114]	Bronchial asthma	30 children (suffering from partial or uncontrolled mild persistent allergic asthma despite long-term treatment with 400 μ g budesonide equivalent), 2 groups (6–11 yr)	2 $\times$ 5 mL (corresponding to 70 mg extract) 28–30 d	Randomized, double blind, placebo-controlled, cross-over study	Improvement of MEF75-25, MEF25 and VC
Korean red ginseng extract[115]	Influenza-like illness	100 healthy adults, 2 groups (30-70 yr)	9 capsules/d. 3 m	Placebo-controlled trial	Reduced the incidence of influenza-like illness
Modified ginseng extracts (GS-3K8 and GINST)[116]	Acute respiratory illness	45 healthy applicants, 3 groups (39-65 yr)	Capsules: 500 mg; 6 capsules/d; 8 wk	Randomized, double-blind, placebo-controlled pilot study	Reduction in acute respiratory illness development and symptom duration
<i>Panax quinquefolius</i> extract CVT-E002[117]	Acute respiratory illness and Chronic Lymphocytic Leukemia	293 patients, 2 groups ($\geq$ 18 yr)	2 $\times$ 200 mg extract. 3 m	Randomized, double-blind, placebo-controlled study	Reduction intense acute respiratory illness and moderately-severe sore throat. Increased antibody responses.

<i>Panax ginseng</i> [118]	Chronic obstructive pulmonary disease	14 participants, 2 groups (57–73 yr)	2 × 200 mg 4 wk	Clinical trial protocol and pilot study	One participant in <i>P. ginseng</i> group reported events of sore throat, cough and fever
<i>Panax ginseng</i> root extract [119]	Chronic obstructive pulmonary disease	168 participants, 2 groups	2 × 100 mg capsules. 24 wk	Randomized, multi-center, double-blind, placebo controlled	Reduction in symptoms
<i>Pelargonium sidoides</i> extract EPs® 7630 [120]	Chronic obstructive pulmonary disease	199 adults, 2 groups (18 yr and older)	30 drops. 24 wk	Randomized, double-blind, placebo-controlled, parallel group trial	Improvement in HRQoL (health-related quality-of-life) and PRO (Patient-reported outcomes)
<i>Pelargonium sidoides</i> extract EPs® 7630 [121]	Acute bronchitis	220 patients (1–18 yr)	1–6 yr: 3 × 10 drops; 6–12 yr: 3 × 20 drops; 12–18 yr: 3 × 30 drops; 7 d	Randomized, double-blind, placebo-controlled clinical trial	Reduction in the total score of bronchitis-specific symptoms (especially cough and rales at auscultation)
<i>Pelargonium sidoides</i> extract EPs® 7630 [122]	Upper respiratory tract infections	28 children with a diagnosed transient hypogammaglobulinemia of infancy (1–5 yr)	3 × 10 drops; 7 d	Randomized, placebo controlled, prospective, monocentric pilot study	Increased appetite. Reduction of nasal congestion
<i>Pelargonium sidoides</i> root extract EPs® 7630 [123]	Upper respiratory tract- asthma attacks	61 children (1–14 yr)	1–5 yr: 3 × 10 drops; 6–12 yr: 3 × 20 drops; 12 yr and above: 3 × 30 drops; 5 d	Randomized, placebo controlled	Reduction the severity of symptoms (especially cough and nasal congestion). Shortening of the duration of upper respiratory viral infections. Reduction asthma attack frequency
<i>Pelargonium sidoides</i> preparation EPs® 7630 [124]	Acute non-streptococcal tonsillopharyngitis	126 children, 2 groups (6–10 yr)	3 × 20 drops. 6 d	Double-blind, placebo-controlled clinical trial	Decrease in tonsillitis severity score compared to placebo in the EPs® 7630 group after 4 d of treatment
<i>Pelargonium sidoides</i> extract EPs® 7630 [125]	Common cold	207 adults (18–55 yr)	SD: 3 × 30 drops; HD: 3 × 60 drops; 10 d	Prospective, double-blind, parallel-group, placebo-controlled, phase 3, 2 parts, 2-arm, clinical trial	After 10 d, clinical treatment in 90.4% of the active drug group. Reduction the severity of symptoms and short the duration of the disease. Higher full recovery rates or greater recovery for HD treatment on day 5
<i>Sambucus nigra</i> extract [126]	Influenza	64 patients (16–60 yr)	Lozenge: 175 mg extract; 4 lozenges/ d; 2 d	Randomized, double-blind, placebo-controlled, pilot clinical trials	Significant improvement in most symptoms within 24 h (fever, headache, muscle aches and nasal congestion). Significant improvement in all investigated symptoms within 48 h (cough and mucus discharge)
<i>Sambucus nigra</i> extract [127]	Respiratory health	312 adults, 2 groups	Capsules: 300 mg. Before travel: 2 capsules/ d. During travel and after arrival: 3 capsules/ d. 14 d	Randomized, double-blind placebo-controlled clinical trial	Reduction of cold duration and severity in air travelers. Low symptom score

SD: Standard dose; HD: High dose.

the effect of eucalyptol (1.8 cineol), which is a component of eucalyptus essential oil, on Mpro. They showed that eucalyptol/Mpro complexes produce hydrophobic interactions, strong ionic interactions, hydrogen bond interactions, and eucalyptol may be a potential inhibitor of COVID-19 Mpro. Similarly, M pro/3CL pro/eucalyptol complexes have been shown to form hydrophobic interactions[39]. In another study, Sharma and Kaur[40] suggested jensenone, the component of eucalyptus essential oil, as a potential COVID-19 Mpro inhibitor. In a molecular docking study of 12 active ingredients of eucalyptus essential oil, all of these ingredients were found to bind effectively to the COVID-19 S-protein. Especially the toruatone component was effectively bound and the Spike (S) protein/Toruatone complexes formed hydrogen and hydrophobic interactions[41]. Muhammad *et al*[42], in a study of the molecular

Table 3 Plants that can have an impact on coronavirus disease 2019 symptoms

Plant name	Effects	Ref.
<i>Allium sativum</i> (Garlic)	Analgesic	Dehghani <i>et al</i> [128], 2018
	Anti-inflammatory	Arreola <i>et al</i> [129], 2015
	Anti-platelet	Hiyasat <i>et al</i> [130], 2009
	Heart protection	Sultana <i>et al</i> [131], 2016
	Hepatic protection	Aprioku <i>et al</i> [132], 2017
	Improving GI function	Chen <i>et al</i> [133], 2018
	Renal protection	Seckiner <i>et al</i> [134], 2014
<i>Curcuma longa</i> (Turmeric)	Analgesic	Henrotin <i>et al</i> [135], 2020
		Eke-Okoro <i>et al</i> [136], 2018
	Antiemetic	Liu <i>et al</i> [137], 2018
	Antifatigue	Huang <i>et al</i> [138], 2015
	Anti-inflammatory	Shimizu <i>et al</i> [139], 2019
	Antifibrotic	Gouda <i>et al</i> [140], 2019
	Antipyretic	Haider <i>et al</i> [141], 2013
	Bronchodilator	Ram <i>et al</i> [142], 2003
	GI protection	Haider <i>et al</i> [141], 2013
<i>Glycyrrhiza glabra</i> (Licorice)		Dulbecco and Savarino[143], 2013
	Hepatic protection	Dulbecco and Savarino[143], 2013
	Antitussives	Nosalova <i>et al</i> [144], 2013
		Kuang <i>et al</i> [145], 2018
	Anti-inflammatory	Kao <i>et al</i> [146], 2010
<i>Nigella sativa</i> (Black cumin)	Respiratory system protection	Shi <i>et al</i> [147], 2011
	Analgesic	Rushmi <i>et al</i> [148], 2017
	Anticoagulant	Muralidharan-Chari <i>et al</i> [149], 2016
	Antihistaminic	Ansari <i>et al</i> [150], 2010
<i>Panax ginseng</i> (Ginseng)		Alsamarai <i>et al</i> [151], 2014
	Anti-inflammatory	Majdalawieh and Fayyad[152], 2015
		Mahdavi <i>et al</i> [153], 2016
	Bronchodilation	Boskabady <i>et al</i> [154], 2010
		Salem <i>et al</i> [155], 2017
<i>Panax ginseng</i> (Ginseng)	Adaptogenic	Ratan <i>et al</i> [156], 2021
<i>Pelargonium sidoides</i> (Pelargonium)	Antitussives	Bao <i>et al</i> [157], 2015
	Secretolytic activity	Bao <i>et al</i> [157], 2015
<i>Scutellaria baicalensis</i> (Chinese skullcap)	Antiemetic	Aung <i>et al</i> [158], 2005
	Anti-inflammatory	Hong <i>et al</i> [159], 2013
	GI protection	Mehendale <i>et al</i> [160], 2007
		Cui <i>et al</i> [161], 2021
	Hepatic protection	Thanh <i>et al</i> [162], 2015
	Neuroprotective	Dai <i>et al</i> [163], 2013
	Regulation of histamine release-Anti allergic	Bui <i>et al</i> [164], 2017
<i>Thymus vulgaris</i> (Thyme)	Analgesic	Laub[165], 2018

<i>Withania somnifera</i> (Ashwagandha)	Anticoagulant	Salmalian <i>et al</i> [166], 2014
	Anti-inflammatory	Okazaki <i>et al</i> [167], 2002
	Adaptogenic	Habashy <i>et al</i> [168], 2018
	Analgesic	Salve <i>et al</i> [169], 2019
	Anticoagulant, antithrombotic	Murthy <i>et al</i> [170], 2019
	Anti-inflammatory	Ku <i>et al</i> [171], 2014
	Antitussives	Gupta and Singh[172], 2014
<i>Zingiber officinale</i> (Ginger)	Stress-relieving	Nosalova <i>et al</i> [144], 2013
	Analgesic	Lopresti <i>et al</i> [173], 2019
		Maghbooli <i>et al</i> [174], 2014
		Bartels <i>et al</i> [175], 2015
	Antiemetic	Tóth <i>et al</i> [176], 2018
	Anti-inflammatory	Khan <i>et al</i> [177], 2015
	Antiplatelet, antithrombotic	Lee <i>et al</i> [178], 2017
	Antitussives	Bera <i>et al</i> [179], 2016
	GI protection	Nanjundaiah <i>et al</i> [180], 2011
	Hepatic protection	Ajith <i>et al</i> [181], 2007
	Nephroprotective	Ajith <i>et al</i> [182], 2007

insertion of eucalyptus active ingredients into Mpro, showed that the α -gurjune of eucalyptus, aromadene and allo-aromadene components have strong binding energy.

Glycyrrhiza glabra

Sinha *et al*[43] conducted molecular docking simulation studies of two antiviral drugs (lopinavir and ribavirin) and 20 compounds of *Glycyrrhiza glabra*. Two protein targets from COVID-19 have been identified: Non-structural protein-15 endoribonuclease and spike glycoprotein. Glycyrrhizic acid prevented the virus from entering the host cell, due to its bulky structure. Gliasperin A showed high affinity to Nsp15 endoribonuclease and inhibited its activity. The authors suggested that glycyrrhizic acid disrupts the connection of the virus with the ACE2 receptor at the input level, and Gliasperin A inhibits the replication process of the virus after it enters the host cell. Another study showed that glycyrrhizin can be highly bound to Mpro[44].

Scutellaria baicalensis

Liu *et al*[45] investigated the *in vitro* effect of *Scutellaria baicalensis* and its components on COVID-19. Baicalein (its main ingredient) and the ethanol extract of the plant inhibited the 3CLpro activity and replication of COVID-19. The ethanol extract also inhibited viral entry. Udrea *et al*[46] suggested the benefit *Scutellaria baicalensis* flavones (especially baicalein) against respiratory damage caused by COVID-19. Flavones bound to 3CLpro. strongly bound to wogonin flavone, nitric oxide synthase and cyclooxygenase 2. In addition, norwogonin and baicalein arachidonate modulated 15-lipoxygenase and lysine-specific demethylase 4D analogue.

Thymus vulgaris

In a randomized clinical study conducted on patients suffering from COVID-19, it was found that *Thymus vulgaris* strengthens the immune system and can be used to reduce COVID-19 symptoms. In the study, 83 COVID-19 patients were randomly divided into the control group and the group receiving thyme (TRG). TRG was given as thyme essential oil three times a day for seven days. A questionnaire asking about symptoms such as fever, cough, fatigue, and loss of appetite was completed before and at the end of treatment to determine the effect of thyme on symptoms. Thyme essential oil significantly reduced the severity of symptoms such as fever, cough, shortness of breath, dizziness, muscle pain, anorexia, weakness and lethargy and fatigue. Additionally, thyme increased lymphocyte count and calcium while decreasing blood urea nitrogen and neutrophil count[47]. Carvacrol, a component of thyme, has been

Table 4 Angiotensin-converting enzyme inhibitor plant

Plants	The compound under study	Results	Ref.
<i>Ammoides verticillata</i> essential oil	Isothymol	SARS-CoV-2/ ACE2 inhibition	Abdelli <i>et al</i> [183], 2021
<i>Allium sativum</i> essential oil	Organosulfur compounds (99.4% of its essential oil)	SARS-CoV-2/ ACE2 inhibition. Garlic essential oil can prevent protein maturation of the virus and the spread of infection	Thuy <i>et al</i> [184], 2020
<i>Apium graveolens</i>	Apigenin	Kidneys of spontaneous hypertensive rats/Regulation in ACE2 expression	Sui <i>et al</i> [185], 2010
<i>Camellia sinensis</i>	Black tea; Dark tea; Green tea; Oolong tea; White tea	ACE inhibition: Green < oolong < white < black < dark teas	Dong <i>et al</i> [186], 2011
<i>Citrus aurantium</i> <i>Erigeron breviscapus</i> <i>Glycine max</i> <i>Glycyrrhiza radix</i> <i>Scutellaria baicalensis</i>	Hesperetin. Scutellarin. Nicotianamine. Glycyrrhizin. Baicalin	SARS-CoV-2/Connecting to ACE2 and blocking the SARS-CoV-2 input	Chen and Du[187], 2020
Geranium and lemon essential oils	Citronellol and limonene	SARS-CoV-2/ ACE2 inhibition	Senthil Kumar <i>et al</i> [188], 2020
Ginseng <i>Glycyrrhiza uralensis</i>	Ginsenoside Rg6; Ginsenoside F1; Monoammonium glycyrrhizinate; Glycyrrhizic acid methyl ester	SARS-CoV-2/ ACE2 kinase inhibition	Zi <i>et al</i> [189], 2020
<i>Glycine max</i> (soybean)	Nicotianamine	ACE2 inhibition	Takahashi <i>et al</i> [190], 2015
<i>Glycyrrhiza glabra</i>	Glycyrrhizic acid	SARS-CoV-2/Glycyrrhizic acid disrupts the connection of the virus with the ACE2 receptor at the entry level	Sinha <i>et al</i> [43], 2021
<i>Hibiscus sabdariffa</i> anthocyanins	Delphinidin- and cyanidin-3-O-sambubiosides	ACE inhibition	Ojeda <i>et al</i> [191], 2010
<i>Linum usitatissimum</i> (Flaxseed)	Secoisolariciresinol diglucoside	ACE inhibition	Prasad <i>et al</i> [192], 2013
<i>Melaleuca cajuputi</i> essential oil	Components (70.9% of the oil)	SARS-CoV-2/ ACE2 and PDB6LU7 proteins inhibition	My <i>et al</i> [193], 2020
<i>Nicotiana benthamiana</i>	Recombinant ACE2-Fc fusion protein produced from <i>N. benthamiana</i>	SARS-CoV-2/Strong binding to the RBD of SARS-CoV-2 and inhibition	Siriwattananon <i>et al</i> [194], 2020
<i>Withania somnifera</i>	Withanone	SARS-CoV-2/Docking to the connector interface of the AEC2-RBD complex	Balkrishna <i>et al</i> [51], 2020

ACE: Angiotensin-converting enzyme; RBD: Receptor binding domain; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; ACE2: Angiotensin-converting enzyme-2.

shown to inhibit Mpro by *in silico* study. It can be a potential inhibitor of controlling viral replication[48].

Withania somnifera

W. somnifera components withanolides have potential antiviral properties on COVID-19[49]. Patel *et al*[50] demonstrated that *W. somnifera*'s Withanoside VI components have positive interactions at the binding site of protein targets of SARS-CoV-2. Withanone reduced the electrostatic interaction between ACE2 and receptor binding domain[51]. Withaferin A, which is found in the *W. somnifera* plant, has been shown to interact with Mpro and Glucose regulated protein 78 (GRP78) receptor[52].

CONCLUSION

In this study, the concept of “being effective against COVID-19” for herbal treatments was discussed from the angles of antiviral effect and control of symptoms, specifically related to GI system.

Antiviral effects on COVID-19

Since COVID-19 is a virus that mainly affects the respiratory tract, the antiviral effects of medicinal plants against respiratory viruses have been examined firstly. The structure similarities of SARS-CoV-2 have been found with SARS-CoV and Middle East respiratory syndrome coronavirus. Therefore, it can be suggested that plants and their compounds affecting these viruses may also be potential treatment options for COVID-19. Here firstly, clinical studies supporting antiviral effects of 22 plant on respiratory viruses has been reviewed which determined that glycyrrhizic acid derivatives obtained from *Glycyrrhiza* sp, *Nigella sativa*, *Scutellaria baicalensis* and *Torreya nucifera* have anti-COVID-19 effects. Plants such as *Allium sativum*, *Glycyrrhiza glabra*, *Melaleuca* sp, *Withania somnifera* have been shown to bind to ACE2 receptors that are imperative for COVID-19 replication. Focusing on these plants might be a logical way to go for herbal treatment against COVID-19.

This review also showed the antiviral effects of essential oils obtained from plants have the potential to affect COVID-19. The treatment involves using inhaled steam supplemented by essential oils possessing natural antimicrobial properties, oropharyngeal sanitization, as well as they are remedies for symptomatic relief. Inhalation of antimicrobial essential oils may help attenuate the virus in the nasal cavity, nasopharynx, oropharynx, and laryngopharynx. Antiseptic mouthwashes and gargles can also help to sanitize the oral cavity and oropharynx, whereas antiseptic lozenges can help to sanitize the oro- and laryngopharynx as well. The steam will carry the tiny particles of the antimicrobial constituents from these essential oils into the respiratory tract and is likely to improve the efficacy of the steam treatment. The steam supplemented by antimicrobial volatile oils may help to provide a local antimicrobial effect within the airways.

There are computer model studies showing that some botanicals and active ingredients are effective in COVID-19. *Allium sativum*, *Curcuma longa*, *Eucalyptus globulus*, *Glycyrrhiza glabra*, *Melaleuca* sp, *Thymus vulgaris*, *Withania somnifera* is among these plants. These studies with commonly found plants will guide future studies to develop effective supplements or drugs for COVID-19.

Symptomatic treatment of COVID-19

Since the symptoms of COVID-19 seriously affect the quality of life, herbal options to eliminate them were also evaluated in this review. Previously, herbs such as garlic, echinacea and ginseng were found to reduce the symptoms of cold in healthy individuals. Plants with their pharmacological effects are natural options for eliminating the symptoms of COVID-19. Based on the effects described in Table 3, *Allium sativum*, *Curcuma longa*, *Scutellaria baicalensis* and *Zingiber officinale* are easily found as prominent plants to eliminate the GI symptoms of COVID-19. For example, ginger can eliminate the negative effects of COVID-19 on the GI system with its antiemetic and hepatic protective properties. A clinical study was conducted with thyme essential oil on COVID-19. Thyme essential oil was found to significantly reduce COVID-19 symptoms. This revealed an option that thyme and essential oil have potential effects for consideration in treatment of COVID-19. Studies on more essential oils of eucalyptus reveal more effects of eucalyptus on respiratory system symptoms. *Eucalyptus globulus*, *Hedera helix*, *Pelargonium sidoides*, *Sambucus nigra*, *Thymus vulgaris* can be recommended for relief of respiratory symptoms. ACE2 receptors are found in tissues other than the lung, such as the intestine. Based on this fact, we concluded that the use of herbs binding to ACE2 receptors can eliminate the side effects that may occur in variety of organs including GI tract. As shown in Table 4 these plants are *Ammoides verticillate*, *Allium sativum*, *Apium graveolens*, *Camellia sinensis*, *Citrus aurantium*, *Erigeron breviscapus*, *Glycine max*, *Glycyrrhiza glabra*, *Hibiscus sabdariffa*, *Linum usitatissimum*, *Melaleuca* sp., *Nicotiana benthamiana*, *Withania somnifera*.

Based on these studies, herbal treatments offer several potential treatments of COVID-19. Plants may be an option for the treatment of COVID-19 and its symptoms, as well as protection from COVID-19. Even though these data point to good outcomes there is always the possibility of interaction between drugs used and these herbs. For instance, herbs such as ginger with antithrombotic effects can be beneficial on COVID-19 symptoms, but one might be cautious about escalated risk of bleeding when it is used together with antithrombotic or anticoagulant drugs. Therefore, it is extremely important to avoid the indiscriminate use of plants.

For a plant to be used as a medicine, its effect must be supported by clinical studies. COVID-19 is just emerging, and more research are needed for its treatment. Yet, herbal therapies are potential options for both antiviral effects and the control of COVID-19 symptoms. Since plants with multiple pharmacological effects can affect many systems

(respiratory, GI, and nervous), herbs might be more effective against COVID-19 than synthetic drugs. But first, all aspects of SARS-CoV-2 need to be examined. Then, the effects of plants on this virus should be determined by further studies.

The strengths and weaknesses of this review

Unlike other studies, in this report, the effect of plants on COVID-19 was evaluated in several ways. Preclinical studies, clinical studies and silico studies are included in this review. Moreover, the efficacy on COVID-19 symptoms has been addressed by including different systems. On the other hand, the focus is on the respiratory and GI systems. The effects, not only of botanicals but also active metabolites of have been studied.

The biggest limitation of this study is the lack of sufficient studies on the efficacy of botanicals. Since botanical studies are generally preclinical studies, results may vary due to conducting and including clinical studies. In clinical studies showing the effects of the plants in Table 2 on respiratory tract infections, the results were generally obtained with questionnaire studies. Placebo effects and breadth of study may be effective in positive results.

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