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Herbal remedies and COVID-19: where is the evidence?

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Abstract: The novel coronavirus disease 2019 (COVID-19) was widely regarded due to an unpredictable, imminent pandemic posing a significant threat to humanity. This new virus has high infectivity, mortality, and variable latency. The recurrent modification in the virus' genetic (antigenic) structures poses a challenge in successful vaccine development. While several vaccine trials are underway, many conventional drugs are repositioned (i.e. repurposing) and used for prophylactic and therapeutic purposes. However, the results were not very encouraging and often causing serious adverse effects. To come down the grimness and duration of acute disease and complexities, safe alternative remedies are, thus, needed. In symptomatic SARS-COV-2 patients, the traditional Chinese medicine (TMC) with allopathic drugs and Moroccan medicinal plant extract showed significant benefit. Traditional medicine derived from Indian herbal plants used since ancient times to treat human diseases in India is easily available and cost-effective without any side effects. Some compounds from Indian herbal plants such as phytonutrients, flavonoids, phytomelatonin, and others have been demonstrated to possess anti-inflammatory, immunomodulatory, and antiviral bioactivities. In this review, we discuss some of the potential herbal plants with antiviral properties based on the history of usefulness in either treating COVID-19 or other potential viral infections. Considering the benefits of these preparations, government agencies must take interest in these preventive therapies and allot more funding. More evidence-based, experimental (basic, translational, and clinical) studies are needed to establish its efficacy and safety of these ingredients either alone or in combination.

***Keywords*:** Antioxidants, antiviral, COVID-19, herbal, immunoenhancement, plants, virus

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INTRODUCTION

The world community faces an unheard-of pandemic of new coronavirus disease (COVID-19) caused by Coronavirus 2 Severe Acute Respiratory Syndrome (SARS-CoV-2). One report on April 8 2020 stated that about 1.43 million people were infected and 82,100 casualties occurred. The number of infected and deaths were increasing day by day despite taking all the preventive measures in all the infected country except the lack of therapeutic medicine. The Coronavirus infection is now caused by the deadly situation throughout the globe after its pandemic nature. While officially licensed pharmacological agents are not yet available for COVID-19 therapy, several international health agencies are actively interested in clinical trials of different compounds [1–4]. Moreover, among the immigrant community and ethnic minorities, it is not unusual to try cost-effective "alternative" therapies to avoid or treat COVID-19. Some of these supposed remedies include, but are not limited to, herbal therapies like Ashwagandha, Artemisia annua, Capsaicin, Curcumin, Favipiravir, Guduchi (*Tinospora cordifolia*), Kabasurakudineer (Table 1), Vitamin C, Vitamin D, and Zinc. Homeopathic formulations such as Arsenicum Album 30 (Ars Alb 30C) and Camphor 1 m are used as anti-COVID-19 prophylactic agents. Other compounds used as prophylactics were tested either alone or in combination, assessing their effectiveness and safety as a potential antiviral agent. Such compounds include chloroquine (CQ), hydroxychloroquine (HCQ), azithromycin, metformin [5,6]. So far, the therapeutic and investigative approaches for COVID-19 have focused primarily on agents for attacking or immunizing against the virus. Most of the antiviral and herbal drugs in COVID-19 are important because of their antioxidant and immunomodulatory properties.

However, every medical specialty claims they have some help available to either prevent, treat, or cure potential infectious viral pathogens. This includes, but is not limited to, Siddha, Ayurveda, Unani, complementary and alternative medicine (CAM) therapies, and indigenous tribal preparation around the world [7]. Besides, there are many unproven and fraudulent claims concerning prevention, cure, and management for COVID-19. When patients and consumers resort to any of these alternative treatment modalities, care must be taken to avoid side effects and/or potential death. The health agencies such as the World Health Organization (WHO) has released warning against the use of unproven treatment [8]. Hence, patients and consumers are advised to consult appropriate medical specialties and avoid self-medication. As CAM therapies evolving due to some factors and lacunae in the health care system, more research is needed on this front (Fig. 1). In our report, we have highlighted some of these available options mainly CAM therapies that need to be researched further.

This review reveals the outbreak of the coronavirus pandemic, the mechanism of infection, and finding the most suitable medicinal plants from the floral diversity of South Asian countries. From ancient times, many medicinal plants are being used for different diseases including ~~thse~~ viral infection ~~also~~. The recent pharmacology industry also mainly depends upon the plant-related drug formulation for most of the evolved diseases in the globe. Therefore, with preventive measures such as the use of hand sanitizer, washing hands, social distance, etc., to fight with this pandemic, now, the time for therapeutic drug development. The cognition of medicinal plants, which have ~~the~~ antiviral properties, may be applicable for the new drug formulation or may consume at the society level to make the human immune system strong.

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Table 1 The composition of Kabasurakudineer, an herbal concoction.

The composition of KabaSuraKudineer, a herbal concoction		
Botanical name	English name	Plant part being used
Zingiberofficinale	Ginger	Rhizome, ginger root or ginger
Piper longum	Indian long pepper or Pipli	Dried fruit
Syzygiumaromaticum	Cloves	Flower bud
Tragiainvolucrata	Indian stinging nettle	Root
Anacyclus pyrethrum	Pellitory, Spanish chamomile, or Mount Atlas daisy or Akarkara	Root
Solanumanguivi	Forest Bitterberry or African Eggplant	Root
Terminalia chebula	black- or chebulicmyrobalan	Small, ribbed and nut-like fruit rind
Justiciaadhatoda	Malabar nut, adulsa, adhatoda	Leaf
Plectranthusamboinicus (formally known as Coleus aromaticusBenth.)	Indian mint	Leaf
Saussureacostus	Costus or Kuth	Root
Tinosporacordifolia(Thunb.) Miers (Guduchi)	Heart-leaved moonseed, Guduchi, orGiloy	Stem
Clerodendrumserratum (L.) Moon.	Turk's turban moon, Blue glory, Beetle killer	Root
Andrographispaniculata	Creat or green chireta	Aerial parts
Cissampelospareira L.	Velvet-leaf, Abuta	Root
Cyperusrotundus	Coco-grass, Java grass, Nut grass, Red - or Purple nut sedge, Khmer kravanhchruk	Root tuber
Preparation of decoction: An equal part of these 15 ingredients must be made into a coarse powder.8 gm powder in 4-glass water, boiled and reduced into 1 glass. May be taken twice or thrice according to the severity of the fever and other respiratory symptoms. Since the recipe is recently promoted as prophylaxis for COVID-19, for prophylaxis, it may be taken once a day for three days, if required it may be taken after a gap of 3-4 days. No need to take it continuously.		

Etiopathogenesis of COVID-19: Severe acute respiratory syndrome corona virus-2 (SARS-CoV2) caused novel coronavirus disease 2019 (COVID-19). SARS-CoV2 is a single-stranded, β coronavirus-containing RNA. Viral host cell infection triggered by endocytosis liaised by the receptor. Receptor binding domain (RBD) is located in virus spike protein attached to the target cell via angiotensin-converting enzyme-2 (ACE-2) receptor, which is highly enriched distribution in the alveolar epithelium in the human lung. An analysis of the structural model shows that SARS-CoV2 has a 10 times more binding affinity than SARS CoV that has a similar spike protein RBD [9]. RBD ACE-2 complex formation mediates the coalition between the host cell membrane and viral envelope during virus-host interaction and ultimately grants the viral genome to entry in the host cell

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[10]. Many herbal compounds inhibit infection and propagation of COVID-19 by blocking the complex RBD ACE-2.

SARS CoV 2 remains unknown to have pathological mechanisms for organ damage. COVID-19's potential mechanism for ARDS may be immune disruption and inflammatory process. The peripheral blood examination and quantification of extreme COVID-19 patients with plasma cytokine have shown depletion of cytotoxic T-lymphocytes and a massive increase in IL-10, IL-6, IL-2, and IFN-α. This 'cytokine storm' causes damage to the alveolar epithelium and therefore respiratory distress [11].

Scope of Ayurveda against COVID-19: For nearly 5000 years Ayurveda, an ancient Indian medicine method, has been practiced in India, relying heavily on plants to formulate it. Ayurvedic herbal supplements and immunity boosters showing the way to a broad-spectrum antiviral drug that is the need of the hour. For plants namely *Glycyrrhiza glabra, Andrographis paniculata, Phyllanthus spp., Zingiber officinale,Withania somnifera*, and *Curcuma longa* antiviral properties have been reported. Whereas, others have the properties to enhance immunity, such as *Tinospora cordifolia* and *Emblica officinalis* [12]. It has been previously shown that *Coptidis rhizome, Meliae cortex, Sanguisorbae radix, Cimicifuga rhizome,* and *Phellodendron cortex* exhibit anti-coronavirus activity. *Sophorae radix*, *Torilis fructus,* and *Acanthopanacis cortex* decreased intracellular viral RNA levels with corresponding viral protein decreases [13]. Therefore, Ayurveda has a tremendous to attenuate this pandemic but the trials should be implemented substantially which will simplify learning, produce proof, and provide a way forward [14].

Efficacy of medicinal plants against COVID-19: From ancient times, medicinal plants have been in use for the treatment and prevention of various diseases including viral infections (Table 2). Studies on plant antiviral activity, however, were minimal compared with other antimicrobial efficiencies such as antibacterial and antifungal activities. Some of the plants and plant products were investigated for their effectiveness against pathogenic viruses in general, and particularly COVID. Table 2 presents some of the major preventive and prophylactic medicinal plants with recorded effectiveness against COVID-19.

Research on *Vitex trifolia* and *Sphaeranthus indicus* for coronaviral anti-mouse activity reported inhibiting the NF-kB pathway after reducing the inflammatory cytokines which are involved in SARS-CoV respiratory distress [59,60]. *Clitoria ternatea* has the metalloproteinase inhibitory effect in ACE shredding that is primarily associated with virus replication. *Strobilanthes cusia* plant reportedly blocks the HCoV infection [61]. Amber et al. [62] reported that *Justicia adhatoda, Verbascum Thapsus*, and *Hyoscyamus niger* that is traditionally used in bronchitis, have been found to reduce influenza virus infections. Kambizi et al. [63] demonstrated that *Aconitum ferox* and *Withania somnifera* aqueous extracts have anti-HSV-1 activity.

Thus, several medicinal plants, including *Cynara scolymus, Punica granatum*, *Coscinium fenestratum, Boerhaavia diffusa, Cassia occidentalis, Embelia ribes,* and *Coriandrum sativum* can inhibit the activity o ACE [64–66]. One study on *Salacia oblonga* reported that it has the anti angiotensin II activity [67]. *Andrographis paniculata* commonly known as Kalmegh has been credited for its efficacy against viral respiratory infections [68]. The interleukin-1β molecules, caspase-1, and high NOD-like receptor protein 3 (NLRP3) were suppressed after the application of this plant [11]. *Glycyrrhiza glabra, Clerodendrum inerme,* and *Allium sativum* have the potential to inactive the viral replication [69–71].

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Table 2 Medicinal plants having anti-viral properties

Sl. No.	Medicinal Plants	Virus Name	References
	Achyranthus aspera	Herpes simplex virus	[15]
	Allium cepa	SARS-COV2	[16]
	Allium porrum	SARS-COV2	[17]
	Allium sativum	SARS-COV2	[18]
	Alnus japonica	SARS-COV2	[19]
	Andrographis paniculata	H1N1, H9N2, H5N1	[20]
	Andrographis paniculata	Dengue virus	[20]
	Andrographis paniculata	Dengue virus	[21]
	Angelica keiskei	SARS-COV2	[22]
	Azadirachta indica	Dengue virus	[23]
	Betula pubescens	SARS-COV2	[24]
	Canthium coromandelicum	HIV	[25]
	Carissa edulis	Herpes simplex virus	[26]
	Cassiae semen	SARS-COV2	[27]
	Chamaecyparis obtusavar formosana	SARS-COV2	[24]
	Cinnamomum cassia	SARS-COV2	[28]
	Cryptomeria japonica	SARS-COV2	[24]
	Curcuma longa	H1N1, H6N1	[20]
	Dioscoreae rhizoma	SARS-COV2	[27]
	Emblica officinalis	Influenza Virus	[20]
	Ficus religiosa	Human rhino virus	[29]
	Galla chinensis	SARS-COV2	[30]
	Gentianae radix	SARS-COV2	[27]
	Glycine max	Human adenovirus	[31]
	Glycyrrhiza glabra	Respiratory Syncytial virus	[20]
	Glycyrrhiza glabra	Herpes type 1 and 2 viruses	[32]
	Glycyrrhiza glabra	SARS-COV2	[33]
	Guazuma ulmifolia Lam	Polio virus	[34]
	Hippophae rhamnoides	Dengue virus	[35]
	Isatis indigotica	SARS-COV2	[36]
	Juniperus oxycedrus	SARS-COV2	[37]
	Laurus nobilis	SARS-COV2	[37]
	Linum usitatissimum	SARS-COV2	[38]
	Loranthi ramus	SARS-COV2	[27]
	Mangrove plant	HIV	[39]
	Moringa oleifera	HIV	[40]
	Moringa oleifera	Epstein bar virus	[41]
	Myrica faya	SARS-COV2	[42]
	Nicotiana tabacum	SARS-COV2	[43]
	Nigella sativa	SARS-COV2	[44]
	Nilavembu kudineer	Chikungunya virus	[31]
	Paulownia tomentosa	SARS-COV2	[45]
	Phyllanthus amarus	Human immuno deficiency virus	[46]
	Phyllanthus amarus	Human Immunodeficiency Virus	[20]

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	Phyllanthus amarus	Hepatitis B	[47]
	Phyllanthus urinaria	Herpes Simplex Virus	[20]
	Psoralea corylifolia	SARS-COV2	[48]
	Pterocarpus santalinus	SARS-COV2	[24]
	Rheum officinale	SARS-COV2	[49]
	Rheum palmatum	SARS-COV2	[50]
	Rhodiola kirilowii	SARS-COV2	[51]
	Salvia miltiorrhiza	SARS-COV2	[19]
	Scutellaria baicalensis	SARS-COV2	[52]
	Scutellaria lateriflora	SARS-COV2	[42]
	Sesbania grandiflora	Herpes simplex virus	[53]
	Stephania cepharantha	SARS-COV2	[54]
	T. nucifera	SARS-COV2	[55]
	Terminalia belerica	HIV-1	[56]
	Terminalia bellerica	HIV-1	[57]
	Thuja orientalis	SARS-COV2	[37]
	Tinospora cordifolia	Human Immunodeficiency Virus	[20]
	Toona sinensis	SARS-COV2	[27]
	Triterygium regelii	SARS-COV2	[55]
	Utrica dioica	SARS-COV2	[58]
	Veronica linariifolia	SARS-COV2	[51]
	Withania somnifera	Herpes Simplex Virus 2	[20]

In Brazil, *Acmella oleracea* is a well-known herb that belongs to the asteraceae family. It is used for the local 'Jambu tea' preparation consumed daily in every home in Brazil. This plant contains a lot of phytomolecules, among which Spilanthol, undeca-2,7,9-trienoic acid isobutyl amide, and undeca-2-en-8,10-diynoic acid isobutyl amide are well known. It has been proved that the extract of this plant has anti-microbial properties [72].

Ocimum sanctum, *Acacia nilotica*, *Ocimum kilimandscharicum*, *Euphorbia granulate, Eugenia jambolana*, *Solanum nigrum*, and *Vitex negundo* inhibited HIV and *Sambucus ebulus* reversed transcriptase activity inhibiting enveloped virus activity [73–79]. All these plants may be applicable as the effective agents against SARS-CoV-2.

Cinnamomum camphora (Camphor): In India, herbal product camphor is commonly used as a white crystalline substance derived from camphor laurel wood (*Cinnamomum camphora*), a tree belongs to the lauraceae family. Camphor is obtained by distilling steam, purifying, and sublimating wood [80]. This is distributed in India, Taiwan, Japan, China, Mangolia, and especially in Florida. This product has a very fine history as the antispasmodic, odontalgic, anti-rheumatic, and rubifacient medication. The Chinese oil for sassafros obtained from *C. Camphora*. The camphor is composed of camphor, sofrole, linalool, borneol, dipentene, terpeneol, and cineole [81]. It is also well established that Camphors has antihistaminic activity, antibacterial activity, anti-inflammatory activity, bronchitis antioxidant activity, sprain, rheumatic pain, etc., immunoglobulin-E suppressing allergic disease activity [82]. A characteristic organized feature of camphor molecule is its rigid structure of cage-hydrocarbons such as amantadine, rimantadine, most potent antiviral drugs [83]. These compounds' antiviral activity is due to the blockage of virally encoded protein-M2, which acts as a protein channel necessary for the hemmagglutinin cleavage and adhesion of host cell membranes and viral envelope [84]. New biologically active antiviral compounds are obtained by

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chemical modification of the natural compounds that occur. The camphecene (Fig. 1) is a recent camphor amino derivative, with high antiviral activity and low toxicity [85]. The camphecene is based on hepten-2-ylidene-aminoethanol-1,7,7-trimethylbicyclo(2.2.1); Amino camphor derivatives are an important influenza A inhibitor of M2 ion channels (viral haemagglutinin) [86]. Bananins are potent antiviral compounds close to classical adamantanes (trioxa-admantene moiety covalently linked to pyridoxal derivatives). Tanner et al. [87] reported that bananin and its derivatives are potent inhibitors of both SARS-Coronavirus ATPase and helicase activities, thus inhibiting the replication of SCVs. In Iran, triggered by the use of homeopathic medication Camphor-1 M, COVID-19 related deaths dramatically reduced. In India, the ministry of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy (AYUSH) has recommended the use of Arsenicum Album 30 (Ars Alb 30C) and Camphor 1 m (homeopathic formulations) in COVID-19 under physician supervision for prophylaxis usage. Thus, these drugs were issued to several Indian states and police forces.

Ocimum sanctum (Tulasi): Because of its medicinal and spiritual values, Tulasi (*Ocimum sanctum*) belongs to the plant family Lamiaceaeis widely used in the Indian medicinal system; also known as holy basil, Mother Natural Medicine, and "The Queen of Herbs" This is found in the Himalayas in all of India climbing up to 1800 m. Tulasi's main bioactive molecules are oleanolic acid, rosmarinic acid ursolic acid, carvacrol, eugenol, and caryophyllene. There are hundreds of scientific studies showing that this plant has a special combination of behavior including anti-diarrheal, anti-oxidant, antimicrobial (including antifungal, anthelmintic, antibacterial, antiviral, antimalarial, antiprotozoal), hepato-protective, anti-inflammatory, neuroprotective, antidiabetic, cardioprotective, analgesic, anti-allergic, antipyretic, immunomodulatory, cardioprotective, and anti-inflammatory. Extract from *Ocimum sanctum* has considerable potential to inhibit the produced free radicals in the cell. There was strong antioxidant activity in the phenolic compounds, i.e., apigenin and rosmarinic acid, isothymusin, cirsimaritin, cirsilineol, and large amounts of eugenol from stems and leaves [77]. *Ocimum sanctum* demonstrates its immunomodulatory effect by increasing the number of IL-‘4, NK cells, IFN-γ, T-helper cells. This helps to reduce the increasing population of neutrophils, and lymphocytes and thereby increasing phagocytic activity and phagocytic index. In bovine sub-clinical mastitis, the aqueous extract also exhibited immunotherapeutic potential by inhibiting mast cell degranulation and histamine release in the presence of an allergen. This is more effective for treating acute viral encephalitis than dexamethasone [88]. Since the 1990s, the flavonoid molecules (6-hydroxyflavone, Apigenine (Fig. 1), tangeritin, wogonin, scutellarein, chrysin, and luteoline) of the plant extract has increased antiviral effect in cell culture on herpes simplex virus types 1 and 2 [89]. Pandey et al. [90] reported naturally extracted flavonoids have the evidence to inhibit the helicase activity of SARS-CoV due to suppression of ATPase activity.

Zingiber officinale (Ginger): *Zingiber officinale* (Ginger) belongs to the Zingiberaceae family and is among the most commonly used herbs. The Rhizome is the eaten portion of the ginger. It has been developed as a spice for a long time. From the last decade, it is being used as a traditional medicine in the different medicinal system [91]. Ginger includes various substances, such as gingerol, gingerdiol, and gingerdione, which have anti-inflammatory, anti-diabetic, anti-cancer, chemopreventive and chemotherapeutic effects, anti-microbial and anti-oxidant properties of ginger [92–94].

Tinospora cordifolia (Giloy): *Tinospora cordifolia* is commonly known as Giloy or Guduchi. Three major species *of Tinospora viz., Tinospora candifolia, Tinospora malabarica,* and *Tinospora*

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crispa are found primarily in Myanmar, mainly tropical and subtropical regions of India, Sri Lanka, and China [95]. Flavonoids, glycosides, phytosterols, alkaloids, polysaccharides, and others are the active constituents of the plants. Several chemical components, such as giloin, tinosporic acid, tinosporite, berberine, palmatin, isocolumbin, columbin, choline, tinochordifolin, and others were extracted from the various parts of tinospora [95]. This plant is also recognized for anti-allergic, anti-oxidant, anti-inflammatory, anti-pyretic, anti-oxidant, anti-spasmodic, and anti-cancer properties [96]. Tinospora is a potent natural immunomodulator. It induces chemotaxis, phagocytosis of macrophages, and activates B- lymphocytes and other immune controlling cells [97]. Giloy root extracts have shown positive modulation of the immune system in HIV patients. It was reported that *T. Chordifolia* has a protective effect against swine flu [96]. *T. Chordifolia* has a high potential for anti-stress and antioxidant [98]. Giloy's phytochemicals such as tinocodiside could be potent against COVID-19. Exactly within the ACE2-RBD complex, in-silico model tinocodisides dock has been found which suggests that rich giloy extracts of Tinochordiside may be the best options to inhibit the host cell entry of COVID-19. Giloy's immunomodulatory property will strengthen innate immunity to COVID-19 infections [99].

Glycyrrhiza glabra (Mulethi): Several in vivo and in vitro studies reported that Licorice and glycyrrhizine have the potential as the therapeutic agent against several viral diseases including vaccina virus, chronic hepatitis A, B and C, respiratory syncytial virus, human immunodeficiency (HIV) virus, SARS-related coronavirus, arboviruses, and vesicular stomatitis virus (VSV) [100–103].

Nyctanthes arbortristis (Tree of sorrow or Harsingar): *Nyctanthes arbortristis* also known as Harsingar or Parijatha belongs to the family of Oleaceae/Nyctanthaceae. Leaves from the *N. Arbortristis* contains oleanolic acid, methyl salicylate, astragalin, iridoid glycosides, amorphous resin, flavanol glycosides, nicotiflorin, a trace of volatile oil, carotene, β-sitosterol, benzoic acid, and nyctanthic acid. *Nyctanthes arbortristis* seeds contain Arbortristoside A&B, oleic acid, glycerides, lignoceric acid, linoleic acid, and 3-4 secotriterpene acid. The bark of *N. Arbortristis* contains both glycosides and alkaloids [104]. The bronchodilatory effect of this plant ethanolic extract was demonstrated in in-vitro circumstances [105]. Stabilizing mast cell and bronchodilating activity of *N. Arbortristis* bark has been shown to treat asthma [106]. Administration of doses of 0.25 and 0.5 g/kg body weight of plant ethanolic extract found that there was a significant increase in splenic antibody-secreting cells, leukocyte count, phagocytic index [107]. Plant ethanolic extract along with arbortristoside C and arbortristoside A; have inhibitory activity against Semliki Forest Virus (SFV) and encephalomyocarditis virus (EMCV). The *in-vivo* ethanol extract of *N. Arbortristis* and n-butanol fraction protected EMCV infected mice against SFV [108].

Camellia sinensis (Herbal Tea): Tea leaves (*Camellia sinensis*) are rich in polyphenol (catechins and flavonoids) [109]. Green tea contains six primary catechin compounds such as epigallocatechin, epicatechin, epicatechingalate, catechin, gallocatechin, and epigallocatechin gallate (Fig. 1).Polyphenols vary from 30% to 40% and from 3% to 10%, respectively in green tea and black tea. The health benefits of tea consumption are well known and widely reported in the literature [110]. There has recently been hype concerning the usefulness of tea in the treatment of COVID-19. Preliminary evidence in the past has suggested that tea components could be a potential antiviral agent that could potentially inhibit coronavirus (COVID-19) proliferationin the human body [111]. This led to the assumption that the consumption of tea could be beneficial against SARS Cov-2 due to its abundant chemical constituents. Polyphenolic compounds like Prodelphinidine B-2 39-gallate inhibited the entry of HSV type 2, HIV-1 into target cells. ECGC has also been reported to prevent influenza virus infection by binding to viral hemagglutinin [112]. Catechins have anti-influenza virus activity [75]. Epigallocatechin gallate has a higher activity than the epicatechingalate activity against

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viral infection after suppressing the viral DNA and RNA polymerases. However, the strongest inhibition of these compounds was observed with HIV reverse transcriptase [113,114]. Epigallocatechin gallate has reported blocking the binding of HIV-1 glycoprotein 120 to CD4 molecules on T-cells [115].

Withania somnifera (Ashwagandha): *Withania somnifera*, a family shrub of Solanaceae, is generally used as an immunosuppressive agent in folk medicines. Its medicinal properties have been attributed to its major bioactive constituent steroidal lactones called anolides. This is oxygenated steroidal molecules. About 130 anolides have been isolated from *Withania sp*. and they are well established for the anti-inflammatory, anti-tumor, antioxidant, and anti-microbial properties have been demonstrated. Infectious Bursal Disease Virus Replication was stunned after the application of hydro-alcoholic extract of *W. Somnifera* [116].

Antiviral Herbs as Potential Anti-COVID Agent: The unsung Himalayan floral diversity is known as the storage house of the medicinal plants [62]. From ancient times, the ethnomedicinal properties of the available plats were known. Recently, numerous plants found in this region have reported that they have the properties as anti-SARSCoV-2, anti-influenza virus infections, and other anti-viral infections [59,60,117,118]. The extract of these plants mainly inhibits the virus entry to the cell, inhibition of viral replication, inhibiting the NF-kB pathway, immunomodulation in the host cell, etc [60,66]. The herb lemongrass is known as *Cymbopogon sp.*, mainly found in Asian and African countries, and commonly found in Australia. Lemongrass extracted essential oil (EO) has great potential as an antimicrobial agent. Studies have shown that lemongrass EO affects the antimicrobial resistance of pathogens [119,120]. Other studies also reported an extract of Cymbopogon sp. possible antiviral activity. Bahtiar et al. [121] reported that the ethanol extract of *Cymbopogon nardus* attenuated the activity of herpes simplex virus serotype 1 (HSV-1), anti-measles activity, anti-dengue virus serotype 1, anti-hepatitis-A virus, anti norovirus murine [122–125].

Antiviral phytochemicals: Phytochemicals provide eco-friendly and substantially applicable in the public health sector as anti-viral agents. Several pure individual bioactive chemical constituents from different plants have been investigated for their antiviral activity, with a particular focus on anti-COVID action. The reported antiviral and anti-COVID activity of various phytochemicals are summarized in Table 3 and Fig. 14. Curcumin is well known bioactive pigment present in *Curcuma longa* (. It is well established the curcumin anti-inflammatory, anti-viral, antioxidant, and anti-cancer, anti-bacterial properties. This has the inhibitory effects of the HIV replication process in the host cell, inhibiting HIV kinase-related enzymes, inhibition of several cell signaling mechanisms, etc. [169]. Withaferin A and Withanone (Fig. 1) are the main phytochemical of *Withania somnifera*; a well-known medicinal plant. These molecules have the capabilities to reduce H1N1 influenza neuraminidase activity, inhibiting the effect of viral DNA polymerase activity, reduce the bonding between the viral RBD and host ACE2 receptor [170]. Therefore, these molecules may reduce the infective power of COVID-19 [99] Caffeine, theobromine, and theophylline (Fig. 1) are the main bioactive molecules in the tea leaf. Theaflavins-1, Theaflavins-2, and Theaflavins-3 (Fig. 1) are also present in the black tea and they are now known for the SARS-COV-2 viral replication process in the host cell [111]. Artemisinin (ART), dihydroartemisinin (DHA), and artesunate (AS) (Fig. 1) are the active ingredients derived from *Artemisia annua*. For a very long time, this is used in Chinese traditional medicine [75]. These molecules reported their antiviral effect in the fibroblast cell model by measuring viral DNA synthesis in cell lysates, antimalarial, anti-bovine viral diarrhea virus (BVDV) [171,172]. Artemether is often used alongside lumefantrin. One clinical version of this formulation is Coartem®. The combination of artemether-lumefantrine has also been used in

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patients diagnosed with EBOV and has shown a decreased efficacy in reducing the risk of death [173]. The study of *Arisaema tortuosum* plants found that the extract of this plant has a proven mechanism for attenuating the HSV-2 replicative cycle. Apigenin and luteolin had high inhibitory activity against the HSV-2 replicative cycle [174]. Phytomolecules such as isorhapontigenin, gnetupendin B, shegansu B, and gnetin D have significant anti-influenza viral activity in the in vitro condition [175]. The use of icetexane diterpenoids, namely perovskatones B–D, α-hydroxybrussonol, and α-hydroxypisiferanol (Fig. 1); isolated from *Perovskia atriplicifolia*, has been used against inhibitory hepatitis B virus activity in the HepG 2.2.15 cell line. The results suggest that phytomolecules have inhibitory activity against in vitro hepatitis B virus activity [176]). The root of the *Marsdenia tenacissima* plant was used for the extraction process and marstenacissides B10–B17, marstenacissides A8-A12, polyoxypregnane glycosidesmarsdenosides M, and L, isolatedmarstenacissides A1–A7 and B1–B9 (Fig. 1) were isolated and identified. The anti-HIV activity was reported [177]. *Naphthoquinone droserone* is a natural product found in dicotyledonous plants. Lieberherr et al. [178] have shown that this molecule has great potential for entry into cells of the measles virus.

Table 3 Bioactive phytochemicals with virus inhibiting action

Bioactive compounds	Source Plants	Virus inhibiting action	References
1, 8-cineole	*Vitex trifolia*	Inhibition of SARS-CoV-2 virus	[126]
10-Methoxycamptothecin	*Camptotheca acuminata*	Inhibit adenovirus, Herpes and vaccinia viruses	[127]
6-deoxyglucose-diphyllin	*Justicia gendarussa*	Inhibition of Zika Virus, Human Immunodeficiency Virus -1	[128]
6-gingerol	*Zingiber officinalis*	Anti-viral action against Avian influenza virus H9N2	[129]
7′R,8′S,7″R,8″S)-Erythrostrebluslignanol G	*Streblus asper Lour.,Moraceae*	Inhibition of Hepatitis B	[130]
Actinophnine	*Actinodaphne hookeri*	Herpes simplex virus type 1↓	[131]
Aranotin, Gliotoxin	*Arachniotus aureus*	Coxsackievirus A 21, poliovirus, rhinovirus, influenza virus, para-influenza virus type 3↓	[132,133]
Azadirachtin	*Azadirachta indica*	Virucidal activity against FMDV	[50]
Bicyclol	*Schisandra rubriflora*	Inhibition of Hepatitis B, Hepatitis C	[134]
Buchapine	*Euodia roxburghiana*	HIV-1-reverse transcriptase ↓	[135]
Camptothecin	*Ophiorrhiza mungos*	Herpes virus ↓	[136]
Canavanin	*Carnavalia ensiformis* L.	Influenza virus, Semliki Forest virus ↓	[137]
Caribine	*Hymenocallis arencola*	Antiviral activity	[138]
Carinatine	*Zephyranthes carinata*	Antiviral activity	[138]
Carnosic acid	*Rosmarinus officinalis*	Blocks replication of Human Respiratory syncytial virus (hRSV)	[139]
Castanospermine, Australine	*Castanospermum australe*	HIV↓	[140]
Chelidonine	*Chelidonium majus* L.	Herpes virus, influenza virus ↓	[138]
Cordycepin	*Cordyceps militaris*	Picornavirus, poliovirus, vaccinia, Newcastle disease virus, Herpes simplex, and influenza viruses ↓	[141]
Cryptopleurine	*Bochneria cylindrica* L. Sw. & *Cryptocarya pleurosperma*	Herpes simplex type 1 ↓	[142]
Diphyllin	*Justicia gendarussa*	Inhibition of Zika Virus	[143]
Ellagic acid, Isoquercetin, Kaemferol	*Eugenia jambolana*	Inhibition of protease activity in Avian Influenza	[66]
Emetine	*Cephaelis ipecacuanha* A	MERS, SARS	[144]
Fagaronine	*Fagara zanthoxyloides* Lam	Reverse transcriptase activity of retrovirus ↓	[145]
Flavonoids and Alkaloids	*Hyoscyamus niger*	Inhibition of Ca^{2+} channels and Bronchodilator SARS-CoV-2	[146]
Flavonol glycosides	*Clitoria ternatea*	Inactivation of SARS-CoV-2	[147]
Glaucine fumarate, *N*-Methyllaurotetanine, Isoboldine,	Herpes simplex virus	*Corydalis cava, Glaucium flavum, Peumus boldo*↓	[148]

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Nuciferine HCl			
Glycyrrhizin	*Glycyrrhiza glabra*	Induces nitrous oxide synthase which in turn blocks replication of SARS-CoV	[30]
Harmaline, Harmine	*Peganum harmala*	DNA-containing herpes virus type 1 (HSV-1) ↓	[149]
Harmine	*Peganum harmala*	Inhibit replication of Influenza Avirus	[33]
Hinonkin	*Chamaecyparis obtusa*	Inhibition of Human Cytomegalo Virus, SARS-CoV	[24]
Hypoxanthine	*Beta vulgaris*	Viral diseases ↓	[150]
Luteolin	*Reseda luteola*	Inhibit entry of SARS-CoV, have great affinity for S2 protein thus interfere virus-cell fusion process in SARS-CoV	[151]
Menthol and essential oils	*Mentha piperita*	Virucidal impact on IBV by incrementing virion density	[152]
Nordihydroguaiaretic acid	*Larrea tridentata*	Inhibition of Hepatitis C virus, West Nile virus, Zika virus	[153]
Ochropamine, epi-16-Ochropamine	*Cabucula erythrocarpa* Vatke Mar	Influenza virus ↓	[154]
O-Demethyl-buchenavianine	*Buchenavia capitata*	Cytopathic effect of HIV ↓	[155]
Odorinol	*Aglaia roxburghiana*	Ranikhet disease virus ↓	[156]
Oleanane triterpenes	*Camellia japonica*	Block replication of PEDV-CoV via affecting key structural protein synthesis	[157]
Oliverine	*Polyathia oliveri*	Herpes simplex virus type 1 ↓	[131]
Oxostephanine	*Stephania japonica*	Herpes simplex virus type 1 ↓	[131]
Pachystaudine	*Pachypodanthium staudti*	Herpes simplex virus type 1 ↓	[131]
Papaverine	*Papaver somniferum*	Cytomegalovirus (CMV), measles and HIV ↓	[154]
Phenolics	*Acacia nilotica*	Inhibition of HIV-PR	[158]
Phytosterols and Phenolics	*Strobilanthes callosa*	Blocking of HCoV-NL63 virus	[69]
Platycodin D	*Platycodon grandiflorum*	Inhibit viral replication and proinflammatory cytokine expression in PRRSV	[159]
Polyphenols	*Rheum palmatum*	Significant inhibition of protease activity SARS-3CL	[160]
Psychotrine	*Cephaelis acuminata*	HIV-1 ↓	[135]
Punicalagins and Ellagitannin	*Punica granatum*	Inhibition of ACE SARS-CoV-2	[161]
Quercetin	*Houttuynia cordata*	Virucidal activity against MHV, DENV-2, inhibits ATPase of multidrug resistance-protein	[162]
Quercetin and kaempferol	*Moringa oleifera*	Blocks initial stages of replication of FMDV	[163]
Quinazolinone, alkaloids and monoterpenes	*Strobilanthes cusia*	Blocking of replication of HCoV-NL63 virus	[69]
Resveratrol	*Vitis vinifera*	Reduced expression of nucleocapsid (N) protein, also lowers the apoptosis induced by MERS-CoV virus	[164]
Rifampin	*Streptomyces mediterranei*	Vaccinia, pox viruses ↓	[53]
Schumannificine	*Schumanniophyton magnificum*	HIV and anti- Herpes simplex (anti-HSV) ↓	[155]
Solasonine	*Solanum nigrum & S. khasianum*	Tobacco mosaic virus and sunnhemp rosette virus ↓	[165]
Taspine	*Croton lechleri* M.	RNA-directed DNA polymerase activity of avian myeloblastosis virus ↓	[154]
tetra-O-methylnordihydroguaiaretic acid	*Larrea tridentata*	Inhibition of Herpes Simplex Virus, Human Influenza Virus	[166,167]
Yatein	*Chamaecyparis obtusa*	Inhibition of Herpes Simplex Virus 1	[168]

Nocchi et al. [179] found that *Schinus terebinthifolia* plant's bark extract reduces infections of the Herpes simplex virus in cells.

CONCLUSION

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Currently, effective treatments against Covid-19 are unavailable. There may or may not be one in the near future. In such circumstances, medications commonly used for other viral infections such as Malaria, Ebola Virus Disease (EVD), Severe Acute Respiratory Syndrome (Sars-CoV), Middle East coronavirus-related respiratory syndrome (MERS-CoV) are considered (repurposing/repositioning) as therapeutic options. Every medical specialty around the world claims they have some help available to either prevent, treat, or cure potential infectious viral pathogens. This includes, but is not limited to, Siddha, Ayurveda, Unani, Complementary and alternative medicine (CAM) therapies, natural and indigenous tribal medicine. Several communities eschew drugs for Covid-19 but resort to natural medicine as it is believed that the home-made remedies are much safe without mush side-effects, and additionally have great preventive curing capabilities. For example, native South American from Amazonia uses 'toothache plant' (*Acmella oleracea*) to prepare an herbal tea (jambú tea) home remedy. Traditional herbal remedies from India and other countries and Traditional Chinese Medicine (TCM) are currently being explored. In India, the Ministry of Ayurveda, Yoga & Naturopathy, Unani, Siddha, and Homoeopathy (AYUSH) has been involved in the research and dissemination of indigenous alternative medicine systems. However, the aim was to promote traditional healing therapies and to list various practices that prevent infectious agents from occurring, strengthen the immune system, thereby improving the overall health and well-being of the individual, but not promoting it as a primary treatment.When patients and consumers resort to any of these alternative supportive therapies, care must be taken to avoid potential side effects. The World Health Organization (WHO) has released a general warning against the use of unproven treatment. Besides, there are many fraudulent claims concerning prevention, cure, and management for COVID-19. Hence, patients and consumers are advised to consult appropriate medical specialties and avoid self-diagnosis and treatment or while using over-the-counter preparations.

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CONFLICTS OF INTERESTS

The authors have read the journal's policy and have the following potential conflicts: This study was not industry-supported. S.R. Pandi-Perumal is a stockholder and the President and Chief Executive Officer of Somnogen Canada Inc., a Canadian Corporation. This does not alter his adherence to all of the journal policies. Pandi-Perumal has edited several academic volumes for which he receives occasional annual royalties. He declares that he has no competing interests that might be perceived to influence the content of this article.

Other remaining authors declare that they have no proprietary, financial, professional, nor any other personal interest of any nature or kind in any product or services and/or company that could be construed or considered to be a potential conflict of interest that might have influenced the views expressed in this manuscript.

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