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Review

Immunity-Boosting Natural Herbs to Combat COVID-19 Pandemic: A Narrative Review

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Abstract

Coronaviruses cause some severe forms of respiratory infections such as Severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and Coronavirus disease 2019 (Covid-19). These viruses cause diarrhea in pigs and cows and upper respiratory disease in chickens, while other symptoms may differ. In humans, a total of six coronaviruses have been identified HCoVs-NL63, HCoVs-OC43, HCoVs-229E, HCoVs-HKU1, MERS-CoV, and SARS-CoV. The world health organization (WHO) has done a great deal of hard work regarding combating the monstrous effects of this virus. So far, no specific antiviral drugs have been developed for the treatment of Covid-19. Therefore, the medicinal plants used for the previous epidemic outbreaks are getting attention for their potential treatment against the virus. It has been reported that 70 to 80% of people in developing countries depend on medicinal plants or phytomedicine compared to allopathic drugs for their primary healthcare. The south Asian subcontinents have used almost up to 25,000 formulations and extracts obtained from medicinal plants for treatment in folk medicine. The present review discusses an overview of the coronavirus, its immune responses, and some immunity-boosting herbs to combat Covid-19.

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INTRODUCTION

Recently, pandemic diseases have become of great importance in terms of enormous morbidity even with the extensive facilities available in medical sciences[1]. More importantly, the antiviral drugs have failed to give the requisite results due to the more resistant mutant forms of viruses that have emerged over time[2]. Due to the fast urbanization and improved availability of travel facilities, contagious diseases have been spread more easily, posing a danger to communal safety and health integrity[3]. In the twenty-first century, two fatally devastating viral outbreaks have been observed by humans: The Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) population of our planet[4]. Recently, coronavirus disease 2019 (Covid-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the third most important disease that originated from an animal source and spread worldwide after starting in Wuhan, China[5].

Experts have studied the clinical presentation of this virus, and it has been confirmed that it resembles much pneumonia and therefore has been named the novel coronavirus (2019-nCoV). Investigations have acquired that in sequence homology SARS-CoV resembles bat coronavirus. The spike glycoproteins of the virus are seen to have a massive affinity for Angiotensin-converting enzyme 2 (ACE2) receptors in humans. This property enables the virus to undergo human-to-human transmission[6]. The virus diagnosis and transmission ability vary in comparison with SARS-CoV despite the huge resemblance they share. The distinction lies mainly in the nucleotide pattern of spike proteins as well as its receptor-binding domains[7].

World Health Organization (WHO) has done a great deal of hard work regarding combating the monstrous effects of this virus. For example, they have made the populations aware of how to halt the spread of the disease by minimization of physical contact, isolating and screening the infected people in the early stages, as well as recognizing and reducing the transmission from the animals[8]. The virus is known to spread through aerosol pathways as well as through saliva and the nose. As long as no vaccine is available, scientists worldwide have been putting a significant number of efforts into finding out the best way to prevent the spread of this fatal disease[9]. On the other hand, manufacturers have been working on manufacturing sanitizers and masks, which have been profitable to ordinary people and health care professionals. With the diseases still spreading at an incredible speed, it is imperative to unveil the pathogenesis of the virus so that suitable drugs and vaccines can be designed[10].

Many treatment options are being discovered, but there is a severe lack of valid evidence to support their use. Multiple drugs are in the waiting of clinical trials. While that is to be done, the already available antiviral drugs such as lopinavir, nitazoxanide, chloroquine, ritonavir, tocilizumab, hydroxychloroquine, and azithromycin have been used for management and are seen to dwindle the replication and reduce the load of the virus[11,12]. Scientists are working fast to achieve their target of protecting the public. Monoclonal antibodies, steroids, peptides, oligonucleotides, interferons, enzyme inhibitors have been suggested to restrain the spread of disease[13,14]. To manage the clinical presentation of SARS-CoV-2 unproven vaccines, antiviral drugs, and other alternatives have been tried imposing stress on symptoms management and precautions[15]. The discovery of a new drug requires months to years as the drug is tested through clinical trials and improved based on the results[16]. However, there is a great demand to combat the Covid-19 outbreak, bring relief to those suffering, and save lives for which natural medicines, medicinal plants, and herbal formulations should now be sent for warfare. They are feasible and cost-effective, eco-friendly, efficacious, with almost no side effects when used accordingly[17].

One herb contains plenty of phytochemicals that are very effective pharmacologically, either collectively or singlehandedly[18]. These naturally occurring constituents are isolated and modulated into new drugs used to treat different ailments. In recent years, medicinal plants are the way to go for managing the symptoms and treating their cause, and research is being done to encourage their usage for treating patients with Covid-19 as these herbs possess antioxidant, anti-inflammatory, and antiviral characteristics[19]. Through this review, we suggest using phytomedicine as an alternative approach to treat and manage the diseases caused by these fatal viruses as described in **Figure 1**.

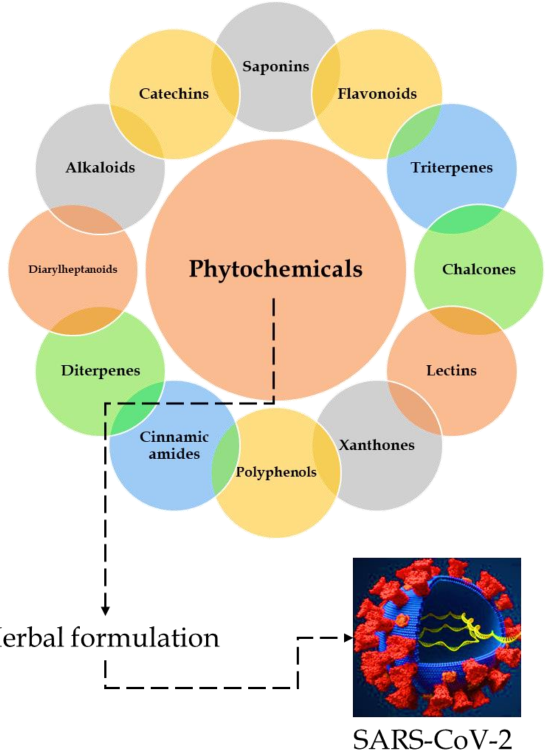

Figure 1. Isolated phytochemical compounds inhibiting the SARS-CoV-2

GENERAL OVERVIEW

Coronavirus is derived from the Latin word Orthocoronavirinae is one subfamily from the two of Coronaviridae family and is known to cause ailments in mammals and birds. Because of its specific crown-like shape, the virus is called a corona. Serologically and genotypically, the subfamily of coronavirus constitutes four specific types: alpha, beta, gamma, and delta coronavirus[20]. There are also four different subgroups of coronavirus, including A, B, C, and D. As of today, the total of identified coronaviruses infecting mammals, poultry, humans, and other animals has reached up to thirty and cause various ailments of hepatic, gastrointestinal, neurological, and particularly the respiratory types[21]. In humans, a total of six coronaviruses have been identified HCoVs-NL63, HCoVs-OC43, HCoVs-229E, HCoVs-HKU1, MERS-CoV, and SARS-CoV[22]. It is already reasonably known that the diameter of the virus is 120 nanometers. A pair of electron-dense cells make up the envelope of the virus, as seen through electron microscopy[23].

Coronavirus is a ribonucleic acid (RNA) virus of a single strand. Only the alpha and beta coronaviruses cause infectious diseases in humans[5]. The survival of the virus depends upon its medium and can survive at room temperature on dry surfaces and in feces for two to three days and two to four days, respectively[24]. The genomic RNA of the virion is seen to be embedded in double layers of a phospholipid, and two different kinds of nucleocapsid protein coat the virion. The membrane protein (M protein) is a transmembrane glycoprotein of type-3. Both the M protein and the envelope protein are included in the surface proteins (S proteins) of the virus's envelope[25]. In the early steps of viral infection, the multifunctional S protein plays a vital role by interacting with the proteases and receptors of the host cell. As a result of these interactions, human cells containing contain hACE2 transmembrane proteins are infected[26].

IMMUNOPATHOLOGY

The infection caused by coronavirus is classified into three stages. The first is the asymptomatic stage, while the second and third are the symptomatic stages of the viral disease, with the second being non-severe and the third being the severe stage[27]. Most patients recover before progressing to the third severe stage of the disease, while the few develop multiorgan failure or acute respiratory distress syndrome (ARDS). When SARS-CoV-2 attaches with ACE2 receptors and lets out the viral RNA for the process of replication, the host's immunity begins to respond to the invader[28].

In response to the viral invasion, both the adaptive and innate immune responses can be produced[29]. However, the immune responses depend on the severity of the infection. It has been shown that in the blood samples of hospitalized patients with mild to moderate symptoms of SARS-CoV-2 infection before the symptoms resolved, several immunological changes were observed, such as an increase in the number of active CD8+ killer T cells and CD4+ helper T cells, antibody-secreting cells, follicular helper T cells, and immunoglobulin (Ig) G and IgM antibodies were detected[30]. In contrast to this, in severely ill patients, there is a decrease in the numbers of B cells, natural killer cells, CD3+ T cells, CD8+ killer T cells, CD4+ helper T cells, as well as a rise in the neutrophil-to-lymphocyte ratio (NLR) and levels of C-reactive protein. Moreover, in serum samples of critically ill patient's tumor necrosis factor (TNF)-α, granulocyte-colony stimulating factor, interleukin (IL)-2, IL-6, IL-7, IL-8, IL-10, macrophage inflammatory protein-1α, and monocyte chemoattractant protein-1 are reported to be elevated in contrast with non-severe patients[31,32].

The NLR is a biomarker for the systemic inflammatory response and indicates the devastating inflammatory stage of critically ill patients[33]. An overactive inflammatory response is produced in response to the uncontrolled levels of chemokines and cytokines and is also called a cytokine storm. The impairment of the adaptive immune response along with these hyperactive responses of immune systems leads to pulmonary injury, viral sepsis, ARDS, and complications of organ failure, and in some cases, death[34].

SIGNS AND SYMPTOMS

According to the Centers for Disease Control and Prevention (CDC), the median incubation period for Covid-19 is four to five days. It varies from person to person. However, it can range anywhere from two to 14 days. It affects a different person in different ways[1]. The most infected person will develop mild to moderate illness and recover without hospitalization; not every person with a Covid-19 infection will feel unwell. It is possible to have the virus and not develop any symptoms. When symptoms are present, they are typically mild and develop slowly[35].

According to researchers in China, these were the most common symptoms like fever, fatigue, nausea and vomiting, cough, runny or stuffy nose, mucus/phlegm, sore throat, lack of appetite (anorexia), muscle aches and pains (myalgia), shortness of breath (dyspnea), headache, diarrhea, chills, loss of taste or smell, and conjunctivitis[36]. The severity of Covid-19 symptoms can range from very mild to severe. Some people may experience severe or worsened symptoms, such as difficulty breathing or shortness of breath, pneumonia, chest pain, loss of speech or movement, about a week after symptoms start. Older people with pre-existing chronic medical conditions have a higher risk of serious illness from Covid-19, and the risk increases with age[37].

DIAGNOSIS

Upon diagnosis with the suspected infection, a patient gets to confirm whether a suffering from Covid-19 or not. The CDC recommends two testing strategies for SARS-CoV-2. In the first strategy, a patient's blood sample is screened for the possible presence of antibodies against the virus, and in the second strategy, viral deoxyribonucleic acid (DNA) is screened for a sputum sample. The virus can be detected in case of infection, but to make sure polymerase chain reaction (PCR) is performed, PCR takes a more extended hour than the screen of patient blood method[38].

The collection of an appropriate specimen is the crucial step in the laboratory diagnosis of Covid-19. The specimens are accepted from the upper respiratory tract, lower respiratory tract, stool, whole blood, and serum, and the respiratory secretions are the most frequent sample for diagnosis. Nowadays, SARS-CoV-2 has been detected in the swabs of nasopharyngeal, oropharyngeal, throat, sputum, bronchoalveolar lavage fluid (BALF), whole blood, serum, stool, urine, saliva, rectal and conjunctival[39]. A comparison of different nucleic acid amplification of SARS-CoV-2, including laboratory-based tests and point-of-care tests, is shown in **Table I**.

Table I. Characteristics and the merits-demerits of different laboratory diagnostic methods for SARS-CoV-2[40-42]

SARS-CoV-2 tests	Methods	Testing strategies	Merits	Demerits
Neutralization tests	Virus neutralization test and pseudo-virus-based virus neutralization test	Bio-safety level-2 (BSL-2) or BSL-3 laboratory, pathogen laboratory	Authoritative, simple, low cost, reliable, highly sensitive	Time-consuming, long period, laborious, perform in BSL-3 or BSL-2 laboratory
PCR	Quantitative reverse transcription-PCR (qRT-PCR)	BSL-2 laboratory, public health institutes, quarantine depots	High specificity, not require expensive equipment, time-saving	Complex pre-treatment steps require skillful, false negative
	Portable benchtop sized analyzers	Clinical laboratory, physician's office, emergency departments	Automatic, portable, rapid, not require trained staff	Inconsistent performance may lack sensitivity in weakly positive samples
	Reverse transcription-loop mediated isothermal amplification	Basic laboratory, community nursing sites	Time-saving, thermostatic, sensitive, user-friendly, sophisticated equipment free	Easy to be contaminated and cause false positive, non-specific amplification cannot be easily identified, require skillful
	Nanoparticles based amplification	BSL-2 laboratory, environment testing institutions	High sensitivity, adopted in fully automated RNA extraction systems, excellent RNA binding performances	Complex pre-treatment steps require skillful, expensive than qRT-PCR, with the risk of photobleaching
	Nested RT-PCR	BSL-2 laboratory, prefectural and municipal public health institutes, quarantine depots	High sensitivity, specificity was higher than that of RT-PCR, suitable for detecting low copy number viruses, time-saving	Complex pre-treatment steps require skillful, manpower, the second PCR amplification may cause cross-contamination
	Droplet digital-PCR	BSL-2 laboratory, public health institutes, quarantine depots	Quantitative, sensitive, suitable for detecting samples with low viral load, independent of a traditional standard curve	Susceptible to exogenous contamination, expensive than qRT-PCR, calibrant materials need to be defined
Immunological diagnostic	Enzyme-linked immunosorbent assay	Clinical laboratory, public health institutes	Quantitative detection, simple, a low risk of infection, convenient, stable reagent	Time-consuming, low sensitivity, cross-reactivity, expensive monoclonal antibody, low throughput
	Lymphocyte function-associated antigen	Clinical laboratory, physician's offices emergency departments, community service stations	Rapid, convenient, onsite screening, inexpensive, small sample volume	Low sensitivity, cross-reactivity, inconsistent performance, not suitable for early diagnosis, low throughput
	Microarray and microfluidic chip	Clinical laboratory, emergency departments, community service stations	Small size, high sensitivity, automatic, high throughput, portable	Core technologies lack norms and standards, high cost, non-specific binding of proteins
	Immunofluorescence assay	Clinical laboratory, pathogen laboratory, public health institutes	Avoid the interference of endogenous biotin and contamination of antigens in the blood	Non-specific fluorescence, subjective, low throughput, time-consuming

	Chemiluminescence immunoassay	Clinical laboratory, public health institutes	Automatic, rapid, quantitative, high sensitivity, broad linear range, stable results	Sophisticated instruments, high requirements for equipment and environment, not suitable for detecting whole blood samples
Genome sequencing	Metatranscriptomic sequencing	BSL-2 laboratory, genetic testing centers, research laboratory	Simple, reduce the cost, does not claim a reference sequence	Increase cost, sophisticated instruments, insufficient coverage, and depth
	Hybrid capture-based sequencing	BSL-2 laboratory, genetic testing centers, research laboratory	High sensitivity, suitable for detecting intraindividual variations	Sophisticated instruments, not to be used to sequence highly diverse or recombinant viruses
	Nanopore targeted sequencing	BSL-2 laboratory, genetic testing centers, research laboratory	Broad detection range, rapid turnaround time, long read, high accuracy, monitor the variation	Increase cost, sophisticated instruments, requires skillful
	Amplicon sequencing	BSL-2 laboratory, genetic testing centers, research laboratory	Convenient, high sensitivity, suitable for detecting samples with low viral load, economical	Sophisticated instruments, not to be used to sequence highly diverse recombinant viruses

MEDICINAL PLANTS FOR COVID-19

So far, no specific drugs (antiviral) therapy or vaccines have been developed to treat Covid-19; the medicinal plants used for the previous epidemic and pandemic outbreaks are getting attention for their potential treatment against the virus[43]. Chinese herbal medicine is an essential part of Chinese traditional medicine and has been one of the most robust models of herbal medicine for about 2000 years by using about 10,000 medicinal plants as extracts of warm water to control contagious diseases[44]. It has been reported that 70 to 80%of people in developing countries depend on medicinal plants or phytomedicine compared to allopathic drugs for their primary healthcare[45]. The benefits obtained from the medicinal herbs are contributed by the presence of the plant's secondary metabolites such as steroids, diterpenes, alkaloids, glycosides, and aliphatics, and others[46].

The investigations for discovering a plant metabolite with antiviral activity have been ongoing but not very successful due to the ability of viruses to mutate and adapt resistance and undergo latency and the persistence of infections in patients with a weak immune system[47]. Moreover, the antiviral therapy modules are mostly not specific for viruses while exerting their antiviral activity[48]. Medical research has been working hard to develop novel antiviral mediators at present. The antiviral constituents of the various medicinal plants play an essential role in combating viral diseases by exerting effects at the various stages of viral replication and growth[49].

Traditional medicine has been used for a long time in the Indian subcontinent and has played important roles in fighting off the various ailments and providing primary healthcare to communities at a much efficient and affordable cost[50]. The traditional subcontinental medicines include Ayurveda, Unani, Homeopathy, Siddha, Naturopathy, and Yoga and are being used to treat various infectious ailments[50]. Animals, plants, and minerals have been used for treatment by these medical models[51]. The south Asian subcontinents have used almost up to 25,000 formulations and extracts obtained from medicinal plants for treatment in folk medicine[52]. Following are some of the antiviral, immunostimulant, and immunomodulating agents, which belong to medicinal plants. Various studies have recommended their isolated compounds to potentially use in the battle against the Covid-19, as shown in **Tables II** and **III**.

Cannabis sativa

A study carried out by Wang *et al*.[53] on cannabinoid and cannabidiol reported that an active constituent of *C. sativa* showed that the constituent has anti-inflammatory properties as it modulates the gene expression of ACE2, the protein required for the coronavirus entry into the host cell and transmembrane protease, serine 2. It can be used as an adjunctive therapy and as a mouthwash as well as throat gargle because it reduces the entry of the virus through the oral mucosa.

Glycyrrhiza glabra

A study carried out by Bailly and Vergoten[54] on glycyrrhizin, liquiritin, glycyrrhizic acid, and isoliquiritin; active constituents of *G. glabra*, showed that the plant has antiviral properties and can be used as a potential antiviral herbal drug against Covid-19.

Citrus species

A study was carried out by Meneguzzo *et al*.[55] on essential oils, naringin, pectins, and hesperidin (flavonoids) belonging to citrus species showed that they have a high affinity of binding with the SARS-CoV-2 cellular receptors, which puts a halt to the overreaction of the immune system before the inflammatory process begins. This particular action enables it to be used as prophylaxis as well as a potential treatment for Covid-19. Another study on citrus species showed that naringin, hesperetin, naringenin, and hesperidin have an inhibitory effect on the pro-inflammatory cytokines (inducible nitric oxide synthase, cyclooxygenase-2, IL-1β, IL-6) expression belonging to the cell line of macrophage, and also halted the effect of cytokines by inhibition of expression of high mobility group box protein 1 in a model of mouse and hindered the ACE2 receptor binding affinity of coronavirus[56]. The anti-inflammatory activity of the citrus species owing to the phytochemicals derived from flavonoids ensures the usage of the species as a potential treatment module of Covid-19[57].

Nigella sativa

Banerjee *et al*.[58] reported that *N. sativa* could be used as a potential treatment against the infection of SARS-CoV-2 as two of its active constituents; α-hederin and nigelledine, act as the CoVs proteases inhibitors by docking into their active sites.

Camellia sinensis

Polyphenols of *C. sinensis* or black tea act as protease inhibitors by targeting the main protease of Covid-19, which is involved in the replication and transcription of the virus. This way, the plant can hinder the growth of the virus inside the host cell. Black tea can be used in the diet to help the body fight against Covid-19 when the disease is still in the early stages[59].

Zingiber officinale

Zingiber officinale can be used as a potential treatment drug against Covid-19 as it inhibits the Covid-19 main protease R7Y by binding with its active sites. The active ingredient attributing to this particle property is 6-gingerol[57,60].

Cnidoscolus aconitifolius

The plant is reported to have the most potent inhibitory effect on the ACE2 enzyme, modulated expression of α-gene for the production of TNF in macrophages, and anti-inflammatory properties. These plant characteristics are attributed to the presence of phenols, flavanones, flavonoids, and dihydroflavonols[61].

Scutellaria baicalensis

The plant is reported to inhibit replication and SARS-CoV-2 3-chymotrypsin-like cysteine protease and can be effective for inhibiting the virus[62].

Ginkgo biloba

Ginkgo biloba is reported to dwindle protein and Deoxyribonucleic acid synthesis by binding with the cell receptors of the host and is due to the presence of ginkgolic acids and can be used for the treatment of coronavirus infections[63]. Moreover, another study shows that terpenoids and ginkgolide have a strong binding affinity with the coronavirus proteases and therefore can be used as potential antiproteases for Covid-19[64].

Allium sativum

The plant's essential oils and active constituents, such as allyl disulfide and allyl trisulfide, are reported to be involved in ACE2 receptor inhibition as well as inhibition of SARS-CoV-2 main proteins. Essential oils help restrain the entry of viruses into the body by acting as antiviral compounds and can be used for the fight against Covid-19[65].

Table II. List of the 46 isolated phytochemical compounds inhibiting the coronaviruses[66-70]

Phytochemical compounds	Plant source	Chemical groups	EC_{50}/IC_{50} values	Types of coronaviruses
Glycyrrhizin	*Glycyrrhiza glabra*	Saponin	EC_{50}: 364.5 μM	Severe acute respiratory syndrome-coronavirus
Saikosaponin B2	*Bupleuri radix*	Saponin	EC_{50}: 1.7±0.1 mmol/L	
Saikosaponin A	*Bupleuri radix*	Saponin	EC_{50}: 8.6±0.3 mmol/L	
Tetra-O-galloyl-β-D-glucose	*Phyllanthus emblica*	Polyphenol	EC_{50}: 4.5 μM	
Luteolin	*Reseda luteola*	Flavonoid	EC_{50}: 10.6 μM	
Sinigrin	Brussels	Polyphenol	IC_{50}: 217 μM	
β-sitosterol	*Leucaena leucochepala*	Phytosterol	IC_{50}: 1210 μM	
Hesperetin	Citrus	Flavonoid	IC_{50}: 8.3 μM	
Amentoflavone	*Gingko biloba*	Flavonoid	IC_{50}: 8.3 μM	
Luteolin	*Reseda luteola*	Flavonoid	IC_{50}: 20.2 μM	
Quercetin	*Allium cepa*	Flavonoid	IC_{50}: 23.8 μM	
Apigenin	Citrus	Flavonoid	IC_{50}: 280.8 μM	
Isobavachalcoone	*Psoralea corylifolia*	Flavonoid	IC_{50}: 7.3±0.8 μM	
Psoralidin	*Psoralea corylifolia*	Flavonoid	IC_{50}: 4.2±1.0 μM	
Tomentin A	*Jatropha curcas*	Flavonoid	IC_{50}: 6.2±0.04 μM	
Tomentin B	*Jatropha curcas*	Flavonoid	IC_{50}: 6.1±0.02 μM	
Tomentin E	*Jatropha curcas*	Flavonoid	IC_{50}: 5.0±0.06 μM	
3'-O-methyldiplacol	*Pawlonia tomentosa*	Flavonoid	IC_{50}: 9.5±0.10 μM	
Isoliquiritigenin	*Glycyrrhiza uralensis*	Flavonoid	IC_{50}: 61.9±11.0 μM	
Quercetin	*Allium cepa*	Flavonoid	IC_{50}: 52.7±4.1 μM	
Kaempferol	*Kaempferia parviflora*	Flavonoid	IC_{50}: 116.3±7.1 μM	
Kazinol F	*Broussonetia kazinoki*	Flavonoid	IC_{50}: 43.3±10.4 μM	
Broussochalcone B	*Broussonetia papyrifera*	Flavonoid	IC_{50}: 57.8±0.5 μM	
Papyriflavonol A	*Broussonetia papyrifera*	Flavonoid	IC_{50}: 103.6±17.4 μM	
Terrestrimine	*Tribulus terrestris*	Cinnamic amide	IC_{50}: 15.8±0.6 μM	
Tingenone	*Maytenus guianensis*	Triterpene	IC_{50}: 9.9±0.1 μM	
Iguesterin	*Catha cassinoides*	Triterpene	IC_{50}: 2.6±0.3 μM	
Pristimererin	Celastrus	Triterpene	IC_{50}: 5.5±0.7 μM	
Dihydrotanshinone I	*Salvia miltiorrhiza*	Diterpene	IC_{50}: 4.9±1.2 μM	
Cryptotanshinone	*Salvia miltiorrhiza*	Diterpene	IC_{50}: 0.8±0.2 μM	
Tanshinone IIA	*Salvia miltiorrhiza*	Diterpene	IC_{50}: 1.6±0.5 μM	
Xanthoangelol	*Angelica keiskei koidzumi*	Chalcone	IC_{50}: 11.4±1.4 μM	
Hirsutenone	*Boerhavia repens*	Diarylheptanoid	IC_{50}: 3.0±1.1 μM	
Rubranoside	*Alnus glutinosa*	Diarylheptanoid	IC_{50}: 7.2±2.2 μM	
Curcumin	Curcuma	Diarylheptanoid	IC_{50}: 5.7 μM	
Allium porrum agglutinin	*Allium cepa*	Lectin	EC_{50}: 0.45±0.08 μg/mL	
Urtica dioica agglutinin	Utricularia	Lectin	EC_{50}: 1.3±0.1 μg/mL	
Lycorine	*Calophyllum blancoi*	Alkaloid	EC_{50}: 15.7 IU/mL	
Blancoxanthone	*Calophyllum blancoi*	Xanthone	EC_{50}: 3 μg/mL	Human coronavirus 229E
Pyranojacareubin	*Calophyllum inophyllum*	Xanthone	EC_{50}: 15 μg/mL	
Tylophorine	*Incertae sedis*	Alkaloid	EC_{50}: 58±4 nM	Trans-missible gastro-enteritis virus
7-methoxy-cryptopleurine	Boehmeria	Alkaloid	EC_{50}: 20±1 nM	
Jubanine G	*Zizyphus jujuba*	Alkaloid	EC_{50}: 13.41±1.13 μM	Porcine epidemic diarrhea virus
Jubanine H	*Zizyphus jujuba*	Alkaloid	EC_{50}: 4.49±0.67 μM	
Nummularine B	*Berberis nummularia*	Alkaloid	EC_{50}: 6.17±0.50 μM	
Schimperinone	*Biblioteca civica*	Triterpene	EC_{50}: 0.28±0.09 μM	

Table III. Summary of the 15 promising medicinal plants and their isolated bioactive compounds against the Covid-19[53,62,65,71-75]

Medicinal plants (Bioactive compounds)	Mechanism of action	Therapeutic effects
Gingko biloba (ginkgolide A, terpenoids)	Stronger bond and high affinity with proteases	Compounds may be considered as effective SARS-CoV-2 antiproteases drugs
Citrus, *Curcuma longa* (hesperidin, rutin, diosmin, apiin, diacetyl curcumin)	Inhibitory action against SARS-CoV-2 main proteases (M^{pro})	Medicinal potential to cure SARS-CoV-2
Zingiber officinale (6-shogaol, 6-gingerol)	Binding potential with active residues of ACE2 that mediate host viral interface	The future systemic investigation could validate the efficacy before the recommendation
Allium sativum (allyl disulfide, allyl trisulfide)	Acted as ACE2 receptor inhibitor for resistance against SARS-CoV-2 along with activity against main proteases of SARS-CoV-2	Essential oil as valuable natural antivirus source, contributing towards preventing the invasion of SARS-CoV-2 into the human body
Scutellaria baicalensis (baicalein)	Anti-SARS-CoV-2 activity via suppressing SARS-CoV-2 3C-like proteases ($3CL^{pro}$)and replication	Effective compounds as anti-SARS-CoV-2 inhibitors
Betula pubescens (herbacetin, isobavachalcone, quercetin, betulinic acid)	Inhibitory compounds against MERS-CoV $3CL^{pro}$	Flavonoids with these characteristics can be used as templates to develop potent MERS-CoV $3CL^{pro}$ inhibitors

Camellia sinesis (epigallocatechin gallate)	Targets include main proteases SARS-CoV-2, the post-fusion core of SARS-CoV-2 S2 subunit, prefusion spike glycoproteins, and non-structural protein 15 endoribonucleases from SARS-CoV-2	Future drug candidate SARS-CoV-2
Eucalyptus sp. (jensenone)	SARS-CoV-2 M^{Pro} inhibitor	Eucalyptus oil could be used for prevention and cure
Cannabis sativa (cannabinoid, cannabidiol)	Anti-inflammatory action by via modulation of gene expression of anion exchange protein 2 enzymes, transmembrane protease, serine 2, protein pre-requisite for SARS-CoV-2 invasion into host cells	Adjunct therapy and utilized as mouthwash and throat gargle products clinically and home use owing to their potential to decrease viral entry via the oral mucosa
Citrus sp. (essentials oils, pectins, naringin, and hesperidin (flavonoids))	Binds with high affinity to cellular receptors of SARS-CoV-2 that restrain the pro-inflammatory overreaction of the immune system	Prophylaxis and treatment of SARS-CoV-2
Lawsonia inermis (fraxetin 1[3H]-isobenzofuranone)	Phytochemical, cytotoxicity, and anti-inflammatory actions confirmed infractions of extract as observed as a potent-constituents	Cytotoxic compounds, warrant research to fabricate suitable formulations comprising these constituents
Cnidoscolus aconitifolius (phenols, flavonoids, flavonones, and hydroflavonoles)	Highest ACE2 enzyme inhibition, anti-inflammatory activity, the modulated α-gene expression for TNF-production in macrophages	Bioactive compounds could be used for drug formulations
Nilavembu Kudineer (benzene 123 triol)	Immuno-modulatory activity against ACE2 enzyme receptor, that routes virus entry in the pathogenesis of novel coronavirus	Potent anti-viral capacity for drug development
Porphyridium sp. (sulfated polysaccharides (carrageenan))	Potent inhibitors of coronaviruses that inhibit the binding or internalization of the virus into the host cells	Biocompatible compounds can be used as a coating material on sanitary items for SARS-CoV-2 prevention
Ocimum sanctum (oleonolic acid, urosolic acid)	Higher binding affinity with viral and host macromolecular targets and other human pro-inflammatory mediators, SARS-CoV-2 main proteases, spike, human ACE2, and furin proteins	Regularly consumed in the form of Ayurvedic Kadha to boost immunity and dwindle chances of SARS-CoV-2 infection

CONCLUSION

Scientists are burning night oils in finding out the ways to treat Covid-19. However, due to higher ability of the virus to mutate and adaptation to resistance has imposed several limitations. Plant extracted formulations are cost-effective, eco-friendly, and have nil to rare side effects. Several plant extracts are used in the treatment of several diseases. Scientists can work on finding out the efficacy of the mentioned drug on the SARS-CoV-2. Some of these formulations might be proved a treatment measure. They may also reduce the lethality of the disease, along with helping in alleviating the symptoms. These extracts might be proved helpful singly or taken along with other medications.

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All authors have equal contributions to this article.

DATA AVAILABILITY

None.

CONFLICT OF INTEREST

The authors declare that they do not have a conflict of interest regarding article publication.

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