Journal of Pharmacognosy and Phytochemistry
Available online at www.phytojournal.com

E-ISSN: 2278-4136
P-ISSN: 2349-8234
www.phytojournal.com
JPP 2021; 10(5): 147-157
Received: 21-07-2021
Accepted: 23-08-2021

Parul Goel
Assistant Professor, Department of Bioscience, MLSM College, Himachal Pradesh, India

Monika Bhuria
Council of Scientific and Industrial Research - Institute of Himalayan Bioresource Technology Palampur, Himachal Pradesh, India

Mamta Kaushal
Council of Scientific and Industrial Research - Institute of Himalayan Bioresource Technology Palampur, Himachal Pradesh, India

Corresponding Author:
Parul Goel
Assistant Professor, Department of Bioscience, MLSM College, Himachal Pradesh, India

Efficacy of medicinal plants in combating COVID-19

Parul Goel, Monika Bhuria and Mamta Kaushal

Abstract
The Severe Acute Respiratory Syndrome-related Coronavirus 2 (SARS-CoV-2) has been declared as a global pandemic by WHO (World health organization). Till now the SARS-CoV-2 has affected nearly 213 countries and claimed four million deaths. Medicinal plants and plant based drugs plays a pivotal role in boosting the immune system of the body. The apt use of medicinal plants can successfully cure several diseases in humans. This review discusses about the several aspects related to COVID-19 with special focus on medicinal plants that have been use since ancient time and are proven to be effective against COVID-19. Here, we also discuss the recent research on medicinal plant that can act against deadly SARS-CoV-2. We have also focussed on the medicinal plants that could be potentially used to prevent and cure the life threatening symptoms associated with COVID-19. Keeping in view the importance of medicinal plant, the current review will open a province for the development of plant based drugs or herbal formulation as an alternative strategy to combat the present COVID-19 situation.

Keywords: COVID-19, medicinal plants, ACE2, lung inflammation

1. Introduction
Every pandemic has affected thousand to millions of life. The emergence of world pandemic Coronavirus disease 2019 (COVID-19) is caused by novel corona virus named as Severe Acute Respiratory Syndrome-related Coronavirus 2 (SARS-CoV-2) .The SARS-CoV-2 is the seventh known virus that belongs to Coronaviridae family. Two of the viruses belonging to this family namely Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS) were already responsible for major epidemics that took place in year 2003 and 2012, respectively (Zhou *et al*., 2020; Zhu *et al*., 2020) [1, 2]. The COVID-19 pandemic has turned out to be more deadly than above mentioned coronaviruses. The first outbreak of COVID-19 was from Wuhan city of China in December 2019 (WHO, 2020) [3]. All of these coronaviruses have zoonotic origin (Ye *et al*., 2020) [4]. Using viral genome sequencing and evolutionary analysis, the natural origin of SARS-CoV-2 is Chinese horseshoe bats of genus Rhinolophus (Grahm *et al*., 2020) [5]. Countries throughout the world are taking strict actions such as complete lockdown, social distancing in combating the spread of this disease. Moreover, our day to day life has affected by COVID-19. The insistence of taking extensive hygiene such as washing hands, wearing masks has been done to avoid the infection of this virus.

Coronaviruses are positive single-strand RNA enveloped viruses having largest RNA genome ranging from 26-32 kilobases (Pal *et al*., 2020) [6]. SARS-CoV-2 belongs to the beta-coronavirus group. SARS-CoV-2 directly binds to the epithelial cell of oral and nasal cavities. The virus later migrates from respiratory tract to alveoli tissue of the lungs. In moderate infection the virus infection is limited to upper respiratory tract [7](Mason *et al*., 2020). However under sever conditions, the alveoli cells of the lungs get damage thus impairing gas exchange. Common symptoms of COVID-19 include fever, cough, and shortness of breath and may cause pneumonia and/or even death under severe condition (WHO, 2020) [3]. The major mode of transmission is airborne droplets, respiratory secretions and direct contact with the infected patient (Jayaweera *et al*., 2020) [9]. The mortality rate of this disease is much higher in patients having hypertension, diabetes and other cardiovascular diseases (Wu *et al*., 2019) [10]. The incubation period is between 2-14 days or even longer. SARS-CoV-2 not only infects the respiratory system but may develop disorders in digestive system, heart and kidney (Liu *et al*., 2020) [11]

Boosting the immune system has become topmost priority since the outbreak of COVID-19. At present COVID-19 situation, several studies have shown that people with strong immunity has high recovery rate against COVID-19 (Chowdhury *et al*., 2020) [12]. The phytoconstituents such as steroids, alkaloids, diterpenes, triterpenes, aliphatics and glycosides etc.

present in medicinal plants are one of the key players in boosting host immune response (Chikezie *et al*., 2015) [13]. Their anti-inflammatory, antioxidant and anti-viral properties make them as good candidate for the treatment of COVID-19. The anti-viral property of medicinal plant is attributed by their role in preventing virus entry and its replication in host cell. The medicinal plants can not completely cure the COVID-19 but perhaps it could minimize the severity of this disease by boosting up the immune response. As the present pandemic situation is neither the first nor last. The world may keep on facing such pandemics in future but we can minimise the effect and one of the way is to healthify our life style by introducing herbal formulations, plant based nutraceuticals etc. that will strengthen our immune response. By this review, we enlighten the role of medicinal plants in combating this dreadful virus.

2. Insight to biology of SARS-CoV-2

The SARS-CoV-2 is enveloped single stranded positive-sense RNA virus having genomic size ~30 kb [14] (Guo *et al*., 2020). SARS-CoV-2 belongs to the β- genus of Nidovirales order of the Coronaviridae family [15] (Paules *et al*., 2020). The genome of SARS-CoV-2 encodes both structural and non-structural proteins (Table1). The structural protein includes envelop (E), glycoprotein spikes (S), nucleocapsid (N) and membrane protein (M). Spike proteins are involved in attaching the virus to the host cell, envelop is required for virion assembly, membrane protein is required for providing morphology to the virions and the nucleocapsids are for packaging the subgenomic RNA. In addition to, the virus genome also encode 16 non-structural proteins (NSP1-NSP16) (Yadav *et al*., 2021) [16]. Papain-like proteases (PLP) and 3CL-proteases encoded by NSP3 and NSP5 respectively, are non-structural proteins vital for virus replication and itsspread in host cell. Another crucial non-structural protein is RNA-dependent RNA polymerase (RdRp) that enables replication and transcription of viral genome. The entry of virus in host cell is first of all initiated by the binding of spike protein to the cellular receptors mainly angiotensin-converting enzyme 2 (ACE2) (Sungnak *et al*., 2020) [17]. This is thought to be the most critical step for virus entry. ACE2 is mainly expressed by epithelial cells of the lungs, small intestine, kidney and heart (Hamming *et al*., 2004) [18]. After binding, the next step is the cleavage of S protein by cell surface-associated transmembrane protease serine 2 (TMPRSS2) and cathepsin. This further promotes the invasion of virus into host cell via endocytosis. After the entry of viral genome in the host cytoplasm,a positive-sense RNA genome translates into two polyproteins 1a, b (pp1a, pp1b).Polyproteins formed via translation is further processed into functional proteins by 3CLpro and PLpro. PLpro also leads to immune suppression of the host cell (Ziebuhr *et al*., 2000) [19]. Functional proteins mainly helicase, RdRp, and NTPase are the integral part of replication-transcription complex (RTC)that participates in replicating virus genome. In addition to virus own machinery, host cellular enzymes like human proteases, cathepsins B and L, trypsin are critically important (Millet *et al*., 2015) [20].

3. Human Immune response towards SARS-CoV-2

Activation of human immune response towards SARS-CoV-2 is very crucial step in deciding the severity of COVID disease. The entry of virus inside human cell triggers both innate and adaptive immune response (Fig. 1). Several toll-like receptors (TLR) specifically TLR3, TLR7, TLR8 firstly binds to the virus and then activates array of immune response which includes release of inflammatory factor, activation of dendritic cells and also initiates the production of type I Interferons (IFN-α/β) (Kawai and Akira, 2010) [21]. All these factors are crucial in preventing the virus spread in body. Cascade of pro-inflammatory cytokines mainly IL -1, -2, -4, -7, TNF-α and free radicals were also observed in COVID-19 patients (Chien *et al*., 2006) [22]. This in turns leads to local damage of organs mainly lungs. However sever infection may sometimes leads to multiple organ failure that results in death (Zaim *et al*., 2020) [23]. The T-cells (CD4+ and CD8+) of adaptive immune response was also activated against SARS-CoV-2 infection**.** Additionally**,** the production of SARS-CoV-2 specific antibodies mainly IgG, IgM and IgA was also reported during early stage of infection (Jacofsky *et al*., 2020) [23]. The C3a and C5a protein of compliment system also comes to action in combating the viral infection (Mellors *et al*., 2020) [24].

4. Potential role of some important medicinal plants against viral infection

Medicinal plants are those plants that are mostly used in treating and preventing diseases harmful to humans. Traditional system of medicines relies on using medicinal plants for curing several diseases. Medicinal plants play a pivot role in strengthening human health. Two-thirds of word's plant species contain medicinal property (Krishnaiah *et al*., 2011) [25] Worldwide, people are using medicinal plants as a plant-based drug or herbal formulation for disease remedy (Agbor *et al*., 2005) [26]. Non-toxicity, ease in availability and low-cost are some other factors that makes them people first choice when it comes to improve health issues.Active phytochemicals such as flavonoids, tannins reducing sugars, triterpenoids, sugars, alkaloids, steroids, phenolic compounds, catechins, saponins, , anthroquinons present in medicinal plants are reported to act as a antimicrobial agent (Adhikari *et al*., 2020) [27]. Medicinal plants are act as a immunomodulator means they can alter our immune response (Mukherjee*et al*., 2013) [28]. In general the medicinal plants boost-up our immune system by enhancing or stimulating the components of both adaptive and innate immune response. Several medicinal plants have been already tested for their anti-viral activity against several awful viruses such as HIV, SARS, MERS, poxvirus, dengue virus, and influenza viruses (Adhikari *et al*., 2020) [27]. The biological active compounds isolated from medicinal plants have always been a great interest of research for scientists. Examples of medicinal plants along with their immunomodulatory mechanism have been shown in Table 2. Few of the medicinal plants that are part of our ancient medicinal system and also act as immune enhancer are separately discussed below.

4.1 Tulsi (*Ocimum sanctum* L): Tulsi, holy basil is popularly known for its eminent medicinal properties. The immunomodulatory effect of tulsi leaves is associated with the enhancement of both helper and natural killer (NK) cells that are effective against antibacterial and antiviral infection (Singh *et al*., 2021) [50] Two active ingredients found in tulsi are Apigenin and Ursolic acid. Tulsi is mostly used for curing COVID-19 related symptoms mainly fever and cough (Goothy *et al*., 2020) [51]. The antiviral property of tulsi is effective against both RNA and DNA-viruses (Mondal *et al*., 2011) [52]. The tulsi leaf extract is effective against asthma and bronchitis.

4.2 *Tinospora cordifolia* (Giloy, Guduchi): It is an esteemed medicinal plant having curative properties against fever, gout, respiratory infections, diabetes, asthma, piles. The plant also has anti-oxidant, anti-inflammatory, anti-cancer effect.The plant extract contain several bioactive compounds such as berberine and furanolactone, tinosporone, tinosporic acid. Herbal formulation of giloy, tulsi, ginger is effective against COVID-19 (Srivastava *et al*., 2020) [53].

4.3 *Zingiber officinalis* (Ginger, Adrakh): Ginger roots are used to treat common diseases mainly headache, cold and nausea. Bioactive compounds of ginger mainly 6-gingerol, 8-gingerol, and 6-shogaol are effective against respiratory disorder by relaxing the human airway smooth muscles (Mangprayool *et al*., 2013) [54]. High concentration of fresh ginger stimulates mucosal cells to secrets IFN-β that can prevent virus entry.

4.4 *Curcuma domestica* (Turmeric, Haldi): It has excellent anti-septic properties. The rhizome part of *C. domestica* is mainly use in food and also consider as a best remedy to treat cold, cough and throat infection. Its main photochemical namely curcumin exhibits anti-inflammatory response. Curcumin can improve breathing problem in patients facing bronchitis by clearing the mucous in lungs (Rocha *et al*., 2020; Benzieand Wachtel-Galor 2011) [55]

4.5 *Glycyrrhiza glabra* (Liquorice): The roots of *G. glabra* are mainly utilised to cure asthma and cold. It is also consume as anti-oxidant, anti-diuretic, anti-diabetic and anti-inflammatory herb. Its main bioactive constituent glycyrrhizin is reported to prevent viral replication and also effective against SARS-CoV virus (Hoever *et al*., 2005) [56]

4.6 *Withania somnifera* (Ashwagandha): It is a small shrub commonly known as Indian ginseng. One of the important bioactive compounds of Ashwgandha is Withaferin-A which possess anti-viral activity against influenza virus (Kumar *et al*., 2020) [57]. This medicinal plant also known to stop the cytokine storm that activates during viral infection (Bani *et al*., 2006) [58]. The roots possesses high antiviral activity.

4.7 *Cinnamomum zeylanicum*: The bark of *C. zeylanicum*has many medicinal properties especially in curing digestive disorders. The bioactive compound namely cinnamaldehyde significantly slow down the inflammatory cytokines mainly TNF-α, IL-6, IL-13 and IL-1β in covid-19 patients (Asif *et al*., 2020) [59]

4.8 *Piper nigrum* (Black pepper): The bioactive compound of black pepper named as piperine has widespread pharmacological role as anti-inflammatory, anti-oxidant, anti-tumor and anti-microbial (Singh *et al*., 2021) [50]. The *P. nigrum* is found to be useful in respiratory congestion (Chopra *et al*., 2020) [60].

4.9 *Phyllanthus emblica* L. (Amla): The amla fruit possess antibacterial, antifungal and antiviral properties. It is an excellent source of vitamin C. Phenolics from amla found to inhibit Herpes simplex virus HSV-1 and HSV-2 infection (Xiang *et al*., 2011) [61].

5. Evidences of medicinal plants effective against SARS-CoV infection

The therapeutic potential of several medicinal plants against SARS-CoVinfection have been tested globally. In order to explore the potential of medicinal plants for use in COVID-19 management several parameters such as antiviral, anti-inflammatory, immunomodulatory, safety, toxicity are taken into consideration. In a recent article Lim *et al*., 2021 [62] has suggested four medicinal plants *A. indica, E. longifolia, N. sativa*, and *V. amygdalina* that could be further investigated to unearth their role against this viral infection. Proteins like ACE2, 3CL-pro, PL-pro, RdRp etc are considered to be the promising targets of antiviral drugs to act against CoV infection. Therefore, medicinal plants that could inhibit these proteins could be used to treat the SARS-CoV-infection. Natural products isolated from medicinal plants also act as dual inhibitors for e.g a monoterepenoid, Carvacrol present in ajwain, oregano, black cumin could target both ACE2 and SARS-CoV 3C-like protease (Javed *et al*., 2020) [63]. Tannic acid present in fruits like berries, citrus, grape, and apples also act as potential inhibitor of both ACE2 and TMPRSS (Wang *et al*., 2020) [64]. Such compounds could have more impact in treating COVID-19. Medicinal plants that have potential for inhibiting the SARS-CoV2 proteins are discussed below.

5.1 Medicinal plants targeting ACE-2 receptor

Angiotensin-converting enzyme 2 (ACE-2) is a receptor protein expressed in cell and tissues of lung, kidney, heart and liver. ACE-2 is an entry receptor for SARS-CoV-2 in human cells (Salamanna *et al*., 2015; Hoffmann *et al*., 2020) [65, 66]. Therefore to tackle the present pandemic situation one of the most promising approach is to identify those medicinal plants that could block the entry of SARS-CoV-2 by targeting ACE-2 receptors. Medicinal plant such as *Rheum palmatum* L., *Citrus aurantium* L., *Rubia tinctorum* L., *Quercus infectoria* has been tested and found to have good potency against ACE-2 receptor (Ho *et al*., 2007; Yang *et al*., 2020; Heidary *et al*., 2020; Sharifi *et al*., 2013) [67-70]. Studies have shown that most of the abovementioned plants contains a bioactive compound named as emodin that could blocks the interaction between SARS coronavirus spike protein and ACE2 (Ho *et al*., 2007; Schwarz *et al*., 2014) [67, 71]. A bioactive compound named as naragennin present in several citrus fruits is considered as powerful inhibitor of ACE-2 receptor [72] (Clementi *et al*., 2020). Some important bioactive compound namely baicalin and scutellarin obtained from some Chinese herbs (Scutellaria spp.) are reported to act as ACE-2 inhibitor (Deng *et al*., 2012; Wang *et al*., 2016) [73, 74]. Potent components in *A. sativum* (Garlic) and *Quercus infectoria* have also been found to effective against ACE-2 receptor through *in vitro* studies (Zaidi *et al*., 2009; Sharifi *et al*., 2013) [75, 70]. It is also reported that the aqueous solution of Indian medicinal plant *Withania somnifera* L. prevents the entry of SARS-CoV by blocking host ACE2 receptor (Balkrishna *et al*., 2020) [76].

5.2 Medicinal plants targeting transmembrane proteinase Serine 2 (TMPRSS2)

TMPRSS2 is a transmembrane proteinase Serine 2 that promotes the virus entry in host cell. Being as protease TMPRSS2 cleaves the spike protein of SARS-CoV and activate it to promote virus fusion at cell surface (Shirato *et al*., 2013) [77]. The entry of SARS-CoV-2 is firstly governed by its interaction with ACE2 receptor followed by the cleavage of SARS-CoV-2/ACE2 complex by TMPRSS2 (Matsuyama *et al*., 2005) [78]. Therefore one of the propitious approaches to prevent coronavirus infection is to target and inhibit the expression of TMPRSS2 (Schlagenhauf *et al*., 2020) [79]. *In silico* interaction study of 97 alkaloid compounds present in African medicinal plant with TMPRSS2 protein has

recognised cryptospirolepine, 10-hydroxyusambarensine, and cryptoquindoline as potential inhibitor of TMPRSS2 (Gyebi *et al*., 2020) [80]. In one of the molecular modelling tool, Withaferin-A, Withanone compounds obtained from Ashwgandha were considered to have stronger inhibitory effect towards TMPRSS2 (Kumar *et al*., 2020) [57].

5.3 Medicinal plants targeting RdRp enzyme

RNA-dependent RNA polymerase (RdRp) is involved in corona virus replication process inside host cell. The enzyme is also crucial in transcription of subgenomic rna (sgRNA). RdRp is also prime target of antiviral drugs. *In-silico* analysis has revealed four plant derived polyphenols (Epigallocatechin gallate, theaflavin-3'-O-gallate, theaflavin-3'-gallate, theaflavin 3,3'-digallate) that could inhibit RdRp activity and effective against COVID-19 (Singh *et al*., 2020) [81]. Using virtual screening of 92 phytochemicas from 20 medicinal plants of south America, has identified hesperidin as a lead candidate to inhibit RdRp activity [82] Mosquera *et al*., 2020. Anti-SARS activity of Chinese herbal plant *Houttuynia cordata* Thorn (HCT) is mainlydue to its property of inhibiting RdRp enzyme (Lau *et al*., 2008) [83].

5.4 Medicinal plants targeting SARS-CoV 3C-like protease and Papain-Like proteinase (PLpro)

SARS-CoV 3C-like protease and PAPAIN-LIKE PROTEINASE (PLpro) are non-structural protein or cysteine proteases encoded by SARS-CoV-2 genome. Both these proteases are involved in processing and maturation of viral proteins that are vital for virus replication and transcription in host cell (Baez-Santos *et al*., 2015) [84]. A 3C-like protease (3CLpro) sometimes referred to as main protease (Mpro) is required in cleaving viral polyprotein into functional protein , whereas PAPAIN-LIKE PROTEINASE (PLpro) has an additional role in evading or supressing host immune response by targeting interferon production (Yuan *et al*., 2015) [85]. These proteases are considered as accepted targets for antiviral drugs to block virus replication.

In silico study has suggested six phytochemicals Baicalin, Rutin, Biopterin, Licoleafol, Luteolin and Quercetin that have potential to use against PAPAIN-LIKE PROTEINASE (PLpro) (Laskar and Choudary, 2021) [86]. Bioactive compounds especially rutin and rocymosin b isolated from *Glycyrrhiza glabra*were found to be effective inhibitor of papain-like protease (PLpro) using molecular docking analysis (Shawky *et al*., 2020) [87]. Phytochemical studies revealed the inhibitory effect of potent flavonoids namely psoralidin and sobavachalcone isolated from the seeds of *Cullen corylifolium* L. towards SARS-CoV- 3CL(PLpro) (Kim *et al*., 2014) [88]. Moreover bioactive cinnamic amides extracted from the fruit of *Tribulus terrestris* also inhibits SARS-CoV PLpro enzyme (Song *et al*., 2014) [89]. Inhibitory effect of four biflavonoids (amentoflavone, bilobetin, ginkgetin, and sciadopitysin) isolated from the leaves of *Torreya nucifera* (L.) Siebold & Zucc. was proven to be effective against SARS-CoV- 3CL(pro) (Ryu *et al*., 2010) [90]. The popular red sage plant *Salvia miltiorrhiza* Bungewas also exhibited inhibitory effect on SARS-CoV- 3CL(pro) (Park *et al*., 2012) [91]. The potent bioactive compound found in this plant is Dihydrotanshinone. Moreover, an alkylated chalcone xanthoangelol E extracted from *Angelica keiskei* (Miq.) Koidz was found to be potent SARS-CoV- 3CL (pro) and SARS-CoV- PLpro inhibitor (Park *et al*., 2016) [92]. Molecular docking study has revealed the dual role of Verbascoside compound isolated from plants like *Cichorium intybus*, *Olea europaea* and *Marrubium vulgare* in inhibiting SARS-CoV-3CL (pro) and SARS-CoV- PLpro activity (Shawky *et al*., 2020) [87]. The whole plant extracts of Chinese medicinal plant *Artemisia annua* L.was reported to act against SARS-CoV-2 infection by inhibiting enzymatic activity of 3CLPro (Law *et al*., 2020; Benatouil, *et al*., 2020) [93, 94]. Phenolic compounds of *Isatis indigotica* also block the enzyme activity of 3C-like proteases (Lin *et al*., 2005) [95]. Molecular docking analysis has also suggested lupinifolin as a potent inhibitor of SARS-CoV- 3CL(pro) (Mosquera *et al*., 2020) [82]

6. Use of medicinal plants against life threatening symptoms associated with COVID-19

People suffering from COVID-19 show wide array of symptoms including fever, dry cough, fatigue, muscle aches, sore throat, headaches, runny nose, nasal congestion, loss of taste or smell, pink eye, skin rash or discoloration of finger or toes, nausea, vomiting, gastrointestinal disturbances like diarrhoea (Tenforde *et al*., 2020) [96]. Specific organ dysfunction primarily lungs, kidney and heart has been also observed during acute COVID-19 infection (Carfi *et al*., 2020) [97]. Moreover, patient suffering from cancer, type 1 or type 2diabetes, high blood pressure, severe obesity, cardiovascular disease, chronic kidney disease, asthma are at high risk of COVID-19 infection. In a recent report of 44,672 COVID-19 patients, the highest mortality rate was observed for patients with a cardiovascular disease (10.5%) followed by patient with diabetes (7.3%), respiratory disease (6.3%) and hypertension (6%) (Wu *et al*., 2020) [98]. Morbidity associated with COVID-19 can be reduced by making use of medicinal plants that can help to minimize the severity of life threatening symptoms. Some of the medicinal plants that have potential against life threatening symptoms associated with COVID-19 are discussed below.

6.1 Lung inflammation and fibrosis

ACE2 is highly expressed in the lungs and alveolar cells that catalyses the conversion of angiotensin II to vasodilator angiotensin. The binding of Spike protein of SARS CoV-2 results in the reduced expression of ACE2 leading to the accumulation of angiotensin II responsible for pulmonary hypertension, acute lung injury (ALI), and lung fibrosis. Curcumin treatment has been shown to improve several lung diseases including pulmnory fibrosis, allergic asthma, chronic obstruction pulmnory disease (COPD) and ALI/acute respiratory distress syndrome (ARDS) (Venkatesan *et al*., 2007; Ram *et al*, 2003) [99, 100]. These infections might also develop in patients suffering from COVID19 that can become life threatening. Curcumin also provide protection against bleomycin induced lung fibrosis in rats by stabilizing the lung architecture, maintaining the redox balance, inhibiting leukocyte infiltration and release of proinflammatory cytokine including TNF-α (Venkatesan *et al*., 2007) [100]. Curcumin inhibited the replication and budding of respiratory syncytial virus (RSV) which is the cause of asthma, bronchitis and severe lower respiratory tract disease in young children and infants. *C. alata* a medicinal herb *is* reported to produce variety of secondary metabolites including major flavonoid, kaempferol-3-O-gentiobioside and kaempferol-3-O-β-d-glucopyranoside. The root powder of *Withaniasomnifera* was reported to be effective in treating the rats with pulmonary hypertension by reducing the inflammation, endothelial dysfunction and oxidative stress (Kaur *et al*., 2015) [101]. Withaferin A has shown to improve pulmonary fibrosis and lung damage by suppressing the expression of pro-

inflammatory (NF-κB p65, IL-1β, TNF-α), pro-fibrotic (CTGF, collagen 1A2, collagen 3A1, fibronectin) and pro-angiogenic factors (VEGF, FAK, p38 MAPK, PLC-γ1) in animal studies (Bale *et al*., 2018) [102].

6.2 Renal Damage

In a clinical study, acute kidney failure was reported in the 5 to 15 % of COVID-19 patients with a 60-90% mortality rate (Cheng *et al*., 2020) [103]. In a study related to diabetic mice, ACE2 expression was enhanced in glomerulus. Moreover, ACE2 inhibition resulted in the higher urinary albumin excretion (UAE) by regulating the angiotensin II levels through its degradation (Ye *et al*., 2006) [104]. ACE2 inhibition might result in renal damage in diabetic patients. Since ACE2 acts as receptor for SARS-CoV2 viruses, use of ACE2 inhibition therapy might put the diabetic patients at high risk for severe kidney damage. Several studies have highlighted the anti-inflammatory role of curcumin, which suppresses the activation of of NF-κB responsible for the buildup of IL-1, IL-2, IL-6, TNF-α and MCP-1 (Quiao *et al*., 2012) [105]. CK have shown to increase epithelial of permeability along with a decrease in intestinal alkaline phosphatase (IAP) caused due to reduction of epithelial tight junction protein (ZO1, Claudins). Curcumin was reported to play protective role in the renal fibrosis at the priming and activation stages byrestoring the redox balance,inhibiting the inflammation reaction and the deposition of extracellular matrix in animal models. These changes are brought about though inhibition of production of inflammatory molecule (MCP1, NF-κB, TNF-α, IL-1β, COX-2, and cav-1) and induction of expression of anti-inflammatory molecules (HO-1; heme oxygenase-1, M6PRBP1; mannose-6-phosphate receptor binding protein 1 and NEDD4; neural precursor cell expressed developmentally down-regulated protein 4). Curcumin also blocks the TGF-β/Smads, and MAPK/ERK pathways, and stimulates PPAR-γ pathway (Sun *et al*., 2017) [106].

Phyllantus sp. is a traditional medicine used in the treatment of jaundice, diabetes, liver and gall bladder disease (Calixto *et al*., 1998; Dhiman *et al*., 2005) [107, 108]. Its plant extract contains various secondary metabolite including flavonoids, lignins, alkaloids, terpene, tannins, and phenols. The hepatoprotective effect was shown to be associated with two major lignin, phyllanthin and hypophyllanthin (Syamsunder *et al*., 1985) [109]. *P. urinaria* and *P. maderaspatensis*reportedto exhibit significant hepatoprotective activity in HepG2 cells that were devoid of phyllanthin and hypophyllanthin (Sharma *et al*., 2011) [110].

6.3 Diabetic symptoms

A combination of ethanolic extract of *G. amygdalinum* and *Azadirachta indica* was reported to reduce and maintain a steady level of blood glucose in diabetic rats (Atangwho *et al*., 2012) [111]. The phytochemical kaempferoland its major glycoside kaempferol-3-O-gentiobioside present in the *C. alata*possess moderate α-glucosidase activity andexhibited antidiabetic action by inhibiting the carbohydrate digestion (Varghese *et al*., 2012) [112]. The type 2 diabetic rats treated with *W.somnifera*exhibited reduced blood glucose level with reduction in the number and size of pancreatic beta cells (Anwer *et al*., 2012) [113].

6.4 Asthmatic symptoms

Nigella sativa commonly known as black cumin (Kalonji in Hindi) is a traditional medicine used in the treatment of respiratory diseases like bronchial asthma. In animals or cellular models, *N. sativa* have shown to reduce asthmatic symptoms owed to its ability to promote bronchodilation and to reduce hypersensitivity and inflammatory reactions (Ikhsan *et al*., 2018, Koshak *et al*., 2017) [114, 115]. The immunomodulatory function of *N. sativa*is due to its bioactive compound thymoquinone which is reported to enhance the survival of the activated $CD8^+$ T cells (Salem, *et al*., 2011) [116]. At higher doses (2-3g/kg), thymoquinone have been associated with several toxic effects in mice including hypoglycaemia and hepatic enzyme disturbances (Badary *et al*., 1998) [117].

6.5 Hypoxic symptoms

Adhatodavasica is a medicinal shrub popularly known as Malabar nuts. It is also known by other names such as *Adhatodazeylanica* Medic. and *Justiciaadhatoda* L. and vasaka in Sanskrit. It has been traditionally used as plant drug in Ayurvedic and Unani medicinal system (Claeson *et al*., 2000) [118]. In a recent study, aqueous extract of *A. vasica*has shown to alleviate inflammatory and hypoxic effects in mice by reducing the levels of transforming growth factor-β (TGF-β). *Adhatodavasica*extract was also able to decrease the viral load in vero cell line infected with SARS-CoV2 (Gheware *et al*., 2021) [119]. This study highlighted the potential of *A. vasica*in treating the hypoxic symptoms present in the severely infected COVID-19 patients.

Figures 1: COVID-19 pathogenesis: SARS-CoV-2 enters the epithelial cell via endocytosis or by membrane fusion through binding to ACE2 receptor and releasing its RNA into the cytoplasm. Once the virus enters inside the cell, it will activate the component of host innate and adaptive immune response. This results in activation of pro-inflammatory cytokines mainly Interleukin (IL) -1, -2, -4, -7, Tumor-necrosis factor (TNF)-α. This leads to local damage of lungs. The organ cross-talk between the injured lungs, the kidneys, and the heart further spread the injury to multiple organ.

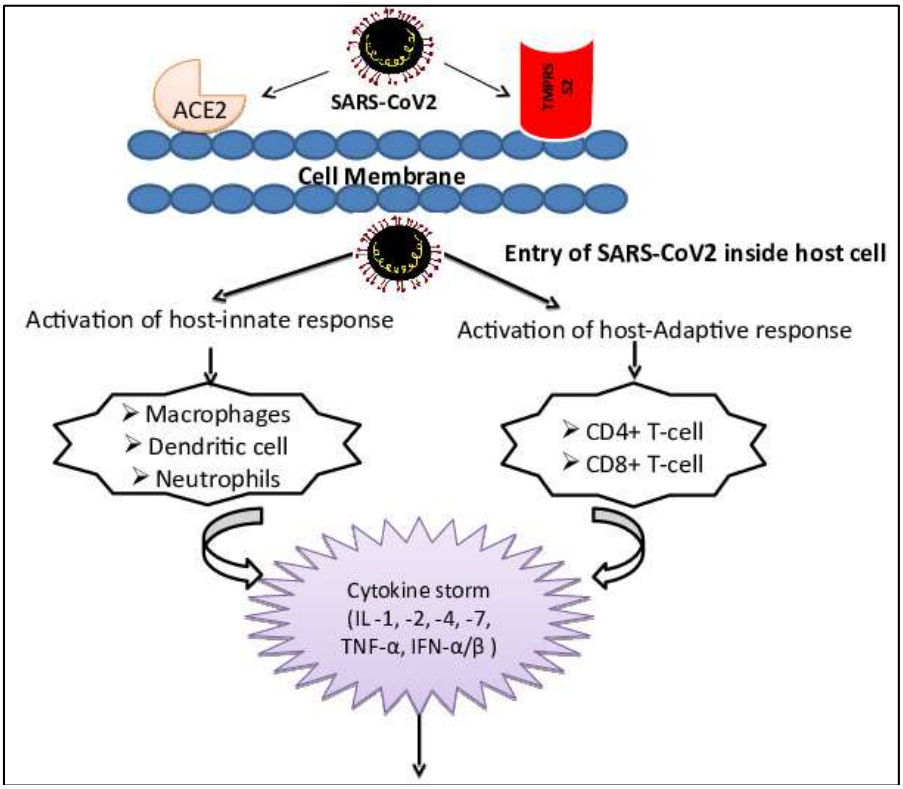

Fig 1: Inflammatory responses characterised by symptoms such as cough, fever, dyspnea, diarrhoea, multiple organ failure

Table 1: Structural and Non-structural proteins encoded by SARS CoV-2 genome.

	Protein name	Function
Structural Protein	1. Envelop	Virion assembly and release
	2. Spike	Binds to host cell receptor
	3. Nucleocapsid	Packaging and release of RNA particle
	4. Membrane protein	Virion shape
Non-structural Protein (NSP)	1. Nsp1 (Endonuclease)	It acts as host translation inhibitor and also degrade host mRNA
	2. Nsp2 (N-terminal product)	disruption of intracellular host signaling
	3. Nsp3 (Papain-like proteinase)	Activates Nsp1, Nsp2, Nsp3 Suppress host immune response
	4. Nsp4 (Membrane protein)	important for the virus-induced membrane rearrangement
	5. Nsp5 (3CL-protease)	Protease activity
	6. Nsp6 (Transmembrane protein)	Involves in formation of ER-derived autophagosomes
	7. Nsp7 (RNA polymerase)	It form complex with Nsp8 and Nsp12 to activates the Nsp 8 primase activity
	8. Nsp8 (Primase)	*De novo* synthesis of short RNA primer in presence of Nsp7
	9. Nsp9 (Replicase)	In association with Nsp8 Involves in virus replication
	10. Nsp10 (Cofactor)	Act as cofactor for both Nsp14 and Nsp16
	11. Nsp11 (Endoribonuclease)	Essential for replication
	12. Nsp12 (RNA-dependent RNA polymerases)	Involves in replication and transcription of virus RNA
	13. Nsp13 (Helicase)	Involves in replication and transcription
	14. Nsp14 (Methyl transferase/Exoribonuclease activity)	Involves in viral RNA synthesis
	15. Nsp15 (Endoribonuclease)	Vital for evading host antiviral defense
	16. Nsp16 (2'-O-ribose methyltransferase)	In complex with Nsp10, it methylates the mRNA cap

Table 2: Medicinal plants traditionally used in enhancing immune response

Scientific Name	Common name	Bioactive compound	Used organ	References
Aloe vera	Ghritkumari	Aloin, hydroxyaloins, phenol, vanillic, homovanillic, protocatechuic	Leaves, roots	Andrea et al., 2020 [29]
Allium sativum	Garlic, Lahsun	diallylpolysulfides, vinyldithiin, ajoene, S-allyl cysteine, alliin	Bulb	Shang et al., 2019 [30]
Azadirachta indica	Neem	nimbidin, gedunin, cyclic trisulfide, nimbidin, gedunin, cyclic trisulfide	Leaves, root, fruit, bark, oil and seed a	Bhowmik et al., 2010; Alzohairy et al., 2016 [31, 32]
Curucuma domestica	Turmeric, Haldi	curcumin, demehoxycurcumin and bisdemethoxycurcumin, germacrone, turmerone, atlantone and zingiberene	Rhizome	Prasad et al., 2011[33]
Capparis moonii wight	Rudanti, Rudravanti	Rutin, quercitin	Fruit	Nagar et al., 2019 [34]
Cinnamomum	Dalchini	cinnamaldehyde, cinnamic acid, and cinnamate.	bark, leaves,	Khan et al., 2011[35]

zeylanicum			flowers, fruits and roots,	
Cinchona officinalis	Chinchona	Quinine, Cinchonine, Cinchonidine	Bark	Cinatl et al., 2003 [36]
Elettaria cardamomum	Cardamom, Elaichi	Terpineol, myrcene, heptane	Dried fruit	Saleem et al., 2005[37]
Glycyrrhiza glabra	Mulethi	glycyrrhizic acid, isoflavaneglabridin, isoflaveneglabrene	Rhizome	Jamshidi et al., 2017[38]
Nigella sativa L.	Black seed or Kalonji	Steroids, tannins, courmarin	Seed	Majdalawieh et al., 2015 [39]
Ocimum sanctum	Holi basil, Tulsi	Apigenin and Ursolic acid	Leaves	Cohen 2014 [40]
Panax ginseng	Ginseng	Genosides	Root	Mancuso et al., 2017[41]
Picrorhiza kurroa	Kutki	Picrorhizaoside, Sweroside, Veronicoside	Rhizomes, Leaves	Prakash et al., 2020[42]
Piper nigrum	Black pepper, Kaalimirch	piperine and piperamides	Dry unripe fruit	Ahmad et al., 2015[43]
Phyllanthus emblica	Amla	quercetin, phyllemblic compounds, gallic acid	Fruit	Jai et al., 2016[44]
Syzygium aromaticum	Clove, Laung	Eugeniin, eugenol, thymol	Fruit	Gulcin et al., 2012[45]
Tinospora cordifolia	Giloy	g lactones, alkaloids, glycosides, steroids, sesquiterpenoid, diterpenoid, aliphatic compounds, phenolics, polysaccharides and flavonoid, tinosporin, tetrahydropalmatine, choline, palmatine and magnoflorine,	Stem	Singh et al., 2017; Saha et al., 2012 [46,47]
Withania somnifera	Ashwgandha, Indian ginseng	withaferin-A (WA), 12-deoxywithastramonolide (WO), withanolide-A (WD)	Root	Saiyed et al., 2016 [48]
Zinziber officinalis	Ginger, adrak	Zingerone and gingerols along with [6]- gingerol (1-[4'-hydroxy-3'-methoxyphenyl]-5-hydroxy-3-decanone)	Rhizome	Rahmani et al., 2014 [49]

7. Conclusion

COVID-19 pandemic is one of the greatest threats to human health and need to be eradicated as soon as possible. In a present scenario, people have become more conscious of their health and are taking extra measures to slow down the risk of infection. Majority of infectious diseases attack our immune system. Medicinal plants have wide potential in curing several diseases in human. Owing to their long lasting use since ancient time and enough research evidences related to their safety and clinical efficacy, they become first choice when it comes to boost up the immunity. This review is focused on medicinal plants showing anti-viral or anti-COVID-19 properties and could be used in drug discovery program in nearby future.

8. References

1. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, *et al*. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270-273.
2. Zhu Z, Lian X, Su X, Wu W, Marrao GA, Zeng Y. From SARS and MERS to COVID-19: a brief summary and comparison of severe acute respiratory infections caused by three highly pathogenic human coronaviruses. Respiratory Research 2020;21:224.
3. World Health Organization. Timeline: WHO's COVID-19 response. World Health Organization 2020.
4. Ye ZW, Yuan S, Yuen KS, Fung SY, Chan CP, Jin DY. Zoonotic origins of human coronaviruses. International Journal of Biological Science. 2020;16(10):1686-1697.
5. Graham RL, Donaldson EF, Baric R.S. A decade after SARS: strategies for controlling emerging coronaviruses. Nature Review Microbiology 2013;11:836-848.
6. Pal M, Berhanu G, Desalegn C, Kandi V. Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2): An Update. Cureus 2020;12(3):e7423.
7. Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. European Respiratory Journal 2020; 55: 2000607
8. Jayaweera M, Perera H, Gunawardana B, Manatunge J. Transmission of COVID-19 virus by droplets and aerosols: A critical review on the unresolved dichotomy. Environmental Research. 2020;188:109819.
9. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. The Journal of the American Medical Association 2020;323(13):1239-42.
10. Liu C, Zhou Q, Li Y, Garner LV, Watkins SP, Carter LJ *et al*. Research and development on therapeutic agents and vaccines for COVID-19 and related human coronavirus diseases. Journal of the American Chemical Society 2020; 6(3):315-31.
11. Chowdhury MA, Hossain N, Kashem MA, Shahid MA, Alam A. Immune response in COVID-19: A review. Journal of Infection and Public Health 2020; 13:1619-29.
12. Chikezie PC, Ibegbulem CO, Mbagwu FN. Bioactive principles from medicinal plants. Research Journal of Phytochemistry 2015;9(3):88-115.
13. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ *et al*. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status. Military Medical Research 2020;7(1):11.
14. Paules CI, Marston HD, Fauci AS. Coronavirus infections-more than just the common cold. The Journal of the American Medical Association 2020;323(8):707-8.
15. Yadav R, Chaudhary JK, Jain N, Chaudhary PK, Khanra S, Dhamija P, Sharma A, Kumar A, Handu S. Role of Structural and Non-Structural Proteins and Therapeutic Targets of SARS-CoV-2 for COVID-19. Cells 2021;10(4):821.

16. Sungnak W, Huang N, Bécavin C, Berg M, Queen R, Litvinukova M, Talavera-López C, *et al*. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nature medicine 2020;26(5):681-87.
17. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis GV, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland 2004;203(2):631-37.
18. Ziebuhr J, Snijder EJ, Gorbalenya AE. Virus-encoded proteinases and proteolytic processing in the Nidovirales. Microbiology 2000; 81(4):853-79.
19. Millet JK, Whittaker GR. Host cell proteases: critical determinants of coronavirus tropism and pathogenesis. Virus Research 2015;202:120-34.
20. Kawai T, Akira S. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. Nature immunology 2010;11(5):373-84.
21. CHIEN JY, HSUEH PR, CHENG WC, YU CJ, YANG PC. Temporal changes in cytokine/chemokine profiles and pulmonary involvement in severe acute respiratory syndrome. Respirology 2006;11(6):715-22
22. Zaim S, Chong JH, Sankaranarayanan V, Harky A. COVID-19 and multiorgan response. Current problems in cardiology 2020;45(8):100618.
23. Jacofsky D, Jacofsky EM, Jacofsky M. Understanding antibody testing for COVID-19. The Journal of arthroplasty 2020;35(7):S74-81.
24. Mellors J, Tipton T, Longet S, Carroll M. Viral evasion of the complement system and its importance for vaccines and therapeutics. Frontiers in Immunology 2020;11:1450.
25. Krishnaiah D, Sarbatly R, Nithyanandam R. A review of the antioxidant potential of medicinal plant species. Food and Bioproducts Processing 2011;89(3):217-33.
26. Agbor AG, Ngogang YJ. Toxicity of herbal preparations. Cameroon Journal of Ethnobotanical 2005;1(1):23-8.
27. Adhikari B, Marasini BP, Rayamajhee B, Bhattarai BR, Lamichhane G, Khadayat K *et al*. Potential roles of medicinal plants for the treatment of viral diseases focusing on COVID-19: A review. Phytotherapy Research 2021;35(3):1298-312.
28. Mukherjee PK, Nema NK, Bhadra S, Mukherjee D, Braga FC, Matsabisa MG. Immunomodulatory leads from medicinal plants. Indian Journal of Traditional knowledge 2014;13:235-256
29. Andrea B, Dumitrița R, Florina C, Dulf F, Veres A, Sonia S *et al*. Comparative analysis of some bioactive compounds in leaves of different Aloe species. BMC Chemistry. 2020;14:67.
30. Shang A, Cao SY, Xu XY, Gan RY, Tang GY, Corke H, *et al*. Bioactive Compounds and Biological Functions of Garlic (Allium sativum L.). Foods 2019;8:246.
31. Bhowmik D, Chiranjib, Yadav J, Tripathi KK, Kumar KPS. Herbal remedies of Azadirachta indica and its medicinal application. Journal of Chemical and Pharmaceutical Research 2010;2:62-67.
32. Alzohairy M. Therapeutics Role of Azadirachta indica (Neem) and Their Active Constituents in Diseases Prevention and Treatment. Evidence-based Complementary and Alternative Medicine 2016; eCAM 2016.
33. Prasad S, Aggarwal BB. Turmeric, the Golden Spice: From Traditional Medicine to Modern Medicine. In: Benzie IFF, Wachtel-Galor S, editors. Herbal Medicine: Biomolecular and Clinical Aspects. 2nd edition. Boca Raton (FL): CRC Press/Taylor & Francis 2011, 13.
34. Nagar L, Lamo R, Dwivedi KN. Comprehensive ethnopharmacological review of rudanti (*Capparis moonii* Wight). International Journal of Pharmaceutical Sciences and Research 2019;11:556-562.
35. Khan A Ullah, Khan QJ, Gilani AH. Pharmacological Basis for the Medicinal Use of Cardamom in Asthma. Bangladesh Journal of Pharmacology 2011;6:34-37
36. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr HW. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. Lancet 2003;361:2045-2046.
37. Salem ML. Immunomodulatory and therapeutic properties of the *Nigella sativa* L. seed. Int Immunopharmacol 2005;5:1749-1770.
38. Jamshidi Negar, Marc M Cohen. The Clinical Efficacy and Safety of Tulsi in Humans: A Systematic Review of the Literature. Evidence-based complementary and alternative medicine : eCAM 2017, 9217567.
39. Mancuso C, Santangelo R. Panax ginseng and Panax quinquefolius: From pharmacology to toxicology. Food Chem Toxicol 2017;107(Pt A):362-372.
40. Prakash V, Kumari A, Kaur H, Kumar M, Gupta S, Bala R. Chemical Constituents and Biological Activities of Genus Picrorhiza: An Update. Indian Journal of Pharmcy Science. 2020;82(4).
41. Ahmad N, Fazal H, Abbasi BH, Farooq S, Ali M, Khan MA. Biological role of Piper nigrum L. (black pepper): a review. Asian Pac J Trop Biomed 2015, S1945-S1953.
42. Jain PK, Das D, Pandey N, Jain P. Traditional Indian herb Emblica officinalis and its medicinal importance. International Journal of Pharmacy and Pharmaceutical Sciences 2016, 1-15.
43. Gulcin I, Elmasta M, Aboul-Enein HY. Antioxidant activity of clove oil – a powerful antioxidant source. Arabian Journal of Chemistry 2012;5:489-499.
44. Singh D, Chaudhuri PK. Chemistry and Pharmacology of Tinospora cordifolia. Natural Product Communications 2017.
45. Saha Soham, Shyamasree Ghosh. Tinospora cordifolia: One plant, many roles." Ancient science of life 2012;31:151-159.
46. Saiyed A, Jahan N, Majeedi SF, Roqaiya M. Medicinal properties, phytochemistry and pharmacology of Withania somnifera: an important drug of Unani Medicine. Journal of Scientific and Innovative Research 2016;5(4):156-160
47. Rahmani AH, Shabrmi FM, Aly SM. Active ingredients of ginger as potential candidates in the prevention and treatment of diseases via modulation of biological activities. International journal of physiology, pathophysiology and pharmacology 2014;6:125-136.
48. ain PK, Das D, Pandey N, Jain P. Traditional Indian herb Emblica of□cinalis and its medicinal importance. Innov J Ayurvedic Sci. 2016;4(4):1-15
49. Singh NA, Kumar P, Kumar JN. Spices and herbs: Potential antiviral preventives and immunity boosters during COVID-19. Phytotherapy Research 2021;35(5):2745-57.
50. Goothy SS, Goothy S, Choudhary A, Potey GG, Chakraborty H, Kumar AH *et al*. Ayurveda's holistic

lifestyle approach for the management of Coronavirus disease (COVID-19): possible role of tulsi. International Journal of Research in Pharmaceutical Sciences 2020;16-18.
51. Mondal S, Varma S, Bamola VD, Naik SN, Mirdha BR, Padhi MM *et al*. Double-blinded randomized controlled trial for immunomodulatory effects of Tulsi (Ocimum sanctum Linn.) leaf extract on healthy volunteers. Journal of Ethnopharmacology 2011;136(3):452-56.
52. Shrivastava R. Immunity boosters: Solutions from nature–Herbs and spices. Journal of Renal Nutrition and Metabolism 2020;6(2):35.
53. Mangprayool T, Kupittayanant S, Chudapongse N. Participation of citral in the bronchodilatory effect of ginger oil and possible mechanism of action. Fitoterapia 2013;89:68-73.
54. Rocha FA, de Assis MR. Curcumin as a potential treatment for COVID-19. Phytotherapy Research 2020;34:2085-87.
55. Hoever G, Baltina L, Michaelis M, Kondratenko R, Baltina L, Tolstikov GA *et al*. Antiviral activity of glycyrrhizic acid derivatives against SARS− coronavirus. Journal of Medicinal Chemistry 2005;48(4):1256-59.
56. Kumar V, Dhanjal JK, Kaul SC, Wadhwa R, Sundar D. Withanone and caffeic acid phenethyl ester are predicted to interact with main protease (Mpro) of SARS-CoV-2 and inhibit its activity. Journal of Biomolecular Structure and Dynamics 2020, 1-13.
57. Bani S, Gautam M, Sheikh FA, Khan B, Satti NK, Suri KA *et al*. Selective Th1 up-regulating activity of Withania somnifera aqueous extract in an experimental system using flow cytometry. Journal of Ethnopharmacology 2006;107(1):107-15.
58. Asif M, Saleem M, Saadullah M, Yaseen HS, Al Zarzour R. COVID-19 and therapy with essential oils having antiviral, anti-inflammatory, and immunomodulatory properties. Inflammopharmacology 2020;28:1153-61.
59. Chopra D, Bhandari B, Dwivedi S. Beneficial role of Indian medicinal plants in COVID-19. MGM Journal of Medical Sciences 2021;8(2):166.
60. Xiang Y, Pei Y, Qu C, Lai Z, Ren Z, Yang K *et al*. *In vitro* anti-herpes simplex virus activity of 1, 2, 4, 6-Tetra-O-galloyl-β-d-glucose from Phyllanthus emblica L.(Euphorbiaceae). Phytotherapy Research 2011; 25(7):975-82.
61. Lim XY, Teh BP, Tan TY. Medicinal Plants in COVID-19: Potential and Limitations. Frontiers in Pharmacology 2021;12:355.
62. Javed H, Meeran MF, Jha NK, Ojha S. Carvacrol, a Plant Metabolite Targeting Viral Protease (Mpro) and ACE2 in Host Cells Can Be a Possible Candidate for COVID-19. Frontiers in Plant Science 2020, 11.
63. Wang SC, Chen Y, Wang YC, Wang WJ, Yang CS, Tsai CL *et al*. Tannic acid suppresses SARS-CoV-2 as a dual inhibitor of the viral main protease and the cellular TMPRSS2 protease. American Journal of Cancer Research 2020;10(12):4538-46.
64. Salamanna F, Maglio M, Landinin MP, Fini MBody Localization of ACE-2: On the Trail of the Keyhole of SARS-CoV-2. Fronitier in Medicine 2021;7:594495.
65. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S *et al*. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020;181:271-280.e8.
66. Ho TY, Wu SL, Chen JC, Li CC, Hsiang CY. Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. Antiviral Research. 2007;74:92-101.
67. Yang KL, Gao Y, Yang FW, Liu M, Shi SZ, Chen YM. *et al*. Analysis of traditional Chinese medicine from patent information sharing platform of coronavirus disease 2019 (COVID-19). China Journal of Chinese Materia Medica. 2020;45:3001-3006.
68. Heidary F, Varnaseri M, Gharebaghi R. The Potential Use of Persian Herbal Medicines Against COVID-19 Through Angiotensin-Converting Enzyme 2, Archives Of Clinical Infectious Diseases. Online ahead of Print; 15(COVID-19):e102838
69. Sharifi N, Souri E, Ziai SA, Amin G, Amanlou M. Discovery of new angiotensin converting enzyme (ACE) inhibitors from medicinal plants to treat hypertension using an *in vitro* assay. DARU Journal of Pharmaceutical Sciences 2013;21(1):1-8.
70. Schwarz S, Sauter D, Wang K, Zhang R, Sun B, Karioti A, *et al*. Kaempferol derivatives as antiviral drugs against the 3a channel protein of coronavirus. Planta Med 2014;80:177-182.
71. Clementi N, Scagnolari C, D'Amore A, Palombi F, Criscuolo E, Frasca F *et al*. Naringenin is a powerful inhibitor of SARS-CoV-2 infection *in vitro*. Pharmacological research 2020;163:105255.
72. Deng YF, Aluko RE, Jin Q, Zhang Y, Yuan LJ. Inhibitory activities of baicalin against renin and angiotensin-converting enzyme. Pharmaceutical Biology 2012; 50(4):401-6.
73. Wang W, Ma X, Han J, Zhou M, Ren H, Pan Q *et al*. Neuroprotective effect of scutellarin on ischemic cerebral injury by down-regulating the expression of angiotensin-converting enzyme and AT1 receptor. PloS one 2016;11(1):e0146197
74. Ziadi SA, Heidari MR, Amin GH, Kochmeshki A, Heidari M. Inhibitory effects of germinal angiotensin converting enzyme by medicinal plants used in Iranian traditional medicine as antihypertensive. Journal of Kerman University of Medical Sciences 2009;16(2):134-43.
75. Balkrishna A, Pokhrel S, Singh H, Joshi M, Mulay VP, Haldar S *et al*. Withanone from Withania somnifera attenuates SARS-CoV-2 RBD and host ACE2 interactions to rescue spike protein induced pathologies in humanized zebrafish model. Drug Design, Development and Therapy 2021;15:1111-33.
76. Shirato K, Kawase M, Matsuyama S. Middle East respiratory syndrome coronavirus infection mediated by the transmembrane serine protease TMPRSS2. Journal of Virology 2013;87(23):12552-61.
77. Matsuyama S, Ujike M, Morikawa S, Tashiro M, Taguchi F. Protease-mediated enhancement of severe acute respiratory syndrome coronavirus infection. Proceedings of the National Academy of Sciences 2005;102(35):12543-47.
78. Schlagenhauf P, Grobusch MP, Maier JD, Gautret P. Repurposing antimalarials and other drugs for COVID-19. Travel Medicine and Infectious Disease 2020;34:101658.
79. Gyebi GA, Adegunloye AP, Ibrahim IM, Ogunyemi OM, Afolabi SO, Ogunro OB. Prevention of SARS-CoV-2 cell entry: insight from in silico interaction of drug-like alkaloids with spike glycoprotein, human ACE2, and

TMPRSS2. Journal of Biomolecular Structure and Dynamics 2020, 1-25.
80. Singh S, Sk MF, Sonawane A, Kar P, Sadhukhan S. Plant-derived natural polyphenols as potential antiviral drugs against SARS-CoV-2 via RNA-dependent RNA polymerase (RdRp) inhibition: an in-silico analysis. Journal of biomolecular structure & dynamics 2020, 1-16. Advance online publication.
81. Mosquera-Yuqui F, Lopez-Guerra N, Moncayo-Palacio EA. Targeting the 3CLpro and RdRp of SARS-CoV-2 with phytochemicals from medicinal plants of the Andean Region: molecular docking and molecular dynamics simulations. Journal of Biomolecular Structure and Dynamics 2020, 1-4.
82. Lau KM, Lee KM, Koon CM, Cheung CS, Lau CP, Ho HM *et al*. Immunomodulatory and anti-SARS activities of Houttuynia cordata. Journal of Ethnopharmacology 2008;118(1):79-85.
83. Baez-Santos YM, St John SE, Mesecar AD. The SARS-coronavirus papain-like protease: structure, function and inhibition by designed antiviral compounds. Antiviral Research 2015;115:21-38.
84. Yuan L, Chen Z, Song S, Wang S, Tian C, Xing G *et al*. p53 degradation by a coronavirus papain-like protease suppresses type I interferon signaling. Journal of Biological Chemistry 2015;290(5):3172-82.
85. Laskar MA, Choudhury MD. Search for therapeutics against COVID 19 targeting SARS-CoV-2 papain-like protease: An in silico study.
86. Shawky E, Nada AA, Ibrahim RS. Potential role of medicinal plants and their constituents in the mitigation of SARS-CoV-2: identifying related therapeutic targets using network pharmacology and molecular docking analyses. RSC Advances 2020;10(47):27961-83.
87. Kim DW, Seo KH, Curtis-Long MJ, Oh KY, Oh JW, Cho JK *et al*. Phenolic phytochemical displaying SARS-CoV papain-like protease inhibition from the seeds of Psoralea corylifolia. Journal of Enzyme Inhibition and Medicinal Chemistry 2014;29(1):59-63.
88. Song YH, Kim DW, Curtis-Long MJ, Yuk HJ, Wang Y, Zhuang N *et al*. Papain-like protease (PLpro) inhibitory effects of cinnamic amides from Tribulus terrestris fruits. Biological and Pharmaceutical Bulletin 2014;37(6):1021-28.
89. Ryu YB, Jeong HJ, Kim JH, Kim YM, Park JY, Kim D *et al*. Biflavonoids from Torreya nucifera displaying SARS-CoV 3CLpro inhibition. Bioorganic and Medicinal Chemistry 2010;18(22):7940-47.
90. Park JY, Kim JH, Kim YM, Jeong HJ, Kim DW, Park KH *et al*. Tanshinones as selective and slow-binding inhibitors for SARS-CoV cysteine proteases. Bioorganic and Medicinal Chemistry 2012;20(19):5928-35.
91. Park JY, Ko JA, Kim DW, Kim YM, Kwon HJ, Jeong HJ *et al*. Chalcones isolated from Angelica keiskei inhibit cysteine proteases of SARS-CoV. Journal of Enzyme Inhibition and Medicinal Chemistry 2016;31(1):23-30.
92. Law S, Leung AW, Xu C. Is the traditional Chinese herb "Artemisia annua" possible to fight against COVID-19? Integrative Medicine Research 2020;9(3):100474.
93. Benatouil CP, Reanimator A. Action of Artemisia annua on adaptive immunity in COVID-19 infections 2020, 1-24.
94. Lin CW, Tsai FJ, Tsai CH, Lai CC, Wan L, Ho TY *et al*. Anti-SARS coronavirus 3C-like protease effects of Isatis indigotica root and plant-derived phenolic compounds. Antiviral Research 2005;68(1):36-42.
95. Tenforde MW, Kim SS, Lindsell CJ, Rose EB, Shapiro NI, Files DC *et al*. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network—United States, March–June 2020. Morbidity and Mortality Weekly Report 2020;69(30):993-98.
96. Carfì A, Bernabei R, Landi F. Gemelli against COVID-19 post-acute care study group. Persistent symptoms in patients after acute COVID-19. The Journal of the American Medical Association 2020;324(6):603-5.
97. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. The Journal of the American Medical Association 2020;323(13):1239-42.
98. Venkatesan N, Punithavathi D, Babu M. Protection from acute and chronic lung diseases by curcumin. The Molecular Targets and Therapeutic Uses of Curcumin in Health and Disease 2007, 379-05.
99. Ram A, Das M, Ghosh B. Curcumin attenuates allergen-induced airway hyperresponsiveness in sensitized guinea pigs. Biological and Pharmaceutical Bulletin 2003;26(7):1021-24.
100. Kaur G, Singh N, Samuel SS, Bora HK, Sharma S, Pachauri SD *et al*. Withania somnifera shows a protective effect in monocrotaline-induced pulmonary hypertension. Pharmaceutical Biology 2015;53(1):147-57.
101. Bale S, Venkatesh P, Sunkoju M, Godugu C. An adaptogen: withaferin A ameliorates *in vitro* and *in vivo* pulmonary fibrosis by modulating the interplay of fibrotic, matricelluar proteins, and cytokines. Frontiers in Pharmacology 2018;9:248.
102. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L *et al*. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney International 2020;97(5):829-38.
103. Ye M, Wysocki J, William J, Soler MJ, Cokic I, Batlle D. Glomerular localization and expression of angiotensin-converting enzyme 2 and angiotensin-converting enzyme: implications for albuminuria in diabetes. Journal of the American Society ofNephrology 2006;17(11):3067-75.
104. Qiao Q, Jiang Y, Li G. Curcumin improves the antitumor effect of X-ray irradiation by blocking the NF-κB pathway: an in-vitro study of lymphoma. Anti-Cancer Drugs 2012;23(6):597-05.
105. Sun X, Liu Y, Li C, Wang X, Zhu R, Liu C *et al*. Recent advances of curcumin in the prevention and treatment of renal fibrosis. BioMed Research International 2017.
106. Calixto JB, Santos AR, Filho VC, Yunes RA. A review of the plants of the genus Phyllanthus: their chemistry, pharmacology, and therapeutic potential. Medicinal Research Reviews 1998l;18(4):225-58.
107. Dhiman RK, Chawla YK. Herbal medicines for liver diseases. Digestive Diseases and Sciences 2005;50(10):1807-12.
108. Syamasundar KV, Singh B, Thakur RS, Husain A, Yoshinobu K, Hiroshi H. Antihepatotoxic principles of Phyllanthus niruri herbs. Journal of Ethnopharmacology 1985;14(1):41-44.
109. Sharma SK, Arogya SM, Bhaskarmurthy DH, Agarwal A, Velusami CC. Hepatoprotective activity of the Phyllanthus species on tert-butyl hydroperoxide (t-BH)-

induced cytotoxicity in HepG2 cells. Pharmacognosy Magazine 2011;7(27):229-33.
110. Atangwho IJ, Ebong PE, Eyong EU, Asmawi MZ, Ahmad M. Synergistic antidiabetic activity of Vernonia amygdalina and Azadirachta indica: Biochemical effects and possible mechanism. Journal of Ethnopharmacology 2012;141(3):878-87
111. Varghese GK, Bose LV, Habtemariam S. Antidiabetic components of Cassia alata leaves: identification through α-glucosidase inhibition studies. Pharmaceutical Biology 2013;51(3):345-49.
112. Anwer TA, Sharma M, Pillai KK, Khan G. Protective effect of Withania somnifera against oxidative stress and pancreatic beta-cell damage in type 2 diabetic rats.Acta poloniae pharmaceutica 2012;69(6):1095-101.
113. Ikhsan M, Hiedayati N, Maeyama K, Nurwidya F. *Nigella sativa* as an anti-inflammatory agent in asthma. BMC Research Notes 2018;11(1):1-5.
114. Koshak A, Koshak E, Heinrich M. Medicinal benefits of *Nigella sativa* in bronchial asthma: A literature review. Saudi Pharmaceutical Journal 2017;25(8):1130-36.
115. Salem ML, Alenzi FQ, Attia WY. Thymoquinone, the active ingredient of *Nigella sativa* seeds, enhances survival and activity of antigen-specific CD8-positive T cells *in vitro*. British Journal of Biomedical Science. 2011;68(3):131-37.
116. Badary OA, Al-Shabanah OA, Nagi MN, Al-Bekairi AM, Elmazar M. Acute and subchronic toxicity of thymoquinone in mice. Drug Development Research 1998;44(2-3):56-61.
117. Claeson UP, Malmfors T, Wikman G, Bruhn JG. Adhatoda vasica: a critical review of ethnopharmacological and toxicological data. Journal of Ethnopharmacology 2000;72(1-2):1-20.
118. Gheware A, Dholakia D, Kannan S, Panda L, Rani R, Pattnaik BR *et al*. Adhatoda Vasica attenuates inflammatory and hypoxic responses in preclinical mouse models: potential for repurposing in COVID-19-like conditions. Respiratory Research 2021;22(1):1-5.