Potential Immunity Boosting Plant Candidates Effective against SARS-CoV-2

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Abstract

Global pandemic caused by the virus named SARS-CoV-2 created havoc and resulted in worldwide lockdown. COVID-19 disease caused by novel coronavirus results in severe symptoms and mainly infects the respiratory system of humans. If the infection is not dealt appropriately, it can lead to severe complications and may even result in death. Immunity to COVID-19 has proven to be the biggest weapon against the deadly virus while everyone struggled to find the cure. Immunity helps the body to resist, withstand the severity of disease as well as prevent its manifestation. The human immune system mainly comprises of B and T cells, natural killer cells, macrophages, neutrophils along with cytokines. The immune system functions by producing

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antibodies to fight infection. Ayurveda is an ancient medical science and is known to be practised for several years. It uses herbal plants as a source of Ayurvedic medicines which can treat several diseases and boost immunity. Moreover, there are lot of studies and scientific data available in the public domain on the various properties of herbs and their phytoconstituents. *In silico* studies were performed to analyse the interaction of herbal plant extracts against SARS-CoV-2. The results are promising but need more scientific evidence to substantiate and establish their safety and effectiveness. In this chapter, medicinal plants and their phytoconstituents that can be used in future for developing drugs against SARS-CoV-2 have been discussed.

Keywords

Antiviral, Covid-19, Docking, Immunity, Medicinal plants, Phytochemicals, SARS-CoV-2

1. Introduction

The COVID-19 pandemic has been spreading at worrying rates to almost every part of the world. As per reports of WHO (2021), it has diseased more than 82 million people and resulted in more than 3.9 million deaths across the globe in 2020 alone. COVID-19 cases still remain high in many countries of the world (e.g. India), where rate of administering of vaccines is low (https://www.who.int/news-room/spotlight/the-impact-of-covid-19-on-global-health-goals). World Health Organization (WHO) declared this outburst as a health emergency on 30th January, 2020, and further confirmed it pandemic on 11th March, 2020.

The history of coronaviruses infecting humans dates back to 1965 when Tyrrell and Bynoe (1966) cultivated viruses from the patients suffering from cold. COVID-19 is an acutely infectious disease triggered by the newly discovered coronavirus called SARS-CoV-2 (+ssRNA virus). Coronavirus first appeared in December 2019 in Wuhan, Hubei Province, China (Zhu et al. 2020a). This family of virus is known to exclusively cause respiratory diseases like SARS and MERS which have high rate of mortality and were first reported in 2003 and 2012 respectively (Origin of SARS-CoV-2, https://apps.who.int/iris/handle/10665/332197). SARS-CoV-2 is an animal virus and present studies indicate that bats, pangolins and snakes might act as host for this virus. According to the whole genome sequencing data, bats shows 96% homology with bat coronaviruses and thus suggests that bats are acting as host for this virus. However, the intermediate host for SARS-CoV-2 is yet unidentified (Zhu et al. 2020b). Coronaviruses belongs to the family of single stranded (ss), enveloped RNA viruses (Weiss 2020). Transmission electron microscopy studies reported CoVs to be spherical in shape with spike like proteins projecting from the surface of the virions giving it a crown like appearance and henceforth it was named 'coronavirus' (Ashour et al. 2020).

The pandemic is an outcome of speedy growth in urbanization, increased travel and trade, limited facility and inadequate access to health care and environmental destruction. Despite the development of vaccines and immunization, people are still wondering what post pandemic new norm of life would look like? The government are struggling with new lockdown measures, imposing strict quarantine and enforcing strict restrictions on movement to control and prevent the further spread of this highly communicable disease (World Bank, 2020; https://www.worldbank.org/en/news/feature/2020/06/08/the-global-economic-outlook-during-the-covid-19-pandemic-a-changed-world#).

SARS-CoV-2 virus mainly kills through immune system's overreaction and generally attacks people with low immunity and especially people of under and over ages. The immune system is a protective system of the body that provides protection against foreign bodies like viruses. Therefore, people with low or weak immunity are more susceptible to viral infections (Khabour and Hassanein 2021; Li et al. 2020). Thus it is recommended to strengthen the immune system by maintaining good nutrition to prevent infection. Since ancient times the medicinal plants including herbs and spices are distinguished for their medicinal properties. In Ayurvedic system of medicine, the probable role of plant extracts in strengthening the immune system is well documented. Besides these, there are many other benefits of these herbal plants like they are non-toxic, accessible and safe to use compared to allopathic/synthetic medicines. Thus, the use of medicinal plants can strengthen our immunity naturally and prevent and/or lessen the risks and complications associated with COVID-19.

There are many medicinal plants and herbs that have the potential to boost our immunity which would help in management of COVID-19. For example, *Azadirachta indica, Allium sativum, Astragalus glycyphyllos,* Black cumin*, Cinnamomum verum,* *Curcuma domestica, Curcuma longa, Daucus maritimus, Moringa oleifer, Ocimum sanctum, Phyllanthus emblica, Piper betel, Piper nigrum, Syzygium aromaticum, Sambucus nigra, Tinospora cordifolia, Withania somnifera,* etc. These plants are storehouse of antioxidants, alkaloids, steroids, antiviral and antibacterial phytochemicals, proteins, vitamins, carbohydrates, dietary amino acids, fibres and minerals that help in restoring the immune system and provide protection against viruses (Patil and Kakde 2020). People in India have been using herbal preparations in different forms (diet, powder, eea, kadha) which boost their immunity in natural way. It is also very imperative to consume nutrient supplements like vitamin A, C, E, D, B-complex, copper and zinc as they help in defence response against the pathogens (Tamboli et al. 2021). There are reports of increased use of some medicinal plants like *Curcuma longa*, *Carum carvi, Glycyrrhiza glabra*, *Ocimum basilicum*, *Origanum majorana, Pimpinella anisum* and *Zingiber officinale* during the pandemic in Egypt (Khabour and Hassanein 2021). These plants have antibacterial, antiviral, anti-inflammatory properties and also act as modulators of the immune system. The use of natural immune boosters might be an effective approach to combat COVID-19 disease (Khabour and Hassanein 2021; Tamboli et al. 2021).

The Ministry of AYUSH has set up task force to devise and plan research at various levels like clinical, preclinical and observational etc. for COVID-19 disease management. WHO is also focussing on innovations all around the world including traditional medicines, repositioning drugs i.e. to identify new therapeutic use for available and approved drugs as well to develop new therapies for potential treatments for COVID-19 (Kotecha 2021; WHO 2021, https://www.afro.who.int/news/who-supports-scientifically-proven-traditional-medicine).

The present chapter highlights different natural immunity boosting medicinal plants, herbs and spices as well as their potential role in developing appropriate drugs and thus curing and contributing in prevention of the spread of COVID-19 pandemic.

2. Immunity: The Biggest Weapon

Immunity acts as one of the most important shields to fight against coronavirus. Several studies have suggested that people with strong immunity are able to fight the virus more efficiently. Immune System consists of different kinds of cells namely lymphocytes (T cells, B cells and natural killer cells), macrophages and neutrophils. The chief proteins of immune system include cytokines and antibodies. Human immune memory system consists of antibodies, memory B cells, memory CD8+ T cells, and memory CD4+ T cells. A spike in all four of them is observed when a person is infected with SARS-CoV-2 virus and the information was retained even after 6 months of recovery (Dan et al. 2021). Other reports also proposed that the exposure to SARS-CoV-2 virus can result in the virus-specific T cell responses in both symptomatic and asymptomatic patients (Gallais et al. 2021). However, in asymptomatic patients an increased production of IFN-γ and IL-2 along with the excretion of IL-10 and proinflammatory cytokines was observed whereas an inconsistent secretion of inflammatory cytokines was observed in symptomatic individuals (Le Bert et al. 2021).

2.1 Types of immunity

Immunity is the capability to fight against pathogen and the disease caused by them (https://www.merriam-webster.com/dictionary/immunity). Immune system is subdivided into two categories namely innate and adaptive immune system. The first line of protection against pathogens is the innate immunity while adaptive immunity also called as specific or acquired immunity is the second line of protection. Another classification of immune responses includes natural and artificial immunity. When immune responses are generated due to infection caused by known pathogen, it is termed as 'Natural Immunity'; whereas, if the immune responses are generated by injecting attenuated form of pathogens (vaccination), it is called as 'Artificial Immunity' or acquired immunity or adaptive immunity (Ariful Kabir and Tanimoto 2021).

2.1.1 Innate immunity

Frequent exposure to viruses and other infections leads to innate immunity. It consists of complement system, nonspecific phagocytic and cytolytic leukocytes, interferons and cytokines. Innate immune system is not responsible for specific and enduring responses (Weber 2021). Type-1 interferons (IFN) are signalling molecules produced after viral infection and they further activate the neighbouring cells and turn them recalcitrant to infection (Huang et al. 2019). Innate immunity causes either tissue inflammation or phagocytosis and results in direct excretion of biologically active signals or indirectly stimulates immune responses (adaptive) by secretion of antigen presenting cells (APC) (Sun et al. 2020). Toll-like receptors are also a part of innate immune responses and are used in recognizing molecular patterns of pathogens (Huang et al. 2021). The responses of adaptive immunity are regulated by innate immune system. The SARS-CoV2 virus has the capability to escape the innate immune system and thus can replicate and produce multiple copies in humans. It results in hyper inflammation and cytokine storm (Felsenstein et al. 2020).

2.1.2 Adaptive Immunity

Sensing of pathogens and their elimination is an important function performed by innate immune system. However, the adaptive immunity provides higher efficiency in recognizing self and non-self-antigens. Function of adaptive immunity comprises of mobile T and B lymphocytes and is responsible for pathogen specific responses (Bonilla and Oettgen 2010). Adaptive immune system is dependent on cytokines. IFN-γ (a type of cytokine) is involved in both adaptive and immune responses. IFN-γ is also responsible for activation of NK cells, dendritic cells and differentiation of cytotoxic T cells and B cells (Prokopiev 2021).

2.1.3 Herd Immunity

Herd immunity addresses the immunity present at population level, where sufficient individuals are immune to the pathogen causing a disease. Herd immunity depends on various factors associated with disease like its mode of transmission, infection and exposure of immune system of the individuals to disease. If herd immunity fails to establish then it is usually due to loss of acquired maternal immunity (Smith 2019).

The larger proportion of population gains immunity against the pathogen by either vaccination or recovering from infection. This helps in preventing the infection at larger scales (Fontanet and Cauchemez 2020). Since human population is heterogenous, there is a possibility that herd immunity can be achieved but at the cost of large proportion of loss of lives (Britton et al. 2020).

2.2 Immune system response against SARS-CoV-2

Many researchers are presently exploring the possible response of immune system to SARS-CoV-2 viral infection. Important drug targets which help in viral replication or in signalling pathways are 3-chymotrypsin-like protease ($3CL^{pro}$; control viral replication), papain-like protease (PL^{pro}; facilitate viral spread), S protein (viral spike glycoprotein; important for attachment of virus), RdRp (RNA-dependent RNA polymerase; vital enzyme for viral RNA replication), angiotensin-converting enzyme 2 (ACE2; receptor for entry of virus) and transmembrane protease serine 2 (TMPRSS2; responsible for priming viral S glycoprotein).

The entry receptor for SARS-CoV2 in human is ACE2 (angiotensin-converting enzyme 2). The C terminal of the viral spike (S) protein shows higher affinity for the human ACE2 receptor (Wang et al. 2020). The attachment of the virus to the ACE2 receptor is the probable cause of unexpected spread of COVID-19 (Ortega et al. 2020).

The 3-chymotrypsin-like protease ($3CL^{pro}$) is responsible for the virus replication (Gyebi et al. 2021) whereas RNA-dependent RNA polymerase (RdRp) also plays a crucial part in completing the life cycle of the virus (Molavi et al. 2021). Papain-like cysteine protease (PL^{pro}) was reported to play an important role in virus development and impairment of host inflammation, and negatively control antiviral immune responses (Huang et al. 2021)

The major protease enzyme M^{pro} and papain-like protease of the virus recognizes specific cleavage sites and are also involved in replication of the virus (Gurung et al. 2020).

3. Ayurveda and Herbal Medicines

Ayurveda is the ancient science of Indian medicine and it takes advantage of using phytocompounds for therapeutics. It uses plants and deals with the root cause of the health problems. Herbal medicines have existed since ancient times in countries like China, Greece, Egypt and India and still continue to do so. In India, about 15,000 plants are reported to be as medicinal herbs. Indian Ayurvedic culture uses the concept of polyherbalism i.e., use of many herbs to treat a disease. The herbal medicines have antimicrobial properties and have potential to combat infections caused by pathogens. Such herbs can also be included in a day-to-day diet for building immunity and consequently prevention of diseases (Tambekar and Dahikar 2011). Ayurvedic medicines prepared form multiple herbs can treat chronic ailments such as cancer, diabetes, arthritis and asthma. These herbal medicines are especially useful in rural areas all over the world in underdeveloped countries because they have minimal side effects and are cost-effective. Ayurvedic medicines are now backed with recent researches. In a recent study, it was revealed that the patients tested positive for COVID-19, when treated with ayurvedic medicine showed substantial decrease in their symptoms as compared to combined treatment of ayurvedic and allopathic medicines (Balkrishna et al. 2021a).

4. Plants with Immunomodulatory and Antiviral Potential

Severity of on-going coronavirus pandemic has compelled us to take extra precautionary measures to keep ourselves safe from the viral infection. Therefore there is need to strengthen our immune system. Plants can also be used as antiviral agents for counteracting the viral infections. Many medicinal plants have been reported to possess anti-viral bioactivities and also modulate the immune system (Table 1). Some of the important plants that can be applied to boost immunity especially against SARS-CoV2 virus are discussed.

4.1 *Allium sativum*

Allium sativum commonly called garlic belongs to the family Amaryllidaceae. Bulb (cloves), flowers and leaves are used in preparation of medicine and for culinary purposes. The major phytoconstituent of garlic includes organosulphur compounds (more than 33) like allin, allicin, ajoene etc. and these phytochemicals are accountable for its pungent nature (Zhang et al. 2020). It possesses different pharmacological properties like antifungal, antibacterial, anticancerous, anti-inflammatory, immunomodulatory, antioxidant, anti-diabetic, neuroprotective, antihypertensive, anticoagulant etc. (Bisen and Emerald 2016). Garlic can be used in treatment of bronchitis, diabetes, cardiovascular diseases, cancer, liver disorders, toothache, cough, indigestion and other infectious diseases (Bayan et al. 2014). It has also been reported to modulate the immune system by activating macrophages, NK cells, eosinophils etc. It also regulates cytokine secretion and production of immunoglobins (Arreola et al. 2015). Many researchers have also stated the antiviral activities of garlic against animal, human and plant viral infections. Pre-clinical data analyses showed that garlic combats the viral infection by blocking the entry of the virus, foiling viral replication and by down regulating the signal transduction pathway. Rouf et al. (2020) have hypothesised that garlic can be used as a preventive measure for COVID-19 as it can boost the immune system by decreasing the excretion of inflammatory cytokines and leptin. Molecular docking studies showed that organosulphur compounds present in garlic can interact with ACE2 and main protease PDB6LU7 proteins (Thuy et al. 2020) Using *in silico* approach, Pandey et al. (2021b) also proposed that garlic can be used as an effective inhibitor of SARS-CoV main protease.

4.2 Aloe vera

Aloe belongs to family Asphodelaceae. The plant holds great value in Ayurveda, Homeopathic and Allopathic medicines. It is widely distributed and its gel which is of great importance has several compounds in its latex (Sharma 2021). The main phytoconstituents are anthraquinones, chromones, naphthalene derivatives, coumarins, benzofurans, phenyl pyrans and pyrones (Abouelela et al. 2021). Emodin a phenolic compound found in plant is identified for its anti-neoplastic, anti-inflammatory, antidiabetic, and anti-angiogenic properties. The compound acemannan can heal oral-dental problems, cardiovascular diseases, oncology and wounds. The plant is also useful for colon, liver, duodenum, skin, pancreas, lungs and kidney (Puia et al. 2021).

The reports suggested that the compounds of *Aloe* showed affinity for the main protease of the SARS-CoV-2 virus (Mpiana et al. 2020). Molecular docking analysis showed that 2′-oxo-2′-O-(3,4-dihydroxy-*E*-cinnamoyl)-(2′*R*)-aloesinol-7-methylether, 2′-oxo-2′-O-(4-hydroxy-3-methoxy-(*E*)-cinnamoyl)-(2′*R*)-aloesinol-7-methylether and rutin showed maximum affinity for the main protease of the virus, 2″-O-(4-10 methoxycinnamoyl)-(*S*)-aloesinol, rabaichromone and aloeribide showed maximum binding affinity for spike glycoprotein and rabaichromone (Abouelela et al. 2021).

4.3 *Azadirachta* sp.

Azadirachta commonly known as Neem belongs to family Meliaceae and is used to cure many ailments such as dental and digestion problems, malaria, skin diseases, headache, heat burn, fever, cough, diarrhoea and stimulates appetite. The tree is also referred as "the wonder tree" or "nature's drug store" and is part of Ayurveda and Siddha medicines. The plant also has insecticidal properties and is widely used in cosmetic industry (Sujarwo et al. 2016). Leaves, bark, flowers, roots, fruits, and seeds are different parts of neem plant which can be used for medicinal purposes. The plant exhibits several phytocompounds such as azadirachtins, azadirachtol (a tetranortriterpernoid), 2,3′-dehydrosalanol gedunin, nimbin, azadironolide, isoazadironolide etc. (Atawodi and Atawodi 2009). Phytochemicals present in neem confers antiallergic, antidermatic, antiviral, antimicrobial, anti-inflammatory and anticancerous properties (Ogbuewu et al. 2011).

The plant has antiviral activities against poliovirus type 1, dengue virus type 2, avian influenza virus and many other viruses. It increases both humoral and cell mediated immune system (Roy and Bhattacharyya 2020). Docking and simulation methods showed that several compounds from neem binds to the membrane and envelope proteins of SARS-CoV-2 virus and inhibit their function (Borkotoky and Banerjee 2020). Different phytocompounds of neem (epoxyazadiradione and gedunin) also showed higher affinity for SARS-CoV-2 main protease (6Y84) required for its replication (Kumar 2020). Molecular docking studies also showed highest binding of desacetylgedunin (DCG; a compound present in seeds of neem) with Papain like protease (PL^{pro}) of the SARS-CoV-2 (Baildya et al. 2021).

4.4 *Curcuma longa*

Curcuma longa (commonly known as turmeric) belongs to family Zingiberaceae and is considered as the 'golden spice' or the 'Indian saffron'. Turmeric powder is the dried and ground rhizome of the *Curcuma longa* and is used for flavouring and in traditional medicines. Many phytochemicals have been extracted from turmeric; the main compounds are turmerone present in its volatile oil and curcuminoids (curcumin, dihydrocurcumin, demethoxycurcumin etc.) giving it the specific color (Ruby et al. 1995). Turmeric exhibits anti-inflammatory, anti-diabetic, anti-allergic, antioxidant, antiseptic, antitumor activities etc. (Yadav and Tarun 2017). It is used for treatment of various ailments like asthma, arthritis, diabetes, cancer, cardiovascular diseases, Alzheimer, digestive disorders etc. (Aggarwal et al. 2007; Prasad and Aggarwal 2011).

Turmeric also exhibits broad spectrum antiviral activities against Zika virus, human immunodeficiency virus (HIV), HSV-2 (Herpes Simplex Virus-2), dengue virus, influenza A virus etc. (Jennings and Parks 2020). Wen et al. (2007) reported that curcumin can prevent replication of SARS-CoV. Based on former studies, curcumin has been hypothesised to regulate SARS-CoV-2 entry, replication and patho-physiological consequences (Soni et al. 2020). Curcumin also modulates the immune system by stimulating T cells, B cells, dendritic cells, macrophages and by reducing the secretion of inflammatory cytokines, NF-κB, and chemokines. At low levels, it increases the antibody responses (Babaei et al. 2020). Molecular docking studies also indicated the interaction of curcumin to viral spike protein and human ACE2 receptor sites (Das et al. 2021). All these properties make curcumin a promising prophylactic candidate effective against COVID-19 (Babaei et al. 2020; Thimmulappa et al. 2021).

4.5 *Phyllanthus* sp.

Phyllanthus emblica commonly called as Indian gooseberry or amla belonging to the family Phyllanthaceae is an important medicinal plant. Its fruits are rich source of vitamin C and all parts of plant can be used for therapeutic purposes. It contains many bioactive phytocompounds like phenols, alkaloids, tannins, ellagic acid, gallic acid, leutolin, chebulinic acid etc. (Gaire and Subedi 2014). It has broad spectrum of therapeutic activities namely hepatoprotective, anticarcinogenic, antimicrobial, antipyretic, anti-inflammatory, antioxidant, antidiabetic, antianemia etc. (Thilakchand et al. 2013). In Ayruveda, it is used as an immunodilator, increases digestion, for constipation, alleviating asthma, fever, cough, improving memory, considered good for eyes etc. (Bhat et al. 2015).

P. emblica exhibits immunostimulatory potential by increasing splenocyte proliferation and NK cell activity (Huabprasert et al. 2012). Other species of *Phyllanthus* have been shown to confer immune stimulating properties (Jantan et al. 2019). Muthulakshmi et al. (2016) observed better antibody responses both primary as well as secondary in *Oreochromis mossambicus* (fish) treated with aqueous extract of *P. niruri*. *Phyllanthus* species have also been recognized to exhibit anti-viral activities. *P. niruri* has been found to be effective against HIV and hepatitis B virus (Bagalkotkar et al. 2006). Anti-HSV activity of *P. emblica* has also been documented (Xiang et al. 2011). *P. emblica* has been shown to inhibit HIV reverse transcriptase (Estari et al. 2012). *In silico* docking investigations revealed that phytochemicals present in *P. amarus* and *P. emblica* can be used as drug for counteracting SARS-CoV-2 infection (Pandey et al. 2021a).

4.6 *Ocimum* sp.

Ocimum, commonly called as tulsi or Holy basil, belongs to the family Lamiaceae. The plant is commonly used in Ayurveda and is grown in old world tropical region. The plant is identified to possess medicinal properties and holds religious values. Active compound eugenol is mainly responsible for its benefits. It contains several bioactive compounds that help to combat diseases and deficiencies. All parts of *O. sanctum* are reported to be useful and has chemical compound named eugenol (1-hydroxy-2-methoxy-4-allylbenzene). It exhibits antifertility, anticancer, anti-inflammatory, anti-diabetic, antimicrobial, hepatoprotective, palliative and cardioprotective actions properties (Prakash and Gupta 2005). It aids in fighting against cancer, bronchitis, diabetes mellitus, hypertension, liver injuries and gastric ulcers. It also regulates cellular and humoral immunity. The plant possesses beneficial functions due to presence of eugenol, carvacrol, ursolic acid, β-caryophyllene and rosmarinic acid (Kamyab and Eshraghian 2013). The presence of terpenoids in the plant results in reducing virus copies. This effect can last up to 3 days of consumption (Ghoke et al. 2018). Orientin and vicenin-1 are two types of flavonoids present in plant that bind to the amino acid residue of the SARS-CoV-2 virus essential for its functioning. Flavonoids present in tulsi plant are capable of docking with viral S proteins, RdRP and the main protease (Baruah et al. 2021). *In silico* analysis showed the binding of phytochemical orientin to the Glucose Regulating Protein 78 (GRP78 protein), an important region where virus can bind to gain entry into the host (Bhowmik et al. 2021). In another report, bioinformatics studies revealed that flavonoid luteolin-7-O-glucuronide and polyphenolic chlorogenic acid binds with the Cys145 of viral protease and can permanently inhibit its activity (Mohapatra et al. 2020).

4.7 *Tinospora cordifolia*

Tinospora cordifolia, commonly called as giloy or guduchi, belongs to the family Menispermaceae. It is an essential herbal medicinal plant used for treatment of different diseases. Important bioactive compounds isolated from *Tinospora* roots, stem and whole plant are alkaloids, phenolic compounds, glycosides, terpenoids (diterpenoids, sesquiterpenoids), steroids etc. (Reddy and Reddy 2015). It possesses many therapeutic properties ranging from antidiabetic, anti-inflammatory, antimicrobial, antipyretic, hepatoprotective, immunomodulatory etc. (Nair et al. 2019). It can be used for treatment of heart diseases, fever, typhoid, malaria, leprosy, diabetes, dysentery, helmenthiasis, jaundice, skin related ailments, improving memory etc. (Reddy and Reddy 2015).

Different phytoconstituents of *Tinospora* have been reported to confer immunomodulatory properties (Sachan et al. 2019). Upadhyaya et al. (2011) showed that aqueous extract of *Tinospora* can activate macrophages and stimulate the excretion of nitric oxide and cytokines. *T. cordifolia* has also been indicated to modulate immune system via toll receptor like pathway (Sachan et al. 2019). Antiviral properties of *Tinospora* have been well documented (Pruthvish and Gopinatha 2018). It is shown to be effective against HIV virus (Akhtar 2010), Herpes Simplex Virus (HSV; Pruthvish and Gopinatha 2018) and bursal disease virus (Sachan et al. 2019). *In silico* analysis via molecular docking studies showed the phytochemical berberine of *T. cordifolia* can be used as potential drug to inhibit SARS-CoV-2 (Chowdhury 2020). Krupanidhi et al. (2020) also identified anti-SARS-CoV-2 lead molecules from *T. cordifolia* using 3CL main protease as the ligand. Rakib et al. (2020) examined the interaction of bioactive phytochemicals of *T. cordifolia* with main protease enzyme, M^{pro} of SARS-CoV-2 via docking studies. Balkrishna et al. (2021b) showed that pro-inflammatory alterations and tissue damage caused by SARS-CoV-2 in zebra fish can be reversed on treatment with Giloy ghanvati.

4.8 *Withania somnifera*

Withania somnifera, normally known as Ashwagandha or Indian winter cherry, is a herbaceous plant that belongs to family Solanaceae. The most important plant parts are leaves and roots. The main phytoconstituents are withanolides (steroidal lactones). These constitute a group of steroidal lactone triterpenoids and mainly includes withaferin A, withanolide (A-Y, WS-1, IV and V), withanone, withasomniferin A, somnirol, etc. and polyphenols like catechin, p-coumaric acid, syringic acid, etc.

It exhibits various pharmaceutical properties and thus, is widely recommended in auyrvedic treatments (antimalarial, antidiabetic, anti-inflammatory, antimicrobial, antibacterial, immunomodulator, antioxidant, antihypertensive, reduces stress and anxiety, anti-covid 19 activities, etc.). It suppresses pro-inflammatory cytokines, and also plays role in organ protection (nervous system, liver, heart, kidney and lung). There are scientific data which supports its activity in maintaining of immune homeostasis (inflammatory and infectious diseases). It can also be used for treatment of tumors, insomnia, dyspnea, emaciation and traditionally has been in use as energy and immune boosters (Saggam et al. 2021).

There are various *in silico*, *in vivo*, *in vitro*, and clinical data available which suggest its usage in treatment of COVID-19 infection. The antiviral property of this plant might interfere with the viral entry into host cell and its subsequent life cycle. Molecular docking studies have predicted the probable role of withanoside V and somniferin as inhibitors of SARS-CoV-2 M^{pro}. Studies have shown that withaferin A and withanone most likely binds to the viral spike (S-) protein of SARS-CoV-2. They block the main protease M^{pro} and TMPRSS2 and thus block the ability of spike proteins to fuse with host cell receptor-ACE-2 and subsequently impede with the viral entry and its replication. This result was further strengthened by an *in vitro* study that revealed that withanone decreases the TMPRSS2 mRNA level in MCF7 cells. Withanolide B and withacoagin are also found to obstruct the RdRp and enzyme viral spike protein. Molecular docking studies have further revealed that withaferin A inhibits the host cell receptor-GRP78. Moreover, its level was found to increase in COVID-19 infected patients (Kumar et al. 2020; Shree et al. 2020; Straughn and Kakar 2020). Thus, together these studies indicate that it holds potential role in treatment of COVID-19 disease management.

4.9 *Zingiber officinalis*

Zingiber officinalis commonly called as ginger is a member of family Zingiberaceae. The rhizome of ginger is reported to be used for medicinal purposes and as a spice. Phytochemical constituents of ginger have been categorised into volatile and non-volatile compounds. Distinct flavour and aroma of ginger is due to the presence of volatile compounds namely monoterpenoid hydrocarbons and sesquiterpenes. Non-volatile compounds consist of shogaols, zingerone, paradols and gingerols (Jolad et al. 2004). It possesses different therapeutic properties like anti-inflammatory, anticarcinogenic, antioxidant, antimicrobial, antifungal, antiviral immunomodulatory etc. (Al-Awwadi 2017). It is recommended for curing cough, sore throat, asthma, nausea, balancing blood circulation, indigestion, increasing appetite, arthritis, etc. (Al-Awwadi 2017; Dissanayake et al. 2020).

Many studies have reported the antiviral activity of ginger (Ahmed et al. 2017). Lyophilised extract of ginger repressed the replication of Hepatitis C virus (Abd El-Wahab et al. 2009). By analysing plaque reduction assays on respiratory mucosal cell lines, San Chang et al. (2013) showed that fresh ginger extract inhibited the internalization and attachment of human respiratory syncytial virus. They concluded that higher levels of ginger could induce secretion of IFN-β (interferon) from mucosal cells for combating the viral infection (San Chang et al. 2013). Aqueous ginger extract has been shown to increase IgM levels which might results in robust antibody response for counteracting viral infections (Mahassni and Bukhari 2019). Aqueous plant extract of ginger rhizome displayed significant anti-chikungunya activity (Kaushik et al. 2020). Molecular docking studies have revealed that phytoconstituents of ginger can interact with viral spike proteins and host ACE-2 receptors for averting the spread of virus (Haridas et al. 2021). *In silico* studies also indicated that phytochemical shogaol can be used as a drug for prevention of COVID-19 (Afrida et al. 2021). Prasanth et al. (2020) also showed that phytoconstituents of *Zingiber* can interact with SARS CoV-2 main protease which is important for the spread of virus.

Table1: Different medicinal plants that can be used as antiviral agents against COVID-19

S. No.	Plant species (common name)	Plant part used	Phytochemicals present	Pharmacological properties	References
1.	*Allium cepa* (Onion)	Bulb	Flavonoids, phytosterols, saponins	Antimicrobial, antioxidant, palliative, anti-inflammatory, antidiabetic	Marrelli et al. (2018); Teshika et al. (2018)
2.	*Alpinia galanga* (Galangal)	Rhizome	Alpinin, gallic acid, galangin, β-sitosterol, zerumbone, kampferide	Anti-inflammatory, aphrodisiac, antipyretic, antidiabetic, hepatoprotective	Kaushik et al. (2011)
3.	*Alstonia scholaris* (Devil's tree)	Leaves, stem, bark	Lupeol, betulin, betulinic acid, oleanolic acid, ursolic acid	Aphrodisiac, anti-choleric, anti-dysentery, antipyretic, anti-cancerous	Khyade et al. (2014); Wang et al. (2016)
4.	*Andrographis paniculate* (Bitterweed)	All parts	Ent-labdane diterpenoids, quinic acids, xanthones, noriridoids	Antioxidant, anti-dysentry, cardioprotective	Hossain et al. (2014)
5.	*Cinnamomum* (Cinnamon)	Bark	Cinnamaldehyde, cinnamic acid	Antibacterial, antidiabetic, antioxidant, anti-inflammatory, palliative, anti-tumor	Dorri et al. (2018)
6.	*Cuminum cyminum* (Cumin)	Seeds	Terpenes, phenols, flavonoids	Hepatopotective, anti-inflammatory, antidiabetic, antitumor	Srinivasan (2018)
7.	*Daucus carota* (Wild carrot)	Root	Phenolics, carotenoids, polyacetylenes	Antioxidant, anti-inflammatory, anti-tumour, cardioprotective	Ahmad et al. (2019)
8.	*Elettaria cardamom* (Cardamom)	Fruit	1, 8-cineole, catechin, kaempferol, lutein, myricetin, quercetin	Antioxidant, antidiabetic, antimicrobial, antitumor, insecticidal, cardioprotective anti-diarrhoea	Ashokkumar et al. (2020)

9.	*Moringa oleifera* (Horseradish tree/drumstick tree)	Leaves, bark, seeds, roots, flowers, plant sap	Essential amino acids, isothiocyanate, vitamin A	Antihypertensive, anti-inflammatory, hepatoprotective, antioxidant, antitumor, antidiabetic	Stohs and Hartman (2015); Kou et al. (2018)
10.	*Piper longum* (Indian Long)	Fruits	Alkaloids, essential oils, flavonoids, steroids	Anti-inflammatory, anti-microbial, antitumor, anti-obesity, antipyretic, cardioprotective, anti-diarrhoea	Subramaniam et al. (2021)
11.	*Piper nigrum* (Black Pepper)	Fruits	Pinene, phellandrene, thujene, bisabolene, caryophyllene, limonene, sabinene	Antioxidant, anti-obesity, anti-inflammatory, antitumor, antidiabetic, antibacterial gastroprotective, insecticidal	Ashokkumar et al. (2021)
12.	*Syzigum aromaticum* (Clove)	Dried flower buds, oil	β-caryophyllene, eugenyl acetate, eugenol, terpenes	Palliative, antioxidant, antitumor, antibacterial, anti-inflammatory, antiviral, anti-pathogenic	Batiha et al. (2020)
13.	*Terminalia bellirica* (Baheda)	Fruits	Termilignan, gallic acid, arjunolic acid, ellagic acid, bellericanin galloyl, corilagin, chebulagic acid	Antioxidant, antimicrobial, immunomodulatory, hepatoprotective, anticancer, antifungal, anti-inflammatory, nephroprotective	Gupta et al. (2020)
14.	*Trigonella foenum-graecum* (Fenugreek)	Leaves, stem and seeds	Hederagenin glycoside, trigonelline, coumarin, nicotinic acid	Antidiabetic, immunomodulating, anti-oxidant, anti-inflammatory, antitumor	Nifras et al. (2021)

5. Conclusion

In order to overcome the deadly effects of COVID-19 disease, there is an urgent need for discovery of newer remedial drugs for curing as well as preventing the viral infection. Medicinal plants have a wide scope and have been used as pharmaceutical agents against a variety of viruses. Different studies have indicated that medicinal plants can be used as potential candidates for developing anti-SARS-CoV-2 drugs. Phytoconstituents of most of the plants have been shown to interact with the main protease of SARS-CoV-2 (Figure 1). *In silico* analyses have also given promising leads but direct evidence is required by performing wet laboratory experiments. Therefore, more research is required for untangling the role of phytochemicals in controlling, curing and/or preventing viral infection.

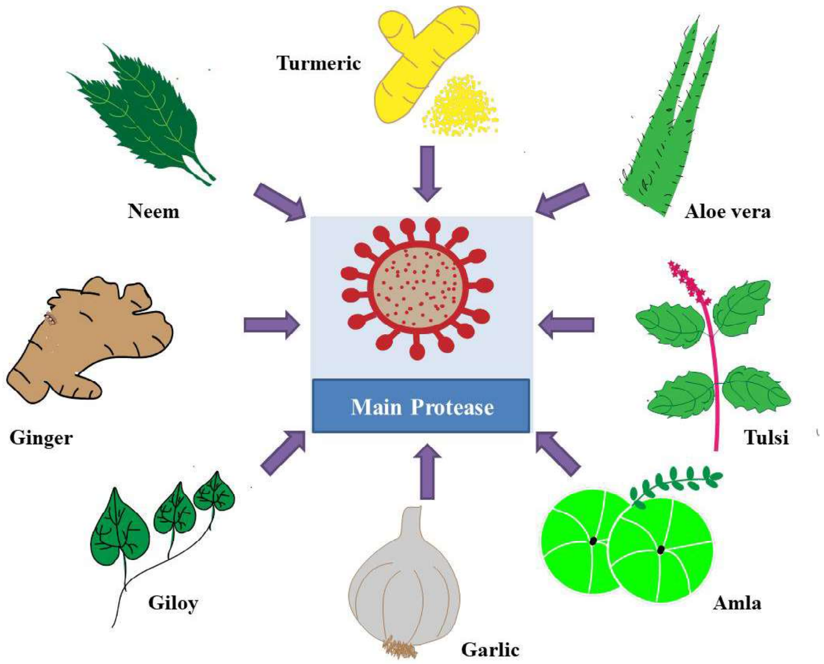

Figure 1: Some of the medicinal plants that can be used to target SARS-CoV-2 main protease responsible for its spread.

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