Neurological disorders of COVID-19: insights to applications of natural products from plants and microorganisms

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Abstract In addition to the typical respiratory manifestations, various disorders including involvement of the nerve system have been detected in COVID-19 ranging from 22 to 36%. Although growing records are focusing on neurological aspects of COVID-19, the pathophysiological mechanisms and related therapeutic methods remain obscure. Considering the increased concerns of SARS-CoV-2 potential for more serious neuroinvasion conditions, the present review attempts to focus on the neuroprotective effects of natural compounds as the principle source of therapeutics inhibiting multiple steps of the SARS-CoV-2 infection cycle. The great majority of the natural products with anti-SARS-CoV-2 activity mainly inhibit the attachment, entry and gene expression rather than the replication, assembly, or release. Although microbial-derived natural products comprise 38.5% of the known natural products with neuroprotective effects following viral infection, the neuroprotective potential of the majority of microorganisms is still undiscovered. Among natural products, chrysin, huperzine A, ginsenoside Rg1, pterostilbene, and terrein have shown potent in vitro neuroprotective activity and can be promising for new or repurpose drugs for neurological complications of SARS-CoV-2.

Keywords Natural products · Drug discovery · Neurological complications · SARS-CoV-2

Introduction

The evolutionally optimized scaffold diversity and structural complexity can highlight natural products (NPs) critical importance in drug discovery. Nature provides a rich resource of novel therapeutic compounds including antivirals affecting different viral life cycle steps of viruses like the influenza virus, hepatitis B and C viruses, human immunodeficiency virus, MERS and SARS-CoV-1 (Mohan et al. 2020). The biodiversity and variability of commercially available microbial bioactive compounds compared to those discovered from other natural sources (Abdel-Razek et al. 2020) highlight the position of microbial products as one of the most momentous leads in the future of natural drug discovery.

Unlike the common, not lethal respiratory infections caused by some human coronaviruses (hCoVs) comprising HCoV-OC43, HCoV-229E, HCoVNL63, and HCoVHKU1 (Coerd and Khachemoune 2021), at the end of 2019, an unknown virus from this family surprised the world once more and with exceeding 554 million cases and 6.3 million victims (Roser et al. 2020), made this viral strain as one of the most continues disastrous infection in recent years, regrettably.

The treatment options for COVID-19 are in three classes which include antiviral, immunomodulatory and other supporting drugs. Notably, the vast majority of clinical studies...
have been conducted in emergency settings suffering from methodology and clinical limitations leading to poor consistency across studies. Therefore, it is difficult to draw some valid conclusions on drug efficacy in COVID-19 disease treatments. Certainly, further higher quality study designs on larger populations are urgently demanded to establish the most efficient drug. The latest guideline recommends Ritonavir-boosted nirmatrel (paxlovid), Remdesivir and bebtelovimab when hospitalization is not essentially required and Molnupiravir, baricitinib, Remdesivir and dexamethasone in severe cases (Jirjees et al. 2021).

Considering that the pulmonary system is not the exclusive target of SARS-CoV-2, varied clinical manifestations of COVID-19 mainly neurological disorders have been reported (da Rosa Mesquita et al. 2021). Understanding how the virus affects the nervous system and its long-term consequences should be considered more seriously at a rapid speed. Accordingly, the most common neurological disorders of SARS-CoV-2, the probable entry routes to the nerve system mainly the blood–brain barrier disruption, and also, the impact of the virus on these neurological disorders are discussed in this review. The conducted review aims to give an overview of SARS-CoV-2 general virology features, the CNS entry routes of SARS-CoV-2, its related neurological manifestations recorded so far and the efficiency of natural including microbial compounds on neurological complications of COVID-19. The probable mechanisms of action of these bioactive compounds and the pharmaceutical assays for the discovery of neuroprotective compounds are also discussed.

SARS-CoV-2 general features and the infection of neural cells

The spherical enveloped coronaviruses (CoVs) with the greatest genome size among all studied RNA viruses (26 to 32 kb) within the family Coronavirusidae include four (alpha, beta, gamma, and delta) genera. SARS-CoV-2 is categorized as beta-CoVs. Currently, alpha and beta-CoVs as the two largest genera have attracted more attention because of their ability to cross biological barriers and become major human pathogens (Poyiadji et al. 2020). The region preceding 3′ end of the viral RNA encodes four main structural proteins including spike (S), nucleocapsid (N), membrane (M), and envelope (E) proteins. The spike (S) polypeptide contains three chains with numerous functional domains like N-terminal domain (NTD), receptor binding domain (RBD), furin cleavage site, etc. The RBD domain interacting with the angiotensin-converting enzyme 2 (ACE2) receptor, facilitates cell recognition and binding (Satarker and Nampoothiri 2020). Besides, furin cleavage site might be cleaved by the TMPRSS2 (cellular serine protease) which is needed for complete viral entrance into the host cell. Activation of immune responses and viral pathogenesis due to the S protein (Hoffmann et al. 2020), indicate any mutational modifications could cause varied pathogenesis. Other structural proteins mainly facilitate the viral assembly. The life cycle and protein components of SARS-CoV-2 have been comprehensively reviewed previously (Almasi and Mohammadipanah 2021; Yadav et al. 2021).

Although the level of ACE2 expression in the entire brain is relatively low and other receptors rather than ACE2 adsorbs SARS-CoV-2 to nerve cells, its expression and function in neural cells as the SARS-CoV-2 entry receptor is reported numerously (Song et al. 2021). Further, some reports indicate a high level of ACE2 expression in some parts of the brain, like the striatum (Poyiadji et al. 2020) and the choroid plexus (Moriguchi et al. 2020). Different infection routes including receptor based pathways by which SARS-CoV-2 reaches the brain are discussed below.

Mechanism of SARS-CoV-2 entry into the nervous system

Neuroinvasive potential of CoVs specially SARS-CoV-2 and their presence in cerebrospinal fluid (CSF) or brain have been demonstrated via numerous experimental and clinical researches (Mao et al. 2020a; Moriguchi et al. 2020; Paniz-Mondolfi et al. 2020; Jackson et al. 2022; Reza-Zaldivar et al. 2021; Swain et al. 2021). Although it is not elucidated how SARS-CoV-2 enters the brain and if it directly affects the CNS or participates in other related mechanisms, four hypotheses have been proposed based on other coronaviruses infections: (i) receptor based, (ii) hematogenous spread, (iii) neuronal, and (iv) lymphatic pathways (Fig. 1).

Receptor pathway

The ACE2 receptor is widely expressed in different organs and its expression is even higher in the heart, kidney and digestive system compared to the lungs and trachea (Zou et al. 2020). Besides, recent studies have identified many neutralizing human antibodies that bind to S protein of SARS-CoV-2 but do not bind the receptor binding domain (RBD) of ACE2 (Chi et al. 2020). These results suggest that ACE2 as a critical known receptor should not be considered as the only functional SARS-CoV-2 receptor and other/or co-critical receptors might play role in the viral entry in varied host cells.

In addition to numerous reports on the role of serine protease 2 and furin (Wang et al. 2020b) in triggering the fusion process of SARS-CoV-2, more recently, CD147 (Basigin) was proposed as an emerging receptor of SARS-CoV-2 (Wang et al. 2020a). Another probable receptor could be CD209L (L-SIGN) which will be discussed in
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Neuronal pathway

Some types of viruses including CoVs can travel in a retrograde way invading from peripheral nerve ends specially olfactory neurons via microtubules and known motor proteins mainly kinesin and dynein to reach the CNS (Bohmwald et al. 2018). This trans-synaptic pathway is considered

the lymphatic pathway. Neuropilin-1 (NRP-1) can also be considered as another receptor that remarkably potentiates viral infectivity especially in olfactory epithelial cells. Its elevated level of mRNA in lung and olfactory epithelium of COVID-19 cases and human cell culture examinations propose a strong probability that NRP1 promotes the interaction of SARS-CoV-2 with ACE2 (Kyrou et al. 2021).

**Fig. 1** Mechanism of SARS-CoV-2 entry into the nervous system. SARS-CoV-2 can enter to the CNS via four plausible routes. Receptor pathway: spike protein of SARS-CoV-2 binds and infects cells via ACE2 while other enzymes like the TMPRSS2 and furin are needed for the viral membrane fusion. Several proteins with much higher expression levels in brain like cathepsin L (CTSL), CD 147 and NRP1 can affect viral endocytosis and the spreading of SARS-CoV-2 in the brain; Neuronal pathway: one of the probable retrograde pathways of SARS-CoV-2 entry to CNS is the olfactory pathway. SARS-CoV-2 can enter the olfactory bulb through the olfactory nerves and finally, through the olfactory tract, it enters different parts of the brain. There are reports indicating the probable transfer of SARS-CoV-2 to CNS via the trigeminal and vagus nerves; The hematogenous pathway: beside entrance to blood stream and affecting different tissues, SARS-CoV-2 can disrupt BBB. In addition, it can penetrate to CNS via endothelial cells of the blood-cerebrospinal fluid barrier (BCSFB). Lymphocytes and monocytes infected by SARS-CoV-2 could also be considered as a probable vehicle for CNS entry; and the lymphatic network around bronchus and trachea tissues expressing another SARS-CoV-2 receptor named CD209L confirm the lymphatic entry route of SARS-CoV-2. Some parts of Figure were created in Biorender (https://app.biorender.com/)
one of the possible mechanisms of SARS-CoV-2 virus since the olfactory nerve correlates with both the nasal epithelium and the olfactory bulb. The in vitro neuroinvasive capability determination of inhaled CoVs such as MHV (Bohmwald et al. 2018), SARS-CoV-1 (McCray Jr et al. 2007), and HCoV-OC43 (Dubé et al. 2018) support the olfactory pathway indicating the presence of CoVs in the olfactory bulb before the CNS infection. In addition, infection of local peripheral nerves of GI tract and communication of the vagus nerve and the GI might play a role in trans-synaptic CNS entry of the SARS-CoV-2 (Zhang et al. 2020b).

**Hematogenous pathway**

Although CoVs are mainly respiratory viral pathogens, they can potentially disrupt the epithelium cells and enter the bloodstream causing viremia before reaching the CNS (Gonzalez-Scarano and Tyler 1987). The other probable hematogenous routes are the blood-neural barriers (BNBs) mainly the blood-cerebrospinal fluid barrier (BCSFB) and the blood brain barrier (BBB) recognized as ‘gatekeeper’ networks Once SARS-CoV-2 enters the blood stream, binds to the endothelium expressing ACE2 receptors, disrupts the barrier and finally penetrates to the CNS (Paniz-Mondolfi et al. 2020). Additionally, the presence of viral-like particles of SARS-CoV-2 in the brain endothelial cells, as well as pericytes and astrocytic, strongly support the hematogenous entry route for SARS-CoV-2 (Paniz-Mondolfi et al. 2020). Increased levels of inflammatory mediators (chemokines, cytokines), and hypoxemia mediate the destabilization or disruption of the BBB affecting its tight junctions promoting the entry of SARS-CoV-2 to CNS (Lima et al. 2020).

The blood stream immune cell transmigration mainly monocytes and macrophages is another proposed mechanism for SARS-CoV-2 entry to CNS known as the ‘trojan horse’ mechanism. SARS-CoV-1 infects monocytes, macrophages and T lymphocytes leading to a consistent reduction level of these cells named lymphopenia which has also been reported for SARS-CoV-2 cases (Mao et al. 2020a). The infected immune circulating cells can diffuse into other tissues and the CNS.

**Lymphatic pathway**

Spreading of the SARS-CoV-2 in the brain lymphatic drainage system could be implicated as another route, although it is contradictory at the moment (Bostancıklıoğlu 2020). Foremost, ACE2 and TMPRSS2 are expressed on the endothelial cells of this system. In addition, perineural spaces of nasal lymphatic tissue and olfactory nerves are substantial for drainage of the CSF (Lima et al. 2020).

As discussed before, CD209L is another receptor of SARS-CoV-2 expressed in lymphatic endothelial cells, kidney and liver tissues. Amraei et al. demonstrated the independent action or heterodimerization of CD209L with ACE2 in the entry process of SARS-CoV-2 (Amraei et al. 2021).

**Associated neurological disorders with SARS-CoV-2 infection**

**CNS related manifestations**

**Headache and dizziness**

Headache, dizziness, and malaise are the most usual primary symptoms in SARS-CoV-2 infected patients (Bolay et al. 2020; Mao et al. 2020a). with relatively high prevalence (3–17% of the studied cases) with sever/moderate intensity (Kase and Okano 2021; Vacchiano et al. 2020). these symptoms are also common in a number of neurological pathologies (encephalitis, meningitis, and vasculitis, etc.) or systemic viral infections. Considering the pain was reported to be in the temporo-parietal or forehead and periorbital regions, direct or indirect invasion of SARS-CoV-2 to the trigeminal nerves could be the most probable suggested underlying mechanism (Mao et al. 2020a).

**Cerebrovascular complications**

According to reports gathered in the middle of SARS-CoV-2 pandemic, COVID-19 cases are at low risk for different subtypes of cerebrovascular problems comprising intracerebral hemorrhage (ICH), acute ischemic stroke (AIS), subarachnoid hemorrhage (SAH), transient ischemic attack (TIA), and cerebral venous sinus thrombosis. Based on large population studies, different subtypes of stroke like AIS, ICH and venous sinus thrombosis have been reported in approximately 0.5–17% of SARS-CoV-2 cases (Romero-Sánchez et al. 2020).

**Demyelinating diseases**

COVID-19 cases with demyelinating diseases such as acute myelitis and encephalomyelitis (Kim et al. 2021a), acute disseminated encephalomyelitis (Jan et al. 2021) and optic neuritis (Romero-Sánchez et al. 2020) have currently a low prevalence (one report for optic neuritis and 4–5 case reports for other demyelinating diseases). Notably, no evidence indicating the effect of COVID-19 on MS worsening and exacerbation is reported yet (Berger et al. 2020).
Impaired consciousness

Encephalopathy is described as the acute disturbance of brain function leading to the alteration of consciousness level, with varying subtypes and prevalence (up to 30%) (Hayashi et al. 2020).

Encephalitis and anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis (Monti et al. 2020) could be considered as other disorders leading to consciousness impairment following SARS-CoV-2 infection as its presence has been confirmed in CNS.

Seizure

Seizure can be considered as one of the most prevalent neurological disorders in COVID-19 cases as detected in SARS-CoV-1 (Lau et al. 2004) and MERS-CoV (Saad et al. 2014) infected patients. The viral invasion to the CNS, hypoxia and neuro-inflammatory pathway activation are the proposed mechanisms causing seizures (Hepburn et al. 2021).

Miscellaneous

There are a few reports on other neurological manifestations in COVID-19 infections like movement disorders, vasculitis in CNS and several other organs (skin, kidney, lung, and liver), cranial nerves abnormalities (nerves related to anosmia and ageusia) and a case report of CNS related visual impairments after SARS-CoV-2 infection (Romero-Sánchez et al. 2020).

Peripheral nervous system (PNS) related manifestations

Cranial nerve abnormalities

Oculomotor and trigeminal cranial nerve malfunction lead to impaired eye movement (Pascual-Goñi et al. 2020) and trigeminal neuropathy (Ferreira et al. 2020), respectively which are among the rare disorders related to PNS.

Guillain-Barré Syndrome (GBS) and its variants

GBS is an autoimmune disorder that is reported in several COVID-19 cases causing peripheral neuronal dysfunction due to cross reaction with peripheral nerves (Romero-Sánchez et al. 2020). Besides, GBS has been repeatedly observed following SARS-CoV-2 vaccination (Loza et al. 2021).

There are only seven sporadic reports on COVID-19 cases associated with Miller Fisher syndrome (MFS) as a rare variant of GBS (Li et al. 2021b). Therefore, there is no sufficient evident MFS is not rational to assume any relation or mechanism connecting MFS to SARS-CoV-2 infection and more reports are required to confirm an epidemiologic correlation.

Neuromuscular junction (NMJ) related manifestations

Data regarding myopathy, myalgia and NMJ dysfunction following SARS-CoV-2 infection are scarce (Mao et al. 2020a; Romero-Sánchez et al. 2020), but long-term physical disabilities due to the growing number of COVID-19 must be assessed. The ACE2 receptors mediated muscle entry, inflammation, and cytokine storms are the main proposed mechanisms mediating muscle damage (Madia et al. 2020).

A summary of the estimated prevalence of major SARS-CoV-2 neurological complications adopted from a comprehensive meta-analysis study (Vitalakumar et al. 2021) is illustrated in Fig. 2.

Natural based therapeutics for inhibition of SARS-CoV-2 infection

After the outbreak of SARS-CoV-1 and MERS-CoV, screening of agents against hCoVs increased dramatically while the majority of identified antiviral were naturally based. Out of the total of 185 antiviral agents identified by 2019, synthetic drugs have the least portion (15.1%) (Newman and Cragg 2020). Besides the high rate of SARS-CoV-2 mutations, the exorbitant therapeutics with limited availability, and various side effects (Kumar et al. 2021a) shifted the research focus to natural treasures mainly herbal and microbial sources. In addition, natural compounds with demonstrated worthiness introduced via virtual (molecular dynamics simulations) are feeding the experimental screening assays. In the following, we overview the natural compounds which have shown perspective in the management of SARS-CoV-2 infection through acting on diverse hypothetical targets involved in the viral cell cycle by in vitro methods (alone or combined with other methods) (Table 1).

Targeting cell attachment and entry

Targeting S glycoprotein

As discussed before, the club-shaped spike glycoprotein of coronaviruses (150–220 kDa) plays a salient role in cell binding, membrane fusion and also interaction with TMPRSS2 and host antibodies. Therefore, natural compounds acting on this protein have been introduced as promising drug candidates for treating COVID-19 and its complications like neurological disorders via blocking nerve cell entrance.
Considering the abundance of the virtual-based introduced natural compounds with effectivity on SARS-CoV-2 some like a flavonoid named H69C2 capable of attaching to the RBD domain of SARS-CoV-2 via in silico has shown in vitro antiviral activity as well (IC₅₀ of 85.75 µM) (Wang et al. 2021). Kobophenol A (Gangadevi et al. 2021), isorhamnetin (Zhan et al. 2021), and demethylzeylasteral (Zhu et al. 2021) are some of the natural S protein blockers impairing the interaction between S protein and ACE2 being examined through in vitro assessments (Table 1) like ELISA, cell membrane chromatography, SPR, molecular-biology chromatography (MBC) (Lv et al. 2021), etc.

**Host receptors**

Flavonoids are a diverse group of natural compounds with ACE2 inhibitory activity like quercetin, nympholide A, naringenin, hesperetin, baicalin, nicotinamin, etc. Based on reports, hesperidin potentially interferes with ACE2-mediated host cell entry (Muchtaridi et al. 2020). In addition, Liu et al. demonstrated the human recombinant ACE2 inhibitory activity of quercetin and its metabolites including tamarixetin, rutin, quercetin-3-O-glucoside, and 3,4-dihydroxyphenylacetic acid, which quercetin with IC₅₀ of 4.48 µM was the most strong inhibitor at physiologically relevant concentrations (Liu et al. 2020b). Furthermore, the antiviral effect of resveratrol in Vero E6 cells has been evaluated (ter Ellen et al. 2020). There are also some clinical trials for resveratrol are undergoing (NCT04542993, NCT04536090, and NCT04377789).

In addition, other enzymes like the TMPRSS2 and several proteins with much higher expression levels like cathepsin L (CTSL) and furin can cause modifications of viral proteins, affecting the spreading of SARS-CoV-2 in the brain (Coutard et al. 2020). Inhibition of TMPRSS2 by a triterpenoid named platycodin D present in *Platycodon grandiflorum* (Kim et al. 2021b), theaflavin from *Camellia sinensis* var. assamica (Wu et al. 2020b), and tannic acid (Wang et al. 2020b) are limited natural examples being examined by in vitro screening assays. Diethyl ether fraction of *Aframomum melegueta* with IC₅₀ of 0.03 mg/L is the only natural extract being in vitro validated for furin inhibition (Omotuyi et al. 2021).

Following the cleavage of S protein by furin, C-end Rule (CendR) motif forms at the C-terminal of S protein. Then, this motif interacts with NRPI and this phenomenon could be the reason for neurological symptoms in COVID-19 cases since the expression of NRPI is higher than ACE2 or TMPRSS2 in the brain (Kyrou et al. 2021). Hence, inhibiting NRPI could be another promising approach for developing drugs for neurological aspects of SARS-CoV-2. Alhadrami et al. reported cnicin from the *C. benedictus* can inhibit neuropilin 1 (NPR-1) and replication of SARS-CoV-2 (Alhadrami et al. 2021). Improving cognitive and memory, preventing the Aβ aggregation and reducing the oxidative stress by an encapsulated quercetin with BBB crossing ability have been reported in mouse models (Ramalho et al. 2020).
### Table 1: Natural products with reported effectiveness on SARS-CoV-2 in experimental assessments

| Targeted cell cycle step | Chemical class | Source | Natural product/extract | Potential target(s) | Screening method(s) | References |
|-------------------------|----------------|--------|-------------------------|---------------------|---------------------|------------|
| Cell attachment and entry | Flavonoids | Bupleurum chinense DC | Quercetin | Binding to ACE2 | In silico, in vitro | Pan et al. (2020) |
| | | Cyathula officinalis Kuan | | | | |
| | | Hippophae rhamnoides | Isonhamnetin | Binding to the S protein | In silico, in vitro | Zhan et al. (2021) |
| | | Pueraria lobata (Willd.) Ohwi | Puerarin | Impairing the interaction between ACE2 and S protein | In silico, in vitro | Pan et al. (2020) |
| | | Bupleurum chinense DC | Rutin | Binding to ACE2 | In silico, in vitro | Joshi et al. (2021) |
| | | Astragalus membranaceus (Fisch.) Bge. var. mongholicus (Bge.) Hsiao | | | | |
| | | Scutellaria baicalensis-Georgi | Oxyrorylin a | Binding to ACE2 | In silico, in vitro | Gao et al. (2021) |
| | | Camellia sinensis (L.) O. Kuntze | Epigallocatechin-3-gallate | Binding to S protein | In silico, in vitro | Gowrishankar et al. (2021) and Henss et al. (2021) |
| | | Not determined | h69c2 | Binding to the RBD domain of S protein | In vitro, in silico | Wang et al. (2021) |
| Terpenoids | Tripterygium wilfordii Hook.f | Demethylyze-lasteral | | Impairing the interaction between ACE2 and S protein | In silico, in vitro | Zhu et al. (2021) |
| | Glycyrrhiza uralensis Fisch | Glycyrrhizic acid | | Binding to S protein | In vitro in silico | Yu et al. (2021) |
| | Astragalus membranaceus (Fisch.) Bge. var. mongholicus (Bge.) Hsiao | Astragaloside iv | | Binding to ACE2 | In silico, in vitro | Ye et al. (2021) |
| Phenols | Salvia miltiorrhiza Bge | Salvianolic acid a | | Binding to S protein and ACE2 | In silico, in vitro | Hu et al. (2021) |
| | Caragana sinica (Buc’hoz) Rehder | Kobophenol a | | Binding to S protein | In silico, in vitro | Gangadevi et al. (2021) |
| | Lonicera japonica Thunb | Neochlorogenic acid | | Binding to ACE2 | In vitro in silico | Chen et al. (2021) |
| | Caesalpinia spinose | Tannic acid | | Binding to TMPRSS2 protease | In vitro | Wang et al. (2020b) |
| Quinones | Rheum palmatum L | Rhein | | Binding to ACE2 | In silico, in vitro | Chen et al. (2021) |
| Alkaloids | Ephedra sinica Stapf | Ephedrine | | Binding to ACE2 and S protein | In silico, in vitro | Lv et al. (2021) |
| Glycosides | Forsythia suspensa (Thunb.) Vah | Forsythoside a55 | | Binding to ACE2 | In silico, in vitro | Chen et al. (2021) |
| Sesquiterpene lactone | Carduus benedictus | Cnicin | | Binding to NRP-1 | In vitro | Alhadrami et al. (2021) |
| Targeted cell cycle step | Chemical class | Source                                      | Natural product/extract | Potential target(s) | Screening method(s) | References                     |
|-------------------------|----------------|---------------------------------------------|-------------------------|---------------------|---------------------|--------------------------------|
| Replicase protein       | Flavonoids     | Scutellaria baicalensis Georgi              | Baicalin                | Binding to 3CLpro   | In vitro            | Su et al. (2020a)              |
| expression              |                | Citrus fruits                               | Naringenin              | Binding to 3CLpro   | Insilico, in vitro  | Abdallah et al. (2021)         |
|                         |                | Pimenta dioica (L.) Merr                    | Rutin                   | Binding to 3CLpro   | In silico, in vitro, in vivo | El Gizawy et al. (2021) |
|                         |                | Scutellaria baicalensis                     | Baicalein               | Binding to 3CLpro   | In vitro            | Liu et al. (2021a)             |
| Replication             | Phenol         | Curcuma longa                               | Curcumin                | Binding to 3CLpro   | In silico, in vitro | Guijarro-Real et al. (2021)    |
|                         |                | Caesalpinia spinosa                         | Tannic acid             | Binding to 3CLpro   | In vitro            | Coelho et al. (2020)           |
|                         | Terpene        | Andrographis paniculata                     | Andrographolide         | Binding to 3CLpro   | In vitro            | Shi et al. (2020)_ ENREF_89    |
|                         | Flavonoids     | Scutellaria baicalensis Georgi              | Baicalin                | Binding to the RdRp | In vitro            | Su et al. (2020a)              |
|                         |                | Scutellaria baicalensis                     | Baicalein               | Binding to the RdRp | In vitro            | Liu et al. (2021a)             |
|                         | Terpene        | Andrographis paniculata                     | Andrographolide         | Binding to the RdRp | In vitro            | Shi et al. (2020)_ ENREF_89    |
|                         | Sesquiterpene  | Carduus benedictus                          | Cnicin                  | Binding to the RdRp | In vitro            | Alhadrami et al. (2021)        |
| lactone                 | Macrocyclic    | Streptomyces avermitilis                    | Ivermectin              | Binding to the RdRp | In silico, in vitro | Heidary and Gharebaghi (2020) |
| lactone                 | Alkaloid       | Lycoris radiata                            | Lycorine                | Binding to the RdRp | In vitro            | Min et al. (2021)              |
| Viral protein           | Phenol         | Brassica oleracea                           | Sinapic acid            | Binding to the E protein | In silico, in vitro | Orfali et al. (2021)           |
| assembly and release    |                |                                            |                         |                     |                     |                                |

Table 1 (continued)
Targeting replicase protein expression

Following the viral entrance and the uncoating, two processed polyproteins (pp) (pp1a and pp1ab) are formed by viral protease, named papain-like proteinase (PLpro) and chymotrypsin-like protease (Guijarro-Real et al. 2021) (also called the main protease, MPro). The crucial function of these proteases in replication and life cycle of SARS-CoV-2 renders them as valuable targets in the development of therapeutics against SARS-CoV-2. Using computational approaches, a few reports suggest potential PLpro inhibitors compared to various 3CLpro inhibitors (Wu et al. 2020a).

Abdollah et al. evaluated in vitro 3CL protease, untagged (SARS-CoV-2) assay of the top eighteen hits from virtual screening of some commercially available natural agents. Finally, the most potent compound, naringenin showed moderate activity on a SARS-CoV-2 Egyptian strain (IC_{50} value of 28.347 μM) (Abdallah et al. 2021).

Based on experimental screening, baicalin (IC_{50} 6.41 μM) and baicalein (IC_{50} 0.94 μM) are flavonoids inhibiting 3CLpro, as well as SARS-CoV-2 replication inhibition in Vero E6 cells (Su et al. 2020a). SARS-CoV-2 3CLpro inhibitory activity of baicalein as the main component of the S. baicalensis, and the crude ethanol extract was also reported with IC_{50} of 0.39 μM and 8.52 μg/ml, respectively (Liu et al. 2021a).

In another in vitro assay, the butanol fractions of two traditional Chinese medicinal plants (Reynoutria sachalinensis with IC_{50} of 4.031 μg/mL and R. japonica with IC_{50} of 7.877 μg/mL showed the strongest 3CLpro inhibitory activity. Replication inhibition was also demonstrated for both of them (Nawrot-Hadzik et al. 2021).

| Targeted cell cycle step | Chemical class | Source | Natural product/extract | Potential target(s) | Screening method(s) | References |
|-------------------------|----------------|--------|-------------------------|---------------------|---------------------|------------|
| Multi steps             | Terpenoid      | *Salvia miltiorrhiza* | Cryptotanshinone | Inhibitory effects on virus propagation | In vitro | Zhang et al. (2020d) |
|                         | Terpene        | *Salvia miltiorrhiza* | Tanshinone iia | PLpro, 3CLpro, S protein, PDK1/Akt/Flt dual pathway inhibition | In vitro | Elebeedy et al. (2021) |
|                         | Flavonoids     | *Psoralea sp.* | Isobavachalcone | Not identified | In vitro | Zhang et al. (2020d) |
|                         |                | *Psoralea sp* | Bavachin | Not identified | In vitro | Zhang et al. (2020d) |
|                         | Coumarins      | *Psoralea sp* | Psoralidin | Not identified | In vitro | Zhang et al. (2020d) |
|                         | Alkaloids      | *Stephania tetrandra* | Tetrandrine | Inhibiting viral replication, expression of S and N protein, activating the p38MAPK pathway | In vitro | Zhang et al. (2020d) |
|                         |                | *Stephania tetrandra* | Cepharanthine | Inhibiting viral replication, entrance and N protein expression | In vitro | Zhang et al. (2021) |
|                         |                | *Lycoris sp* | Lycorine | Inhibiting replication, probably modulating host factors | In vitro | Zhang et al. (2020b) |
|                         |                | *Rauvolfia serpentina* | Reserpine | Inhibition of replication, 3CLpro and entry | In vitro | Zhang et al. (2020d) |
andrographolide isolated from *Andrographis paniculata* (Shi et al. 2020), tannic acid (Coelho et al. 2020) and quercetin (Liu et al. 2020b) are SARS-CoV-2 3CLpro inhibitors proved in experimental screenings. Recently Guijarro-Real et al. evaluated the methanolic extract of 17 fruits and traditional plants for anti-3CLpro activity using fluorescence based in vitro assay. They demonstrated that extracts of *Curcuma longa* rhizomes, *Brassica nigra* seeds, and *Diplotaxis erucoides* leaves produced the highest reduction in SARS-CoV-2 3CLpro activity. The rhizome of *Curcuma longa* mainly contains curcumin. Curcumin is a compound found in the root of *Curcuma longa* and recent studies proved its efficiency in neurological manifestations mainly neurodegenerative disease (Guijarro-Real et al. 2021).

Despite its highly hydrophobic structure and low oral bioavailability, different targeted delivery researches of curcumin showed enhanced biodistribution in the brain (Ramalho et al. 2020). Recently, Gizaw et al. evaluated anti-3CLpro activity of four bioactive compounds from the leaves of *Pimenta dioica* (L.) Merr (ferulic acid, rutin, gallic acid, and chlorogenic acid) (El Gizawy et al. 2021). According to in silico, in vitro and in vivo analysis, rutin with IC\(_{50}\) values of 31 µg/mL showed notable inhibitory activity. Based on some in silico and in vitro reports, epigallocatechingallate (IC\(_{50}\) 73 µM), galloctachingallate (IC\(_{50}\) 47 µM) and quercetin (IC\(_{50}\) 73 µM) are the most potent inhibitors of the SARS-CoV-2 3CLpro. Neuroinflammatory properties and inhibition of beta amyloid oligomerization by galloctachingallate have also been reported (Ghosh et al. 2020; Chakravarti et al. 2021).

Screening a library with more than 3000 natural compounds using virtual and cell based assays, Jan et al. identified 15 active molecules targeting SARS-CoV-2 3CLpro enzyme. In the in vivo assay, melquine and extract of *M. haplocalyx* significantly decreased viral load compared to the control. The extract of *Ganoderma lucidum* (RF3) was also a potent SARS-CoV-2 3CLpro inhibitor (Jan et al. 2021).

**Targeting replication**

The high sequence similarity of RNA-dependent RNA polymerase (RdRp) of SARS-CoV-1 and 2, the conserved active site of RdRp, and importantly, no counterpart with human polymerase resembles indicates RdRp inhibitors as a promising therapeutic strategy (Elfiky 2021).

Based on cell culture assays, an anti-parasitic microbial product named ivermectin could inhibit the RdRp of SARS-CoV-2 with an IC\(_{50}\) of 2.2–2.8 µM (Heidary and Gharebaghi 2020) and the clinical trials of ivermectin is in progress (www.ClinicalTrials.gov -NCT04390022, NCT04602507). Recently Raihan et al. (Raihan et al. 2021) reported a comprehensive review on antiviral microbial metabolites, their classification and the viral targets. According to their report, fungi are responsible for 67% of microbial derived antivirals followed by bacteria (28%). Ivermectin, a bacterial-derived macrocyclic lactone (Table 1) has been approved for emergency usage during the pandemic of SARS-CoV-2.

Digoxin is another natural compound with a high affinity to RdRp and its SARS-CoV-2 RdRp inhibitory activity in Vero cells is demonstrated by research groups (Zhang et al. 2020d). Silibinin, a flavonolignan extracted from the milk thistle seeds, rapamycin, novobiocin, produced by *Streptomyces niveus* and ergotamine are other natural inhibitors of SARS-CoV-2 replication machine. Cnicin from *Cardus benedictus* extract is another promising replication inhibitor of SARS CoV-2 (IC\(_{50}\) 1.18 µg/mL) targeting ADP ribose phosphatase and RdRp (Alhadrami et al. 2021).

Recently, Yin et al. investigated the RdRp inhibitory activity of a known natural derived drug suramin. SARS-CoV-2 cellular entrance prevention by this compound was also evaluated (Salgado-Benvindo et al. 2020). Accordingly, suramin at low concentrations (100 µM) completely blocks the formation of RdRp–RNA complex with IC\(_{50}\) of 0.26 µM. According to results of cell-based assay of RdRp activity, lycorine, a natural alkaloid, blocked SARS-CoV-2 RdRp activity more effectively than remdesivir at 4.4 µM (IC\(_{50}\) of 1.465 ± 0.033 µM) (Min et al. 2021). Overall, the virtual and experimental findings propose the natural compounds as notable RdRp binders.

**Targeting viral protein assembly and release**

The only structural protein linked to the membrane-associated viral replicase-transcriptase complex (RTC) is N protein which can be considered an important target of anti-SARS-CoV-2 drug discovery. It attaches to RNA and is the main component of ribonucleoprotein complex. Additionally, it has a critical function in the virus structural organization by interacting with the genome, M and other N proteins and finally viral assembly and release. Although recognized natural N protein inhibitors are limited compared to the other targets discussed before, Rani et al. reported three natural compounds by screening natural antiviral agents against all structural proteins of SARS-CoV-2 (Rani et al. 2021). Recently, Orfali et al. introduced sinapic acid with IC\(_{50}\) of 2.69 µg/mL as an efficient anti-SARS CoV-2 natural agent inhibiting membrane proteins (Orfali et al. 2021).

**Entire/multi steps of viral cell cycle**

Some natural products have been recognized to be effective in the inhibition of cytopathic effect (CPE), aiming to find antivirals affecting any steps of the SARS-CoV-2 life cycle.
cycle. Recently, Zhang et al. screened a large library (more than 1050 compounds) in a high throughput cell based assay (Vero-E6 cells) and introduced bruceine A, bufalin, and digoxin as active natural compounds against SARS-CoV-2. Although intracellular ion homeostasis regulator proteins like Na+/K+-ATPase may be the probable targets, more investigation identifying the exact mechanism is required (Zhang et al. 2020d). Resveratrol is another natural compound that strongly reduced SARS-CoV-2 production in cell based assays. It likely interferes with SARS-CoV-2 replication cycles including genome translation cycle and/or viral RNA replication and/or viral protein synthesis. Although the exact mechanism is not clear, the compound act prior to virus assembly and release (ter Ellen et al. 2020).

Natural products entry to the nerve system

The high potential of natural compounds for the treatment of CNS disorders like neurodegenerative diseases, brain tumors, cerebrovascular diseases, glioblastoma, etc., have been extensively investigated due to their well-known properties applicable to CNS disorders, such as anti-inflammatory, antioxidant, and neuroprotective effects. Nevertheless, poor pharmacokinetic or physicochemical characteristics cause low bioavailability, aqueous solubility, and gastrointestinal/hepatic elimination, which are the remarkable issues leading to limited BBB crossing.

Lipophilicity, polar surface area (PSA) and molecular weight (MW) are principle indicators for CNS exposure determining the extent and rate of BBB penetration of natural products with activity against SARS-CoV-2. Generally, moderate lipophilic natural compounds with Log P of 2–5 (Wager et al. 2010) and other proper indicators are centrally active. Considering the fast clearance and low tissue/plasma concentration of oral or parenteral administrated natural compounds, bypassing the BBB via intranasal transport into the brain through the olfactory and trigeminal nerves and also, nanocarrier systems are being investigated to improve their access to the brain (Bicker et al. 2020). Some of the natural candidates for the treatment of CNS manifestations, include the rographolide (Log P 1.62), baicalin (Log P 0.31), curcumin (Log P 2.92), kaempferol (Log P 2.05), puerarin (Log P 1.95), quercetin (Log P 1.5), resveratrol (Log P 3.14), rutin (Log P 1.76), and scutellarin (Log P −0.46), have been reported to have anti-SARS-CoV-2 activities (Table 1).

Natural products from plants and microorganisms with neuroprotective effects

SARS-CoV-2 damages the nervous system mainly because of the outbreak of inflammation storm in the brain, which will activate immune cells and cause secondary damage. Many natural products from plants and microorganisms have been reported to have neuroprotective effects through anti-neuroinflammatory, anti-Aβ deposition, acetylcholinesterase inhibitory, and monoamine oxidase inhibitory actions, etc. (Moraga-Nicolás et al. 2018; Dhiman et al. 2020; Wang et al. 2013). The summary of 151 so far reported natural products with neuroprotective effects is shown in Table 2. Compounds 1–132, including flavonoids (1–33), alkaloids (34–55), terpenoids (56–80), phenylpropanoids (81–97), quinone (98–103), and miscellaneous (104–131), have been found from herbal medicines. In addition, small-molecular microbial products (132–151) are listed in Table 2. The characteristics of these compounds with neuroprotective activity are summarized in Fig. 3. We will review the neuroprotective effects of various representative components by structural types. The chemical structures of compounds 1–151 and the related references are provided in the supplementary file.

Flavonoids

The neuroprotection effect of flavonoids has been reported so far through the regulation of monoamine oxidase (MAO), quinone reductase (NQO1) and P2X7 receptor (Gao et al. 2019; Carradori et al. 2014). MAO catalyzes monoamines oxidative deamination reaction in the body and its inhibitors can reduce or eliminate various monoamine substances to reduce the activity of monoamine oxidase. Biochanin A (5) is a competitive inhibitor for both hMAOs, making it a potential candidate molecule for neurodegenerative disease (Zarmouh et al. 2017). In addition, (-)-epicatechin (22) and (+)-catechin (23) showed inhibitory activities on rat MAO-B, with IC50 values of 88.6 and 58.9 μM (Hou et al. 2005).

Neuroprotective abilities of monochloropivaloylquercetin (11) and 2S-5, 7, 3′, 5′ -tetrahydroxyflavanone (24) have also been reported. In LPS-induced toxicity in N9 cell model, pretreatment and post treatment with 20 μM 2S-5, 7, 3′, 5′ -tetrahydroxyflavanone could significantly inhibit the expression of NQO1 (Li et al. 2015). Monochloropivaloylquercetin has been demonstrated to act as an antioxidant and NQO1 inhibitor to improve the survival of BV2 cells after Aβ challenge (Cumaoglu and Yerer 2018). Cardamonin (9) could play a neuroprotective role by inhibiting the expression of cell membrane CD14 protein. Furthermore, chrysin (6) reduced neuroinflammation by inhibiting the expression of CCAAT/enhancer binding protein δ and nuclear factor kappa-B (NF-κB) signaling pathway in interferon (IFN)-γ-induced primary microglia (Gresa-Arribas et al. 2010; Chow et al. 2012).
| Compound | Phytochemical class | Natural source | Targets/pathways |
|-----------|---------------------|----------------|------------------|
| Apigenin-7-glucoside (1) | Flavonoids | Plant | GABAa↓, transient receptor potential vanilloid 1↓ |
| Baicalein (2) | Flavonoids | Plant | Homo monoamine oxidase (hMAO)-B↓, nuclear factor kappa-B (NF-κB)↓ |
| Baicalin (3) | Flavonoids | Plant | GABAa↓ |
| bilobetin (4) | Flavonoids | Plant | β-secretase↓ |
| Biochanin A (5) | Flavonoids | Plant | hMAO-B↓ |
| Chrysin (6) | Flavonoids | Plant | C/EBP δ↓ |
| Hesperidin (7) | Flavonoids | Plant | NF-κB↓, Mitogen-activated protein kinase (MAPK)↓, miRNA-132↑ |
| Isoquercitrin (8) | Flavonoids | Plant | hMAO-B↓ |
| Cardamonin (9) | Flavonoids | Plant | NQO1↓ |
| Kaempferol-7-O-β-D-Glucopyranoside (10) | Flavonoids | Plant | NQO1↓ |
| Monochloropivaloylquercetin (11) | Flavonoids | Plant | aldose reductase↓ |
| Naringin (12) | Flavonoids | Plant | P2X3 receptor↓ |
| Mangiferin (13) | Flavonoids | Plant | Nrf2-OH-1↓, NF-κB↓, NLRP3↓ |
| Pinostrobin (14) | Flavonoids | Plant | hMAO-B↓ |
| Procyanidins (15) | Flavonoids | Plant | NLRP3↓ |
| Quercetin (16) | Flavonoids | Plant | hMAO-B↓, aldose reductase↓, tyrosine kinase -2↓, NQO1↓ |
| Quercetagetin-7-O-β-D-glucopyranoside (17) | Flavonoids | Plant | NQO1↓ |
| Robustaflavone (18) | Flavonoids | Plant | β-secretase↓ |
| Rutin (19) | Flavonoids | Plant | Glutathione peroxidase, hMAO-B↓ |
| Silibinin (20) | Flavonoids | Plant | NF-κB↓ |
| Wogonin (21) | Flavonoids | Plant | Janus kinase-signal transducer and activator transcription (JAK/Stat)↓, tyrosine kinase -2↓ |
| (−)-Epicatechin (22) | Flavonoids | Plant | hMAO-B↓ |
| (+)-Catechin (23) | Flavonoids | Plant | hMAO-B↓ |
| 2S-5, 7, 3′, 5′-Tetrahydroxyflavanone (24) | Flavonoids | Plant | NQO1↓ |
| 2′, 4′-Dihydroxy-6′-methoxochalcone (25) | Flavonoids | Plant | NF-κB↓ |
| Myricitrin (26) | Flavonoids | Plant | NF-κB↓, MAPK↓ |
| Dihydromyricetin (27) | Flavonoids | Plant | NLRP3↓ |
| 3, 5, 7, 3′, 4′-Pentahydroxyflavone (28) | Flavonoids | Plant | NF-κB↓, MAPK↓ |
| Eriodictyol (29) | Flavonoids | Plant | NF-κB↓, MAPK↓ |
| 7-Methoxylavone (30) | Flavonoids | Plant | MAPK↓ |
| Cudraflavanone B (31) | Flavonoids | Plant | NF-κB↓ |
| Sophoraflavanone G (32) | Flavonoids | Plant | Phosphatidylinositol-3-kinases /protein kinase B (PI3K/Akt)↓, Jak-Stat↓ |
| Mgricitrin (33) | Flavonoids | Plant | NF-κB↓, MAPK↓ |
| Isoliquiritigenin (34) | Alkaloids | Plant | NF-κB↓ |
| Formononetin (35) | Alkaloids | Plant | NF-κB↓ |
| Loganin (36) | Alkaloids | Plant | Tyrosine hydroxylase, NF-κB↓ |
| Huperzine A (37) | Alkaloids | Plant | Acetylcholinesterase (AChE)↓, NF-κB↓ |
| Berberine (38) | Alkaloids | Plant | NF-κB↓ |
| Mitragynine (39) | Alkaloids | Plant | AChE↓ |
| Mitragynine oxide B (40) | Alkaloids | Plant | AChE↓ |
| Lycoramine (41) | Alkaloids | Plant | AChE↓ |
| Norpluvine diacetate (42) | Alkaloids | Plant | AChE↓ |
| 6α-Deoxytazettine (43) | Alkaloids | Plant | AChE↓ |
| Geissospermine (44) | Alkaloids | Plant | AChE↓ |
| Matrine (45) | Alkaloids | Plant | Aβ↓ |
| Piperine (46) | Alkaloids | Plant | hMAO-A/B↓ |
Table 2 (continued)

| Compound | Phytochemical class | Natural source | Targets/pathways |
|----------|---------------------|----------------|------------------|
| β-Carbolene (47) | Alkaloids | Plant | hMAO-A/B↓ |
| Tetrandrine (48) | Alkaloids | Plant | NF-κB↓ |
| Coumaroylaminobutanol Glucopyranoside (49) | Alkaloids | Plant | NF-κB↓ |
| Tryptanthrin (50) | Alkaloids | Plant | NF-κB↓, MAPK↓ |
| Canthin-6-one (51) | Alkaloids | Plant | GABA↓ |
| Hirustine (52) | Alkaloids | Plant | PI3K/Akt↓ |
| Delavatine A (53) | Alkaloids | Plant | NF-κB↓ |
| Betanin (54) | Alkaloids | Plant | NF-κB↓ |
| Cannabinin F (55) | Alkaloids | Plant | Brain derived neurotrophic factor† |
| Catalpol (57) | Terpenoids | Plant | hMAO-B↓ |
| Geniposide (58) | Terpenoids | Plant | hMAO-B↓ |
| Farfarone D (59) | Terpenoids | Plant | inducible nitric oxide synthase (iNOS)↓ |
| Rhynchophylline (56) | Terpenoids | Plant | iNOS↓ |
| Artemisinin B (63) | Terpenoids | Plant | NF-κB↓ |
| Ginsenoside Rg3 (64) | Terpenoids | Plant | NF-κB↓, MAPK↓ |
| Ginsenoside Rd (65) | Terpenoids | Plant | P2X↓, receptor↓, P2X↓ receptor↓ |
| Ginsenoside Rg1 (66) | Terpenoids | Plant | NF-κB↓, MAPK↓ |
| Triptolidine (67) | Terpenoids | Plant | AP-1 DNA binding site↓ |
| β-Caryophyllene (68) | Terpenoids | Plant | Cannabinoid type-2 G protein-coupled receptor↑ |
| β-Amyrin (69) | Terpenoids | Plant | Human monoacylglycerol lipase↓, 2-arachidonoyl glycerol hydrolysis↓ |
| Genipin (70) | Terpenoids | Plant | PI3K/Akt↓ |
| Kanshine B (71) | Terpenoids | Plant | NF-κB↓, MAPK↓ |
| Kanshine E (72) | Terpenoids | Plant | NF-κB↓, MAPK↓ |
| Isonardosinone (73) | Terpenoids | Plant | NF-κB↓, MAPK↓ |
| Nardosinone (74) | Terpenoids | Plant | NF-κB↓, MAPK↓ |
| Alismol (75) | Terpenoids | Plant | NF-κB↓ |
| Glycyrrhizic acid (76) | Terpenoids | Plant | NF-κB↓ |
| Ginsenoside Rg18 (77) | Terpenoids | Plant | MAPK↓, PI3K/Akt↓, Jak-Stat↓ |
| Ginsenoside Re (78) | Terpenoids | Plant | MAPK↓ |
| β-Sitosteryl (79) | Terpenoids | Plant | NF-κB↓, MAPK↓ |
| Saikosaponin B3 (80) | Terpenoids | Plant | NF-κB↓ |
| Pseudoginsenosides-F11 (81) | Terpenoids | Plant | PI3K/Akt↓ |
| Ferulic acid (82) | Phenylpropanoids | Plant | indoleamine 2, 3-dioxygenase↓ |
| honokiol (83) | Phenylpropanoids | Plant | Krüppel-like factor 4↑ |
| 4′-O-Methylhonokiol (84) | Phenylpropanoids | Plant | Cannabinoid type-2 G protein-coupled receptor↑ |
| 2′-Hydroxycrenamic acid (85) | Phenylpropanoids | Plant | Low-density lipoprotein receptor-related protein 1↓ |
| 2′-Hydroxycrenamic acid (86) | Phenylpropanoids | Plant | Low-density lipoprotein receptor-related protein 1↓ |
| 9-Hydroxy-6, 7-dihydroxysal ergi quinol (87) | Phenylpropanoids | Plant | Heme oxygenase-1↑ |
| 4′-Hydroxy Pd-C-III (88) | Phenylpropanoids | Plant | ACh↓, BCh↓, β-secretase↓ |
| Decursidin (89) | Phenylpropanoids | Plant | ACh↓, BCh↓, β-secretase↓ |
| tannic Acid (90) | Phenylpropanoids | Plant | NF-κB↓ |
| Magnesium lithospermate B (91) | Phenylpropanoids | Plant | NF-κB↓ |
| Compound                  | Phytochemical class | Natural source | Targets/pathways                          |
|--------------------------|---------------------|----------------|------------------------------------------|
| Osthole (92)             | Phenylpropanoids    | Plant          | NF-κB↓                                   |
| Auraptene (93)           | Phenylpropanoids    | Plant          | MAPK↓                                    |
| Kellerin (94)            | Phenylpropanoids    | Plant          | MAPK↓, NLRP3                             |
| 4’-Methoxyl-Pd–C-I (95)  | Phenylpropanoids    | Plant          | AChE↓, BChE↓, β-secretase↓               |
| 3-Hydroxy-4-methoxyl cinnamic aldehyde (96) | Phenylpropanoids | Plant          | AChE↓, BChE↓, β-secretase↓               |
| 4-Hydroxy cinnamic aldehyde (97) | Phenylpropanoids | Plant          | AChE↓, BChE↓, β-secretase↓               |
| Tanshinone I (98)        | Quinone             | Plant          | Aβ↓                                     |
| Tanshinone IA (99)       | Quinone             | Plant          | hMAO-A↓                                  |
| Abtusin (100)            | Quinone             | Plant          | hMAO-A↓                                  |
| Alatermin (101)          | Quinone             | Plant          | hMAO-A/β↓                                |
| Aloeemodin (102)         | Quinone             | Plant          | Aβ↓                                     |
| Questin (103)            | Quinone             | Plant          | hMAO-A↓, BChE↓, β-secretase↓             |
| Resveratrol (104)        | Miscellaneous       | Plant          | P2X7 receptor↓                           |
| Pterostilbene (105)      | Miscellaneous       | Plant          | NF-κB↓                                   |
| α-Viniferin (106)         | Miscellaneous       | Plant          | Heme oxygenase-1↑                        |
| 2,3,6-Tribromo-4,5-dihydroxybenzyl alcohol (107) | Miscellaneous | Plant          | hMAO-A↓, dopamine D3/D4 receptor↑        |
| 2,3,6-Tribromo-4,5-dihydroxybenzyl methyl ether (108) | Miscellaneous | Plant          | hMAO-A↓, dopamine D3/D4 receptor↑        |
| bis-(2,3,6-Tribromo-4,5-dihydroxybenzyl) ether (109) | Miscellaneous | Plant          | hMAO-A↓, dopamine D3/D4 receptor↑        |
| Cannabidiol (110)        | Miscellaneous       | Plant          | Metallothionein 2↑, N-myc-downstream regulated gene 1↑, matrix metallopeptinase 23↑ |
| Δ⁹-Tetrahydrocannabinol (111) | Miscellaneous     | Plant          | Cannabinoid type-1/2 G protein-coupled receptor↑ |
| Corilagin (112)          | Miscellaneous       | Plant          | Lactate dehydrogenase↓                   |
| 2,4-bis(p-Hydroxyphenyl)-2-butenal (113) | Miscellaneous | Plant          | β-secretase↓, γ-secretase↓               |
| Arturmerone (114)        | Miscellaneous       | Plant          | Nrf2-OH-1↑                               |
| Arbutin (115)            | Miscellaneous       | Plant          | Ninjurin1↓                               |
| Domoic acid (116)        | Miscellaneous       | Plant          | Brain derived neurotrophic factor↑, tyrosine kinase receptor B↑ |
| Paconol (117)            | Miscellaneous       | Plant          | Adenosine monophosphate-activated protein kinase-α↑, glycogen synthase kinase 3 α/β↑ |
| (Z)-9,17-Octadecadienal (118) | Miscellaneous     | Plant          | hMAO-A↓                                  |
| Samurai shodown (119)    | Miscellaneous       | Plant          | hMAO-A/β↓                                |
| Emodin-1-β-D-Glucopyranosyl (120) | Miscellaneous | Plant          | Nf-κB↓                                  |
| Zerumbone (121)          | Miscellaneous       | Plant          | Jak-Stat↓                                |
| 5, 8-Dihydroxy-10-methoxy-2-methyl-4H-naphtho [1, 2-b]pyran-4-one (122) | Miscellaneous | Plant          | MAPK↓                                   |
| 4-(1,2-Dimethoxyethyl) benzene-1,2-diol (123) | Miscellaneous | Plant          | MAPK↓                                   |
| Bakuchiol (124)          | Miscellaneous       | Plant          | MAPK↓                                   |
| Macelignan (125)         | Miscellaneous       | Plant          | MAPK↓                                   |
| Isodojaponin D (126)     | Miscellaneous       | Plant          | MAPK↓                                   |
| trans-Caryophyllene (127) | Miscellaneous       | Plant          | MAPK↓                                   |
| Macrolactin A (128)      | Miscellaneous       | Plant          | β-secretase↓                            |
| 4-(1, 2-Dimethoxyethyl) benzene-1, 2-diol (129) | Miscellaneous | Plant          | Nrf2-OH-1↑                             |
| S-Allyl cysteine (130)   | Miscellaneous       | Plant          | hMAO-A↓, MAPK↓                          |
| Curcumin (131)           | Miscellaneous       | Plant          | NF-κB↓                                  |
| Brevicompanine E (132)   | Alkaloids           | Microorganism  | NF-κB↓, PI3K/Akt↓, Activator protein-1↓ |
| 8-O-Methylbostrycoidin (133) | Alkaloids          | Microorganism  | AChE↓                                   |
| Beauvericin (134)         | Alkaloids           | Microorganism  | AChE↓                                   |
Alkaloids

Alkaloids are naturally occurring organic compounds that usually carry at least one nitrogen atom within a heterocyclic ring. The nitrogen atoms in alkaloids are in a negative oxidation state, giving the alkaloids their essential properties. The indole alkaloids, mitragynine (39) and mitragynine oxide B (40), have been identified as acetylcholinesterase (AChE)
inhibitors by computational chemistry techniques. In the experiment on AChE inhibitory activity, the inhibitory effect of mitragynine on AChE was dose-dependent, and the IC_{50} value was 3.57 μM (Innok et al. 2021).

Tryptanthrin (50) blocked the expression of mRNAs of pro-inflammatory cytokines and the production of inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2 via regulating mitogen-activated protein kinase (MAPK) and NF-κB signal pathways to reduce the lipopolysaccharide (LPS)-induced neuroinflammation in BV-2 cell model (Lee et al. 2018). Brevicominanine E (132), isolated from fungus Penicillium sp. of deep ocean sediments, was found to be able to block the production of tumor necrosis factor-α, inducible iNOS and COX-2 induced by LPS. In addition, the electrophoretic mobility shift assay in LPS-induced microglia proved that brevicominanine E weakened NF-κB and activator protein-1 (AP-1) DNA-binding activity (Yang et al. 2009).

**Terpenoids**

In addition to alkaloids and flavonoids, terpenoids are other phytochemicals with neuroprotective effects. Genipin (70) and 4-(1, 2-dimethoxyethyl) benzene-1, 2-diol (129) were isolated from Eucommia ulmoides, which is a commonly used herb for the treatment of cardiovascular and cerebrovascular diseases in China. Genipin can stimulate the phosphorylation of phosphatidylinositol-3-kinase (PI3K)/ protein kinase b (Akt) in microglia in a dose-dependent manner, leading to anti-inflammatory effect, while the neuroprotective function of 4-(1, 2-dimethoxyethyl) benzene-1 and 2-dio was produced by inhibiting p38-MAPK signal pathway (Luo et al. 2014). In addition, genipin could also play a neuroprotective role by inhibiting the production of mitochondrial reactive oxygen species (ROS) and NF-κB signaling pathway (Nam et al. 2010).

Artemisinin B (63) inhibited the expression of MyD88 and NF-κB in the abnormally activated microglia, reduced inflammation and amyloid production by regulating toll-like receptor (TLR)4-NF-κB signaling pathway (Qiang et al. 2018a).

Four nardosinone-type sesquiterpenes, kanshone B (71), kanshone E (72), isonnardosinone (73), and nardosinone (74) inhibited the production of inflammatory cytokines and COX-2 enzymes in LPS-induced BV2 model by regulating NF-κB, JNK, p38-MAPK, and other signal pathways, showing an excellent anti-inflammatory potential (Ko et al. 2018).

Asperterpenes A (135) and asperterpenes B (136), two 3,5-dimethylserrinic acid-based meroterpenoids, were obtained from Aspergillus terreus. Asperterpenes A and B mediated neuroprotection by exhibiting promising inhibitory activities against β-secretase (Qi et al. 2016).

**Phenylpropanoids**

Phenylpropanoids are one of the main chemical constituents in plants and fungi (Kernan et al. 1998). A simple phenylpropanoid, ferulic acid (82) was shown to inhibit the production of inflammatory factors in BV2 cells induced by benzoprene and LPS and subsequently inhibit the overactivation of microglia (Zhou et al. 2016; Bao et al. 2019). Also, 3-hydroxy-4-methoxy cinnamic aldehyde (96) and 4-hydroxy cinnamic aldehyde (97) effectively reduced the production of NO in inflammatory cells by inhibiting the overactivation of microglia with IC_{50} values of 2.18 and 2.39 μM, respectively (Lu et al. 2020).

Honokiol (83) and 4′-O-methylhonokiol (84), were renowned lignans and also the most important component of Houpoea officinalis. Honokiol and 4′-O-methylhonokiol were proved to possess anti-neuroinflammatory effects by inhibiting NF-κB pathway and increasing kruppel-like factor 4 in LPS-induced astrocytes and microglia models (Lee et al. 2012; Rickert et al. 2018). In addition, 4′-O-methylhonokiol could play a useful function in the process of Alzheimer’s disease (AD) by regulating the role of cannabinoid type-2 G protein-coupled receptor on the surface of microglia (Gertsch and Anavi-Goffer 2012).

Magnesium lithospermate B (91), a water-soluble active component of traditional Chinese medicine Salvia Miltiorrhiza, could significantly improve the neurological defects of cardiac and cerebrovascular patients. Magnesium lithospermate B increased intracellular Ca^{2+} levels in SH-SY5Y cells by effective inhibition of cardiac glycosides on Na^{+}/K^{+}-ATPase. Moreover, detailed molecular interactions showed that magnesium lithospermate B formed five intermolecular H-bonds and strong hydrophobic interactions with hydrophobic residues around the binding pocket of Na^{+}/K^{+}-ATPase (Chen et al. 2010).

**Miscellaneous**

Resveratrol (104) could reduce the cell injury induced by oxygen-glucose exclusion in primary neurons at a concentration of 30 μmol/L (Lanzillotta et al. 2013). Moreover, resveratrol protected mouse embryonic brain cells from damage caused by tert-butyl peroxide free radicals (Karlsson et al. 2000). In addition, resveratrol reduced the hyperphosphorylation of tau protein Ser396 site, and prevented the formation of neuronal fiber tangles by inhibiting the extracellular signal-regulated kinase (ERK)1/2 and GSK-3β signaling pathways to delay the occurrence and development of AD (Magistri et al. 2016).

Three bromophenol compounds from Symphyocladia latiscula, 2,3,6-tribromo-4,5-dihydroxybenzyl alcohol (107), 2,3,6-tribromo-4,5-dihydroxybenzyl methyl ether (108), and bis-(2,3,6-tribromo-4,5-dihydroxybenzyl) ether...
were shown to possess significant dopamine D3/D4 receptor-activating effects in cells and exhibiting good therapeutic potential for PD (Paudel et al. 2020).

Flaviligeranin (137) is a secondary metabolite of intestinal microorganisms. It regulated cellular protein hydrolysis by inhibiting the upregulation of proteasome autophagy and the activity of cathepsin β, finally reducing the number of Aβ1-42 in the central system to prevent Alzheimer’s disease (AD) (Hayakawa et al. 2010).

6, 8, 1’-tri-O-methylaverantin (138) is an anthraquinone isolated from marine fungus Aspergillus sp, inducing the expression of HO-1 protein in primary microglia and activating nuclear factor (erythroid-derived 2)-like 2 (Nrf2)-related signal pathways (Kim et al. 2018).

Terrein (144), isolated from the Aspergillus, Penicillium and Pestalotopsis, exhibited inhibitory activity against the iNOS and COX-2. It inhibited LPS-induced translocation of p65/p50 heterodimer to the nucleus, and induced HO-1 protein expression in primary microglia cells (Kim et al. 2020).

Trienomycin A (149), rienomycin D (150), and trienomycin J (151) are 21-membered macrocyclic benzenoid ansamycins isolated from Streptomyces cacaoi subsp, significantly inhibiting the production of NO in LPS-induced BV2 model (IC50 = 0.1, 0.02 and 0.03 μM, respectively). Researchers used molecular docking techniques to simulate their interactions with iNOS (Tang et al. 2018).

Potential natural medicines for neurological disorders of SARS-CoV-2

As mentioned above, both central and peripheral nervous system disorders are present in patients with SARS-CoV-2, while some of them like stroke, movement disorders, seizures and low levels of consciousness are more common in severe cases. Here, we review in vivo and in vitro studies that highlight the preclinical study use of natural products for the protection of the nervous system in COVID-19 cases. The structures of key compounds are shown in Fig. 4.

Treatment of cerebrovascular diseases

Some severe SARS-CoV-2 cases showed uncontrolled inflammation and compromised immunity, which can develop into stroke, septicemia, and meningoencephalitis. It is worth noting that the virus has not been detected in the CSF of SARS-CoV-2 patients. Direct brain infection might be responsible for meningoencephalitis, peri-infectious inflammation, and altered neurotransmission (Huang et al. 2020). Currently, researchers speculate that SARS-CoV-2 may cause cerebrovascular disease through the following pathways: I. It is probable that attachment of SARS-CoV-2 to ACE2 blocks the activity of angiotensin-(1–7) in the renin angiotensin pathway. Subsequent effects can cause more vasoconstriction and thrombosis, resulting in cerebrovascular disease; II. Cytokine storms in SARS-CoV-2 lead to IL-6-dependent changes in the expression of vascular endothelial growth factor and endothelial cell e-cadherin, leading to stroke and hypertension in SARS-CoV-2 patients; III. SARS-CoV-2 can result in severe damage to the BBB through initiate a proinflammatory response via an increase in matrix metalloproteinases by interacting with tight junction-associated protein stardust. On this basis, we reviewed the reported compounds related to the treatment of SARS-CoV-2-mediated cerebrovascular diseases and those with therapeutic potential (Mao et al. 2020b; Andrabi and Andrabi 2020).

Curcumin (132), the major bioactive component isolated from the rhizome of Curcuma longa, can inhibit viral infection and attenuate oxidative stress and inflammation (Yang et al. 2014). Curcumin has been observed to inhibit SARS-CoV-20-post-covid thromboembolic events in clinical studies. Curcumin could accelerate symptom recovery, shorten hospital stay and reduce the occurrence of inflammatory storms as observed in hospitalized COVID-19 patients (Hassaniazad et al. 2020). The COVID-19 patients treated with formulations containing curcumin and piperine (46), which is a biological enhancer to increase absorption of curcumin, required less mechanical ventilator support and fewer episodes of thromboembolic than those in the control group (Pawar et al. 2021). In vivo studies revealed that curcumin could down-regulate the expression of ACE and angiotensin type 1 receptors in brain tissue and vascular smooth muscle cells, and inhibit hypertension and oxidative stress effects mediated by angiotensin II angiotensin type 1 receptor in rats (Li et al. 2017a). Furthermore, curcumin has been proved to inhibit p38MAPK/PKC and NF-κB signaling pathways in erythrocytosis-induced overactivated microglia and reduce the expression of M1 markers and increase the expression of M2 markers (Zhang et al. 2019; Yang et al. 2014).

Resveratrol and pterostilbene (105) are promising antiviral compounds to inhibit SARS-CoV-2 infection. The antiviral mechanism of resveratrol and pterostilbene is most likely through interference with genomic translation and the early steps of viral RNA replication/protein synthesis (Ter Ellen et al. 2021). Pterostilbene also has been approved to prevent ischemic stroke-induced SH-SY5Y cell death, restore tissue structure, and reduce infarct area in mice. The primary mechanism is inducing miR-21-5p and inhibiting programmed cell death 4 (Tu et al. 2020). Moreover, pterostilbene could reduce brain water content and infarct volume in middle cerebral artery occlusion and reperfusion rats by inhibiting the over-expression of phosphorylated IκBα and ROS (Liu et al. 2020a). It was also found that the blood–brain barrier index of pterostilbene group was 0.49, which was higher than that of the
Fig. 4 Chemical structures of isolated from plant and microorganism with the potential of being used against neurological complications of SARS-CoV-2
resveratrol group (0.18). Therefore, pterostilbene might be an ideal candidate for the treatment of neuroinflammation and cerebrovascular diseases (Meng et al. 2019).

Mangiferin (13) is another bioactive molecule that can reverse neurological deficit and brain edema in subarachnoid perforation rat model. Mangiferin mediated neuroprotection through multiple mechanisms, including modulation of nuclear factor erythroid-2-related actor 2/heme oxygenase 1 (Nrf2-Oh-1), NF-κB, and NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammatory bodies (Wang et al. 2017b).

Huperzine A (37) has been developed as a promising neuroprotective agent, antagonizing many steps in the inflammatory cascade, including the activation of NF-κB, MAPKs, and AChE (Wang et al. 2010). Furthermore, huperzine A could cross the BBB to reduce inflammation and neuronal degeneration (Li et al. 2017b). Huperzine A could also improve cerebrovascular function by inhibiting AChE activity, activating NF-κB and decreasing the density of tight junctions (Ruan et al. 2014). Oral administration of huperzine A could significantly reduce the memory impairment in the transient global ischemia in gerbils. Further study has shown that huperzine A could reduce neuronal degeneration in the CA1 region, and partially restore hippocampal choline acetyltransferase activity (Zhou et al. 2001). In addition, huperzine A reduced the cognitive impairment of isoflurane anesthetized rats by inhibiting hippocampal inflammatory factors and increasing hippocampal neurotrophic factors (Cai et al. 2020).

A sesquiterpene coumarin, kellerin (95), isolated from Ferula sinkiangensis, has drawn greater attention because of its biological potential (Xing et al. 2017). Kellerin exhibited an inspiring therapeutic potency for ischemic stroke through the alleviation of the cognitive impairment of bilateral common carotid artery occlusion mice by transforming microglia from pro-inflammatory M1 phenotype to anti-inflammatory M2. Furthermore, LPS-induced microglial polarization could be regulated by kellerin by inhibiting NLRP3 and MAPK signaling pathways (Zhang et al. 2020a).

Naringenin (12) is a flavanone found in citrus plants and has been found to prevent oxidative damage in high-risk diseases such as microbial infection, heart diseases, and neurodegenerative diseases (Erlund 2004). Naringenin was observed to reduce oxidative stress and apoptosis by activating the Nrf2 signaling pathway in the middle cerebral artery occlusion model (Wang et al. 2017a). Additionally, naringenin may play a therapeutic role for SARS-CoV2 by inhibiting the SARS-CoV2 main protease 3CLpro and decreasing the activity of ACE2 receptor (Tutunchi et al. 2020). Thus, naringenin seems to be a promising natural product for the treatment of both SARS-CoV2 and its neurological complications.

### Treatment of nerve demyelination diseases

Coronaviruses can result in neuroinvasion due to their tropism for the CNS and inflammatory infiltrates, resulting in demyelinating diseases. Multiple sclerosis and Guillain–Barré syndromes which are characterized by inflammatory components, demyelination and plaques, and axonal damage, have been diagnosed in SARS-CoV-2 patients (Harapan and Yoo 2021).

Chrysin, a flavonoid existing in many higher plants, has anti-neuroinflammatory and antiviral effects and therefore might be used to prevent/treat SARS-CoV-2 (Kumar et al. 2021b). Accumulating in vitro and in vivo data has shown that chrysin can be a candidate for the prevention or treatment of nerve demyelination-related diseases like multiple sclerosis and Guillain–Barré syndrome. In in vitro studies, chrysin suppressed dendritic cells and Th1 cells and the expression of IFN-γ, IL-12, and p35 in an experimental autoimmune neuritis mice model (Zhang et al. 2015). A recent report revealed that chrysin reduces the inflammatory cell infiltration and demyelination of sciatic nerves by inhibiting the expression of iNOS, COX-2, and NF-κB (Xiao et al. 2014).

Flavonoidolignoid, siliibinin (20), is the most important component of Silibum marianum. Siliibinin possesses multiple biological functions including immune-boosting, hepatoprotective, antioxidant, antiviral activity, and neuroprotective activities (Castellaneta et al. 2016). Consistently, a study of siliibinin has shown its potential inhibitory effects on SARS-CoV2 main protease using the molecular docking approach (Kumar et al. 2021b). Siliibinin also reduced the histological signs of demyelination and inflammation in experimental autoimmune encephalomyelitis through nonspecifically down-regulating and up-regulating of the secretion of pro-inflammatory Th1 and the anti-inflammatory Th2 cytokines, respectively (Min et al. 2007). Therefore, taking into account siliibinin’s ameliorating effects against neuroinflammation and its related antiviral properties, siliibinin could be a candidate phytochemical combating nerve demyelination complications of COVID-19.

A vital alkaloid matrine (45) is isolated from various plant species including Sophora flavescens and Sophora tonkinensis. It has a wide range of pharmacological effects, including neuroprotective, anti-viral, antioxidant functions and immunomodulatory effects (Gong et al. 2016). Recently, a clinical case report of a group of COVID-19 patients showed that the effective cure rate of matrine-NaCl treatment for COVID-19 was 100% (Zhang et al. 2020c). In terms of neuroprotection, matrine could reduce the numbers of macrophages, microglia and CD4+T cells in experimental autoimmune encephalomyelitis rats by inhibiting NF-κB and MAPK-protein kinase B (Akt) signaling pathways and mitigating the myelin damage by inhibiting the extravasation.
of the BBB (Kang et al. 2021; Luo et al. 2021; Zhang et al. 2013).

Treatment of consciousness impairment

The resilience of the human brain is evaluated by high levels of sedation, and there is also growing recognition that patients with severe SARS-CoV-2 are at risk for particular forms of consciousness impairment (Edlow et al. 2020). A flavanone glycoside, hesperidin (7) is isolated from citrus fruits after extraction. The key effects of hesperidin include immune boosting, antiviral, anticancer, and neuroprotective functions (Lv et al. 2015). Recent reports confirmed that hesperidin can inhibit helicase of SARS-CoV-2 and be used for COVID-19 treatment based on molecular docking mutation studies and experimental validation results (Su et al. 2020b; Pandey et al. 2021). The neuroprotective activity through suppressing inflammatory mediators as well as antiviral effects of hesperidin make it a promising therapeutic agent for the treatment of consciousness impairment in COVID-19. Hesperidin was reported for its anti-neurodegenerative effects mediating by reduced inflammatory cytokine levels by attenuating Akt, high mobility group box-1 receptor for advanced glycation end-products /NF-κB, and brain derived neurotrophic factor/tyrosine kinase receptor 2 pathways and increasing miRNA-132 expression (Li et al. 2016; Fu et al. 2019; Justin-Thenmozhi et al. 2018). Moreover, hesperidin pretreatment could modulate the AChE activity to improve the memory consolidation process as tested by Morris water maze (Javed et al. 2015).

A flavanone glycoside, baicalin (3) is isolated from various plants and fruits. Baicalin could reverse the decrease of GABAAR/tyrosine kinase receptor B/AKT expression and prevent synaptic dysgenesis and memory impairment in MHE rats. In addition, baicalin can enhance the interaction of GABAAR with tyrosine kinase receptor B and improve the downstream Akt expression (Ding et al. 2018). It’s worth noting that baicalin has significant antiviral activity against SARS-CoV-2 in in vitro studies. Baicalin could inhibit SARS-CoV-2 RdRp activity by acting as an inhibitor of SARS-CoV-2 RdRp (Zandi et al. 2021). Myricitrin (26), is known to possess dose-dependent neuroprotective effects. Myricitrin could reduce the activity of NF-κB and MAPK signal pathways in LPS-induced substantia nigra striatum models. Also, dihydromyricetin (27), the reduction product of myricitrin, could effectively inhibit the activation of NLRP3 inflammatory bodies in APP/PS1 mice (Feng et al. 2018).

SARS-CoV-2 infection may be followed by some long-term neurological complications with a potential association with the progression of neurodegenerative diseases and even delayed neurological effects including AD (Beauchamp et al. 2020). Artemisinin B (63) has exhibited a significant effect on the decrease in Aβ25-35 activity and reduced the inflammatory levels in AD dementia mice. The primary mechanism is inhibiting TLR4/Myd88/NF-κB signal pathway to protect the learning and memory ability of the dementia model of AD (Qiang et al. 2018b). In addition, eriodictyol (29) is another bioactive molecule that can improve the impairment of spatial learning and memory by modulating MAPK, PI3K/Akt, and NF-κB pathways (He et al. 2018).

Glycyrrhizic acid (75) is the major bioactive component isolated from Glycyrrhiza uralensis. Glycyrrhizic acid may play an important role in the treatment of COVID-19 as molecular docking has shown that glycyrrhizic acid can interact with a recombinant S protein and block S protein binding to host cells (Vardhan and Sahoo 2022). Pretreatment with glycyrrhizic acid can reduce the loss of TH-ir neurons and the density-loss of striatal nerve endings by directly quenching free radicals, enhancing the activity of antioxidant enzymes, and inhibiting the expression of NF-κB (Ojha et al. 2016).

S-allyl cysteine (130) could significantly inhibit the production of inflammatory factors in the brain of rats induced by LPS, and improve the cognitive function and learning ability of the rat model group. Besides, s-allyl cysteine could play a neuroprotective role by inhibiting the expression of TLR4 and inducing the activation of Nrf2 signal pathway (Zarezadeh et al. 2017).

The ApoE e4e4 allele is associated with the Aβ peptide levels in CSF and plasma and a 14-fold increased risk of development of Alzheimer’s disease compared to the common e3e3 genotype. The e4e4 genotype has been reported to enhance the risk of severe SARS-CoV-2 infection (Kuo et al. 2020). Therefore, regulation of APOE and Aβ are associated with neurological complications of SARS-CoV-2, and therefore can be considered as another mechanism of natural product-mediated neuroprotection. For example, oral administration of quercetin (16) greatly increased brain ApoE and decreased insoluble Aβ levels in the cortex of 5xFAD amyloid model mice (Zhang et al. 2016). Quercetin was also found to inhibit both the activity and expression of NLRP3 inflammatory bodies by regulating the expression of sirtuin1 (Li et al. 2021a; Kang et al. 2020).

Treatment of seizures

Another neurologic complication observed in patients with SARS-CoV-2 is convulsive seizures (Mao et al. 2020b). Inflammation, impaired immune responses and, neurotransmitter damage have been found in patients’ brain, assumed to be important targets for the treatment and prevention of SARS-CoV-2 post-infection seizure (Boison and Steinhauser 2018).

The crucial function of GABAa and transient receptor potential vanilloid 1 in the activity of neurons makes them
prevalent targets in the development of drug bioassays for seizure treatment. Recently, some flavonoids and alkaloids such as apigenin-7-glucoside (1), chrysin (6), and canthin-6-one (51), were demonstrated to be GABAa and transient receptor potential vaniloid 1 inhibitors (Pasch et al. 2016; Zhu et al. 2006).

The regulation of some ion channels is a vital target in seizure processes. Activation of conductance Ca2+-activated K+ channel (BKCa) can reduce the excitability of nerve cells, playing an important role in reducing Ca2+ influx and excitatory amino acid release.

Tanshinone IIA (99), isolated from the rhizome of Salvia miltiorrhiza, can be used as a therapeutic agent for cardiovascular and cerebrovascular diseases in clinic (Zhu et al. 2020). Tanshinone IIA suppressed glutamate release and reduced the excitability of the nervous system through the enhanced BKCa (Sharifi-Rad et al. 2021). Rynchophylline (91), a famous molecule from traditional Chinese herbal medicine Uncaria rhynchophylla, reducing kainic acid-induced seizures in rats by decreasing the expression of IL-1β and brain derived neurotrophic factors (Ho et al. 2014).

Miscellaneous

As mentioned above, another key factor in central system injury is damage to the vascular wall, which may be the result of a virus directly invading the vascular epithelium and replicating in the blood vessels (Romero-Sánchez et al. 2020). Tanshinone IIA significantly inhibited the formation of Colony Forming Unit-Megakaryocytes (CFU-MK) and the serum levels of inflammatory cytokines, and tumor necrosis factor-α of bone marrow cells of BALB/c mice in a dose-dependent manner (Li et al. 2009). In vivo studies revealed that tanshinone IIA could significantly reduce the number of megakaryocytes and the formation of CFU-MK in rabbits with immune vasculitis (Cao et al. 2015).

Several pathways like the MAPKs are involved in central system inflammation and apoptosis by promoting the activation and proliferation of microglia. For example, xyloketal B (148), isolated from Xyloraria sp. is reported to increase the anti-apoptotic proteins and survival of neurons through inhibition of phosphorylation of ERK and Akt (Li et al. 2013). Triptolide (67), a major bioactive ingredient of a widely used herbal medicine Tripterygium wilfordii, has shown neuroprotective functions. Triptolide could reduce the expression of NF-κB signal pathway by interacting with xeroderma pigmentosum group B/TFIIH, therefore inhibiting the process of neuroinflammation in the brain (Cheng et al. 2014).

P2X7 receptor is widely distributed in many tissues and organs as a signaling complex coupled with multiple downstream components in multiple cellular events like proliferation, protein synthesis, and apoptosis. Recent findings suggest that P2X7 receptor may play important roles not only in physiological transmitter communication but also in pathological neural injury (Melani et al. 2006). The expression regulation of P2X7 receptor and glial fibrillary acidic protein is reported by resveratrol, influencing P2X7 receptor-mediated Ca2+ signals, ERK1/2 phosphorylation levels, and eventually the released level of IL-6 (Wu et al. 2017). A recent report revealed that several ginsenosides like ginsenoside Rg3 (64), ginsenoside Rd (65), and ginsenoside Rg1(66) functioned as potent allosteric modulators of P2X7 channels to block eATP, tumor necrosis factor-α and IL-1β expressions (Liu et al. 2021b; Helliwell et al. 2015). Moreover, ginsenoside Rg3 could elicit a significant inhibitory effect on neuroinflammation by inhibiting TLR4-mediated transforming growth factor-β activated kinase-1/IKK/NF-κB signaling pathway (Kang et al. 2017; Joo et al. 2008).

An increasing number of reports have indicated that sudden anosmia or hyposmia are concurrent symptoms of SARS-CoV-2 infection. The SARS-CoV-2 pathogen can cause severe olfactory dysfunction by penetrating the sieve plate and olfactory bulb neurons (Butowt and Bilinska 2020). Propolis is a resinous substance composed of flavonoids, polyphenolics, and terpenes. It has been approved that propolis prevented MnCl2-induced with irregular damaged nuclear membrane, rupture of myelin fiber on rat olfactory bulb by inhibiting H2O2-triggered mitochondria ROS generation and nuclear DNA damage (Mahmoud et al. 2020).

Conclusion

The SARS-CoV-2 infection is often accompanied by neurological complications, which have a negative impact on the survival and prognosis of patients and greatly increase the difficulty of treatment. Due to the urgent need for drugs against SARS-CoV-2, virtual screening has been widely employed up to now and various inhibitors have been discovered from different classes of natural compounds mostly alkaloids, terpenoids, flavonoids, phenylpropanoids and polyketides. Interestingly, there are some agents like curcumin, epigallocatechin gallate, and quercetin whose effectiveness and their ability to penetrate the BBB with nanocarriers have been studied in various neurological diseases. Most of the natural products with anti-SARS-CoV-2 activity mainly mediate their anti-viral activity by inhibiting attachment, entry and gene expression rather than the replication, assembly or release.

Although not any SARS-CoV-2 specific natural compound has been approved by any global regulatory systems, some antiparasitic drugs like a bacterial-derived macrocyclic lactone named ivermectin (Table 1) have been approved for emergency usage during the pandemic of SARS-CoV-2 capable of inhibiting SARS-CoV-2...
replication. Besides in silico studies have introduced some potential microbial-derived anti-SARS-CoV-2 agents. However, experimental validation is required for them. In addition, there are numerous microbial derived antivirals mainly.

those acting against viral respiratory infections which could be promising candidates for repurposing against SARS-CoV-2. However, more time is needed to identify effective natural compounds and extensive studies are going worldwide to find anti SARS-CoV-2 natural drugs.

Natural compound discovery with both SARS-CoV-2 inhibition activity and ability to reach the brain (alone or incorporated into nanocarriers) promise the effectiveness of these compounds in treating the neurological disorders of SARS-CoV-2. Despite these promising results, the natural compounds with poor oral bioavailability like quercetin should also be optimized for acceptable bioavailability.

In our current search for neuroprotective agents from the secondary metabolites of plants and microorganisms, natural products representing the flavonoids, alkaloids, terpenoids, stilbenes, and polycyclic compounds have been identified as promising leads. Among these compounds, chrysin, hyperzine A, ginsenoside Rg1, pterostilbene, and terrein showed potent in vitro neuroprotective activity and promising in vivo neural injury treatment potential.

Tanshinone IIA has undergone cerebrovascular clinical trials in the People’s Republic of China and several new dosage forms have been developed. Other compounds isolated from microorganisms, including xyloketal A, xyloketal B, terretrem D, and terretrem E, have shown limited neuroprotective activity, but they exhibited interesting structures for further investigations. It is worth noting that most of the active compounds identified in our in vitro experiments have not yet been evaluated in animal studies, so in vivo and clinical validation of the therapeutic effects of these potential neuroprotectants remains to be done.

It is expected that characterizing the exact mechanism and developing efficient brain-targeted delivery systems for natural compounds is one of the future challenges in the field of drug delivery and treatment of neurological disorders specially, SARS-CoV-2 related neurological disorders. Referring to the encouraging results from intranasal delivery of natural compounds in treating CNS disease, this route can be considered a promising approach for the treatment COVID-19 related neurological disorders.

Thus, the discovery of more effective and safer natural drugs must be programmed, which can bring a breakthrough for both the treatment of SARS-CoV-2 neurological complications and other neurodegenerative diseases.

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Declarations

Competing interests Authors state no relevant financial or non-financial interests to disclose on the content of the paper.

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