CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.5517770

Available online at: http://www.iajps.com *Review Article*

ROLE OF NATURAL PRODUCT IN PREVENTING COVID-19.

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Article Received: August 2021 **Accepted:** August 2021 **Published:** September 2021

Abstract:
The current pandemic of COVID-19 that is spreading across countries originated in Wuhan, China. The single cause of this highly communicable disease is a novel coronavirus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is the seventh known virus of the Coronaviridae family capable of infecting humans. The World Health Organization (WHO) welcomes innovations around the world including repurposing drugs, traditional medicines and developing new therapies in the search for potential treatments for COVID-19. In this study the effectiveness of certain medicinal plants for mild and moderate Covid-19 patients were analyzed literately. Thirty number of plants were studied according to their phytochemical properties, traditional uses, therapeutic actions and certain in-vitro studies from articles published in international multidisciplinary journals, newspapers, books, recognized health organizations websites and interviews from the clinicians. The results showed that the plants possess certain phytochemicals which would be effective to boost the immune system, preventing the viral load in the human host, reduce the inflammatory cytokines and improve the blood cells. However pre-clinical and clinical studies should be conducted to prove the efficacy in scientific manner.
Kew words: Covid 19, Medicinal plants, Traditional medicines,

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Please cite this article in press Piratheepkumar. R and Vijitha. P, ***Role of Natural Product In Preventing Covid-19..,*** *Indo Am. J. P. Sci, 2021; 08(9).*

1. INTRODUCTION:

The new Corona virus disease (Covid 19) pandemic has caused global socioeconomic disturbances with a worri-some number of deaths and health issues, and the world has been struggling to find medicine to treat and prevent Covid-19 (WHO, Corona Virus disease Covid 19). Fresh novel coronavirus infections are declining, but the post-Covid-19 complications have become a major cause of worry for healthcare workers across the globe (Gopesh Mangal, et al., 2020). Health workers who had SARS experienced even more marked adverse impact (Nagi J C, et al., 2010). Another study revealed that 40% of people recovering from SARS still had chronic fatigue symptoms 3.5 years after being diagnosed (Lam M H, et al., 2009).

The current pandemic of COVID-19 that is spreading across countries originated in Wuhan, China. The single cause of this highly communicable disease is a novel coronavirus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is the seventh known virus of the Coronaviridae family capable of infecting humans. There are 7 Human Corona Virus (HCoV) strains identified so far and categorized into a-CoV (229E and NL63) and b-CoV (OC43, HKU1, SARS, MERS, and COVID-19 HCoVs). Among these, MERS, HCoV and SARS were reported to be more virulent and have the highest mortality (Elfiky, 2020). The latest report from the World Health Organization cited that there are now over 19 million confirmed cases and over 700,000 deaths worldwide caused by this virus. Further the World Health Organization has declared novel Coronavirus disease 2019 (COVID-19) to be a pandemic that went on to affect more than 219 countries with 44,002,003 confirmed cases and killed more than 1,167,988 people (WHO as of Oct 29, 2020) (Velavan and Meyer, 2020). The fast propagation of this disease is mainly through close contact with infected individuals via respiratory droplets from either sneezing or coughing. Furthermore, there are two other ways of transmitting the virus, including contact and aerosol transmission (Rhea Veda Nugraha, et al., 2020). In Sri Lanka, 373,165 cases have been reported until 19.08.2021 and 6790 deaths also have been reported (Epidemiology unit report 2021).

Among infected patients, COVID-19 shows various unspecific symptoms, ranging from mild to severe. A report from Huang, et al mentioned that fever (98%) is the most frequent manifestation that is reported by patients, followed by cough (76%), myalgia or fatigue (44%), sputum production (28%), and headache (8%). Also, some fatal cases have been reported in certain patients experiencing progressive respiratory failure due to the virus activity that attacks the alveolar epithelial cells. This damage is initiated by the receptor-binding domain (RBD) attachment of the virus to the receptor on the respiratory tract, known as the angiotensin-converting enzyme-2 (ACE2) receptor. Some of these proinflammatory cytokines, including IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1a, and TNF-α, are highly elevated in the blood of severely ill COVID-19 patients. Thus, there may be an association between this elevated level of cytokines and the severity of a patient's manifestations.

Currently, there is no specific treatment for COVID-19. Furthermore, people in the community and researchers are trying to find the best way to cure or prevent the disease, including using herbal medicine. Since the immune status of patients plays an essential role in COVID-19 infection, an herbal medicine, which has an immunomodulatory effect, could have potential as a preventive measure and even therapeutic agent for patients with COVID-19 infection. A recent trend in the community is the consumption of herbal medicines containing certain active compounds, which have antimicrobial or antiviral, anti-inflammatory, and immunostimulatory activities, such as echinacea, quinine, and curcumin. These herbal compounds are assumed to have the capacity to modulate the immune response and, therefore, they are believed to have beneficial effects on preventing or treating COVID-19 (Rhea Veda Nugraha, et al., 2020)

Studies indicate that the patients recovered from Covid-19 face different health issues. This has made the Post Covid treatment of paramount importance. The treatment method should aim to strengthen the body & thus prevent further illness and discomforts. By implementing healthy practices to improve metabolic activities and the absorption of nutrients, the body will resist attacks from antigens. The treatment protocol for Post Covid syndrome is fortifying the inner strength & rejuvenating the immune system and through which only we would able to regularize the detoxification, enhancing the blood circulation, blood purification, reenergizing the body cell. If we maintain the all mentioned processes patient becomes stronger to counter the ill effects of Covid-19.

The World Health Organization (WHO) welcomes innovations around the world including repurposing drugs, traditional medicines and developing new therapies in the search for potential treatments for COVID-19. WHO is working with research institutions to select traditional medicine products which can be investigated for clinical efficacy and safety for COVID-19 treatment. In addition, the

Organization will continue to support countries as they explore the role of traditional health practitioners in prevention, control, and early detection of the virus as well as case referral to health facilities.

After acute Covid 19 illness, recovered patients may continue to report a wide variety of signs and symptoms including cough, low grade fever and fatigue, all of which may relapse and remit. Other reported symptoms include SOB, CP, headache, neurocognitive difficulties, muscular pain and weakness, gastro intestinal upset, rashes, metabolic disruption (such as poor diabetic control), thromboembolic conditions and depression and other mental health condition. Skin rashes can take many forms including vesicular, maculopapular, urticarial or chilblain – like lesion on the extremities (So called Covid toe). There seems to be no need to refer or investigate these if the patient is otherwise well (Greenhalgh Trisha, et al, 2020). These symptoms can be divided into two categories as common symptoms and less common symptoms. Common symptoms include fatigue, dyspnoea, joint pain, chest pain, cough, change in sense of smell or taste and Less common symptoms includes insomnia, low-grade fevers, headaches, neurocognitive difficulties, myalgia and weakness, gastrointestinal symptoms, rash and depression (https://www.who.int/docs/default-source/coronaviruse/risk-comms-updates/update-36-long-term-symptoms.pdf?sfvrsn=5d3789a6_2).

Covid 19 can result in prolonged illness and persistent symptoms even in young adult and persons with no underlying medical conditions who were not hospitalized. As of now, there is limited evidence of post covid sequlae and further research is required and is being actively pursued. A holistic approach is required to follow up care and wellbeing of all post Covid recovery patients (Gopesh Mangal, et al., 2020).

There is an urgent need to develop an alternative method to prevent novel SARS-CoV2 infection. Siddha Medicine, an Indian medical system, uses specific polyherbal formulations for the treatment of infectious diseases (Zysk, 2009; Rajantheran et al., 2014). Diet has very important role in the management of post Covid 19 and it should be with all six tastes and may include ginger, turmeric, pepper, cinamum and amla, mint in their diet to boost immunity (Gopesh Mangal, et al., 2020).

Researchers such as Rastogi et al. (2020) and Vellingiri et al. (2020) have claimed that medicinal Plant-based treatments should be beneficial to treat and prevent COVID-19. Yang et al. reported that plant species traditionally used as food can help to enhance the immune system of the body and help to prevent the manifestation of COVID-19. In the past, medicinal plants were combined with western medicine to treat a similar disease, severe acute respiratory syndrome (SARS). There is no effective medicine available so far for the treatment of COVID-19; medicinal plants are being used globally that might have increased the demand for medicinal plants. Some plants are useful to treat viral disease, but COVID-19 is a new disease, and the effectiveness of the medicinal plants to cure it has not been tested yet. Therefore, the excessive use of medicinal plants, however, could be problematic and is a matter of concern.

Various herbs and herbomineral drugs including Rasayana drugs which play a vital role in Post Covid 19 and specially herbomineral drugs according to the quicker action of drug, easy for administration, act as a Rasayana with high potency. The herbometallic formulations containing gold bahsma plays a key role in overall efficacy. Research work had been proved that the herbo metallic formulations containing gold bhasma helps to regulate antigen specific immune response as nano particles of gold possess immune modulatory, free radical scavenging, antisepsis, analgesic, and antioxidant property (Yadav M, et al., 2020).

Vitiations of tridhosha is variable owing to magnitude of infection or individual immunity of the affected person. Depending on the condition of Dhatu and Dosha, Shamana in the form of *Brimhana chikitsa* can be adopted to restore the function of *Tridosha* beside this *Satvavajaya Chikitsa* (ayurvedic psychotherapy) Sadvritta, and Achara *Rasayana* (behavioral therapy) can play an important role to manage post covid symptoms these are the non-pharmacological approach aimed to maintain mental health. Regular practice of *yogasana* and *pranayama* with *achara rasayana* is useful for mental stability (Gopesh Mangal, et al., 2020). The ancient traditional principals of management in the pandemic diseases can be preciously understand through the integrative method. Performing panchakarma in the preliminary stage which may fight the viral entry into the body or may reduce viral load in the infected individual. Administration of rasayana may delay the process of the pathogenesis by increasing the immunity and eliminating the viral toxic effects on the body. The specific herb therapy may help in completely alleviating the residual viral load.

2. Methodology followed to reviewed the selected papers

The selected papers were reviewed in detail to find out the necessary information for the analyses. Specifically, to analyze the contents of the selected papers, an excel sheet was designed with selected papers on the rows, and columns for collecting data on a wide range of items and issues. The review was conducted in three steps. First, each co-author reviewed a number of papers and collected the necessary data. Then the lead author checked the collected data, divided the articles into several themes based on commonalities, and coded the data. At the final stage, the authors double checked the reviewed articles to ensure accuracy of the collected and coded data. This data was then used for writing up the review.

3. Data collections and discussion

3.1. Immune ration after infection

The initial site of SARS-CoV-2 infection remains unknown, and the pathogenesis of COVID-19 is under investigation. In most patients with COVID-19, it may affect only the lung, because this disease is a respiratory disease. However, in some patients with certain comorbidities, the clinical symptoms might be worse. The mode of infection is human to human transmission through close contact. Close contact increases the risk of transmission via droplets, such as from an infected person through coughing or sneezing or the interaction between health workers and patients with COVID-19. This disease has an incubation period of about 2–14 days, and during this time, the virus can be transmitted. Thus, this mode of infection makes the rate of spread of this disease ranges from 2.2 to 2.6, which means one infected person can infect from 2.2 to 2.6 people (Wu Z., et al, 2020).

Recently, in some patients, several viruses might have caused an emerging situation because of an immune reaction. This emerging threat is known as cytokine release syndrome or a cytokine storm. This condition happens after infection with some influenza viruses (Du Y, et al., 2020). It might also occur in infections caused by SARS-CoV-2. A study provided evidence to suggest that a subgroup of patients with severe COVID-19 might have cytokine release syndrome (CRS) or a cytokine storm. A cytokine storm became the second leading cause of death of COVID-19 because of an under-recognized and hyperinflammatory syndrome that leads to hypercytokinaemia with multi-organ failure (Gao Y, et al., 2020).

A definitive therapeutic agent for managing COVID-19 has not been recommended for humans until now. Current preventive and treatment efforts for COVID-19 have focused developing vaccines and specific therapeutic agents targeting SARS-CoV-2 (Livingston E., et al, 2019).

There are some potential therapeutic agents for COVID-19 management, such as antiviral agents, chloroquine/hydroxychloroquine, dexamethasone, and convalescent plasma transfusion, but most of them still show inconsistent results. Several antiviral agents are under investigation as a treatment for COVID-19. Remdesivir is one of the antiviral agents that used for COVID-19 and known as an adenosine analogue that can be merged into viral RNA chains resulting in their early termination (Dong Y., et al, 2019).

3.2. Role of therapeutic agents from herbs and Siddha Medicine

Herbal medicines are frequently used by many people in the community. According to the characteristics of the SARS-CoV-2 virus, a molecular mechanism of the host is involved in the immune response. The following herbs, medicines, and foods were analyzed based on the data collected from books, journals, articles, and data collected from ola leaves, traditional medical practitioners and allopathic consultants to find out the effective useful and enhance the safety use for Covid 19 prevalence and post covid-19 syndrome peoples.

3.2.1. Medicinal plants:

3.2.1.1. *Echinacea purpurea*:

Contain alkamides, caffeic acid derivatives, polysaccharides, and glycoproteins with purported stimulating effects on the immune system. Nicotiflorin is the dominant flavonoid followed by the flavonoid Rutin. It helps to stimulate the immune system, leading to renewed interest for treating immunodeficiency, lowering the glycemia and boosting healthy immune system during periods of stress or pandemic. It has an ability to mobilize leucocytes, activate phagocytosis and stimulate fibroblast formation. However no scientific evidences are available that it would be effective for Covid-19 (Rhea Veda Nugraha, et al., 2020).

3.2.1.2. *Curcuma xanthorrhiza*:

This plant has some effects as an antimicrobial, anti-inflammatory, antioxidant, antihyperglycemic, antihypertensive, antiplatelet, nephroprotective, anticancer, and supplemental agent for systemic lupus erythematosus (SLE). *C. xanthorrhiza* contains curcuminoids (1%–2%), volatile oil (3%–12%), xanthorrhizol (44.5%), and camphor (1.39%). Curcumin, monodemethoxycurcumin, and bisdemethoxycurcumin belong to curcuminoids. The

most common compound is xanthorrhizol (Baroni A., et al, 2007). The xanthorrhizol treatment inhibits inflammatory cytokine production in adipose tissue and Tumor Necrosis Factor (TNF-α) expression. Further it prevents the recruitment of immune cells to adipose tissue to down regulate the inflammatory cytokine gene. Xanthorrhizol also reduced interleukin (IL-1β) gene expression in muscle. Another study suggested that xanthorrhizol can decrease the serum level of IL-6 and increase serum Transforming Growth Factor (TGF-β) in patients with SLE with hypovitamin D. Taken together, xanthorrhizol can inhibit proinflammatory cytokines and promote the production of anti-inflammatory cytokines. The xanthorrhizol could suppress the generation and secretion of proinflammatory cytokines, such as IL-6 and TNF-α. This inhibition process is the result of inhibited inducible Nitric Oxide Synthase (iNOS) and decreased production of Nitric oxide (NO). Taken together, xanthorrhizol as an immunomodulatory is an immunosuppressant. Therefore Xanthorrhizol may be used as a treatment for COVID-19 because of its ability to inhibit proinflammatory cytokines. Patients with COVID-19 are susceptible to CRS. So, the use of xanthorrhizol may lower the proinflammatory response in a patient with COVID-19 with or without CRS (Ayala S., et al, 2018).

3.2.1.3. Mushroom:

The *Agaricomycota* among the *Bacidiomycetes* mushrooms, AbM, HE and GF, have anti-inflammatory property, and have also been found to induce enhanced Th1 cellular immune response, as demonstrated by increase in IFNγ, IL-2 and IL-12 cytokines. Cells participating in the Th1 response are activated NK cells and cytotoxic Th1 cells and γ/δ T cells, which besides tumor attack, also destroy virus-infected cells. Moreover, γ/δ T cells play an important role in bridging the gap between innate and adaptive immunity. The extract seems to have both a prophylactic and a therapeutic effect against pneumococcal disease. Hence it seems possible that the related medicinal *Basidiomycetes* mushrooms, AbM, HE and GF would have merit as prophylactic or therapeutic add-on remedies in COVID-19 infection, especially as countermeasures against a pneumococcal superinfection, even when caused by multi-resistant bacteria, as well as for the immune overreaction and damaging inflammation that occurs with COVID-19 attack (Hetland G., et al, 2020).

3.2.1.4. *Phylanthus emblica*:

Contain high amount of natural Vitamin C with wide variety of Bioflavanoids which further enhance the effectiveness of the natural Vitamin C. It contains antioxidant, anti-inflammatory activity in rich. Also it has an ability of enhancing the immune system. If it take with Zinc contain food or supplements the effectiveness will be high. Further it contains tannin, phosphorus, calcium, and iron also in rich amount. Vitamin B5, B6, Vitamin E, Phytonutrients, Copper, Manganese, and Potassium are also presents in considerable amount. The main phytonutrients are Flavonols, which are linked to heart health and may have stroke-reducing, cancer-fighting, and antiviral effects. The main types in gooseberries are quercetin, myricetin, kaempferol, and isorhamnetin. The Anthocyanins, one of the phytonutrient**,** are the colored pigments in fruit, and they're associated with eye and urinary tract health, improved memory, healthy aging, and a lower risk of some cancers. Further it has been reported to significantly relieve chromium-induced immunosuppressive effect on lymphocyte proliferation and led to restoration in production of IL-2 and INFγ (Sai Ram, et al., 2002). Phenolics from emblica has been found to increase splenocytes proliferation. Geraniin and isocorilagin showed significant immunostimulatory effects (Liu et al., 2012). Ethanolic extract of amla strongly reduced levels of pro-inflammatory cytokines and increased levels of anti-inflammatory cytokine (Bandyopadhyay, et al., 2011). An isolated compound (1, 2, 4, 6-tetra-*O*-galloyl-β-d-glucose) of *P. emblica* showed antiviral potential against HSV by HSV-1 inactivation, which leads to inhibition of early infection indulging attachment and penetration of virus, suppression of intracellular growth and inhibited gene expression of HSV-1 E and L along with DNA replication (Xiang, et al., 2011).

3.2.1.5. Nuts:

Unless you have a nut allergy, peanuts are a great source of vitamin E, a powerful antioxidant, and phosphorous, a mineral that maintains body tissue.

3.2.1.5.1. *Almonds*:

Contain rich in vitamin E. Vitamin E is one of the antioxidants that can reduce the risks of cancers, slow down the signs of aging, and also save you from inflammation. Furthermore, vitamin E is one of the supplements that may directly affect cells of the immune system. Therefore, it can improve it and prevent diseases that occur due to the vulnerability of the immune system. Almonds have the highest amount of vitamin E in every serving. It can provide 7.27 mg of vitamin E, which is almost half a person's daily requirement.

3.2.1.5.2. *Walnut*:

It is loaded with the highest level of omega-3, which can help you get a good sleep at night and acts like a natural stress relief. It's not only the omega-3 fatty acids that make this nut a superfood. It also contains copper, manganese, potassium, iron, zinc, calcium, and selenium. They are all great immunity boosters and also can improve heart health, skin, and bone health.

3.2.1.5.3. *Pistachios*:
It contains high level of protein. 100 grams of pistachios contain 20 grams of protein, which can give the body 40% of the protein it needs during the day.

3.2.1.5.4. *Cashews*:
Cashews are rich in monounsaturated fats. Moreover, it contain vitamin B6, niacin, magnesium, and also tryptophan, which are mood-stabilizing as a combination. B6 helps convert the tryptophan into serotonin, which is essential for the brain's well-being and happiness.

3.2.1.5.5. *Chestnuts*:

The high amount of copper in this nut helps the body strengthens the bones and boosts the immune system. The low level of cholesterol and sugar in this nut helps with heart diseases and digestion. Moreover, chestnuts contain vitamin B, which can produce red blood cells and improve brain function. The high amount of carbohydrates in this nut also increase the energy level, which is needed even if you are working from home (Nut consumption in the time of COVID-19, Ratinkhosh R&D Team, https://ratinkhosh.com/covid-19-and-nut-consumption)

3.2.1.6. Legumes:
They are rich in iron, zinc, vitamins, selenium, and essential amino acids like Lysiene, which helps with calcium absorption, and regulates appetite. People suffering from COVID should definitely consume more pulses as it will help boost the immune system.

3.2.1.7. *Curcuma longa*:
Contains curcumin has antibacterial, antiviral, antifungal, antioxidant and anti-inflammatory activities. It inhibits the production of pro-inflammatory cytokines. Curcumin exerts antiviral effect on a broad range of viruses including influenza virus, adenovirus, hepatitis, human papilloma virus (HPV), human immunodeficiency virus (HIV), herpes simplex virus−2 (HSV-2) and Zika viruses. It exerts antiviral effect by various mechanisms ranging from inhibiting the virus entry into cells, inhibiting encapsulation of the virus and viral protease, inhibiting the virus replication, as well as modulating several signaling pathways. Recent study has shown that curcumin potentially inhibits ACE2, modulates characteristics of lipid bilayer, as well as viral S protein inhibiting entry of virus into cells, inhibits the viral protease, stimulates host interferon production to activate the host innate immunity, etc. Furthermore, curcumin is a potent antioxidant. It exerts its antioxidant effects both by neutralizing free radicals and enhancing the production of antioxidant enzymes. These studies reveal potential immune-boosting, antioxidant and anti-SARS-CoV-2 effects of curcumin. Therefore, curcumin could be a potential supplement in combating the COVID-19 pathogenesis. Further aqueous extract of *C. longa* decreased relative spleen weight and modulation in hematological changes indicating the potential of *C. longa* as an immunomodulator in cyclophosphamide-immunosuppressed *in vivo* model. The study observed promising effects of turmeric as an immunomodulator by representing spleen cells in younger mice (Mustafa and Blumenthal, 2017). *C. longa* extract also showed antiviral potential against dengue virus in *in vitro* and *in vivo* studies on Huh7it-1 cells and a remarkable reduction in viral load has been observed by in *in vivo* model (Ichsyani et al., 2017). Water and ethanolic crude extracts have been found to be antiviral in H5N1 also showed up regulated TNF-α as well as IFN-β mRNA expression, highlighting its promising role in the inhibition of the replication of viruses (Sornpet, et al., 2017). Turmeric extract has been found to be anti-allergic in mice immunized with ovalbumin and alum. Attenuation of food allergy by maintaining balance of Th1/Th2 has been reported. Extract has been found to cause reduction in Th2 and increase in Th1 cell-related cytokines. Further, increased levels of IgE, IgG1 and mMCP-1 levels were also decreased proving effects of turmeric in allergic disorders mainly, asthma and food allergies (Shin et al., 2015). Various other studies also reported anti-inflammatory effects of *C. longa* either alone or in combination (Lee et al., 2020).

3.2.1.8. *Cinnamomum verum*:
Contains cinnamaldehyde which is a naturally present organic compound abundantly found in essential oils in cinnamon. Cinnamaldehyde is a well-known dietary phytonutrient, known to possess anti-inflammatory properties. It inhibits the TNF-α-induced inflammation through suppression of NF-κB activation. Further it can suppress endotoxin-mediated hyperexpression of TLR4 and NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome signaling pathways (Lee SC., et al, 2018).

Cinnamaldehyde is also known to downregulate the production of prostaglandins (PGEs) by downregulating IL-1β-induced COX-2 activity thus lowering the chances of hyper inflammation in a dose-dependent manner (Guo JY., et al, 2006). The evidences show cases that cinnamaldehyde is a potential anti-inflammatory bioactive compound and could be useful in mitigation of SARS-CoV-2 induced hyper inflammation in the lung.

3.2.1.9. *Allium sativum*:

The predominant thiosulfinate in fresh garlic extract identified as allicin, having anti-inflammatory, antioxidant and antiviral properties. Allicin suppresses the inflammation *via* inhibiting the TNF-α induced expression levels of IL-1β, IL-8, IP-10, and IFN-γ and also through suppression of degradation of NF-κB inhibitory protein IκB in intestinal epithelial cells (Lang A, et al, 2004). It inhibits inducible nitric oxide synthase expression in activated macrophages (Shin JH, et al., 2013) (Dirsch VM, et al., 1998). Several garlic associated compounds have found to possess a strong viricidal activity against a wide range of viruses including para-influenza virus type 3, human rhinovirus, herpes simplex virus (HSV)-1, HSV-2, and vesicular stomatitis virus (VSV). Some of the garlic compounds that show viricidal activity are ajoene, allicin, allyl, methythiosulfinate and methylallyl thiosulfinate (Galabov AS, 2007) (Weber ND., et al, 1992). Most of the above-mentioned functional effects were observed at 200 ng/ml concentrations. Studies also have found that only fresh samples with no processing such as heat induction or drying were successful to induce most of the biological activities of garlic (Siegers CP, et al., 1996). Therefore, fresh garlic extract may be useful as a prophylactic against COVID-19. Garlic contains selenium also that plays a vital role in various physiological processes and on the immune system. Selenium exerts its biological effect through incorporation into selenoproteins in the body. It promotes enhanced T cell proliferation, NK cell activity and innate cell functions. Further supports stronger vaccine response and robust immunity to pathogens. Also, suppresses severe inflammation in tissues such as lungs and intestine (Avery JC., et al, 2018). Studies have shown that selenium supplementation modulates the inflammatory response in respiratory distress syndrome patients by restoring the antioxidant status of the lungs and suppressing the IL-1β and IL-6 levels (Mahmoodpoor A, et al., 2019). Selenium supplementation suppresses pathogen induced activation of NF-κB and its downstream pro-inflammatory cytokine release (Dhanjal NI kaur., et al, 2017). The antiviral properties of selenium have found to be mediated through its antioxidant effects. On the other hand, selenium supplementation demonstrates the improved CD+ T cell counts (Stone CA, et al., 2010) and improves glutathione peroxidase and other antioxidant selenoenzymes along with catalase activities (Dworkin BM, et al., 1994).

3.2.1.10. *Piper nigrum*:

Piperine that is obtained from ethanolic extract of black pepper and is a major alkaloid in the group of cinnamamides (Bang JS, et al., 2009). Piperine possesses a strong anti-inflammatory function and therefore can be repurposed for suppression of hyper inflammation induced during COVID-19. It downregulates PGEs by inhibiting the expression levels of IL-6 and matrix metalloproteinases (MMP-13) (Bang JS, et al., 2009). Piperine promotes innate immunity by promoting the phagocytic activity of phagocytes and is known to inhibit LPS-induced expression of IRF-1 and IRF-7 mRNA, phosphorylation of IRF-3, type 1IFN mRNA, and down-regulation of STAT-1 activity (Bae GS., et al, 2010). Few studies conducted on microglial cells have shown that piperine inhibits LPS-Induced TNF-α, IL-6, IL-1β, and PGE2 production in BV2 cells (Wang-Sheng C., et al, 2017). Also, it found to inhibit the production of IL-2, and IFN-γ in human peripheral blood mononuclear cells (PBMCs) (Chuchawankul S., et al, 2012). Furthermore, piperine treatment found to reduce the production of pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α, COX-2, nitric oxide synthase-2, and NF-κB in the cerebral ischemia-reperfusion-induced inflammation rat model (Vaibhav K., et al, 2012). Further, piperine is a potent antioxidant and protects against oxidative damage by neutralizing free radicals, ROS, and hydroxyl radicals. It scavenges superoxide radicals with IC_{50} of 1.82 mM and inhibits lipid peroxidation with IC_{50} of 1.23 mM. Because of these properties, piperine can be tried as a prophylactic or therapeutic compound to protect from the oxidative stress and hyper inflammation induced during the COVID-19. Piperamides isolated from *P. nigrum* fruits showed significant inhibition of coxsackie virus type B3 in a cytopathic effect inhibition assay (Mair et al., 2016). Aqueous extract of *P. nigrum* acted as a potent modulator of the macrophages and significantly enhanced splenocyte proliferation in a dose-dependent manner (Majdalawieh and Carr, 2010). The isolated alkaloid from *P. nigrum* exhibited anti-inflammatory effect in RAW 264.7 cells stimulated by LPS and significant inhibition in iNOS-mediated NO and IL-1β, IL-6, and TNF-α.

3.2.1.11. Propolis:

Propolis produced by honeybees and known to have a broad spectrum of biological properties, including anti-microbial, anti-inflammatory, dermatoprotective, laxative, anti-diabetic, anti-tumor, and immunomodulatory activity (Wolska K., et al, 2019). The immunomodulatory activity is attributed to flavonoids and some phenolic acids mainly caffeic acid phenethyl esters and artepillin C (3,5-diprenyl-4-hydroxycinnamic acid). Propolis exhibits immunomodulatory effects on a broad spectrum of immune cells mediated by the modulation of extracellular signal-regulated kinase 2 and MAPK signaling pathways. Further, it also modulates nuclear factor of activated T cells (NFAT) and NF κB signaling pathways (Wolska K., et al, 2019) (Sforcin JM., et al, 2011). Propolis also stimulates greater antibody production, suggesting that it could be used as an adjuvant in vaccines. Propolis at higher concentration inhibits lymphoproliferation while at low concentrations the effect is reversed, causing lymphoproliferation (Sforcin JM, 2007). Further, compounds in honey propolis inhibits various viruses such as dengue virus type 2, herpes simplex virus, human cytomegalovirus, influenza virus A1 (Amoros M., et al, 1994).

3.2.1.12. Curd:

Contain commonly used probiotics are *Bifido bacterium* and *Lactobacillus* species, followed by the *Streptococcus, Enterococcus, Bacillus, and Escherichia coli*. Probiotics not only support the health of the gut but also improves system functioning and regulation (Schreck Bird A., et al, 2017). In general, it is observed that the gut microbiome impacts systemic immune responses as well as local immune responses at distal mucosal sites, including lungs (Zelaya H., et al, 2016). Consumption of *Bifido bacterium* and *Lactobacillus* have found to help in clearing the influenza virus in the respiratory tract (Baud D., et al, 2020). Levels of interferons, mucosal antibodies of lung and activity of NK cells, antigen presenting cells (APCs) are improved by probiotics (Mortaz E., et al, 2013). *Lactobacillus plantarum* DR7 strain has shown to have suppressing effect on the pro-inflammatory cytokines TNF-α, IFN-γ, enhances anti-inflammatory cytokines IL-10, IL-4 and also known to reduce plasma peroxidation levels as well as modulate immune system (Chong HX., et al, 2019). *Bifidobacterium longum* BB536 strain prevents infection from influenza and improves innate immunity (Namba K., et al, 2010). Considering the role of probiotics in improving the host innate immune response as well as anti-inflammatory effects, and considering the fact that gut involvement and enterocytes (Lin L., et al, 2020) can be reservoirs of SARS-CoV-2 infection, probiotics can be repurposed as prophylactics as well as adjuvants to combat the pathogenesis of COVID-19.

3.2.1.13. Milk:

Lactoferrin (Lf) is a naturally occurring and non-toxic glycoprotein present in the milk that has been studied against a broad range of viruses, including SARS-CoV, which is closely related to SARS-CoV-2. It inhibits viral entry *via* binding to cell surface molecules or viral particles or both. Therefore, it plays a crucial role in preventing the virus entry and replication (Rosa L., et al, 2017). Further it exerts immunomodulatory and antioxidant effects by inducing the T-cell activation, suppressing the levels of interleukins including IL-6, TNF-α, and downregulating the ferritin (Ishikado A., et al, 2005). Furthermore, zinc saturated Lactoferrin exerts a more potent antiviral effect (Li S., et al, 2009).

3.2.1.14. *Allium cepa*:

Contains quercetin is a well-known antioxidant with anti-inflammatory and antiviral bioactive. It inhibits TNF-α production in LPS-induced macrophages (Manjeet KR., et al, 1999), IL-8 production in lung A549 cells (Geraets L., et al, 2007), and mRNA levels of TNF-α and IL-1α in glial cells (Bureau G., et al, 2008). It also limits the production of cyclooxygenase (COX) and lipoxygenase (LOX) enzymes in rat liver epithelial cells (Lee KM., et al, 2010). Studies have also shown that quercetin has antiviral effects on both RNA and DNA viruses. It inhibits the virus entry and viral-cell fusion (Wu W., et al, 2015) and reduces the expression of pro-inflammatory cytokines and lung inflammation induced by rhinovirus in mice (Ganesan S., et al, 2012). Studies have also found that quercetin-3β-galactoside due to the presence of hydroxyl group, it binds to viral protease $3CL_{pro}$ and inhibits its proteolytic activity (Chen L., et al, 2006). Furthermore, as observed in prediction models that quercetin binds SARS-CoV-2 S-protein at its host receptor region or to the S-protein-human ACE2 interface interfering the virus entry into cells indicating its therapeutic potential (Smith M., et al, 2020). This prediction is consistent with the reports that both quercetin and a structurally similar luteolin inhibits the SARS-CoV virus infection (Yi L., et al, 2004). Additionally, other studies have also found that quercetin in combination with VC induces synergistic antiviral and immunomodulatory effects against COVID-19 (Colunga Biancatelli RML., et al, 2020).

3.2.1.15. *Zingiber officinale*:

Ginger has anti-inflammatory properties that help in removing toxins from the respiratory tract. It contains many vitamins and minerals including potassium, magnesium, beta-carotene, and zinc. It also has antioxidants to help support your immune system. Fresh ginger aqueous extract showed antiviral activity against human respiratory syncytial virus in human respiratory tract cell lines (HEp-2 and A549) and decreased the plaque counts in a dose-dependent manner. It also stimulated the secretion of IFN-β that contributes to counteracting against viral infection (Chang et al., 2013). It also showed antiviral potential against avian influenza virus H9N2 on Vero cells in a dose-dependent manner (Rasool et al., 2017). Oral administration of Soft gel capsules containing a *Z. officinale* in combination showed immunomodulatory and anti-inflammatory properties parallel to those exerted by positive control, and gene expression data highlighted overall same transcriptional remodeling (Dall'Acqua et al., 2019). A study on essential oil of ginger reported immunomodulatory effects by improving the humoral immunity in cyclophosphamide-immunosuppressed mice in a dose-dependent manner (Carrasco et al., 2009). Oral administration of alcoholic ginger extract to allergic rhinitis patients showed significant reduction in total nasal symptom scores (TNSS), with overall improvement in rhino conjunctivitis quality of life questionnaire (Yamprasert et al., 2020). The aqueous and alcoholic extracts of rhizome decreased goblet cell hyperplasia, infiltration of inflammatory cells in airways with reduced total and differential counts of eosinophils and neutrophils in mouse model (Khan et al., 2015).

3.2.1.16.*Illicium verum*:

The flower of *Illicium verum* contains shikimic acid used for antiinfluenza, Tamiflu. Shikimic acid using fermentation of Ecoli bacteria discovered in 2005 and applied in the 2009 for swine flu pandemic. As of 2018 fermentation of Ecoli was the manufacturing process of choice to produce shihimic acid for synthesis of Tamiflu.

3.2.1.17.*Abutilon indicum*:

It has anti-mouse corona viral activity which is a surrogate of human SARS virus. It's extract was found active against influenza and sindbis virus which is a surrogate to Hepatitis B virus.

3.2.1.18.*Piper longum*:

A pilot study showed that Piper longum as an add to standard of care using modern medicine with satandard of care alone. It was used to treat mild to moderate case and the outcome was that reduced the length of hospital stay and improved the recovery time. General feeling of wellbeing and activity levels were better in the 3 month follow-up post discharge.

3.2.1.19.*Tinospora Cordifolia*:

The molecular docking study of Tinocordiside from this plant contain inhibitors against SARS-CoV-2 Mpro (Main protease). The secondary metabolites of Tinospora cordifolia capable of inhibiting the SARS-CoV-2 main protease with high binding efficiency. Taken in to the account of site of inhibition, the strength of the binding affinity, the interaction with the conserved catalytic dyad residues (CYS-145 and HIP-41), and the favorable predicted ADME parameters these metabolites can help as an antidote for SARS-CoV-2. *In vitro* screening of *T. cordifolia* silver nanoparticles against chikungunya virus cell showed significant antiviral potential (Sharma V. et al., 2019). Alcoholic leaves extract of *T. cordifolia* significantly decreases intracellular reactive oxygen species (ROS) in chikungunya patients with high levels of intracellular ROS in persisting polyarthralgia by *ex vivo* treatment (Banerjee et al., 2018). An *in vitro* study revealed the antiviral potential of crude stem extract of *T. cordifolia* against HSV in Vero cell lines by inhibiting the growth of HSV (Pruthvish and Gopinatha, 2018). Aqueous extract of *T. cordifolia* stem significantly increase INFγ and IL levels (IL-1, IL-2, IL-4) in isolated chicken peripheral blood mononuclear cells (PBMCs) against infectious bursal disease virus. Further, immunomodulatory potential via the toll like receptor (TLR)-mediated pathway was also concluded (Sachan et al., 2019). The hydro-alcoholic extract of *T. cordifolia* stem in drinking water caused enhancement of cellular immunity as well as humoral immunity in broiler chicks (Nety et al., 2017). Chloroform extract significantly prevented pro-inflammatory biomarkers (IL-6, IL-1β and PGE2) and decreased paw oedema ($p \leq 0.05$) with no toxicity reported when conducted in RAW264.7 macrophages (Philip et al., 2018).

3.2.1.20.*Andrographis paniculata*:

It's a main ingredient in Nilavembu Kudineer (NVK). The studies with NVK showed reduction in viral load of SARS-CoV-2. Further it reduced the time taken to convert Patient from symptomatic to Asymptomatic based on Reduction in clinical symptoms. Further it was effect on the drugs inflammatory markers (IL6,) at the end of treatment and reduction in hospital stay time based on RT PCR CT Values on 3rd, 6th and 10th day. The secondary outcomes were reduction in use of Intensive Supportive Care, reduction in incidence of complications (Acute Respiratory Distress Syndrome, other systemic complications),

MuLBSTA score for viral pneumonia (multinodular infiltration, hypo-lymphocytosis, bacterial co infection, Total Leucocyte Count (TLC ≤ 0.8 x 10^9/L), smoking history, hyper-tension and age) score, laboratory markers (Haematological & Biochemical Markers), adverse events/effects Siddha-based measurements and Siddha Udaliyal assessment by using Yakkai Ilakkanam.

3.2.1.21. *Justicia adathoda*:
The efficacy of Adathoda's primary active alkaloid vasicine was evaluated by in Silico screening studies on virus proteins ACE 2 Receptor, 3CL protease and Spike protein SARS HR1 motif using PyRx tool and AutoDoc 1.5.6. Based on PyRx results, Vasicine with ACE 2 Receptor shown higher docking affinity score -7.1 K/cal respectively when compared to other virus proteins. AutoDoc 1.5.6 screening study report showed that vasicine promotes good inhibitory constant 486.54 mM on 3CL protease more than others. Therefore it indicates that the vasicine could be a potential target for the treatment of COVID 19

3.2.1.22. *Alpinia galangal*:
The potential of compounds contained in Alpinia galangal (Galangin) as anti SARS-CoV-2 through its binding to 3 protein receptors. The selected protein targets are RBD-S (PDB ID:6LXT), PD-ACE2 (PDB ID: 6VW1), and SARS-CoV-2 protease (PDB ID:6LU7). It showed considerably lower docking score for all three protein receptors representing the high affinity to bind the receptors. Moreover, galangin possess good affinity to the respected receptors, indicating that it perform inhibitory potential for the viral infection and replication. It could be consumed in daily life as prophylaxis of COVID-19.

3.2.1.23. *Linum usitatissimum*:
Heteropolysaccharide, extracted from flax seed hull possessed immunomodulatory activity and anti-hepatitis B virus potential. It significantly stimulated mRNA expression of TNF-α, NO and IL exhibiting immune responses in murine macrophages. Antiviral activity has been reported through inhibition of expression of surface antigen as well as envelop antigen and also interfered with DNA replication. The study suggested its promising potential as an immunostimulant and vaccine adjuvant (Liang et al., 2019). It showed anti-inflammatory and immunomodulatory potential in obesity-associated insulin resistance. Its oil in co-culture with 3T3-L1 adipocytes-RAW 264.7 macrophages of C57BL/6 mice reported shifting the cytokines toward anti-inflammatory with a decrement in TNF-α. Immunomodulation has been observed through an increase in levels of Th2-related cytokine (IL-4), serum anti-ova IgG1, and IgE, and a decrease in Th-1 related cytokines (TNF-α and IFN-γ) and anti-ova IgG levels (Palla et al., 2015). Another study reported the immunomodulatory activity of phenolic components of flax seed mainly through reduction in cell-mediated immune responses (Kasote et al., 2012).

3.2.1.24. *Nigella sativa*:
It's bioactive compounds have been observed as potential inhibitors of COVID-19 in molecular docking studies. Nigellidine gave energy complex at active site (6LU7) with energy scores closest to chloroquine and better than hydroxychloroquine and favipiravir whereas α-hederin gave energy complex at the active site (2GTB) with energy scores better than chloroquine, hydroxychloroquine, and favipiravir (Salim and Noureddine, 2020). The alcoholic seed extract has shown immunosuppressive activity on a phytohemagglutinin and immunostimulating effect on non-phytohemagglutinin (PHA) stimulated proliferation (Alshatwi, 2014). The thymoquinone-rich oil showed suppression of cytokine signaling molecules, and PGE_2 in T-lymphocytes as well as enhanced PGE2 release in adrenocarcinomic human alveolar basal epithelial A549 cells (Koshak et al., 2018).

3.2.1.25. *Ocimum sanctum*:
Hydro-alcoholic extract of *Ocimum sanctum* inhibited intracellular multiplication of virus. It also inhibits non-specific interference with virus-cell interactions in H9N2 viruses. (Ghoke et al., 2018). The immunomodulatory potential of alcoholic leaves extracts at IC_{50} value of 73.3 µg/ml showed reduction in hepatic parasite and, skewing of the humoral response toward Th1 type (Bhalla et al., 2017). *O. sanctum* inhibits leukotriene-C4-synthase, leukotriene-A4-hydrolase and cyclooxygenase-2 activities in cultured HL-60 cells and causes a significant reduction in OVA-induced lung inflammation (Soni et al., 2015).

3.2.1.26. *Withania somnifera*:
Multiple studies have proved that Ashwagandha has antiviral and immunomodulatory potential. Very recently, an *in silico* study concluded that Withaferin-A exhibits antiviral potential against SARS-CoV-2 through inhibiting RNA polymerase with higher binding energy than hydroxychloroquine and other drugs used against SARS-CoV-2. Another study on withanone showed blockage of SARS-CoV–2 entry and also its subsequent infection by interrupting electrostatic interactions between the RBD and ACE2 (Balkrishna et al., 2020). Grover and colleagues

through molecular docking reported the potential of withaferin A against HSV through inhibition of DNA polymerase enzyme (Grover et al., 2011). *W. somnifera* molecular mechanism has been elucidated by using network ethnopharmacological technique and reported that withanolide-phytosterol combination is a good immunomodulator (Chandran and Patwardhan, 2017). *W. somnifera* formulation (supplemented with minerals) has been reported to improve both cellular and humoral immunity as well as hematological profile in addition to the significant inhibition in mouse splenocytes (Trivedi et al., 2017). Aqueous root extract of *W. somnifera* attenuates production of pro-inflammatory cytokines and transcription factor in collagen-induced arthritis (Khan et al., 2018). A study in 2018 showed that *W. somnifera* significantly inhibited mRNA expression of inflammatory cytokines and promotes the mRNA expression of the anti-inflammatory cytokine in HaCaT cells (Sikandan et al., 2018).

4. CONCLUSION:

There were lot of literature and photochemical evidences to say the above listed medicinal plants would be effective to manage the mild and moderate level Covid patients and would be used as preventive aspect too. However pre-clinical or clinical study should be conducted to prove.

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