



Therapeutic opportunities of edible antiviral plants for COVID-19

Bhoomika Patel¹ · Supriya Sharma² · Nisha Nair² · Jaseela Majeed² · Ramesh K. Goyal² · Mahaveer Dhobi² 

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Abstract

The pandemic of Serious Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2) that produces corona virus disease (COVID-19) has challenged the entire mankind by rapidly spreading globally in 210 countries affecting over 25 million people and about 1 million deaths worldwide. It continues to spread, afflicting the health system globally. So far there is no remedy for the ailment and the available antiviral regimens have been unsatisfactory for the clinical outcomes and the mode of treatment has been mainly supportive for the prevention of COVID-19-induced morbidity and mortality. From the time immortal the traditional plant-based ethno-medicines have provided the leads for the treatment of infectious diseases. Phytopharmaceuticals have provided potential and less toxic antiviral drugs as compared to conventional modern therapeutics which are associated with severe toxicities. The ethnopharmacological knowledge about plants has provided food supplements and nutraceuticals as a promise for prevention and treatment of the current pandemic. In this review article, we have attempted to comprehend the information about the edible medicinal plant materials with potential antiviral activity specifically against RNA virus which additionally possess property to improve immunity along with external and internal respiration and exhibit anti-inflammatory properties for the prevention and treatment of the disease. This will open an arena for the development of novel nutraceutical herbal formulations as an alternative therapy that can be used for the prevention and treatment of COVID-19.

Keywords Antiviral · Nutraceutical · Edible plants · Coronavirus · COVID-19

Introduction

In Wuhan, China in December 2019, a newly emergent novel coronavirus SARS-CoV-2 was reported to cause severe acute respiratory tract infections, coronavirus disease 2019 (COVID-19) [1]. After the first case of corona reported from Wuhan, there has been an unprecedented outbreak of COVID-19. As of the last week of August 2020, over 25 million cases of this disease have been reported from 210 countries with 3.32% deaths [2, 3]. The United Nations called the pandemics of COVID-19 as the worst global humanitarian crisis since World War II. Countries all over the world are taking aggressive steps and adopting all possible preventive measures to combat the spread of this disease. The disease is

associated with high mortality risk (2–8% in different countries), a very high transmission rate combined with the lack of WHO or FDA approved specific prophylactic vaccines or therapeutic protocols for the effective prevention, treatment or management of the disease. A typical viral disease mechanism involves the entry of virus into the host via specific receptor, followed by uncoating, transcription and genome synthesis finally forming viral assembly and releasing of multiple copies in the host. The antiviral drugs are designed to act on such varied targets (Fig. 1).

The current treatment appears to be mainly supportive in nature [4, 5]. From time immemorial, herbal medicine has provided remedies for majority of the diseases, for e.g., digitalis and reserpine for cardiac patients, artemisinin and quinine for malaria, vincristine and vinblastine for cancer. Some potential drug candidates including blockbuster antivirals like Remdesivir, Hydroxychloroquine, Lopinavir, Ritonavir, APN01 or Favipiravir are being tested for clinical trials across the globe. Still no therapy has been found to be effective or devoid of deleterious effects against COVID-19 as of now [6–8]. Keeping in view the shortcomings

✉ Mahaveer Dhobi
mahaveer.pharma@gmail.com

¹ Institute of Pharmacy, Nirma University, Ahmedabad, Gujarat 382481, India

² Delhi Pharmaceutical Sciences and Research University, New Delhi 110017, India

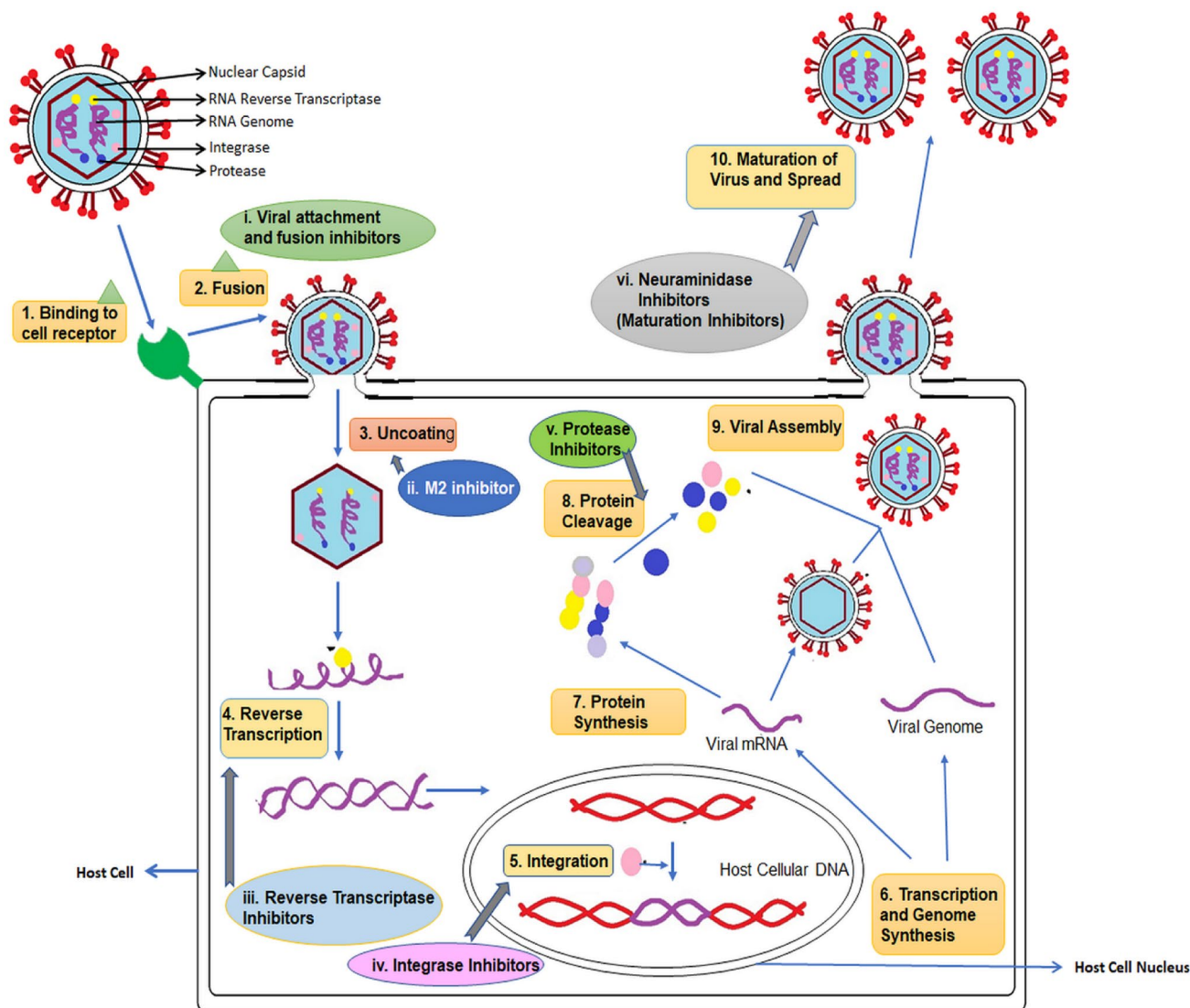


Fig. 1 Typical viral disease mechanism and various targets for antiviral drugs

associated with available antiviral drugs therapies, i.e. viral resistance coupled with the problem of viral latency and conflicting efficacy in recurrent infection in immunocompromised patients, there is an increasing need for search of new compounds and therapy with antiviral activity that are highly efficacious and cost-effective for the management and control of viral infections. Moreover, the viral infections caused by Coronaviruses, Human immunodeficiency virus, Ebola virus, Nipah virus, Influenza virus, Enterovirus, Swine flu, Bird flu, Zika Virus, Hepatitis B and C, etc. have risen significantly and natural products play a vital role in the cure for some with no or less harmful effects [9, 10]. Novel bioactive phytomolecules bearing credible therapeutic potential against such viral diseases is the prime focus of the current medical research in order to gain an upper edge over such widespread infections and prevent the future ones [11,

12]. Identification of the antiviral mechanisms from these natural agents has shed light for further research targeting virus–host-specific interactions.

Indian subcontinent has been recognized as a treasure home for various plant species due to its varied agro-climatic zones and suitable topographical conditions and is placed among the list of top 12 mega diversity countries of the world. The Indian subcontinent is endowed with rich and diverse flora about which the ethnobotanical literature describes use as plant extracts, infusions and powders for diseases of infectious nature [13]. These medicinal herbs provide a wide approach in managing several diseases, including viral respiratory infections by modulating immune system and inflammatory responses. AYUSH system of medicine has provided a basic approach on prevention of infection through dietary modification, lifestyle management,

remedies to boost immune system and preventive interventions based on the symptom [14]. Around 65–80% of the world population residing in developing countries utilizes traditional herbs in their primary health treatment. Additionally, the interest in the study of herbs have aroused due to their phytoactive/phytotherapeutic agents which can be utilized in the form of nutraceuticals, which possess drug-like actions, and in some cases can be traced directly through the existing links between a local and biomedical use [15]. The lack of preventive and curative treatment of COVID-19 till date compels the researchers to look onto therapeutic alternatives that can be added in our daily diets in order to both prevent and cure such life-threatening infections and provide long-term protection. For centuries, numerous plants have been used in daily diets which serve as folk remedies by supporting the body system in one way or the other [16].

This review aims to bring focus on the detailed information about herbal flora with antiviral activities that can be explored for development of novel nutraceutical herbal formulations. Advancement in separation technologies, adoption of modern drug discovery and the development of vector-based strategies for antiviral screening purposes offers a promise for edible medicinal plants usage in daily diet, and may serve as an alternative therapy for treatment of this pandemic and prevention of another one. The article also aimed to merge the ethnopharmacological knowledge with the modern technologies to devise drug targets for the SARS-CoV-2 virus and identification of potential candidates from natural sources which may offer some preventive or even therapeutic value.

Pathogenesis of COVID-19 and strategy for using edible plants

For a better insight on how nutraceuticals or phytomolecules can effectively work against novel coronaviruses, it is imperative to understand the structural characteristics and culpable targets and receptors associated with it. Moreover, understanding the mechanism of action of conventional antivirals and liable targets for drug designing may be useful for development of therapy regimen for COVID-19 from natural sources. SARS-CoV-2 like other HCoV is positive-sense single-stranded RNA viruses with two groups of protein forming its characteristic markers: structural protein, such as Spike (S), Nucleocapsid (N), Matrix (M), Envelope (E); and non-structural proteins such as nsp12-RNA-dependent RNA polymerase (RdRp), Nsp3- Papain-like proteinases, Nsp5-3C-like main protease and nsP13 SARS-CoV helicase [17, 18]. Primarily, nsP13 helicase, 3CL protease, nsp12-RNA-dependent RNA polymerase (RdRp) become primary target for drug development. Apart from these proteins, the viral spike glycoprotein (S) initial attachment and internalization

within host cells ACE-2 receptor can also be targeted to prevent viral entry into newer host cells [19]. SARS-CoV-2 recognizes human angiotensin-converting-enzyme-2 (ACE-2), thereby proving its essentiality for host cell entry by invasion of alveolar epithelial cells, subsequent viral replication and primary host lung cells infection as ACE-2 is highly expressed in the heart, lungs, intestine, kidney and blood vessels [20]. The expression of ACE-2 is substantially increased in patients with diabetes and hypertension and the connecting link to this associated comorbidity has been the angiotensin-converting-enzyme-2 (ACE-2) receptor as it is the site of virus multiplication, and thus a strategy has been devised to develop antiviral newer drugs considering the ACE-2 as an attractive target [21]. Various plants produce phytomolecules that can be utilized in targeting these viral targets and so has been done previously in case of other viral diseases like SARS, HIV, HCV, etc. [22–24].

At the molecular level, the virus SARS-CoV-2 binds to the angiotensin-converting-enzyme-2 (ACE-2) present in the lungs of the human host. Binding of the virus to the host cells through its trimeric spike glycoprotein makes this protein a key target for potential therapies and diagnostics. It was reported that in SARS-CoV-2, the S2 subunit in each spike monomer contains a fusion peptide, a transmembrane domain, and cytoplasmic domain which is highly conserved and could be a possible target for antiviral (anti-S2) compounds [25]. There occurs multiplication of the viruses that induces cellular responses. There occurs infiltration of huge number of inflammatory cells which comprise innate immune cells and adaptive immune cells [26, 27]. Neutrophils are majorly the innate immune cells which produce injury to lungs [28]. On the other hand, the adaptive immune cells are majorly the T cells viz. cytotoxic CD8+ T cells which not just kill virus but again contribute injury to lungs [29]. This accelerates the progression of systemic inflammatory response, leading to extensive increase in various cytokines like TNF α , IL1, IL6, IL10, etc. This is termed as the cytokine surge. Due to increase in various cytokines, there occurs inflammation and apoptosis of Type-1 and Type-2 cells in the alveoli. This interrupts the functions of oxygen transport resulting in cell death in alveoli of the lungs and causing Acute Respiratory Distress or syndrome (ARDS) [30]. Figure 2 depicts the pathogenesis of disease leading to cytokine storm and multiple organ dysfunction and ultimately death.

Among the proposed mechanisms of pulmonary injury caused by SARS-CoV-2, there is a “cytokine storm” triggered by an imbalanced response by type-1 and type-2 T helper (Th) cells leading to an uncontrolled and generalized inflammatory response [31]. Increased pro-inflammatory cytokines (Interferon γ , interleukin (IL-) 1 β , IL-6, IL-12) and chemokines (CXCL10 and CCL2) circulating in the body are associated with pulmonary inflammation

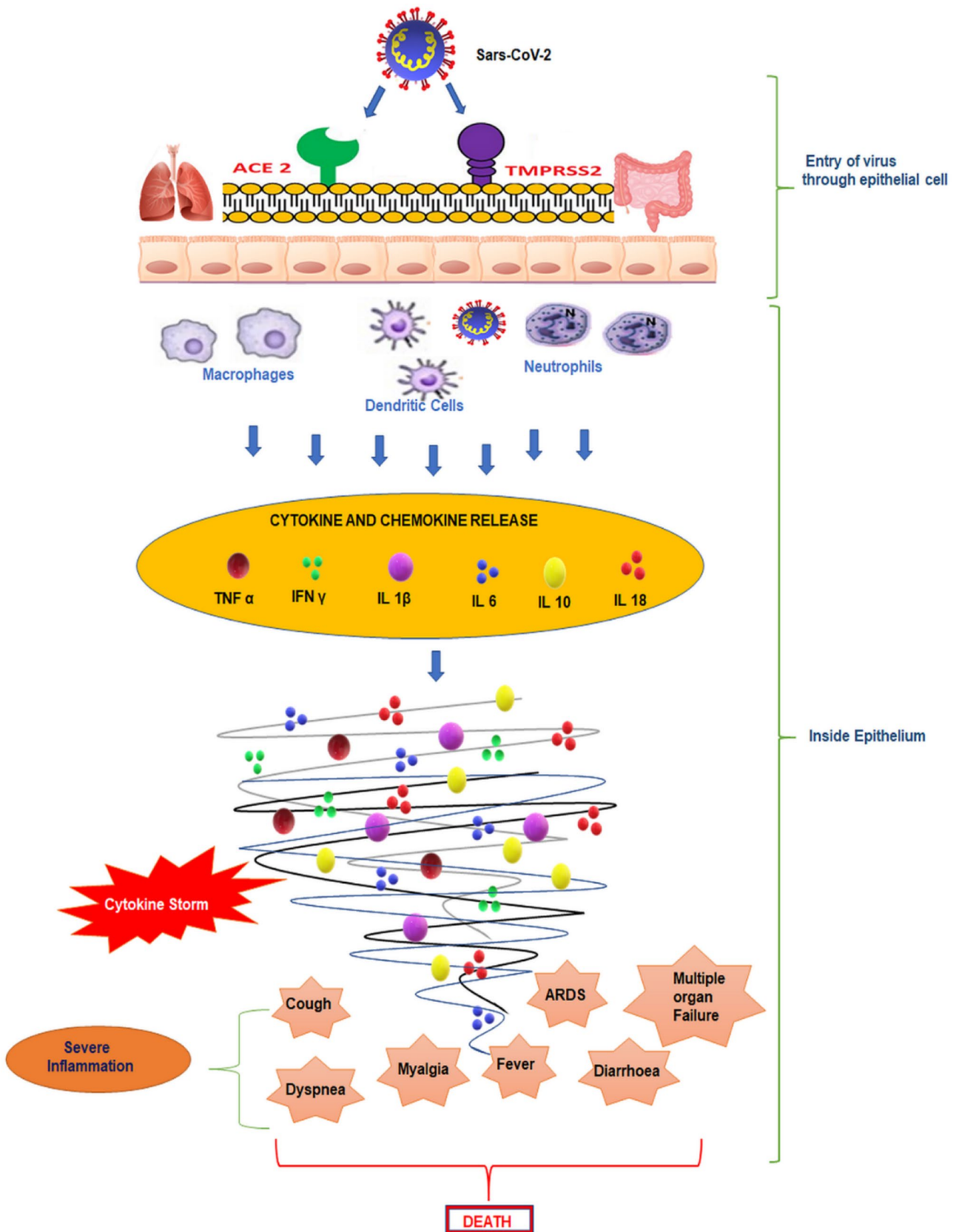


Fig. 2 Pathogenesis of COVID-19

and ARDS pathogenesis due to inflammatory injury to the alveolar-capillary membrane, resulting in increased lung permeability and the exudation of protein-rich pulmonary edema fluid into the airspaces culminating into respiratory insufficiency and the main causes of complications leading to multi-organ failure [32]. Antiviral plants with added anti-inflammatory properties protecting the lung against infections can be investigated, for that matter, to have a synergetic therapy.

Weak immune mechanisms coupled with cytokine surge is one of the major causes that finally leads to decreased cellular oxygenation at the level of alveoli, has been reported to be the main cause of death in COVID-19. Apart from this respiratory damage there occurs thrombotic events involving open reading frames (ORFs) especially the ORF8 proteins which upon binding with SARS-COV2 leading to dissociation of iron from the β -chain of hemoglobin getting attached to the surface glycoprotein porphyrin and thereby resulting in failure of internal respiration [33].

SARS-CoV2 has a longer incubation period of 2–14 days on an average inside the human body, probably due to their immune evasion properties, efficiently escaping host immune detection at the early stage of infection [34]. Herbal preparations that possess immunomodulatory activity may serve as prophylactic treatment, if added in daily diet, for prevention of infection acquisition during this spell of critical community level spread and help contain the disease in community as well as help faster healing post infection. Considering the above strategies for treatment, management and prevention of COVID-19, a search for potential plants with above properties can help to devise natural plant-derived antiviral agents against the pandemic disease.

Edible plants exhibiting antiviral property against RNA viruses: initial signals for COVID-19

The secondary metabolites obtained from herbal drugs can also be utilized as nutraceuticals and can become a lead compound in the treatment therapy [35]. Studies have also shown promising results of nutraceuticals and phytochemicals in various pathological complications such as diabetes, atherosclerosis, cardiovascular diseases (CVDs), cancer and neurological disorders [14]. Since ages, herbs of Indian origin have been implemented in treatment and as preventive strategies for several diseases that include respiratory viral infections as the benefit of usage of these herbs against viral respiratory infections lies in immune stimulation and inflammation modulating effects. The AYUSH systems of medicine also promotes prevention of COVID-19 through lifestyle modification as well as dietary management and prophylactic interventions for improving the immunity

[31]. All these have led to a revival of interest in herbal medicines, novel nutraceuticals and herbal formulations with antiviral potency based on any of the potential plants. Looking into the results of previously deciphered phytochemical-directed researches, a wide variety of phytochemicals present in Indian forest biodiversity can point towards their capability to be manipulated into devising antiviral drugs for SARS-CoV-2. Table 1 provides detailed information on edible plants used as food or nutraceutical showing antiviral activity against RNA viruses, their potential to be explored against COVID-19 on the basis of antiviral activity against various RNA viruses, their active phytoconstituents bearing potential anti-coronaviral activity and mechanism of action.

Plants preventing entry of virus in the host

It has been reported that flavonoids can bind to the functional domains of the SARS-CoV-2S protein, a viral surface glycoprotein required for initial attachment and internalization within host cells. Emodin from plants of family polygonaceae can block the interaction with the SARS-coronavirus spike protein by inhibiting the 3a ion channel of SARS-CoV and HCoV-OC43 [36]. Lectins, the natural proteins, also target the sugar moieties of a SARS-CoV spike protein. In time-of-addition assay conducted to understand mechanism of antiviral action, glucose-, galactose-, N-acetyl glucosamine- and N-acetyl galactosamine binding lectins and most importantly mannose binding lectin indicated their interference with virus attachment to spike protein making them early entry inhibitors. Lectins also carry prophylactic potentials as it agglutinates viral particles by binding to it, thereby not allowing it to bind to human cell receptors and complete its pathogenic cycle [37]. As SARS-CoV-2 also uses host receptor ACE-2 for the cellular entrance similar to SARS-CoV [38], medicinal herbs with the capacity to target ACE-2 therefore holds a promising effect in the prevention and infection of SARS-CoV-2. Various edible medicinal plants, including *Cynara scolymus* [39], *Cassia occidentalis* [40] and *Punica granatum* [41], have shown ACE inhibitory effects, and the same can be explored for inhibition of ACE2 also.

Plants inhibiting viral replication

Studies on edible plants, such as *Glycyrrhiza glabra* [42], *Allium sativum* [43], showed the inhibition of viral replication of SARS-CoV that can be further utilized as leads against SARS-CoV-2, due to similar homology between SARS-CoV and SARS-CoV-2 [44]. Edible antiviral plants like *Aloe vera* [45], *Ginkgo* [46], *Olea europaea* [47], *Cicer arietinum* [48], *Nigella sativa* [49], *Agrimonia Pilosa* [50], *Commelina communis* [51], *Mangifera indica* [52], *Syzygium cumini* [53] that showed effects against influenza virus

Table 1 Edible plants present in Indian biodiversity being used as food or nutraceutical showing anti-retroviral activity

S. No.	Plant species /family	Common name	Major chemical constituents	Used as	Virus type	Extract type/active compound	Mechanism of action
1	<i>Abutilon indicum</i> L. (Sweet)/Malvaceae	Indian lantern flower, Indian mallow, Kanghi	β -Sitosterol, asparagine [86]	Food [87]	Anti-mouse coronavirus activity (a surrogate of SARS-CoV) [66]	Aerial parts methanol extract [66]	Mechanism not clear
2	<i>Acalypha indica</i> L./ Euphorbiaceae	Indian-nettle, Copper-leaf, Kuppi, Kuppik-hokhali	Acalyphin, kaempferol [88]	Food [89]	Vesicular stomatitis virus [90]	Ethanol leaf extract [90]	Inhibitory activity by protein interaction [90]
3	<i>Aegle marmelos</i> (L.) Correa/Rutaceae	Bael	Marmin, marmesin [62]	Food [91]	Human coxsackieviruses B1-B6 infection [62]	Methanolic and aqueous methanolic (1:1) extract of Leaves, stem, bark, root, root bark/Marmelide [62]	Inhibits viral replication [62]
4	<i>Agrimonia pilosa</i> Ledeb./Rosaceae	Hairy agrimony	Catechin, hyperoside [50]	Food [92]	Influenza virus [50]	Whole plant ethanol extract/Flavonoids (catechin, hyperoside, quercetin, and rutin) [50]	Reacts with viral membrane, inhibits viral replication and viral mRNA synthesis [50]
5	<i>Allium sativum</i> L./Amaryllidaceae	Garlic	Allicin, Alliin [43]	Nutraceutical [93], Spice [94]	SARS-CoV [37] Parainfluenza-3, Human rhinovirus, Vesicular stomatitis virus [43]	Lectin (ASA, ASA1) [37], fresh garlic clove extract/Ajoene, alliin, allyl methyl thiosulfinate, methyl allyl thiosulfinate [43]	Interfere with the glycans on the spike protein during virus entry and virus release [37]. Inhibits viral adsorption or penetration [43]
6	<i>Aloe vera</i> (L.) Burm. f./ Asphodelaceae	Aloe vera, Gwarpatha, Ghritkumari	Polysaccharides, aloin [95]	Food [95]	Influenza A virus [96]	Aqueous leaf extract/polysaccharide [96]	Inhibits viral attachment to host cell [96]
7	<i>Areca nut</i> L./Arecaceae	Supari, Betelnut	Arecoline, guvacine [97]	Mouth fresher [98]	Human immunodeficiency virus type 1 [2]	Aqueous and methanolic seed extract/arecatanins [2]	Inhibition of HIV type-1 protease enzyme [2]
8	<i>Artemisia annua</i> L. / Asteraceae	Sweet sagewort	Artemisinin [99]	Spice [100]	SARS-CoV [67]	Whole plant ethanol extract [66]	Mechanism not clear
9	<i>Azadirachta indica</i> A. Juss./Meliaceae	Neem, Indian-lilac	Azadirachtin [101]	Nutraceutical [101]	Group B Coxsackieviruses [72]	Methanolic leaf extract/Flavonoids, triterpenes [72]	Inhibits viral replication [72]
10	<i>Camellia sinensis</i> (L.) Kuntze/Theaceae	Black tea, Common tea, Green tea	Epigallocatechin gallate [102]	Beverage [103]	Bovine coronavirus [75], Influenza virus [104], HIV-1 [102]	Epigallocatechin gallate [75], Aqueous leaf extract/Catechins [104], Hot aqueous leaf extract/Epigallocatechin gallate [102]	Inhibitory effect by interacting with spike glycoprotein [75]. Inhibits various virus lifecycle steps [104, 102]

Table 1 (continued)

S. No.	Plant species /family	Common name	Major chemical constituents	Used as	Virus type	Extract type/active compound	Mechanism of action
11	<i>Cassia occidentalis</i> L./ Fabaceae	Coffee senna	Rhein, emodin [105]	Food [106]	Human immunodeficiency virus [40]	Methanolic leaf extract [40]	Inhibiting HIV reverse transcriptase activity [40]
12	<i>Cicer arietinum</i> L./ Fabaceae	Chick Pea, Bengal gram	Dietary minerals [107]	Food [107]	Parainfluenza-3 virus [48]	Methanolic extract of seed, fruit skin and aerial part/Phenolic compounds [48]	Inhibits parainfluenza-3 virus [48]
13	<i>Commelina communis</i> L./ Commelinaceae	Asiatic dayflower	Homonojirimycin [108]	Food [109]	Influenza virus [108]	Ethanol leaf and stem extract/Homonojirimycin [108]	Prevents inflammatory responses and strengthens host resistance against viral infection by activating secretion of IFN- and IL-10 [108]
14	<i>Curcuma longa</i> L./ Zingiberaceae	Haldi, turmeric	Curcumin [110]	Spice [111]	Respiratory syncytial virus [110]	Curcumin [110]	Inhibit viral replication [110]
15	<i>Cynara Scolymus</i> L./ Asteraceae	Globe artichoke, Sharifa	Cynaropicrin [39]	Food, nutraceutical [112]	Hepatitis C virus [39]	Cynaropicrin [39]	Inhibits viral cell-entry [39]
16	<i>Embelia ribes</i> Burm. f./ Primulaceae	Vidanga	Embelin [59]	Nutraceutical [113]	Influenza A virus (H1N1) [59]	Ethyl acetate fruit extract/Embelin [59]	Inhibits viral replication [59]
17	<i>Eugenia jambolana</i> Lam./ Myrtaceae	Jamun, Jambul	Delphinidin, petunidin [114]	Food [114]	Influenza virus (H5N1) [115]	Methanolic, hydromethanolic and aqueous leaf extract; aqueous bark extract [115]	Interferes with viral envelop that are necessary for adsorption or entry into host cells [115]
18	<i>Ginkgo biloba</i> L./ Ginkgoaceae	Maidenhair-tree, Ginkgo	Ginkgetin [46]	Nutraceutical [116]	Influenza virus [46]	Ginkgetin [46]	Inhibition of viral sialidase activity [46]
19	<i>Glycyrrhiza glabra</i> L./ Fabaceae	Liquorice, Mulethi	Glycyrrhizin [42]	Nutraceutical [117], sweetener [118]	SARS- CoV [42]	Glycyrrhizin [42]	Inhibits viral adsorption, penetration and replication [42]
20	<i>Gymnema sylvestre</i> (Retz.) Schult./ Apocynaceae	Gymnema, miracle-fruit, Gudmar	Gymnemic acid [119]	Nutraceutical [119]	Anti-mouse coronavirus activity (a surrogate of SARS-CoV) [66]	Aerial parts methanol extract [66]	Mechanism not clear
21	<i>Hibiscus sabdariffa</i> L./ Malvaceae	Roselle, Indian-sorrel, Lal ambari	Hibiscus acid, citric acid [120]	Food [120]	H5N1 highly pathogenic avian influenza virus [121]	Aqueous tea extract [121]	Inhibited viral replication and viral antigens and genes expression [121]
22	<i>Leucas aspera</i> (Wild.) Link/Lamiaceae	Tumba, Chota halkusa	Asperphenamate, sitosterol [122]	Food [122]	Anti-mouse coronavirus activity (a surrogate of SARS-CoV) [66]	Aerial parts methanol extract [66]	Mechanism not clear

Table 1 (continued)

S. No.	Plant species /family	Common name	Major chemical constituents	Used as	Virus type	Extract type/active compound	Mechanism of action
23	<i>Mangifera indica</i> L./ Anacardiaceae	Mango	Mangiferin [123]	Food [124]	H2N2 influenza A virus, coxsackie B3 virus [52]	Hydroalcoholic stem bark extract/Penta-O-galloyl-glucose, tetra-O-galloyl-glucose [52]	Inhibits influenza neuraminidase and coxsackie virus 3C protease [52]
24	<i>Momordica charantia</i> L./Cucurbitaceae	Karela, Bitter gourd, Bitter melon	Momordicine, Charantin [125]	Food [125]	Human immunodeficiency virus [126]	MAP30 protein [126]	Inhibit various stages of viral life cycle [126]
25	<i>Moringa oleifera</i> Lam./ Moringaceae	Drumstick tree	Quercetin, Linolenic acid [76]	Food [127]	Human immunodeficiency virus type-1 [128]	Methanolic, ethyl ether and aqueous extract of leaves/Saponins, tannins, flavonoids [128]	Inhibits viral replication [128]
26	<i>Myrica esculenta</i> Buch.-Ham. Ex D. Don/ Myricaceae	Kaphal, Bayberry	Myricetin, gallic acid [54] [129]	Food [130]	SARS-CoV [54]	Myricetin [54]	Inhibits helicase protein [54]
27	<i>Nigella sativa</i> L./Ranunculaceae	Black Cumin, Kalonji	Thymoquinone, thymol [49] [131]	Spice [132]	H9N2 avian influenza virus [49]	Dried seeds/Thymoquinone [49]	Inhibit viral replication [49]
28	<i>Ocimum sanctum</i> L./ Lamiaceae	Basil, Tulsi	Eugenol, linolenic acid [133]	Herbal tea [133]	Human immunodeficiency virus [57]	Aerial parts methanolic extract/Flavonoids [57]	Inhibit protease enzyme [57]
29	<i>Olea europaea</i> L./ Oleaceae	Olive	Oleuropein [47]	Edible oil [134]	Viral hemorrhagic septicemia virus [47]	Ethanol leaf extract/Oleuropein [47]	Direct inactivation, interferes with viral envelope [47]
30	<i>Phaseolus vulgaris</i> L./ Fabaceae	Bean, Rajma	Phaseolin [135]	Food [135]	Human immunodeficiency virus type-1 [58]	Crude bean extract/Homodimeric lectin [58]	Inhibits HIV reverse transcriptase and alpha-glucosidase [58]
31	<i>Phyllanthus emblica</i> L./ Phyllanthaceae	Amla, Indian Gooseberry	Phyllanthidine, phyllanthine [136]	Food [137]	Human immunodeficiency virus [138]	Methanolic fruit extract [138]	Inhibits HIV reverse transcriptase [138]
32	<i>Punica granatum</i> L./ Lythraceae	Pomegranate	Polyphenols, ursolic acid [139] [140]	Food [139]	Influenza A virus [141]	Ethanol peel extract [141]	Inhibits viral replication [141]
33	<i>Solanum nigrum</i> L./ Solanaceae	Black Nightshade, Makoi	Solanine, solamargine [142]	Food [142]	Hepatitis C virus [65]	Chloroform and methanol seed extract [65]	Inhibits NS3 protease [65]
34	<i>Syzygium cumini</i> (L.) Skeels/Myrtaceae	Jaman, Jambolan	Ellagic acid, gallic acid [143]	Food [143]	Avian influenza virus (H5N1) [53]	Aqueous leaf extract, aqueous bark extract [53]	Interfere with viral envelop or mask viral structures which are necessary for adsorption or entry into host cells [53]

Table 1 (continued)

S. No.	Plant species /family	Common name	Major chemical constituents	Used as	Virus type	Extract type/active compound	Mechanism of action
35	<i>Terminalia chebula</i> Retz./Combretaceae	Black myrobalan	Chebularic acid, Chebulonic acid [144]	Food [145]	Respiratory syncytial virus [69]	Chebularic acid [69]	Anti-inflammation, suppression of iNOS, COX-2 and PGE2 expressions and suppression of IKK-NF- κ B and MAPK signaling pathway [69]
36	<i>Trachyspermum ammi</i> (L.) Sprague ex Turill/Apiaceae	Ajwain, Bishop's weed	Thymol, carvacrol [146]	Spice [147]	Hepatitis C virus [64]	Methanolic fruit extract [64]	Inhibits viral protease enzymes [64]
37	<i>Withania somnifera</i> (L.) Dunal./ Solanaceae	Ashwagandha	Withaferin A [148]	Nutraceutical [149]	Influenza virus (H1N1) [148]	Withaferin A [148]	Inhibit neuraminidase, the key enzyme in the life cycle of influenza virus [148]
38	<i>Zingiber officinale</i> Roscoe./Zingiberaceae	Ginger	6-Gingerol, 6-shogaol [150]	Nutraceutical [151], Spice [152]	Human respiratory syncytial virus [150]	Hot aqueous rhizome extract/Gingerols [150]	Inhibits viral attachment and penetration [150]

can be studied rigorously to investigate any reliable target between SARS-CoV-2 and influenza virus.

Myricetin and scutellarein can act as novel chemical inhibitors of the SARS coronavirus helicase, nsP13 [54]. Flavonoids isolated from medicinal plants have been reported to show antiviral activity. Quercetin, epigallocatechin gallate and gallic acid showed inhibitory activity against 3CLpro of SARS-CoV [55]. Plants showing inhibitory effects on HIV proteases, such as *Eugenia jambolana*, *Areca nut* [56], can be investigated for their effects on SARS-CoV-2. Similarly, plants like *Ocimum sanctum* [57], *Phaseolus vulgaris* [58], *Phyllanthus emblica* [59] having HIV reverse transcriptase activity can also be studied against SARS-CoV-2. Plants like *Solanum nigrum* [60] have been known to target the reverse transcriptase activity of HIV and can be studied for activity against SARS-CoV-2 as well; betulinic acid, savinin and some plant-based phenolic compounds are competitive inhibitors of SARS-CoV 3CL protease [61]. *Azadirachta indica* inhibits viral replication in Group B Coxsackieviruses virus and can be investigated for their possible effects against SARS-CoV-2 [62]. Another herb *Aegle marmelos* inhibited viral replication in human coxsackieviruses B1-B6 infection and can be used in the study against SARS-CoV-2 [62]. Another potential target that can be utilized for the inhibition of CoV replication is proteases [63]. *Trachyspermum ammi* [64] and *Solanum nigrum* [65] inhibited viral protease enzymes in hepatitis C virus (HCV) infection. *Acalypha indica* showed selective anti-VSV activity by protein interaction [64], and *Ocimum sanctum* also inhibited HIV protease enzyme [57]; therefore these plants can be studied against SARS-CoV-2 as they may target protease enzymes.

Plants inhibiting viral envelop formation

Sambucus ebulus has been known to inhibit the activity of enveloped viruses and can also be used to target this virus. Though the detailed mechanism remains unclear, *Sambucus ebulus* is indicated to inhibit the entry of enveloped viruses owing to the presence of lectins that block viral entry. Phenolic compounds like quercetin 3-*O*-glucoside and isorhamnetin present in the plant have previously demonstrated the prophylactic potential against Ebola virus. The flavonoids, diosgenin and yomogenin of *Sambucus* species also showed viral entry inhibition against Hepatitis C viruses [61].

Antiviral plants with unknown mechanism

A study on *Abutilon indicum*, *Gymnema sylvestre*, *Leucas aspera* showed anti-mouse coronaviral activity which is a surrogate of human SARS virus but its mechanism of action is still unexplored and requires more research in this area [66]. *Leucas aspera* has been shown to have anti-MCV and

anti-HSV activities, *Abutilon indicum* extract was found active against influenza virus and Sindbis virus which is a surrogate to Hepatitis B virus. Gymnemic acid from *Gymnema sylvestre* has virucidal activity against Asian influenza virus, whereas *Artemisia annua* showed inhibitory effects against SARS-CoV and likely against SARS-CoV-2 but their mechanism of action is still unknown [67].

Plants used in respiratory distress

As SARS-CoV-2 causes respiratory distress, plants used in human respiratory syncytial virus (HRSV) infection, such as *Zingiber officinale* [68], *Olea europaea* [47], *Terminalia chebula* [69], might act as a preventive treatment in COVID-19. Aqueous rhizome extract of *Zingiber officinale* contains allicin which acts against HRSV by reducing the plaque formation in respiratory mucosa induced by stimulation of the respiratory mucosal cells to secrete IFN- β . *Olea europaea* act via multiple antiviral mechanisms: interfering with critical amino acid production essential for viruses, preventing virus assembly at the cell membrane, penetrating infected cells and stopping the viral replication or else primarily by neutralizing the production of reverse transcriptase and protease [47, 68]. On the other hand, Chebulagic acid and chebulinic acid from *Terminalia chebula* have shown efficacy to inhibit virus attachment and penetration comparable to Acyclovir as well as implement neuraminidase-mediated viral release similar to the antiviral drug oseltamivir [69]. Curcumin (diferuloylmethane), which is found in the spice *Curcuma longa*, exhibits anti-inflammatory as well as immunomodulatory activity by inhibiting PHA-induced T-cell proliferation, interleukin-2 production, NO generation, and lipopolysaccharide-induced nuclear factor-kappa B (NF-kappa B), augments NK cell cytotoxicity as well as inhibits cell proliferation and cytokine production by inhibiting NF-kappa B target genes involved in the induction of these immune parameters [70].

Edible antiviral plants with additional activity against Covid-19

Medicinal plants such as *Hibiscus sabdariffa* [71], *Ocimum sanctum* [57], *Azadirachta indica* [72], contain flavonoids which can be exploited for the development of the active compounds against COVID-19. Although numerous plants have been studied, a lot of scientific data are required to confirm their effects and hence further research needs to be maneuvered towards this direction. It should be noted that increased inflammatory responses occurs in the patients with COVID-19 which increases the death rate of the patients [73]; therefore anti-inflammatory herbal drugs like *Withania somnifera* [74], *Zingiber officinale* [68], *Camellia sinensis* [75], *Nigella sativa* [49], *Moringa oleifera* [76], *Agrimonia*

Pilosa [50], *Momordica charantia* [77] can be investigated in supportive treatment against COVID-19 and can be incorporated in daily routine diet of patients, which could produce a reduction in the severity and mortality rate of the patients suffering from the disease. A study on herbal formulas also suggested that immunomodulators might show preventive effects against viral infections and likely COVID-19 [78, 79]. Edible herbs and nutraceuticals such as *Allium sativum*, *Zingiber officinale*, *Glycyrrhiza glabra*, *Olea europaea*, *Cicer arietinum*, *Camellia sinensis* can boost immune system, preventing the body from invading viruses [37]. As mentioned earlier, ACE2 is the entry point for the SARS-CoV-2. Considering this, search for the antiviral plants with added ACE2 inhibition property, anti-inflammatory and immunomodulatory activity should be the future line for research. Table 2 provides the details of the antiviral plants that show potential ACE inhibition, anti-inflammatory and/or immunomodulatory activity.

Clinical evidence of SARS treatment using herbals: paving the way for optimistic future

An epidemic of severe acute respiratory syndrome (SARS) that began in 2002 saw extensive usage and treatment with phytomolecules as auxiliary therapy to conventional medicine. Several anti-SARS formulae were recommended by the Ministry of Health of China to be used along conventional antiviral drugs. The very fact is that SARS-CoV-2 virus shares a striking similarity of 79.5% genetic homology to the SARS-CoV and MERS coronavirus as both are descendants of bat coronaviruses within the beta coronavirus genus [38]; this high genetic similarities between SARS-CoV-2 and SARS or MERS point towards the notion that similar-to-yester-years, administration of auxiliary therapy with plant-based product will prove effective and beneficial against novel coronavirus-generated pandemic too. As a matter of fact, phytomolecules and plant products as well as their analogues are already being employed as an early line of defense against SARS-CoV-2 also. In this section, we have described certain clinical studies for SARS-CoV and SARS-CoV-2 using herbal drugs.

Chen et al. (2007) studied and reported that treatment with herbal drugs which consisted of more than different herbal medicines mainly including *Anemarrhena asphodeloides* Bunge, *Atractylodes macrocephala* Koidz., *Aspidium*, *Artemisia annua* L., *Bupleurum chinense* DC., *Paeonia moutan* (L.) Mill., *Coptis chinensis* Franch., *Coptis deltoidea*, *Coptis teeta* Wall., *Curcuma*, *Salvia miltiorrhiza* Bunge, *Fritillaria* was more effective in clearing up the lung infiltrate as well as shortening the time to abatement of a fever in SARS-infected patients than conventional treatment alone. The study also suggests that adjunctive use of medicinal

Table 2 Plants having anti-inflammatory, immunomodulatory and/or ACE inhibitory activity

S. No.	Plant species/family	Anti-inflammatory	Immunomodulatory	ACE inhibitor
1.	<i>Abutilon indicum</i> L. (Sweet)	Yes [153]	Yes [154]	No
2.	<i>Acalypha indica</i> L	Yes [88]	Yes [155]	No
3.	<i>Aegle marmelos</i> (L.) Correa	Yes [156]	Yes [157]	No
4.	<i>Agrimonia pilosa</i> Ledeb	Yes [158]	No	No
5.	<i>Allium sativum</i> L	Yes [159]	Yes [160]	Yes [161]
6.	<i>Aloe vera</i> (L.) Burm. f	Yes [162]	Yes [163]	No
7.	<i>Areca nut</i> L	Yes [97]	No	Yes [56]
8.	<i>Artemisia annua</i> L	Yes [99]	Yes [164]	No
9.	<i>Azadirachta indica</i> A. Juss	Yes [165]	Yes [166]	Yes [167]
10.	<i>Camellia sinensis</i> (L.) Kuntze	Yes [168]	Yes [169]	Yes [170]
11.	<i>Cassia occidentalis</i> L	Yes [171]	Yes [105]	Yes [41]
12.	<i>Cicer arietinum</i> L	Yes [172]	Yes [173]	Yes [174]
13.	<i>Commelina communis</i> L	Yes [175]	No	No
14.	<i>Curcuma longa</i> L	Yes [176]	Yes [177]	Yes [178]
15.	<i>Cynara Scolymus</i> L	Yes [179]	No	Yes [41]
16.	<i>Embelia ribes</i> Burm. f	Yes [180]	Yes [181]	Yes [41]
17.	<i>Eugenia jambolana</i> Lam	Yes [182]	Yes [183]	Yes [184]
18.	<i>Ginkgo biloba</i> L	Yes [185]	Yes [186]	Yes [187]
19.	<i>Glycyrrhiza glabra</i> L	Yes [188]	Yes [189]	No
20.	<i>Gymnema sylvestre</i> (Retz.) Schult	Yes [190]	Yes [191]	No
21.	<i>Hibiscus sabdariffa</i> L	Yes [192]	Yes [193]	Yes [194]
22.	<i>Leucas aspera</i> (Wild.) Link	Yes [195]	Yes [196]	No
23.	<i>Mangifera indica</i> L	Yes [197]	Yes [198]	Yes [123]
24.	<i>Momordica charantia</i> L	Yes [77]	Yes [199]	Yes [200]
25.	<i>Moringa oleifera</i> Lam	Yes [76]	Yes [201]	Yes [202]
26.	<i>Myrica esculenta</i> Buch.-Ham. Ex D. Don	Yes [203]	No	Yes [204]
27.	<i>Nigella sativa</i> L	Yes [205]	Yes [206]	Yes [207]
28.	<i>Ocimum sanctum</i> L	Yes [208]	Yes [209]	Yes [210]
29.	<i>Olea europaea</i> L	Yes [211]	Yes [212]	Yes [213]
30.	<i>Phaseolus vulgaris</i> L	Yes [214]	Yes [78]	Yes [215]
31.	<i>Phyllanthus emblica</i> L	Yes [136]	Yes [216]	No
32.	<i>Punica granatum</i> L	Yes [217]	Yes [218]	Yes [41]
33.	<i>Solanum nigrum</i> L	Yes [219]	Yes [220]	No
34.	<i>Syzygium cumini</i> (L.) Skeels	Yes [221]	Yes [183]	Yes [184]
35.	<i>Terminalia chebula</i> Retz	Yes [144]	Yes [222]	Yes [223]
36.	<i>Trachyspermum ammi</i> (L.) Sprague ex Turrill	Yes [146]	Yes [224]	No
37.	<i>Withania somnifera</i> (L.) Dunal	Yes [225]	Yes [226]	Yes [227]
38.	<i>Zingiber officinale</i> Roscoe	Yes [228]	Yes [229]	Yes [230]

plants and phytomolecules could significantly bring the average daily use of corticosteroids for reducing inflammatory responses as well as in tackling the issue of low counts of CD4⁺ and CD8⁺. The patients who had received integrative medicine in the study showed to recover the lymphocyte cells with marked higher CD4⁺ counts at the end of study [80].

In another study by Hsu et al., four of the severely confirmed SARS patients received routine supplementary treatment with combination of herbs: *Bupleurum chinense*,

Gardenia jasminoides, *Siler divaricatum*, *Scutellaria baicalensis*, *Notopterygium incisium*, *Schizonepeta tenuifolia*, *Poria cocos*, *Paeonia lactiflora* Pallas, *Paeonia veitchii* Lynch, *Pinellia ternata*, *Platycodon grandiflorum* and *Ophiopogon japonicus* showed less morbidity than the patient on western medicine and placebo [81]. While in a controlled clinical study by Hsu et al. (2006), the adjuvant treatment with plant-derived pharmaceuticals resulted in marked improvement of symptoms and shortened the disease course [82], in another study by Cinatl et al. (2003)

Glycyrrhizin, an active constituent in liquorice root, showed potential inhibition of replication of clinical isolates of SARS virus [42]. Chloroquine phosphate extracted from the bark of cinchona trees and hydroxychloroquine are being currently used for treating COVID-19 patients [83]. Qingfei Paidu Decoction (QPD), a Chinese decoction of medicinal plants comprising *phedra sinica*, *Glycyrrhiza glabra*, *Prunus armeniaca* Linne var. *ansu* Maximowicz, *Prunus mandshurica* Koehne var. *glabra* Nakai, *Cinnamomum cassia* (L.) Presl, *Alisma orientale* (Sam.) Juzep, *Polyporus*, *Aster tataricus* L., *Atractylodes macrocephala* Koidz, *Poria cocos* (Schw.) Wolf., *Bupleurum chinense* DC., *Bupleurum scorzonerifolium* Willd., *Scutellariae baicalensis* Georgi, *Pinellia ternate* (Thunb.) Breit, *Zingiber officinale* Rosc, *Tussilago farfara* L., *Belamcanda chinensis* (L.) DC., *Asarum* spp, *Dioscorea opposita* Thunb, *Citrus aurantium* L., *Citrus sinensis* Osbeck, *Citrus reticulata* Blanco and *Pogostemon cablin* (Blanco) Benth., are being promoted in China and as per report of clinical studies there are already seem to be some promising results [84] and some of these plants belongs to Indian origin. In the trial study by Xu et al.(2020), 701 confirmed cases were treated by QPD; among them 130 cases were cured as well as discharged, whereas clinical symptoms of 51 cases disappeared, symptoms of 268 cases showed improved and 212 of the cases had stable symptoms without aggravation [85].

Summary and conclusion

Despite the fact that a number of drug candidates are being tested for clinical trials for COVID-19 across the globe, no therapy has yet been found to be effective. Thus, there is need to look into any alternative solutions. Natural compounds have been used since decades in controlling infectious diseases. Based on previous experiences of coronavirus outbreaks (SARS-CoV in 2002 and MERS CoV in 2012), seasonal epidemics caused by various viruses showing effectiveness of natural products in the treatment of HIV, HCV and Influenza, herbal drugs and their phytoconstituents could be developed as a potential drug candidate against SARS-CoV-2. To be an effective therapy in treatment of COVID-19, the phytoconstituents need to have anti-inflammatory, antioxidants, antiviral activity and effects on cardiovascular targets in lieu of renin-angiotensin system being involved in COVID-19, with ACE-2 as the major target. Such herbal formulations can be used as complementary treatment for prevention of infection acquisition without causing any ill effects, provided the intake is on evidence-based protocols.

In the present review, a total of 38 plant species of Indian flora and biodiversity have been identified that are edible plants. They have potential antiviral activities on the basis

of inhibition against various RNA viruses. Many of them contain phytoconstituents that possess the potential anti-coronaviral activity. The clinical spectrum of COVID-19 starts from simple cough, fever, chills, sore throat and headache. The edible nutraceuticals are being used in most countries with the history of complementary ancient medicine system and still being practiced to the extent of over 50%.

To conclude, there are several edible plants available as a source of natural antiviral agents and have a potential to develop as a nutraceutical for the COVID-19. More rigorous scientific research is needed to understand mechanistically their therapeutic value. The nutraceuticals thus developed may serve as adjuvant and complementary treatment to help the population in coping with such maliciously infectious pandemics and thereby protect the global population from current and future pandemics.

Compliance with ethical standards

Conflicts of interest The authors declare that there is no conflict of interest regarding the publication of this article.

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