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Role of medicinal plants in inhibiting SARS-CoV-2 and in the management of post-COVID-19 complications

Pulok K Mukherjee\textsuperscript{a,c,*}, Thomas Effert\textsuperscript{h}, Bhaskar Das\textsuperscript{c}, Amit Kar\textsuperscript{a}, Suparna Ghosh\textsuperscript{c}, Seha Singha\textsuperscript{a}, Pradip Debnath\textsuperscript{c}, Nanaocha Sharma\textsuperscript{a}, Pardeep Kumar Bhardwaj\textsuperscript{a}, Pallab Kanti Haldar\textsuperscript{c}

\textsuperscript{a} Institute of Bioresources and Sustainable Development, Imphal-795001, India
\textsuperscript{b} School of Natural Product Studies, Department of Pharmaceutical Technology, Jadavpur University, Kolkata -700 032, India
\textsuperscript{c} Department of Pharmaceutical Biology, Institute of Pharmaceutical and Biomedical Sciences, Johannes Gutenberg University, Mainz, Germany

\textbf{ABSTRACT}

\textbf{Background:} The worldwide corona virus disease outbreak, generally known as COVID-19 pandemic outbreak resulted in a major health crisis globally. The morbidity and transmission modality of COVID-19 appear more severe and uncontrollable. The respiratory failure and following cardiovascular complications are the main pathophysiology of this deadly disease. Several therapeutic strategies are put forward for the development of safe and effective treatment against SARS-CoV-2 virus from the pharmacological view point but till date there are no specific treatment regimen developed for this viral infection.

\textbf{Purpose:} The present review emphasizes the role of herbs and herbs-derived secondary metabolites in inhibiting SARS-CoV-2 virus and also for the management of post-COVID-19 related complications. This approach will foster and ensure the safeguards of using medicinal plant resources to support the healthcare system. Plant-derived phytochemicals have already been reported to prevent the viral infection and to overcome the post-COVID complications like parkinsonism, kidney and heart failure, liver and lungs injury and mental problems.

\textbf{In this review, we explored mechanistic approaches of herbal medicines and their phytocomponents as antiviral and post-COVID complications by modulating the immunological and inflammatory states.}

\textbf{Study design:} Studies related to diagnosis and treatment guidelines issued for COVID-19 by different traditional system of medicine were included. The information was gathered from pharmacological or non-pharmacological interventions approaches. The gathered information sorted based on therapeutic application of herbs and their components against SARS-CoV-2 and COVID-19 related complications.

\textbf{Methods:} A systemic search of published literature was conducted from 2003 to 2021 using different literature database like Google Scholar, PubMed, Science Direct, Scopus and Web of Science to emphasize relevant articles on medicinal plants against SARS-CoV-2 viral infection and Post-COVID related complications.

\textbf{Results:} Collected published literature from 2003 onwards yielded with total 625 articles, from more than 18 countries. Among these 625 articles, more than 95 medicinal plants and 25 active phytomolecules belong to 48 plant families. Reports on the therapeutic activity of the medicinal plants belong to the Lamiaceae family (11 reports), which was found to be maximum reported from 4 different countries including India, China, Australia, and Morocco. Other reports on the medicinal plant of Asteraceae (7 reports), Fabaceae (8 reports), Piperaceae (3 reports), Zingiberaceae (3 reports), Ranunculaceae (3 reports), Meliaceae (4 reports) were found, which can be explored for the development of safe and efficacious products targeting COVID-19.

\textbf{Abbreviations:} 3CL, Pro-3-chymotrypsin-like protease; ACE-2, Angiotensin-converting enzyme 2; AYUSH, Ayurveda, yoga & naturopathy, unani, siddha and homeopathy; Bcl-xL, B-cell lymphoma-extra large; BH3, Bcl-2 homology 3; CD, Cluster of differentiation; CFR, Case fatality rate; COVID-19, Coronavirus disease 2019; CSIR, Council of Scientific & Industrial Research, DNA, Deoxyribonucleic acid; FDA, Food and Drug Administration, IFNγ, Interferon gamma, IL, Interleukin; IP10, Inducible protein 10; MCP1, Monocyte chemoattractant protein 1; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K, Papain-like protease; RdRp, RNA-dependent RNA polymerase; RNA, Ribonucleic acid; SARS-CoV, Severe acute respiratory syndrome coronavirus; TCM, Traditional Chinese medicine; TH1, T helper type 1; WHO, World Health Organization.

\textbf{* Corresponding author at: Institute of Bioresources and Sustainable Development, Dept. of Biotechnology, Ministry of Science and Technology, Govt. of India, Takyelpat, Imphal-795001, India, Tele-Fax: +91 385 2446121}

\textbf{E-mail addresses:} naturalproductm@gmail.com, director.ibsd@nic.in (P.K. Mukherjee).

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Introduction

In 2002-2003, a surveillance definition was established following the outbreak of SARS-CoV-2. At the end of December 2019, a pneumonia patient with unidentified etiology was found positive for pan-β-coronavirus which has the closest resemblance to another coronavirus, Bat CoV-RaTG13 (Zhou et al., 2020). This new virus was termed SARS-CoV-2, and the disease it causes was termed coronavirus disease 2019 (COVID-19). Whole genome sequencing analysis of clinical SARS-CoV-2 isolates from COVID-19 patients revealed a total of 104 different viral strains as of yet (Hu et al., 2021). It generally is transmitted during close unprotected contact with infected persons via virus-loaded droplets and aerosoles. Due to its novel nature, there is no immune defence present in host. Globally 178,202,610 confirmed cases of COVID-19 were reported to the World Health Organization (WHO) including 3,865,738 deaths as of June 21, 2021 (Anonymous 2021, WHO coronavirus disease COVID-19 Dashboard 2021).

The symptoms of COVID-19 are non-specific and can be asymptomatic to severe pneumonia characterized by fever, coughing, shortness of breathing and also death. Headache, fatigue, anosmia, sore throat, increased sputum production, rhinorrhea, anorexia, dyspnea, pleurisy, skin sensitivity, hemoptysis, myalgias, and diarrhea can be developed as COVID-19 symptoms (Anaya et al., 2021; Rehman et al., 2021). On a mean incubation period of 5-6 days after infection, an infected person may develop pathological symptoms such as mild respiratory complications with fever. Many case reports showed that the mortality rate increases with age, people over 80 years of age having highest mortality rate and people over 60 years of age with other disorders including diabetes, hypertension, chronic respiratory disease, cardiovascular disease, and cancer. The case fatality rate (CFR) is also higher among males compared to female individuals at any age (Anonymous, 2020a; Lee et al., 2021; Report of the WHO-China Joint Mission on Coronavirus Disease 2019).

With the outbreak of COVID-19, the uses of medicinal plant and their product or traditional herbal preparation increased dramatically around the world (Peng et al., 2020). Based on preliminary clinical reports, FDA approved chloroquine sulfate and hydroxychloroquine sulfate as first-line treatment (Gao et al., 2020; Gautret et al., 2020; Naserghandi et al., 2020). Unfortunately, these conventional drugs are not as effective against COVID-19 infection as expected (Cao et al., 2020; Ferner and Aronson, 2020).

Antiviral drugs such as favipiravir, remdesivir and kaletra (lopinavir and ritonavir combination drug) have also been put forward to improve the condition of COVID-19 patients (Guo, 2020; Misruf et al., 2019; Sheshan et al., 2020). Drug Controller General of India approved 2-deoxy-D-glucose (2-DG) for emergency use as add-on therapy in moderate to severe coronavirus patients (Balkrishna et al., 2020a; Verma et al., 2020). However, the outcome of large randomized clinical trials was not very encouraging (Tu et al., 2020). The most common preventive and effective approach to combat the COVID-19 pandemic is the use of vaccines (Khodadadi et al., 2020). Approximately, 78 vaccine candidates have already been developed worldwide and are at different stages of clinical evaluation (Liu et al., 2020; Thanh Le et al., 2020). Up to now, several vaccine candidates are approved through Emergency Use Authorization (EUA) including the Pfizer/BioNTech Comirnaty vaccine (BNT162b2), the Oxford–AstraZeneca COVID-19 vaccine (AZD1222) sold under brand name Covishield, the Moderna (mRNA 1273) vaccine by the American Pharmaceutical and Biotechnology Company, CoronaVac by a Chinese company named Sinovac Biotech, Sinopharm in collaboration with the Wuhan Institute of Virology and Beijing Institute of Biological Products developed inactivated Chinese Corona Virus (CVC) vaccine and BBIBP-CoV, EpiVacCorona by a Russian company named Federal Budgetary Research Institution State Research Center of Virology and Biotechnology, China. Covaxin (BBV152) was developed by Bharat Biotech in collaboration with the Indian Council of Medical Research (ICMR) and National Institute of Virology (NIV). Sputnik V is a viral vector COVID-19 vaccine developed by the Russian Gamaleya Research Institute of Epidemiology and Microbiology (Logunov et al., 2021; Mishra and Tripathi, 2021). Still there are many vaccine candidates under clinical investigation. JNJ-78436735 formerly known as Ad26.COV2.S was developed by Johnson & Johnson, CanSino Biologics developed a recombinant vaccine called Ad5-nCoV and NVX-CoV2373 was developed by Novavax (Kashte et al., 2021).

Methodology

Specific information on the topic was collected from the literature available from search engines such as Google Scholar, PubMed, Science Direct, Scopus, and Web of Science for retrieving published data (from 2003 to 2021) using different combination of keywords i.e., COVID-19/ SARS-CoV-2, diagnosis/treatment guideline issued for COVID-19, cytokine storm, immunomodulation/anti-inflammatory/antiviral, post-COVID complications etc. The inclusion criteria limited to full text articles on pharmacological or therapeutic approaches for COVID-19 based on in-vivo, in-vitro, and in-silico and clinical trial reports on herbal drugs. News reports, editorial, peer review articles were also retrieved and to recent updates were included. The collected literature was electronically checked for duplicates using EndNote software. On the contrary, the exclusion criteria for the collected literature include, predatory journals source, non-english language.

Guidelines from different traditional system of medicine to combat COVID-19

The World Health Organization (WHO) welcomes initiatives to develop COVID-19 therapies, including drug repositioning and traditional medicines. In many countries, traditional medicine has a long history and plays an important role in healthcare. Nowadays, WHO in collaboration with several research institutions is working on the medicinal plant-based products used in traditional medicinal systems, in order to explore their scientific and clinical potential for the treatment and management of COVID-19. In many countries, WHO provided support to perform clinical COVID-19 trials for traditional medicinal products (Anonymous 2020b), WHO, Africa CDC push for COVID-19 traditional medicine research in Africa). The disease is almost controlled in China (Salzberger et al., 2020), but still widespread in Europe, USA, India, Brazil and other countries, which have emerged as new epicentres of COVID-19 (Grasselli et al., 2020). TCM is playing an important role to control the death rate. Along with TCM, Ayurveda might also help to manage COVID-19 (Sawarkar and Sawarkar, 2020; Patwardhan et al., 2020). However, there is not much solid evidence yet to prove this hypothesis. One may critically ask, why is the outbreak not under control in India, if Ayurveda would really help. The same is true for all other traditional medicines worldwide in a similar manner. Currently the data from www.clinicaltrials.gov and http://www.chictr.org.cn include 46 plant-derived phytomolecules and 64 traditional Chinese medicinal preparations are under clinical investigations targeting both management and prevention of COVID-19 viral infection (Jin et al., 2020). But still, it requires reliable and high-quality clinical
evidence due to small sample size and long time line (Luo et al., 2020; Nile and Kai, 2021; Pang et al., 2020; Wang et al., 2021; Wei et al., 2020; Xu et al., 2020; Zhu et al., 2020). Randomized clinical trials, which reach international visibility and recognition concerning this issue, are urgently required to answer this question. The Ministry of AYUSH has come up with several preventive measures against COVID-19 infection. These preventive measures are published officially as Guidelines for Practitioners in Naturopathy, Siddha, Homeopathy, Unani, Ayurveda, Yoga and for Public Health and Health care Practitioners for COVID-19 (AYUSH Guidelines for COVID-19 2020)AYUSH Guidelines for COVID-19 (Interdisciplinary committee for integration of ayurveda and yoga interventions in the 'National clinical management protocol: COVID-19' 2020). The Unani system of medicine may offer potential candidates for controlling the disease burden. The textbooks of Unani medicine focused explicitly on air-borne respiratory infections. In Unani medicine, epidemics and pandemics were described with the common term waha, which means diseases affecting a large geographical area. Most of the Unani herbal drugs are cheap, easy to administer and easily available. As an example, vinegar is recommended made from Saccharum officinarum L., Rosa damascena Herrm., Tamarindus indica L., Rheum austral D. Don, Viola odorata L., Terminalia chebula Retz., Cassia fistula L. and Punica granatum L. (Nikhut and Fazil, 2020).

Ayurveda can prevent the disease progression by regulating the immune-inflammation state in COVID-19 patients. The Ministry of AYUSH, India, recommended different preventive measures to improve the quality of life of individual patients. Daily practice of Yoga, Dhyanayana, and Pranayama practices may help to withstand psychological perturbations in COVID-19 patients (Tillu et al., 2020). The use of spices such as Curcuma longa L., Cuminum cyminum L., Coriandrum sativum L., and Allium sativum L. is recommended for daily use. The consuming herbal decoctions of Ocimum sanctum L., Piper nigrum L., Zingiber officinale Roscoe, Cinnamonum verum J. Presl, Vitis vinifera L. are also recommended as teas to improve the immunity in COVID-19 patients. Taking Emblica officinalis Gaertn., Tinospora cordifolia (Willd.) Miers and Tribulus terrestris L. in equal ratio with honey suggested having benefits in post-COVID related complications. Daily consumption of ashwagandha (Withania somnifera (L.) Dunal) also having benefits in prophylactic care. An ayurvedic herbo-mineral preparation known as Chyawanprasha is also recommended due to its immunoboosting properties and in the management of post-COVID related complications. Patients with sore throat and cough are advised as steam inhalation with Mentha arvensis L. or Trachyspermum ammi L. with Syzygium aromaticum L. powder (Gupta et al., 2021a; Gupta et al., 2021b).

Based on the traditional and scientific evidence, the Ministry of AYUSH recommended the consumption of a poly-herbal decoction (Kadha) containing five different herbs namely, Tulsi (Ocimum tenuiflorum L.), Dalchini (C. verum), Kalmirich (P. nigrum), Shunthi (Z. officinale) and Munakka (V. vinifera) for boosting immunity. The network pharmacology analysis data of this immunomodulatory formulation showed to modulate several signaling pathways involved in the regulation of immunity in biological systems such as HIF-1, Estrogen, Rap1, p53, PISK-Akt, Toll-like receptor, MAPK, cAMP, Ras, Wnt, Adipocytokine, NOD-like receptor, Chemokine, NF-kB, IL-17, TNF, Sphingolipid, and cGMP-FKG. Along with Kadha, it is also recommended to take raisins (dried Munakka) and golden milk (C. longa powder in hot milk) as a prophylactic against COVID-19 to boost immunity in the subjects with compromised immunity (Khanal et al., 2020; Schuster et al., 2017).

Global perspective of herbs and herbal formulae from different traditional systems of medicine to inhibit SARS-CoV-2 virus

Soon after the outbreak of COVID-19, the National Health Commission of the People’s Republic of China announced a combination of TCM and commercial medicines to treat COVID-19 patients (Lin and Li, 2020). After the global spread of COVID-19, rushes for traditional herbal medications against COVID-19 have been reported in different parts of the world (Ang et al., 2020; Benarba and Pandiella, 2020; Mani et al., 2020; Mukherjee, 2019; Paudyal et al., 2021).

The exploration of herbs and herbal preparations used in traditional medicine, followed by bioassay-guided isolation of lead compounds from medicinal herbs, represent an attractive approach in combat this pandemic (Tahir et al., 2020). In several African countries, home remedies are used as alternative healthcare remedies to manage COVID-19. Natural spices and leaves of medicinal plants having the antioxidant and anti-inflammatory properties were reported to be effective (Orisakwe et al., 2020).

Many natural products have broad-spectrum antiviral activity, may inhibit multiple steps in viral infection and replication and have been used in the treatment of SARS, MERS, influenza, and dengue virus. Fig. 1 represents the chemical structures of the bioactive phytomolecules to be useful for the management of COVID-19 related complications. Moreover, they have been reported as immunomodulators, inhibiting inflammatory effect concerned for the significant morbidity and mortality of COVID-19 infection (Khan and Al-Balushi, 2021; McKee et al., 2020) (Tables 1–3). Medicinal plants that showed to be effective in the management of post-COVID related complications have been tabulated in Table 4. Fig. 2 represents the probable inhibition mechanism of medicinal plants/products against SARS-CoV-2 viral replication. However, the phytochemicals could be toxic at certain levels, and hence in vitro and in vivo researches are needed to evaluate the safe and therapeutic levels for each natural compound before human clinical studies can be conducted (Mani et al., 2020). Infusino et al., (2020) focuses the possible role of supplements, probiotics, and nutraceuticals in reducing the risk of SARS-CoV-2 infection or mitigating the symptoms of COVID-19 in their study.

In this Review, the importance of medicinal herbs from different traditional medicine systems together with herbs-derived secondary metabolites are summarized based on the mechanistic point of view for post-COVID related complications.

Herbal formulae from different traditional systems of medicine

During the first outbreak of SARS in China (2002-2003), TCM showed a great potency in reducing the fatality rate (Yang et al., 2021; Chen and Nakamura, 2004; Yang et al., 2020). After the outbreak of COVID-19, several TCM formulations have been frequently prescribed, e.g., Lianhua Qingwen capsule, Yu Ping Feng San decoction, Guishu- and Mahuwan decoction, Shuang-Huang-Lian, Sang Ju Yin and Yu Ping Feng San, Dong Gai Long Hai pill, Shufeng Jiedu capsule, Qingfei Paidu decoction, Huashi Baidu decoction, Huoxiang Zhengqi, Jinhua Qinggan granules, Xuebijing injection, Reduning injection, Tanreqing injection, Shufeng Jiedu capsule, Xuanfei Baidu decoction, Shenmai injection and Ma Xin Gan Shi Tang etc (Table 2). These herbal formulations have significant antiviral, anti-inflammatory and immunomodulatory activity to combat COVID-19 (Chan et al., 2018; Ding et al., 2017; Du et al., 2014; Fu et al., 2018; Gao et al., 2014; Huang et al., 2020; (Liu et al., 2015) Liu, 2020; Poon et al., 2006; Runfeng et al., 2020; Yang et al., 2020).

Based on recent updates, several herbs and isolated phytomolecules were found to inhibit the SARS-CoV-2 viral infection through different mechanisms (Table 3). Through the binding between SARS-CoV-2 spike protein and Angiotensin-converting enzyme 2 (ACE-2) receptor of the host is the major reason of viral entry into the cells of the nasal and bronchial epithelium. SARS-CoV-2 virus infection, replication can easily be inhibited by inhibiting human ACE-2 receptor (Galani and Andreakos, 2021). Weng et al. (2019) showed that the phenol-rich extract of Sambucus formosana Nakai inhibited viral replication of human coronaviruses NL63, Triterpenoids and flavonoid glycosides isolated from the ethanolic extract of Euphorbia nertifolia L. exhibited antiviral activity against human coronavirus. The molecular docking study of isolated 3β-friedelanol showed that the friedelane skeleton could be a potential scaffold for developing new anti-HCoV-229E drugs (Chang et al., 2012). In another study, the methanol extract of Strobilanthes cusia (Nees)
Kuntze blocked the cytopathic effect of HCoV-NL63-infected cells (Tsai et al., 2020). Mechanism based inhibition of medicinal plants/products through regulation of cytokine storm in SARS CoV-2 infection has been represented in Fig. 3.

The Ministry of AYUSH in collaboration with the CSIR started clinical trials of four ayurvedic herbs with immunoboosting properties to alleviate the symptoms caused by SARS-CoV-2. These are *W. somnifera*, *T. cordifolia*, *Glycyrrhiza glabra* L. and *Piper longum* L. with AYUSH-64. This polyherbal formulation is used against malaria-related fever (*Vishamjvara*), inflammation and joint pains (Gundeti et al., 2020).

Based on a clinical trial on patients with bronchial asthma, the polyherbal formulation DCBT4567-Astha-15 reduced clinical symptoms such as dyspnoea, wheezing, cough, expectoration, disability, and sleep disturbances (Murali et al., 2006). This formulation is under clinical investigation to be used against COVID-19.

Fig. 1. Chemical structure of the compounds found to be active against COVID-19 virus.
Role of natural products in the management of post-COVID complications

Parkinsonism

SARS-CoV-2 has been detected in the brain and it has been also isolated from the cerebrospinal fluid of affected patients (Papa et al., 2020). The dynamic pro-inflammatory state of COVID-19 accompanies abnormal accumulation of α-synuclein in nerve fibres, neurons and glial cells, which leads to increased oxidative stress and causes neuro-inflammation (Stefanis, 2012; Achbani et al., 2020) and Parkinson’s disease symptoms. During viral infections, α-synuclein participates in the innate immune response and acts as inhibitor of viral RNA and growth in neurons (Chana-Cuevas et al., 2020; McCann et al., 2014).

*Bacopa monnieri* (L.) Wettst. reduced dopaminergic neurodegeneration by decreasing α-synuclein aggregation and might, thus, be used as a potent anti-parkinsonian agent (Jadiya et al., 2011). *Cinnamonum zeylanicum* Blume bark and *Centella asiatica* (L.) Urb. leaves extract inhibit α-synuclein aggregation, stabilized and disintegrate the oligomers and fibrils (Berrocal et al., 2014; Khotimah et al., 2015; Shaltiel-Karyo et al., 2012). The flower petals of *Carthamus tinctorius* L. improved the behavioral dysfunction in a Parkinson’s induced rat model by inhibiting α-synuclein aggregation and astrogliosis (Ren et al., 2016). The stigma of *Crocus sativus* L. inhibited the fibril dissociation and

Fig. 1. (continued).
α-synuclein aggregation (Inoue et al., 2018). Crocin-1, crocin-2, and crocetin present in the extract were the major components responsible for the anti-Parkinson’s effect. Leaves of Corema album (L.) D.Don ex Steud. promoted the formation of non-toxic α-synuclein species in vitro and inhibited its toxicity and aggregation in cells, by promoting the autophagic flux and reducing oxidative stress (Macedo et al., 2015). Geum urbanum L. inhibited α-synuclein fibrillation in a concentration-dependent way and partly disintegrated α-synuclein fibrils (Lobbens et al., 2016). The root of Panax ginseng C.A.Mey. prevented dopaminergic loss by attenuating α-synuclein aggregation, microgliosis and apoptosis (Van Kampen et al., 2003). The root of Scutellaria pinnatifida A.Ham. also attenuated α-synuclein aggregation (Sashourpour et al., 2017). Trichosanthes kirilowii Maxim., Prunus japonica Thunb., Perillae Ramulus, Pogostemon cablin (Blanco) Benth. and Cuscuta chinensis Lam. displayed detoxification effects on α-synuclein-induced damage in a yeast model of Parkinson’s disease (Fu et al., 2014; Sohn et al., 2012). The alkaloid acetylcorynoline from Corydalis bungeana Turcz. reduced α-synuclein aggregation leading to decreased lipid peroxidation which also maintained efficient cellular signaling (Folmer, 2020). Curcuminoids prevented neuroinflammation by reducing pro-inflammatory cytokine levels (Ojha et al., 2012). Medicinal plants that showed to be effective for the mangement of...
Table 1  
Herbs found to be effective against COVID-19 through in-vivo/ in-vitro analysis

| Plant Family | Plant name | Antiviral | Anti-inflammatory | Immunomodulation | References |
|--------------|------------|-----------|-------------------|-------------------|------------|
| **Acanthaceae** | *Andrographis paniculata* (Burm. f.) Nees | Binding potential with active residues of ACE2 that mediate host viral interface | Andrographolide reduces the levels of inflammatory cytokines TNFα, IL-12, IL-1β, IL-6, IL-18 in LPS/ IL-4-activated murine macrophages | Andrographolide significantly stimulates the immune response, regulate the production of NK cells and cytokines and stimulate the production of cytotoxic T-lymphocytes | Lu et al., 2019; Wang et al., 2015; Varma et al., 2011; (Zou et al., 2016)Banakere and Pradeep, 2020 |
| **Amaryllidaceae** | *Allium sativum* L. | Aqueous bulb extracts and essential oils restrained viral protease enzyme by inhibiting amino acid synthesis | Allicin inhibit of TNF-induced secretion of IL-1, CXCL8 and IP10 | Crushed garlic extract increase the production of IFNγ and expansion of CD4+ T-cells | Mohammad and Shaghaghi, 2020; Lang et al., 2004; Azizia et al., 2015 |
| **Anacardiaceae** | *Rhizoma Dryopteridis crassirhizoma* Nakai | It clear heat and detoxify, removes lung hotness and having potency against SARS-CoV-2 | Ethanol root extract inhibits TNF-α, IL-6 and IL-1β | Polysaccharides fraction promoted humoral immune response of the body and produces immune effect on KM and Balb/c mice | (Chang et al., 2012) Shan et al., 2015; Chen et al., 2021; Ho and Chang, 2002; Hamburger, 2002 |
| **Asteraceae** | *Echinacea purpurea* L. | Herb and roots ethanol extract act against some viruses with a membrane through direct viralicidal activity against *Japanese encephalitis virus*. | Unpurified fresh pressed juice mediated the increased release of various cytokines, including IL-1, IL-10 and TNF-α by macrophages | Polyacetylene and pteryphyllin from the root showed anti-viral activity | Islam et al., 2020; Wen et al., 2011 |
| **Brassicaceae** | *Sinapis alba* L. | Ethanol extract of gall having the inhibitory activity of SARS-CoV virus into host cell and prevented virus replication | Teta-O-galloyl-β-glucose showed to inhibit SARS CoV-2 virus replication | Tryptanthrin was found to have anti-inflammatory activity. | Wang et al., 2020 |
| **Caesalpinaceae** | *Caesalpinia sappo* L. | Ethanol seed extract inhibits 3CL protease and SARS CoV replication. | Ethanol seed extract induces expression of phosphorylated eIF2α response | Polyacetylene and pteryphyllin from the root showed anti-viral activity | Sharma et al., 2009; Burger et al., 1997 |
| **Catalyphylaceae** | *Calophyllum inophyllum* Planch. | Extracts from leaves and roots showed anti-inflammatory and anti-necroic activity in mice model | Extracts from leaves and roots showed anti-inflammatory and anti-necroic activity in mice model | Extracts from leaves and roots showed anti-inflammatory and anti-necroic activity in mice model | Shen et al., 2005; Filho et al., 2009 |
| **Celastraceae** | *Tripterygium regelii* Sprague | Triptophalin C-2 showed antiviral activity against H1N1 influenza virus and HCMV, measles virus and influenza A virus | Triptophalin C-2 showed antiviral activity against H1N1 influenza virus and HCMV, measles virus and influenza A virus | Triptophalin C-2 showed antiviral activity against H1N1 influenza virus and HCMV, measles virus and influenza A virus | Hayashi et al., 1996; Lee et al., 1995; Lv et al., 2019 |
| **Cibotiaceae** | *Cibotium barometz* (L.) J. Sm. | Methanol and ethanol extract of dried rhizome inhibit viral replication. | The methanol extract of rhizome suppress NO and IL-6 and also decreased iNOS and COX-2 expression | The methanol extract of rhizome suppress NO and IL-6 and also decreased iNOS and COX-2 expression | Islam et al., 2020; Wen et al., 2011; Wu and Yang, 2009 |
| **Compositae** | *Chrysanthemum indicum* L. | The herb found to inhibitory SARS-CoV-2 virus | Flower and bud ethanol extract reduced TNF-α, IL-6 and IL-1β production | The herb found to inhibitory SARS-CoV-2 virus | Kwong et al., 2020; Lee et al., 2009; Cheng et al., 2005 |
| **Dryopterisaceae** | *Dryopteris crassirhizoma* Nakai | It clear heat and detoxify, removes lung hotness and having potency against SARS-CoV-2 | Ethanol root extract diminishes the production of NO and PGE2, down regulate the iNOS synthase, COX-2, and TNF-α mRNA expression and also decrease the level of IL-6 | Ethanol root extract diminishes the production of NO and PGE2, down regulate the iNOS synthase, COX-2, and TNF-α mRNA expression and also decrease the level of IL-6 | Yang et al., 2020; Yang et al., 2013; Cheng et al., 2016 |
| **Fabaceae** | *Muscaea pruriens* (L.) DC. | Peptide fraction has been reported in the treatment of to liver cancer, HCV, and high activities of protecting DNA damages | Essential oil from leaf and flavonoids from seed powder shown anti-inflammatory | The bean extract showed immunomodulatory activity by modulating TNF-α, IL-6, IFN-1, IL-1β, iNOS and IL-2 level in the CNS and also enhanced the activity of the transcription factor NF-kB | Taghizadeh et al., 2021; Avooseh et al., 2020; Javed et al., 2013; Malturw et al., 2006; Eai et al., 2017 |
| **Glycyrrhiza glabra* L. | Glycyrrhizini (i) was shown to inhibit SARS-coronavirus (SARS-CoV) replication | Glycyrrhizic acid, liquiritin and liquiritigenin inhibited iNOS, COX-2, TNF-α, IL-1β and IL-6. | Glycyrrhizic acid, liquiritin and liquiritigenin inhibited iNOS, COX-2, TNF-α, IL-1β and IL-6. | Glycyrrhizic acid, liquiritin and liquiritigenin inhibited iNOS, COX-2, TNF-α, IL-1β and IL-6. | Ciufal et al., 2003; Hoever et al., 2005; Fiore et al., 2008; Bordbar et al., 2012 |

(continued on next page)
| Plant Family | Genus | Compound(s) | Effect | Reference(s) |
|-------------|-------|-------------|--------|--------------|
| Lamiaceae   | Hyptis atrorubens Poit. | Ethyl acetate and water extract of root showed antiviral activity against enterovirus 71 by interrupting viral RNA synthesis and viral entry | Polysaccharides extract enhanced expression of IL-4, IL-6, and IFN-γ | Liu et al., 2013; Chen et al., 2017; Han et al., 2018; Wu et al., 2007 |
|             | Salvia officinalis L. | Essential oils from fruits was found to be active against SARS-CoV and HSV-1 replication | The polysaccharide fractions showed immunomodulatory activity | Loizzo et al., 2008; Ghorbani and Esmailizadeh, 2017; Capek et al., 2003 |
| Scutellaria | baicalensis Georgi | The root aqueous extract inhibited the production of NO, IL-3, IL-6, IL-10, IL-12p40, IL-17, IP-10 | Baicalin suppresses TNF-α and IL-12p70 secretion and expressions of CD80, CD86 and MHC II | Liu et al., 2021; Wu et al., 2019; Yoon et al., 2009; Lin et al., 2017 (Chen et al., 2018) |
| Lauraceae   | Cinnamomum zeylanicum L. | Methanol bark extract showed anti-inflammatory activity in vivo animal models | Polyphenolic fractions of bark extract stimulate lymphocytes proliferation, immunoglobulin production and IL-1β production. The oil and bark extract having immunosuppressive potential | Zhuang et al., 2009; Kubo et al., 1996; Balekar et al., 2014 |
|             | Laurus nobilis L. | Essential oils inhibited SARS-CoV and HSV-1 replication in vitro | Hydro-alcoholic extracts of leaves and seeds showed anti-inflammatory activity in mice | Loizzo et al., 2008; Eora et al., 2007 |
|             | Azadirachta indica A. Juss | Ethanol seed extract inhibited SARS virus replication acting on papain-like protease (PLpro) | Bakuchiol inhibited the expression of iNOS in RAW 264.7 macrophages cells | Mohamed et al., 2017; Pae et al., 2001; Kim et al., 2014 |
|             | Toona sinensis (Juss.) M. Roem. | Stem and leaf hexane extract inhibited viral replication in SARS-CoV-infected Vero E6 cells | Aqueous stem extract inhibits the production of NO and TNF-α and possesses anti-inflammatory activity | Zhang et al., 2013; Wen et al., 2011; Wen et al., 2011; Ding et al., 2013 |
|             | Broussonetia papyrifera (L.) L’Her. ex Vent | Nimboloid (terpenoid lactone) is effective in regulating the ARDS, is a key pathological feature of COVID-19 | Flowers aqueous stimulated both specific and non-specific immune responses, humoral and cell mediated response | Shetty et al., 2020; Schumacher et al., 2011; Shah et al., 2005; Das, 2021 |
|             | Polyphenols from ethanol root extract markedly inhibited 3CL and PL CoV proteases. The isolated compounds exerted significant SARS-CoV PLpro | The plant root ethanol extract reduced IgG-dependent passive cutaneous anaphylaxis | | Park et al., 2017; Ryu et al., 2019; Wang et al., 2012 |

(continued on next page)
Table 1 (continued)

| Family | Genus | Species | Plant Part | Activity/Effect |
|--------|-------|---------|------------|-----------------|
| Myrtaceae | Syzygium | aromaticum (L.) Merr. | Root ethanol extract | Inhibitory activity through noncompetitive inhibition |
| | | | | Higher binding affinity with viral and host macromolecular targets and other human proinflammatory mediators, SARSCoV-2 main proteases, spike, human ACE2 and furin proteins |
| | | | | Eugenol prevent increase in IL-4, IL-5 and the down regulation of proinflammatory cytokines IL-6 and TNFs |
| | | | | Eugenol found immunomodulatory activity |
| | | | | Maurya and Sharma, 2020; Bachega et al., 2012; Barbosa et al., 2018; Pramod et al., 2010; Dibazar et al., 2015 |
| | | | | Ji et al., 2015; Jo and Kim, 2019; Lee et al., 2018; Yang et al., 2019 |
| | | | | Maurya and Sharma, 2020; Dowey et al., 2017; Gorgani et al., 2017 |
| | | | | Kim et al., 2008; Guo et al., 2017; Li and Yu, 2006 |
| Rutaceae | Apigenin from methanol flower extract | | Root ethanol extract | Higher binding affinity with viral and host macromolecular targets and other human proinflammatory mediators, SARSCoV-2 main proteases, spike, human ACE2 and furin proteins |
| | | | | Stem bark methanol extract reduced the production of IL-6 and TNF-α in LPS-stimulated RAW264.7 cells |
| | | | | The flower polysaccharides extracts enhanced lymphocyte proliferation, serum antibody titer and serum IFN-γ concentrations |
| | | | | Maurya and Sharma, 2020; Dowey et al., 2017; Gorgani et al., 2017 |
| | | | | Kim et al., 2008; Sun et al., 2019 |
| Urticaceae | Urtica dioica L. | | Lactic acid | Hydrolyzable tannins from leaf ethanol extract having antiviral property against influenza A by blocked the viral replication and RNA-dependent RNA polymerase |
| | | | | Hydroalcoholic extract of aerial part decreased IL-6 and High Sensitive C-Reactive Protein (hs-CRP) |
| | | | | Flavonoid fraction and flavonoid glycosides from methanol extract of aerial part showed immunostimulatory activity |
| | | | | Day et al., 2009; Semal et al., 2017; Akbay et al., 2003 |
| Zingiberaceae | Zingiber officinalis | | | 6-gingerol binds at active sites of R7Y COVID-19, main protease essential for replication and reproduction of SARS-CoV-2 |
| | | | | 6-gingerol inhibits the production of proinflammatory cytokines IL-1β, IL-12, TNFs |
| | | | | 6-gingerol possess immunomodulatory properties |
| | | | | Rashinavel et al., 2020; Tripathi et al., 2007; Sharifi-Rad et al., 2016 |
| | | | | Tilwari et al., 2011; Lee et al., 2017; Malik et al., 2018 |

**Notes:**
- *Phytomedicine 98 (2022) 153930*
Table 2: Herbs derived secondary metabolites found to be effective against COVID-19 through molecular docking analysis.

| Plant Family Molecular docking study | Plant name | Antiviral | Anti-inflammatory | Immunomodulation | References |
|--------------------------------------|------------|-----------|------------------|------------------|------------|
| **Apocynaceae**                      | Nerium oleander L. | Digitoxigenine (ix) and Calarene (x) interact with Coronavirus spike protein. | The flower aqueous extract inhibited NO production and ERK phosphorylation. Oleandrin blocked TNF-α induced activation of NF-κB. Andrographolide significantly reduced production of IL-1β, IL-6, CXCL-1, MCP-1. | Stimulate the cell-mediated and the humoral mediated immune systems, specifically stimulates T and B lymphocytes. | Aansouz et al., 2021; Atay Balkan et al., 2018; Manna et al., 2000; |
| **Acanthaceae**                      | Andrographis paniculata (Burm. f.) Wall. ex Nees | Andrographolide (xxvi) inhibits main protease of SARS-COV-2 (Mpro) through in silico studies | Andrographolide was reported to stimulate an innate immune response in in-vivo model. Ethanol extract induced phagocytic activity and peritoneal macrophages and Increases lymphocytes cell proliferation | | Emsonni et al., 2021; Shen et al., 2002; Puri et al., 1993; Basnerjey et al., 2021; Churiyah et al., 2015 |
| **Amaranthaceae**                    | Amaranthus tricolor L. | Amaranthin (xxiv) may inhibit SARS-CoV-2 3CLpro activity and hence virus replication | The hydroalcohol extract of leaves showed anti-inflammatory activity in in-vivo repisation | | Ul-Qamar et al., 2020; Bilhani et al., 2013; Srivastava, 2017 |
| **Amaryllidaceae**                   | Allium sativum L. | Allyl disulfide, allyl trisulfide, allyl (E)-1-propenyl disulfide, allyl methyl trisulfide, diallyl tetrasulfide, 1,2-dithiole, allyl (Z)-1-propenyl disulfide, 2-vinyl-4H-1,3-dithiine, 3-vinyl-1,2-dithiacyclohexane-4-ene, carvone, trisulfide, 2-propenyl propyl, methyl allyl disulfide, diacetonolcarb, trisulfide, (1E)-1-propenyl 2-propenyl, allyl sulfide, 1-propenyl methyl disulfide, trisulfide, (1Z)-1-propenyl 2-propenyl showed inhibition of the ACE2 protein Allicin (xxv) may act as potential inhibitors of the COVID-19 Mpro binding with spike protein | DMSO extract of Garlic powder reduced NF-κB, IL-1β, IL-6, TNF-α and diallyldisulfide also significantly reduced IL-1β and TNF-α | | Thuy et al., 2020; Rhaerunnsita et al., 2020; Keis et al., 2003; Zamani et al., 2011 |
| **Apiaceae**                         | Angelica keiskei (Miq.) Koidz. | Nine alkylated chalcones and four coumarins exhibited 3CLpro and PLpro inhibitory activity in a dose dependent manner | The n-hexane bark extract down regulate NF-κB-dependent gene products. Compounds present in the plant showed potent inhibition of IL-6 production in TNF-α-stimulated MG-63 cell. Ethanol root extract decreased IL-1β, IL-6 and TNF-α level. | Xanthoangelol B, xanthoangelol C, and xanthoangelol E are immunological stimulators. *Selinidin suppress LTC4 synthesis and TNF-α production | Islam et al., 2021; Caesar and Cech, 2016; Kil et al., 2017 |
| **Asteraceae**                       | Aster tataricus L. | The phytomolecules may inhibit 3CLpro or viral entry through binding with spike protein | Scutellarin reduced IL-18, and IL-1β. Brevicarpine down-regulated IL-6 in-vivo | | Zhang et al., 2020d; Rho et al., 2020 |
| **Asteraceae**                       | Erigeron brevicaespus (Vaniot) Hand.-Mazz. | The phytomolecules may inhibit 3CLpro or viral entry through binding with spike protein | Ethanol bark extract inhibit NO and COX-2 production. Triterpenoid present in the plant inhibit IL-1β and IL-6 levels induced by LPS in macrophage cells. | Ethanollic extract of leaves and barks of A. japonica possesses immunomodulatory activity | Demeke et al., 2021; Choi et al., 2011; Kim et al., 2005 |
| **Betulaceae**                       | Alnus japonica (Thumb.) Steud. | Diarylheptanoids (Hirsutene) inhibited replication of SARS-CoV PLpro by inhibiting Papain like protease. | Citrooxygenone B, citrooxygenone C, citrooxygenone D, and Cech, 2016; Kil et al., 2017 | | Zhang et al., 2020d; Zhu et al., 2018 |
| **Brassicaceae**                     | Isatis indigotica Fortune | Indigo, sinigrin, aloe emodin (xxiii) and hesperetin blocked the cleavage processing of the 3CLpro | The root aqueous extract with DNA vaccine has adjuvant effect on the immune response against foot-and-mouth-disease-virus | | Liang et al., 2020; Meng et al., 2017; Lin et al., 2005; Chen et al., 2012 (Ryu et al., 2010) |
| **Celastraceae**                     | Tripterygium regelii Sprague & Takeda | Quinone-methide triterpenes celastrol, pristimerin, tingenone, iguasterin and dihydrocelastrol showed potent inhibitory activities against SARS-CoV 3CLpro | The aqueous fruit extract suppress COX-2, iNOS, IL-16, IL-6 and reduced TNF-α, IL-1β | | Yin et al., 2021; Wu et al., 2020a; (Wang et al., 2017) |
| **Euphorbiaceae**                    | Phyllanthus emblica L. | Phyllaemblicin B (xiv) and phyllaemblicin showed binding affinity to Spike protein, ACE2 protein Phyllaemblicin G7 showed binding affinity to Spike protein, ACE2 protein Phyllaemblicin exhibited binding affinity to 3CLpro, Phyllaemblicin B found to | The aqueous fruit extract enhance NK cell activity and antibody dependent cellular cytotoxicity | | Suresh and Vasudevan, 1994 |

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### Table 2 (continued)

| Order         | Family       | Genus                        | Species            | Active Compound(s)                                                                                   | Effect                                      |
|---------------|--------------|------------------------------|--------------------|-----------------------------------------------------------------------------------------------------|---------------------------------------------|
| Legumes       | Phaeoleus    | vulgaris L.                  |                    | The navy bean or black bean flour-containing diet significantly reduced IL-1β, TNF-α, and IL-6.       | The lectin crude extract has immunomodulatory effect |
| Magnoliaceae  | Magnolia     | officinalis Rehd & E.H.Wilson|                    | Magnolol (xvi) showed potential PLpro inhibition.                                                   | polyphenol rich aqueous extract from bark reduced serum NO, IL-6 and TNF-α, inhibiting pneumonia, decreasing lung viral tilters and sensitizing IVA induced apoptosis |
| Menispermace  | Tinospora    | cordifolia (Willd.) Miers    |                    | Chloroform stem extract prevented IL-6, IL-1β and PGE2                                             | Aqueous and methanolic stem extract stimulate production of IFN-γ, TNF-α, and IL-1β |
| Myricaceae    | Myrica       | corylifera L.                |                    | Myricitrin (xi) showed good interaction potential with SARS-CoV-2 3C108 receptor.                  | Myricidine down-regulate the NF-κB |
| Oleaceae      | Olea         | Europea L.                   |                    | Oleuropein inhibit IL-1β production and down regulated NOX, COX-2, NFKB, and JNK, and IL-6 and IL-1β | The hydroalcohol leaf extract reduced IL-1β, IL-6, IL-8, TNF-α and INOS expression |
| Oxalidaceae   | Averrhoa     | bilimbi Linn.                |                    | The methanol fruit extract decreased IL-1β, IL-6, TNF-α levels                                      | Methanol fruit extracts significantly inhibited the CD18/11a expression |
| Piperaceae    | Piper         | longum L.                    |                    | Dichloromethane fraction suppress IL-1β, IL-6, and TNF-α                                           | Piperine having anti-apoptotic and restorative ability against splenic B and T cell population and IL-2 and gamma-interferon release |
| Ranunculaceae | Nigella      | sativa L.                    |                    | The aqueous seed extract improves both cellular immunity and humoral immunity by stimulating CD4+ |
| Solanaceae    | Withania     | somnifera (L.) Dunal          |                    | Withanol (xvii) block or weaken COVID-19 infection and its subsequent infectivity                      | A herbo mineral formulation containing aswagandha significantly increased the CD4+ and CD8+ |
| Taxaceae      | Torreya      | nucifera (L.) Siebold & Zacc.|                    | The leaves reduced secretion of IL-1β, IL-6, NO and PGE2                                           | The leaves reduced secretion of IL-1β, IL-6, NO and PGE2 |
| Theaceae      | Camellia     | sinensis (L.) Kunze          |                    | Ethanol leaf extract and epigallocatechin gallate suppressed the production of NO, COX-2, IL-6, IL-1β, and TNF-α | Hot water extract of leaves significantly increased blood leukocyte, lymphocyte count, peritoneal macrophages, spleen and thymic lymphocytes count, lung macrophages count |
| Zingiberaceae | Zingiber     | officinale Roscoe            |                    | Rhizome supplement reduced TNF-α, IL-6 level.                                                      | Ginger essential oil recovered the humoral immune response |

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post-COVID complications have been represented in Table 4.

Olfactory dysfunctions are very common among COVID-19 patients. A considerable portion of patients experienced with the loss of smell and taste, while one third additionally suffered from rhinitis. Hyposmia is a common non-motor symptom of early stages of Parkinson’s disease (Bocksberger et al., 2020; Xiao et al., 2014). Hyposmia without nasal dysfunction and rhinorrhea was also documented (Giacomelli et al., 2020; Lechien et al., 2020; Lovato and Filippis, 2020).

### Mental problems

SARS-CoV-2 can appear as being both neuro-invasive and neuro-virulent. One in every three patients recovering from COVID-19 suffers from neuropsychological problems ranging from headache, dizziness, memory disorder, seizures, depression and lingering loss of smell or taste to mood disorders and deeper cognitive impairment. Those patients with insomnia feature stress, anxiety, depressive symptoms, denial, anger, mental breakdown, and those with pre-existing mental illness experience worsening of their conditions (Anaya et al., 2021; Czeisler et al., 2020; Roy et al., 2021; Schäfer et al., 2020). The demyelination syndrome troubles COVID-19 patients, in which the protective coating of nerve cells is attacked by the immune system. This is an autoimmune disease causing weakness, numbness, tingling, spurring psychosis and also hallucinations (Coony, 2020).

COVID-19 patients are challenged by severe stressors, including fear of death from life-threatening illness, pain from medical interventions, endotracheal intubation, limited ability to communicate, and the feeling to loose control (Kaseda and Levine, 2020). The Chicago medical center reported that more than 40% of COVID-19 patients exhibited neuropsychologic manifestations and more than 30% of those had impaired cognition. Sometimes, the neurological manifestations can be calamitous and can even lead to death.

Implementation of Indian herbs and herbal formulations such as Brahmi (B. monnieri), Shankphuphi (Convolvulus prostratus Forsk.), Giloy (T. cordifolia), Malkangni (Celastrus paniculatus Willd.), Tulsi (O. tenuiflora), Ashwagandha (W. somnifera) etc. can help managing psychological post-COVID conditions. Bacoside from B. monnieri induced an antioxidant environment in brain, and its neuroprotective potential was documented (Anaya et al., 2021; Abdelrezek et al., 2018).

### Table 2 (continued)

| Plant Family | Herb name | Common Name | Use in Traditional Formulation | Antiviral | Anti-inflammation | Immunomodulation | References |
|--------------|-----------|-------------|--------------------------------|-----------|------------------|------------------|------------|
| Fabaceae     | Astragalus | Urad bean   | Urad bean used for the treatment of SARS-CoV-2 infection | Isoliquiritigenin and liquiritigenin inhibited IL-6 and IL-12 productions | Polysaccharide-enriched fraction suppressed IL-1β, IL-6 expression and TNF-α level in LPS-induced macrophages | Aqueous root extract enhances IL-1α and IL-12 expression | Lee et al., 2003; Gong et al., 2018; Li et al., 2014 |
| Zygophyllaceae | Tribulus terrestris L. | Tribulus | Tribulus extract used for the treatment of SARS-CoV-2 infection | Inhibit COX-2 | Inhibit PGE2 and NO production by inhibiting the production of TNF-α, IL-1β, IL-6 | Inhibit TNF-α and IL-10 | Yang et al., 2020; Tanaka et al., 2009; Tanemoto et al., 2015; Ayeka et al., 2017 |
| Labiatae | Schizonepeta tenuifolia L. | Yin Qiao San | Schizonepeta tenuifolia L. used as ingredient in Yin Qiao San | The ethanol extract of the aerial part significantly decreased COX-2, PGE2 and NO production by inhibiting the production of TNF-α, IL-1β, IL-6 | The ethanol extract of aerial part inhibited Ig-E, IL-4, IL-6 and IL-10 | The ethanol extract of aerial part inhibited Ig-E, IL-4, IL-6 and IL-10 | 1999; Lee et al., 2017; Chen et al., 2017 |
| Lamiaeae | Menispermum haplocalyx Briq. | Menispermum | Menispermum haplocalyx Briq. used as ingredient in Menispermum haplocalyx Briq. | Phenolic fraction and linarin from ethanol extract of aerial part decreased NO, TNF-α, IL-1β, IL-6 expression and suppress mRNA expression levels of iNOS, TNF-α, IL-1β, and IL-6 | The ethanol extract of aerial part inhibited IFN-γ, TNF-α, IL-4 and IL-5 production | The ethanol extract of aerial part inhibited IFN-γ, TNF-α, IL-4 and IL-5 production | Yang et al., 2020; Lee et al., 2017; Chen et al., 2017 |
| Moraceae | Morus alba L. | Hua Qing Wen Capsule | Morus alba L. used as ingredient for the treatment of SARS-CoV-2 infection | The aqueous and ethanol root bark extract suppressed the expression of TNF-α, C-Fox, p-p38, and pNF-kB p65. Restored INOS, COX-2, IL-10, and IL-1β expression | Kusnanon G significantly decreased the levels of IgE and IL-4, IL-5, and IL-13 in the sera and BAL fluids | Polysaccharides from aqueous root bark extract increased lymphocyte proliferation and decreased antibody production from B cells | Kwon et al., 2020; Yan et al., 2020; Zhang et al., 2020; Bayazid et al., 2020; Kavitha and Geetha, 2018; Kim et al., 2000 |
| Rosaceae | Arminia sibirica (L.) Lam. | Lian Hua Qing Wen | Arminia sibirica (L.) Lam. used as ingredient in Lian Hua Qing Wen Capsule | Aqueous seed extract used for the treatment of SARS-CoV infection | Phenolic fraction from root extract used as an ingredient in Lian Hua Qing Wen Capsule | The methanol seed extract able to inhibit Ig-E, IL-4, IL-6 and IL-12 expression | Erdogan-Orhan and Kartal, 2011; Yang et al., 2020; Chang et al., 2005 |
| Family Name | Plant Name | Mechanism of Action | Disease | Reference |
|-------------|------------|---------------------|---------|-----------|
| Acanthaceae | Andrographis paniculata (Burm.f.) Nees | Andrographolide improved cell apoptosis, collagen deposition and epitelial-mesenchymal transition in HK-2 cell line. It also improved renal tubular cell apoptosis, tubulointerstitial fibrosis, epithelial-mesenchymal transition, NLRP3 inflammasome activation and mitochondrial dysfunction in high glucose treated rats | Kidney complications | (Liu et al., 2021) |
| | | Hydroalcohol extract improved lung injury condition by harmonizing the inflammatory responses, NF-κB p65 protein expression and nuclear translocation, and phosphorylation of IkBα in male Wistar rats | Lung complications | Yao et al., 2021 |
| | | Water extract of whole plant improved myocardial inflammation pathway, reduced the chances of cardiac hypertrophy and myocardial apoptosis in high fat diet obese mice | Cardiac complications | Hsieh et al., 2016 |
| | | Andrographolide improved GSK-3β activity, β-catenin and NeuroD1 levels in vivo. Thus, it can be used to improve deregulation like behaviours | Mental Problem | Varela-Nallar et al., 2015 |
| | | Hydroalcohol extract of aerial parts restored glutatione xglutamatergic transaminase, glutamate pyruvate transaminase, alkaline phosphatase, superoxide dismutase, glutathione peroxidase and lipid peroxides level in paracetamol treated rat liver | Liver related problem | Nagalekshmi et al., 2011 |
| | | Androgrpholide reported to protect mesencephalic neurons by reducing dopaminergic neurodegeneration in vivo and also inhibited in vivo microglial inhibition, ROS and pro-inflammatory cytokine production in lipopolysaccharide treated rats | Parkinsonism | Wang et al., 2004 |
| Amaranthaceae | Amaranthus tricolor L. | Leaves extracts with organic solvents (methanol, petroleum ether, dichloromethane) improved gene expression of the pro-inflammatory cytokines, TNF-α, IL-1 and IL-6 in AEGs-induced oxidative stress and neuroinflammation associated with the risk of brain aging and developing Parkinson’s disease | Parkinsonism | Amornrit and Sanitryanont, 2015 |
| | | Ethanol leaves extract improved serum GOT, GPT, GGT, ALP, bilirubin, and MDA level in CCl4 treated rats | Liver related problem | Al-Dosari, 2010 |
| Amaryllidaceae | Allium sativum L. | Allicin isolated from bulbs improved acute lung injury and inflammation, oxidative stress, apoptosis condition in lipopolysaccharide treated neonatal rats and as a traditional medicine in Peru it used to treat cough, cold and sore throat | Lung related complications | Villena-Tajeda et al., 2021 |
| | | Diallyl trisulfide improved liver injury by reducing the serum aspartate transaminase, alanine aminotransferase levels, sterol regulatory element binding protein and cell apoptosis in ethanol treated rat | Liver related problem | Wang et al., 2018 |
| Anacardiaceae | Rhus chinensis Mill. | Aqueous extract of fruit pulp reduced calcium oxalate crystal formation, aggregation and crystal density in in-vitro calcium oxalate crystallization | Kidney complications | Heirrangkhamjiam and Ngaseppam, 2021 |
| | | Dammarane-type triterpenoids isolated from the root extract prevented heart failure in zebra fish by enhancing heart dilatation, venous congestion, cardiac output, blood flow velocity and heart rate | Cardiac complications | Ye et al., 2020 |
| | | Phenolic compound of fruit extract improved serum lipid level, steatosis and liver damage in high-fat and ethanol treated rat model | Liver related problem | Wu et al., 2019 |
| Apiaceae | Angelica keiskei (Micq.) Koidz. | Ethanol extract of aerial parts its active principle, 4-hydroxyderricin improved myosin heavy chain degradation by suppressing expressions of MAFbx, MuRF-1 and myostatin | Cardiac complications | Kweon et al., 2019 |
| | | Ethanol extract of aerial parts improved apoptosis via intrinsic and extrinsic pathways against AAP treated hepatotoxicity | Kidney complications | Choi et al., 2017 |
| | | Xanthoangelol isolated from the hydroalcohol extract of aerial parts (1) inhibited monoamine oxidase and dopamine β-hydroxylase in rats | Mental problem | Kim et al., 2013 |
| | | A double blind, placebo-controlled study (clinical study) decreased anxiety conditions | Kidney related problem | Rezaie et al., 2013 |
| Asteraceae | Echinacea purpurea L. Moench | Hydroalcohol extract of aerial part decreased serum AST, BUN, total and direct bilirubin content and improved histopathological changes of kidney tissue by early fibrosis and proliferation | Mental problem | Haller et al., 2019 |
| | | Scutellarin showed potent hepatoprotective effects by improving CYP2E1 and IkBα/NF-κB signaling pathways in carbon tetrachloride treated mice | Liver related problem | Miao et al., 2021 |
| | | Scutellarin improved lung damage due to its antioxidant, antiinflammatory and antiapoptotic effects in a bilateral hind limb ischemia-reperfusion rat model | Lung related complications | Ibrahim et al., 2019 |
| | | Scutellarin improved renal function by reducing serum creatinine, blood urea nitrogen, urine total protein and microglobulin content | Kidney complications | Wu et al., 2018 |
| | | Ethanol whole plant extract, ethyl acetate and aqueous fraction potently and noncompetitively inhibited GABA transaminase and succinic semialdehyde dehydrogenase enzymes in in-vitro assay due to the presence of flavonoids | Parkinsonism | Tao et al., 2008 |
| Brassicaceae | Isatis indigotica Fortune ex Lindl. | Erucic acid isolated from the ethanol extract improved lung injured condition by reducing CDA- cytoxic T lymphocyte, pro-apoptotic, hyperactivity signalling pathways and the immune inflammation | Lung related complications | Liang et al., 2020 |
| Caesalpinaceae | Cassia tora L. | | Mental Problem | Shrivastava et al., 2020 |

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Table 4 (continued)

| Family         | Genus                     | Species                        | Plant Description                                                                                     | Condition                          | Complication              |
|----------------|---------------------------|--------------------------------|------------------------------------------------------------------------------------------------------|------------------------------------|---------------------------|
| Euphorbiaceae  | Phyllanthus               | Emblica                        | Methanol extract exhibited protective action against pulmonary fibrosis lung                           | Kidney complications               | (Park et al., 2019)       |
|                |                           |                                | Aqueous flower extract showed hepatoprotective activity against acetaminophen induced HepG2 cell death | Liver related problem              | (Choi et al., 2010)       |
| Celastraceae   | Dryopteris                | Cuspidata                       | Ethanol extract improved p53 expression in porcine kidney cell line and also improved histopathological alterations and apoptosis in cisplatin treated rats | Mental Problem                     | (Hong et al., 2012)       |
| Compositae     | Chrysanthemum             | Indicum                        | Aqueous flower extract showed hepatoprotective activity by decreasing glutamic oxaloacetic transaminase and pyruvic transaminase level in hepatocellular carcinoma cells | Liver related problem              | (Kim et al., 2011)        |
| Dryopteridaceae| Dryopteris                | Crassirhiza                    | Ethanol extract improved in-vivo allergic asthma condition and airway inflammation by inhibiting the activation of NF-κB signalling | Lung related complications         | (Piao et al., 2020)       |
| Euphorbiaceae  | Phyllanthus               | Emblica                        | Ethanol fruit extract suppressed neuroinflammation in Microglia and promoted neurite outgrowth in Neuro2a cells | Cardiac complications              | (Phochantachinda et al., 2021) |
|                |                           |                                | Aqueous fruit extract prevented precancerous lung lesions through regulating the IκB-α/β/miR-i101/Lin28B signaling pathway in benzopyran treated mice | Lung related complications         | (Usharani et al., 2019)   |
| Fabaceae       | Glycyrrhiza               | Glabra                         | Aqueous extract suppressed tyrosine hydroxylase and acetylcholine transferase expression in the brain of repeated stress treated depressed rats | Mental Problem                     | (Uddin et al., 2016)      |
|                |                           |                                | Glycyrrhizin reduced thrombin-fibrinogen clotting time, thrombin-induced platelet aggregation and improved plasma recalcification duration | Kidney complications              | (Tanasanrong et al., 2014) |
|                |                           |                                | Glycyrrhizin isolated from the aqueous root extract possessed anti-depressant activity in mice model | Kidney complications              |                           |
|                |                           |                                | Glycyrrhizin acid isolated from fermented root extract showed hepatoprotective activity in alcohol treated mice by decreasing lipid accumulation and increasing the hepatic glutathione level | Liver related problem              | (Jung et al., 2016)       |

(continued on next page)
| Family       | Species                                    | Effects                                                                                                                    | Complications | References                          |
|--------------|--------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|---------------|-------------------------------------|
| Gulateae     | Mucuna pruriens                           | Aqueous seed extract improved protection of kidney by decreasing serum ALT and other kidney enzyme levels in arsenic treated rats | Kidney        | Concessus et al., 2020              |
|              | Glycyrrhiza uralensis Fisch.               | Hydroalcohol extract of leaves improved serum ALT, AST, ALP, and bilirubin levels in isoniazid-rifampicin treated rats       | Liver related | Obegwu et al., 2014                |
|              | Salvia officinalis L.                     | Hydroalcohol extract improved anti-depressant activity by reducing immobility time and showed potent activity against chronic unpredictable mild stress in rats | Mental problem | Rana and Galani, 2014              |
|              | Gentiana scabra Bunge                     | Seed powder can improve long term management of Parkinson’s disease and provide symptomatic relieve from PD.                 | Parkinsonism   | Katzenschläger et al., 2004         |
|              | Gentiana lutea (L.) DC.                   | Polyphenolic compounds isolated from aqueous extract exhibited hepatoprotective activity in CCl4 induced mice model by reducing oxidative stress and liver injury | Liver related | Ko et al., 2011                     |
|              | Schizonepeta tenuifolia (Benth.) Briq.    | Hydroalcohol extract inhibited pro-inflammatory cytokines and oxidative stress, and activated the Nr2-H0-1 axis in lipopolysaccharide treated mice | Lung related complications | Lee et al., 2021                   |
|              | Mentha haplocalyx Briq.                   | In TCM system Lian Hua Qing Wen Capsule containing the plant along with some other plant clear heat and relaxes lungs    | Lung related   | Yang et al., 2020                   |
|              | Salvia miltiorrhiza Bunge                 | Aqueous extract of the plant improved lung injured condition by inhibiting the production of TNF-a, IL-6 and the protein and mRNA expression of toll-like receptors 4, nuclear factor-KB, IL-1 receptor-associated kinase-1 | Lung related complications | Qin et al., 2018 (Chen et al., 2017) |
|              | Salvia miltiorrhiza Bunge                 | Essential oil from the aerial parts showed improved anxiolytic condition by increasing the intracellular G1 concentration in vitro cell culture and also improved the anxiolytic effect and social interaction in vivo model | Mental problem | Liu et al., 2015                    |
|              | Salvia officinalis L.                     | Leaves extract showed hepatoprotective activity in oestrogen deficient ovariectomized rats by altered plasma transaminases and lipid profile activities of liver | Liver related | Koubba-Ghobrel et al., 2020a        |
|              | Scutellaria barbata D. Don                | Essential oils improved liver biochemical marker, cholesterol, body weight and renal dysfunction in high fat diet treated rats | Kidney        | Koubba-Ghobrel et al., 2020b        |
|              | Cinnamomum zeylanicum L.                  | Essential oils potentially reduced aspartate transaminase, alanine transaminase, γ-glutamyltranspeptidase and lactate dehydrogenase activities and total cholesterol, triglycerides, total lipids, and low-density lipoprotein cholesterol level in high fat diet induced mice | Cardiac        | Koubba-Ghobrel et al., 2020b        |
|              | Lauraceae                                 | Leave infusion inhibited lung fibrosis in rats and normalized lipid peroxidation, superoxide dismutase and catalase activities | Lung related   | Bahri et al., 2020                  |
|              | Laurus nobilis L.                         | In a clinical study the ethanol extract of dried leave improved anxiety, alertness, calmness and contentedness on the Bond-Lader mood scales | Mental problem | Kennedy et al., 2005                |

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Table 4 (continued)

| Family          | Genus/Taxonomy                        | Description                                                                                         | Control                                                                 |
|-----------------|---------------------------------------|-----------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Leguminosae     | Psoralea corylifolia L.               | Corilin isolated from the whole plant extract reduced LPS-induced dopaminergic toxicity by increasing cell survival rate and decreasing intracellular ROS levels | Parkinsonism                                                           |
|                 |                                       | Psoralidin from the seed extract improved 5-HT, 5-hydroxyindoleacetic acid and dopamine secretion in mice brain and also improved the stress condition by improving the release of adrenal corticotropin hormone, corticosterone and serum corticotropin-releasing factor | Mental Problem                                                        |
| Lobanaceae      | Ecklonia cava                         | Ethanol extract of leaves reduced serum aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl-transpeptidase levels in 6-hydroxydopamine treated rat model | Mental Problem                                                        |
| Magnoliaceae    | Magnolia officinalis Rehder & E.H.Wilson | Magnolol improved dopamine transporter and tyrosine hydroxylase protein levels in the striatum. Magnolol improved the number of total cells, neutrophils, macrophages in the bronchoalveolar lavage fluid. Magnolol decreased the production of total NO in the brain of treated mice. | Mental Problem                                                        |
| Meliaceae       | Azadirachta indica A. Juss.           | Ethyl acetate fraction of bark improved sedative and anxiolytic effect on adult zebrafish through serotonergic and GABAergic systems due to its phenolic and flavonoid content | Mental Problem                                                        |
| Menispermae     | Tinospora cordifolia (Willd.) Miers    | Leaves extract showed hepatoprotective activity by reducing liver fibrosis, TGF-beta1 and collagen in chloacetamide treated rat | Parkinsonism                                                          |

(continued on next page)
| Family       | Species                          | Activity                                                                                                                                            | Disease/Problem                          |
|--------------|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| Oleaceae     | Broussonetia papyrifera          | Root bark extract showed hepatoprotective effect by prevention of hepatic steatosis in high fat diet treated mice                                      | Liver related problem                    |
|              |                                  | Traditionally the fruit extract used to treat various ailments related to heart disease                                                            | Cardiac complications                    |
|              |                                  | The plant along with L. japonica reduced in vivo septic inflammation and TNF-α, IFN-γ, IL-1β levels and also inhibited cell recruitment in bronchoalveolar lavage fluid | Lung related complications               |
|              |                                  | Chloroform extract of twigs possessed improved Parkinson’s condition in mushroom tyrosinases                                                         | Parkinsonism                             |
|              | Morus alba L.                    | Ethanol extract of root bark prevented endothelial dysfunction in rat aorta                                                                     | Cardiac complications                    |
|              |                                  | Root bark extract improved depression like behaviour condition in high fat diet treated rats and also reduced brain-derived neurotrophic factor expression and extracellular signal-regulated kinase phosphorylation | Mental Problem                           |
| Myricaceae   | Myrica cerifera L.               | Myricetin increased glutathione, monoamine oxidase, glutathione-S-transferase, protein carbonyl content and lipid peroxidation                  | Parkinsonism                             |
|              | Syzygium aromaticum (L.) Merr. & L.M.Perry | Hydroalcohol extract of buds improved acute kidney injury by ameliorating necrosis, degeneration, dilatation and flattening in rats             | Kidney complications                     |
|              |                                  | Essential oil isolated from the buds showed potent in vivo anticonvulsant activity by improving the threshold of clonic seizures in chemical treated rats | Parkinsonism                             |
|              |                                  | Alcohol and water extract of leaves improved serum glutamate pyruvate transaminase, glutamate oxaloacetate transaminase, alanine phosphatase and bilirubin and histological changes in carbon tetrachloride treated rats | Liver related problem                    |
|              |                                  | Ethanol extract of root barks inhibited production of pro inflammatory cytokines IL-6, TNF-α, infiltration of inflammatory cells in lung epithelial cells and NO production in lung macrophages | Lung related complications               |
|              |                                  | Hydroalcohol fruit protected dopaminergic neurons in in-vitro cells. In-vivo treatment of the extract protected brain from bradykininesia dopaminergic neuronal damage | Mental Problem                           |
|              |                                  | Alcohol and water extract of leaves improved serum glutamate pyruvate transaminase, glutamate oxaloacetate transaminase, alanine phosphatase and bilirubin and histological changes in carbon tetrachloride treated rats | Parkinsonism                             |
|              | Olea Europaea L.                 | Leaf extract decreased IL-6, IL-8 and TNFs in hypertensive patients                                                                               | Kidney complications                     |
|              |                                  | Oleuropein and hydroxytyrosol decreased NF-κB and TNF-α expression by p38 signaling pathway in bisphenol A-treated rats                         | Liver related problem                    |
|              |                                  | Olive oil reduced behavioral deficits via altering 5-HT and DA metabolism level in in-vivo models on Wistar rats                                      | Mental problem                           |
| Paulowniaceae| Paulownia tomentosa Steud.       | Chloroform fruit extract and ursolic acid showed potent hepatoprotective activity against hepatocarcinogenesis on MCF-7 and HepG2 cell line and restored various biochemical parameters | Liver related problem                    |
|              |                                  | Methanol extract of stem bark reduced the production of pro-inflammatory cytokine IL-6, TNF-α in LPS-stimulated RAW 264.7 macrophages. It also reduced in-vivo neutrophils, macrophages, nitric oxide and inducible nitric oxide synthase levels, inflammatory cells infiltration and monocyte chemoattractant protein-1 in lipopolysaccharide treated mice | Lung related complications               |
|              |                                  | Piperine improved plasma concentrations of creatinine, urea-nitrogen, expression of pro-inflammatory factors, oxidative stress and renal histopathological injuries in ischemia-reperfusion rat | Kidney complications                     |
|              | Piper longum L.                  | Piperine potentially reduced activation of microglia and blocked release of proinflammatory cytokines thus, protected dopaminergic neurons damage     | Parkinsonism                             |
|              |                                  | Methanol extract of fruits inhibited monoamine oxidase activity and increased monoamine neurotransmitters levels in β-amyloid treated rat     | Mental Problem                           |
|              |                                  | Alcohol fruit extract inhibited bronchospasm and blocked the release of histamine in in-vitro guinea-pig ileum preparation and histamine treated guinea-pig | Liver related problem                    |
|              |                                  | Piperine showed negative isotropic and negative chronotropic effect by blocking the action of adrenalin in isolated frog heart                   | Cardiac complications                    |
|              |                                  | Piperine improved glutathione and peroxyde level in the liver cell in tert-butyl hydroperoxide and carbon tetrachloride treated mice            | Liver related problem                    |
|              |                                  | Ethanol extract of seed showed nephroprotective activity by improving serum biochemical parameter and histopathological changes in para-aminosalicylic acid treated rats | Kidney complications                     |

(continued on next page)
| Family       | Genus               | Species                  | Description                                                                                                                                                                                                                      | Effect                                                                 | Reference                  |
|--------------|---------------------|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|---------------------------|
| Taxaceae     | Torreya nucifera    | Siebold & Zucc.          | Hydroalcohol leaf extract elevated depression condition, improve immobility condition, oestrogen level and glucose metabolism in brain                                                                                       | Mental Problem                                                      | Ye et al., 2019            |
| Taxaceae     | Camellia sinensis   | (L.) Kuntze              | In repeated stress induced rats model the hydroalcohol leaf extract elevated depression condition, improve immobility condition, oestrogen level and glucose metabolism in brain                                                                      | Mental Problem                                                      | Ye et al., 2019            |
| Rosaceae     | Armeniaca sibirica  | Lam.                     | Root extract increased dopamine, 3,4-dihydroxy-phenylacetic acid, homovanillic acid, lipid peroxidation marker level in the corpus striatum Root extract exhibited nephroprotective effect by improving antioxidant activity in gentamicin treated animal | Kidney complications                                               | Kim et al., 2003           |
| Rutaceae     | Phellodendron cortex|                         | Alkaloids derived from the plant improved mental depression condition, noradrenaline, dopamine and monoamine oxidase-A levels and provide protection against Alzheimer’s disease Quercetin reduced the symptoms of heart failure and improved coronary heart disease condition Berberine isolated from n-butyl alcohol extract showed bronchodilation effect by inhibiting high K⁺ and acetylcholine-induced precontraction of airway smooth muscle in tracheal rings and lung slices | Mental Problem                                                      | Kong et al., 2019          |
| Ranunculaceae| Cimicifuga racemosa | (L.) Nutt.                | Nigella sativa Nutt. Torreya nucifera Dunal Lam. Toddalia asiatica Lam. Arctigenin, traxillagenin, and 49-demethyltraxillagenin improved activity in gentamicin treated animal Thymoquinone induced a significant positive baseline isotropic effect in the rat heart Quercetin-3-O-α-L-rhamnopyranoside, quercetin-7-O-β-D glucopyranoside, tauroside E. and sapindoside B isolated from hydroalcohol extract of seeds improved antidepressant condition by inhibiting the uptake of norepinephrine, serotonin, and dopamine in mice Thymoquinone afforded neuroprotection against 6-OHDA neurotoxicity in neurodegenerative disorders Thymoquinone decreased serum creatinine, blood urea nitrogen, thiobarbituric acid reactive substances, total nitrate/nitrite level and increased glutathione, glutathione peroxidase, catalase and ATP levels in kidney tissues in gentamicin treated rats | Cardiac complications, Liver related problem, Kidney complications, Mental Problem | Gorach, 2018; Asoom and Al-Hariri, 2019; Elkhayat et al., 2016; Sayed-Ahmed and Nagi, 2007; Vardi et al., 2013; Sun et al., 2019; Jeng et al., 2021; Sharma et al., 2021; Logie and Vanden Berghe, 2020; Raja Sankar et al., 2009; Jeyanthi and Subramanian, 2009; Ye et al., 2019 |
| Solanaceae   | Withania somnifera  | (L.) Dunal                | Aqueous root extract showed hepatoprotective activity by the antioxidant activity in CCl₄ treated rats Withaferin A improved lung inflammation by blocking NF-κB and nuclear factor erythroid2 related factor 2 signalling pathway Root extract increased dopamine, 3,4-dihydroxy-phenylactic acid, homovanillic acid, lipid peroxidation marker level in the corpus striatum Root extract exhibited nephroprotective effect by improving antioxidant activity in gentamicin treated animal Arctigenin, traxillagenin, and 49-demethyltraxillagenin improved hepatocytes condition by maintaining the GSH level CCl₄ treated rats | Cardiac complications, Lung related problem, Mental Problem, Kidney complications | Daba and Abdel-Rahman, 1998; Oguz et al., 2013; Shyu et al., 2020; Raj et al., 2016; Zodape and Gaikwad, 2019; Sayed-Ahmed and Nagi, 2007 | Daba and Abdel-Rahman, 1998; Oguz et al., 2013; Shyu et al., 2020; Raj et al., 2016; Zodape and Gaikwad, 2019; Sayed-Ahmed and Nagi, 2007 |
Table 4 (continued)

| Family          | Species                  | Activity                                                                 | Effect                                         |
|-----------------|--------------------------|--------------------------------------------------------------------------|-----------------------------------------------|
| Zingiberaceae   | Curcuma longa L.         | Aqueous plant extract showed cardioprotective activity in isolated Langendorff perifused rat heart by decreasing heart rate and increasing left ventricular pressure | Cardiac complications                         |
|                 |                          | Curcumin showed hepatoprotective activity against alcohol induced liver disease by preventing apoptosis and inhibition of NF-κB in in-vivo models | Liver related problem                         |
|                 |                          | Curcumin improved anti-immobility action in forced swim test and also enhanced the anti-immobility effect of monoamine oxidase inhibitors such as translocypramine, selegiline | Mental Problem                                |
|                 |                          | Curcumin improved loss of dopaminergic neurons in Parkinson’s disease induced rat model | Parkinsonism                                  |
|                 |                          | Curcumin improved renal ischemia reperfusion injury and antioxidant gene expression in in-vivo model | Kidney complications                          |
|                 |                          | Curcumin protected rats from adriamycin-induced myocardial toxicity and inhibited the development of atherosclerosis in apoE/LDLR-double knockout mice | Cardiac complications                         |
|                 |                          | Curcumin inhibited in-vitro allergen-induced lymphocyte, proliferation and production of IL-2, IL-5, GM-CSF, IL-4 model and also reduced airway constriction | Lung related complications                    |
| Zingiber officinalis Roscoe | Hydroalcohol extract of rhizome showed potent anxiolytic activity in mice models | Mental Problem                                |
|                 |                          | Ethanol extract of rhizome improved renal dysfunction, kidney tissue damage and oxidative damage by increasing serum creatinine, urea level and decreasing the creatinine clearance and reabsorption of urine albumin. It also decreased total antioxidant status and DNA content in cadmium treated rats | Kidney complications                          |
|                 |                          | Pre-treatment with aqueous ethanol extract of rhizome decreased cardiac enzyme troponin, creatine kinase, lactate dehydrogenase, alanine transaminase and aspartate transaminase activity thus improved myocardial injury in isoprotanol treated rats | Cardiac complications                         |
|                 |                          | 6-shogaol isolated from rhizome improved Parkinson’s disease condition in rat mesencephalic cell culture. In-vivo treatment of 6-shogaol inhibited Bradykinin and restored MPTP-induced changes in motor coordination | Parkinsonism                                  |
| Zygophyllaceae  | Tribulus terrestris L.   | Ethanol extract of rhizome showed protective hepatotoxic activity against thioacetamide-treated rat and Hep-G2 cells | Liver related problem                         |
|                 |                          | Methanol extract of the fruit improved muscular strength, catatonia, locomotor functions and also restored the levels of CAT, SOD, GSH, and GPx. It also reduced the mRNA expression and IL-1β, α-synuclein, TNF-α, and AChE production | Parkinsonism                                  |
|                 |                          | Oral administration of the hydroalcohol extract of root improved renal injury in mercuric chloride treated rats and decreased the accumulation of mercury in kidney tissue | Kidney complications                          |
|                 |                          | Whole plant methanol extract exerted potent activity against cardiac ischemia by improving various cardiac biomarker levels like serum creatinine kinase, serum lactate dehydrogenase, serum glutamic oxaloacetic transaminase, serum creatinine kinase, myocardial B fraction, serum glutamic pyruvic transaminase in both in-vitro and in-vivo models | Cardiac complications                         |
|                 |                          | Terrestrosin D isolated from the plant reduced in-vivo inflammatory cell infiltration, macrophages number, neutrophils, lymphocytes and percentage of macrophages in the monocyte-macrophage system. It also reduced the production of TNF-α and pro-inflammatory cytokine IL-6, IL-8, TGF-β1, PDGF-AB | Lung related complications                    |
|                 |                          | Saponins extracted showed significant antidepressant activity and increased the cortisol and corticotropin-releasing factor levels in stress induced rats | Mental Problem                                |
|                 |                          | Hydroethanol extract of the plant showed potent hepatotoxic activity in acetaminophen treated rat | Liver related problem                         |

activity was attributed to the regulation of mRNA transcription and surface expression of AMPA, NMDA and GABA neuroreceptors in the brain. Acorus calamus L. is another plant, which is used as nerve tonic, tranquilizer, sedative etc. by reducing AChE levels and interaction with GABA receptors. It showed antidepressant properties by induction of α1, α2 and 5-HT1A receptors. Flowers of Convolvulus pluricaulis Choisy showed anxiolytic activity and are also used as brain tonic in mental aberration and neurosis. The plant possesses strong antioxidant activity towards brain cells. It also inhibited AChE and 5-LOX, which are involved in neurodegenerative disorders. The seed oil of Curcuma longa showed significant antidepressant-like effects by interaction with dopamine D2 receptors, serotonergic and GABA receptors. It also inhibited MAO-A and caused reduction in plasma corticosterone levels (Joshi and Pandya, 2020).

TCM plants including Lily bulb, Rehmannia, Anemarrhena and Ganma Dazao decoctions were incorporated to treat depression. G. Dazao decoction was used to treat hysteria, whose symptoms were sadness, crying, mood disorders, and abnormal behaviour. It is composed of G. glabra, Triticium aestivum L. and Ziziphus jujuba Mill. According to the TCM theory, this decoction nourishes Yin of heart and calms mind (Ma et al., 2020). G. Dazao decoction combined with Lily bulb and Rhizoma Anemarrhena decoction is also used to treat depression, which effectively reduced the depression symptoms of patients and improved their sleep status. This modified G. Dazao decoction is clinically efficient and safe in the treatment of perimenopausal patients with severe depression, because of the regulation of monoamines and amni-noacid neurotransmitters, regulation of immune inflammation, and also the reduction of the level of inflammatory factors (Li and Gao, 2014). Suansaozen decoction, Huang lien E jiao secction, Zhiqi Chi decoction were also incorporated in the drug treasure trove to treat the anxiety of internal heat and Yin deficiency syndrome. Suansaozen decoction is made from Ziziphus spinosa Hu, liquorice root, R. Anemarrhena, Poria

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cocos (Schw.) and Chuanxiong Rhizoma. Huang lian E jiao decoction is composed of Coptidis Rhizoma, Scutellariae Radix, Paeoniae Radix Alba, Colla Corii Asini and fresh egg yolk. The anti-anxiety properties of the Suanzaoren decoction was related to an increased NO concentration in the blood and the decrease of IL-1β and TNF-α level in serum (Wang and Xie, 2004; Liu, 2018). In another study, the combination of Suanzaoren decoction and Zhizi Chi decoction was significantly improved anxiety-related insomnia (Liu et al., 2014). The anti-anxiety activity of Suanzaoren decoction and Huanglian E jiao decoction was related to elevated γ-GABA levels (Zhao, 2012). Lily bulb, Rehmannia decoction and Guilu Erxian decoction were useful against post-traumatic stress disorder (PTSD; internal heat and Yin deficiency syndrome) by regulating synaptic plasticity, anti-apoptosis, anti-inflammation and reducing fear memory (Li et al., 2020).

Kidney failure

The CDC reported that of the adults hospitalized for COVID-19 with underlying conditions in USA, 74.8% had chronic renal disease, but patients with chronic renal disease consisted of only 3% of the total cases (Abbott, 2020). A recent clinical study with 701 patients from a hospital in Wuhan found that 5.1% of patients admitted for COVID-19 developed acute kidney injury (Cheng et al., 2020). During the infection, the virus circulated in the blood to reach the kidney and caused damage to renal resident cells, which was manifested by proteinuria, hematuria, and elevated levels of blood urea nitrogen, serum creatinine, uric acid as well as D-dimer (Cheng et al., 2020; Henry and Lippi, 2020; Li et al., 2020). The mortality rate of COVID-19 patients with AKI was significantly higher (5.3 times higher in acute kidney injury than 1.5 times in chronic illnesses) (Alberici et al., 2020; Su et al., 2020; Xu et al., 2020). The main binding site for SARS-CoV-2 is the ACE2 protein, which is expressed in the kidney much more than the lungs (Serfozo et al., 2020; Ye et al., 2006). Targeting of ACE2 by SARS-CoV-2 results in angiotensin dysregulation, innate and adaptive immune pathway activation, and hyper-coagulation to result in organ injury and AKI associated with COVID-19. SARS-CoV-2 might cause tubular damage through infiltrating renal parenchyma by an exaggerated and often uncontrolled surge of plasma pro-inflammatory factors (IL2, IL7, IL-10, GSCF, IP-10, MCP-1, MIP1A and TNF-α) known as “cytokine storm” (Wen et al., 2020). Inflammatory cells such as CD68+ macrophages, CD4+ T cells, and CD56+ natural killer cells can be present in tubulointerstitium of affected patients. The hyper-activation of these immune cells may eventually promote fibrosis, induce epithelial cell apoptosis, and cause microvasculature change. Moreover, C5b-9 complex expression and disposition on tubular cells causes renal interstitial damage (Diao et al., 2021; Rodríguez et al., 2018; Saffarzadeh et al., 2012).

Thirty-eight patients with moderate chronic renal failure were treated with 1 g Rheum palmatum L. (Chinese rhubarb) root extract per day, which led to significant decreases in serum BUN and creatinine level (Sanada, 1996). Tincture of lespedea (Lespedeza capitata Michx.) showed beneficial effect in patients with acute and chronic renal failure (Yarnell and Abascal, 2007). The effect may be due to the compound proanthocyanidins present in the plant extract showing angiotensin-converting enzyme (ACE) inhibition effects (Wagner and Elbl, 1992). A study showed that Urtica dioica L. seed might be an effective herbal treatment for renal failure patients, as it lowers the serum creatinine levels and also reduces the symptoms (Treasure, 2003). Roots of Andrographis paniculata (Burm.f.) Nees significantly reduced
blood proteinemia and uremia (Rao, 2006). Rheum officinale Baill. combined with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and and Chinese patented medicine Rheum (CPM-Rheum) might be used to improve the condition of impaired renal function (Yang et al., 2018).

Heart failure

Some patients having problems related to heart even exhibited signs related to mild to severe heart damage in post-COVID infection due to an overactive immune response with abnormal heart rhythms, heart muscle disease and also heart failure in severe cases of myocarditis (Sharma, 2020). A report of the University of Frankfurt in Germany showed that more than 78% patients exhibited cardiac issue and 60% patients, who had COVID-19, exhibited cardiac inflammation (Puntmann et al., 2020). In severe cases, elevated troponin levels in the blood were seen in infected patients. Multi-drug therapy may cause serious cardiovascular complications due to drug-drug interactions. The antiviral drug remdesivir reduced blood pressure and caused unusual heart rhythm (Citroner, 2020; Healthline.com; https://www.healthline.com/health-news/how-covid-19-may-damage-your-heart).

The ACE2 receptor plays an important role in regulating blood vessel dilation and blood pressure. The anti-hypertensive therapy could raise the number of ACE2 receptors expressed on cells, generating more molecular gates for SARS-CoV-2 to enter (Pesheva, 2020). In Ayurveda, Rasayana acts as antioxidant, anti-stress, anti-inflammatory drug and improves the cardiac health of patients (Rastogi et al., 2020). Cucurmin from C. longa blocked cytokine release, specifically IL-1, IL-6, pro-inflammatory cytokines and TNF-α possesses anti-inflammatory activity in COVID-19 patients (Khanna et al., 2021). Naringin, naringenin and hesperidin present in Citrus sp. inhibited the expression of pro-inflammatory cytokines in macrophages, restrained cytokines via inhibiting HMGB1 expression and obstructed binding affinity of the ACE 2 receptor to the coronavirus (Cheng et al., 2020). G. glabra root also exhibited anti-inflammatory properties, which induces interferon production in the body and prevents heart disease. Cannabis sativa L. shows anti-inflammatory actions by modulation of expression of ACE2 and the serine protease TMPRSS2, which is a pre-requisite for SARS-CoV-2 invasion into host cells. Triterpenoids and flavonoids in Glycyrrhizae radix is used as anti-inflammatory and cardioprotective drug. Aconiti lateralis radix praeparata was widely used to treat heart failure in COVID-19 patients (Ang et al., 2020). For cardiovascular and circulatory disorders, Salvia miltiorrhiza Bunge and T. terrestris can be used in infected and recovered patients (Benarba and Pandiella, 2020). Uncaria tomentosa (Willd. ex Schult.) DC. exhibited immunostimulating and cardiovascular protective activity. Uncaria rhynchophylla (Miq.) Miq. ex Havil. possesses anti-inflammatory and antioxidative effects by inhibition of the TLR4/NF-kB/NLRP3 pathway in murine alveolar macrophages (Firenzuoli et al., 2020). P. longum contains phenanthrenes, phenylpropionic acids, diarylheptanoids, piperidines, oxanes showing cardioprotective activity. T. cordifolia is well known for its cardiotonic activity and is used to treat heart diseases (First Report and Recomendation, 2020, ayush.)
Lever injury

Some studies reported higher serum pro-inflammatory cytokine and chemokine levels in infected patients with abnormal liver function (Duan et al., 2003; Feng et al., 2020; Zhang et al., 2020; Li et al., 2020). Hepatic cells can be directly infected due to the ACE2 expression in the liver, bile duct cells and cholangiocytes, which may explain dysregulated liver function in COVID-19 patients (Chai et al., 2020; Hamming et al., 2004). Liver biopsies in infected patients showed a significant increase in mitotic cells and ballooned hepatocytes, causing apoptosis of liver cells (Chau et al., 2004). The SARS-CoV-specific protein 7a affects the liver tissue by inducing apoptosis via a caspase-dependent pathway (Tan et al., 2004).

Besides, application of high-dose antibiotics along with hepatotoxic antiviral drugs and steroids led to liver abnormalities and liver injury in 76% of COVID-19 patients (Ali, 2020), as documented by elevated serum levels of ALT, AST, GGT, and TB (Cai et al., 2020; Guan et al., 2020; Zhang et al., 2020b Zhao et al., 2020). Pre-existing liver disease among COVID-19 patients showing comorbidities such as hypertension (68%) and diabetes (48%) increased the risk of mortality (Singh and Khan, 2020; Zhang et al., 2020a).

T. cordifolia (leaf, stem and root), Momordica charantia L. (fruit), M. arvensis (leaves), Lawsonia inermis L. (leaves), E. officinalis, Eclipta alanswari et al., (L.) Hassk. (leaves), Clitoria ternatea L. (leaves), Cassia angustifolia M. Vahl (leaves), Argemone mexicana L. (leaves), Abrus precatorius L. (seeds) normalized elevated levels of ALT, ALP and bilirubin in vivo (Battua and Kumara, 2009; Beedimani and shetkar, 2015; Bhuvaneswari et al., 2014; Kavitha and Geetha, 2018, 2013; Mohamed et al., 2017; Nithiannantham et al., 2011; Shanmugasundaram et al., 2010; Sourabie et al., 2012; Zahr et al., 2012). The fruits of Solanum xanthocarpum Schrad. & H. Wendl. normalized the serum parameters (SGOT, SGPT, ALP, TB) better than Juniperus communis L. fruit in paracetamol- and azithromycin-induced liver toxicity in rats (Singh et al., 2015).

Lung injury

The heterogeneity of the clinical COVID-19 presentation has prompted the conceptualization of novel paradigms to individualize clinical management of COVID-19 (Gattinoni et al., 2020). The Berlin Criteria define the acute respiratory distress syndrome (ARDS) by acute hypoxaemic respiratory failure following an acute event (such as viral respiratory infection) that presents as bilateral pulmonary infiltrates on lung imaging in the absence of a purely cardiogenic or hydrostatic etiology (Definition Task Force et al., 2012). Nevertheless, a recent cohort study reported that 85% ICU patients with COVID-19 meet the Berlin Criteria definition of ARDS and that is a well-established supportive intervention for ARDS, such as low tidal volumes and prone ventilation, resulted in significant improvement in oxygenation and lung compliance (Ziehr et al., 2020). Mortality attributable to SARS-CoV-2 infection occurs mainly through the development of viral pneumonia-induced ARDS.

The virus could cause lung parenchymal injury resulting in pneumonia barring interstitial lung and/or alveolar inflammation features. Moreover, the virus could directly bind to the ACE-2 receptors facilitating endothelial dysfunction. The deregulated inflammatory response of cells (e.g., polymorphonuclear neutrophils, macrophages, vascular endothelial cells and alveolar epithelial cells) activated the production of pro-inflammatory factors (e.g., TNF-α, IL-1, IL-9 and IL-8), inflammatory mediators (e.g., elastin, cathepsins, collagenases and gelatinases, cytokines, chemokines) and other inflammatory transmitters, which cause damage to the alveolar epithelial cells. The associated cytokine release syndrome could exacerbate both lung parenchymal and microvascular inflammation, promoting refractory forms of ARDS with associated hypercoagulable states and microthrombosis (Klok et al., 2020; Tang et al., 2020; Zhang et al., 2020c). Several signal transduction pathways such as NF-κB, mitogen-activated protein kinase (MAPK), nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing 3 (NLRP3), toll like receptors (TLRs), adrenergic receptors and JAK/STAT signaling pathways are involved in this inflammatory process (Chang et al., 2018; Li et al., 2019; Sun et al., 2018a). Hence, it can be stated that the COVID-19-associated cytokine release syndrome may be the catalyst of two parallel inflammatory pathways: one promoting parenchymal lung injury and another one facilitating thromboembolic phenomena, resulting in a “dual-hit” lung injury (Fraisset al., 2020; Hekimian et al., 2021; Menter et al., 2020). Another cause is lung edema and lung dilatation due excess production of reactive oxygen species (ROS), which cause damage to the cell membrane by unsaturated fatty acids (Fu et al., 2017; Imai et al., 2008).

Several plant-derived phytomolecules were reported to be effective in acute lung infection through modulation of NF-κB, MAPK and Nrf2 signaling pathways owing to their anti-inflammatory and anti-oxidant activities (He et al., 2021).

Discussion

Traditionally used Indian medicinal herbs/herbal preparations are promising candidates for the treatment and management of various illnesses through rejuvenating human wealth (Gomathi et al., 2020; Mukherjee et al., 2017). Ayurveda and Siddha practices are still widely used among the Indian population for maintaining human well-being (Mukherjee et al., 2019). By identifying certain phytocomponents, it is possible to effectively characterize medicinal herbs that could help to alleviate the SARS-CoV-2 viral infection. Hence, by repurposing Indian medicinal plants, more innovative treatment options can be penned down to defeat this viral pandemic and post-COVID related complications (Balachandar et al., 2020). In this review, we systematically summarized and analyzed the pharmacological importance of herbs and herbs-derived secondary metabolites which may be effective against COVID-19 related infections and by the traditional practice recommended by all available guidelines.

Several therapeutic strategies were put forward for the development of treatments against COVID-19 from the pharmacological point of view such as antivirals (e.g., ribavirin, sofosbuvir, lopinavir/ritonavir, remdesivir, favipiravir etc.) (Clercq, 2007) and antiinflammatory drugs (e.g., baricitinib) (Stebbing et al., 2020), and monoclonal antibodies (Zheng and Song, 2020). In China, three patent herbal drugs, Lianhuaqingwen capsules and Jinhuaxinqinggan granules for mild conditions and Xuebijing (injectable) for severe conditions were approved to treat COVID-19 symptoms. These herbal formulations can effectively relieve symptoms, such as fever, cough, and fatigue, and reduce the probability of patients developing severe conditions (A report by National Health Commission of Chinese). Glycyrrhizin from liquorice root is the most frequently used Chinese herb, which inhibited the replication of clinical isolates of the SARS virus (Cinatl et al., 2003). T. cordifolia aqueous extract twice a day for 15 days can be effective against chronic fever, provided by AYUSH, Government of India as therapeutic approach against COVID-19 (Vellingiri et al., 2020). AYUSH also suggested that the extract of Eupatorium perfoliatum L. may be helpful to treat COVID-19-related respiratory symptoms (Vellingiri et al., 2020). After the acute phase of COVID-19, majority of the patients developed persistent and prolonged clinically significant physical and mental adverse outcomes affecting the quality of life. It was observed that such adverse outcomes were not confined; rather it is recognized as a multi-organ disease and increased risk of indolent death (Oronsky et al., 2021). The reviewed data shows that A. paniculata, Cassia tora L., Phyllanthus emblica L., G. glabra, Azadirachta indica A.Juss., Morus alba L., P. longum, Nigella sativa L., Camellia sinensis (L.) Kuntze, U. dioica, C. longa, T. terrestris, Chrysanthemum indicum Thunb., Astragalus propinquus

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Schischkin, S. millorhiza, Salvia officinalis L., C. eylanicum, P. nigrum, Z. officinale, Mucuna pruriens (L.) DC., Psoralea coriylsifolia L., Ecklonia cava, T. cordifolia, Syzygium aromaticum (L.) Merr. & L.M.Perry. W. somnijera were found to have enriched biological benefits due to their varied secondary metabolites. This may provide a more rational phytotherapeutic choice to improve the general well-being effectively by counteracting the biological complications caused by for patients affected with COVID-19.

Conclusion and perspectives

As a matter of fact, the pandemic is far from over. There are more questions than answers about diagnosis, treatments, and, what we need most, effective cures and aftercare. This review may serve as reference in traditional herbal medicine for COVID-19 treatment. The present review compiled pharmacological information of more than 50 herbal medicines, which potentially combat the viral infection and post-COVID complications through different mechanisms. Most information is rather based on some in-vitro and in-silico investigations and anecdotal clinical data. The basic molecular mechanisms are also unexplored yet. It should be noted that there is still no convincing clinical evidence on the activity of most herbal products. Unlike modern medicines, herbs are often claimed to be non-toxic, due to their natural origin and long-term use as traditional medicines. However, numerous difficulties can be occurred due to the adulteration, substitution, contamination, misidentification, intrinsic toxicity, drug-herb interactions and lack of standardization. For that reasons, pre-clinical evaluation of therapeutic effectiveness is a great concern for the further development of safe and standardization. For that reasons, pre-clinical evaluation of therapeutic effectiveness is a great concern for the further development of safe and effective herbal treatments. As the COVID-19 pandemic continues, substantial progress has been made in pathogen monitoring, identifying sources, basic etiology, and clinical treatment. Herbs from traditional system of medicine may be useful in alleviating the disease symptoms but it requires more research works to unravel their therapeutic potential. The integration of traditional medicine into conventional treatment may be an alternative approach for the treatment of COVID-19 in the future. However, the global situation is very serious, and numerous questions remain unanswered. It will take combined efforts of traditional and western medical systems worldwide to ultimately extinguish this pandemic.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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