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Usefulness of herbal medicines in the prevention and management of coronavirus disease-2019 (COVID-19) and its symptoms: A review

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Abstract

Background: Various studies have been conducted to identify drug candidates to combat the virus, meanwhile some persons believe that consuming herbal medicines or medicinal plants that act as immunomodulators can prevent or even cure COVID-19. It was reported that about 85% of COVID-19 patients in China received combined treatment with Traditional and Complementary Medicine and regular medication. Recent systematic review has shown that herbal medicines can be significantly effective in alleviating different disease symptoms, including COVID-19.

Objectives: The study was conducted to identify different herbal preparations and medicinal plants used in the prevention of COVID-19 and its symptoms.

Methods: About twenty-five (25) different journal articles obtained from Pubmed, Elsevier, Hindawi, PLOS ONE, African Journals Online (AJOL), Lancet, Research gate, Google scholar and other journal hubs, relating to the use of herbal medicines and medicinal plants on prevention management of COVID-19 and related infection and its symptoms were reviewed and summarized to generate useful data and document the various herbs and medicinal plants employed in managing COVID-19.

Results: From the results obtained, various plants have been tested across the globe as possible candidate in the prevention and management of COVID-19 symptoms. Some of the notable medicinal plants reported to have such properties include *Artemisia annua*, neem tree (*Azadirachta indica*), Garlic (*Allium sativum*), Lime or Lemon (*Citrus limonum*), Ginger (*Zingiber officinale*), Xanthorrhizol (*Curcuma xanthorrhiza*), Cinchona bark (*Cinchona sp.*), purple coneflower (*Echinacea purpurea*), among others.

Conclusion: Herbal medicines might have the capabilities to regulate the production and release of proinflammatory cytokines, interfere with the development of the virus in host cells, and modify certain molecular pathways related to the RAA system; hence many herbal agents might be useful in the prevention and possible treatment of COVID-19.

Keywords: Herbal medicine, coronavirus, COVID-19, pandemic, medicinal plants, traditional medicine

Introduction

Significant interest and attention has been given to traditional, complementary and integrative medicine (TCIM) over past few decades, and a growing body of evidence indicates the usefulness of such approaches in combating emerging infectious diseases (Arora *et al.*, 2011; Liu *et al.*, 2012) [7, 41]. Coronavirus disease 2019 (COVID-19) is a new infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that belongs to the coronavirus family (Hayat *et al.*, 2020) [27]. Impaired immune regulation is one of the factors that play a role in its pathogenesis and results in poor outcomes of COVID-19 patients (Nugraha *et al.*, 2020) [57]. In patients with Coronavirus disease 2019 (COVID-19), the most common clinical symptoms are fever and cough, shortness of breath, and other breathing difficulties in addition to other nonspecific symptoms, including headache, dyspnea, fatigue, and muscle pain (Mo, Xing & Xiao, 2020; Wang *et al.*, 2020) [53]. Also, some patients also report digestive symptoms such as diarrhea and vomiting (Huang, Wang, & Li, 2019; Wang *et al.*, 2020). Fever occurred in 98-100% of patients with SARS or MERS, compared to 81.3% of patients with COVID-19 (Assiri, al-Tawfiq, & al-Rabeeah, 2013; Yin & Wunderink, 2018; Mo *et al.*, 2020). 18.7% of patients had no fever at admission, suggesting that the absence of fever could not rule out the possibility of COVID-19 (Mo *et al.*, 2020). Although patients initially have fever with or without respiratory symptoms, various degrees of lung abnormalities develop later in all patients, and these can be seen on chest CT (CT) (Huang *et al.*, 2019;

Wang Hu & Hu, 2020) [28]. Although diarrhea is present in approximately 20-25% of patients infected with MERS-Cov or SARS-Cov, intestinal symptoms have rarely been reported in patients with COVID-19 (Sahin, Erdogan & Agaoglu, 2020) [66].

Various studies have been conducted to identify drug candidates to combat the virus, from natural and synthetic sources, with different individuals metabolizing such drugs in diverse manners as results of their genetic makeup (Bunu *et al.*, 2020) [15]. For the meantime, some persons believe that consuming herbal medicines or medicinal plants that act as immunomodulators can prevent or even cure COVID-19 infection (Nugraha *et al.*, 2020) [57]. It was reported that about 85% of COVID-19 patients in China received combined treatment with Traditional and Complementary Medicine and regular medication (Yang *et al.*, 2020) [42]. Recent systematic review has shown that herbal medicines can be significantly effective in alleviating different disease symptoms, including COVID-19 (Ang *et al.*, 2020) [6]. In one of such reviews, twelve databases were searched through 12 May 2020. Randomized controlled trials (RCTs) and quasi-RCTs assessing the effects of herbal medicines for the treatment of COVID-19 were eligible (Ang *et al.*, 2020) [6]. Consistent with previous analysis, the World Health Organization (WHO) concluded that, there is no specific medicine recommended to prevent or treat COVID-19 infection (Luo *et al.*, 2020). Hence, Traditional Chinese Medicine (TCM) that has been used in the control of infectious diseases for thousands of years may have some beneficial effects on COVID-19. There is clear room for the intervention of TCM as a complementary therapy for COVID-19 patients. It was reported that the patients with SARS-CoV or COVID-19 infection have benefited from TCM treatment (Tong *et al.*, 2004) [77], such as amelioration of side effect of conventional therapeutics (Zhang, Liu, & He, 2004; Liu *et al.*, 2012) [41]. Based on these factors, there is a general expectation that traditional medicine would be a valuable weapon in the armory against COVID-19 infection and its symptoms (Yang *et al.*, 2020) [42]. Therefore, this current review was conducted to extensively identify different herbal preparations and medicinal plants used in the prevention and management of COVID-19 and its symptoms.

Method

This is a review study, about twenty-five (25) different journal articles obtained from Pubmed, Elsevier, Hindawi, PLOS ONE, African Journals Online (AJOL), Lancet, Research gate, Google scholar and other journal hubs, relating to the use of herbal medicines and medicinal plants on the prevention and management of COVID-19, related infections and its symptoms were reviewed and summarized to generate useful data and document the various herbs and medicinal plants employed in managing COVID-19 globally. This was conducted September, 2021. Search keywords such as COVID-19 and Herbal medicinal, Use of herbal medicines in COVID-19, etc were used in for articles related to the review.

Results and Discussion

From the extensive review, various plants have been used across the globe in management of COVID-19 symptoms. Some of the notable medicinal plants reported to have such properties include *Artemisia annua*, neem tree (*Azadirachta indica*), Garlic (*Allium sativum*), Lime or Lemon (*Citrus medica*), Ginger (*Zingiber officinale*), Xanthorrhizol (*Curcuma xanthorrhiza*), Cinchona bark (*Cinchona sp.*),

Purple coneflower (*Echinacea purpurea*) *Curcuma longa*, among others. Significant effects of the combined therapy of herbal medicine with Western medicine has been found, and this have revealed the potential role of herbal medicine in treating COVID-19 (Ang *et al.*, 2020) [6]. In this regard, high-quality clinical trials are needed to evaluate the efficacy and safety of herbal medicine or medicinal plants combined with conventional therapy in the treatment of adults with mild to moderate COVID-19 in the future (Du *et al.*, 2021) [21]. Some, preliminary studies have been conducted in some these plants, thus, some of them may acceptable preventive measure against COVID-19 infection to boost immune system cells and to repress the production and secretion of proinflammatory cytokines as well as an adipose tissue derived hormone leptin having the proinflammatory nature. Some specific plants employed in the management of COVID-19 include the following:

Artemisia annua

A multinational research group has been the first to show the excellent activity of artemisinin-based treatment against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in human cell lines – including a specific type of lung cells. Notwithstanding the increasing availability of vaccines against the coronavirus disease 2019 (COVID-19), the world is still in need for effective and affordable treatments. There were many attempts to repurpose drugs that we already use for a myriad of different indications but to not much avail. Artemisinin is one of many bioactive compounds present in the plant known as *Artemisia annua*, and is currently used as an active ingredient to treat malaria. Moreover, its derivatives, artesunate, and artemether come with even better pharmacokinetic traits, which is why they are pervasively used in various anti-malaria combination treatments around the world. Considering their excellent safety profiles in humans, as well as their potential for worldwide distribution at relatively low costs, artemisinin-based drugs appear to be an attractive repurposing drug candidate for COVID-19 (Zhou, Y., 2021) [93].



Fig 1: Leaves of *Artemisia annua*

A study by Yuyong *et al.*, (2021) [91] on the effective and affordable treatments for patients suffering from coronavirus disease 2019 (COVID-19), reported the *in vitro* efficacy of *Artemisia annua* extracts as well as artemisinin, artesunate, and artemether against SARS-CoV-2. Concentration-response antiviral treatment assays, based on immunostaining of SARS-CoV-2 spike glycoprotein, revealed that treatment with all studied extracts and compounds inhibited SARS-CoV-2 infection of VeroE6 cells, human hepatoma Huh7.5 cells and human lung cancer A549-hACE2 cells, without obvious influence of the cell type on antiviral efficacy. In treatment

assays, artesunate proved most potent (range of 50% effective concentrations (EC50) in different cell types: 7–12 µg/mL), followed by artemether (53–98 µg/mL), *A. annua* extracts (83–260 µg/mL) and artemisinin (151 to at least 208 µg/mL). The selectivity indices (SI), calculated based on treatment and cell viability assays, were mostly below 10 (range 2 to 54), suggesting a small therapeutic window. Time-of-addition experiments in A549-hACE2 cells revealed that artesunate targeted SARS-CoV-2 at the post-entry level. Peak plasma concentrations of artesunate exceeding EC50 values can be achieved. Clinical studies are required to further evaluate the utility of these compounds as COVID-19 treatment (Yuyong *et al.*, 2021) [91].

Echinacea purpurea (*E. purpurea*) is one of the most popular herbal medicines in Europe and North America because it shows promising effects against viral infections. Its common name is Purple coneflower. The preparation of *E. purpurea* can be made in the form of extracts, tinctures, teas, and sprays. Many Native Americans use this kind of herb for respiratory infections (Sharma *et al.*, 2009; Hudson & Vimalanathan, 2011) [70, 29]. It contains several bioactive compounds like chicoric acid and caffeic acids, alkylamides, and polysaccharides. The utilisation of *E. purpurea* extracts for the treatment of virus-induced diseases expanded in the community after some studies reported that it had advantages as antiviral activity (Barnes *et al.*, 2005) [13]. Some commercial products containing echinacea claim that they have an immunomodulatory effect and act mainly as an immunostimulatory rather than an immunosuppressor. This claim is supported by a study in the USA, and demonstrated that echinacea mediated the increased release of various cytokines, including IL-1, IL-10, and TNF-α by macrophages (Burger *et al.*, 1997) [16]. Macrophages may have a minimal number or no ACE2 receptors on their surface. They are considered to have the constant capability for the phagocytosis of SARS-CoV-2 and release TNF-α with other proinflammatory cytokines through the humoral immune response (Prompetchara, Ketloy, & Palaga, 2020) [62].



Fig 2: Leaves of *E. purpurea*

Under certain conditions, these cytokines can help to support immune cell activities, yet they may sometimes lead to various unwanted effects on tissues. TNF-α is a central cytokine that plays an important role in local tissue inflammation, such as an increase in vascular permeability, adhesion, and migration of leukocytes and secretion of other cytokines including IL-1 and IL-6 by activated leukocytes. It can be considered when a series of cytokines are liberated in COVID-19 with the supplementation of echinacea. So, it certainly will increase the number of proinflammatory cytokines induced by Echinacea (Tisoncik *et al.*, 2012; Kumar *et al.*, 2019; Nugraha *et al.*, 2020) [57, 76, 36].

Java turmeric or Curcuma xanthorrhiza Roxb (*C. xanthorrhiza*) is an herbal plant that is widely used in Southeast Asian countries. This plant belongs to the Zingiberaceae and Curcuma genus. Java turmeric originates from Indonesia and has been spread and grown wild in Thailand, Philippines, Sri Lanka, and Malaysia. It also has been used as a food additive to enhance the flavor of food (Vesely *et al.*, 2015) [80]. In addition, this plant has been utilized in the medicine world, and its benefits have been scientifically proven. This plant is used to treat some diseases and as a supplement (Kim *et al.*, 2014; Vesely *et al.*, 2015; Singih *et al.*, 2017; Shimizu *et al.*, 2019) [80, 73, 34].



Fig 3: Parts of *Curcuma xanthorrhiza*

C. xanthorrhiza is widely used as a medication and supplement for specific diseases. This plant has some effects as an antimicrobial, anti-inflammatory, antioxidant, antihyperglycemic, antihypertensive, antiplatelet, nephroprotective, anticancer, and supplemental agent for systemic lupus erythematosus (SLE) (Maldonado *et al.*, 2017; D'alessandro *et al.*, 2020) [18-19]. *C. xanthorrhiza* is a dried rhizome and contains curcuminoids (1%–2%), volatile oil (3%–12%), xanthorrhiza (44.5%), and camphor (1.39%). Curcumin, monodemethoxycurcumin, and bisdemethoxycurcumin belong to curcuminoids. The presence of xanthorrhizol is specific and can distinguish this plant from *C. longa* (Ayala *et al.*, 2018) [10-11]. The most common compound in java turmeric is xanthorrhizol. The study about xanthorrhizol active compounds suggested that this compound could decrease inflammatory genes in adipose tissue, liver, and muscle in patients with diabetes mellitus. This study showed that xanthorrhizol treatment inhibited inflammatory cytokine production in adipose tissue and tumour necrosis factor (TNF-α) expression. The results showed that xanthorrhizol prevents the recruitment of immune cells to adipose tissue to down regulate the inflammatory cytokine gene. In the liver, xanthorrhizol inhibited CRP, a nonspecific

marker of systemic inflammation. Xanthorrhizol also reduced interleukin (IL-1 β) gene expression in muscle (Kim *et al.*, 2014) [34]. 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 (Singgih *et al.*, 2017) [73]. Taken together, xanthorrhizol can inhibit proinflammatory cytokines and promote the production of anti-inflammatory cytokines. A study about the anti-inflammatory and antioxidant effects of xanthorrhizol in hippocampal neurons and primary culture microglia was in line with the previous study in patients with diabetes mellitus and SLE. It showed that 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) (Ismail *et al.*, 2005; Lim *et al.*, 2005; Van & Kroes, 2014) [30, 38, 79]. Taken together, xanthorrhizol as an immunomodulatory is an immunosuppressant. Xanthorrhizol is an immunosuppressant that 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. However, the administration of xanthorrhizol needs to be done carefully and with consideration because at present, no study has been conducted with xanthorrhizol in COVID-19. There is still a chance that the administration of xanthorrhizol may worsen the conditions of patients with COVID-19. Using xanthorrhizol for treatment and prevention in COVID-19 still requires more evaluation, especially in the clinical trial setting (Nugraha *et al.*, 2020) [57].

Neem (*Azadirachta indica*) is a medicine which seems to cure so many aspects of Covid 19. Neem can be a very effective option against Covid 19 due to its broad-spectrum antiviral, antibacterial, antiretroviral, antioxidant and antimalarial effect as well as proinflammatory cytokine inhibition, immunomodulation, hepatoprotective effects, thrombolytic, its action as an ACE inhibition and as per its docking study, Neem has shown high inhibitory action against COVID-19 virus (Subramanian S., 2020) [74].



Fig 4: Leaves Neem (*Azadirachta indica*)

Neem leaves have not shown toxicity even at the dose of 6g/kg of body weight *in vitro* studies (Shirish, 2010) [72]. As Neem improves immunity and has antioxidant action, it can be advised to healthy people to take it in minimum dose. COVID-19 is responsible for severe cytokine storm induced complications and coagulopathies and Neem has been reported to inhibit proinflammatory cytokines, it has also shown thrombolytic properties. Hence, Neem can be a single

silver bullet due to its immunomodulator as well as thrombolytic properties other than its broad-spectrum antiviral action in mild, moderate and severe cases of COVID-19. Yet it is unclear whether virus lingers in the body for a longer duration after acute infection. Neem has anti-inflammatory properties and protective action on alveolar cells which may prevent lung fibrosis. It may help in the healing of alveolar cells if taken over a more prolonged duration of time in post COVID-19 cases. Hence, Neem can have a possible role as prophylactic medicine, curative medicine and to avoid long term effects on lungs in post COVID-19 cases. It may help in the healing of alveolar cells in post COVID-19 cases (Md Irfan *et al.*, 2019; Subramanian S., 2020) [74, 49]. Another study found that, there was a reduced risk of COVID-19 infection in patients receiving Neem capsules, thus, this demonstrates its potential as a prophylactic treatment for the prevention of COVID-19 infection ().

Cinchona sp. Cinchona trees (*Chincona L., Raiatea*) from the Andean mountain forests have valuable benefits as a particular component of the trees contains bioactive compounds used in managing fever. This beneficial effect was first discovered by Jesuit missionaries and gradually expanded throughout the world (Maldonado, Barnes, & Cornett, 2017) [46].



Fig 5: Parts of Cinchona tree

The bark of the trees produces quinine alkaloids, which were also an effective treatment of malaria for more than several centuries. Quinine has a mode of action that is similar to that of chloroquine, a synthetic antimalarial agent to treat malaria, thus, it is known as a chloroquine analogue (Abolghasemi *et al.*, 2012) [1]. Recently, quinine sulphate has become one of the most wanted drugs in the society for COVID-19 treatment. Inappropriate statements had been made by state officials and doctors that caused public panic. So, people looked for quinine-containing drugs competitively. The behavior of the people was triggered by a spontaneous reaction because of the high incidence and mortality rate of COVID-19 worldwide (D'alessandro *et al.*, 2020). Chloroquine showed an antiviral effect against the SARS-CoV infection (Vincent, Bergeron, & Benjannet, 2005). A clinical trial proved that hydroxychloroquine improves the SARS-CoV-2 viral load in COVID-19 patients when combined with azithromycin. The effect of quinine as an antiinfluenza virus infection has been extensively conducted (Seeler *et al.*, 1946). Moreover, the antiviral effect of quinine was described later by a group of scientists. In their report, quinine sulphate was evaluated on HSV-1 HaCat cells infected, which suggested that quinine acts to inhibit the viral infection through indirect pathways, such as activating the

protein heat shock response, interfering with multiple pathways during virus replication, and inhibiting NF- κ B by blocking the expression of the gene (Baroni, Paoletti, & Ruocco, 2007) [14]. A recent study invariably mentioned that the proposed antiviral mechanism of quinine is indirectly killing off viruses. Previous research investigated the effect of quinine sulphate on dengue virus-infected cells. As the relative similarity of dengue virus and SARS-CoV-2 structures, it may be possible that SARS-CoV-2 uses some relative methods to infect the cell and trigger cytokines to combating the virus (Ayala, Sreelatha, & Dechtawewat, 2018) [10-11]. The host cells infected by viruses will initiate the release of viral RNA and interfere with normal protein synthesis. However, an expression of a pathogen recognition receptor (PRR) known as RIG-I in the infected host cell increases minimally to promote the IFN-I signaling pathway rather than to elevate gene expression of IFN-stimulated genes (RNase L, PKR) that inhibit the synthesis of the protein, thereby blocking viral replication (Sadler & Williams, 2008). The RNase L pathway can eliminate ssRNA in virus infected cells, while PKR blocks the translation and affect signal transduction (Noisakran *et al.*, 2009) [56]. The target of quinine action is the inhibition of genome replication and translation of infected host cells and increased expression of RIG-I and IFN- α . It has been proven that IFN- α is the cytokine secreted by host cells to fight the viruses (Ayala *et al.*, 2018) [10-11].

Sambucus nigra L. Adoxaceae (Dried Flowers). This is indicated for fever and inflammation of the respiratory tract (WHO, 2002; BRASIL, 2011). Other indications are to relieve cold and flu symptoms, to alleviate headaches, and as expectorant (EMA, 2018e; Torabian *et al.*, 2019). It consist of flavonoids, such as kaempferol, astragalol, quercetin, rutin, isoquercitrin, hyperoside; triterpenes (α - and β -amyrin, ursolic acid, oleanolic acid); sterols (β -sitosterol, campesterol, stigmasterol); phenolic acids and their corresponding glycosides (chlorogenic, ferulic, caffeic and *p*-coumaric acids); and essential oil (Sidor and Gramza-Michałowska, 2015).



Fig 6: Parts of *Sambucus nigra* L. Adoxaceae

It has been experimentally proven for fever. The active constituents inhibit the biosynthesis of the inflammatory cytokines IL-1a, IL-1b, and tumor necrosis factor- α in

human peripheral mononuclear cells *in vitro* (Yeşilada *et al.*, 1997; Torabian *et al.*, 2019). Several *in vitro* and *in vivo* experiments have shown the antiviral effects of extracts from elderberries, against Influenza virus (Serkedjieva *et al.*, 1990; Zakay-Rones *et al.*, 1995; Krawitz *et al.*, 2011; Kinoshita *et al.*, 2012; Porter and Bode, 2017). Two randomized studies with a standardized extract, involving patients presenting influenza symptoms and positive reaction for Influenza virus type A or B, showed the reduction of the symptoms after the second day of treatment, without significant adverse effects (Zakay-Rones *et al.*, 1995; Zakay-Rones *et al.*, 2004). In another randomized study with air travelers, the group using *S. nigra* presented less cold episodes than the placebo group (Tiralongo *et al.*, 2016). A meta-analysis of randomized clinical studies led to the conclusion that *S. nigra* supplementation reduces upper respiratory symptoms of common cold and influenza (Hawkins *et al.*, 2019).

Ginger (*Zingiber officinale*) belongs to the family of Zingiberaceae. The herb is one of the most valued medicinal plant in Ayurvedic, Chinese and Unani to treat different kinds of diseases (Jayawardena *et al.*, 2020) [31]. The nutritional components present in ginger/100g contains, vitamin C (1.0 mg), magnesium (43 mg), manganese (0.229 mg), iron (279.7 mg), copper (8.8 mg), calcium (280 mg), folate (0.2 mcg), niacin (0.750 mg), choline (0.6 mg), zinc (64.0 mg), omega-3-fatty acids, (0.7 mg), omega-6- fatty acids (2.4 mg), gingerols, shogaols and paradols (Wagesho and Chandravanshi, 2015) [82].



Fig 7: Part of *Zingiber officinale* Zingiberaceae

According to Jayawardena *et al.* (2020) [31], magnesium including other vitamins are important to enhance immunity in viral infections, with special emphasis on COVID-19. Magnesium deficiency can increase the risk of high blood pressure, heart disease and type 2 diabetes (Geiger and Wanner, 2012) [25], and all these are comorbidities associated with COVID-19 deaths. Gingerol: Gingerol in ginger can be best described as capsaicin, a compound that gives chilies their spiciness and piperine found in black pepper. Gingerol is an active compound that has exhibited numerous healing activities against respiratory syncytial virus (RSV) (Mao *et al.*, 2019) [48], type-2 diabetes (Vagedes *et al.*, 2018) [78], osteoarthritis and rheumatoid arthritis through a mechanism which inhibits the formation of inflammatory cytokines and chemical messengers of the immune system (Terry *et al.*, 2011). Khaerunnisa *et al.* (2020) [75], reported that gingerol showed the highest binding affinity of -15.7591 kJ/mol with 5R7Y COVID-19 main protease essential for replication and reproduction of SARS-CoV-2. The researchers further revealed that gingerol exhibited binding affinity of -11.4082 kJ/mol, -12.9523 kJ/mol and -12.8835 kJ/mol with COVID-19 viral RNA binding protein (6W4B), N-terminal RNA binding

protein (6VSB), spike glycoprotein (6M3M) respectively. Thus, the compound could be a promising drug candidate to treat COVID-19 infection and its symptoms.

Citrus limonum; Lemon belong to the family of Rutaceae, with a scientific name *Citrus limonum risso*. It is one of the healthiest fruit on planet earth with wide range of health benefits (Omoruyi *et al.*, 2021) [58]. Lemon is chock-full of essential vitamins and minerals. According to the United States Department for Agriculture database, 124g squeezed lemon contains vitamin A (45 IU), vitamin C (112 mg), vitamin E (0.4 mg), vitamin B3 (0.2 mg), vitamin B1 (0.01 mg), vitamin B2 (0.01 mg), vitamin B5 (0.06 mg), vitamin B6 (0.1 mg), folate (31.7 mcg), pantothenic acid (0.3 mg), choline (12.4 mg), potassium (303 mg), calcium (17.1 mg), sodium (2.4 mg), magnesium (14.6 mg), copper (0.1 mg), phosphorus (14.6 mg), selenium (0.2 mg), zinc (0.1 mg) and iron (0.1 mg). Hesperidin, a natural compound that occupies the membrane peel of lemon, forms the highest concentration of crystals which appear as white flakes when lemon juice is extracted (Xiong *et al.*, 2019) [87]. Hesperidin in lemon, helps in maintaining the healthy thin walls of the small capillary blood vessels (Xiong *et al.*, 2019) [87]. The compound does this by protecting the endothelium against hypoxia via the stimulation of mitochondrial enzymes. Hesperidin was recently shown to bind to COVID-19-spike protein (Spro) and interfered with the re-folding of spike and then inhibits the viral infection process (Adem *et al.*, 2020) [3]. The researchers concluded that the compound could become a meaningful medicine for the treatment of SARS-CoV-2 infections. Another research revealed that hesperidin antiviral activity also exhibited a high binding affinity to COVID-19-3CLpro, indicating that the compound should be used as 3CLpro inhibitor (Wu *et al.*, 2020).



Fig 8: Parts of *Citrus limonum* Rutaceae

According to Jia *et al.* (2019), SARS-NsP13 sequence is a conserved multi-functional protein, which include N-terminal metal binding domain (MBD) and helicase domain (Hel) necessary for the replication of coronavirus. Based on structure modeling or helicase protein, hesperidin showed high binding affinity to the SARS-NsP13 target Jia *et al.* (2019). As the ACE2 remains the host specific target receptor in which COVID-19 gain access to the body, it has also been considered as the major target for the treatment of coronavirus infection to block SARS-CoV-2 from entering host cells.

Allium sativum; Garlic also known as *Allium sativum* is an edible bulb herb, consisting of 10-20 smaller sections of cloves, enclosed in a white parchment-like-skin (Ouroudi *et al.*, 2017). Each clove contains valuable amount of nutritional components. Three crush garlic cloves can contain vitamin C (8 mg), vitamin B6 (1 mg), calcium (16 mg), potassium (36

mg), phosphorus (13 mg), quercetin (2 mg), omega-3 fatty acids (8 mg), carbohydrates (3 g), calories (13 mg), trace amount of vitamin A and K, allicin, ajoene, S-allyl-cysteine (SAC) and its derivative, S-allylmercapto-L-cysteine (SAMC) (Lawson and Hunsaker, 2018). Garlic is an ancient natural herb that have received support from both the scientific community and natural healers from around the world (Petrovskal and Cekovska, 2010). Because of its medicinal properties, it has kept many people healthy.



Fig 9: Parts of *Allium sativum*

According to Parcival, (2016), the vitamins, minerals and other phyto-compounds in garlic have the power to boost the immune system, fight common virus infections and reduce inflammation. Garlic has many potent chemical constituents including allicin. Allicin is released by an enzyme known as alliinase when garlic is crushed or chopped (Livingstone *et al.*, 2019). It becomes highly volatile as it oozed out its pungent odor in garlic (Kotheri *et al.*, 2019). The breakdown of allicin forms other varieties of fat- and water-soluble sulfur-containing compounds, known as ajoene, S-allyl-cysteine and S-allyl-mercapto-L-cysteine. Allicin is a blood thinner that has drastically reduced the lead levels in blood clots, allowing better blood flow. Garlic allicin has been found to significantly decrease the blood sugar levels of individuals suffering from diabetes (Mikaili *et al.*, 2013). Allicin is also well known for its antiviral activity against viruses capable of causing respiratory diseases worldwide, including, herpes simplex virus type 1 and 2, parainfluenza virus type 3, vaccine virus, vesicular stomatitis virus, cytomegalovirus and human rhinovirus type 2 (Al-Snafi, 2019). Allicin was recently found as a potential inhibitor of the COVID-19 3CLpro/Mpro (Khaerunnisa *et al.*, 2020). The result obtained from the docking experiment showed that allicin binding affinity to the 6LU7 COVID-19 amino acids was -4.30 kcal/mol. According to Bezerra *et al.* (2018), allicin in garlic have shown to decrease virus replication by reducing the production of proteins involved in HIV replication. Also quercetin, a flavonoid compound found in garlic, has been tested to have a broad spectrum of antiviral activities, including COVID-19. Liu *et al.* (2020) [41] recently crystallized the main protease (Mpro) active site (3-chymotrypsin-like protease (3CLpro) of COVID-19. They observed that Mpro in CoV regulates the proteolytic maturation of the virus and hence should be the potential target protein to prevent the spread of infection (Liu *et al.*, 2020) [41]. Phyto-medicinal products, including quercetin were tested on COVID-19 Mpro, using a molecular docking approach (Khaerunnisa *et al.*, 2020). The result of the docking analysis shows that quercetin H-bonds interacted with 6LU7 amino acids (His164, Glu166, Asp187, Gln192 and Thr190)

in the COVID-19 Mpro active site (Khaerunnisa *et al.*, 2020). The high affinity binding of quercetin was comparable to the commercial nelfinavir used as positive control (Khaerunnisa *et al.*, 2020). Hence, the authors concluded that quercetin may be a potential inhibitor of COVID-19 Mpro, and should be explored in future research. The high doses of quercetin treatment injected in mice infected with lethal dose of the Ebola virus, survived Ebola infection compared with the placebo control group that were not given quercetin treatment (Qui *et al.*, 2016). Another research study conducted by Lopes *et al.* (2020), observed that quercetin may have immunomodulating properties that prevents viruses from replicating and reduces resistance to treatment with antiviral medication. It was also observed that quercetin derivatives have similar molecular structures and biological activities as nelfinavir, an antiviral drug used to treat HIV/AIDS (Khaerunnisa *et al.*, 2020).

Ganoderma Lucidum and Others

A study conducted among 632 Hong Kong residents, where individuals of least 18 years of age and could comprehend written traditional Chinese participated. The most popular forms of traditional, complementary and integrative medicine (TCIM) were vitamins or other dietary supplements (n = 160, 25.3%) and Chinese herbal medicine (n = 122, 19.3%) during the COVID-19 pandemic. The most frequently reported indication was strengthening the immune system, especially for vitamins or other dietary supplements (n = 142/160, 88.8%). The most popular herbal products that were reported to be used frequently in the prevention and management of COVID-19 symptoms include Lingzhi (*Ganoderma Lucidum*) (n = 7/278, 2.5%), *Chrysanthemi Flos* (n = 5/278, 1.8%), *Isatidis Radix* (n = 5/278, 1.8%), and *Glycyrrhizae Radix Et Rhizoma* (n = 5/278, 1.8%) etc., (Chun *et al.*, 2021). Also, Among various herbal medicines, Soshihotang (SSHT, Xiao Chai Hu Tang in Chinese) has also been prescribed to treat various viral diseases and is used in combination with other herbal medicines depending on the patient's symptoms (Seungwon *et al.*, 2020).

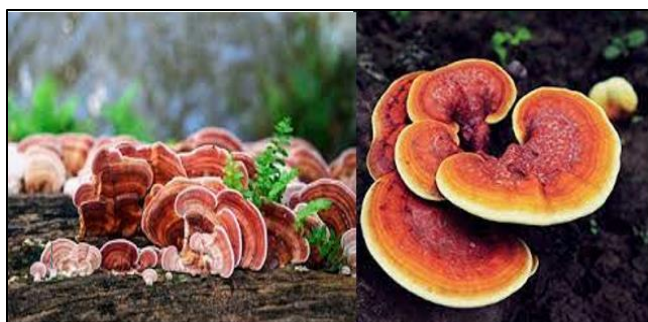


Fig 10: Parts of *Ganoderma Lucidum*



Fig 11: Parts of *Chrysanthemi Flos*



Fig 12: Soshihotang (SSHT, Xiao Chai Hu Tang in Chinese)



Fig 13: Parts of *Glycyrrhizae Radix Et Rhizoma*

Reports has shown the use of SSHT in the treatment of infectious diseases caused by various bacteria and, particularly, viruses. With respiratory system infections, in particular, there have been reports of SSHT used to treat viral infections such as influenza or the common cold. In a study comparing the effects of oseltamivir in patients with influenza A (Yaegashi, 2010).

Use of Vitamin D in COVID-19: Vitamin D has been reported to modulate the systemic inflammatory response through interaction with immune system. As such, it has a possible protective role against the risk of respiratory tract infections and other diseases (Fausto *et al.*, 2021). It may be useful in particular, during COVID-19 pandemic. In a systematic review, on the use of vitamin D in COVID-19, Asma *et al.*, (2021), investigated the relation between Vitamin D or 25-hydroxyvitamin-D [25(OH)D], concentrations and risk of SARSCoV-2 infection and COVID-19 severity. They systematically reviewed and, where appropriate, meta-analyzed the related retrospective, cohort, cross-sectional, and clinical trial studies that assessed the association of 25(OH)D concentrations and the risk of SARS-CoV-2 infection, composite severity. From their results, higher risk of SARS-CoV-2 infection was observed in Vitamin D deficiency (VDD) and serum concentrations of 25(OH)-D were lower in COVID-19 patients compared with healthy counterparts, as indicated by pooled results of both adjusted and non-adjusted studies. Among the 3 adjusted studies, 2 measured 25(OH)-D in the preceding year before SARS-CoV-2 infection (Merzon *et al.*, 2020; Meltzer *et al.*, 2020). The sample sizes in one of these studies were sufficiently powered (case/control: 782/7025) (Merzon *et al.*, 2020). The non-adjusted studies measured 25(OH)-D at admission and the sample sizes were sufficient in 4 studies (186/2700, 197/197, 128/219, 335/560) (Ferrari, & Locatelli, 2020) respectively. Moreover, concentrations of 25(OH)-D were lower in COVID-19 patients compared with healthy subjects. Based on these findings, VDD is associated with increased risk of SARS-CoV-2 infection; however, caution should be made in interpreting these results, since the studies have inherent limitations (Asam *et al.*, 2021). All of the studies indicated a lower concentration of 25(OH)-D with more severe status

(composite severity) of disease. Furthermore, VDD was associated with composite severity in studies that were both adjusted and not adjusted for confounders. In addition, due to the highly expressed concentrations of vitamin D receptors (VDRs) in B- and T-lymphocytes (Gruber-Bzura, 2018), vitamin D may affect immune system function. VDR is a member of the nuclear hormone receptor (NHR) family, a known transcription factor that is present in both T and B immune cells and regulates a variety of metabolic pathways, such as those involved in the immune response and cancer (Adorini, Daniel, & Penna, 2006; Evans *et al.*, 2020) [4]. High concentrations of transforming growth factor β (TGF- β) have been reported in the acute phase of COVID-19, where TGF- β signaling is closely related to SARS-CoV-2 and is suppressed by VDR via genomic competition with Mothers against decapentaplegic homolog 3 (Smad3) occupancy on proinflammatory (e.g., IL-6) genes and therefore creating a stable physiologic situation (Ding *et al.*, 2013). Another probable mechanism is that vitamin D can induce cathelicidin, IL-37, and defensins as antimicrobial peptides, and promote cellular innate immunity and reduce virus replication (Liu *et al.*, 2006; Adams *et al.*, 2009; Barlow *et al.*, 2011) [41, 2]. It has been postulated that vitamin D can enhance the expression of some genes related to antioxidant systems, such as the glutathione reductase gene (Lei *et al.*, 2017); accordingly, some studies have reported that vitamin D metabolites have vascular-related functions including anticoagulant effects through modifying the expression of thrombomodulin and tissue factor in monocyte and aortic cells (Wu-Wong *et al.*, 2006; Ruth Wu-Wong, 2009) [64]. Because of the global prevalence of COVID-19 pandemic, it is therefore important to investigate potential antiviral treatments or preventions (Asam *et al.*, 2021). Also, A double-blind, randomized, placebo-controlled trial in Brazil conducted by Murai *et al.* (2020) [54] showed an effect of a single dose of 200 000 IU of vitamin D3 supplementation to hospital stay in severely ill COVID-19 patients. During the trial, 240 patients were equally randomized either in vitamin D supplementation or in placebo arm. The baseline demographic and clinical characteristics were comparable between both the arms. Though the supplementation was found to be safe and it improved serum 25-hydroxyvitamin D levels, it did not translate into any clinical benefits to the patient in the form of reduced hospital stay, the requirement of ICU support or mortality rate. Hence, the authors recommended against the use of vitamin D as adjuvant therapy in hospitalized COVID patients. Though it was found that requirement of oxygen therapy was low in patients treated with vitamin D as compared to placebo group (65.5% vs. 85.9%; P=0.008). Removal of this study from overall analysis resulted in lowering of heterogeneity in cumulative findings of meta-analysis and yielded beneficiary effect on ICU needs with vitamin D (Murai *et al.*, 2020; Shah *et al.*, 2021) [54, 69].

Conclusion

Based on this review, herbal medicines might have the capabilities to regulate the production and release of proinflammatory cytokines, interfere with the development of the virus in host cells, and modify certain molecular pathways related to the RAA system; hence many Herbal agents might be useful as treatments to fight COVID-19. Patients that are still not recommended to use the supplementation containing one of these compounds to prevent COVID-19 or to heal the disease without the specific advice or under the direct supervision of a clinician, suggestion should be given to

clinicians for the administration of these herbal medicines carefully to patients, even if they are healthy

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