

# Chapter 11

## Therapeutic Potential of Selected Medicinal Plants for Neurological Disorders after the Infection of COVID-19



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### 11.1 Introduction

World Health Organization statistics indicate that 14% of the global disease burden is caused by neurological disorders, and 85% of global deaths are caused by cerebrovascular diseases. Lower-middle-income countries have a higher death rate (16.8%) than high-income countries (13.2%) ([https://www.who.int/mental\\_health/neurology/neurological\\_disorders\\_report\\_web.pdf](https://www.who.int/mental_health/neurology/neurological_disorders_report_web.pdf)). WHO also stated that COVID-19-related mental health system upheavals are mostly affecting preexisting mental health issues (Lancet 2020). According to a United Nations study, COVID-19 affects more than one in five people mentally and is associated with a number of neurological disorders (Brief 2020). The mechanism behind the evolution of SARS-CoV-2, which causes the severe acute respiratory syndrome, is unclear. Several of the claims are based on research conducted at Wuhan University, and others are based on ecological evidence (Boni et al. 2020; Xiao et al. 2020; Lam et al. 2020; Latinne et al. 2020). Several neurological disorders have been reported in patients infected with the SARS-CoV-2 virus, including heart, liver, and brain infections (Karuppan et al. 2021). Blood clotting and cytokine storms in the peripheral and

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central nervous systems are responsible for a number of these neurological disorders (Fotuhi et al. 2020). SARS-CoV-2 may cause neuroinvasive respiratory disease in COVID-19 patients who exhibit respiratory failure (Sellner et al. 2020). In the nasal mucosa, lamina cribrosa, and olfactory bulb, as well as retrogressive axonal movement, ACE-2 receptors enable SARS-CoV-2 entry into the central nervous system (Hartung and Aktas 2020). The high levels of angiotensin II observed in COVID-19-infected patients are associated with several disorders, including vasoconstriction, kidney failure, heart disease, apoptosis, and oxidative stress, all of which accelerate aging and lead to cognitive decline (Vidrio et al. 2022; Elrayess et al. 2022; Amezcua-Guerra et al. 2022). There are a number of biomarkers associated with COVID-19, including interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-7 (IL-7), granulocyte colony-stimulating factor (GCSF), and tumor necrosis factor-alpha (TNF-alpha) (Azizi Jalilian et al. 2022; Chaumont et al. 2020). The exact mechanisms responsible for coronavirus entry into the nervous system are unknown (Susilawathi et al. 2021).

Several patients have reported blood clots in their brains and multiple organs as a result of COVID-19 infection. This protocol does not specifically treat neurological disorders associated with COVID-19 infection (Tang et al. 2021). In this study, herbs were examined for their potential to aid the early recovery of COVID-19 patients from neurological disorders. The discovery of new drugs for infectious diseases, such as cancer, kidney and heart disease, and neurological disorders, can be attributed to nature and its derivatives. Plant derivatives are thought to contribute to early recovery. It is critical to identify potential drugs from traditional medicines without harming nature's database. Scientists must rethink and rearrange nature's database compassionately. More than 50 million people are suffering from dementia, a neurological disease associated with aging (<https://www.alz.co.uk/research/WorldAlzheimerReport2019.pdf>). In addition to ensuring that the elderly and corona warriors maintain social distance, it is also critical to provide mental health and psychosocial support (Wang et al. 2020). According to COVID-19 data in Wuhan, fatigue (63%), sleep disorder (26%), and anxiety/depression (13%) were the most commonly reported disorders (Nalbandian et al. 2021).

## 11.2 Methodology

In this study, we reviewed the available literature related to the clinical and neuropathological findings of COVID-19 patients. This study examined specific herbs associated with neurological complications observed in patients with SARS-CoV-2 infection and afterward. PubMed, MEDLINE, Scopus, EMBASE, Google Scholar, EBSCO, Web of Science, Cochrane Library, WHO database, and [ClinicalTrials.gov](https://www.clinicaltrials.gov) were searched for the neuroprotective potential of herbs for post-COVID-19 patients. For Boolean search, the terms are herbs and neuroprotective potential, post-COVID-19 symptoms, etc. Assessing the pathobiological mechanisms

involved in neurological complications associated with COVID-19 using biomarkers that indicate an immune response to SARS-CoV-2.

### 11.3 Discussion

Studies have been done on COVID-19 and post-COVID-infected patients (Leach et al. 2021). Unfortunately, there is no scientific evidence proving the effectiveness of herbs in treating neurological disorders in COVID-19 patients. However, there are widely recognized literature about the use of herbal drugs in many neurodegenerative disorders and cerebrovascular accidents (Ding and He 1986; Akhondzadeh 2007; Wu et al. 2010; Makkar et al. 2020). The most common drug for treating Parkinson's disease is Leva-dopa, which is found in the seeds of the *Mucuna pruriens* plant (Katzenschlager et al. 2004). It is expected that the findings of this study will have a significant impact on the management of COVID-19 patients and post-COVID patients. Some neurological disorders like migraine headaches, loss of smell, etc., might be cured by the use of herbal remedies (Sen 2020).

#### 11.3.1 Neurological Disturbances in COVID-19 Patients

The majority of people with COVID-19 infections experience neurological symptoms such as muscle pain, headaches, confusion, dizziness, and loss of taste and smell (Koralnik and Tyler 2020; Acharya et al. 2020; Liguori et al. 2020). In a study of 236,379 patients with COVID-19 disease, 14 neurological and psychiatric disorders were observed in six months, including intracranial hemorrhage (0.56%), ischemic stroke (2.10%), parkinsonism (0.11%), Guillain-Barré syndrome (0.08%), nerve, nerve root, and plexus disorders (2.85%), myoneural junction and muscle disease (0.45%), encephalitis (0.10%), dementia (0.67%), mood disorder (13.66%), anxiety disorder (17.39%), psychotic disorders (1.40%), substance use disorder (6.58%), and insomnia (5.42%) (Taquet et al. 2021). The neurological symptoms of patients who have a higher risk of neurological disorders due to COVID-19 are described in Table 11.1 and Fig. 11.1.

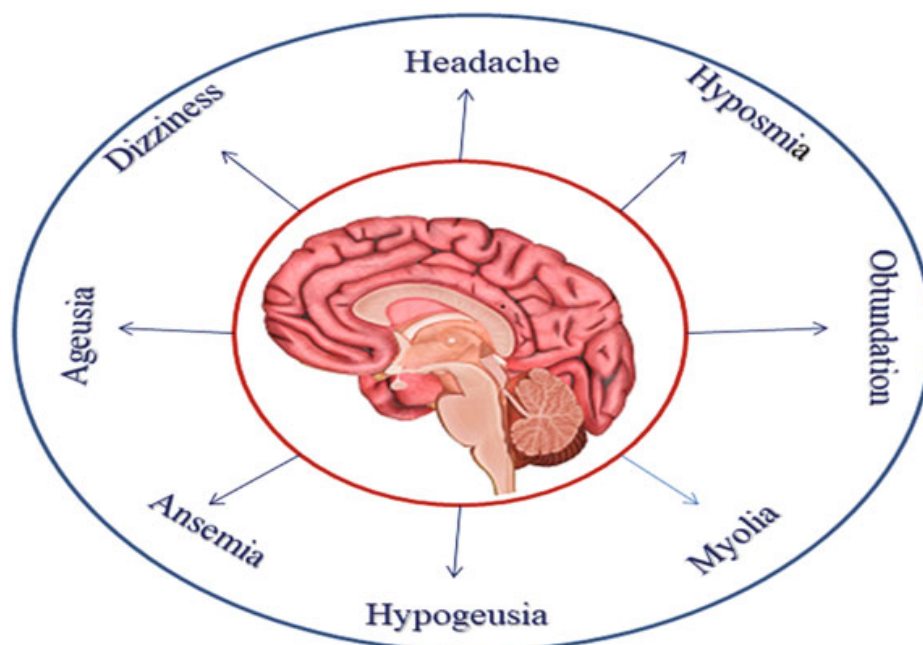
### 11.4 Immune Response and Brain

An inherent immune response exists in the central nervous system (CNS). A CNS response to infection or disease involves an innate immune reaction. Several types of injuries to the CNS system are observed, including acute injuries (mechanical trauma, strokes, etc.), chronic neurodegenerative diseases (multiple sclerosis, Alzheimer's, etc.), brain tumors (gliomas), and infections (HIV, E. coli, etc.)

**Table 11.1** Neurological patients at higher risk due to COVID-19

S. No.	Name of disease	COVID-19 effects	Reference
1	Alzheimer's disease and related dementias (ADRD)	Mental hygiene, trauma, and stigma	Brown et al. (2020)
2	Parkinson's disease (PD)	Mitochondrial dysfunction, proteostasis, lipid metabolism, and stress responses	Gonzalez-Latapi et al. (2021)
3	Motor neuron disease (pwmND)	Proximal muscle weakness of acute or subacute onset and high creatine kinase levels	Barp et al. (2021)
4	CNS disorder with reduced mobility or immobility	Movement disorders, frontal syndrome, brainstem impairment	Lambrecq et al. (2021)
5	Neuromuscular disorder with reduced mobility and compromised respiratory function	Exacerbation, ventilatory muscle weakness, or cardiomyopathy	Tseng and Chen (2021)
6	Autoimmune condition (a) Multiple sclerosis (b) Neuromyelitis optica spectrum disorder (c) Myasthenia gravis (d) Guillain-Barre syndrome (e) Chronic dysimmune neuropathies	(a) Comorbidities, obesity, and black/African ancestry (b) Vomiting and hiccoughs (area postrema syndrome) (c) Diaphragmatic task failure (d) Presence of <i>Campylobacter jejuni</i> (e) –	Reder et al. (2021), Ghosh et al. (2021), Galassi and Marchioni (2021), Vogrig et al. (2021), Younger (2021)

(Lampron et al. 2013). During the course of SARS-CoV-2 infection, the endothelium is able to detect circulating IFN type 1 signaling and thus limit the entry of SARS-CoV-2 into the central nervous system (Iadecola et al. 2020). In terms of stress and neurological disorders, nuclear factor erythroid 2-related factor 2 (Nrf2) is a dominant biomarker (Johnson and Johnson 2015). Study results suggest that deregulation of the NF- $\kappa$ B pathway may modulate T cell activation, which may lead to autoimmune and inflammatory responses. It is the activation of CD4<sup>+</sup> T-helper cells that is the main feature of inflammation (Guisado-Vasco et al. 2020). In pathogenic diseases, immune response promotes the development of macrophages, dendritic cells, and proinflammatory cytokines (IL-1, IL-6, IL-12, and tumor necrosis factor- $\alpha$ ) (Zhang et al. 2017a). Parkinson's disease (PD) is related to immune responses in the central nervous system (Su and Federoff 2014). The presence of CD4<sup>+</sup> and CD8<sup>+</sup> T cells is a strong immune response biomarker associated with PD. Researchers have observed that regulatory T cells (Tregs) in PD patients are less effective in suppressing effectors T cells (Saunders et al. 2012).



**Fig. 11.1** Neurological symptoms in COVID-19 patients

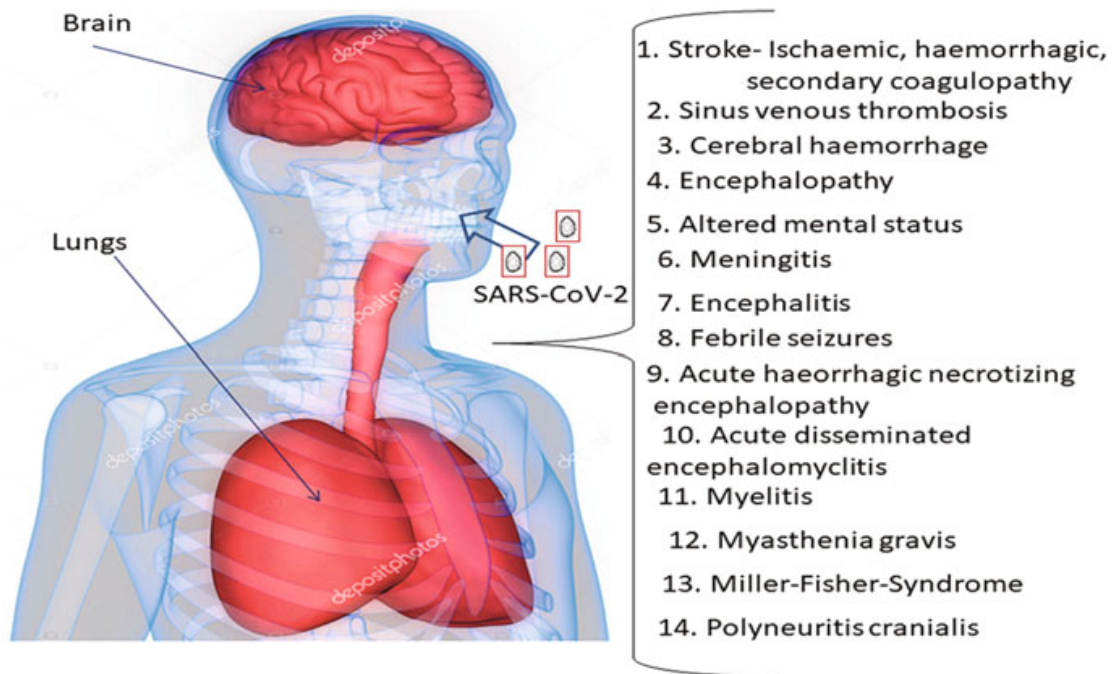
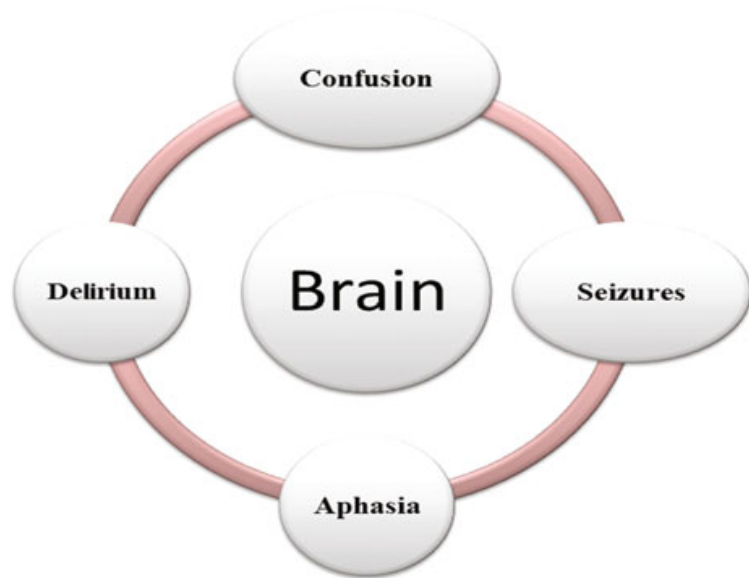
Amyloid- $\beta$  directly activates microglia in Alzheimer's disease (AD) through the NALP3 inflammasome pathway and production of IL-1 $\beta$ . In Alzheimer's disease, amyloid- $\beta$  directly activates microglia through the NALP3 inflammasome pathway and production of IL-1 $\beta$ . This may intensify neurodegeneration (Fuhrmann et al. 2010; Masters and O'Neill 2011). Pathologic inflammation in the CNS is integral to diseases like multiple sclerosis (MS), AD, PD, stroke, and traumatic brain injury (Ransohoff and Brown 2012).

#### ***11.4.1 Evidence of Clinical Trials for Neurological Disorders in COVID-19 Patients***

The clinical trial of patients with neurological symptoms concluded that altered mental status (42%), headache (42%), central (21%), and peripheral weakness (32%). For mild to critical COVID-19 patients, increases in NfL protein, total tau, and GFAP levels were observed in 63%, 37%, and 16% of patients, respectively (Virhammar et al. 2021). A study that examined the neurological manifestations of 901 patients found encephalopathy, Guillain-Barré syndrome, and stroke to be the most prevalent disorders among COVID-19 patients (Ellul et al. 2020). Figures 11.2 and 11.3 show the effects of cytokine storms on the brain and neurological disorders associated with COVID-19.

A study found some COVID-19 neurological patients exhibit SARS-CoV-2 in the central nervous system, while others do not (Mitra et al. 2022). The eight drugs (hydroxychloroquine, baricitinib, ruxolitinib, remdesivir, tocilizumab, lopinavir/

**Fig. 11.2** Cytokine storm effects on the brain



**Fig. 11.3** Neurological disorders reported occurring with COVID-19

ritonavir, favipiravir, and azithromycin) were tested for penetrating capacity in a well-tolerated brain, and hydroxychloroquine and baricitinib were found to be most likely to penetrate the brain (Richardson et al. 2020). COVID-19-infected patients' MRI studies confirm abnormalities in the cerebral parenchyma (Nuzzo et al. 2021).

### 11.4.2 Herbs for Neurological Disorders

Traditionally, *Bacopa monnieri* Linn. is used as a biomedicine for treating neurological disorders and psychiatric disorders (Russo and Borrelli 2005). No clinical studies have been conducted on the effects of *Bacopa monnieri* on the improvement of memory in healthy adults and older adults with age-related memory problems. *Bacopa monnieri* and its bioactive components have shown neuroprotective properties in reducing ROS, neuroinflammation, aggregation, inhibiting amyloid- $\beta$  and improving cognitive abilities (Dubey and Chinnathambi 2019; Abdul Manap et al. 2019). The treatment of Alzheimer's disease has been reported in a few studies, but no studies have examined *Bacopa monnieri* alone in patients with depression (Brimson et al. 2021). Scientists have supported *Mucuna pruriens* as a treatment for PD, but the most common Parkinson's drug is Leva-dopa, which is abundant in *Mucuna pruriens* (Fothergill-Misbah et al. 2020; Cassani et al. 2016; Cilia et al. 2018; Khazdair et al. 2021). *Mucuna pruriens* treated Parkinson's patients show positive effects (<https://clinicaltrials.gov/ct2/show/NCT02680977>).

*Withania somnifera* is a neuroprotective herb. Withanone extracted from *Withania somnifera* inhibits amyloid  $\beta$ -42 and modulates proinflammatory cytokines (Pandey et al. 2018; Dar et al. 2017; Kuboyama et al. 2014; Lopresti and Smith 2021). The main phytochemicals in *Withania somnifera* are sitoindoside VII–X, withaferin A, withanosides IV, withanols, withanolide A, withanolide B, anaferine, beta-sitosterol, and withanolide D. These compounds are effective in treating anxiety disorders, Alzheimer's, Parkinson's, schizophrenia, Huntington's disease, dyslexia, depression, autism, addiction, amyotrophic lateral sclerosis, attention deficit hyperactivity disorder, and bipolar disorders (Zahiruddin et al. 2020). Table 11.2 shows the herbs commonly used in neurological disorders with their biomarkers for immune response to diseases.

A recent survey shows that 61.9% of herbal treatments and 25.3% of herbal-drug combinations are used by COVID-19 patients with mental illness or psychiatric issues (Alonso-Castro et al. 2021). Study outcomes have not been published for herbal treatments for neurological disorders in COVID-19 patients. An ongoing clinical trial on "Functional Assessment of Ashwagandha Root Extract during Weight Loss" evaluates the effect of Ashwagandha root extract capsule on nervous system disease (ClinicalTrials.gov identifier, NCT03112824) (<https://www.clinicaltrials.gov/ct2/show/NCT03112824>). Nuclear factor erythroid 2-related factor 2 (Nrf2) is a dominant biomarker for stress and associated neurological disorders. The combination of drugs (carnosol, withaferin A, and luteolin), rosemary, ashwagandha, and sophora japonica is undergoing a clinical trial (<https://clinicaltrials.gov/ct2/show/NCT04638387>). The study reported neuroprotective effects of ethanolic extract of *Acorus calamus* (Shukla et al. 2002). In Ayurveda, roots and rhizomes of the plant are used for the treatment of epilepsy, neurosis, insomnia, and other diseases (Vohora et al. 1990; Martis et al. 1991). An *Acorus calamus* leaf extract modulates the characteristics of interleukin-8 (IL-8), (IL-6), RNA protein level, and interferon regulatory factor 3 (IRF3), as well as nuclear

**Table 11.2** Herbs used in neurological disorder and their biomarker for the immune response against diseases

S. No.	Herbs	Important phytochemicals	Biomarkers related to immune response	Neurological effects
1	<i>Acorus calamus</i> (Bach)	Galloylquinic acid, Bacopaside III and Bacopaside, $\alpha$ -asarone and $\beta$ -asarone (trans and cis forms, respectively, of 2,4,5-trimethoxy 1- propenyl benzene) acorenone, iso-acorone, (Z)- sesquilavandulol and dehydroxy isocalamendiol acofuran, a sesquiterpenoid, coumarine, saponin, asamyl alcohol, methyl eugenol, calamenol, $\alpha$ - pinene, acorine, acoretine, lucenin, acoradin (Yende et al. 2008)	Nitric oxide, interleukin-2 (IL-2), and tumor necrosis factor- $\alpha$ (TNF- $\alpha$ ) (Mehrotra et al. 2003)	CNS depressant, anticonvulsant, anti-spasmodic, hypolipidemic, immunosuppressive, anti-inflammatory, cryoprotective, and antioxidant (Rajput et al. 2014)
2	<i>Asparagus racemosus</i> (Shatavari)	Shatavarins, sarsapogenin, quercetin, rutin (quercetin 3-O-rutinoside) and hyperoside (quercetin 3-O-galactoside), quercetin 3-glucuronide, ferulic, caffeic, and chlorogenic acids (Srivastava et al. 2018)	Significant increase of CD <sup>3+</sup> and CD <sup>4+</sup> /CD <sup>8+</sup> , percentages effect on T cell activation. Significant upregulation of Th1 (IL-2, IFN-g) and Th2 (IL-4) cytokines suggesting its mixed Th1/Th2 adjuvant activity (Gautam et al. 2009)	Antidepressant activity (Meena et al. 2011)
3	<i>Bacopa monnieri</i> (Brahmi)	Damarane-type triterpenoid saponins with jujubogenin and pseudojujubogenin as the aglycones including bacosides A1-A3, bacopa saponins A-G and bacopasides I-V (Shahid et al. 2017)	TNF- $\alpha$ and IL-6 from activated N9 microglial cells, caspase 1 and 3, matrix metalloproteinase-3 (Nemetchek et al. 2017)	Alzheimer's and Spinocerebellar ataxia (SCA) (Jeyasri et al. 2020)
4	<i>Blumea balsamifera</i> (Ngai camphor)	l-borneol, 10-epi- $\gamma$ -eudesmol, $\gamma$ -eudesmol, $\beta$ -eudesmol, $\alpha$ -eudesmol, limonene, l-camphor, palmitic acid, and d-camphor (Pang et al. 2014)	LPS-induced RAW264.7 cells by decreasing activity of TLR4-NF- $\kappa$ B signaling pathway and inhibiting NLRP3 inflammasome activation (Liao et al. 2021)	Improve drugs delivery to the blood-brain barrier in the central nervous system (Zhang et al. 2017b)

5	<i>Cannabis</i> (Bhang)	$\Delta^9$ -tetrahydrocannabinol, $\Delta^8$ -tetrahydrocannabinol, cannabidiol, and cannabidiol (Ashton 2001)	IFN- $\gamma$ producing CD8+ T cells, glyco-gen synthase kinase 3 $\beta$ (GSK-3 $\beta$ ) hyperphosphorylation caused by A $\beta$ (Nichols et al. 2021; Li et al. 2020)	Epilepsy and Alzheimer's disease (Hosami et al. 2021)
6	<i>Centella asiatica</i> (Mandookparmi or Gotu kola)	triterpenoid saponins, asiaticoside, asiatic acid, madecassic acid, aglycones, saponins-asiaticoside B, brahminoside, centelloside, indcentelloside, thankuni side, isothankuniside, brahamic acid, betulic acid and alkaloid hydrocotyline, madecassic acid, glucose, rhamnose, sitosterol, Stigmasterol (Samy and Chow 2011)	Reduces amyloid- $\beta$ pathology and activates NRF2-regulated antioxidant response pathway (Zweig et al. 2021)	Memory enhancement, Alzheimer's (Boondam et al. 2019)
7	<i>Convolvulus prostratus</i> (Shankha pushpi)	Microphylllic acid, kaempferol, kaempferol-3-glucoside, 3,4-dihydroxycinnamic acid, scopoletin, convolamine, convolidine, sitosterols, 2-butanone, pentanoic acid, cinnamic acid, silane, decanoic acid, 2-pentanol, ascorbic acid, 10-bromodecanoic acid, tridecane, phthalic acid, eicosane, octatriacontyl pentafluoropropionate, 1-octadecene sulphonyl chloride, squa-lene, pyrimidine, heneicosane, 1,2-benzenedicarboxylic acid, cyclononasiloxane, octadecamethyl, nonacosane, sulfurous acid pentadecyl 2-propyl ester, straight chain hydrocarbons (C22–C33), fatty acids (C14–C28), fatty alcohols (C24–C32), vitamin E, and cyclononasiloxane (Salehi et al. 2020)	Regulate the neuronal factor and proteins by inhibiting acetyl-cholinesterase and regulate the neuronal cascades, cytokine- IL-6, MCP-1, ICAM-1 (Balkrishna et al. 2020)	Enhance memory or as a brain and nerve tonic, Alzheimer's disease (Semwal et al. 2021)

(continued)

Table 11.2 (continued)

S. No.	Herbs	Important phytochemicals	Biomarkers related to immune response	Neurological effects
8	<i>Curcuma longa</i> (Turmeric)	Demethoxycurcumin (2, DMC), bisdemethoxycurcumin (3, BDMC) and cyclocurcumin (4, CYC), tetrahydrocurcumin (5, THC) (Randino et al. 2016)	PI3K/Akt, NF- $\kappa$ B, TNF- $\alpha$ , modulating tau oligomers (Mathew and Hsu 2018; Panaro et al. 2020)	Alzheimer agents (Cascio et al. 2019)
9	<i>Mucuna pruriens</i> (Velvet beans)	1-3,4-dihydroxyphenylalanine, pentadecanoic acid, 14-methyl-, methyl ester, dodecanoic acid, 9, 12-octadecadienoic acid (Z, Z)-methyl ester, 9,12-octadecadienoic acid, and 2-myristynoyl-glycinamide (Saikarthik et al. 2017; Lampariello et al. 2012)	(TNF- $\alpha$ ), (IL-1 $\beta$ ), IL-6, and enzymes such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and cyclooxygenase-2 (COX-2) (Rai et al. 2017)	Parkinson's disease (Cilia et al. 2017)
10	<i>Nyctanthes-arbor tristic</i> Linn. (Har Singar or Parijat)	4-hydroxy hexahydro benzofuran-7-one, 6 $\beta$ -hydroxyloganin, and arboortristoside, diterpenoids, nycanthin, nycanthoside, rengyolone, astragalin, flavonoids, anthocyanins, d-mannitol, essential oils, glycosides, carotenoids (Parekh and Soni 2020; Bharshiv et al. 2016)	Splenocytes proliferation and increased production of cytokines, especially IL-2 and IL-6 (Bharshiv et al. 2016)	Anti-epileptic and anxiolytic (Srikalyani and Ilango 2009)
11	<i>Ocimum tenuiflorum</i> (Tulsi)	Oleanolic acid, ursolic acid, rosmarinic acid, eugenol, carvacrol, linalool, B-caryophyllene (Singh and Chaudhuri 2018)	Increased Natural Killer (NK) and T-helper cells (Jamshidi and Cohen 2017)	Anti-stress, loss of memory, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD). Oxidative stress and mitochondrial dysfunction (Singh and Chaudhuri 2018; Jamshidi and Cohen 2017)

12	<i>Phyllanthus emblica</i> (Ambla)	Ascorbic acid (vitamin C), gallic acids, amlaia acid, arginine, aspartic acid, astragallic acid, $\beta$ -carotene, $\beta$ -sitosterol, chebulagic acid, chebulic acid, chebulaginic acid, chebulinic acid, corilagic acid, corilagin, cysteine, ellagic acid, emblicol, gibberellins, glutamic acid, glycine, histidine, isoleucine, kaempferol, leucodelphinidin, methionine, phenylalanine, phyllanthidine, phyllemblic acid, quercetin, riboflavin, rutin, thiamin, threonine, tryptophan, tyrosine, valine, zeatin (Habib-ur-Rehman et al. 2007)	Epithelial barriers, phagocytes (neutrophils, macrophages), B- and T-lymphocytes, modulate cytokine production, decrease histamine levels, reduced proinflammatory cytokine, (TNF- $\alpha$ ) and (IL-1 $\beta$ ) levels, and appreciably upregulate the anti-inflammatory cytokine (IL-10) concentration (Chatterjee et al. 2010)	Memory deficit, Alzheimer's disease (Ashwlayan and Singh 2011; Biswas et al. 2015)
13	<i>Swertia chirata</i> (Chirayita)	Secoiridoid bitters, triterpenoids, xanthones, and alkaloids. Swertiamarin, gentiopicroside, amarogentin, and amaroswerin, amarogentin (Karan et al. 1999)	Inflammatory mediators by blocking the expression of COX-2 and phosphorylation of Akt, IKK- $\beta$ , MAPK, and NF- $\kappa$ B, activation in LPS-stimulated macrophages (Hu et al. 2019)	Antidepressant properties, CNS stimulant, Parkinson's disease (Shikha et al. 2010)
14	<i>Vitex negundo</i> (Nirgundi)	Benzoic acid 3-hydroxy, Ledol, 9,12,15-octadecatrienoic acid, and Vitamin E, 4HPyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl caryophyllene, and n-hexadecanoic acid (Kumar et al. 2010)	Suppressed expressions of inflammatory Th1/Th2 cytokines, chemokines, endopeptidases (MMPs), oxidative effector enzyme (iNOS), adhesion molecules, IL-4/IFN- $\gamma$ release with simultaneous enhancement in levels of IL-10, IFN- $\gamma$ , MUC3, and enhanced phosphorylation of NF- $\kappa$ B, PI3K, Akt and p38MAPKs and downregulated AMPK (Tirpude et al. 2021)	Anti-stress (Tirpude et al. 2021)

(continued)

Table 11.2 (continued)

S. No.	Herbs	Important phytochemicals	Biomarkers related to immune response	Neurological effects
15	<i>Withania somnifera</i> (Ashwagandha)	Withanolides, withaferin A, alkaloids, steroidal lactones, tropine, cuscohygrine, rutin, hyperoside, quercitrin, myricetin, quercetin, kaempferol, rhamnetin, gallic acid, caffeic acid, chlorogenic acid, ferulic acid, p-coumaric acid, p-hydroxybenzoic acids, caffeine, theobromine, theophylline, harmine, harmaline, yohimbine, berberine, noscapine, and papaverine (Tripathi et al. 2020; Tiwari et al. 2015)	TNF- $\alpha$ -induced increases in CCL5 while attenuating the increase in CCL2 expression and NF- $\kappa$ B activation increase in dendrite growth markers, KLK8, and MAP2 (Grunz-Borgmann et al. 2015; Konar et al. 2019)	Alzheimer's disease (Konar et al. 2019)

factor  $\kappa$ B (NF- $\kappa$ B) activation (Kim et al. 2009; Sharma et al. 2020). Vitamin E and C intake are inversely associated with the risk of PD (Hantikainen et al. 2021). *Phyllanthus emblica* is an excellent source of vitamin C. Research indicates that *Phyllanthus emblica* reduces kainic acid-induced elevations of TNF- $\alpha$  in the brain, improving cognitive function levels in the brain and improving the cognitive deficit (Gaire and Subedi 2014). In neurodegenerative disorders, *Phyllanthus emblica* has proved to be beneficial due to its antioxidant, cholesterol-lowering, and anti-inflammatory properties (Husain et al. 2019; Uddin et al. 2016).

Borneol is a natural compound found in *Blumea balsamifera* that acts as blood–brain barrier permeability in the central nervous system. Borneol is an effective agent that can improve drug delivery to the brain: neurological function scores (NFS) and the cerebral infarction area (Kulkarni et al. 2021; Chen et al. 2019). Thus, *Blumea balsamifera* has the potential to provide neuroprotection for a variety of neurological disorders.

*Asparagus racemosus* ethanolic extract has been shown to enhance brain-derived neurotrophic factor (BDNF), as well as estrogen receptors (ERs) (Lalert et al. 2018). In molecular docking study involving *Asparagus racemosus* (Wild.), SARS-CoV-2, the NSP15 Endoribonuclease and Spike Receptor-binding domain was identified. In terms of their effectiveness against the spike receptor-binding domain and NSP15 endoribonuclease, asparoside-C, asparoside-D, and asparoside-F are the most effective (Chikhale et al. 2020). *Asparagus racemosus* phytochemicals exhibit adaptogenic, neuroprotective, antioxidant, anti-inflammatory, and nootropic properties without causing side effects. It may be a possible treatment for neurological disorders such as stress, anxiety, depression, and epilepsy (Majumdar et al. 2021).

*Cannabis sativa L* is a medicinal herb used in treating a variety of diseases and neurological disorders (Mechoulam 2019). The main neuroprotective ingredients found in cannabis are  $\Delta$ 9-tetrahydrocannabinol (THC) and cannabidiol (CBD). The neuroprotective properties of cannabinoids have led to them being referred to as the “Aspirin of the 21st century” (Baker et al. 2003). A hypothesis study on cannabidiol against SARS-CoV-2 proposed that it exerts immunomodulatory and anti-inflammatory effects, as well as decreasing uncontrolled cytokine production responsible for acute lung injury (Esposito et al. 2020). Cannabidiol has been suggested as a support drug against the COVID-19 pandemic with precaution (Paland et al. 2021; Anil et al. 2021).

*Convolvulus prostratus* is commonly known for its neuro-modulating properties. A number of phytochemicals from *Convolvulus prostratus*, including 4'-methoxy kaempferol, 7-methoxy quercetin, convolamine, scopoletin, and hydroxy-cinnamic acid, are responsible for neuroprotective effects in the brain (Alshoushan et al. 2021). An extract of *Convolvulus prostratus* modulates IL-1b, IL-6, TNF-a, alanine transaminase, and aspartate transaminase. Ayurveda shows that *Convolvulus prostratus* improves anxiety, irritability, inability to relax, lack of concentration, disturbed sleep, loss of memory, palpitations, headaches, dry mouth, upset stomach, and restlessness (Belwal et al. 2020).

*Swertia chirata* has traditionally been used in India to boost appetite and as a febrifuge (Liu et al. 2017). The herb's methanol extract is reported to have anti-

diabetic activity because it contains mangiferin, amarogentin, amaroswerin, sweroside, and swertiamarin as active constituents (Suryawanshi et al. 2009). Chirata sweat is known to be effective in the treatment of hepatitis, liver disorders, inflammation, chronic fever, malaria, anemia, GIT disorders, hypertension, mental disorders, and diabetes (Kumar and Van Staden 2016). The therapeutic potential of bellidifolin from *Swertia chirayita* has been explored for the treatment of inflammatory-mediated immune deficiency (Hu et al. 2019).

Traditional Indian medicine uses *Vitex negundo* Linn., for treating respiratory and inflammatory disorders. Vitegnoside extracted from *Vitex negundo* inhibited p38 MAPK/MK2, JNK/c-Jun, and downstream NF- $\kappa$ B inflammatory transduction. In a study on the effect of vitegnoside from *Vitex negundo* on Alzheimer's disease, it was found that vitegnoside promoted neuroprotection by enhancing cell viability, maintaining cytomembrane integrity, and maintaining nuclear homogeneity (Wang et al. 2019).

Physiochemical analyses have demonstrated that crude extracts from *Nyctanthes arbor-tristis* have potential anti-inflammatory, anti-malarial, anti-viral, and immunostimulatory properties (Agrawal and Pal 2013). Researchers note that aqueous leaf extracts from *Nyctanthes arbor-tristis* are the most potent immunomodulators (Bhatia and Kaur 2001).

The herb *Centella asiatica* is well-known for its use in treating mental disorders in India and China. It is believed that triterpene derivatives like asiatic acid, madecassic acid, asiaticoside, madecassoside, and Brahmic acid provide positive effects on the aging brain (Samy and Chow 2011; Orhan 2012). Ethanol extracts have been found to increase neural development (nerve growth factor (NGF) in human SH-SY5Y cell lines) (Soumyanath et al. 2005). This herb was traditionally used in memory enhancers and for treating Alzheimer's disease (Orhan et al. 2013).

*Curcuma longa* has been studied for its antidepressant properties. *Curcuma longa* contains curcumin, which has been found to be effective against neurological disorders such as Alzheimer's and multiple sclerosis (Witkin and Li 2013; Witkin et al. 2013). There is evidence that curcumin can effectively treat fearful or traumatic memories when used alone or in combination with existing medications (Monsey et al. 2015). The curcumin compound interacts directly and indirectly with various transcription factors such as nuclear factor kappa B (NF- $\kappa$ B), activator protein 1 (AP-1),  $\beta$ -catenin, and signal transducer and activator of transcription (STAT) proteins (Witkin et al. 2013; Liu et al. 2014; Shishodia et al. 2007). Additionally, it can act as a partial agonist of peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ), a ligand-activated transcription factor involved in neurological disorders and anti-inflammatory signaling pathways. The nuclear receptor PPAR- $\gamma$  affects metabolism, reproduction, and immune response (Bernardo et al. 2021). In addition to curcumin, other compounds in turmeric include digalloyl-hexoside, caffeic acid, hexoside, curdione, coumaric acid, caffeic acid, sinapic acid, quercetin-3-D-galactoside, casuarinin, bisdemethoxycurcumin, curcuminol, demethoxycurcumin, isorhamnetin, valoneic acid, and curcumin. Their therapeutic value varies according to the disease (Sabir et al. 2021; Maithili KarpagaSelvi et al. 2020). Furthermore, there is scientific evidence that curcumin may have a bioactive role against SARS-

CoV-2 infection as well (Babaei et al. 2020; Zahedipour et al. 2020; Rattis et al. 2021).

*Ocimum tenuiflorum* is a traditional herb used to prevent and treat the common cold, cough, headache, fever, influenza, sore throat, bronchitis, malarial fever, and migraine headaches (Joshi et al. 2017; Iqbal Chowdhury et al. 2020). *Ocimum tenuiflorum* oil contains 50.4% eugenol, ursolic acid, caryophyllene, linalool, and 1,8-cineole (Bhavya et al. 2018). Ocimumoside A and B are used for treating neurological disorders (Singh and Chaudhuri 2018). There is strong evidence that the daily administration of 10 g of an aqueous extract of fresh tulsi leaves for 2 weeks results in symptomatic improvement in patients with acute hepatitis viral infection (Jamshidi and Cohen 2017).

## 11.5 Conclusions

During the COVID-19 pandemic, the demand for medicinal plants was found to increase significantly. Among them, herbs such as *Curcuma longa*, *Ocimum tenuiflorum*, and *Withania somnifera* are gaining popularity as immune boosters against COVID-19 infection. Theoretically, SARS-CoV-2 causes inflammation in the body, which is controlled primarily by adaptive immune responses. The SARS-CoV-2 enters the cell through the ACE-2 receptor and is recognized by the toll-like receptor 7 (TLR-R) present in the endosome (Poulas et al. 2020). As a result, alpha interferon, TNF-alpha, as well as IL-12 and IL-6, are produced, and CD8<sup>+</sup> cytotoxic T cells are formed, and through CD4<sup>+</sup> helper T cells, antigen-specific B cells and antibodies are produced (Ahmadpoor and Rostaing 2020). Antibodies against unknown or known pathogens are produced by B cell receptors (BCRs), which recognize the pathogenic attack, counter-invading pathogens, and provide long-term protection against them (Nielsen and Boyd 2018). The immune system serves as the body's complete defense against pathogens. It is now clear that inborn medicinal herbs promote the immune system through various pathways against infection and inflammation. Many studies support the study objective, but there are still some gaps. Medicinal plants have the potential to treat neurological disorders at an affordable price in COVID-19 or post-COVID-19 patients. It is essential for a clear understanding of comprehensibility to conduct clinical trials on herbs and their secondary metabolisms, as well as their effects on various neurological disorders. Biomarkers, neuroradiological findings, and pathobiological mechanisms need to be re-examined to find the most suitable drugs. The interaction between humans and herbs, and the mechanism of action, should also be re-examined. The therapeutic potential of herbs for neurological disorders requires further mechanistic studies using modern scientific techniques and approaches. It is imperative to conduct further animal studies and clinical trials to explore how these herbs may help alleviate neurological disorders in COVID-19 patients.

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