Arch. Pharm. Res. (2022) 45:909–937
https://doi.org/10.1007/s12272-022-01420-3

Online ISSN 1976-3786
Print ISSN 0253-6269

Archives of Pharmacal Research
www.springer.com/12272

REVIEW

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

Faezeh Almasi[1] · Wen Dang[2] · Fatemeh Mohammadipanah[1] · Ning Li[2]

Received: 4 May 2022 / Accepted: 22 November 2022 / Published online: 28 November 2022

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(Coerdt 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

Faezeh Almasi and Wen Dang have contributed equally to this work.

✉ Fatemeh Mohammadipanah
fmohammadipanah@ut.ac.ir

✉ Ning Li
liningsypharm@163.com

[1] Microbial Biotechnology Lab, School of Biology and Center of Excellence in Phylogeny of Living Organisms, College of Science, University of Tehran, 14155-6455, Tehran, Iran

[2] School of Traditional Chinese Materia Medica, Key Laboratory for TCM Material Basis Study and Innovative Drug Development of Shenyang City, Shenyang Pharmaceutical University, Shenyang 110016, People's Republic of China

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 nirmatre (paxlovid), Remdesivir and bebtelovimab when hospitalization is not essentially required and Molnuppiravir, 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 *Coronaviridae* 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-Zaldívar 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

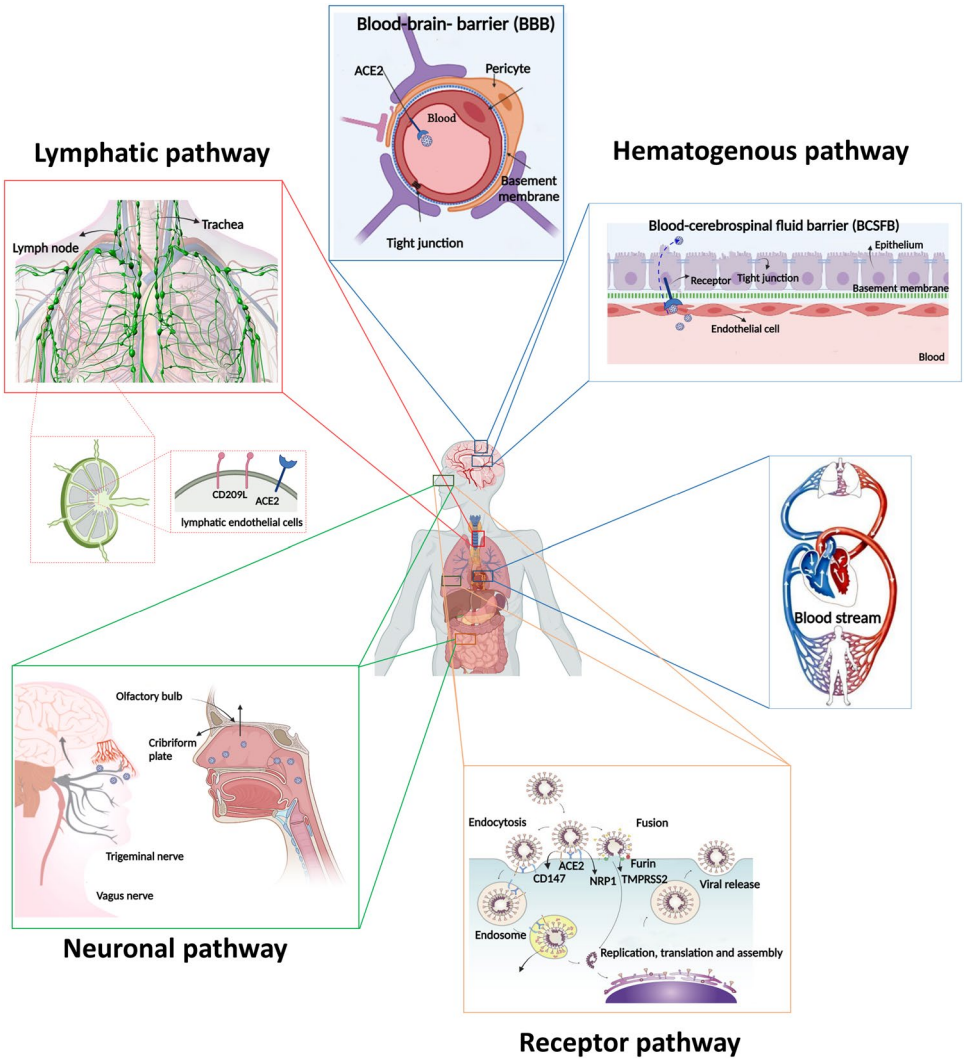

Fig. 1 Mechanism of SARS-CoV-2 entry into the nervous system. SARS-CoV-2 can enter to the CNS via four plausible routes. Receptor pathway: spike protein of SARS-CoV-2 binds and infects cells via ACE2 while other enzymes like the TMPRSS2 and furin are needed for the viral membrane fusion. Several proteins 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/)

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).

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

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 SASR-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 TPMRSS2 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 antivirals 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 naturalcompounds 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.

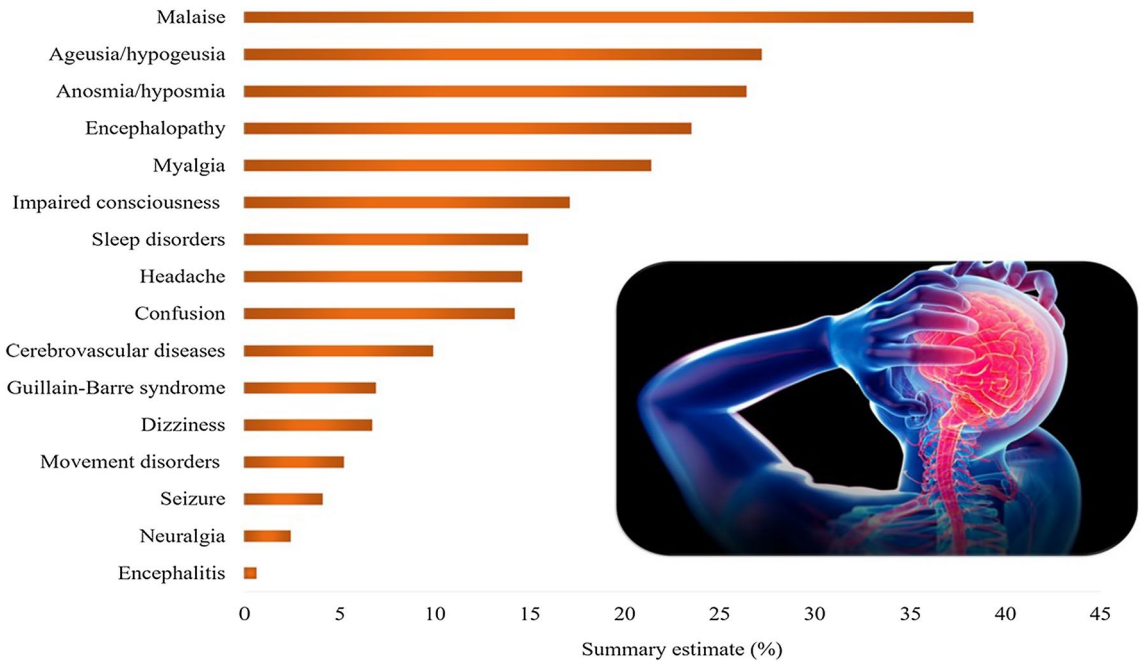

Fig. 2 Estimated prevalence of SARS-CoV-2 neurological complication according to a comprehensive meta- analysis. Data were adopted from Vitalakumar et al. 2021

Considering the abundance of the virtual-based introduced natural compounds with effectivity on SARS-CoV-2some 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 (IC_{50} 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 IC_{50} 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 IC_{50} 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 NRP1 and this phenomenon could be the reason for neurological symptoms in COVID-19 cases since the expression of NRP1 is higher than ACE2 or TMPRSS2 in the brain (Kyrou et al. 2021). Hence, inhibiting NRP1 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 *Cyathula officinalis* Kuan	Quercetin	Binding to ACE2	In silico, in vitro	Pan et al. (2020)
		Hippophae rhamnoides	Isorhamnetin	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 *Astragalus membranaceus* (Fisch.) Bge. *var. mongholicus* (Bge.) Hsiao	Rutin	Binding to ACE2	In silico, in vitro	Joshi et al. (2021)
		Scutellaria baicalensis-Georgi	Oroxylin 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	Demethylzeylasteral	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)

Table 1 (continued)

Targeted cell cycle step	Chemical class	Source	Natural product/ extract	Potential target(s)	Screening method(s)	References
Replicase protein expression	Flavonoids	*Scutellaria baicalensis* Georgi	Baicalin	Binding to 3CLpro	In vitro	Su et al. (2020a)
		Citrus fruits	Naringenin	Binding to 3CLpro	Insilico, in vitro	Abdallah et al. (2021)
		Pimentadioica (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)
	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
Replication	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 lactone	*Carduus benedictus*	Cnicin	Binding to the RdRp	In vitro	Alhadrami et al. (2021)
	Macrocyclic lactone	*Streptomyces avermitilis*	Ivermectin	Binding to the RdRp	In silico, in vitro	Heidary and Gharebaghi (2020)
	Alkaloid	*Lycoris radiata*	Lycorine	Binding to the RdRp	In vitro	Min et al. (2021)
Viral protein assembly and release	Phenol	*Brassica oleracea*	Sinapic acid	Binding to the E protein	In silico, in vitro	Orfali et al. (2021)

Table 1 (continued)

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)

Targeting replicase protein expression

Following the viral entrance and the uncoating, two processed polyproteins (pp) (pp1a andpp1ab) 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 baicaleinas 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). Additionally,

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 *Curcumalonga* 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, Gizawy 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), gallocatechingallate (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 gallocatechingallate 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, mefloquine 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 *Carduus 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. 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-Nicolas 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 $P2X_7$ 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 IC_{50} values of 88.6 and 58.9 μM (Hou et al. 2005).

Neuroprotective abilities of monochloropivaloylquercetin (**11**) and 2*S*-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 2*S*-5, 7, 3′, 5′ -tetrahydroxyflavanon 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).

Table 2 The reported natural products for treatment of neurological implications of SARS-CoV-2

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	NF-κB↓, CD-14↓
Kaempferol-7-*O*-*β*-D-Glucopyranoside (**10**)	Flavonoids	Plant	NQO1↓
Monochloropivaloylquercetin (**11**)	Flavonoids	Plant	aldose reductase↓
Naringin (**12**)	Flavonoids	Plant	$P2X_7$ 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↓
2*S*-5, 7, 3′, 5′ Tetrahydroxyflavanone (**24**)	Flavonoids	Plant	NQO1↓
2′, 4′-Dihydroxy-6′-methoxychalcone (**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-Methoxyflavanone (**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 oxidle B (**40**)	Alkaloids	Plant	AChE↓
Lycoramine (**41**)	Alkaloids	Plant	AChE↓
Norpluvine diacetate (**42**)	Alkaloids	Plant	AChE↓
6*α*-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-Carboline (**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	GABAa↓
Hirsutine (**52**)	Alkaloids	Plant	PI3K/Akt↓
Delavatine A (**53**)	Alkaloids	Plant	NF-κB↓
Betanin (**54**)	Alkaloids	Plant	NF-κB↓
Cannabisin F (**55**)	Alkaloids	Plant	NF-κB↓
Rhynchophylline (**56**)	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)↓
Tussilagonone (**60**)	Terpenoids	Plant	iNOS↓
14-Acetoxy-7*β*-(3-ethyl-cis-crotonoyloxy)-1*α*-(2-methyl-butyryloxy)-notonipetranone	Terpenoids	Plant	iNOS↓
tussilagone (**61**)	Terpenoids	Plant	iNOS↓
7*β*-(3-ethyl-cis-crotonoyloxy)-1*α*-(2-methylbutyryloxy)-3(14)-dehydro-*Z*-Notonipetrane (**62**)	Terpenoids	Plant	iNOS↓
Artemisinin B (**63**)	Terpenoids	Plant	NF-κB↓
Ginsenoside Rg3 (**64**)	Terpenoids	Plant	NF-κB↓, MAPK↓
Ginsenoside Rd (**65**)	Terpenoids	Plant	$P2X_4$ receptor↓, $P2X_7$ receptor↓
Ginsenoside Rg1 (**66**)	Terpenoids	Plant	NF-κB↓, MAPK↓
Triptolide (**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↓
Kanshone B (**71**)	Terpenoids	Plant	NF-κB↓, MAPK↓
Kanshone 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-Sitosterol (**79**)	Terpenoids	Plant	NF-κB↓, MAPK↓
Saikosaponin B3 (**80**)	Terpenoids	Plant	NF-κB↓
Pseudoginsenoside-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′-Hydroxycinnamaldehyde (**85**)	Phenylpropanoids	Plant	Low-density lipoprotein receptor-related protein 1↓
2′-Benzoyloxycinnamaldehyde (**86**)	Phenylpropanoids	Plant	Low-density lipoprotein receptor-related protein 1↓
9-Hydroxy-6, 7-dimethoxydalbergiqu-inol (**87**)	Phenylpropanoids	Plant	Heme oxygenase-1↑
4′-Hydroxy Pd–C-III (**88**)	Phenylpropanoids	Plant	AChE↓, BChE↓, *β*-secretase↓
Decursidin (**89**)	Phenylpropanoids	Plant	AChE↓, BChE↓, *β*-secretase↓
tannic Acid (**90**)	Phenylpropanoids	Plant	NF-κB↓
Magnesium lithospermate B (**91**)	Phenylpropanoids	Plant	NF-κB↓

Table 2 (continued)

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'-Methoxy Pd–C-I (**95**)	Phenylpropanoids	Plant	AChE↓, BChE↓, *β*-secretase↓
3-Hydroxyl-4-methoxyl cinnamic aldehyde (**96**)	Phenylpropanoids	Plant	AChE↓, BChE↓, *β*-secretase↓
4-Hydroxyl cinnamic aldehyde (**97**)	Phenylpropanoids	Plant	AChE↓, BChE↓, *β*-secretase↓
Tanshinone I (**98**)	Quinone	Plant	Aβ↓
Tanshinone IIA (**99**)	Quinone	Plant	Aβ↓
Abtusin (**100**)	Quinone	Plant	hMAO-A↓
Alaternin (**101**)	Quinone	Plant	hMAO-A/B↓
Aloeemodin (**102**)	Quinone	Plant	hMAO-A↓
Questin (**103**)	Quinone	Plant	hMAO-A/B↓ hMAO-A/B↓
Resveratrol (**104**)	Miscellaneous	Plant	$P2X_7$ 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 metalloproteinase 23↑
Δ^9-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↑
Paeonol (**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/B↓
Emodin-1-*β*-D-Glucopyranosyl (**120**)	Miscellaneous	Plant	NF-κB↓ Jak-Stat↓
Zerumbone (**121**)	Miscellaneous	Plant	NF-κB↓
5, 8-Dihydroxy-10-methoxy-2-methyl-4H-naphtho [1, 2-b]pyran-4-one (**122**)	Miscellaneous	Plant	MAPK↓ PI3K/Akt↓
4-(1,2-Dimethoxyethyl) benzene-1,2-diol (**123**)	Miscellaneous	Plant	MAPK↓
Bakuchiol (**124**)	Miscellaneous	Plant	MAPK↓
Macelignan (**125**)	Miscellaneous	Plant	PI3K/Akt↓
Isodojaponin D (**126**)	Miscellaneous	Plant	NF-κB↓
trans-Caryophyllene (**127**)	Miscellaneous	Plant	NF-κB↓
Macrolactin A (**128**)	Miscellaneous	Plant	*β*-secretase↓
4-(1, 2-Dimethoxyethyl) benzene-1, 2-diol (**129**)	Miscellaneous	Plant	PI3K/Akt↓
S-Allyl cysteine (**130**)	Miscellaneous	Plant	Nrf2-OH-1↑
Curcumin (**131**)	Miscellaneous	Plant	NF-κB↓, MAPK↓
Brevicompanine E (**132**)	Alkaloids	Microorganism	NF-κB↓, PI3K/Akt↓, Activator protein-1↓
8-*O*-Methylbostrycoidin (**133**)	Alkaloids	Microorganism	AChE↓
Beauvericin (**134**)	Alkaloids	Microorganism	AChE↓

Table 2 (continued)

Compound	Phytochemical class	Natural source	Targets/pathways
Asperterpene A (**135**)	Terpenoids	Microorganism	*β*-secretase↓
Asperterpene B (**136**)	Terpenoids	Microorganism	*β*-secretase↓
Flaviogeranin (**137**)	Quinone	Microorganism	Aβ↓
6, 8, 1′-tri-*O*-Methylaverantin (**138**)	Quinone	Microorganism	MAPK↓, Nrf2-OH-1↑
Anhydrojavanicin (**139**)	Quinone	Microorganism	AChE↓
Penicitrinone A (**140**)	Quinone	Microorganism	Aβ↓
Butyrolactone I (**141**)	Miscellaneous	Microorganism	NF-κB↓
Fomannoxin (**142**)	Miscellaneous	Microorganism	Aβ↓
Sporothrin A (**143**)	Miscellaneous	Microorganism	AChE↓
Terrein (**144**)	Miscellaneous	Microorganism	NF-κB↓, Nrf2-OH-1↑
Territrem D (**145**)	Miscellaneous	Microorganism	AChE↓
Territrem E (**146**)	Miscellaneous	Microorganism	AChE↓
Xyloketal A (**147**)	Miscellaneous	Microorganism	AChE↓
Xyloketal B (**148**)	Miscellaneous	Microorganism	JAK/Stat↓
Trienomycin A (**149**)	Miscellaneous	Microorganism	INOS↓
Trienomycin D (**150**)	Miscellaneous	Microorganism	INOS↓
Trienomycin J (**151**)	Miscellaneous	Microorganism	INOS↓

Additional information including references of the compounds in this table are mentioned in supplementary file

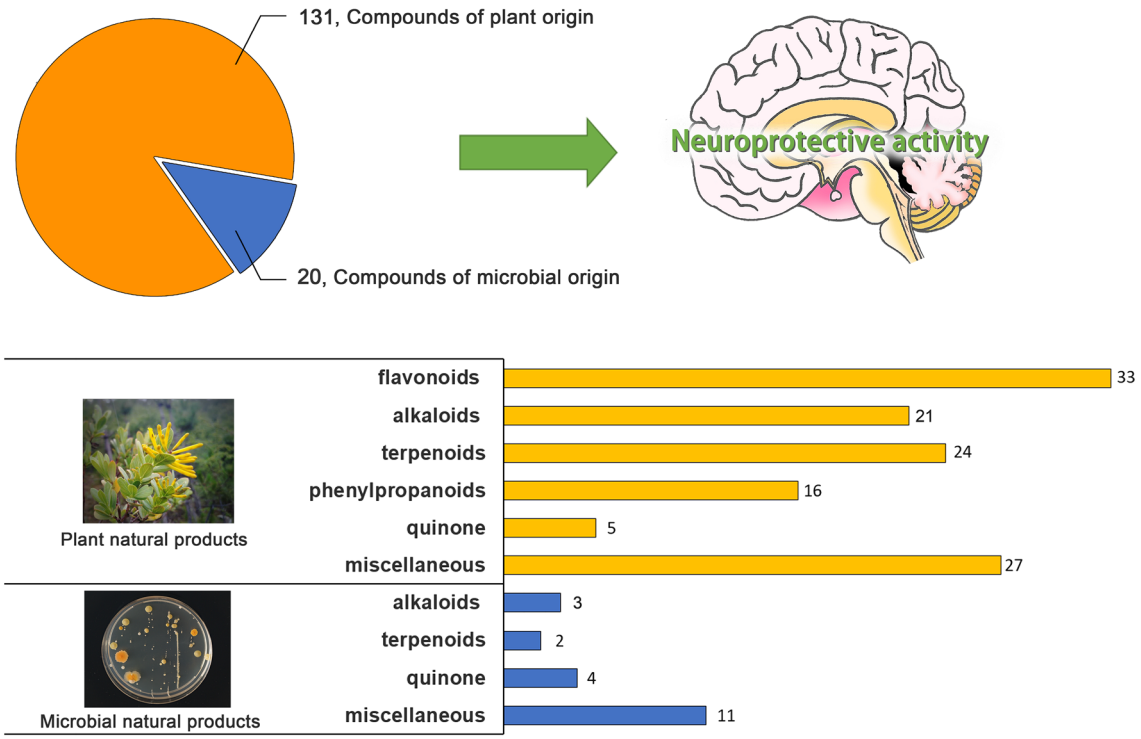

Fig. 3 Structural type of natural products with neuroprotective activity reported form plants and microbial natural products

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 oxidle 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). Brevicompanine 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 brevicompanine 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**), isonardosinone (**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-dimethylorsellinic 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 benzopyrene and LPS and subsequently inhibit the overactivation of microglia (Zhou et al. 2016; Bao et al. 2019). Also, 3-hydroxyl-4-methoxyl cinnamic aldehyde (**96**) and 4-hydroxyl 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 latiuscula*, 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

(**109**) were shown to possess significant dopamine D3/D4 receptor-activating effects in cells and exhibiting good therapeutic potential for PD (Paudel et al. 2020).

Flaviogeranin (**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 $A\beta_{1\text{-}42}$ 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 *Pestalotiopsis*, 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 cacaoisub* sp, significantly inhibiting the production of NO in LPS-induced BV2 model (IC_{50} = 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 erythrocytelysis-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

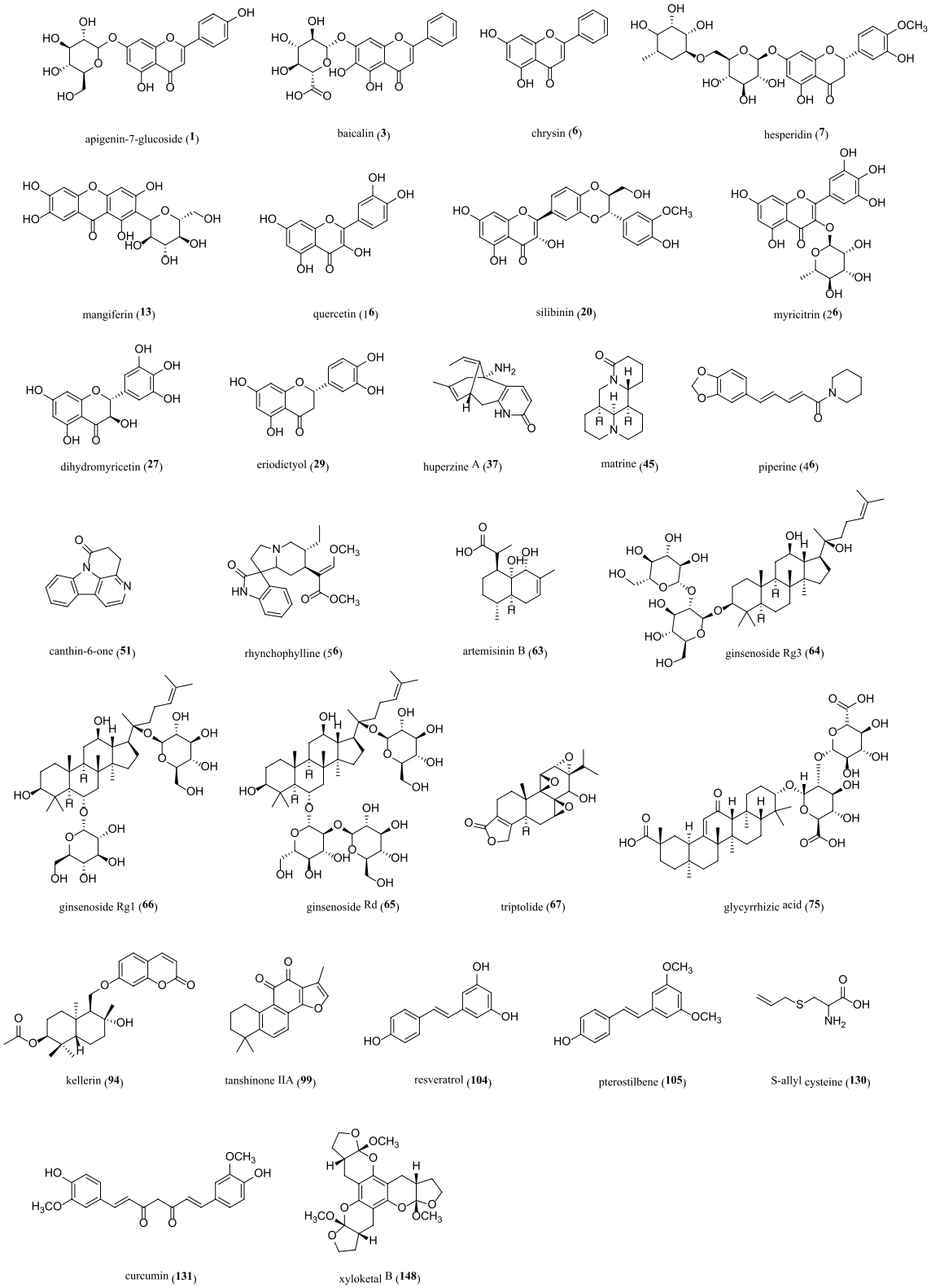

Fig. 4 Chemical structures of isolated from plant and microorganism with the potential of being used against neurological complications of SARS-CoV-2

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, naringin 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, naringin 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 vivo 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, silibinin (**20**), is the most important component of *Silybum marianum*. Silibinin possesses multiple biological functions including immune-boosting, hepatoprotective, antioxidant, antiviral activity, and neuroprotective activities (Castellaneta et al. 2016). Consistently, a study of silibinin has shown its potential inhibitory effects on SARS-CoV2 main protease using the molecular docking approach(Kumar et al. 2021b). Silibinin 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 Thl and the anti-inflammatory Th2 cytokines, respectively (Min et al. 2007). Therefore, taking into account silibinin's ameliorating effects against neuroinflammation and its related antiviral properties, silibinin 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 CD^{4+}T cells in experimental autoimmune encephalomyelitis rats by inhibiting NF-κB and MAPK- proteinkinase 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 $GABA_AR$/ tyrosine kinase receptor B/AKT expression and prevent synaptic dysgenesis and memory impairment in MHE rats. In addition, baicalin can enhance the interaction of $GABA_AR$ 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 $A\beta_{25-35}$ 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 uralen*s. 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 vanilloid 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 Ca^{2+}-activated K^+ channel (BKCa) can reduce the excitability of nerve cells, playing an important role in reducing Ca^{2+} 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 the 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). Rhynchophylline (**91**), is 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).

$P2X_7$ 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 $P2X_7$ 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 $P2X_7$ receptor and glial fibrillary acidic protein is reported by resveratrol, influencing P2X7 receptor-mediated Ca^{2+}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 $MnCl_2$-induced with irregular damaged nuclear membrane, rupture of myelin fiber on rat olfactory bulb by inhibiting H_2O_2-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, huperzine 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, territrem D, and territrem 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.

Acknowledgements The work was not funded by any funding agency.

Data availability The authors confirm that the data of this study are included within the article and its supplementary file.

Declarations

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

References

Abdallah HM, El-Halawany AM, Sirwi A, El-Araby AM, Mohamed GA, Ibrahim SR, Koshak AE, Asfour HZ, Awan ZA, Elfaky MA (2021) Repurposing of some natural product isolates as SARS-COV-2 main protease inhibitors via in vitro cell free and cell-based antiviral assessments and molecular modeling approaches. Pharmaceuticals 14:213. https://doi.org/10.3390/ph14030213

Abdel-Razek AS, El-Naggar ME, Allam A, Morsy OM, Othman SI (2020) Microbial natural products in drug discovery. Processes 8:470. https://doi.org/10.3390/pr8040470

Alhadrami HA, Sayed AM, Hassan HM, Youssif KA, Gaber Y, Moatasim Y, Kutkat O, Mostafa A, Ali MA, Rateb ME (2021) Cnicin as an Anti-SARS-CoV-2: an integrated in silico and in vitro approach for the rapid identification of potential COVID-19 therapeutics. Antibiotics 10:542. https://doi.org/10.3390/antibiotics10050542

Almasi F, Mohammadipanah F (2021) Hypothetical targets and plausible drugs of coronavirus infection caused by SARS-CoV-2. Transbound Emerg Dis 68:318–332. https://doi.org/10.1111/tbed.13734

Amraei R, Yin W, Napoleon MA, Suder EL, Berrigan J, Zhao Q, Olejnik J, Chandler KB, Xia C, Feldman J (2021) CD209L/L-SIGN and CD209/DC-SIGN act as receptors for SARS-CoV-2. ACS Cent Sci 7:1156–1165. https://doi.org/10.1021/acscentsci.0c01537

Andrabi MS, Andrabi SA (2020) Neuronal and cerebrovascular complications in coronavirus disease 2019. Front Pharmacol 11:570031. https://doi.org/10.3389/fphar.2020.570031

Bao Y, Chen Q, Xie Y, Tao Z, Jin K, Chen S, Bai Y, Yang J, Shan S (2019) Ferulic acid attenuates oxidative DNA damage and inflammatory responses in microglia induced by benzo(a)pyrene. Int Immunopharmacol 77:105980. https://doi.org/10.1016/j.intimp.2019.105980

Beauchamp LC, Finkelstein DI, Bush AI, Evans AH, Barnham KJ (2020) Parkinsonism as a third wave of the COVID-19 pandemic? J Parkinsons Dis 10:1343–1353. https://doi.org/10.3233/Jpd-202211

Berger JR, Brandstadter R, Bar-Or A (2020) COVID-19 and MS disease-modifying therapies. Neurol Neuroimmunol Neuroinflamm 7:e761. https://doi.org/10.1212/NXI.0000000000000761

Bicker J, Fortuna A, Alves G, Falcao A (2020) Nose-to-brain delivery of natural compounds for the treatment of central nervous system disorders. Curr Pharm Des 26:594–619. https://doi.org/10.2174/1381612826666200115101544

Bohmwald K, Galvez N, Ríos M, Kalergis AM (2018) Neurologic alterations due to respiratory virus infections. Front Cell Neurosci 12:386. https://doi.org/10.3389/fncel.2018.00386

Boison D, Steinhauser C (2018) Epilepsy and astrocyte energy metabolism. Glia 66:1235–1243. https://doi.org/10.1002/glia.23247

Bolay H, Gül A, Baykan B (2020) COVID-19 is a real headache! Headache 60:1415–1421. https://doi.org/10.1111/head.13856

Bostancıklıoğlu M (2020) SARS-CoV2 entry and spread in the lymphatic drainage system of the brain. Brain Behav Immun 87:122. https://doi.org/10.1016/j.bbi.2020.04.080

Butowt R, Bilinska K (2020) SARS-CoV-2: olfaction, brain infection, and the urgent need for clinical samples allowing earlier virus detection. ACS Chem Neurosci 11:1200–1203. https://doi.org/10.1021/acschemneuro.0c00172

Cai Y, Huang P, Xie Y (2020) Effects of huperzine A on hippocampal inflammatory response and neurotrophic factors in aged rats after anesthesia. Acta Cir Bras 34:e201901205. https://doi.org/10.1590/s0102-865020190120000005

Cao FL, Xu M, Wang Y, Gong KR, Zhang JT (2015) Tanshinone IIA attenuates neuropathic pain via inhibiting glial activation and immune response. Pharmacol Biochem Behav 128:1–7. https://doi.org/10.1016/j.pbb.2014.11.004

Carradori S, D'ascenzio M, Chimenti P, Secci D, Bolasco A (2014) Selective MAO-B inhibitors: a lesson from natural products. Mol Divers 18:219–243. https://doi.org/10.1007/s11030-013-9490-6

Castellaneta A, Massaro A, Rendina M, D'errico F, Carparelli S, Rizzi SF, Thomson AW, Di Leo A (2016) Immunomodulating effects of the anti-viral agent Silibinin in liver transplant patients with HCV recurrence. Transplant Res 5:1. https://doi.org/10.1186/s13737-016-0030-7

Chakravarti R, Singh R, Ghosh A, Dey D, Sharma P, Velayutham R, Roy S, Ghosh D (2021) A review on potential of natural products in the management of COVID-19. RSC Adv 11:16711–16735. https://doi.org/10.1039/D1RA00644D

Chen YC, Jinn TR, Chung TY, Li FY, Fan RJ, Tzen JTC (2010) Magnesium lithospermate B extracted from *Salvia miltiorrhiza* elevats intracellular Ca2+ level in SH-SY5Y cells. Acta Pharmacol Sin 31:923–929. https://doi.org/10.1038/aps.2010.102

Chen X, Wu Y, Chen C, Gu Y, Zhu C, Wang S, Chen J, Zhang L, Lv L, Zhang G, Yuan Y, Chai Y, Zhu M, Wu C (2021) Identifying potential anti-COVID-19 pharmacological components of traditional Chinese medicine Lianhuaqingwen capsule based on human exposure and ACE2 biochromatography screening. Acta Pharm Sin B 11:222–236. https://doi.org/10.1016/j.apsb.2020.10.002

Cheng S, Leblanc KJ, Li L (2014) Triptolide preserves cognitive function and reduces neuropathology in a mouse model of Alzheimer's disease. PLoS ONE 9:e108845. https://doi.org/10.1371/journal.pone.0108845

Chi X, Yan R, Zhang J, Zhang G, Zhang Y, Hao M, Zhang Z, Fan P, Dong Y, Yang Y, Chen Z, Guo Y, Zhang J, Li Y, Song X, Chen Y, Xia L, Fu L, Hou L, Xu J, Yu C, Li J, Zhou Q, Chen W (2020) A neutralizing human antibody binds to the N-terminal domain of the Spike protein of SARS-CoV-2. Science 369:650–655. https://doi.org/10.1126/science.abc6952

Chow YL, Lee KH, Vidyadaran S, Lajis NH, Akhtar MN, Israf DA, Syahida A (2012) Cardamonin from *Alpinia rafflesiana* inhibits inflammatory responses in IFN-gamma/LPS-stimulated BV2 microglia via NF-kappa B signalling pathway. Int Immunopharmacol 12:657–665. https://doi.org/10.1016/j.intimp.2012.01.009

Coelho C, Gallo G, Campos CB, Hardy L, Wurtele M (2020) Biochemical screening for SARS-CoV-2 main protease inhibitors. PLoS ONE 15:e0240079. https://doi.org/10.1371/journal.pone.0240079

Coerdt KM, Khachemoune A (2021) Corona viruses: reaching far beyond the common cold. Afr Health Sci 21:207–213. https://doi.org/10.4314/ahs.v21i1.27

Coutard B, Valle C, De Lamballerie X, Canard B, Seidah NG, Decroly E (2020) The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. Antiviral Res 176:104742. https://doi.org/10.1016/j.antiviral.2020.104742

Cumaoglu A, Yerer MB (2018) The effects of aldose reductase inhibitor quercetin and monochloropivaloylquercetin in amyloid beta peptide (1–42) induced neuroinflammation in microglial cells. Nat Prod Commun 13:693–698. https://doi.org/10.1177/1934578X1801300611

Da Rosa MR, Francelino Silva Junior LC, Santos Santana FM, Farias De Oliveira T, Campos Alcantara R, Monteiro Arnozo G, Da Silva R, Filho E, Galdino Dos Santos AG, Oliveira Da Cunha EJ, Salgueiro De Aquino SH, Freire De Souza CD (2021) Clinical manifestations of COVID-19 in the general population: systematic review. Wien Klin Wochenschr 133:377–382. https://doi.org/10.1007/s00508-020-01760-4

Dhiman P, Malik N, Khatkar A (2020) Natural based piperine derivatives as potent monoamine oxidase inhibitors: an in silico ADMET analysis and molecular docking studies. Bmc Chem 14:ARTN 12. https://doi.org/10.1186/s13065-020-0661-0

Ding S, Zhuge W, Hu J, Yang J, Wang X, Wen F, Wang C, Zhuge Q (2018) Baicalin reverses the impairment of synaptogenesis induced by dopamine burden via the stimulation of GABAAR-TrkB interaction in minimal hepatic encephalopathy. Psychopharmacology 235:1163–1178. https://doi.org/10.1007/s00213-018-4833-8

Dubé M, Le Coupanec A, Wong AH, Rini JM, Desforges M, Talbot PJ (2018) Axonal transport enables neuron-to-neuron propagation of human coronavirus OC43. J Virol 92:e00404-e418. https://doi.org/10.1128/JVI.00404-18

Edlow BL, Claassen J, Victor JD, Brown EN, Schiff ND (2020) Delayed reemergence of consciousness in survivors of severe COVID-19. Neurocrit Care 33:627–629. https://doi.org/10.1007/s12028-020-01133-9

Elebeedy D, Elkhatib WF, Kandeil A, Ghanem A, Kutkat O, Alnajjar R, Saleh MA, Abd El Maksoud AI, Badawy I, Al-Karmalawy AA (2021) Anti-SARS-CoV-2 activities of tanshinone IIA, carnosic acid, rosmarinic acid, salvianolic acid, baicalein, and glycyrrhetinic acid between computational and in vitro insights. RSC Adv 11:29267–29286. https://doi.org/10.1039/D1RA05268C

Elfiky AA (2021) SARS-CoV-2 RNA dependent RNA polymerase (RdRp) targeting: an in silico perspective. J Biomol Struct Dyn 39:3204–3212. https://doi.org/10.1080/07391102.2020.1761882

ElGizawy HA, Boshra SA, Mostafa A, Mahmoud SH, Ismail MI, Alsfouk AA, Taher AT, Al-Karmalawy AA (2021) *Pimenta dioica* (L.) Merr. bioactive constituents exert anti-SARS-CoV-2 and anti-inflammatory activities: molecular docking and dynamics, in vitro, and in vivo studies. Molecules 26:5844. https://doi.org/10.3390/molecules26195844

Erlund I (2004) Review of the flavonoids quercetin, hesperetin, and naringenin. Dietary sources, bioactivities, bioavailability, and epidemiology. Nutr Res 24:851–874. https://doi.org/10.1016/j.nutres.2004.07.005

Feng J, Wang JX, Du YH, Liu Y, Zhang W, Chen JF, Liu YJ, Zheng M, Wang KJ, He GQ (2018) Dihydromyricetin inhibits microglial activation and neuroinflammation by suppressing NLRP3 inflammasome activation in APP/PS1 transgenic mice. CNS Neurosci Ther 24:1207–1218. https://doi.org/10.1111/cns.12983

Ferreira ADF, Romão TT, Macedo YS, Pupe C, Nascimento OJ, Neurology FOTaaO (2020) COVID-19 and herpes zoster co-infection presenting with trigeminal neuropathy. Eur J Neurol 27:1748–1750. https://doi.org/10.1111/ene.14361

Fu HL, Liu L, Tong Y, Li YJ, Zhang X, Gao XJ, Yong JJ, Zhao JJ, Xiao D, Wen KS, Wang HQ (2019) The antidepressant effects of hesperidin on chronic unpredictable mild stress-induced mice. Eur J Pharmacol 853:236–246. https://doi.org/10.1016/j.ejphar.2019.03.035

Gangadevi S, Badavath VN, Thakur A, Yin N, De Jonghe S, Acevedo O, Jochmans D, Leyssen P, Wang K, Neyts J, Yujie T, Blum G (2021) Kobophenol A inhibits binding of host ACE2 receptor with spike RBD domain of SARS-CoV-2, a lead compound for

blocking COVID-19. J Phys Chem Lett 12:1793–1802. https://doi.org/10.1021/acs.jpclett.0c03119
Gao XQ, Du ZR, Yuan LJ, Zhang WD, Chen L, Teng JJ, Wong MS, Xie JX, Chen WF (2019) Ginsenoside Rg1 exerts anti-inflammatory effects via G protein-coupled estrogen receptor in lipopolysaccharide-induced microglia activation. Front Neurosci 13:1168. https://doi.org/10.3389/fnins.2019.01168
Gao J, Ding Y, Wang Y, Liang P, Zhang L, Liu R (2021) Oroxylin A is a severe acute respiratory syndrome coronavirus 2-spiked pseudotyped virus blocker obtained from Radix Scutellariae using angiotensin-converting enzyme II/cell membrane chromatography. Phytother Res 35:3194–3204. https://doi.org/10.1002/ptr
Gertsch J, Anavi-Goffer S (2012) Methylhonokiol attenuates neuroinflammation: a role for cannabinoid receptors? J Neuroinflamm 9:135. https://doi.org/10.1186/1742-2094-9-135
Ghosh R, Chakraborty A, Biswas A, Chowdhuri S (2020) Evaluation of green tea polyphenols as novel corona virus (SARS CoV-2) main protease (Mpro) inhibitors–an in silico docking and molecular dynamics simulation study. J Biomo Struct Dyn 2020:1–13. https://doi.org/10.1080/07391102.2020.1779818
Gong SS, Li YX, Zhang MT, Du J, Ma PS, Yao WX, Zhou R, Niu Y, Sun T, Yu JQ (2016) Neuroprotective effect of matrine in mouse model of vincristine-induced neuropathic pain. Neurochem Res 41:3147–3159. https://doi.org/10.1007/s11064-016-2040-8
Gonzalez-Scarano F, Tyler KL (1987) Molecular pathogenesis of neurotropic viral infections. Ann Neurol 22:565–574. https://doi.org/10.1002/ana.410220502
Gowrishankar S, Muthumanickam S, Kamaladevi A, Karthika C, Jothi R, Boomi P, Maniazhagu D, Pandian SK (2021) Promising phytochemicals of traditional Indian herbal steam inhalation therapy to combat COVID-19–An in silico study. Food Chem Toxicol 148:111966. https://doi.org/10.1016/j.fct.2020.111966
Gresa-Arribas N, Serratosa J, Saura J, Sola C (2010) Inhibition of CCAAT/enhancer binding protein delta expression by chrysin in microglial cells results in anti-inflammatory and neuroprotective effects. J Neurochem 115:526–536. https://doi.org/10.1111/j.1471-4159.2010.06952.x
Guijarro-Real C, Plazas M, Rodríguez-Burruezo A, Prohens J, Fita A (2021) Potential in vitro inhibition of selected plant extracts against SARS-CoV-2 chymotripsin-like protease (3CLPro) activity. Foods 10:1503. https://doi.org/10.3390/foods10071503
Harapan BN, Yoo HJ (2021) Neurological symptoms, manifestations, and complications associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 19 (COVID-19). J Neurol 268:3059–3071. https://doi.org/10.1007/s00415-021-10406-y
Hassaniazad M, Inchehsablagh BR, Kamali H, Tousi A, Eftekhar E, Jaafari MR, Fathalipour M, Nikoofal-Sahlabadi S, Gouklani H, Alizade H, Nikpoor AR (2020) The clinical effect of Nano micelles containing curcumin as a therapeutic supplement in patients with COVID-19 and the immune responses balance changes following treatment: a structured summary of a study protocol for a randomised controlled trial. Trials 21:876. https://doi.org/10.1186/s13063-020-04824-y
Hayakawa Y, Yamazaki Y, Kurita M, Kawasaki T, Takagi M, Shin-Ya K (2010) Flaviogeranin, a new neuroprotective compound from *Streptomyces* sp. J Antibiot 63:379–380. https://doi.org/10.1038/ja.2010.49
Hayashi M, Sahashi Y, Baba Y, Okura H, Shimohata T (2020) COVID-19-associated mild encephalitis/encephalopathy with a reversible splenial lesion. J Neurol Sci 415:116941. https://doi.org/10.1016/j.jns.2020.116941
He P, Yan S, Zheng J, Gao Y, Zhang S, Liu Z, Liu X, Xiao C (2018) Eriodictyol attenuates LPS-induced neuroinflammation, amyloidogenesis, and cognitive impairments via the inhibition of NF-kappaB in male C57BL/6J mice and BV2 microglial cells. J Agric Food Chem 66:10205–10214. https://doi.org/10.1021/acs.jafc.8b03731
Heidary F, Gharebaghi R (2020) Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen. J Antibiot (Tokyo) 73:593–602. https://doi.org/10.1038/s41429-020-0336-z
Helliwell RM, Shioukhuey CO, Dhuna K, Molero JC, Ye JM, Xue CC, Stokes L (2015) Selected ginsenosides of the protopanaxdiol series are novel positive allosteric modulators of P2X7 receptors. Br J Pharmacol 172:3326–3340. https://doi.org/10.1111/bph.13123
Henss L, Auste A, Schürmann C, Schmidt C, Von Rhein C, Mühlebach MD, Schnierle BS (2021) The green tea catechin epigallocatechin gallate inhibits SARS-CoV-2 infection. J Gen Virol 102:001574. https://doi.org/10.1099/jgv.0.001574
Hepburn M, Mullaguri N, George P, Hantus S, Punia V, Bhimraj A, Newey CR (2021) Acute symptomatic seizures in critically ill patients with COVID-19: is there an association? Neurocrit Care 34:139–143. https://doi.org/10.1007/s12028-020-01006-1
Ho TY, Tang NY, Hsiang CY, Hsieh CL (2014) Uncaria rhynchophylla and rhynchophylline improved kainic acid-induced epileptic seizures via IL-1beta and brain-derived neurotrophic factor. Phytomedicine 21:893–900. https://doi.org/10.1016/j.phymed.2014.01.011
Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu N-H, Nitsche A (2020) SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181(271–280):e8. https://doi.org/10.1016/j.cell.2020.02.052
Hou WC, Lin RD, Chen CT, Lee MH (2005) Monoamine oxidase B (MAO-B) inhibition by active principles from *Uncaria rhynchophylla*. J Ethnopharmacol 100:216–220. https://doi.org/10.1016/j.jep.2005.03.017
Hu S, Wang J, Zhang Y, Bai H, Wang C, Wang N, He L (2021) Three salvianolic acids inhibit 2019-nCoV spike pseudovirus viropexis by binding to both its RBD and receptor ACE2. J Med Virol 93:3143–3151. https://doi.org/10.1002/jmv.26874
Huang YH, Jiang D, Huang JT (2020) SARS-CoV-2 detected in cerebrospinal fluid by PCR in a case of COVID-19 encephalitis. Brain Behav Immun 87:149. https://doi.org/10.1016/j.bbi.2020.05.012
Innok W, Hiranrat A, Chana N, Rungrotmongkol T, Kongsune P (2021) In silico and in vitro anti-AChE activity investigations of constituents from Mytragyna speciosa for Alzheimer's disease treatment. J Comput Aided Mol Des 35:325–336. https://doi.org/10.1007/s10822-020-00372-4
Jackson CB, Farzan M, Chen B, Choe H (2022) Mechanisms of SARS-CoV-2 entry into cells. Nat Rev Mol Cell Biol 23:3–20. https://doi.org/10.1038/s41580-021-00418-x
Jan J-T, Cheng T-JR, Juang Y-P, Ma H-H, Wu Y-T, Yang W-B, Cheng C-W, Chen X, Chou T-H, Shie J-J (2021) Identification of existing pharmaceuticals and herbal medicines as inhibitors of SARS-CoV-2 infection. Proc Natl Acad Sci USA 118:e2021579118. https://doi.org/10.1073/pnas.2021579118
Javed H, Vaibhav K, Ahmed ME, Khan A, Tabassum R, Islam F, Safhi MM, Islam F (2015) Effect of hesperidin on neurobehavioral, neuroinflammation, oxidative stress and lipid alteration in intracerebroventricular streptozotocin induced cognitive impairment in mice. J Neurol Sci 348:51–59. https://doi.org/10.1016/j.jns.2014.10.044
Jirjees F, Saad AK, Al Hano Z, Hatahet T, Al Obaidi H, Dallal Bashi YH (2021) COVID-19 treatment guidelines: do they really reflect best medical practices to manage the pandemic? Infect Dis Rep 13:259–284. https://doi.org/10.3390/idr13020029
Joo SS, Yoo YM, Ahn BW, Nam SY, Kim YB, Hwang KW, Lee DI (2008) Prevention of inflammation-mediated neurotoxicity

by Rg3 and its role in microglial activation. Biol Pharm Bull 31:1392–1396. https://doi.org/10.1248/bpb.31.1392

Joshi RS, Jagdale SS, Bansode SB, Shankar SS, Tellis MB, Pandya VK, Chugh A, Giri AP, Kulkarni MJ (2021) Discovery of potential multi-target-directed ligands by targeting host-specific SARS-CoV-2 structurally conserved main protease. J Biomol Struct Dyn 39:3099–3114. https://doi.org/10.1080/07391102.2020.1760137

Justin-Thenmozhi A, Dhivya Bharathi M, Kiruthika R, Manivasagam T, Borah A, Essa MM (2018) Attenuation of aluminum chloride-induced neuroinflammation and caspase activation through the AKT/GSK-3beta pathway by hesperidin in Wistar rats. Neurotoxicol Res 34:463–476. https://doi.org/10.1007/s12640-018-9904-4

Kang A, Xie T, Zhu D, Shan J, Di L, Zheng X (2017) Suppressive effect of ginsenoside Rg3 against lipopolysaccharide-induced depression-like behavior and neuroinflammation in mice. J Agric Food Chem 65:6861–6869. https://doi.org/10.1021/acs.jafc.7b02386

Kang S, Piao Y, Kang YC, Lim S, Pak YK (2020) Qi-activating quercetin alleviates mitochondrial dysfunction and neuroinflammation in vivo and in vitro. Arch Pharm Res 43:553–566. https://doi.org/10.1007/s12272-020-01238-x

Kang J, Liu S, Song Y, Chu Y, Wang M, Shi Y, Zhang F, Zhu L (2021) Matrine treatment reduces retinal ganglion cell apoptosis in experimental optic neuritis. Sci Rep 11:9520. https://doi.org/10.1038/s41598-021-89086-7

Karlsson J, Emgard M, Brundin P, Burkitt MJ (2000) trans-resveratrol protects embryonic mesencephalic cells from tert-butyl hydroperoxide: electron paramagnetic resonance spin trapping evidence for a radical scavenging mechanism. J Neurochem 75:141–150. https://doi.org/10.1046/j.1471-4159.2000.0750141.x

Kase Y, Okano H (2021) Neurological pathogenesis of SARS-CoV-2 (COVID-19): from virological features to clinical symptoms. Inflamm Regener 41:1–7. https://doi.org/10.1186/s41232-021-00165-8

Kernan MR, Amarquaye A, Chen JL, Chan J, Sesin DF, Parkinson N, Ye Z, Barrett M, Bales C, Stoddart CA, Sloan B, Blanc P, Limbach C, Mrisho S, Rozhon EJ (1998) Antiviral phenylpropanoid glycosides from the medicinal plant *Markhamia lutea*. J Nat Prod 61:564–570. https://doi.org/10.1021/np9703914

Kim KW, Kim HJ, Sohn JH, Yim JH, Kim YC, Oh H (2018) Anti-neuroinflammatory effect of 6,8,1'-tri-O-methylaverantin, a metabolite from a marine-derived fungal strain *Aspergillus* sp., via upregulation of heme oxygenase-1 in lipopolysaccharide-activated microglia. Neurochem Int 113:8–22. https://doi.org/10.1016/j.neuint.2017.11.010

Kim KW, Kim HJ, Sohn JH, Yim JH, Kim YC, Oh H (2020) Terrein suppressed lipopolysaccharide-induced neuroinflammation through inhibition of NF-kappaB pathway by activating Nrf2/HO-1 signaling in BV2 and primary microglial cells. J Pharmacol Sci 143:209–218. https://doi.org/10.1016/j.jphs.2020.01.011

Kim J-W, Abdullayev N, Neuneier J, Fink GR, Lehmann HC (2021a) Post-COVID-19 encephalomyelitis. Neurol Res Pract 3:1–3. https://doi.org/10.1186/s42466-021-00113-4

Kim TY, Jeon S, Jang Y, Gotina L, Won J, Ju YH, Kim S, Jang MW, Won W, Park MG (2021b) Platycodin D, a natural component of *Platycodon grandiflorum*, prevents both lysosome-and TMPRSS2-driven SARS-CoV-2 infection by hindering membrane fusion. Exp Mol Med 53:956–972. https://doi.org/10.1038/s12276-021-00624-9

Ko W, Park JS, Kim KW, Kim J, Kim YC, Oh H (2018) Nardosinone-type sesquiterpenes from the hexane fraction of *Nardostachys jatamansi* attenuate NF-kappaB and MAPK signaling pathways in lipopolysaccharide-stimulated BV2 microglial cells. Inflammation 41:1215–1228. https://doi.org/10.1007/s10753-018-0768-9

Kumar M, Mazumder P, Mohapatra S, Thakur AK, Dhangar K, Taki K, Mukherjee S, Patel AK, Bhattacharya P, Mohapatra P (2021a) A chronicle of SARS-CoV-2: seasonality, environmental fate, transport, inactivation, and antiviral drug resistance. J Hazard Mat 405:124043. https://doi.org/10.1016/j.jhazmat.2020.124043

Kumar S, Kashyap P, Chowdhury S, Kumar S, Panwar A, Kumar A (2021b) Identification of phytochemicals as potential therapeutic agents that binds to Nsp15 protein target of coronavirus (SARS-CoV-2) that are capable of inhibiting virus replication. Phytomedicine 85:153317. https://doi.org/10.1016/j.phymed.2020.153317

Kuo CL, Pilling LC, Atkins JL, JaH M, Delgado J, Kuchel GA, Melzer D (2020) APOE e4 genotype predicts severe COVID-19 in the UK Biobank Community Cohort. J Gerontol A Biol Sci Med Sci 75:2231–2232. https://doi.org/10.1093/gerona/glaa131

Kyrou I, Randeva HS, Spandidos DA, Karteris E (2021) Not only ACE2—the quest for additional host cell mediators of SARS-CoV-2 infection: Neuropilin-1 (NRP1) as a novel SARS-CoV-2 host cell entry mediator implicated in COVID-19. Signal Transduct Target Ther 6:1–3. https://doi.org/10.1038/s41392-020-00460-9

Lanzillotta A, Pignataro G, Branca C, Cuomo O, Sarnico I, Benarese M, Annunziato L, Spano P, Pizzi M (2013) Targeted acetylation of NF-kappaB/RelA and histones by epigenetic drugs reduces post-ischemic brain injury in mice with an extended therapeutic window. Neurobiol Dis 49:177–189. https://doi.org/10.1016/j.nbd.2012.08.018

Lau K-K, Yu W-C, Chu C-M, Lau S-T, Sheng B, Yuen K-Y (2004) Possible central nervous system infection by SARS coronavirus. Emerg Infect Dis 10:342. https://doi.org/10.3201/eid1002.030638

Lee YJ, Choi DY, Choi IS, Kim KH, Kim YH, Kim HM, Lee K, Cho WG, Jung JK, Han SB, Han JY, Nam SY, Yun YW, Jeong JH, Oh KW, Hong JT (2012) Inhibitory effect of 4-O-methylhonokiol on lipopolysaccharide-induced neuroinflammation, amyloidogenesis and memory impairment via inhibition of nuclear factor-kappaB in vitro and in vivo models. J Neuroinflamm 9:35. https://doi.org/10.1186/1742-2094-9-35

Lee S, Kim DC, Baek HY, Lee KD, Kim YC, Oh H (2018) Anti-neuroinflammatory effects of tryptanthrin from *Polygonum tinctorium* Lour. in lipopolysaccharide-stimulated BV2 microglial cells. Arch Pharm Res 41:419–430. https://doi.org/10.1007/s12272-018-1020-8

Li XJ, Zhou M, Li XH, Xu YH, Liu H, Yang M (2009) Effects of Tanshinone IIa on cytokines and platelets in immune vasculitis and its mechanism. Zhongguo Shi Yan Xue Ye Xue Za Zhi 17:188–192

Li ZX, Chen JW, Yuan F, Huang YY, Zhao LY, Li J, Su HX, Liu J, Pang JY, Lin YC, Lu XL, Pei Z, Wang GL, Guan YY (2013) Xyloketal B exhibits its antioxidant activity through induction of HO-1 in vascular endothelial cells and zebrafish. Mar Drugs 11:504–522. https://doi.org/10.3390/md11020504

Li N, Meng DL, Pan Y, Cui QL, Li GX, Ni H, Sun Y, Qing DG, Jia XG, Pan YN, Hou Y (2015) Anti-neuroinflammatory and NQO1 inducing activity of natural phytochemicals from *Coreopsis tinctoria*. J Function Foods 17:837–846. https://doi.org/10.1016/j.jff.2015.06.027

Li M, Shao H, Zhang X, Qin B (2016) Hesperidin alleviates lipopolysaccharide-induced neuroinflammation in mice by promoting the miRNA-132 pathway. Inflammation 39:1681–1689. https://doi.org/10.1007/s10753-016-0402-7

Li HY, Yang M, Li Z, Meng Z (2017a) Curcumin inhibits angiotensin II-induced inflammation and proliferation of rat vascular smooth muscle cells by elevating PPAR-gamma activity and reducing oxidative stress. Int J Mol Med 39:1307–1316. https://doi.org/10.3892/ijmm.2017.2924

Li J, Yue M, Zhou D, Wang M, Zhang H (2017b) Abcb1a but not Abcg2 played a predominant role in limiting the brain distribution of Huperzine A in mice. Food Chem Toxicol 107:68–73. https://doi.org/10.1016/j.fct.2017.06.005

Li H, Chen FJ, Yang WL, Qiao HZ, Zhang SJ (2021a) Quercetin improves cognitive disorder in aging mice by inhibiting NLRP3 inflammasome activation. Food Funct 12:717–725. https://doi.org/10.1039/d0fo01900c

Li Z, Li X, Shen J, Chan MT, Wu WKK (2021b) Miller Fisher syndrome associated with COVID-19: an up-to-date systematic review. Environ Sci Pollut Res Int. https://doi.org/10.1007/s11356-021-13233-w

Lima M, Siokas V, Aloizou A-M, Liampas I, Mentis A-FA, Tsouris Z, Papadimitriou A, Mitsias PD, Tsatsakis A, Bogdanos DP (2020) Unraveling the possible routes of SARS-COV-2 invasion into the central nervous system. Curr Treat Options Neurol 22:1–15. https://doi.org/10.1007/s11940-020-00647-z

Liu J, Xu J, Mi Y, Yang Y, Li Q, Zhou D, Wei K, Chen G, Li N, Hou Y (2020a) Pterostilbene alleviates cerebral ischemia and reperfusion injury in rats by modulating microglial activation. Food Funct 11:5432–5445. https://doi.org/10.1039/d0fo00084a

Liu X, Raghuvanshi R, Ceylan FD, Bolling BW (2020b) Quercetin and its metabolites inhibit recombinant human angiotensin-converting enzyme 2 (ACE2) activity. J Agric Food Chem 68:13982–13989. https://doi.org/10.1021/acs.jafc.0c05064

Liu H, Ye F, Sun Q, Liang H, Li C, Li S, Lu R, Huang B, Tan W, Lai L (2021a) *Scutellaria baicalensis* extract and baicalein inhibit replication of SARS-CoV-2 and its 3C-like protease in vitro. J Enzyme Inhib Med Chem 36:497–503. https://doi.org/10.1080/14756366.2021.1873977

Liu Z, Pan H, Zhang Y, Zheng Z, Xiao W, Hong X, Chen F, Peng X, Pei Y, Rong J, He J, Zou L, Wang J, Zhong J, Han X, Cao Y (2021) Ginsenoside-Rg1 attenuates sepsis-induced cardiac dysfunction by modulating mitochondrial damage via the P2X7 receptor-mediated Akt/GSK-3beta signaling pathway. J Biochem Mol Toxicol. https://doi.org/10.1002/jbt.22885

Loza AMM, Holroyd KB, Johnson SA, Pilgrim DM, Amato AA (2021) Guillain-Barré syndrome in the placebo and active arms of a COVID-19 vaccine clinical trial: temporal associations do not imply causality. Neurology 96:1052–1054. https://doi.org/10.1212/WNL.0000000000011881

Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, Bi Y, Ma X, Zhan F, Wang L, Hu T, Zhou H, Hu Z, Zhou W, Zhao L, Chen J, Meng Y, Wang J, Lin Y, Yuan J, Xie Z, Ma J, Liu WJ, Wang D, Xu W, Holmes EC, Gao GF, Wu G, Chen W, Shi W, Tan W (2020) Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 395:565–574. https://doi.org/10.1016/S0140-6736(20)30251-8

Luo D, Or TC, Yang CL, Lau AS (2014) Anti-inflammatory activity of iridoid and catechol derivatives from *Eucommia ulmoides* Oliver. ACS Chem Neurosci 5:855–866. https://doi.org/10.1021/cn5001205

Luo D, Lin Q, Tan JL, Zhao HY, Feng X, Chen NH, Wu ZN, Fan CL, Li YL, Ding WL, Xiao F, Wang GC, Zhang YB (2021) Water-soluble matrine-type alkaloids with potential anti-neuroinflammatory activities from the seeds of *Sophora alopecuroides*. Bioorg Chem 116:105337. https://doi.org/10.1016/j.bioorg.2021.105337

Lv X, Zhao S, Ning Z, Zeng H, Shu Y, Tao O, Xiao C, Lu C, Liu Y (2015) Citrus fruits as a treasure trove of active natural metabolites that potentially provide benefits for human health. Chem Cent J 9:68. https://doi.org/10.1186/s13065-015-0145-9

Lv Y, Wang S, Liang P, Wang Y, Zhang X, Jia Q, Fu J, Han S, He L (2021) Screening and evaluation of anti-SARS-CoV-2 components from *Ephedra sinica* by ACE2/CMC-HPLC-IT-TOF-MS approach. Anal Bioanal Chem 413:2995–3004. https://doi.org/10.1007/s00216-021-03233-7

Madia F, Merico B, Primiano G, Cutuli SL, De Pascale G, Servidei S (2020) Acute myopathic quadriplegia in patients with COVID-19 in the intensive care unit. Neurology 95:492–494. https://doi.org/10.1212/WNL.0000000000010280

Magistri M, Velmeshev D, Makhmutova M, Patel P, Sartor GC, Volmar CH, Wahlestedt C, Faghihi MA (2016) The BET-bromodomain inhibitor JQ1 reduces inflammation and tau phosphorylation at Ser396 in the brain of the 3xTg model of Alzheimer's disease. Curr Alzheimer Res 13:985–995. https://doi.org/10.2174/1567205013666160427101832

Mahmoud OM, Salem NA, Al Badawi MH (2020) Protective effect of propolis on manganese chloride neurotoxicity of olfactory bulb in adult male albino rat. Folia Morphol (Warsz) 79:672–680. https://doi.org/10.5603/FM.a2019.0127

Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D (2020a) Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 77:683–690. https://doi.org/10.1001/jamaneurol.2020.1127

Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X, Li Y, Hu B (2020b) Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 77:683–690. https://doi.org/10.1001/jamaneurol.2020.1127

Mccray PB Jr, Pewe L, Wohlford-Lenane C, Hickey M, Manzel L, Shi L, Netland J, Jia HP, Halabi C, Sigmund CD (2007) Lethal infection of K18-hACE2 mice infected with severe acute respiratory syndrome coronavirus. J Virol 81:813–821. https://doi.org/10.1128/JVI.02012-06

Melani A, Amadio S, Gianfriddo M, Vannucchi MG, Volonte C, Bernardi G, Pedata F, Sancesario G (2006) P2X7 receptor modulation on microglial cells and reduction of brain infarct caused by middle cerebral artery occlusion in rat. J Cereb Blood Flow Metab 26:974–982. https://doi.org/10.1038/sj.jcbfm.9600250

Meng J, Chen Y, Bi F, Li H, Chang C, Liu W (2019) Pterostilbene attenuates amyloid-beta induced neurotoxicity with regulating PDE4A-CREB-BDNF pathway. Am J Transl Res 11:6356–6369

Min K, Yoon WK, Kim SK, Kim BH (2007) Immunosuppressive effect of silibinin in experimental autoimmune encephalomyelitis. Arch Pharm Res 30:1265–1272. https://doi.org/10.1007/BF02980267

Min JS, Kwon S, Jin Y-H (2021) SARS-CoV-2 RdRp inhibitors selected from a cell-based SARS-CoV-2 RdRp activity assay system. Biomedicines 9:996. https://doi.org/10.3390/biomedicines9080996

Mohan S, Elhassan Taha MM, Makeen HA, Alhazmi HA, Al Bratty M, Sultana S, Ahsan W, Najmi A, Khalid A (2020) Bioactive natural antivirals: an updated review of the available plants and isolated molecules. Molecules 25:4878. https://doi.org/10.3390/molecules25214878

Monti G, Giovannini G, Marudi A, Bedin R, Melegari A, Simone AM, Santangelo M, Pignatti A, Bertellini E, Trenti T (2020) Anti-NMDA receptor encephalitis presenting as new onset refractory status epilepticus in COVID-19. Seizure 81:18. https://doi.org/10.1016/j.seizure.2020.07.006

Moraga-Nicolas F, Jara C, Godoy R, Iturriaga-Vasquez P, Venthur H, Quiroz A, Becerra J, Mutis A, Hormazabal E (2018) Rhodolirium andicola: a new renewable source of alkaloids with acetylcholinesterase inhibitory activity, a study from nature to molecular docking. Braz J Pharmacogn 28:34–43. https://doi.org/10.1016/j.bjp.2017.11.009

Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, Ueno M, Sakata H, Kondo K, Myose N (2020) A first case of meningitis/encephalitis associated with SARS-Coronavirus-2.

IntJ Infect Dis 94:55–58. https://doi.org/10.1016/j.ijid.2020.03.062

Muchtaridi M, Fauzi M, Khairul Ikram NK, Mohd Gazzali A, Wahab HA (2020) Natural flavonoids as potential angiotensin-converting enzyme 2 inhibitors for anti-SARS-CoV-2. Molecules 25:3980. https://doi.org/10.3390/molecules25173980

Nam KN, Choi YS, Jung HJ, Park GH, Park JM, Moon SK, Cho KH, Kang C, Kang I, Oh MS, Lee EH (2010) Genipin inhibits the inflammatory response of rat brain microglial cells. Int Immunopharmacol 10:493–499. https://doi.org/10.1016/j.intimp.2010.01.011

Nawrot-Hadzik I, Zmudzinski M, Matkowski A, Preissner R, Kęsik-Brodacka M, Hadzik J, Drag M, Abel R (2021) Reynoutria rhizomes as a natural source of SARS-CoV-2 Mpro inhibitors-molecular docking and in vitro study. Pharmaceuticals 14:742. https://doi.org/10.3390/ph14080742

Newman DJ, Cragg GM (2020) Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. J Nat Prod 83:770–803. https://doi.org/10.1021/acs.jnatprod.9b01285

Ojha S, Javed H, Azimullah S, Abul Khair SB, Haque ME (2016) Glycyrrhizic acid attenuates neuroinflammation and oxidative stress in rotenone model of Parkinson's disease. Neurotoxicol Res 29:275–287. https://doi.org/10.1007/s12640-015-9579-z

Omotuyi IO, Nash O, Ajiboye BO, Olumekun VO, Oyinloye BE, Osuntokun OT, Olonisakin A, Ajayi AO, Olusanya O, Akomolafe FS (2021) Aframomum melegueta secondary metabolites exhibit polypharmacology against SARS-CoV-2 drug targets: in vitro validation of furin inhibition. Phytother Res 35:908–919. https://doi.org/10.1002/ptr.6843

Orfali R, Rateb ME, Hassan HM, Alonazi M, Gomaa MR, Mahrous N, Gaballah M, Kandeil A, Perveen S, Abdelmohsen UR (2021) Sinapic acid suppresses SARS CoV-2 replication by targeting its envelope protein. Antibiotics 10:420. https://doi.org/10.3390/antibiotics10040420

Pan B, Fang S, Zhang J, Pan Y, Liu H, Wang Y, Li M, Liu L (2020) Chinese herbal compounds against SARS-CoV-2: puerarin and quercetin impair the binding of viral S-protein to ACE2 receptor. Comput Struct Biotechnol J 18:3518–3527. https://doi.org/10.1016/j.csbj.2020.11.010

Pandey P, Rane JS, Chatterjee A, Kumar A, Khan R, Prakash A, Ray S (2021) Targeting SARS-CoV-2 spike protein of COVID-19 with naturally occurring phytochemicals: an in silico study for drug development. J Biomol Struct Dyn 39:6306–6316. https://doi.org/10.1080/07391102.2020.1796811

Paniz-Mondolfi A, Bryce C, Grimes Z, Gordon RE, Reidy J, Lednicky J, Sordillo EM, Fowkes M (2020) Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). J Med Virol 92:699–702. https://doi.org/10.1002/jmv.25915

Pasch L, He SY, Huddleston H, Cedars MI, Beshay A, Zane LT, Shinkai K (2016) Clinician vs self-ratings of hirsutism in patients with polycystic ovarian syndrome: associations with quality of life and depression. JAMA Dermatol 152:783–788. https://doi.org/10.1001/jamadermatol.2016.0358

Pascual-Goñi E, Fortea J, Martínez-Domeño A, Rabella N, Tecame M, Gómez-Oliva C, Querol L, Gómez-Ansón B (2020) COVID-19-associated ophthalmoparesis and hypothalamic involvement. Neurol-Neuroimmunology. https://doi.org/10.1212/NXI.0000000000000823

Paudel P, Park SE, Seong SH, Jung HA, Choi JS (2020) Bromophenols from *Symphyocladia latiuscula* target human monoamine oxidase and dopaminergic receptors for the management of neurodegenerative diseases. J Agric Food Chem 68:2426–2436. https://doi.org/10.1021/acs.jafc.0c00007

Pawar KS, Mastud RN, Pawar SK, Pawar SS, Bhoite RR, Bhoite RR, Kulkarni MV, Deshpande AR (2021) Oral curcumin with piperine as adjuvant therapy for the treatment of COVID-19: a randomized clinical trial. Front Pharmacol 12:669362. https://doi.org/10.3389/fphar.2021.669362

Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B (2020) COVID-19–associated acute hemorrhagic necrotizing encephalopathy: imaging features. Radiology 296:E119–E120. https://doi.org/10.1148/radiol.2020201187

Qi C, Bao J, Wang J, Zhu H, Xue Y, Wang X, Li H, Sun W, Gao W, Lai Y, Chen JG, Zhang Y (2016) Asperterpenes A and B, two unprecedented meroterpenoids from *Aspergillus terreus* with BACE1 inhibitory activities. Chem Sci 7:6563–6572. https://doi.org/10.1039/c6sc02464e

Qiang W, Cai W, Yang Q, Yang L, Dai Y, Zhao Z, Yin J, Li Y, Li Q, Wang Y, Weng X, Zhang D, Chen Y, Zhu X (2018a) Artemisinin B improves learning and memory impairment in AD dementia mice by suppressing neuroinflammation. Neuroscience 395:1–12. https://doi.org/10.1016/j.neuroscience.2018.10.041

Raihan T, Rabbee MF, Roy P, Choudhury S, Baek K-H, Azad AK (2021) Microbial metabolites: the emerging hotspot of antiviral compounds as potential candidates to avert viral pandemic alike COVID-19. Front Molecular Biosci. https://doi.org/10.3389/fmolb.2021.732256

Ramalho MJ, Andrade S, Loureiro JA, Do Carmo Pereira M (2020) Nanotechnology to improve the Alzheimer's disease therapy with natural compounds. Drug Deliv Transl Res 10:380–402. https://doi.org/10.1007/s13346-019-00694-3

Rani J, Bhargav A, Khan FI, Ramachandran S, Lai D, Bajpai U (2021) In silico prediction of natural compounds as potential multi-target inhibitors of structural proteins of SARS-CoV-2. J Biomol Struct Dyn 6:1–17. https://doi.org/10.1080/07391102.2021

Reza-Zaldívar EE, Hernández-Sapiéns MA, Minjarez B, Gomez-Pinedo U, Márquez-Aguirre AL, Mateos-Díaz JC, Matias-Guiu J, Canales-Aguirre AA (2021) Infection mechanism of SARS-COV-2 and its implication on the nervous system. Front Immunol 11:621735. https://doi.org/10.3389/fimmu.2020.621735

Rickert U, Cossais F, Heimke M, Arnold P, Preusse-Prange A, Wilms H, Lucius R (2018) Anti-inflammatory properties of Honokiol in activated primary microglia and astrocytes. J Neuroimmunol 323:78–86. https://doi.org/10.1016/j.jneuroim.2018.07.013

Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, Sánchez-Larsen Á, Layos-Romero A, García-García J, González E, Redondo-Peñas I, Perona-Moratalla AB, Del Valle-Pérez JA (2020) Neurologic manifestations in hospitalized patients with COVID-19: the ALBACOVID registry. Neurology 95:e1060–e1070. https://doi.org/10.1212/WNL.0000000000009937

Roser M, Ritchie H, Ortiz-Ospina E, Hasell J (2020) Coronavirus pandemic (COVID-19)—statistics and research—our world in data. Our World in Data

Ruan Q, Hu X, Ao H, Ma H, Gao Z, Liu F, Kong D, Bao Z, Yu Z (2014) The neurovascular protective effects of huperzine A on D-galactose-induced inflammatory damage in the rat hippocampus. Gerontology 60:424–439. https://doi.org/10.1159/000358235

Saad M, Omrani AS, Baig K, Bahloul A, Elzein F, Matin MA, Selim MA, Al Mutairi M, Al Nakhli D, Al Aidaroos AY (2014) Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. Int J Infect Dis 29:301–306. https://doi.org/10.1016/j.ijid.2014.09.003

Salgado-Benvindo C, Thaler M, Tas A, Ogando NS, Bredenbeek PJ, Ninaber DK, Wang Y, Hiemstra PS, Snijder EJ, Van Hemert MJ (2020) Suramin inhibits SARS-CoV-2 infection in cell culture by interfering with early steps of the replication cycle. Antimicrob

Agents Chemother 64:e00900-e920. https://doi.org/10.1128/AAC.00900-20
Satarker S, Nampoothiri M (2020) Structural proteins in severe acute respiratory syndrome coronavirus-2. Arch Med Res 51:482–491. https://doi.org/10.1016/j.arcmed.2020.05.012
Sharifi-Rad J, Quispe C, Herrera-Bravo J, Martorell M, Sharopov F, Tumer TB, Kurt B, Lankatillake C, Docea AO, Moreira AC, Dias DA, Mahomoodally MF, Lobine D, Cruz-Martins N, Kumar M, Calina D (2021) A pharmacological perspective on plant-derived bioactive molecules for epilepsy. Neurochem Res 46:2205–2225. https://doi.org/10.1007/s11064-021-03376-0
Shi T-H, Huang Y-L, Chen C-C, Pi W-C, Hsu Y-L, Lo L-C, Chen W-Y, Fu S-L, Lin C-H (2020) Andrographolide and its fluorescent derivative inhibit the main proteases of 2019-nCoV and SARS-CoV through covalent linkage. Biochem Biophys Res Commun 533:467–473. https://doi.org/10.1016/j.bbrc.2020.08.086
Song E, Zhang C, Israelow B, Lu-Culligan A, Prado AV, Skriabine S, Lu P, Weizman OE, Liu F, Dai Y, Szigeti-Buck K, Yasumoto Y, Wang G, Castaldi C, Heltke J, Ng E, Wheeler J, Alfajaro MM, Levavasseur E, Fontes B, Ravindra NG, Van Dijk D, Mane S, Gunel M, Ring A, SaJ K, Zhang K, Wilen CB, Horvath TL, Plu I, Haik S, Thomas JL, Louvi A, Farhadian SF, Huttner A, Seilhean D, Renier N, Bilguvar K, Iwasaki A (2021) Neuroinvasion of SARS-CoV-2 in human and mouse brain. J Exp Med 218:e20202135. https://doi.org/10.1084/jem.20202135
Su H-X, Yao S, Zhao W-F, Li M-J, Liu J, Shang W-J, Xie H, Ke C-Q, Hu H-C, Gao M-N (2020a) Anti-SARS-CoV-2 activities in vitro of Shuanghuanglian preparations and bioactive ingredients. Acta Pharmacol Sin 41:1167–1177. https://doi.org/10.1038/s41401-020-0483-6
Su HX, Yao S, Zhao WF, Li MJ, Liu J, Shang WJ, Xie H, Ke CQ, Hu HC, Gao MN, Yu KQ, Liu H, Shen JS, Tang W, Zhang LK, Xiao GF, Ni L, Wang DW, Zuo JP, Jiang HL, Bai F, Wu Y, Ye Y, Xu YC (2020b) Anti-SARS-CoV-2 activities in vitro of Shuanghuanglian preparations and bioactive ingredients. Acta Pharmacol Sin 41:1167–1177. https://doi.org/10.1038/s41401-020-0483-6
Swain O, Romano SK, Miryala R, Tsai J, Parikh V, Umanah GK (2021) SARS-CoV-2 neuronal invasion and complications: potential mechanisms and therapeutic approaches. J Neurosci 41:5338–5349. https://doi.org/10.1523/JNEUROSCI.3188-20.2021
Tang D, Liu LL, He QR, Yan W, Li D, Gao JM (2018) Ansamycins with antiproliferative and antineuroinflammatory activity from moss-soil-derived *Streptomyces cacaoi* subsp. asoensis H2S5. J Nat Prod 81:1984–1991. https://doi.org/10.1021/acs.jnatprod.8b00203
Ter Ellen BM, Kumar ND, Bouma EM, Troost B, Van De Pol DP, Van Der Ende-Metselaar HH, Apperloo L, Van Gosliga D, Van Den Berge M, and Nawijn MC (2020) Resveratrol and pterostilbene potently inhibit SARS-CoV-2 infection in vitro. bioRxiv. https://doi.org/10.1101/2020.09.24.285940
Ter Ellen BM, Dinesh Kumar N, Bouma EM, Troost B, Van De Pol DPI, Van Der Ende-Metselaar HH, Apperloo L, Van Gosliga D, Van Den Berge M, Nawijn MC, Van Der Voort PHJ, Moser J, Rodenhuis-Zybert IA, Smit JM (2021) Resveratrol and pterostilbene inhibit SARS-CoV-2 replication in air-liquid interface cultured human primary bronchial epithelial cells. Viruses. https://doi.org/10.3390/v13071335
Tu QL, Le DS, Wang CY, Mao GH (2020) Pterostilbene attenuates ischemic stroke by modulating miR-21-5p/PDCD4 axis in vivo and in vitro. J Funct Foods 75:104275. https://doi.org/10.1016/j.jff.2020.104275
Tutunchi H, Naeini F, Ostadrahimi A, Hosseinzadeh-Attar MJ (2020) Naringenin, a flavanone with antiviral and anti-inflammatory effects: a promising treatment strategy against COVID-19. Phytother Res 34:3137–3147. https://doi.org/10.1002/ptr.6781
Vacchiano V, Riguzzi P, Volpi L, Tappatà M, Avoni P, Rizzo G, Guerra L, Zaccaroni S, Cortelli P, Michelucci R (2020) Early neurological manifestations of hospitalized COVID-19 patients. Neurol Sci 41:2029–2031. https://doi.org/10.1007/s10072-020-04525-z
Vardhan S, Sahoo SK (2022) Computational studies on the interaction of SARS-CoV-2 Omicron SGp RBD with human receptor ACE2, limonin and glycyrrhizic acid. Comput Biol Med 144:105367. https://doi.org/10.1016/j.compbiomed.2022.105367
Vitalakumar D, Sharma A, Kumar A, Flora S (2021) Neurological manifestations in COVID-19 patients: a meta-analysis. ACS Chem Neurosci 12:2776–2797. https://doi.org/10.1021/acschemneuro.1c00353
Wager TT, Chandrasekaran RY, Hou X, Troutman MD, Verhoest PR, Villalobos A, Will Y (2010) Defining desirable central nervous system drug space through the alignment of molecular properties, in vitro ADME, and safety attributes. ACS Chem Neurosci 1:420–434. https://doi.org/10.1021/cn100007x
Wang J, Zhang HY, Tang XC (2010) Huperzine a improves chronic inflammation and cognitive decline in rats with cerebral hypoperfusion. J Neurosci Res 88:807–815. https://doi.org/10.1002/jnr.22237
Wang QM, Yu X, Patal K, Hu RD, Chuang S, Zhang G, Zheng J (2013) Tanshinones inhibit amyloid aggregation by amyloid-beta peptide, disaggregate amyloid fibrils, and protect cultured cells. Acs Chem Neurosci 4:1004–1015. https://doi.org/10.1021/cn400051e
Wang K, Chen Z, Huang J, Huang L, Luo N, Liang X, Liang M, Xie W (2017a) Naringenin prevents ischaemic stroke damage via anti-apoptotic and anti-oxidant effects. Clin Exp Pharmacol Physiol 44:862–871. https://doi.org/10.1111/1440-1681.12775
Wang Z, Guo S, Wang J, Shen Y, Zhang J, Wu Q (2017b) Nrf2/HO-1 mediates the neuroprotective effect of mangiferin on early brain injury after subarachnoid hemorrhage by attenuating mitochondria-related apoptosis and neuroinflammation. Sci Rep 7:11883. https://doi.org/10.1038/s41598-017-12160-6
Wang K, Chen W, Zhang Z, Deng Y, Lian J-Q, Du P, Wei D, Zhang Y, Sun X-X, Gong L (2020a) CD147-spike protein is a novel route for SARS-CoV-2 infection to host cells. Signal Transduct Target Ther 5:1–10. https://doi.org/10.1038/s41392-020-00426-x
Wang S-C, Chen Y, Wang Y-C, Wang W-J, Yang C-S, Tsai C-L, Hou M-H, Chen H-F, Shen Y-C, Hung M-C (2020b) Tannic acid suppresses SARS-CoV-2 as a dual inhibitor of the viral main protease and the cellular TMPRSS2 protease. Am J Cancer Res 10:4538
Wang L, Wu Y, Yao S, Ge H, Zhu Y, Chen K, Chen W-Z, Zhang Y, Zhu W, Wang H-Y (2021) Discovery of potential small molecular SARS-CoV-2 entry blockers targeting the spike protein. Acta Pharmacol Sin 43:788–796. https://doi.org/10.1038/s41401-021-00735-z
Wu B, Ma Y, Yi Z, Liu S, Rao S, Zou L, Wang S, Xue Y, Jia T, Zhao S, Shi L, Li L, Yuan H, Liang S (2017) Resveratrol-decreased hyperalgesia mediated by the P2X7 receptor in gp120-treated rats. Mol Pain 13:1744806917707667. https://doi.org/10.1177/1744806917707667
Wu C, Liu Y, Yang Y, Zhang P, Zhong W, Wang Y, Wang Q, Xu Y, Li M, Li X (2020a) Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharm Sin B 10:766–788. https://doi.org/10.1016/j.apsb.2020.02.008
Wu CY, Lin YS, Yang YH, Shu LH, Cheng YC, Liu HT (2020b) GB-2 inhibits ACE2 and TMPRSS2 expression: In vivo and in vitro studies. Biomed Pharmacother 132:110816. https://doi.org/10.1016/j.biopha.2020.110816
Xiao J, Zhai H, Yao Y, Wang C, Jiang W, Zhang C, Simard AR, Zhang R, Hao J (2014) Chrysin attenuates experimental autoimmune neuritis by suppressing immuno-inflammatory responses.

Neuroscience 262:156–164. https://doi.org/10.1016/j.neuroscience.2014.01.004
Xing Y, Li N, Zhou D, Chen G, Jiao K, Wang W, Si Y, Hou Y (2017) Sesquiterpene coumarins from *Ferula sinkiangensis* act as neuroinflammation inhibitors. Planta Med 83:135–142. https://doi.org/10.1055/s-0042-109271
Yadav R, Chaudhary JK, Jain N, Chaudhary PK, Khanra S, Dhamija P, Sharma A, Kumar A, Handu S (2021) Role of structural and non-structural proteins and therapeutic targets of SARS-CoV-2 for COVID-19. Cells 10:821. https://doi.org/10.3390/cells10040821
Yang X, Du L, Tang X, Jung SY, Zheng B, Soh BY, Kim SY, Gu Q, Park H (2009) Brevicompanine E reduces lipopolysaccharide-induced production of proinflammatory cytokines and enzymes in microglia by inhibiting activation of activator protein-1 and nuclear factor-kappaB. J Neuroimmunol 216:32–38. https://doi.org/10.1016/j.jneuroim.2009.09.004
Yang Z, Zhao T, Zou Y, Zhang JH, Feng H (2014) Curcumin inhibits microglia inflammation and confers neuroprotection in intracerebral hemorrhage. Immunol Lett 160:89–95. https://doi.org/10.1016/j.imlet.2014.03.005
Ye M, Luo G, Ye D, She M, Sun N, Lu YJ, Zheng J (2021) Network pharmacology, molecular docking integrated surface plasmon resonance technology reveals the mechanism of Toujie Quwen Granules against coronavirus disease 2019 pneumonia. Phytomed 85:153401. https://doi.org/10.1016/j.phymed.2020.153401
Yu S, Zhu Y, Xu J, Yao G, Zhang P, Wang M, Zhao Y, Lin G, Chen H, Chen L, Zhang J (2021) Glycyrrhizic acid exerts inhibitory activity against the spike protein of SARS-CoV-2. Phytomedicine 85:153364. https://doi.org/10.1016/j.phymed.2020.153364
Zandi K, Musall K, Oo A, Cao D, Liang B, Hassandarvish P, Lan S, Slack RL, Kirby KA, Bassit L, Amblard F, Kim B, Abubakar S, Sarafianos SG, Schinazi RF (2021) Baicalein and baicalin Inhibit SARS-CoV-2 RNA-dependent-RNA polymerase. Microorganisms 9:893. https://doi.org/10.3390/microorganisms9050893
Zarezadeh M, Baluchnejadmojarad T, Kiasalari Z, Afshin-Majd S, Roghani M (2017) Garlic active constituent s-allyl cysteine protects against lipopolysaccharide-induced cognitive deficits in the rat: possible involved mechanisms. Eur J Pharmacol 795:13–21. https://doi.org/10.1016/j.ejphar.2016.11.051
Zarmouh NO, Eyunni SK, Soliman KFA (2017) The Benzopyrone Biochanin-A as a reversible, competitive, and selective monoamine oxidase B inhibitor. Bmc Complement Altern Med 17:ARTN 34. https://doi.org/10.1186/s12906-016-1525-y
Zhan Y, Ta W, Tang W, Hua R, Wang J, Wang C, Lu W (2021) Potential antiviral activity of isorhamnetin against SARS-CoV-2 spike pseudotyped virus in vitro. Drug Dev Res 82:1124–1130. https://doi.org/10.1002/ddr.21815
Zhang S, Kan QC, Xu Y, Zhang GX, Zhu L (2013) Inhibitory effect of matrine on blood-brain barrier disruption for the treatment of experimental autoimmune encephalomyelitis. Mediators Inflamm 2013:736085. https://doi.org/10.1155/2013/736085
Zhang K, Ge Z, Xue Z, Huang W, Mei M, Zhang Q, Li Y, Li W, Zhang Z, Zhang Z, Zhang L, Wang H, Cai J, Yao Z, Zhang R, Da Y (2015) Chrysin suppresses human CD14(+) monocyte-derived dendritic cells and ameliorates experimental autoimmune encephalomyelitis. J Neuroimmunol 288:13–20. https://doi.org/10.1016/j.jneuroim.2015.08.017
Zhang X, Hu J, Zhong L, Wang N, Yang L, Liu CC, Li H, Wang X, Zhou Y, Zhang Y, Xu H, Bu G, Zhuang J (2016) Quercetin stabilizes apolipoprotein E and reduces brain Abeta levels in amyloid model mice. Neuropharmacology 108:179–192. https://doi.org/10.1016/j.neuropharm.2016.04.032
Zhang J, Zheng Y, Luo Y, Du Y, Zhang X, Fu J (2019) Curcumin inhibits LPS-induced neuroinflammation by promoting microglial M2 polarization via TREM2/ TLR4/ NF-kappaB pathways in BV2 cells. Mol Immunol 116:29–37. https://doi.org/10.1016/j.molimm.2019.09.020
Zhang W, Mi Y, Jiao K, Xu J, Guo T, Zhou D, Zhang X, Ni H, Sun Y, Wei K, Li N, Hou Y (2020a) Kellerin alleviates cognitive impairment in mice after ischemic stroke by multiple mechanisms. Phytother Res 34:2258–2274. https://doi.org/10.1002/ptr.6676
Zhang Y-N, Zhang Q-Y, Li X-D, Xiong J, Xiao S-Q, Wang Z, Zhang Z-R, Deng C-L, Yang X-L, Wei H-P (2020b) Gemcitabine, lycorine and oxysophoridine inhibit novel coronavirus (SARS-CoV-2) in cell culture. Emerg Microbes Infect 9:1170–1173. https://doi.org/10.1080/22221751.2020.1772676
Zhang Y, Xu Q, Sun Z, Zhou L (2020c) Current targeted therapeutics against COVID-19: Based on first-line experience in China. Pharmacol Res 157:104854. https://doi.org/10.1016/j.phrs.2020.104854
Zhang ZR, Zhang YN, Li XD, Zhang HQ, Xiao SQ, Deng F, Yuan ZM, Ye HQ, Zhang B (2020d) A cell-based large-scale screening of natural compounds for inhibitors of SARS-CoV-2. Signal Transduct Target Ther 5:218. https://doi.org/10.1038/s41392-020-00343-z
Zhang D, Hamdoun S, Chen R, Yang L, Ip CK, Qu Y, Li R, Jiang H, Yang Z, Chung SK (2021) Identification of natural compounds as SARS-CoV-2 entry inhibitors by molecular docking-based virtual screening with bio-layer interferometry. Pharmacol Res 172:105820. https://doi.org/10.1016/j.phrs.2021.105820
Zhou J, Zhang HY, Tang XC (2001) Huperzine A attenuates cognitive deficits and hippocampal neuronal damage after transient global ischemia in gerbils. Neurosci Lett 313:137–140. https://doi.org/10.1016/s0304-3940(01)02265-0
Zhou D, Li N, Zhang Y, Yan C, Jiao K, Sun Y, Ni H, Lin B, Hou Y (2016) Biotransformation of neuro-inflammation inhibitor kellerin using *Angelica sinensis* (Oliv.) Diels callus. RSC Adv 6:97302–97312. https://doi.org/10.1039/c6ra22502k
Zhu WL, Ma SP, Qu R, Kang DL, Liu YD (2006) Antidepressant effect of baicalin extracted from the root of *Scutellaria baicalensis* in mice and rats. Pharm Biol 44:503–510. https://doi.org/10.1080/13880200600878684
Zhu JJ, Wu SH, Chen X, Jiang TT, Li XQ, Li JM, Yan Y, Wu XJ, Liu YY, Dong P (2020) Tanshinone IIA suppresses hypoxia-induced apoptosis in medial vestibular nucleus cells via a Skp2/BKCa Axis. Curr Pharm Des 26:4185–4194. https://doi.org/10.2174/1381612826666200602144405
Zhu Z-L, Qiu X-D, Wu S, Liu Y-T, Zhao T, Sun Z-H, Li Z-R, Shan G-Z (2021) Blocking effect of demethylzeylasteral on the interaction between human ACE2 protein and SARS-CoV-2 RBD protein discovered using SPR technology. Molecules 26:57. https://doi.org/10.3390/molecules26010057
Zou X, Chen K, Zou J, Han P, Hao J, Han Z (2020) Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med 14:185–192. https://doi.org/10.1007/s11684-020-0754-0