

Special invited review article: Open access

Medicinal plants, aromatic herbs and spices as potent immunity defenders: Antiviral (COVID-19) perspectives

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Article Info

Article history

Received 3 September 2020

Revised 26 October 2020

Accepted 29 October 2020

Published online 30 December 2020

Keywords

SARS-CoV-2

COVID-19

Medicinal plants

Aromatic herbs

Spices

Immunomodulators

Abstract

Global health is at risk due to the current SARS-CoV-2 pandemic which has posed a huge challenge. The virus has several protein spikes termed peplomers, on its surface, and is a positive-sense single-stranded RNA enveloped virus. The number of infected people across the globe is in an exponential phase in many of the 220 countries infected by the pandemic, and currently is in its second phase of infection at many places.

Scientists and researchers have set in a global race, the winning stride being successful discovery of a preventive vaccine and a specific treatment for COVID-19. Till such time, centers for ancient civilizations as India and China have intensified their search towards alternative medicine using herbal products, which hold immense pharmacological properties. In case of COVID-19, aromatic plants and herbs downregulate the pre-inflammatory mediators as IL-1, 6, 10 and 18, TNF- α and NF- κ B associated with the cytokine storm, which has proved to be fatal. Simultaneously, enhancement of expression of inducible nitric oxide synthase, production of IgG, IFN- γ and IL-4 and activation of T helper cells, and NK cells, promises to provide protection along with therapeutic potential. These can be instrumental in enhancing the body's immune system along with strengthening and maintaining the health of the respiratory tract, the preferred host for the SARS-CoV-2. Such a modality can reach help to people who are immune compromised due to comorbidities as diabetes, hypertension, cancer, and other related disorders.

The present review focuses on reporting aromatic herbs, medicinal plants and spices with potential antiviral and immunomodulatory properties. To cater to the global health till such time that targeted drugs for the viral infection are made publicly available, these herbal remedies can surely be our best defenders.

1. Introduction

The entire globe has been startled by COVID-19 or the coronaviruses pandemic. Coronavirus is a RNA virus, belonging to the family Coronaviridae. Its nuclear material is positive-sense single-stranded RNA and it is an enveloped virus. 'Corona' is Latin in origin and refers to 'a crown or wreath', and the virus was so named on the appearance of infective form of virus which under an electron microscope appears to have multiple large surface projections or spikes making it appear like a crown or wreath. These projections are due to the proteinaceous viral spike peplomers. This class of virus until the outbreak of the severe acute respiratory syndrome (SARS) in the beginning of 21st century (Guan *et al.*, 2003) and the Middle East respiratory syndrome (MERS) in 2013 (Hemida, *et al.*, 2013), was considered to largely affect the respiratory system and to some extent the gastrointestinal system in animals. These viruses lead to symptoms similar to pneumonia affecting respiratory system.

The SARS and MERS are believed to have been originated from bats and transmitted to humans through other animals like camels and civets (Cui *et al.*, 2019; Hu *et al.*, 2017). The viruses of this family depict large genetic diversity with high rate of recurrent recombination and great possibility of transmittance, thereby suggesting the emergence of variants of these viruses periodically.

November 2019 saw emergence of a new viral strain named SARS-CoV-2 or novel coronavirus or COVID-19, by International Committee on Taxonomy. This viral disease which has gripped the entire globe, originated from the market in Jiangnan District, Wuhan, China which trades in live animals and seafood. Statistics suggest that more than 200 countries across all continents were rapidly infected with this virus within 3 months. World Health Organization (WHO) declared the disease, a pandemic in the second week of March 2020, whose symptoms were alike SARS (WHO, 2020). Globally as per 6th December 2020, the number of reported cases were 65,870,030 with 1,523,583 casualties as per WHO dashboard on COVID-19.

The main clinical manifestations of infection by SARS-CoV-2 studied in 1099 patients by Guan *et al.* (2020), from different areas in China, revealed that the dominant ones include fever and fatigue, sore throat and cough, shortness of breath, myalgia, headache, chills, and sputum production whereas few patients reported vomiting

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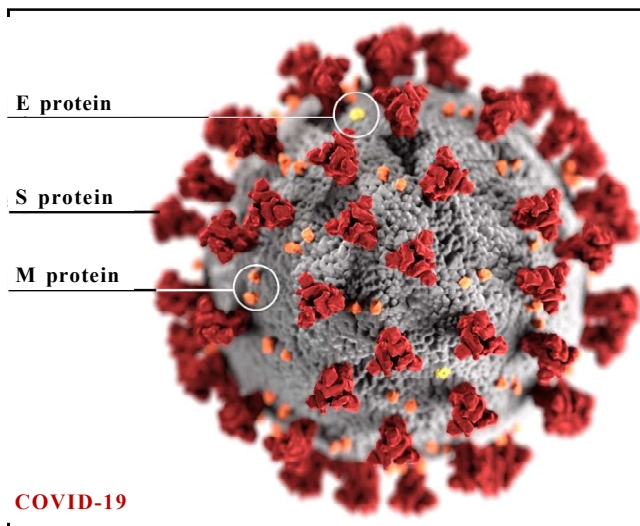
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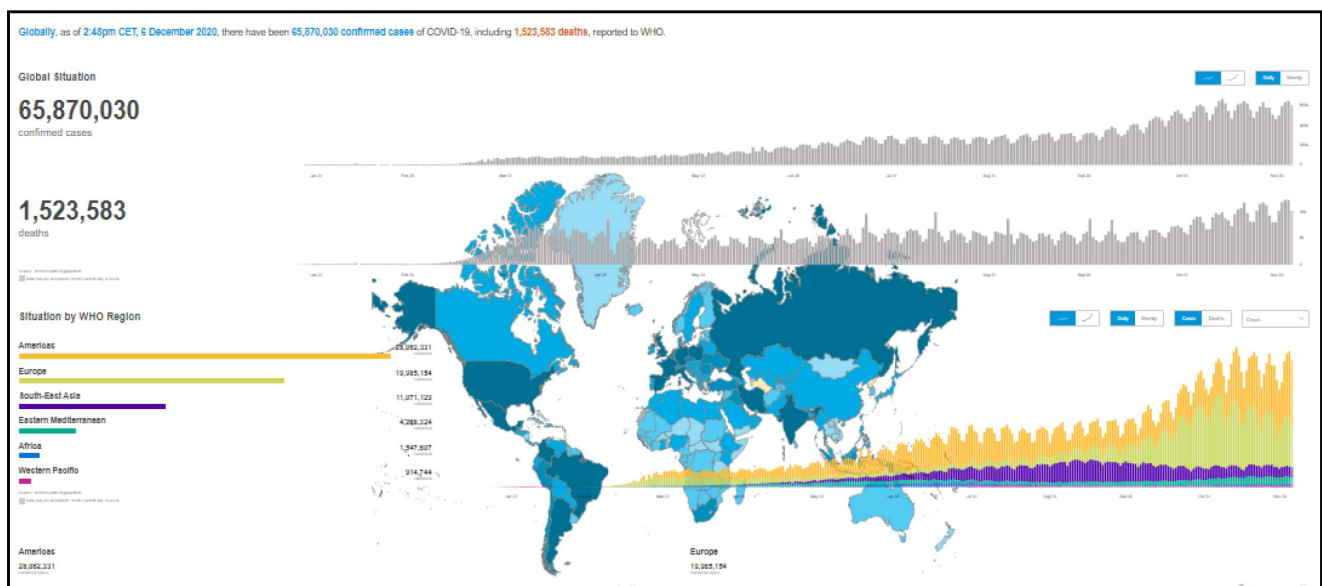
and diarrhea and associated gastrointestinal discomfort. An analysis of patients who contacted the disease suggests that the disease turned fatal in patients above 60 or ones with comorbidities as hypertension, diabetes, cancer, *etc.*, with the number of male patients being higher than females. The rate of infection was elevated in patients with compromised immune system (Li *et al.*, 2020; Hong Kong Centre for Health Protection, 2020; Gao *et al.*, 2020). It was suggested that the best strategy to control and prevent infections were to build and maintain a strong immune system in the body. Thus, a healthy immune system with good holistic wellbeing are crucial factors for assuaging COVID-19 associated risks and increasing rate of survival as well as hastening recovery. Further, the need of the hour is to effectively adopt preventive therapeutic strategies to alleviate the risk of contracting COVID-19 infection till such times that effective antiviral drugs specific for COVID-19 or vaccine are designed, developed and delivered.



Corona virus - Photo credit: CDC/Alissa Eckert, MS; Dan Higgins, MAMS. (Source: Khan *et al.*, 2020: The COVID-19 pandemic: A scoping review.)

The role of innate immunity against viral infections is crucial as the first line of defense. The pathogenicity followed by severity of symptoms and fatality is dependent on the ability of the virus to elude innate immune response. In case of COVID-19, acute respiratory distress syndrome (ARDS) was basically an outcome of dysregulated immune response or ‘cytokine storm’ due to secretion of pro-inflammatory cytokines (Cheng *et al.* 2020) and a moderate reduction in interferon (IFN) response during primary stage could be beneficial. Further, the innate immune response of fighting the virus is related to upregulation of interferon-stimulated genes (ISGs) such as IFIH1, ISG15, OAS1-3, MX1, IFITMs, *etc.* Simultaneously with an increased levels of proinflammatory cytokines like IL-6, IL-2 and IL1 β , tissue damage by the virus is increased. To date, we still are unclear of how the SARS-CoV-2 upsets the host innate immune response and aggravates to lead to severity of infection (Prasad *et al.*, 2020).

Typically, the human body immediately elicits both innate as well as adaptive immune response against a viral infection. The preferred target for the SARS-CoV-2 are the ACE2 receptors. On entering the host cell, the virus releases its nucleic acid, *i.e.*, RNA into the cell and the virus replicates (Cao *et al.*, 2020). Thevarajan *et al.* (2020) investigated hospitalized patients with mild to moderate symptoms and observed an increase in activated CD4⁺, CD8⁺, follicular helper T cells and plasma B cells along with elevated levels of IgG and IgM. In contrast in patients with severe infection, a considerable fall in multiple immune cells as B, T (both CD4⁺ as well as CD8⁺) and NK cells, was observed alongwith lymphocytopenia. The neutrophil to lymphocyte ratio (NLR) as well as C-reactive protein levels, also significantly increased. It was further observed that in critically ill, pro-inflammatory cytokines along with chemokines, *viz.*, TNF- α , IL-2, 6, 7, 8, 10, monocytochemo attractant protein 1 (MCP1), GCSF, and macrophages were found to be elevated (Huang *et al.*, 2020; Qin *et al.*, 2020; Wang *et al.*, 2020a). Elevated NLR, is an effective biomarker of systemic inflammatory response syndrome suggestive of high inflammatory response in the body. This is



(Source: WHO Dashboard, <https://www.who.int/>)

affected through the cytokine storm or uncontrolled release of cytokines and chemokines leading to over active inflammatory responses. Thus, the adaptive immune response is impaired becoming hyperactive and triggers multiple complications as viral sepsis, pulmonary injury leading to acute respiratory distress syndrome (ARDS) and ultimately to organ failure resulting in fatality (Prompetchara *et al.*, 2020).

Since ancient times, across all cultures worldwide, plants have been used as alternative medicines for treatment of many acute as well as chronic infections (Salehi *et al.*, 2019a; Sharifi-Rad *et al.*, 2019; Salehi *et al.*, 2020). In the last 25 years or so, researchers are emphatically making conscious efforts to substantiate potential of plants for health improvement (Sharifi-Rad *et al.*, 2018). Ancient medicinal sciences as those from India, *viz.*, Ayurveda, Siddhi and Unani or those from Chinese, Thai, Persian or Homeopathy, *etc.*, are all being revisited in search for potent antiviral remedies (Yang *et al.*, 2020). Ayurvedic science is a treasure with over 25,000 herbal formulations being used for various ailments, though lack of scientific research on their mechanism of action has hindered their acceptance to the world at large (Pundarikakshudu and Kanaki, 2019). Parasurman *et al.* (2014), rationalized that the medicinal plants contain multiple phytoconstituents which includes secondary metabolites as alkaloids, steroids, glycosides, tannins, terpenoids, saponins, *etc.*, which are pharmacologically effective against various types of infections.

This compilation is aimed at reviewing the immunomodulatory effects of common medicinal plants, aromatic herbs, and spices that can prove beneficial against infections affecting the respiratory tract along with their role as antiviral. The readers can incorporate the usage of these food plants in their dietary regime for improving their overall health and keep them protected in this pandemic.

2. Role of immunity boosters

In current health crisis, efforts to understand the mechanism of natural products towards being antiviral through interruption of virus replication and its life cycle will help evolve a prophylactic along with a therapeutic modality. Ayush Ministry in India in its advisory published in 2020 suggests use of herbal plant products to strengthen immunity to enable one to fight infection. Enhancing the body's immune responses is one of the key factors impeding the virus attack. This will enrich the body's defense mechanism to mediate the desired immune responses as anti-inflammatory, intense cell mediated and regulated antigen presentation and also suppress activity of pro-inflammatory mediators along with proper coordination between the innate and cell mediated responses. The role of cytokines in the pathophysiology of SARS-CoV-2 is crucial as some of these like interleukin-7 and type-I interferon are beneficial while others as TNF- α , interleukin-1 β and 6, appear to lead to cytokine storms which is detrimental. This escalation can be prevented through diet modulation by incorporating plant products with the potential of modulating the immune system along with appropriate sleep and a stress free environment (Jayawardena *et al.*, 2020).

Calder *et al.* (2020) have revealed that the mediators of the immune system namely lymphocytes, helper T cells, natural killer

cells along with secretions as antibodies and interleukins (IL4, 5, 10 and 13), get impaired in presence of stressors, alcoholic and carbonated beverages resulting in higher chances of infection and the transformation of lytic phase of virus into lysogenic one. These are also associated with the release of corticosteroids as epinephrine, norepinephrine and glucocorticoid which further weakens the immunity. The body's requirement for appropriate sleep to recoup its vitality is also an important facet associated with good immunity. Appropriate sleep boosts the immunogenic memory responses by assisting in T cell reorganization towards the lymph nodes. It also boosts immuno-surveillance as it increases count of natural killer cells, neutrophils, T cells and monocytes which thwart the detrimental health prevalence.

Increase in glucose intake or that of CO₂ which is plentiful in beverages delays pathogen removal as it inhibits the activity of phagocytic macrophages. The recruitment of immune cells is increased with supplementation of micronutrients as vitamins. Good supplementation through natural vitamins enriches the immunomodulatory activities of many immune cells. Increase in the immune soldiers can prompt anticorona response. It is expected that these immune cells would activate the anti-coronavirus response through an increase in levels of secreted immunity mediators as secretion of antimicrobial peptides, defensin β and cathelicidin along with activation of processes as chemotaxis, thereby leading to increased phagocytosis and neutrophil migration. This cascade further activates the B and T cell proliferation leading to more antibodies and cytokine synthesis helping curb the infection. The role of diet has been highlighted which can help in recouping from hypovitaminosis which is a fallout of infection (Khanna *et al.*, 2020).

The role of minerals especially micronutrients in immunity is equally significant. These are abundant in the diet comprising of fruits and vegetables and the spices used in cooking. These fortify not only the innate but also the adaptive immune responses as they contain a variety of phytochemicals which facilitate better activity of immune cells. Thus, the role of a balanced diet to collaborate towards attaining optimal immunity is of utmost significance. Physical activities and regular exercises in open areas further assist the body's defense as sunlight is a potent virucide (Martin *et al.*, 2009).

The active phytochemicals in the plant products also contribute to building strong immune responses. Innate immune response against viruses is given a boost by polyphenols as they form receptors which further increases their uptake leading to a signaling of innate immune responses. Nieman and Wentz, (2019) and Lin *et al.* (2017), depicted immune protective action against coronaviruses of much acclaimed resveratrol obtained from grape seeds. Another viable candidate is liquorice with glycyrrhizin as an active component which is known to possess anti-coronaviruses and SARS activity (Chen *et al.*, 2004; Cinatl *et al.*, 2003; Brush *et al.*, 2006), and a potent candidate for trial drug for COVID-19. Well researched phytochemicals obtained from turmeric as curcumin and epigallocatechin gallate from tea are known to protect against allergies as well as grant immunity to gastrointestinal tract (GIT).

Recently Khan *et al.* (2020), cited that plant based products have immense pharmacological potential and they can prove to be crucial resources for developing anti-COVID-19 therapeutic strategies. Figure 1 explains the potential of herbal products in enhancing and maintaining immunity against viral infections.

3. Prospective herbal warriors

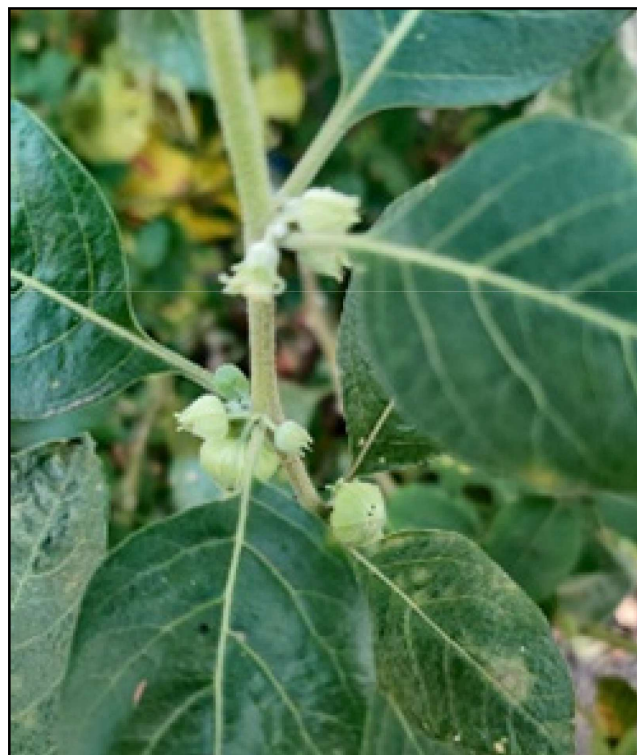
A clear shift in the outlook towards healthy existence is being observed, as with advanced technology, life has become simple and at the same time the incidence of disorders associated with this life style as diabetes, hypertension, hyperlipidemia, *etc.*, have increased. People are now seeking alternative and non-conventional therapies. The science of medicine has a strong foundation in India and Indian origin surgeon, Sushruta, is acclaimed across the world as father of surgery. The traditional Indian plant based therapies are acclaimed to have been one of the oldest health systems.

Multiple practices were followed through branches of Indian healing systems as ayurveda, yoga, siddha, and unani, along with homeopathy for curing various diseases and disorders (Gomathi *et al.*, 2020). These various arms of therapy were founded using products from not only plants but even animals as well as minerals for treatment (Tabuti *et al.*, 2003).

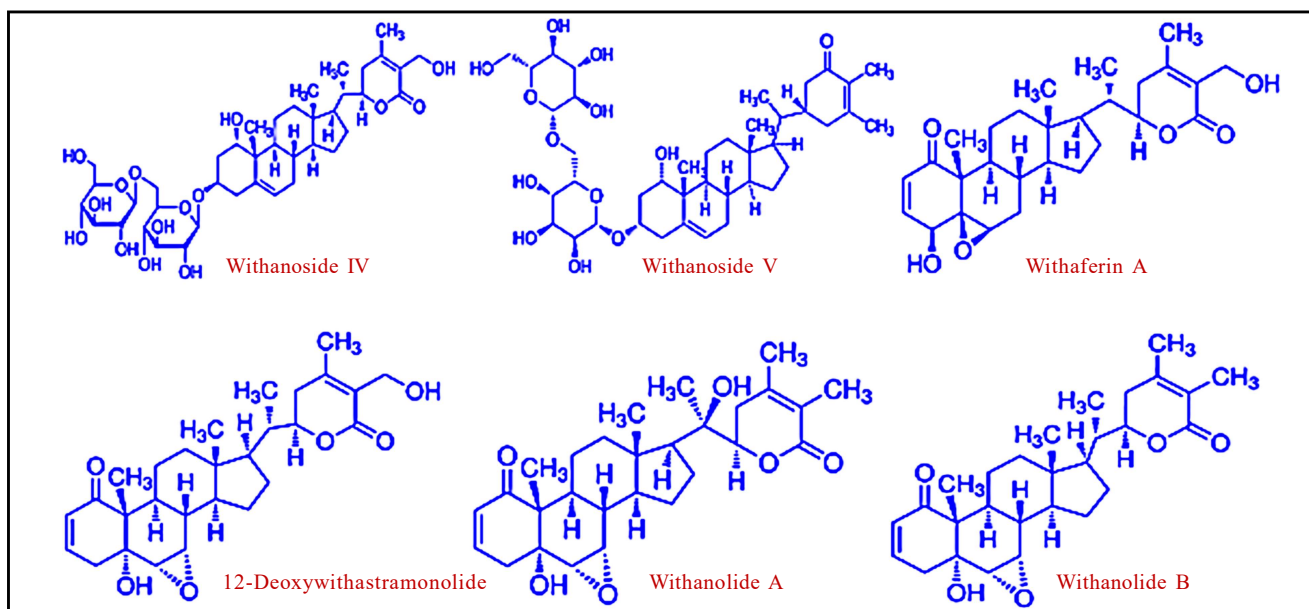
Not only in India, WHO suggests that close to 80% of world population has strong belief in the potential of herbal remedies. Thus, sincere efforts on part of researchers to provide scientific data to support the claim of such non-conventional therapies will go a long way in meeting global health.

4. Medicinal plants and aromatic herbs

4.1 *Withania somnifera* (L.) Dunal (Ashwagandha)



Withania somnifera plant.
(Source: Dr. Bindu Gopalkrishnan)



Major phytochemicals in *Withania somnifera*.
(Source: Nile *et al.*, 2011)

Indian herb *Withania somnifera* (WS) (Ashwagandha) belongs to family Solanaceae and has been used as a traditional medicine by practitioners. Amongst the phytochemicals, the major ones are withaferins, steroid lactones, and steroid alkaloids of the withanolide

series. (Nile *et al.*, 2011). Chengappa, (2018) recorded that the plant acts as an immune booster while Sun *et al.* (2016) found the plant to possess anti-inflammatory activities.

WS extract leads to enhanced phagocytotic activity by macrophages. Iuvone *et al.* (2003) reported that nitric oxide formation increased in presence of WS extract in a concentration dependent manner and resulted in further increase in macrophagal cytotoxic effect against pathogens and tumor cells. Nitric oxide synthase generates inflammatory mediators which inhibit pathogenic growth, and the secretion of this enzyme is increased in presence of WS extract. Other phytochemicals as glycosylated derivatives of withanolides, along with sito-indosides in a WS extract lead to activation of phagocytic activity as number of macrophages increases along with their mobilization. Rasool and Varalakshmi (2006) found the WS extract to possess effective inhibitory activity towards the mitogen induced lymphocyte proliferation, the complement system, and delayed-type hypersensitivity reaction. Vetvicka and Vetvickova, (2011) reported the ability of the herb to be used for its immunomodulatory, as well as rejuvenating and revitalizing properties. Jain *et al.* (2018) reported promising results with the phytochemicals in WS possessing antiinfluenza, antichikungunya, antibursal viral diseases as well as antiherpes simplex virus properties. Withaferin A (WA) is a potent antiviral against infectious bursal disease virus (IBDV) and HSV (Pant *et al.*, 2012), HIV-1 (Shi *et al.*, 2016) and HPV (Munagala *et al.*, 2011). Thus, WS can prove to be a good immune booster by increasing the number of T, B as well as NK cells and modulating the Th-1/Th-2 immunity. The presence of antioxidants facilitates immune homeostasis. Further, it can help induce immunity against viruses by enhanced secretion of IFN- γ responses.

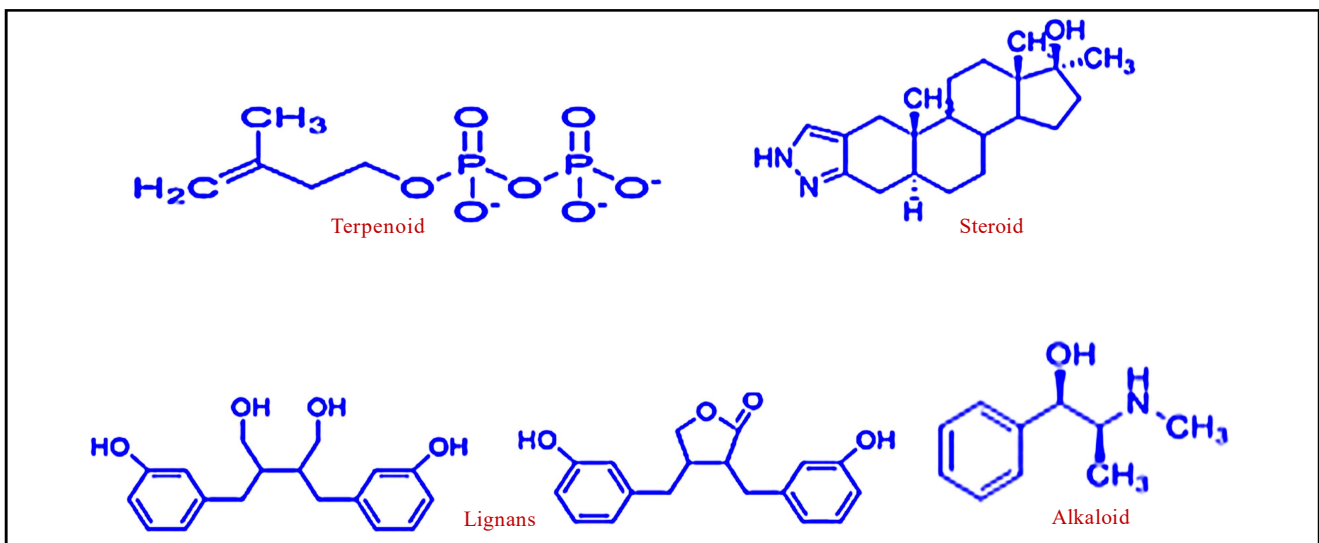
A characteristic effect of coronavirus is the enhanced inflammation which too can be managed by WS extract, as it down regulates various cytokines as IL-1, IL-6, TNF α (Patwardan *et al.*, 2020). Tripathia *et al.* (2020) reported that withanoside V is a potential inhibitor against M^{pro} of SARS-CoV-2 and could prove advantageous to combat COVID-19.

4.2 *Tinospora cordifolia* (Willd.) Miers (Guduchi)



Tinospora cordifolia plant.

(Source: <http://www.flowersofindia.net/extrapics/Gulbel-1.jpg>)



Major phytochemicals in *Tinospora cordifolia*.

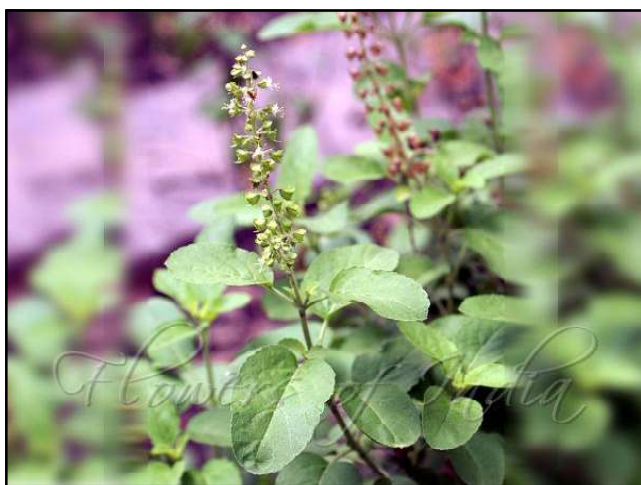
(Source: Sharma *et al.*, 2019)

Popularly termed 'Amrita' suggestive of its role in rejuvenating dead cells, *Tinospora cordifolia* (TC) is another popular herb known also for its immunomodulatory properties, facilitating enhancement of innate immunity against COVID-19 infections. The diterpenoid tinosporin, has antiviral potential and has proved to be effective for therapy of retroviruses and other viruses. The activation of immune cells along with cytokine production is influenced, post viral infection, by guduchi. The extract is rich in antioxidants and it increases the level of bioavailable Vit C which improve immunity (Akhtar 2010).

The proteins in the stem of the plant increase the phagocytic activity of macrophages and, thus it has immunomodulatory properties (Aranha, 2012). The extract of TC inhibits C3 convertase of the complement system, which is an anaphylatoxin, and it prevents release of proinflammatory anaphylactic peptides. Enhancement of IgG was also observed in a dose dependent manner (Kapil and Sharma 1997).

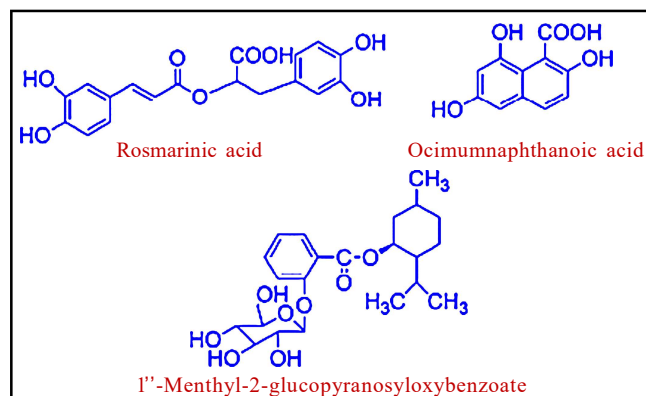
Sagar and Kumar (2020) using *in silico* tools, tested the antiviral activity against targets used by the SARS-CoV-2 for host attachment and replication. The four targets used were the receptor domain (6M0J) and 6VSB, the surface glycoprotein involved in attachment and the 6M71, which is an RNA dependent RNA polymerase and 6Y84 - the protease responsible for viral replication. They suggested that the phytochemicals isocolumbin, berberine, tinocordiside and magnoflorine possessed high binding efficacy for all the targets studied, suggestive of the merits of this plant in management of COVID infection. Another similar study found strong stability of another protease 3CLpro for cardiofolioside B, tinosponone, berberine, xanosporic acid and tembetarine (Krupanidhi *et al.*, 2020). Indian Government's Ayush Ministry (2020), in its health advisory have strongly recommended the use of 500 mg x 2 tablets prepared using aqueous extract of TC as a preventive.

4.3 *Ocimum sanctum* Linn. (Tulsi)



Ocimum sanctum plant.

(Source: <http://www.flowersofindia.net/catalog/slides/Tulsi.jpg>)



Major phytochemicals in *Ocimum sanctum*.

(Source: Singh and Chaudhuri, 2018)

Leaves of tulsi are considered pious and holy in India and it is a versatile herb with immense medicinal properties. For management of pain, fever, cough and cold as well as diarrhea, tulsi has been used since ancient times. One of the best remedies for pneumonia is tulsi along with cow ghee. This plant has proved as an antiviral for vaccinia virus, newcastle disease virus and infectious bursal disease virus (Prakash and Gupta, 2005). Beneficial effects of tulsi leaves decoction has been studied in respiratory disorders as cough and

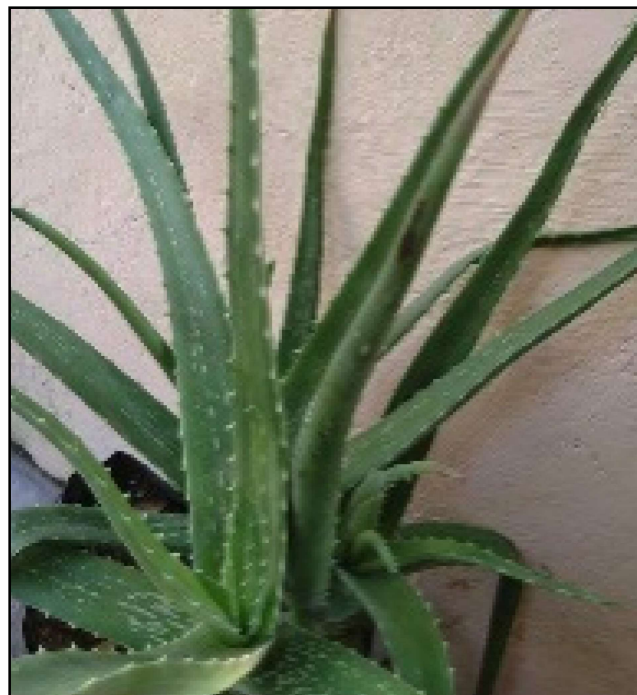
cold, bronchitis, asthma, and influenza and these were attributed to the phenolic content which provides antioxidant properties (Shivananjappa and Joshi, 2012).

An increase in NK and Th cell count and IL-4 secretion has been observed in presence of flavonoids from tulsi. Antiviral properties of the essential oil-eugenol have been found against hepatitis B virus, polio virus type 3 and herpes virus (HSV). An ethanolic extract was found to inhibit polio type 3 virus replication while ursolic and linalool acid depict broad-spectrum antiviral activity against DNA as well as RNA virus (Shrivastav and Saxena, 2020).

Ocimum sanctum seed oil (OSSO) showed immunomodulatory effect on both arms of adaptive immune responses, *viz.*, humoral and cell-mediated, which were associated with GABAergic pathways (Jeba *et al.*, 2011). There was significant decrease in release of histamine and lymphokines due to inhibitory activity as well as leucocyte migration inhibition. It was suggested that it not only had a direct anti-inflammatory effect, but it also inhibited cell-mediated immune response. The leaf extract results in increase in phagocytic activity and increases the number of neutrophils and lymphocytes. Tulsi shows an increment in antibody production as well as the intermediaries of hypersensitivity reactions as the WBC count was increased along with an increase observed in haemagglutination titer (Mukherjee *et al.*, 2005). These immunomodulatory properties can be credited to presence of flavonoids and terpenoids. Mediratta *et al.* (2002) reported that *O. basilicum* modulates both humoral and cell-mediated immune responses.

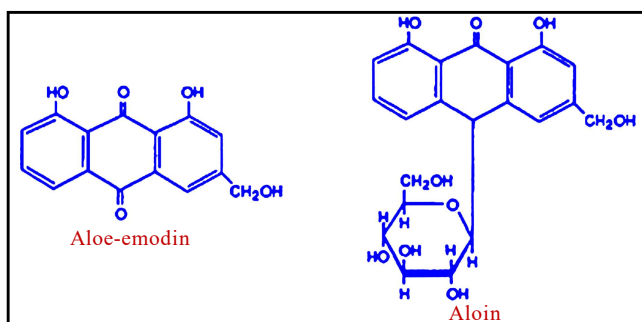
Shree *et al.* (2020) conducted *in silico* studies on 46 active phytochemicals found in *O. sanctum* (Tulsi) for affinity to the ligand N3 against SARS-CoV-2 M^{pro}. The phytochemicals exhibiting high affinity were Vicenin (CID_3084407), Isorientin 42-*O*-glucoside 23-*O*-*p*-hydroxybenzoate (CID_44257986), and Ursolic acid (CID_64945).

4.4 *Aloe vera* (L.) Burm.f



Aloe vera plant.

(Source: Dr. Bindu Gopalkrishnan)



Major phytochemicals in *Aloe vera*.
(Source: Shelton, 1991)

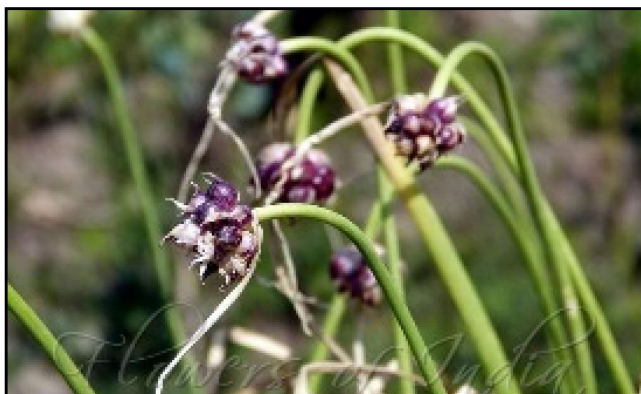
This ‘miraculous or wonder plant’ is known across various world cultures for its medicinal properties. The plant belongs to the family Xanthorrhoeaceae. The phytochemistry and pharmacology of this plant is well documented. The main polysaccharides present are glucomannan and acemannan and the other components are magnesium, calcium, zinc, vitamins A, C, E, plant sterols, cholesterol, carboxypeptidase, prostaglandin precursors as gammalinolenic acid, salicylic acid, lignins and saponins (Sharrif and Sandeep, 2011).

Aloe vera gels’ main polysaccharide, acemannan is known to enhance the count of macrophages and T cells. The polysaccharide along with interferon gamma, facilitates macrophages to release NO and TNF- α which promotes phagocytosis, as the terminal mannose in acemannan is recognized as an antigen by macrophages due to it being similar in structure with polysaccharides present in microorganisms. In combination with interferon- γ , apoptosis was induced in the RAW 264.7 cell line (Tai-Nin Chow *et al.*, 2005).

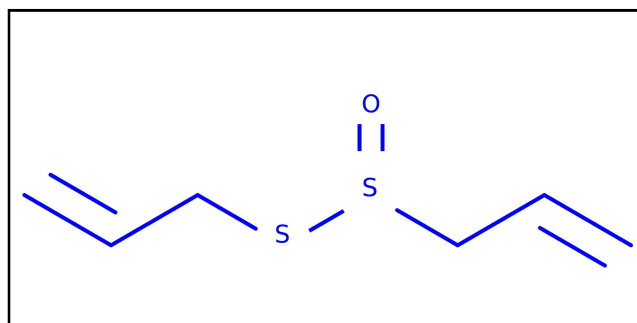
Acemannan upregulates the generation and function and cytotoxic T-cells and induces maturation of dendritic cells. Acemannan also has been found to possess antiviral activity in *in vitro* studies against HIV, influenza virus and newcastle disease, mainly by glycosylation of not only the glycoprotein coats of viruses but that of also virally infected cells (Sierra *et al.*, 2014).

Termination of protein synthesis by the inhibition of nucleic acid biosynthesis was seen in herpes simplex virus type 1 and 2 and in varicella-zoster virus (VZV) by aloe-emodin another component of the aloe gel (Pius *et al.*, 2020a). Molecular docking studies to find the best ligand revealed that reactivity against the COVID-19 main protease (Mpro) was maximal for feralolide, followed by aloesin and aloeresin (Pius *et al.*, 2020b).

4.5 *Allium sativum* L. (Garlic)



Allium sativum plant.
(Source: Picture credits: <http://www.flowersofindia.net>)



Major phytochemical in *Allium sativum*.
(Source: Borlinghaus, 2014)

Allium sativum has been documented to possess multiple medicinal properties since ancient times mainly due to it having good amount of organosulfur compounds and flavonoids. It contains anthocyanin, kaempferol, isorhamnetin and myricetin and organosulfur compounds like quercetin and allicin which is detrimental to the growth of many viruses (Kumar and Pandey, 2013).

Allicin mediates immunomodulatory effect by lymphocyte activation as thioallylation activates p21ras which stimulates phosphorylation of ERK1/2 (Borlinghaus *et al.*, 2014)

The quercetins in garlic inhibits the replication of the virus transcription as RNA polymerase is inhibited due to increase in the uptake of zinc as well as the protein synthesis of the viral genome. Antiviral properties of quercetin derivatives have been documented against rhinovirus, poliovirus, influenza B, Ebola virus, hepatitis C virus, herpes simplex type 1 and 2, vaccinia virus, vesicular stomatitis virus and SARS-CoV which hinders virus attachment to host cell (Chen *et al.*, 2006; Gruhlke *et al.*, 2016). Allicin, ajoene, methyl allyl thiosulfate and allyl methyl thiosulfinate help improve production of neutralizing antibodies. Amongst the most prominent constituents, allicin inhibits multiple thiol enzymes while ajoene helps prevents adhesive interaction of viruses and inhibits leukocytes.

The active components stimulate secretion of pro-inflammatory mediators like IFN- γ and development of CD4⁺ T cells and macrophages. They also inhibit production of cyclooxygenase-2 and prostaglandin E2, *via*, NF- κ B inactivation (Jeong *et al.*, 2016). The anti-inflammatory effect can also be attributed to the signaling cascade activation in macrophages, direct suppression of toll-like receptor 4 (TLR4), lowering of nuclear NF- κ B level and enhancing cytosolic levels of NF- κ B and I κ B. At low doses garlic oil shifts adaptive immune response towards Th1-type and promotes development of anti-inflammatory response while at high doses the Th2 type is favored (Rodrigo *et al.*, 2015).

Molecular docking analysis showed that alliin among other OSCs has higher antiviral potential to prevent COVID-19. This bioactive component alone or in combination with the main therapeutic drug would be an efficient therapy to eradicate SARS-CoV-2 with the lowest side effects and toxicity (Rajgopal *et al.*, 2020).

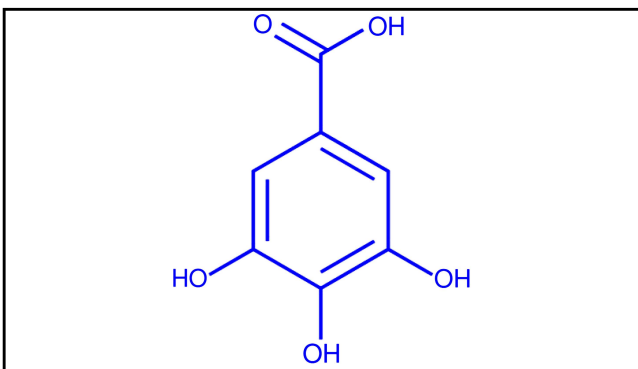
inhibits the activity of ROS activity, apoptosis of neutrophils is regulated along with Th1/Th2 polarization. TF on the other hand down regulates NF- κ B, ICAM-1, VCAM-and inhibits release of IL-6, a proinflammatory cytokines (Chowdhury and Barooah, 2020). The micronutrients in tea further provide additional immunity against the cause of the current pandemic. Selenium acts as immunostimulatory regulating oxidative stress, macrophagic phagocytic activity, enhancing T, lymphocytes, leukocyte and NK cell proliferation and iron promotes activation of NF- κ B cells and enhances host resistance to the intracellular pathogens. Zinc and copper plays a vital role in enhancing phagocyte activities as well as cytokine secretion by macrophages, works against reactive oxygen and nitrogen species and enhances the development and function of neutrophils and NK cells (Street *et al.*, 2006).

Finally, Ghosh *et al.* (2020) have suggested that for the His41 and/or Cys145 in the SARS-CoV-2 3CLPro catalytic pocket, EGCG and GCG displayed strong interaction and had potential as 3CLPro inhibitor.

4.8 *Emblia officinalis* (Amla)



Emblia officinalis plant.
(Source: Dr. Bindu Gopalkrishnan)



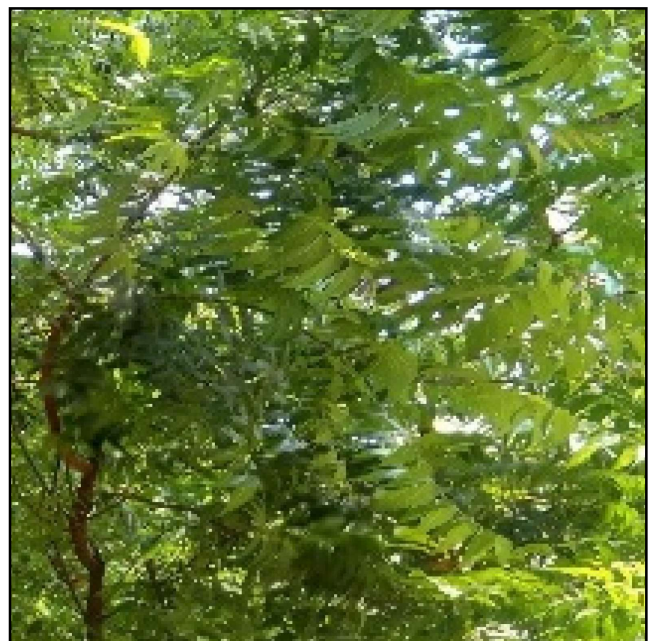
Major phytochemicals in *Emblia officinalis*.
(Source: Meena *et al.*, 2010)

Emblia officinalis comes from the Euphorbiaceae family and is commonly called amla. Studies have shown amla to possess hepatoprotective, antitumor, anti-inflammatory and hypocholesterolemic activities. The fruit has considerably higher concentrations of most minerals, protein and amino acids like aspartic acid, glutamic acid, alanine, proline, cystine and lysine, gallic acid, furosin, β -glucogallin, corilagin, and geraniin. For a long time, it was believed that the amla fresh juice contains good quantity of vitamin C, but it is now known that this activity is due to the emblicanin A, emblicanin B, pedunculagin and puningluconin which are hydrolysable tannins (Sai Ram *et al.*, 2002).

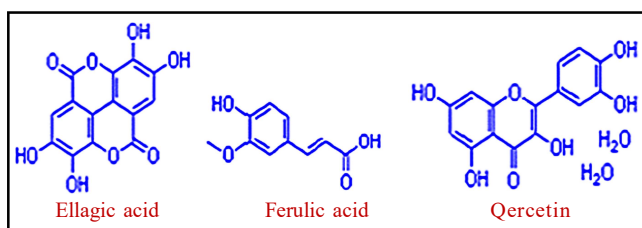
Bhattacharya *et al.* (1999) have shown that amla extract significantly increases the antioxidant enzymes, *viz.*, GPx, catalase, SOD, and reduced lipid peroxidation in the cortical and striatal concentration in the rat brain leading to reduction in free radical-induced oxidative stress. Inhibition of retroviruses as HIV-1 and enhancement of immunity parameters have been attributed to the fruit extracts (El-Mekkawy *et al.*, 1995). Sai Ram *et al.* (2002), demonstrated immunomodulatory and cytoprotective properties of amla along with chromium (Cr) which is believed to be an immunosuppressive agent. The antioxidant status was restored while free radical production was inhibited. Even the Cr associated immunosuppressive effects on lymphocyte proliferation were reversed along with the restoration of IL 2 and gamma IFN production. The activity of NK cell and antibody dependent cellular cytotoxicity was reinstated.

Singh *et al.* (2020) found the potential of using polyphenolic compounds as glucogallin found in amla on SARS-CoV-2, thereby preventing priming of the spike protein and post-translational modification of the viral protein. This polyphenol possessed good absorption and water solubility, no visible effect on essential drugs metabolism and liver enzymes inhibitory effects.

4.9 *Azadirachta indica* A. Juss (syn. *Melia azadirachta*) (Neem)



Azadirachta indica tree.
(Source: Dr. Bindu Gopalkrishnan)



Major phytochemicals in *Azadirachta indica*.
(Source: Pandey *et al.*, 2013)

Azadirachta indica or neem leaves and bark (family, Meliaceae) have been used across civilizations as one of the most versatile medicinal plants serving a wide spectrum of medicinal properties. The United Nations has denoted neem as ‘the tree of the 21st century’ for its multitherapeutic applications. It possesses anti-inflammatory, antioxidant, antipyretic, immune modulatory, antiviral, anticancer, antibacterial and antifungal activities. Amongst the prominent compounds isolated from neem include nimbidin, nimbin, nimbolide, quercetin, β -sistosterol and limonoids. (Bhat *et al.*, 2020; Pandey *et al.*, 2013). It is a potent antiviral inhibiting viral replication in herpes simplex virus type-1, influenza strains coxsackieviruses, *etc.* (Tiwari *et al.*, 2013).

The leaf extract of neem leaf has been used for treatment of especially fever and cough as per Ayurveda. Beneficial effects of neem leaf extract against dengue fever-related symptoms both *in vivo* and *in vitro* conditions were reported. Neem tree branch has potential to relieve cough and asthma (Biswas *et al.*, 2002). Another symptom seen in few COVID-19 patients is diarrhoea and leaves of the plant can treat gastrointestinal disorder. The leaves, flower as well as bark extracts depict strong antioxidant potential and directly scavenge as well as prevent the hydroxyl radical mediated oxidative damage (Roy and Bhattacharyya, 2020).

Neem leaves extract induces both the arms of the adaptive immune response, *i.e.*, humoral as well as cell-mediated response, as the glycoproteins present are effective in maintaining normal immune homeostasis through upregulation of type 1 responses as well as enhancing the antibody production against the infectious bursal disease and newcastle viruses (Bose *et al.*, 2009; Zahid *et al.*, 2013). Enhancement in immunity against HIV/AIDS patients through the increase in CD4⁺ cell count along with induction of dendritic cell maturation and macrophage, mediated antigen presentation has also been observed (Goswami *et al.*, 2010).

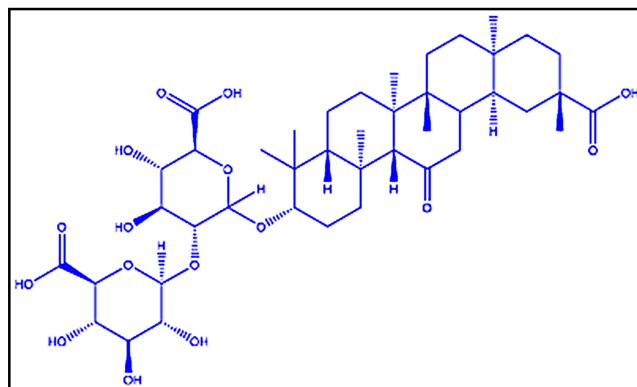
The inhibitory effect on SARS-CoV-19, PLpro protein was noted for the phytochemicals from neem. Potential docking ability was reported, and good prospects were found in comparison with 7 drugs being currently tested against COVID-19, with desacetylgedunin (DCG), depicting the highest docking score. The influence of PLpro and DCG docking, resulted from weak interactions as H-bonds, electrostatic and van der Waals forces and deformation of PLpro structure upon docking with DCG, thus proving its potential for drug development (Baildya *et al.*, 2020).

4.10 *Glycyrrhiza glabra* L. (Licorice/Mulethi)



Glycyrrhiza glabra plant.

(Source: <http://www.flowersofindia.net/extractics/Licorice-1.jpg>)



Major phytochemicals in *Glycyrrhiza glabra*.
(Source: Pastorino *et al.*, 2018)

Glycyrrhiza glabra belonging to Fabaceae family is one of the most important medicinal plants from this family. Also termed licorice or mulethi, it is a native of Mediterranean areas, but present in Asia too. It holds a common remedy for cough, bronchitis gastrointestinal problems, and arthritis. It finds wide application for therapy of peptic ulcers, gastritis, and tremors. Unani folk medicine system asserts it to hold hot as well as wet temperament, as per their standard temperament scale. Its usage for respiratory ailments, due to it being a detoxicant, anti-inflammatory, antipyretic and immune empowering has been well studied. Recent scientific studies added to its foray of activities its potential as anti-microbial, anti-viral, antioxidant, immune modulating, anti-inflammatory and antitumor activities (Pastorino *et al.*, 2018).

Nutritionally, it is rich in all biomolecules along with minerals as sodium, calcium, potassium, phosphorus, iron, selenium, zinc, magnesium, copper, silicon and manganese. Other phytochemicals present are glycyrrhizin, tannins, phytosterols namely sitosterol and stigmasterol, coumarins glabridin, 18-beta-glycyrrhetic acid, liquiritigenin, licochalcone A and licochalcone E, (Wang *et al.*, 2015)

Antiviral property of glycyrrhiza and 18 β glycyrrhetic acid extract was observed against human H5N1 and H3N2 influenza A virus, hepatitis C, coxsackievirus B3 and A16, respiratory syncytial

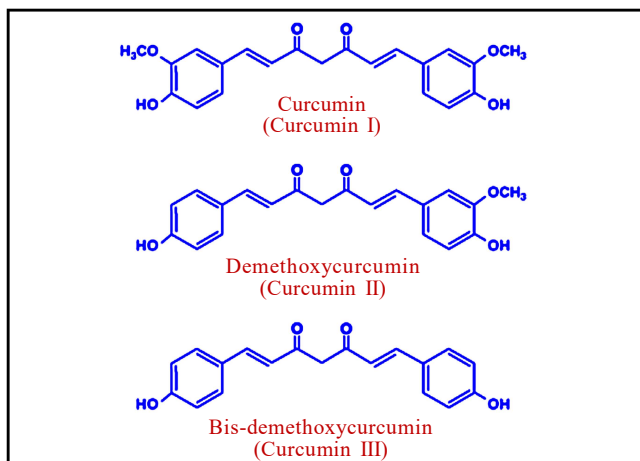
virus, and enterovirus. The extract adversely affects the adhesion of virus and gene expression affecting viral replication. The propagation of cellular response to inflammation due to degradation of κ B enzyme, activation of T lymphocyte proliferation, and suppression of host cell apoptosis has also been found to lead to antiviral activity of glycyrrhiza extract (Wang, 2015). Apoptosis of KSHV infected cells through down regulation in B-cells expression of latency was seen to be affected by glycyrrhizic acid (Damle, 2014). Cellular signaling pathways, *via*, nuclear factor κ B, transcription factors, protein kinase C, casein kinase II, and activator protein 1 were affected by glycyrrhizin. Up regulation of the expression of inducible nitric oxide synthase leading to production of nitric oxide in macrophage along with reduction in the expression of pro-inflammatory cytokines is also affected by glycyrrhizin and 18 β glycyrrhetic acid (Cinatl *et al.*, 2003).

5. Spices

5.1 *Curcuma longa* L. (Turmeric)



Curcuma longa plant.
(Source: Dr. Bindu Gopalkrishnan)



Major phytochemicals in *Curcuma longa*.
(Source: Popuri and Pagala, 2013)

‘Indian saffron’ or turmeric is bright yellow colored herb of the family, Zingiberaceae. Used as a flavoring agent across the Asian continent, it finds great application in ayurvedic science. The dried root is ground to powder and contains all proximate principles along with minerals and curcuminoids. The important ingredients in the plant are curcumin, dihydrocurcumin, and hexahydrocurcumin,

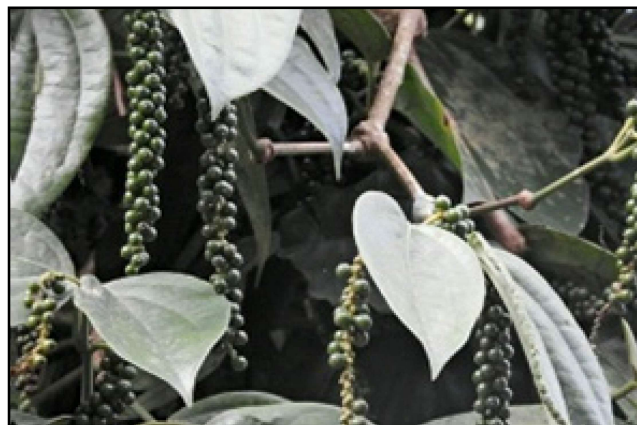
along with volatile compounds as cinol, borneol, zingiberine, α -phellandrene, and many sesquiterpenes (Prasad and Aggarwal, 2011; Popuri, and Pagala, 2013)

Turmeric provides benefits for medical ailments as respiratory infections and curcumin, the most researched natural therapeutic nutrient, bestows preventive and curative effects in multiple disorders, infections, and malignancies (Soni *et al.*, 2020). The immunomodulatory properties are due to interaction of curcumin with cells as B and T lymphocytes, dendritic cells, and macrophages. Curcumin and its derivative, namely; monoacetylcurcumin possess antiviral activity and have been shown to curtail infections of H1N1 and H5N1 influenza, hepatitis B and C, HIV, dengue, chikungunya and zika infections (Divya and Pillai, 2006). It enhances the boosting of T helper-1 mediated immune responses, by inhibiting T helper cytokine profile and suppressing interleukin-12 production by macrophages. Further, curcumin lowers the production of acute phase proteins thereby suppressing cortisol production (Si *et al.*, 2007).

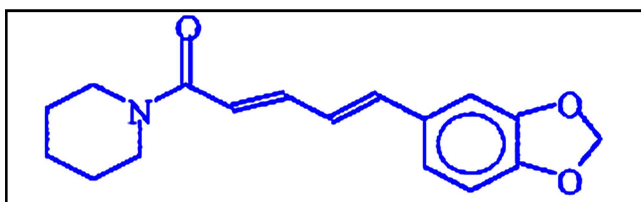
Curcumin impedes the spike protein, namely; ACE-2, furin, basigin, CatB/L and TMPRSS2, and also prevent entry of the virus in the host cells by inhibiting endosomal acidification. It further hampers the replication of SARS-CoV-2 by inhibiting RNA polymerase, MPro- the main protease and also inhibits the release of virions. ACE inhibition leads to a decline in Ang II formation. The inactivation of Ang II is accelerated by enhanced expression of ACE2 by curcumin. Curcumin also downregulates angiotensin receptor inhibiting Ang II and this hampers NF- κ B and MCP-1 activation. Formation of IL-6 and its receptor complex is also prevented as curcumin, which in turn inhibits the ADAM17, dodging adverse effects in COVID-19. Inhibition of STAT3 by curcumin, avoids inflammatory cytokines production. Experimentally supported evidences for the potential of curcumin in prophylactic management and therapy of respiratory infections lead to the recommendation of this spice for its anti-COVID advantage.

In silico studies predict curcumin direct binding with ligands inhibiting entry of virus into the host cells, as well as the modulation of correlated inflammatory events (Chen *et al.*, 2020; Kandeel and Al-Nazawi, 2020; Maurya *et al.*, 2020).

5.2 *Piper nigrum* L. (Black pepper, Kaali mirch)



Piper nigrum plant.
(Source: Dr. Bindu Gopalkrishnan)



Major phytochemicals in *Piper nigrum*.
(Source: Raman and Gaikar, 2002)

Dried unripe fruit of *Piper nigrum* from family Piperaceae, is extensively used in most cuisines across the globe. An extract of black pepper is rich in phytochemicals, the main one being piperine, along with phenolics, alkaloids, flavonoids, steroids, amides, terpenes, lignans, neolignans, chalcones, *etc.*, and their derivatives (Raman and Gaikar, 2002). Four isomers of piperine reported are piperine, isopiperine, chavicine and isochavicine. However, amongst all these compounds isolated, diverse pharmacological activities are seen in piperine, piperamide, pipene and piperamine. Pepper has been studied for its activities like antipyretic, analgesic, anti-inflammatory, antihypertensive, antiplatelets, antitumor, antiasthmatics, antidiarrheal, antispasmodic, antioxidant, antiviral, antibacterial, antifungal, hepatoprotective, immunomodulatory, anxiolytic, antidepressants, antithyroid, antimutagenic, antiapoptotic, antimetastatic and antispermatogenic (Damanhoury and Ahmad, 2014).

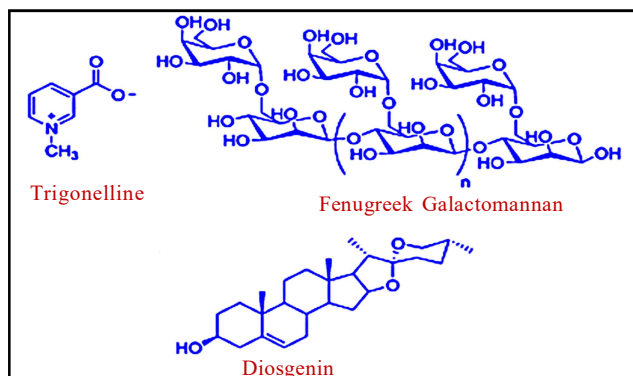
Pepper extract has been used to cater to therapy of viral infections in the respiratory tract, namely; coxsackie virus type B3 (CVB3), human rhinovirus type 2 (HRV2), and influenza virus type A (HK68) and, hence its use in fight against COVID-19 could be beneficial (Mair *et al.*, 2016). Splenocytes proliferation is significantly enhanced by the aqueous extracts of black pepper in a dose-dependent and cooperative manner, suggestive of promotion of proliferative signaling pathways in splenocytes. The release of the Th₂ cytokines, namely; IL-4 and 10 are suppressed by black pepper while that of Th₁ cytokine like IFN γ is enhanced. Further, the aqueous black pepper extracts strengthen the NK cells cytotoxic activity (Majdalawieh and Carr, 2010).

Chaudhary *et al.* (2020) through docking studies have shown that piperine, has high binding affinity towards the RNA-binding pocket of the SARS-CoV-2 nucleocapsid and simulation confirmed it as a potential RNA-binding site inhibitor, suggestive that it is a potential candidate for drug development as it inhibits RNA packaging inhibiting the proliferation of virus.

5.3 *Trigonella foenum-graecum* L. (Fenugreek/Methi)



Trigonella foenum-graecum plant.
(Source: https://cdn.pixabay.com/photo/2017/11/20/11/39/fenugreek-2965214__340.jpg)



Major phytochemicals in *Trigonella foenum-graecum*.
(Source: Venketa *et al.*, 2017)

Fenugreek is member of family Fabaceae and is known as one of the oldest medicinal plant or spice with medicinal properties. Fenugreek seed contains 45-60% carbohydrates, mainly galactomannans-the mucilaginous fiber, proteins, lipids, alkaloids, mainly trigonelline and choline, polyphenols as isovitexin and rhaponticin, saponins and minerals like calcium and iron (Abou-Sheel, 2014; Venketa *et al.*, 2017). It has natural antioxidant properties and has found utility as food for strengthening the immune system. Its utility for relieving sore throat, colds, asthma, sinusitis, influenza, bronchial disorders, pleurisy, pneumonia, laryngitis, cataract, constipation, hay fever and tuberculosis, is well studied. It is also used a gastric stimulant, antidiabetic agent, antibacterial, hepatoprotective, galactagogue and anticancer (Srinivasan, 2006).

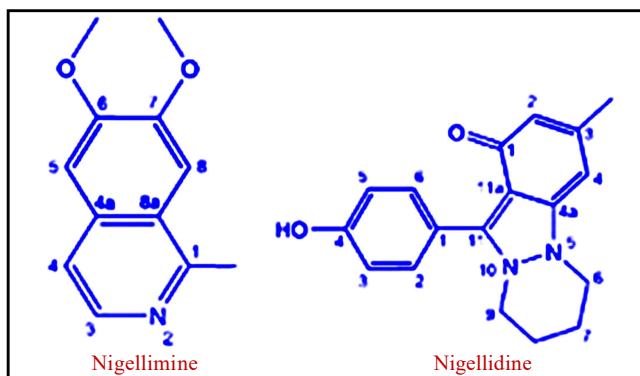
Fenugreek has been acclaimed for its immunomodulatory properties. The cellularity's of thymus and bone marrow along with that of spleen has been found to increase significantly in presence of fenugreek. At low doses, it increases delayed hypersensitivity responses. Plaque-forming cell (PFC) assay results indicative of humoral immunity showed an elevated response at high doses along with significant enhancement in phagocytic potential of macrophages (Rizwanul *et al.*, 2003).

In silico studies with active ingredients in the spice, evaluated them as potential inhibitors of the main protease (Mpro) and spike (S) receptor of SARS-CoV-2, whose role is significant in entry of virus into host and the process of replication and transcription. Quercetin and luteolin from fenugreek are potent ligands for binding to main protease (Mpro) and spike (S) receptor of SARS-CoV-2, respectively (Sen *et al.*, 2020).

5.4 *Nigella sativa* L. (Black cumin)



Nigella sativa L. plant.
(Source: Picture credits: <http://www.flowersofindia.net/catalog/slides/Black%20Seed.jpg>)



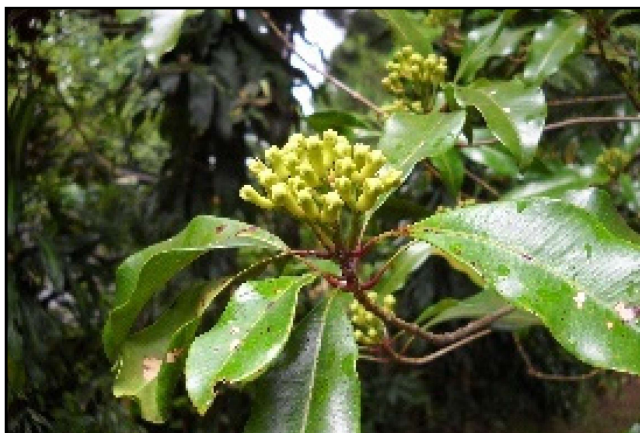
Major phytochemicals in *Curcuma longa*.
(Source: Popuri and Pagala, 2013)

Black cumin or *Nigella sativa* belongs to Ranunculaceae family, possessing a range of medicinal properties. The seeds as well as its oil has potential to treat asthma, inflammatory diseases, rheumatoid arthritis, diabetes and digestive diseases. The main properties in *N. sativa* are due to presence of thymoquinone, though other phytochemicals present are α and β -pinene, p-cymene, dithymoquinone (nigellone), carvacol, longifolene, pinene, thymo-hydroquinone, thymol, nigellidine nigelicine, and nigellimine, saponins and flavonoids (Muhammad *et al.*, 2020).

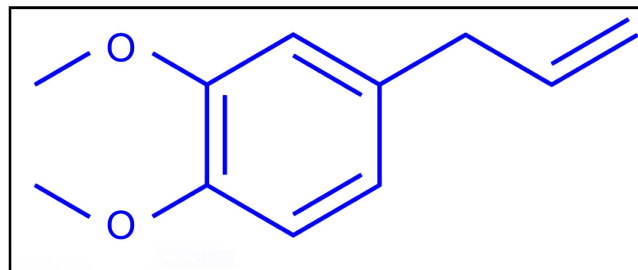
Hossein *et al.* (2008) studied the arachidonic acid metabolism related enzymes against eosinophils and leukocytes suggestive of anti-inflammatory effect. Complexity arises in COVID-19 patients due to elevated pro-inflammatory cytokines like TNF α and IL-6 followed by lymphopenia associated acute respiratory distress syndrome. Inhibition of secretion of IL-6 is an effective treatment modality and thymoquinone inhibits not only IL-6 but also IL-1, 10, 18, along with TNF- α , and NF- κ B, inducible nitric oxide synthase's and transforming growth factor (Srinivasan, 2018). Another active ingredient, α -hederin interferes with secretion of IL-13, thereby suppressing the miRNA-126 expression (Muhammad, *et al.*, 2020).

Docking studies suggest that thymoquinone, thymohydroquinone, nigellidine, hederagenin and α -hederin, depict high to moderate affinity of binding with SARS-CoV-2 enzymes and proteins and carry potential to inhibit viral replication and host cell receptors attachment (Koshak and Koshak, 2020).

5.5 *Syzygium aromaticum* (L.) Merr. and L.M. Perry (Clove)



Syzygium aromaticum plant.
(Source: [https://www.flickr.com/photos/Clous de girofle/](https://www.flickr.com/photos/Clous_de_girofle/))



Phytochemical-Eugenol in *Syzygium aromaticum*.
(Source: Mittal *et al.*, 2014)

S. aromaticum, popularly referred as clove, is a dried flower bud from the Myrtaceae family. Reports document clove to possess antibacterial, antiviral, anti-inflammatory, analgesic, antipyretic, antioxidant and anticarcinogenic properties. It finds use for treatment of burns and wounds, tooth infections and toothache, flatulence, vomiting, liver-bowel and stomach disorders, nausea and nerve stimulant. It is used as appetizer, antipyretic, analgesic, anti-inflammatory decongestant, myorelaxant, antimicrobial, aphrodisiac, anxiolytic, hypnotic, antiemetic and antiepileptic.

Fresh plants are rich in eugenol-the major bioactive molecule, phenolic acids as ellagic, ferulic, caffeic, and salicylic acids, flavonoids as quercetin and kaempferol, gallic acid derivatives and tannins (Batiha *et al.*, 2020; Mittal, *et al.*, 2014).

Eugenol has proved to be antiviral against herpes simplex 1 and 2, as it prevents replication of the virus, thereby reducing chances of infection (Reichling *et al.*, 2018). Cloves show suppression of NF- κ B pathway, prevention of neutrophil and macrophage chemotaxis, inhibition of prostaglandin synthesis and the expression of cyclooxygenase II enzymes leading to anti-inflammatory and immunomodulatory activities (Han and Parker, 2017). Eugenol also downregulates the pro-inflammatory cytokines namely IL-6 and TNF- α expression (Barboza *et al.*, 2018).

6. Conclusion

Conquering COVID-19 is a worldwide challenge as this pandemic has bought not only people but the entire global economy on its toes. Currently, the preventive guidelines revolve around physical distancing, self-hygiene, and self-quarantine. The world of drug design and development is full of zeal towards early development of targeted drugs and a preventive vaccine, however, till the writing of this article, none of the products have hit market for commercial use. However, amongst this darkness, light prevails in use of herbal remedies which can be termed COVID warriors. Table 1 represents a summary of prospective warriors against COVID-19.

Comprehensive research directed towards herbal formulations, can provide lead in this battle. The key players in herbal products mediated therapy for SARS-CoV-2, is the presence of a large number of phytochemicals like aromatic oils, alkaloids, terpenoids, flavonoids, phenols, polyphenols, tannins and saponins, all known to possess innumerable antiviral properties. These aid in blocking not only virus particle invasion and penetration but are equally effective in averting its replication, expression, assembly and release. The key to overcoming the pandemic is working on developing immunity as depicted in Figure 1, for which these herbal defenders can play a vital role. This review on use of herbal

remedies provides a repertoire of candidates which could be leads used for drug development through *in silico* studies. The natural herbal combatants in nature could be developed into frontline

warriors in this battle against COVID-19 due to their potential to not only arrest viral growth in the body but also to develop a strong foundation of the immunity to combat infection.

Table 1: Prospective herbal remedies for COVID-19

Medicinal plant	Common name	Phytochemicals	Antiviral action	References
<i>Withania somnifera</i>	Ashwagandha	Sito-indosides, Withanolide-B, Withanone and Withaferin-A	<ul style="list-style-type: none"> • Host Th1/Th-2 immune response modulation • Upregulation of IFN-gamma responses • Down-regulation of pre-inflammatory mediators as IL-1, 6 and TNF-α 	Patwardhan (2020); Maurya (2020)
<i>Tinospora cordifolia</i>	Guduchi	Alkaloid, terpenoids, lignans	<ul style="list-style-type: none"> • Increase the phagocytic activity of macrophages • Inhibit release of proinflammatory anaphylactic peptides • Enhancement of IgG production 	Kapil and Sharma (1997); Aranha (2012)
<i>Ocimum sanctum</i>	Tulsi	Tulsinol (A, B, C, D, E, F, G), dihydrodieuginol-B, quercetin, eugenol, and apigenin	<ul style="list-style-type: none"> • Potential to inhibit SARS-CoV-2 M^{pro} and papain-like protease associated with viral replication • Upregulation of IFN γ, IL 4, T helper cells, and NK cells 	Varshney <i>et al.</i> (2020); Goothy <i>et al.</i> (2020); Mandal <i>et al.</i> (2020)
<i>Aloe Vera</i>	Aloe vera	Gammalinolenic acid, salicylic acid, lignins and saponins	<ul style="list-style-type: none"> • Enhances macrophages and T cells • Upregulates the generation and function of cytotoxic T-cells 	Tai-Nin Chow <i>et al.</i> (2005)
<i>Allium sativum</i>	Garlic	Allicin, Alliin and S allyl cysteine	<ul style="list-style-type: none"> • Upregulation of IFN-α • Mitigates pulmonary fibrosis, lung injury, and sepsis associated organ 	Bhattacharyya <i>et al.</i> (2007)
<i>Zingiber officinale</i>	Ginger	Zingerone; and multiple forms of gingerol	<ul style="list-style-type: none"> • Beneficial for pulmonary fibrosis and ARDS 	Kulkarni and Deshpande (2016)
<i>Camellia sinensis</i>	Tea	Epigallocatechin gallate, theaflavin and catechins	<ul style="list-style-type: none"> • Inhibition of 3C-like protease of SARS-CoV 	Chen <i>et al.</i> [89]
<i>Emblica officinalis</i>	Amla	Phyllaemblicin-B and phyllaemblinol, gallic acid, furosin, β -glucogallin, corilagin, and geraniin	<ul style="list-style-type: none"> • High binding affinity against spike protein and helicase protein, of COVID-19 • Good antioxidative and anti-inflammatory properties 	Wu <i>et al.</i> (2020)
<i>Azadirachta indica</i>	Neem	Azadirachtin, Nimbolin, Nimbolide, Quercetin, and β sitosterol	<ul style="list-style-type: none"> • Reduction in macrophages and neutrophils infiltration of preventing severe lung damage 	Lee <i>et al.</i> (2017)
<i>Glycyrrhiza glabra</i>	Licorice/Mulethi	Glycyrrhizin, tannins, sitosterol and stigmaterol	<ul style="list-style-type: none"> • Degradation of IκB enzyme • Activation of T lymphocyte proliferation, • Up regulation of the expression of inducible nitric oxide synthase • Reduction in the expression of proinflammatory cytokines 	Cinatl <i>et al.</i> (2003); Wang, <i>et al.</i> (2015); Damle, (2014)
<i>Curcuma longa</i>	Turmeric	Curcumin, Diacetylcurcumin and Dedemethoxycurcumin,	<ul style="list-style-type: none"> • Modification in structure and folding of 3CL-protease • Enhanced effectivity in comparison to Nelfinavir, by diacetylcurcumin, on COVID-19 (Mpro) 	Gonzalez <i>et al.</i> (2020); Adem <i>et al.</i> (2020)
<i>Piper Nigrum</i>	Black Pepper, Kaali Mirch	Piperine, alkaloids, flavonoids, steroids, amides, terpenes, lignans, neolignans, chalcones	<ul style="list-style-type: none"> • Splenocytes proliferation • Suppression of release of IL-4 and 10 • Enhancement of IFNγ 	Majdalawieh and Carr, (2010)
<i>Trigonella foenum-graecum</i>	Fenugreek/Methi	Trigonelline, choline, isovitexin and rhaponticin	<ul style="list-style-type: none"> • At low doses increases delayed hypersensitivity • At high doses increases humoral immunity 	Rizwanul <i>et al.</i> (2003)
<i>Nigella sativa</i>	Black cumin	α and β -Pinene, p-Cymene, Nigellone, Nigellidine Nigelicine, and Nigellimine, and Thymo-hydroquinone	<ul style="list-style-type: none"> • Inhibits IL-6, IL-1, 10, 18, TNF-α, and NF-κB • Induces nitric oxide synthase's and transforming growth factor 	Rinivasan, <i>et al.</i> (2018)
<i>Syzygium aromaticum</i>	Clove	Ellagic, ferulic, quercetin, kaempferol, gallic acid derivatives and tannins	<ul style="list-style-type: none"> • Prevents virus replication • Suppresses NF-κB pathway • Prevention of neutrophil and macrophage chemotaxis, Inhibition of prostaglandin synthesis • Downregulates the pro-inflammatory cytokines 	Barboza <i>et al.</i> (2018); Reichling <i>et al.</i> (2018); Han and Parker, (2017)

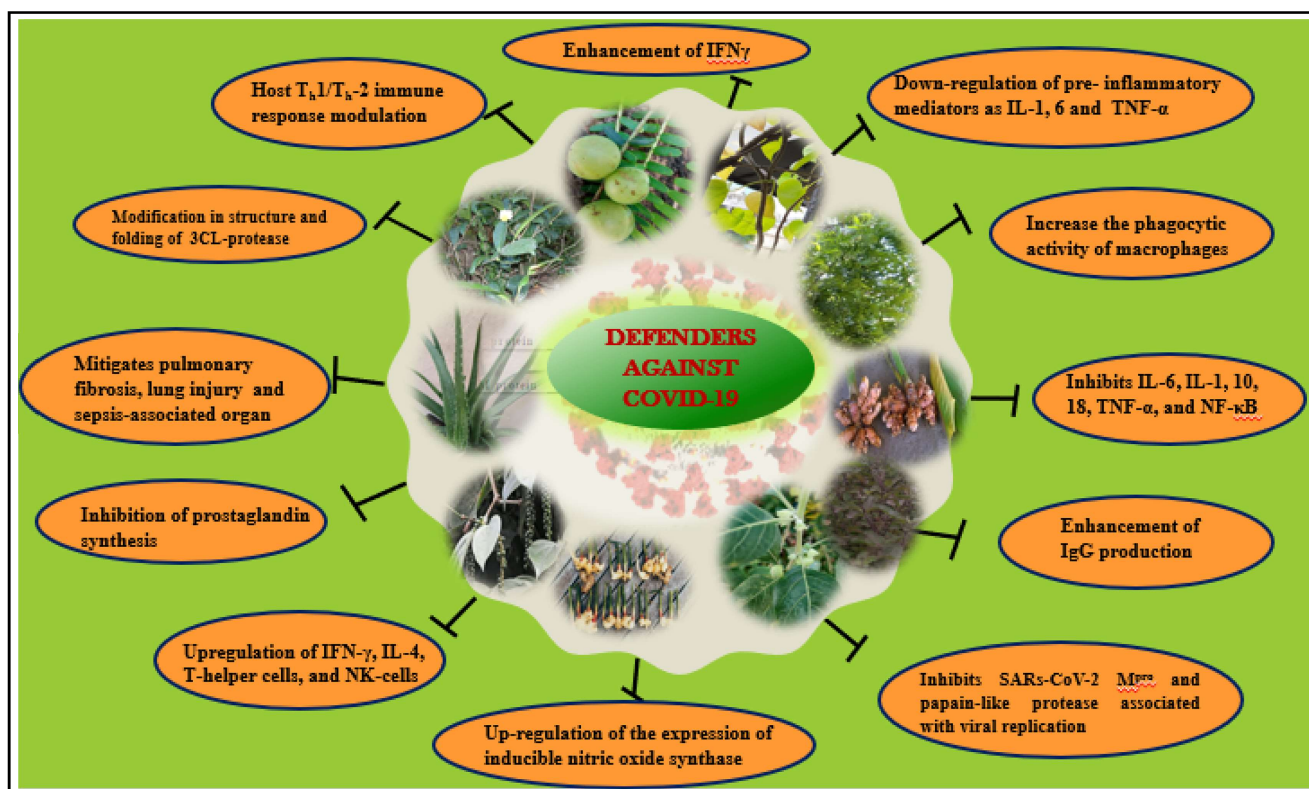


Figure 1: Immunoprotective action of medicinal plants, aromatic herbs and spices.

Acknowledgements

Financial and infrastructural support to the Department of Biochemistry from Shri Vile Parle Kelavani Mandal (SVKM) and Mithibai College (Autonomous) is gratefully acknowledged. I acknowledge the efforts of Dr. Bindu Gopalakrishnan (Department of Botany) for providing pictures of plants.

Conflict of interest

The author declares that there are no conflicts of interest relevant to this article.

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Citation Nupur Mehrotra (2020). Medicinal plants, aromatic herbs and spices as potent immunity defenders: Antiviral (COVID-19) perspectives. Ann. Phytomed., 9(2):30-49. <http://dx.doi.org/10.21276/ap.2020.9.2.4>