Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Herbal Medicine 32 (2022) 100501

Contents lists available at ScienceDirect

Journal of Herbal Medicine

journal homepage: www.elsevier.com/locate/hermed

Review article

Herbal plants as immunity modulators against COVID-19: A primary preventive measure during home quarantine

Kuntal Das *

Dept of Pharmacognosy and Natural Product Chemistry, Krupanidhi College of Pharmacy #12/1, Chikkabelandur, Carmelaram Post, Varthur Hobli, Bangalore, 560035, India

ARTICLE INFO

Keywords:
COVID-19
Immunity
Herbals
Medicine
SARS
Traditional application

ABSTRACT

The novel coronavirus or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a deadly virus which has spread globally and claimed millions of lives. This novel virus transmits mainly through droplets and close human contact. It's impact in different countries varies depending on geographical location, climatic conditions, food habits, and cultural activities. Several precautionary measures, as well as many medicines, are applied in different combinations to limit the spread of infection. This results in a preliminary relief of people infected in the first stage of infection. An alternative approach has been introduced which proposes natural herbs, which have minimal or no side effects, and improve overall immunity. Some essential herbs with their immunomodulatory effects are mentioned in this article along with suggestions for improved immunity and protection.

1. Introduction

The world is enduring a difficult situation during which millions of people are dealing with an infectious outbreak from the novel Coronavirus. Initially, the virus infects the respiratory tract of the human body. The disease is known as an acute and severe respiratory syndrome. The first reported case of respiratory illness was in Wuhan City, Hubei Province, China (Lu et al., 2020) and this was formally announced to the World Health Organization (WHO) on 31st December 2019. Subsequently, on 30th January 2020, the WHO declared the COVID-19 an outbreak and, a global health emergency for the first time and on March 11, 2020, the WHO further declared COVID-19 as a global pandemic (WHO, 2020).

The virus is made up of nucleoprotein, belongs to Betacoronavirus (betaCoV) and possibly originated from bats and rodents (Chan et al., 2013). The virus is spherical or pleomorphic in shape and contains single-stranded RNA in a capsid composed with protein matrix, and has been isolated from animal species (Perlman and Netland, 2009). The outer cover or envelope contains club-shaped glycoprotein projections. These are crown like in appearance under an electron microscope due to the presence of spike glycoproteins on the shell. Commonly, the virus comes in contact with the uncoated host cell and then the genome is transcribed and further translated. Viral transcription takes place in the cytoplasm, and viral replication takes place using both continuous and discontinuous RNA synthesis. The coronavirus replicates via a range of RNA processing enzymes such as sequence-specific endoribonuclease, 3′-to-5′ exoribonuclease, 2′-O-ribose methyltransferase, ADP ribose 1′-phosphatase and, in a subset of group 2 coronavirus, cyclic phosphodiesterase activities which are absent from other RNA viruses (Ziebuhr, 2005; Almazan et al., 2006). The coronavirus has three to four viral proteins in the membrane which are known as conserved genes which are ORF1ab, spike, envelope, membrane and nucleocapsid but among them, membrane glycoprotein (M) is found the most abundantly (Haan et al., 1998). Others such as spike (S), envelope (E), and nucleocapsid (N) proteins are encoded by open reading frames (ORFs) 10, 11 on the one-third of the genome near the 3′-terminus. The spike protein (S) as a type I membrane glycoprotein constitutes the peplomers (Perlman and Netland, 2009). The novel virus is very quick to propagate infection, which immediately causes virulence in humans. It binds to ACE2 (the angiotensin-converting enzyme 2) via its spike and infects the host cells through a mechanism which depends on cellular proteases, human airway trypsin-like protease (HAT), cathepsins and transmembrane protease serine 2 (TMPRSS2) (Bertram et al., 2011). It spreads rapidly to other humans who are in close contact with an infected individual through respiratory droplets or aerosols dispersed through, coughing, and sneezing. The droplets penetrate the host human body especially into the lungs via inhalation through the nose or mouth (Riou and Althaus, 2020; Parry, 2020). The novel virus is active on

* Corresponding author.
E-mail address: drkkdsd@gmail.com.

https://doi.org/10.1016/j.hermed.2021.100501
Received 28 April 2020; Received in revised form 21 June 2021; Accepted 3 August 2021
Available online 5 August 2021

surfaces for around 9 h to several days, hence the chances of infection spread is high. The infection also spreads through various household products, such as plastic, stainless steel, copper, iron items where the virus stays in active mode for up to 4–5 hours. The virus is more active until 40 ° C and slowly loses activity over 56 ° C (Chin et al., 2020). The earlier research reported that finger rings made up of gold, currency notes, silver, or any other metals, are more conductive to the spread of contaminants which people usually neglect when viruses stay active a longer time in the environment.

Infection with SARS-CoV-2 is roughly divided into three stages namely, stage-1, an asymptomatic incubation period with or without detectable COVID virus; stage-2, non-severe symptomatic period with the presence of COVID virus; and stage-3, severe respiratory symptomatic stage with extreme COVID viral load (Wang et al., 2020). Hence, major degradation of the intestine and kidney occurs as the virus propagates throughout the host human body. The impaired cells trigger intrinsic inflammation of the lungs by pro-inflammatory macrophages and granulocytes cause severe respiratory disorders which may become life threatening. This is known as the acute respiratory distress syndrome (ARDS) arising from a rapid onset of widespread inflammation in the lungs, which results in fatality (Xu et al., 2020). Thus, it initially involves the immune defense based protective phase where a boost is needed for immune responses, and then an inflammation-driven damaging phase where it is suppressed. The novel COVID-19 virus is sensitive to heat and ultraviolet rays. In addition, ether (75 %), ethanol, chlorine-containing disinfectant, peroxyacetic acid, and chloroform are effectively used for inactivation of the virus (Cascella et al., 2020). Hence some chemicals mitigate COVID virus exposure.

Other preventive measures include hand washing with soap or alcohol-based sanitizers, maintaining proper social distance, and the

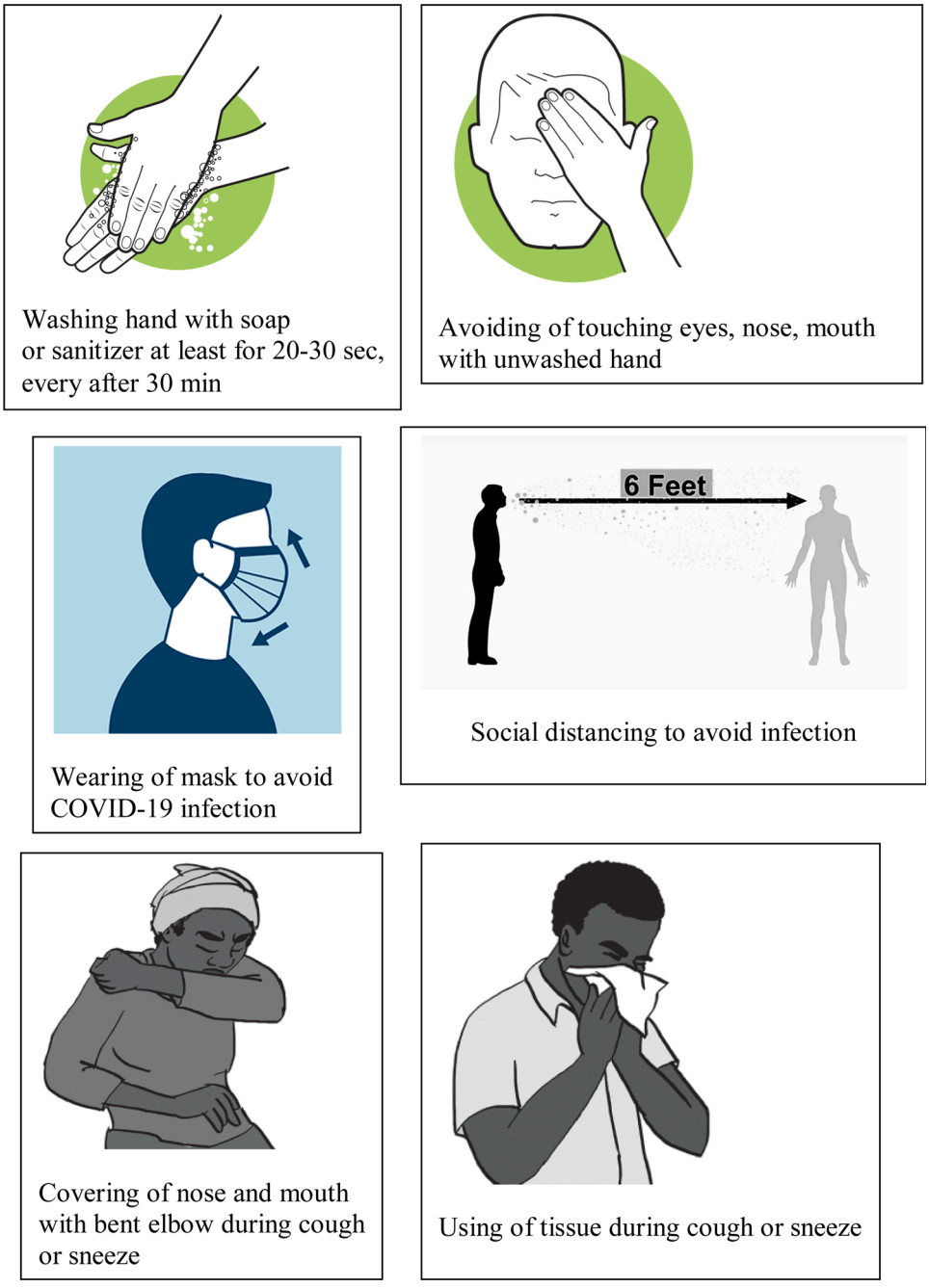

Fig. 1. Preventative measures against COVID-19.

wearing of masks. It is also advisable to avoid touching the eyes, nose and mouth, proper mask wearing without gaps between face and the mask, covering the nose and mouth with a bent elbow or tissue during coughing or sneezing, staying home, if a person has a fever, cough, or breathing problems (Fig. 1).

COVID 19 spreads by droplets and can stay in the air for 3−8 hours and cannot be measured. Drastically it is capable of infecting a large number of people within few hours. Staying at home is the safest choice to prevent infection, as well as isolating sick people away from others so that they don't infect others. This is known as home quarantine and it is the practice of confining a person and restricting movement for a limited time span (14–21 days). The governments of all countries use it to avoid the spread of this deadly novel corona disease.

It is estimated that 194 million people were infected with COVID-19 with the worldwide death count estimated at 4.16 million as of 15th July 2021. Deaths were highest in the United States (0.61 million), followed by Brazil (0.55 million), and India (0.421 million).

There are many possible medicines which have been effective for treating the virus-based symptoms but no comprehensive medicines. The antiviral drug, called favipiravir or Avigan, is an approved drug which used in Japan to treat influenza as well COVID-19. Chloroquine and hydroxychloroquine, approved by the U.S. Food and Drug Administration (FDA) for the treatment of malaria, is used for COVID-19 in various countries. Remdesivir, approved by FDA to treat COVID-19. Antiviral drug Kaletra, a combination of lopinavir and ritonavir, is used to treat COVID-19 in China. A mix of HIV, swine flu, and Malaria, drugs and also anti-HIV drugs, Lopinavir and Ritonavir, have been accepted by Indian Council of Medical Research, India, to treat COVID-19 (Jin et al., 2020). Recently, many multinational companies from India, namely Sanofi, Pfizer & BioNtech, Johnson & Johnson, Vaccitech, Novavax, Vaxart, Heat Biologics Inc. and others, prepared a COVID-19 vaccine and there are now several in use. The first mass vaccination programme started in early December 2020. The Pfizer/BioNtech Comirnaty vaccine was listed for WHO Emergency Use Listing (EUL) on 31 December 2020. The SII/Covishield and AstraZeneca/AZD1222 vaccines were given for EUL on 16th February 2021, and were developed by AstraZeneca/Oxford and manufactured by the State Institute of India and SK Bio, respectively. India's indigenous Covid-91 vaccine, Covaxin was developed by Bharat Biotech in collaboration with the Indian Council of Medical Research (ICMR) - National Institute of Virology (NIV) in June of 2021. The Covaxin has demonstrated 77.8 % vaccine efficacy against symptomatic COVID-19 infections. It is a 2-dose vaccination regimen given 28 days apart. The Janssen/Ad26.COV 2.S was developed by Johnson & Johnson, and was listed for EUL on 12 March 2021. The Moderna COVID-19 vaccine (mRNA 1273) was listed for EUL on 30 April 2021 and the Sinopharm COVID-19 vaccine was listed for EUL on 7 May 2021. The Sinopharm vaccine is produced by Beijing Bio-Institute of Biological Products Co Ltd, a subsidiary of China National Biotec Group (CNBG). The Sinovac-CoronaVac was listed for EUL on 1 June 2021.

Furthermore, various allopathic medicines are initially effective for treatment against the virus but have various side effects which are harmful to the heart, kidneys, and diabetic patients. Plasma therapy for the infected people by isolating plasma from blood from the healed people with viral infections is also an alternate therapy against Covid-19 virus. Therefore, some preventive measures are required and mainly alternative medicines with herbal plants are used to improve the immune system to counter COVID-19. To that end, a recent article identified a few key herbal plants (suggested by AUYSH, India) that provide strong protection, protecting against infection throughout the home quarantine period. It is believed that the herbs suggested support the immunity of the body. Conversely, also in China, alternatively Traditional Chinese Medicines are used with extra care to prevent COVID-19 infection (Givetash, 2020).

2. Methodology

The information in the review is collected from various latest research papers (Journal of the Chinese Medical Association, 2020; WHO report, 2020; Nature Reviews Microbiology, 2021; The Lancet, 2020 & 2021 etc.), bibliographic data base, and information from the various official websites. Databases such as PubMed, PubMed Central., Science Direct, SCIELO, DOAJ, Science alert, Semantic scholar and Google scholar were used for the information. The maximum number of studies (minimum 10 nos.) related to individual plants were selected and tabulated to contain the latest information in this review. All the figures are self-created and were collected from the various images procured through various websites. Data analyses are included with the latest information related to the various Indian medicinal plants effective against COVID-19.

3. Herbal plants as immunomodulatory activities

Several medicinal plants are used as potential therapeutic agents against Covid-19. Indian Ayurveda practitioners suggest few important plants that provide strong immunity in the human body. Some important herbals are neem (*Azadirachta indica* A. Juss), Amalaki (*Emblica officinalis* Gaertn.), Kutki (*Picrorhiza kurroa* Royle ex Benth), Guduchi (*Tinospora cordifolia* (Willd). Miers), Drum stick (*Moringa oleifera* Lam.), Tulsi (*Ocimum sanctum* L.), Ashwagandha (*Withania somnifera* (L.) Dunal), Cinnamon (*Cinnamomum zeylanicum* Blume), Black pepper (*Piper nigrum* L.), Ginger (*Zingiber officinale* Roscoe), Turmeric (*Curcuma longa* L.), Liquorice (*Glycyrrhiza glabra* L.), Aloe (*Aloe barbadensis* Mill), Harsingar (*Nyctanthes arbor-tristis* L.), Satavar (*Asparagus racemosus* Willd.), Almond (*Prunus amygdalus*) and Broccoli (*Brassica oleracea* L.). These are important first- level Ayurvedic herbs which are helpful in building immunity in the human body and preventing infection since the immune system plays an essential and primary role in the defense against this novel viral infection (Fig. 2).

The neem plant belongs to Meliaceae family and has therapeutic implications in the prevention and treatment of diseases with its active ingredients through the modulation of various biological pathways. Various active constituents such as azadirachtin, nimbolinin, nimbin, nimbidin, nimbidol, sodium nimbinate, gedunin, salannin, and quercetin are responsible for various therapeutic effects (Ali, 1993; Hossain et al., 2011). Nimbin ($C_{30}H_{36}O_9$) is the first bitter compound isolated from neem oil which enhances the immune system of the body and helps to fight all kinds of infections. The extract stimulates phagocytic activity and the antigen-presenting ability of macrophages through the stimulation of cytokines, and boosting the immune system. The extract enhances the mitogenic response of spleenocytes to concanavalin-A, and stimulates the production of IL-1, IFN-gamma, and TNF-alpha reflecting activation (Thatte and Dhanukar, 1997). The immunomodulatory activity of the aqueous extract of *Azadirachta indica* flowers on humoral and cell-mediated immune response to ovalbumin, the phagocytic activity evaluated by carbon clearance test and cyclophosphamide-induced myelosuppression model. The result showed significant immunomodulatory activity by triggering both humoral and cell mediated immunity and non specific immune response through phagocytic activity of macrophages (Shah et al., 2009). Not only does neem have immunomodulatory activity but it also has a powerful anti viral activity and because of this neem leaves are the first line herbal choice against COVID-19. An aqueous extract of the bark of the neem plant, acted as a potent inhibitor against Herpes simplex virus type 1 (HSV-1) infection in natural target cells and is considered a novel anti-herpetic microbicide (Tiwari et al., 2010). Recently, it was shown that the phytochemicals of neem leaves are effective against the COVID-19 virus which was affirmed by a molecular docking study where the binding affinity of the constituents was high against COVID-19 main protease (Shanmuga, 2020). In another molecular docking study neem compounds from the seed extract showed a level of inhibitory activity

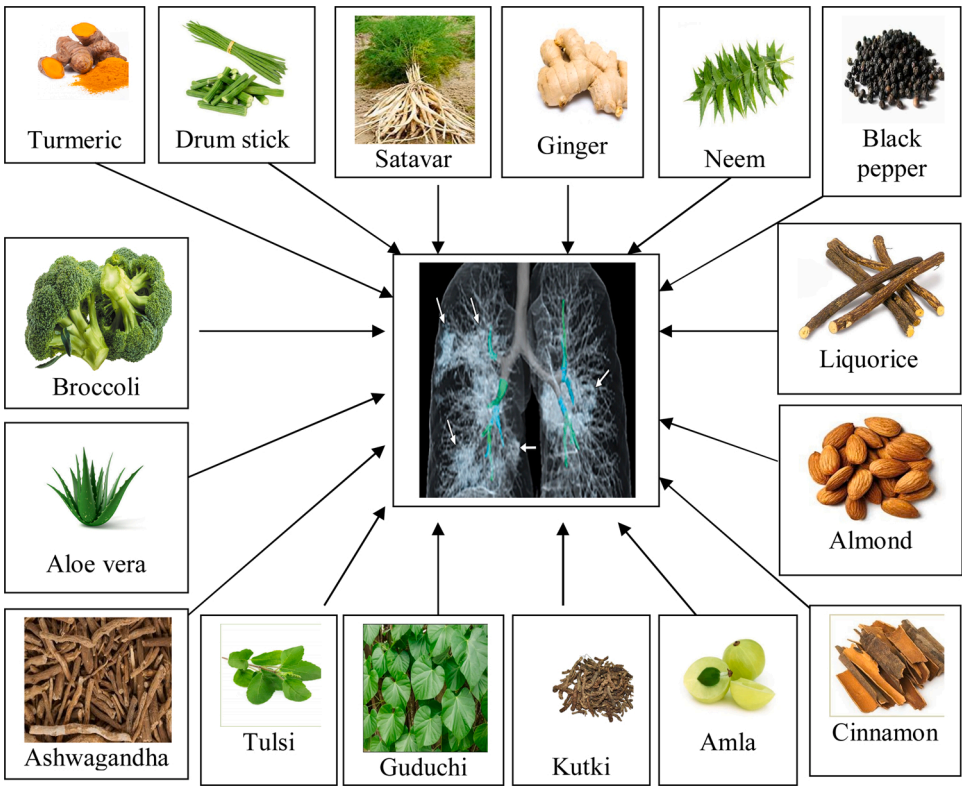

Fig. 2. Herbal plants as immunomodulator against COVID-19 infection.

against Papain like protease (PLpro) of SARS-CoV-2. The compound, desacetylgedunin showed the highest binding affinity towards PLpro (Baildya et al., 2021).

Amalaki belongs to the family- Phyllanthaceae and its fruits are one of the most important fruits to be used as immunomodulators for repeated respiratory infections in humans. The fruit is rich in vitamin C and other active constituents with its main flavonoids being kaempferol, ellagic acid, and gallic acid. The extract acts as an adaptogen and improves immunity. It enhances IL-2, NK (natural killer) cell activity, Antibody-Dependent Cellular Cytotoxicity (ADCC), and gamma-IFN production and inhibits apoptosis (Sai Ram et al., 2002; Sreeramulu and Raghunath, 2009). Currently, the fruit is essentially utilized to improve immunity against COVID-19 due to it being a rich source of vitamin-C. Phyllaemblicin B, the phytoconstituent extracted from the roots showed inhibitory potential for the Coxsackie virus (Wang et al., 2009) while its phenolic content revealed effectiveness against herpes simplex viruses (HSV) 1 and 2. The phytochemical 1, 2, 4, 6-tetra-O--galloyl-ɑD-glucose from *P. emblica* showed antiviral activity for HSV in vitro (Xiang et al., 2011). Pentagalloylglucose inhibited influenza A virus replication through the prevention of adsorption of the virus and the suppression of the release of the virus. *P. emblica* plant extracts also showed anti-HIV properties by inhibiting reverse transcriptase enzyme of the virus (Estari et al., 2012).

Kutki is part of the Scrophulariaceae family and it is an effective immunomodulator and effective against liver and respiratory disorders. The plant extract contains the phytoconstituents kutkin, picroside, vanillic acid, D-mannitol androsin and apocynin (Kumar et al., 2016a). The picroside boosts the immune system by increasing phagocytosis and, cell-mediated and humoral immunity (Sharma et al., 1994). Its immunomodulatory activity was evaluated in Complete Freund's Adjuvant-induced stimulation of a peritoneal macrophage model and lipopolysaccharide-stimulated RAW 264.7 murine macrophages which resulted in significant immunomodulatory activity (Kumar et al., 2016b). Apart from this activity, the plant is also useful against viral infection. Recently, four new bis-iridoid glycosides, saungmaygaosides A–D, and six known iridoid glycosides were isolated from the n-butanol extract of the stems of *Picrorhiza kurroa* and evaluated for viral protein R inhibition activity (Win et al., 2019).

Guduchi is part of the family- Menispermaceae and is a creeper plant widely available in India. The leaves are effective as an immune booster. Some important plant constituents are tinosporone, tinosporic acid, berberine, giloin alkaloids, diterpenoids, flavonoids, and lignins. The isolated cordifolioside A and syringin from the extract show potential immunomodulatory activity with an increase in percentage phagocytosis (Sharma et al., 2012). In a clinical research study the immunostimulant activity of *Tinospora cordifolia* was evaluated in 400 children and resulted in an increase in total leucocyte count and lymphocyte percentage and count (Sharma and Sharma, 2015). The immune-stimulating potential of aqueous and methanol extracts of *Tinospora cordifolia* was determined by measuring the cytokine levels in the culture supernatants of treated murine J774 macrophages (Alsuhaibani and Khan, 2017). The plant also showed immunomodulatory potential via the Toll like receptors mediated pathway and as adjuvants in poultry for viral diseases (Sachan et al., 2019).

The drumstick plant is found in the family- Moringaceae and is distributed throughout India. Its leaves, flowers, and fruits have significant immunomodulatory activity. The leaves contain mainly niaziminin A, and niaziminin B, niaziminin, and the flower contains mainly flavonoids such as quercetin, isoquercetin, kaemopherol, kaempferitin. Its fruits contain isothiocyanate, nitrites, thiocarbamates, beta sitosterol (Sharma et al., 2011). Glucosamine specific lectin from the leaves show an immunomodulatory effect via NK cell activity and Antibody-Dependent Cellular Cytotoxicity (ADCC) (Jayavardhanan et al., 1994). The antiviral activity of the chloroformic leaf extract of *Moringa oleifera* was studied against the Foot and Mouth disease virus and showed potent antiviral activity using the MTT assay (3-(4, 5-Dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide) (Younus et al., 2016). A recent article revealed *Moringa oleifera* contains high levels of potassium (K) which decreases the infection in patients with COVID-19 caused by the SARS-CoV-2 virus (Ignatov, 2020).

Tulsi is considered a holy plant in Ayurveda and is, available everywhere in India. The plant is also known as holy basil and belongs to the family Lamiaceae. The leaves contain mainly ursolic acid ($C_{30}H_{48}O_3$) and apigenin ($C_{15}H_{10}O_5$) and, in addition, it has oil that contains monoterpene 1,8-cineole, and eugenol. The leaves show an immunomodulatory effect by an increase in IFN-Y, IL-4, T-helper cells, NK cells, and enhance phagocytic activity and the phagocytic index (Mondal et al., 2011). The oil also boosts immunity by mediated GABAergic pathways and by the cell- mediated and humoral immunity (Mediratta et al., 2002). An immunomodulatory activity of an aqueous leaf extract of Ocimum sanctum was evaluated by in-vitro and in-vivo methods using delayed type hypersensitivity, humoral antibody titre, total leucocyte count and differential leucocyte count models (Venkatachalam and Rajinikanth, 2013). Recently, the plant is the prime focus in COVID-19 treatment as an antiviral agent. The study revealed the antiviral activity of leaves of its leaves (crude extract, terpenoid and polyphenol) against H9N2 virus using an *in ovo* model and showed potent antiviral efficacy (Ghoke et al., 2018). In another study, the antiviral activity of different extracts of *Ocimum sanctum* was confirmed against orthmyxovirus and paramyxovirus using *in vitro* cytotoxicity assay (Patil, 2018). A study last year revealed that phytochemicals from *Ocimum sanctum* potentially inhibit M^{pro} (main protease) of SARS-CoV-2 using a molecular docking and molecular dynamics (MD) simulation study (Shree et al., 2020).

Ashwagandha is an evergreen shrub found in India. It is in the Solanaceae family and is a master" herb in ayurvedic medicine. The root contains alkaloids like isopelletierine, anaferine, cuseohygrine, anahygrine, steroidal lactones, withanolides, withaferins and saponins (Mishra et al., 2000). Ariel parts also contain 5-dehydroxy withanolide-R and withasomniferin-A (Rahman et al., 1991). The two isolated compounds sitoindoside IX (1) and sitoindoside X (2), show potential immunomodulatory activity through the activation of peritoneal macrophages involved in, phagocytosis (Ghosal et al., 1989). The main constituents of the root are withanolide ($C_{28}H_{38}O_6$) and withaferin A ($C_{28}H_{38}O_6$) and these are steroidal constituents which possess immune-stimulatory activity through enhancing the phagocytic activity of peritoneal macrophages (Davis and Kuttan, 2000). Recently, the plant was also used as an effective COVID-19 treatment as an antiviral agent. The antiviral potential of *Withania somnifera* was screened against Bursal disease virus replication. The hydroalcoholic extract of the root showed the antiviral activity against infectious Bursal disease virus in a cytopathic effect reduction assay (MTT assay) (Pant et al., 2012). The main constituent withaferin A demonstrated the ability to attenuate the neuraminidase of H1N1 influenza (Cai et al., 2015). Previously, a study revealed potent antiviral activity of the aqueous extract of ashwagandha leaf against hepatitis C virus (HCV) using MTT assay. The activity was confirmed by NS5B RNA-dependent RNA and Human protein kinase N2 (PKN2, PRKCL2) using molecular docking (Mofed et al., 2020).

Cinnamon is in the Lauraceae family and is a well known tree in many countries, including India. It is easily available as spices. The bark is a well known flavouring agent but it also shows various therapeutic activities. The bark and leaves contain oils such as cinnamaldehyde, camphor (found in the bark oil), eugenol (found in the leaf oil), as well as others (Wijesekera, 1978). The extract showed immunomodulatory activity by increasing the phagocytic index and serum immunoglobulin levels as well as increasing both cell-mediated and humoral immunity (Niphade et al., 2009). A study showed that silver nanoparticles containing cinnamon bark extract possessed significant antiviral activity against the highly pathogenic avian influenza virus subtype H7N3 using MTT assay (Fatima et al., 2015). *Cinnamon zeylanicum* essential oil and powder showed appreciable immune-stimulatory activity by increasing survival percent (challenge test) lysozyme, phagocytic index and phagocytic activity (Tamam et al., 2017).

Black pepper (Family: Piperaceae) is one of the most widely used spice throughout the world. The fruit is well known for treatment of throat infection, cough and cold. The therapeutic potency is shown due to presence of piperine and other constituents like piperic acid, piperlonguminine, pellitorine, piperolein B, piperamide, piperettine, and (-)-kusunokinin etc. (Takooree et al., 2019). Piperine shows an effective immunostimulant through the increased phagocytic index, proliferation of macrophage cells, and by increasing WBC count (Tripathi et al., 1999; Sunila and Kuttan, 2004; Noor Mohamed et al., 2017). Recently, the fruit of black pepper is extensively used in the treatment of COVID-19 as a powerful antiviral agent. The earlier research revealed an anti-viral assay of the ethanol extract of *Piper longum* Linn. against Hepatitis B virus to possess superior anti- Hepatitis B virus activity in vitro against the secretion of hepatitis B virus surface antigen and hepatitis B virus e antigen (Jiang et al., 2013). Another study showed powerful antiviral activity of a methanolic and chloroform extract from the seeds of *Piper longum* against Vesicular stomatitis virus and human para influenza virus on HeLa cell lines which showed that this may be a strong antiviral agent possibly due to the presence of piperidine (Priya and Kumari, 2017).

Ginger is part of the Zingiberaceae family, and well known as a cooking spice and flavouring agent. The plant is easily available universally. The rhizome is used for throat infections, colds, dry cough, many gastrointestinal infections and influenza. The rhizome contains the main active principles zingiberene, β-bisabolene, α-farnesene, the terpene compounds β-sesquiphellandrene, and, α-curcumene, and the phenolic compounds gingerol, paradols, and shogaol (Phenolic compounds) (Grzanna et al., 2005). The extract increases the production of IL-1β, IL-6 and TNF-α in activated macrophages, as well as splenocyte proliferation and cytokine production (Ryu and Kim, 2004). Gingerol and zingiberene are powerful immune boosters which have been shown to improve humoral and cell-mediated immune response (Carrasco et al., 2009). An *in vitro* study showed the anti-hydatic and immunomodulatory effects of ginger and [6]-gingerol with interferon-gamma (IFN-γ) on PSC which were co-cultured with the mononuclear cells of hydatic patients (Amri and Boukoffa, 2016). A recent study showed ginger root to be an immunomodulator in a herbal formulation which was used for the treatment of respiratory disorders. This was shown through the macrophage phagocytosis and lymphocyte proliferation assay and the measurement of immunoglobulin G (IgG) antibodies (Ikawati et al., 2019). Ginger rhizome is currently one of the first line choices in the management of COVID-19 infections due to its antiviral activity. Earlier research showed it to be a strong antiviral agent against the Chikungunya virus using the MTT assay (Kaushik et al., 2020).

Turmeric is also part of the Zingeberaceae family and is a very common and well established multi-functional plant widely grown and used throughout the world. The rhizome is used for various medicinal purposes as an important blood purifier, immune-stimulant, and general tonic. The activity is mainly due to the presence of the active constituents' curcumin, zingiberene, alpha and beta turmerone. Curcumin ($C_{21}H_{20}O_6$) is the essential compound that has been linked to the activation of T cells, B cells, macrophages, neutrophils, natural killer cells, and dendritic cells. It also enhances the antibody response in low doses (Jagetia and Aggarwal, 2007). Nitric oxide (NO)-induced production in RAW264.7 macrophages was used to assess the immunomodulatory activity of the aqueous extract of turmeric. This resulted in improved cellular immune responses, tissue healing, and lifespan with activated immunity (Pan et al., 2017). Curcumin Phytosome was recently tested for immunomodulatory effects by T cell activation in a non-randomized phase 2 study with seven endometrial cancer patients and resulted in significant immune-stimulanting activity (Tuyaerts et al., 2019). Turmeric has been used with COVID-19 due to its wide ranges of antiviral properties. Earlier scientific data showed that curcumin had an antiviral activity against several different viruses including hepatitis, influenza, and emerging arboviruses like Zika and chikungunya. It has also been reported clinically that curcumin inhibits human immunodeficiency virus, herpes simplex virus 2 and human papillomavirus (Mishra et al., 2015; Rhein et al., 2016; Mounce et al., 2017).

Liquorice is part of the Legiminosae family and its root is used as an

immunomodulator due to the presence of constituents such as glycyrrhizic acid, glabridin, and sterine among others. It is very useful in the treatment of throat infections. Liquorice extract shows a modulatory effect on the complement system through *in vitro* study and inhibits the replication of Severe Acute Respiratory Syndrome (SARS)- associated virus. The clinical study of Glycyrrhizic acid and its aglycone have been shown to modulate NF-kB and IL-10 production which, in turn reduced inflammation in the liver (Yoshikawa et al., 1997). The immunomodulatory properties of a liquorice aqueous root extract was studied with *in* vivo phagocytosis (carbon clearance method) and by leukocyte count (Mazumder et al., 2012). The root has shown antiviral activity when it inhibited SARS-coronavirus (SARS-CoV) replication in vitro by an attachment of 2-acetamido-β-D-glucopyranosylamine into the glycoside chain of glycyrrhizin, which resulted in a ten-fold increased in anti-SARS-CoV activity (Hoever et al., 2005). It has been established as a potent antiviral which is effective against the hepatitis C virus due to the presence of glycyrrhizin using quantitative real time RT-PCR measurement (Ashfaq et al., 2011).

Aloe is in the Liliaceae family and is a plant with multi functionality, which is known throughout the world. The juice contains multiple essential active constituents such as polysaccarides (glucomannan, acemannan,mannose derivatives hemicellulose), aloin, para-coumaric acid, and aldopentose (Bensky and Gamble, 1993). Aloenin ($C_{19}H_{22}O_{10}$) and aloesin ($C_{19}H_{22}O_9$) are extracted from the leaves and active an immune response by augmenting secondary humoral immunity (Halder et al., 2012). The immunomodulatory activity of aloe gel extract was evaluated by phagocytic activity of polymorphonuclear cells on candida cells (Bhalsinge et al., 2018). It has potential antiviral activity. Scientific clinical research showed aloe polysaccharides extracted from the leaves to be effective against the H1N1 influenza virus (Sun et al., 2018). Recently, an ethanolic extract of aloe was reported to cause a significant reduction in the viral replication of green fluorescent protein-labeled influenza A virus in Madin-Darby canine kidney cells (Choi et al., 2019).

The harsingar plant is found in the Oleaceae family and is well known in India. The leaves of this plant have shown to have strong immunomodulatory activity (Bharshiv et al., 2016). The leaves contain tertiary and quaternary alkaloids which increase immune-bioactivities. The following constituents are found primarily in the leaves: nicotiflorin, oleanolic acid, nyctanthic acid, friedeline, lupeol, mannitol, glucose, fructose, and iridoid glycosides. The flowers contain nyctanthin, D-mannitol, carotenoid, β-monogentiobioside ester of α-crocetin, among others. (Bansal et al., 2015). The leaf extract enhances circulating antibodies and increases total white blood cell counts (Kannan et al., 2007), which further boosts immunity. Another study showed the immunomodulatory activities of an aqueous extract of its flowers with splenocytes proliferation and the induction of cytokines (Bharshiv et al., 2016). The harsingar plant is also used as an antiviral agent against COVID-19 due to its antiviral potentiality. An *in vitro* study established it as an antiviral agent when an ethanolic crude extract of the plant and two isolated compounds from the extracts were tested separately against encephalomyocarditis Semliki forest viruses (Gupta et al., 2005). In another research study, the antiviral activity of water, ethanol, and acetone extracts of Nyctanthes arbor-tristis was tested on *enterovirus* 71 and reported as potent antiviral agent (Panda et al., 2017).

Satavar (Family: Liliaceae) root is extremely effective as an immunomodulator. A steroidal sapogenin acid from the root shows a potent immunomodulator (Sharma and Varmal, 2011) by significant increase of CD3+ and CD4/CD8+ % T cell activation and also shows immunoadjuvant action by significant up-regulation of Th1 (IL-2) and Th2 (IL-4) cytokines (Guatam et al., 2004). Another research revealed the bioactivity and immunomodulatory potential of in vitro produced shatavarins from cell cultures of Asparagus racemosus using human peripheral blood lymphocytes which resulted in Shatavarin stimulated immune cell proliferation and IgG secretion in a dose dependent manner (Pise et al., 2015).

Almond (Family: Rosaceae) is commonly known as badam and available in India and many other countries. The almond seed is very effective in chronic cough and pneumonia and has an effective soothing effect on the throat (Khan and Azam, 2012). It is a rich source of vitamin-E which boosts immunity. The seed contains mainly various amino acids, vitamin E, and also oil. From oil, diolein and triolein are isolated (Anonymous, 2003). Thereafter, it revealed that almonds contains high levels of cytokine i.e., interferon-α (INF-α), interleukins (IL-12), INF-gamma and tumour necrosis factor (TNF-α) that improved the immune surveillance of the peripheral blood mono nuclear cells towards viral infections and also significantly decreases in the Herpes simplex virus (HSV-2) replication (Arena and Bisignano, 2010). The extract produces high levels of cytokine i.e., interferon-α (INF-α), interleukins (IL-12), INF-gamma, and tumour necrosis factor (TNF-α) that boosts an immunity in blood mononuclear cells towards viral infections (Jagannadha Rao and Lakshmi, 2012).

Broccoli is in the Brassicaceae family and the flower provides many health-promoting properties, and is cultivated in many countries. The flower contains a high content of flavonoids, glucosinolates, indole-3-carbinol, isothiocyanates, vitamins (especially vitamin E, C, K), mineral nutrients, essential oils, phenolics (such as kaempferol, and quercetin) and polypeptides (Vasanthi et al., 2009; Samy and Gopalakrishnakone, 2010). Sulforaphane, an isothiocyanate isolated from the flower acts as an immune booster through the enhancement of phagocytic activity of the peritoneal macrophages and the reduction of elevated levels of TNF-alpha production by lipopolysaccharide (LPS) stimulated macrophages (Thejass and Kuttan, 2007). The immunomodulatory activity of pectins extracted from broccoli stalks (Brassica oleracea var. italica) were studied *in vivo* and *in vitro* by the activation of macrophages (Busato et al., 2020).

4. Homemade traditional applications

During home quarantine, the adaptation of various traditional practices may strengthen the body's immunity and are considered first-line preventive measures against COVID-19. The Ministry of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy (AYUSH) recommend some self-care guidelines (AYUSH, 2020) which are as follows:

a) Drink warm water in the morning and after 1−2 hours gap, throughout the day.
b) Practice Yogasana, Pranayama, and meditation for at least 30 min daily to build body immunity.
c) Consume homemade food with applied spices such as turmeric (*Curcuma longa*), cumin (*Cuminum cyminum*), coriander (*Coriandrum sativum*), and garlic (*Allium sativum*), will increase immunity.
d) Drink hot herbal tea containing tulsi, cinnamon, black pepper, dried ginger, and raisins once or twice a day.
e) Drink hot milk mixed with half teaspoon turmeric powder, once or twice a day.
f) Apply a few drops of sesame oil, coconut oil, or ghee in both the nostrils each day in morning and evening.
g) Steam inhalation of extremely hot water infused with fresh mint leaves or caraway seeds before bed at night.
h) Clove powder mixed with honey taken 2–3 times a day to reduce cough or throat infections.

Other important traditional applications which are easy to follow in the home include:

i) Ingestion of cinnamon powder with honey in the morning to strengthen the immune system.
ii) Ingestion of one glass of hot water mixed with one spoon of ginger juice to improve throat infections and overall immunity.

iii) Ingestion of half a spoon of black pepper powder mixed with ginger paste, combined with one spoon of ghee in hot rice for cough, cold, and throat infection.
iv) Combine one spoon of honey and garlic in the morning to increase immunity.
v) Ingest one glass of hot water mixed with one spoon of lemon juice to increase immunity.
vi) Take one spoon of honey mixed with one spoon of turmeric powder, half spoon of cinnamon powder and black pepper powder each day for cough, and to soothe a scratchy throat.
vii) Take one glass of hot milk with half a spoon of turmeric and half a spoon of almond powder once daily after dinner to strengthen immunity.
viii) Take black jeera (black cumin) powder with coleus leaf extract one spoon daily in the morning to strengthen immunity.
ix) Take one spoon of tulsi leaf juice with half spoon of honey for throat infections and respiratory tract issues.
x) Ingest hot milk with 2–3 saffron petals mixed with half spoon almond seed powder after dinner will boost immunity.

5. Discussion

Medicinal and aromatic plants (MAPs) are widely regarded as a constant source of safe and effective medicines with potential to develop constituents found in the plants into newer drugs. The potential is currently under threat due to alarming biodiversity loss and over exploitation. The present review discussed seventeen important Indian plants and their main phytoconstituents and how they actively play a role in combating COVID-19 infections and strengthen immunity. Many advanced literatures, including study evidences, are evaluated, and the most relevant findings are highlighted in the current work, which focuses on future researchers and the scientific community as a whole. In this review, the most important guidelines recommended by AYUSH, India during home quarantine are outlined.

6. Conclusion

COVID-19 has spread rapidly and resulted in a global pandemic. Many approaches are being implemented for either prevention or treatment. Some synthetic medicines in various combinations inhibit COVID-19 infections but some countries have not approved their uses due to side effects and toxicity. Many people globally rely upon traditional herbal preparations to manage chronic diseases because of ease of availability, cost-effectiveness, and minimal side-effects. Medicinal plants offer an option for immune support and herbals can build body immunity in the preliminary stage of a COVID-19 infection. Herbals have an enormous role to play with their immunomodulatory mechanism due to the presence of active medical constituents.

Declaration of Competing Interest

There is no conflict of interest.

References

Ali, A., 1993. Textbook of Pharmacognosy. Publication and Information Directorate., New Delhi, India.

Almazan, F., Dediego, M.L., Galan, C., Escors, D., Alvarez, E., Ortego, J., Sola, I., Zuniga, S., Alonso, S., Moreno, J.L., Nogales, A., Capiscol, C., Enjuanes, L., 2006. Construction of a severe acute respiratory syndrome coronavirus infectious cDNA clone and a replicon to study coronavirus RNA synthesis. J. Virol. 80 (21), 10900–10906.

Alsuhaibani, S., Khan, M.A., 2017. Immune-stimulatory and therapeutic activity of Tinospora cordifolia: double-edged sword against salmonellosis. J. Immunol. Res. 2017, 1787803 https://doi.org/10.1155/2017/1787803.

Amri, M., Boukoffa, C.T., 2016. In vitro anti-hydatic and immunomodulatory effects of ginger and [6]-gingerol. Asian Pac. J. Trop. Med. 9 (8), 749–756.

Anonymous, 2003. The Wealth of India. New Delhi: Council of Scientific and Industrial Research, VIII, pp. 250–254.

Arena, A., Bisignano, C., 2010. The immunomodulatory and the antiviral activities of almonds. J.I m let. 132 (1-2), 18–23.

Ashfaq, U.A., Masoud, M.S., Nawaz, Z., Raizuddin, S., 2011. Glycyrrhizin as antiviral agent against hepatitis C virus. J. Transl. Med. 9, 112. https://doi.org/10.1186/1479-5876-9-112.

AYUSH, 2020. AYUSH Reiterates Immunity Boosting Measures for Self-care During COVID 19 Crises.. Available from: Press Information Bureau Government of India AYUSH https://pib.gov.in/newsite/PrintRelease.aspx?relid=201167.

Baildya, N., Khan, A.A., Ghosh, N.N., Dutta, T., Chattopadhyay, A.P., 2021. Screening of potential drug from Azadirachta Indica (Neem) extracts for SARS-CoV-2: An insight from molecular docking and MD-simulation studies. J. Mol. Struct. 1227, 129390.

Bansal, G., Suri, K.A., Grover, P., 2015. A comprehensive review on Nyctanthes arbortristis. Int. J Drug Dev. & Res. 7 (1), 183–193.

Bensky, D., Gamble, A., 1993. Chinese herbal medicine: materia medica. Eastland Press Inc., Seattle, USA.

Bertram, S., Glowacka, I., Müller, M.A., Lavender, H., Gnirss, K., Nehlmeier, I., Niemeyer, D., He, Y., Simmons, G., Drosten, C., Soilleux, E.J., Jahn, O., Steffen, I., Pohlmann, S., 2011. Cleavage and activation of the severe acute respiratory syndrome coronavirus spike protein by human airway trypsin-like protease. J. Virol. 85 (24), 13363–13372.

Bhalsinge, R.R., Rajbhoj, S.R., Limaye, M.V., Vaidya, M.U., Rane, P.S., Tilak, A.V., 2018. Anti-inflammatory and immunomodulatory activity of ethanol extract of Aloe vera gel. Int. J. Pharm. Sci. Res. 9 (2), 832–835.

Bharshiv, C.K., Garg, S.K., Bhatia, A.K., 2016. Immunomodulatory activity of aqueous extract of Nyctanthes arbor-tristis flowers with particular reference to splenocytes proliferation and cytokines induction. Indian J. Pharmacol. 48 (4), 412–417.

Busato, B., Abreu, E.C.A., Petkowicz, C.L.O., Martinez, G.R., Noleto, G.R., 2020. Pectin from Brassica oleracea var. Italica triggers immunomodulating effects in vivo. Int. J of Biol. Macromolecules. 161, 431–440.

Cai, Z., Zhang, G., Tang, B., Liu, Y., Fu, X., Zhang, X., 2015. Promising anti-influenza properties of active constituent of Withania somnifera ayurvedic herb in targeting neuraminidase of H1N1 influenza: computational study. Cell Biochem. Biophys. 72 (3), 727–739.

Carrasco, F.R., Schmidt, G., Romero, A.L., Sartoretto, J.L., Caparroz-Assef, S.M., Bersani-Amado, C.A., Cuman, R.K., 2009. Immunomodulatory activity of Zingiber officinale Roscoe, Salvia officinalis L. And Syzygium aromaticum L. Essential oils: evidence for humor- and cell-mediated responses. J. Pharm. Pharmacol. 1 (7), 961–967.

Cascella, M., Rajnik, M., Cuomo, A., Dulebohn, S.C., Di Napoli, R., 2020. Features, evaluation and treatment coronavirus (COVID-19). StatPearls [Internet]. StatPearls Publishing, Treasure Island (FL). Available from: https://www.ncbi.nlm.nih.gov/books/NBK554776/.

Chan, J.F., To, K.K., Tse, H., Jin, D.Y., Yuen, K.Y., 2013. Interspecies transmission and emergence of novel viruses: lessons from bats and birds. Trends Microbiol. 21 (10), 544–555.

Chin, A., Chu, J., Perera, M., Hui, K., Yen, H.L., Chan, M., Peiris, M., Poon, L., 2020. Stability of SARS-CoV-2 in different environmental conditions. Lancet Microbe. https://doi.org/10.1101/2020.03.15.20036673.

Choi, J.G., Lee, H., Kim, Y.S., Hwang, Y.H., Oh, Y.C., Lee, B., Moon, K.M., Cho, W.K., Ma, J.Y., 2019. Aloe vera and its components inhibit influenza a virus-induced autophagy and replication. Am. J. Chin. Med. 47 (6), 1307–1324.

Davis, L., Kuttan, G., 2000. Immunomodulatory activity of Withania somnifera. J. Ethnopharmacol. 71 (1-2), 193–200.

Estari, M., Venkanna, L., Sripriya, D., Lalitha, R., 2012. Human Immunodeficiency Virus (HIV-1) reverse transcriptase inhibitory activity of Phyllanthus emblica plant extract. Biol. Med. 4 (4), 178–182.

Fatima, M., Zaidi, N.Us.S., Amraiz, D., Afzal, F., 2015. In vitro antiviral activity of Cinnamomum cassia and its nanoparticles against H7N3 influenza A virus. J. Microbiol. Biotechnol. 26 https://doi.org/10.4014/jmb.1508.08024.

Ghoke, S.S., Sood, R., Kumar, N., Pateriya, A.K., Bhatia, S., Mishra, A., Dixit, R., Singh, V. K., Desai, D.N., Kulkarni, D.D., Dimri, U., Singh, P., 2018. Evaluation of antiviral activity of Ocimum sanctum and Acacia arabica leaves extracts against H9N2 virus using embryonated chicken egg model. BMC Complement. Altern. Med. 18, 174.

Ghosal, S., Srivastava, R.S., Bhattacharya, S.K., Upadhyay, S.N., Jaiswal, A.K., Chattopadhyay, U., 1989. Immunomodulatory and CNS effects of sitoindosides IX and X, two new glycowithanolides form Withania somnifera. Phytother. Res. 2, 201–206.

Givetash, L., 2020. China Is Encouraging Herbal Remedies to Treat COVID-19, but Scientists Warn Against It. Available online: https://www.nbcnews.com/news/world/china-encouraging-herbal-remedies-treat-covid-19-scientists-warn-against-n1173041.

Grzanna, R., Lindmark, L., Frondoza, C.G., 2005. Ginger—an herbal medicinal product with broad anti-inflammatory actions. J. Med. Food 8 (2), 125–132.

Guatam, M., Diwanay, S., Gairola, S., Shinde, Y.S., Patki, P., Patwardhan, B., 2004. Immunoadjuvant potential of Asparagus racemosus aqeous extract in experimental system. J. Ethnopharmacol. 91, 251–255.

Gupta, P., Bajpai, S.K., Chandra, K., Singh, K.L., Tandon, J.S., 2005. Antiviral profile of Nyctanthes arbor-tristis L. Against encephalitis causing viruses. Indian J. Exp. Biol. 43, 1156–1160.

Halder, S., Mehta, A.K., Mediratta, P.K., 2012. Augmented humoral immune response and decreased cell-mediated immunity by Aloe vera in rats. Inflammopharmacology 20, 343–346.

Hoever, G., Baltina, L., Michaelis, M., Kondratenko, R., Baltina, L., Tolstikov, G.A., Doerr, H.W., Cinatl, J., 2005. Antiviral activity of glycyrrhizic acid derivatives against SARS−Coronavirus. J. Med. Chem. 48 (4), 1256–1259.

Hossain, M.A., Shah, M.D., Sakari, M., 2011. Gas chromatography–mass spectrometry analysis of various organic extracts of Merremia borneensis from Sabah. Asian Pac. J. Trop. Med. 4 (8), 637–641.
Ignatov, I., 2020. Anti Inflammatory and anti viral effects of Potassium (K) and chemical composition of Moringa. Asian J. Biol. 9 (2), 1–7. https://doi.org/10.9734/AJOB/2020/v9i230081.
Ikawati, Z., Hertiani, T., Izzati, F., 2019. Immunomodulatory activity of an Indonesian herbal formulation for respiratory disorder. Phcog Mag 15, 130–134.
Jagannadha Rao, H., Lakshmi, 2012. Therapeutic applications of almonds (Prunus amygdalus l): a review. J. Clin. Diagn. Res. 6 (1), 130–135.
Jagetia, G.C., Aggarwal, B.B., 2007. Spicing up of the immune system by curcumin. J. Clin. Immunol. 27 (1), 19–35.
Jayavardhanan, K.K., Damodaran, V., Panikkar, K.R., Suresh, K., 1994. Modulatory potency of drum stick lectin on the host defense system. J. Exp. Clin. Cancer Res. 13, 205–209.
Jiang, Z.Y., Liu, W.F., Zhang, X.M., Luo, J., Ma, Y.B., Chen, J.J., 2013. Anti-HBV active constituents from Piper longum. Bioorg. Med. Chem. Lett. 23 (7), 2123–2127.
Jin, Y.H., Cai, L., Cheng, Z.S., Cheng, H., Deng, T., Fan, Y.P., Fang, C., Huang, D., Huang, L.Q., Huang, Q., Han, Y., 2020. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Military medicial Research 7 (1), 4. https://doi.org/10.1186/s40779-020-0233-6.
Kaushik, S., Jangra, G., Kundu, V., Yadav, J.P., Kaushik, S., 2020. Anti-viral activity of Zingiber officinale (Ginger) ingredients against the Chikungunya virus. Virus Dis. https://doi.org/10.1007/s13337-020-00584-0.
Khan, M.A., Azam, M., 2012. New Delhi: CCRUM, Vol. I. Ministry of Health & Family Welfare, Govt. of India, pp. 522–524.
Kumar, V., Chauhan, R.S., Tandon, C., 2016a. Biosynthesis and therapeutic implications of iridoid glycosides from Picrorhiza genus: the road ahead. J. Plant Biochem. Biotechnol. 26 (1), 1–13.
Kumar, R., Gupta, Y.K., Singh, S., Raj, A., 2016b. Anti-inflammatory effect of Picrorhiza kurroa in experimental models of inflammation. Planta Med. 82 (16), 1403–1409.
Lu, H., Stratton, C.W., Tang, Y.W., 2020. Outbreak of pneumonia of unknown etiology in Wuhan, China: the mystery and the miracle. J. Med. Virol. 92, 401–402.
Mazumder, P.M., Pattnayak, S., Parvani, H., Sasmal, D., Rathinavelusamy, P., 2012. Evaluation of immunomodulatory activity of Glycyrhiza glabra L roots in combination with zing. Asian Pac. J. Trop. Biomed. 2 (1), S15–S20.
Mediratta, P.K., Sharma, K.K., Singh, S., 2002. Evaluation of immunomodulatory potential of Ocimum sanctum seed oil and its possible mechanism of action. J. Ethanopharmacol. 80, 15–20.
Mishra, L.C., Singh, B.B., Dagenais, S., 2000. Scientific basis for the therapeutic use of Withania somnifera. (Ashwagandha): a review. Alternative Medicine Reviews 5, 334–346.
Mishra, A., Kumar, R., Tyagi, A., Kohaar, I., Hedau, S., Bharti, A.C., Sarker, S., Dey, D., Saluja, D., Das, B., 2015. Curcumin modulates cellular AP-1, NF-kB, and HPV16 E6 proteins in oral cancer. E-cancer medical science. 9, 525. https://doi.org/10.3332/ecancer.2015.525.
Mofed, D., Ahmed, W., Zekri, A.R., Said, O., Rahouma, M., Faraag, A.H.I., 2020. The antiviral efficacy of Withania somnifera (ashwagandha) against hepatitis C virus activity: in vitro and in silico study. Adv. Microbiol. 10, 463–477.
Mondal, S., Varma, S., Bamola, V.D., Naik, S.N., Mirdha, B.R., Padhi, M.M., Mehta, N., Mahapatra, S.C., 2011. Double-blinded randomized controlled trial for immunomodulatory effects of Tulsi (Ocimum sanctum Linn.) leaf extract on healthy volunteers. J. Ethnopharmacol. 136, 452–456.
Mounce, B.C., Cesaro, T., Carrau, L., Vallet, T., Vignuzzi, M., 2017. Curcumin inhibits Zika and chikungunya virus infection by inhibiting cell binding. Antiviral Res. 142, 148–157.
Niphade, S.R., Asad, M., Gowda, K.C., Emmanuel, T., Deshmukh, P., 2009. Immunomodulatory activity of Cinnamomumzeylanicum bark. Pharm. Biol. 47 (12), 1168–1173.
Noor Mohamed, M.S., Jaikumar, K., Anand, D., Saravanan, P., 2017. Assessment of Cytotoxic and Immunomodulatory Properties of Piper nigrum Linn. (White Pepper) Seed Extract. Int. J. Pharm. Sci. Drug Res. 9 (2), 64–67.
Pan, M.H., Wu, J.C., Ho, C.T., Badmaev, V., 2017. Effects of water extract of Curcuma longa (L.) roots on immunity and telomerase function. J. Complement. Integr. Med. 14 (3) https://doi.org/10.1515/jcim-2015-0107.
Panda, S.K., Padhi, L., Leyssen, P., Liu, M., Neyts, J., Luyten, W., 2017. Antimicrobial, Anthelmintic, and antiviral activity of plants traditionally used for treating infectious disease in the similipal biosphere reserve, odisha. India. Front. Pharmacol. https://doi.org/10.3389/fphar.2017.00658.
Pant, M., Ambwani, T., Umapathi, V., 2012. Antiviral activity of ashwagandha extract on infectious bursal disease virus replication. Indian J. Sci. Technol. 5 (5), 2750–2751.
Parry, J., 2020. China coronavirus: cases surge as official admits human to human transmission. BMJ 368, m236. https://doi.org/10.1136/bmj.m236.
Patil, U., 2018. Studies on antiviral activity of tulsi (Ocimum sanctum) crude extracts on selected viruses of veterinary importance. Int. J. Ayur. Pharm. Res. 6 (4), 17–21.
Perlman, S., Netland, J., 2009. Coronaviruses post-SARS: update on replication and pathogenesis. Nat. Rev. Microbiol. 7 (6), 439–450.
Pise, M.V., Rudra, J.A., Upadhyay, A., 2015. Immunomodulatory potential of shatavarins produced from Asparagus racemosus tissue cultures. J. Nat. Sci. Biol. Med. 6 (2), 415–420.
Priya, N.C., Kumari, S., 2017. Antiviral activities and cytotoxicity assay of seed extracts of Piper longum and Piper nigrum on human cell lines. Int. J Pharm Sci Rev Res 44 (1), 197–202.
Rahman, A.U., Abbas, S., Shahwar, D.E., Jamal, S.A., Choudhary, M.I., Abbas, S., 1991. New withanolides from Withania spp. J. Nat. Prod. 56, 1000–1006.
Rhein, C., Weidner, T., Henb, L., Martin, J., Weber, C., Sliva, K., Schnierle, S., 2016. Curcumin and Boswellia serrata gum resin extract inhibit chikungunya and vesicular stomatitis virus infections in vitro. Antiviral Res. 125, 51–57.
Riou, J., Althaus, C.L., 2020. Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV). Eurosurveillance 25 (4). https://doi.org/10.2807/1560-7917.ES.2020.25.4.2000058.
Ryu, H.S., Kim, H.S., 2004. Effect of Zingiber officinale Roscoe extracts on mice immune cell activation. Korean J. Nutr. 37 (1), 23–30.
Sachan, S., Dhama, K., Latheef, S.K., Samad, H.A., Mariappan, A.K., Munuswamy, P., Singh, R., Singh, K.P., Malik, Y.S., Singh, R.K., 2019. Immunomodulatory potential of Tinospora cordifolia and CpG ODN (TLR21 agonist) against the very virulent, infectious bursal disease virus in SPF chicks. Vaccines 7, 106. https://doi.org/10.3390/vaccines7030106.
Sai Ram, M., Neetu, D., Yogesh, B., Anju, B., Dipti, P., Pauline, T., Sharma, S.K., Sarada, S.K., Ilavazhagan, G., Kumar, D., Selvamurthy, W., 2002. Cyto-protectiveand immunomodulating properties of Amla (Emblica officinalis) on lymphocytes: an in-vitro study. J. Ethnopharmacol. 81, 5–10.
Samy, R.P., Gopalakrishnakone, P., 2010. Therapeutic potential of plants as Antimicrobials for drug discovery. Evid. Complement. Alternat. Med. 7 (283-), 294.
Shah, A.S., Gunjal, M.A., Juvekar, A.R., 2009. Immunomostimulatory activity of aqueous extract of Azadirachta indica flowers on specific and non specific immune response. J. Nat. Remedies 9 (1), 35–42.
Shanmuga, S., 2020. Some Compounds From Neem Leaves Extract Exhibit Binding Affinity As High As -14.3 kcal/mol Against COVID-19 Main Protease (Mpro): a Molecular Docking Study. https://doi.org/10.21203/rs.3.rs-25649/v1.
Sharma, D.N., Sharma, A., 2015. Tinospora cordifolia enhances Vyadhikshamatwa (immunity) in Children. J. Phytopharmacology 4 (4), 227–230.
Sharma, J., Varmal, R., 2011. A review on endangered plant of Mallotus philippensis (Lam.) M.ARg. Pharmacologyonline 3, 1256–1265.
Sharma, M.L., Rao, C.S., Duda, P.L., 1994. Immunostimulatory activity of Picrorhiza kurroa leaf extract. J. Ethnopharmacol. 41 (3), 185–192.
Sharma, V.R., Paliwal, R., Sharma, S., 2011. Phytochemical analysis and evaluation of antioxidant activities of hydro-ethanolic extract of Moringa oleifera Lam. J. Pharm. Res. 4 (2), 554–557.
Sharma, U., Bala, M., Kumar, N., Singh, B., Munshi, R.K., Bhalerao, S., 2012. Immunomodulatory active compounds from Tinospora cordifolia. J. Ethnopharmacol. 141, 918–926.
Shree, P., Mishra, P., Selvaraj, C., Singh, S.K., Chaube, R., Garg, N., Tripathi, Y.B., 2020. Targeting COVID-19 (SARS-CoV-2) main protease through active phytochemicals of ayurvedic medicinal plants – withania somnifera (Ashwagandha), Tinospora cordifolia (Giloy) and Ocimum sanctum (Tulsi) – a molecular docking study. J. Biomol. Struct. Dyn. https://doi.org/10.1080/07391102.2020.1810778.
Sreeramulu, D., Raghunath, M., 2009. Antioxidant activity and phenolic content of roots, tubers and vegetables commonly consumed in India. Food Res. Int. 43, 1017–1020.
Sun, Z., Yu, C., Wang, W., Yu, G., Zhang, T., Zhang, L., Zhang, J., Wei, K., 2018. Aloe polysaccharides inhibit influenza a virus Infection-A promising natural anti-flu drug. Front. Microbiol. 9, 2338. https://doi.org/10.3389/fmicb.2018.02338.
Sunila, E.S., Kuttan, G., 2004. Immunomodulatory and antitumor activity of Piper longum Linn. And piperine. J. Ethnopharmacol. 90, 339–346.
Takooree, H., Muhammad, Z.A., Rengasamy, K.R.R., Venugopala, K.N., Jeewon, R., Zengin, G., Mahomoodally, M.F., 2019. A systematic review on black pepper (Piper nigrum L.): from folk uses to pharmacological applications. Crit. Rev. Food Sci. Nutr. 59 (1), S210–S243.
Tamam, S.M., Abd el, H.M.S., Samah, M.H., Marwa, A.N., 2017. The anti-viral and immunomodulatory activity of cinnamon zeylanicum against "NDV" newcastle disease virus in chickens. Int. J. Sci. Basic Appl. Res. 32 (2), 251–262.
Thatte, U.M., Dhanukar, S.A., 1997. The rasayan concept: clues from immunomoldulatory therapy. In: Upadhayaya, S.N. (Ed.), Immunomodulation. Narosa Publishing House, New Delhi, India, pp. 141–148.
Thejass, P., Kuttan, G., 2007. Immunomodulatory activity of Sulforaphane, a naturally occurring isothiocyanate from Broccoli (Brassica oleracea). Phytomedicine 14 (7-8), 538–545.
Tiwari, V., Darmani, N.A., Yue, B.Y.J.T., Shukla, D., 2010. In vitro antiviral activity of neem (Azardirachta indica L.) bark extract against herpes simplex virus type-1 infection. Phytother. Res. 24 (8), 1132–1140.
Tripathi, D.M., Gupta, N., Lakshmi, V., Saxena, K.C., Agrawal, A.K., 1999. Antigiardial and immunostimulatory effect of Piper longum on giardiasis due to Giardia lamblia. Phytother. Res. 13 (7), 561–565.
Tuyaerts, S., Rombauts, K., Everaert, T., Van Nuffel, A.M.T., Amant, F., 2019. A phase 2 study to assess the immunomodulatory capacity of a lecithin-based delivery system of curcumin in endometrial Cancer. Front. Nutr. 5, 138. https://doi.org/10.3389/fnut.2018.00138.
Vasanthi, H.R., Mukherjee, S., Das, D., 2009. Potential health benefits of Broccoli- A chemico-biological overview. Mini Rev. Med. Chem. 9 (6), 749–759.
Venkatachalam, V.V., Rajinikanth, B., 2013. Immunomodulatory activity of aqueous leaf extract of Ocimum sanctum. In: Malathi, R., Krishnan, J. (Eds.), Recent Advancements in System Modelling Applications. 188. Springer, India. https://doi.org/10.1007/978-81-322-1035-1_37.
Wang, Y.F., Wang, X.Y., Ren, Z., Qian, C.W., Li, Y.C., Kaio, K., Wang, Q.D., Zhang, Y., Zheng, L.Y., Jiang, J.H., Yang, C.R., 2009. Phyllaemblicin B inhibits Coxsackie virus B3 induced apoptosis and myocarditis. Antiviral Res. 84 (2), 150–158.
Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., Wang, B., Xiang, H., Cheng, Z., Xiong, Y., Zhao, Y., Li, Y., Wang, X., Peng, Z., 2020. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA 323 (11), 1061–1069. https://doi.org/10.1001/jama.2020.1585.

WHO, 2020. Director-General's Opening Remarks at the Media Briefing on COVID-19. World Health Organization, 11 March 2020.
Wijesekera, R.O., 1978. Historical overview of the cinnamon industry. CRC Crit. Rev. Food Sci. Nutr. 10, 1–30.
Win, N.N., Kodama, T., Lae, K.Z.W., Win, Y.Y., Ngwe, H., Abe, I., Morita, H., 2019. Bis-iridoid and iridoid glycosides: viral protein R inhibitors from Picrorhiza kurroa collected in Myanmar. Fitoterapia 134, 101–107.
Xiang, Y., Pei, Y., Qu, C., Lai, Z., Ren, Z., Yang, K., Xiong, S., Zhang, Y., Yang, C., Wang, D., Liu, Q., 2011. In vitro anti-herpes simplex virus activity of 1,2,4,6-tetra-O-galloyl-b-D-glucose from Phyllanthus emblica L. (Euphorbiaceae). Phytother. Res. 25 (7), 975–982.
Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C., Liu, S., Zhao, P., Liu, H., Zhu, L., Tai, Y., Bai, C., Gao, T., Song, J., Xia, P., Dong, J., Zhao, J., Wang, F.S., 2020. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir. Med. 8 (4), 420–422.
Yoshikawa, M., Matsui, Y., Kawamoto, H., Umemoto, N., Oku, K., Koizumi, M., Yamao, J., Kuriyama, S., Nakano, H., Hozumi, N., Ishizaka, S., Fukui, H., 1997. Effects of glycyrrhizin on immune-mediated cytotoxicity. J. Gastroenterol. Hepatol. 12, 243–248.
Younus, I., Siddiq, A., Ishaq, H., Anwer, L., Badar, S., Ashraf, M., 2016. Evaluation of antiviral activity of plant extracts against foot and mouth disease virus in vitro. Pak. J. Pharm. Sci. 29 (4), 1263–1268.
Ziebuhr, J., 2005. The coronavirus replicase. Coronavirus Replication Reverse Genetics 287, 57–94.