



A Review on SARS-CoV-2-Induced Neuroinflammation, Neurodevelopmental Complications, and Recent Updates on the Vaccine Development

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Abstract

Coronavirus disease 2019 (COVID-19) is a devastating viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The incidence and mortality of COVID-19 patients have been increasing at an alarming rate. The mortality is much higher in older individuals, especially the ones suffering from respiratory distress, cardiac abnormalities, renal diseases, diabetes, and hypertension. Existing evidence demonstrated that SARS-CoV-2 makes its entry into human cells through angiotensin-converting enzyme 2 (ACE-2) followed by the uptake of virions through cathepsin L or transmembrane protease serine 2 (TMPRSS2). SARS-CoV-2-mediated abnormalities in particular cardiovascular and neurological ones and the damaged coagulation systems require extensive research to develop better therapeutic modalities. As SARS-CoV-2 uses its S-protein to enter into the host cells of several organs, the S-protein of the virus is considered as the ideal target to develop a potential vaccine. In this review, we have attempted to highlight the landmark discoveries that lead to the development of various vaccines that are currently under different stages of clinical progression. Besides, a brief account of various drug candidates that are being tested to mitigate the burden of COVID-19 was also covered. Further, in a dedicated section, the impact of SARS-CoV-2 infection on neuronal inflammation and neuronal disorders was discussed. In summary, it is expected that the content covered in this article help to understand the pathophysiology of COVID-19 and the impact on neuronal complications induced by SARS-CoV-2 infection while providing an update on the vaccine development.

Keywords SARS-CoV-2 · Neurological damage · Coagulation · ACE-2 · S-protein · Vaccine

Abbreviations

COVID-19	Coronavirus disease	RBD	Receptor-binding domain
SARS-CoV	Severe acute respiratory syndrome coronavirus	RBM	Receptor-binding motif
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2	RNA	Ribonucleic acid
CoV	Coronavirus	ORF	Open reading frame
MERS	Middle East respiratory syndrome	Nsp	Non-structural proteins
hCoV	Human coronavirus	S-protein	Spike protein
ACEIs	Angiotensin-converting enzyme inhibitors	N-protein	Nucleocapsid protein
ARBs	Angiotensin II receptor blockers	M-protein	Membrane protein
NTD	N-terminal domain	E-protein	Envelope protein
		DC-SIGN	Dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin
		L-SIGN	Liver/lymph node-specific intercellular adhesion molecules-3-grabbing non-integrin
		DPP4	Dipeptidyl peptidase 4
		HCQ	Hydroxychloroquine
		IFNs	Interferons
		RAS	Renin-angiotensin system
		ACE	Angiotensin-converting enzyme

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AT1R	Angiotensin type 1 receptor
AT2R	Angiotensin type 2 receptor
GPCRs	G-protein-coupled receptors
TMPRSS2	Transmembrane serine protease 2
PAMPs	Pathogen-associated molecular patterns
US-FDA	US Food and Drug Administration
IL	Interleukins
BBB	Blood–brain barrier
BAL	Bronchoalveolar lavage
CNS	Central nervous system
GFAP	Glial fibrillary acidic protein
NfL	Neurofilament light chain
MRI	Magnetic resonance imaging
ICU	Intensive care unit
ARDS	Acute respiratory distress syndrome
PNS	Peripheral nervous system
RT-PCR	Real-time polymerase chain reaction
CSF	Cerebrospinal fluid
BCSFB	Blood-cerebrospinal fluid barrier
CP	Choroid plexus
PD	Parkinson’s disease
OE	Olfactory epithelium
OECs	Olfactory ensheathing cells
EV	Extracellular vesicles
GCSF	Granulocyte colony-stimulating factor
DDC	DOPA decarboxylase
DMTs	Disease-modifying therapies
MS	Multiple sclerosis
A β	Beta-amyloid
AD	Alzheimer’s disease
AMP	Antimicrobial peptide
hiPSCs	human induced pluripotent stem cells
NPCs	Neural progenitor cells
MHV	Mouse hepatitis virus
NTD	N-terminal domain
HR1	Heptad repeat 1
HR2	Heptad repeat 2
CP	Cytoplasmic domain
TM	Transmembrane domain
HT	Hydroxytyrosol
OLE	Oleuropein aglycone
OT	Ozone therapy
GBS	Guillain–Barré syndrome
ADEM	Acute disseminated encephalomyelitis

Introduction

Coronaviruses (CoVs) are RNA viruses, which belong to the Coronaviridae family and Coronavirinae subfamily. They are widely distributed among animals and humans, causing respiratory, enteric, hepatic, and neurological disorders [1, 2]. SARS-CoV, SARS-CoV-2, hCoV-229E, OC43, NL63, and HKU1 are

currently circulating in the human population, causing mild and self-limiting upper respiratory tract infections [3]. Severe acute respiratory syndrome-coronavirus (SARS)-CoV and Middle East respiratory syndrome-coronavirus (MERS)-CoV have emerged as two highly pathogenic CoVs over the past two decades [4]. The outbreak of highly contagious SARS-CoV-2 is a variant of coronavirus, which is currently causing a pandemic infection globally. Infection with SARS-CoV-2 causes a severe respiratory disease referred to as the COVID-19, which is accompanied by the symptoms of fever, cough, pneumonia, dysphonia, and occasional diarrhea, after 3–14 days of incubation [5, 6]. As of April 6th 2021, over 131.8 million confirmed cases and 2.8 million deaths were reported worldwide due to COVID-19 disease (<https://www.who.int>).

Key Insights in to the Structural Features of SARS-CoV-2

Structurally, SARS-CoV-2 is a 65–125 nm in diameter virus with club-shaped spikes on the enveloped surface. The virus contains a helical nucleocapsid, which is bound to a single positive-strand RNA of 27–32 kbp [7, 8]. Phylogenetic studies of the SARS-CoV-2 genome revealed its homology to other beta coronaviruses that were reported in bats. SARS-CoV-2 has a similarity of 79% to SARS-CoV and 50% to the MERS-CoV [9]. The genome of SARS-CoV-2 contains 14 open reading frames (ORFs) [10]. The ORF1a/ORF1ab is located at the 5’ end and encodes two polypeptides, PP1a and PP1ab. Polypeptides upon proteolytic cleavage encode nonstructural proteins (Nsp 1–16) that form a replicase and transcriptase complex, which is required for replication and transcription of the virus [11, 12]. The other 13 ORFs at 3’ encode four main structural proteins and nine putative accessory factors. Structural proteins include: spike (S) protein, nucleocapsid (N) protein, membrane (M), and envelope (E) proteins, which are essential for virus assembly and infection [13] (Fig. 1). “S” protein interacts efficiently with various host receptors and facilitates the attachment of the virus on the host cell surface and mediates the entry of the virus into the host cells. “M” protein maintains the virus in its intact shape [14]. “E” protein is the smallest structural protein that plays a significant role in the viral pathogenesis, viral assembly, and viral release inside the host cells [15]. “N” protein interacts with RNA substrates, transcriptional regulatory sequences, and genomic packing signals and plays a critical role in the pathogenicity [16, 17]. The other essential structural and accessory proteins coded by the open reading frames are hemagglutinin esterase protein, 3a/b protein, and 4a/b protein [8]. Recent research reports have identified many mutations in the genome of SARS-CoV-2, suggesting the ability of viruses to acquire adaptations to their new host. The enhanced infection abilities of the SARS-CoV-2 are believed to be imparted by mutations in NSP2 and NSP3 molecules [18].

Mitigating SARS-CoV-2-Induced COVID-19 Disease: Strategies That Are Under Evaluation

Several basic-, clinical-, and public health research findings have reported the efficacy of several molecules against the target proteins in SARS-CoV-2. Besides, several immunomodulators and drug repurposing strategies have been described as effective against SARS-CoV-2; however, their usage was constrained by adverse drug reactions and systemic toxicity. For instance, the administration of ACE-2 inhibiting anti-malarial drug hydroxychloroquine (HCQ) was proven effective against SARS-CoV-2-induced damage. However, monotherapeutic approaches using HCQ were reported unsuccessful, hence, strategies combining HCQ with other pharmacological agents for treating COVID-19 cases are currently being explored [19]. Also, several novel small molecule inhibitors (NSMIs), antiviral agents such as umifenovir, remdesivir, nitazoxanide, favipiravir, ritonavir, lopinavir, interferons (IFNs), anti-cytokine drugs, anticoagulants, and passive antibody therapies are currently being tested in different stages of clinical development (Table 1) [19].

Key Therapeutic Targets

SARS-CoV-2 Interactions with Host Cells

Angiotensin-Converting Enzyme 2 (ACE-2)

ACE-2 is a zinc-dependent metalloprotease ectoenzyme, which is reported to be a key mediator of SARS-CoV-2 entry into host cells [39]. ACE-2 is located on the apical membrane of polarized cells of the testis, cardiovascular epithelium, cardiac myocytes, cardiac fibroblasts, epithelial cells of the kidney, liver, intestine, brain, and lungs [39–43]. ACE-2 is a type I integral membrane protein sharing 40% homology with ACE (angiotensin-converting enzyme). It is a key player in the renin-angiotensin system (RAS) [44]. ACE activates RAS by converting angiotensin I to angiotensin II. Angiotensin II activity is mediated through selective interactions with angiotensin II type 1 receptor (AT1R) and angiotensin II type 2 receptor (AT2R), a type of G-protein-coupled receptors (GPCRs). However, additional data is currently warranted to delineate the role of ACE in the entry of human CoVs [44].

ACE-2 acts as a functional cellular receptor for coronaviruses, namely, NL63 and SARS-CoV, by facilitating viral entry into the lungs [45, 46]. Studies using fluorescent probes have confirmed that SARS-CoV-2 could act on the same ACE-2 receptor for entering the host cell [47, 48]. ACE-2 consists of an N-terminal peptidase domain and a

C-terminal collectrin-like domain joined together with a single transmembrane helix and an intracellular segment of about 40 amino acid residues [49, 50]. The peptidase domain of ACE-2 cleaves angiotensin II to angiotensin (1–7), which functions in association with a G-protein-coupled Mas-receptor. The ACE-2-angiotensin-Mas receptor axis mediates a regulatory effect, which antagonizes the effects of the ACE-angiotensin II axis and consequently protects the pulmonary and cardiovascular system from the harmful impact of RAS activation [51–53].

In the lungs, ACE-2 is expressed in pulmonary endothelium, type I and type II alveolar epithelial cells, and smooth muscle cells [41]. Several studies have reported that the downregulation of ACE-2 contributes to the development and progression of lung disease accompanied by the changes in vascular permeability, increased edema, neutrophil accumulation in lungs leading to respiratory failure, and death [52]. SARS-CoV-2 spike (S) protein binds to ACE-2, inducing ACE-2 shedding by activating disintegrin and metalloproteinase-17 [54] (Fig. 2). S1 subunit has the receptor-binding domain, which upon binding to ACE-2, undergoes conformational changes facilitating viral attachment to the host [55]. S1 subunit in S-protein undergoes priming by the transmembrane serine protease 2 (TMPRSS2) or pH-sensitive endosomal proteases cathepsin B and L at S1/S2 and S2 sites. S-protein priming mediates the entry of SARS-CoV-2 into the host, by the viral envelope and host cellular membrane fusion thereby triggers endocytosis [33, 56–58]. The enhanced binding affinity of SARS-CoV-2 to the ACE-2 receptor is due to a single N501T mutation in the gene coding for S-protein in SARS-CoV-2, which makes this disease transmission more likely to other organs [59].

The acidic environment in the endosomes is capable of facilitating the fusion of SARS-CoV-2 viral and endosomal membranes, releasing the viral genome to the cytosol [60]. The released positive-strand viral RNA is translated on host ribosomes into a replicase, which upon proteolytic cleavage yields proteins needed for genome replication. The full-length antisense negative-strand viral RNA template is generated by viral RNA-dependent RNA polymerase for replicating positive strands of viral genomic RNA and shorter subgenomic negative-strand RNAs [61]. Negative-strand viral RNA serves as templates for the translation of mRNAs in the endoplasmic reticulum that code for the structural proteins of the virus. In the endoplasmic reticulum, viral proteins get encapsulated and bud into membranes. Upon viral assembly, virions form vesicles are released through exocytosis [61].

ACE-2 gene polymorphism plays a crucial role in inducing severe lung damage, as it accounts for the differences in the ACE expression level in the general population [62]. ACE-2 polymorphism is identified by the insertion (I) or

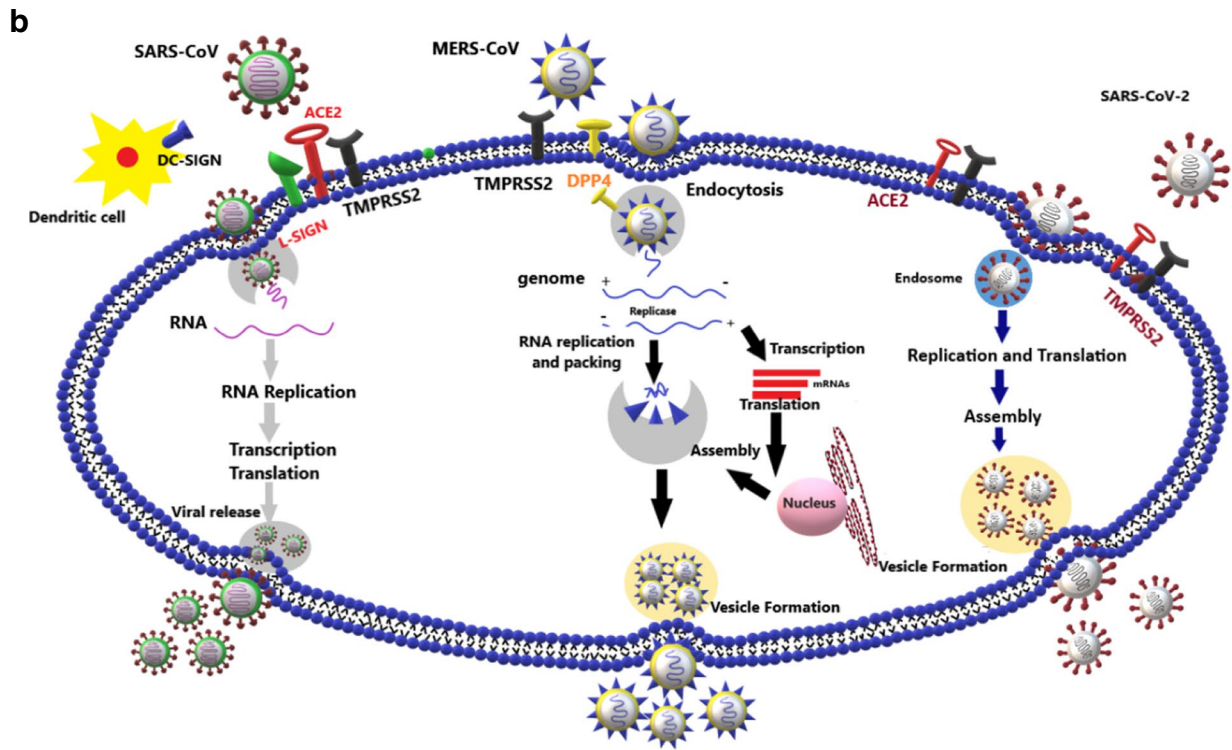
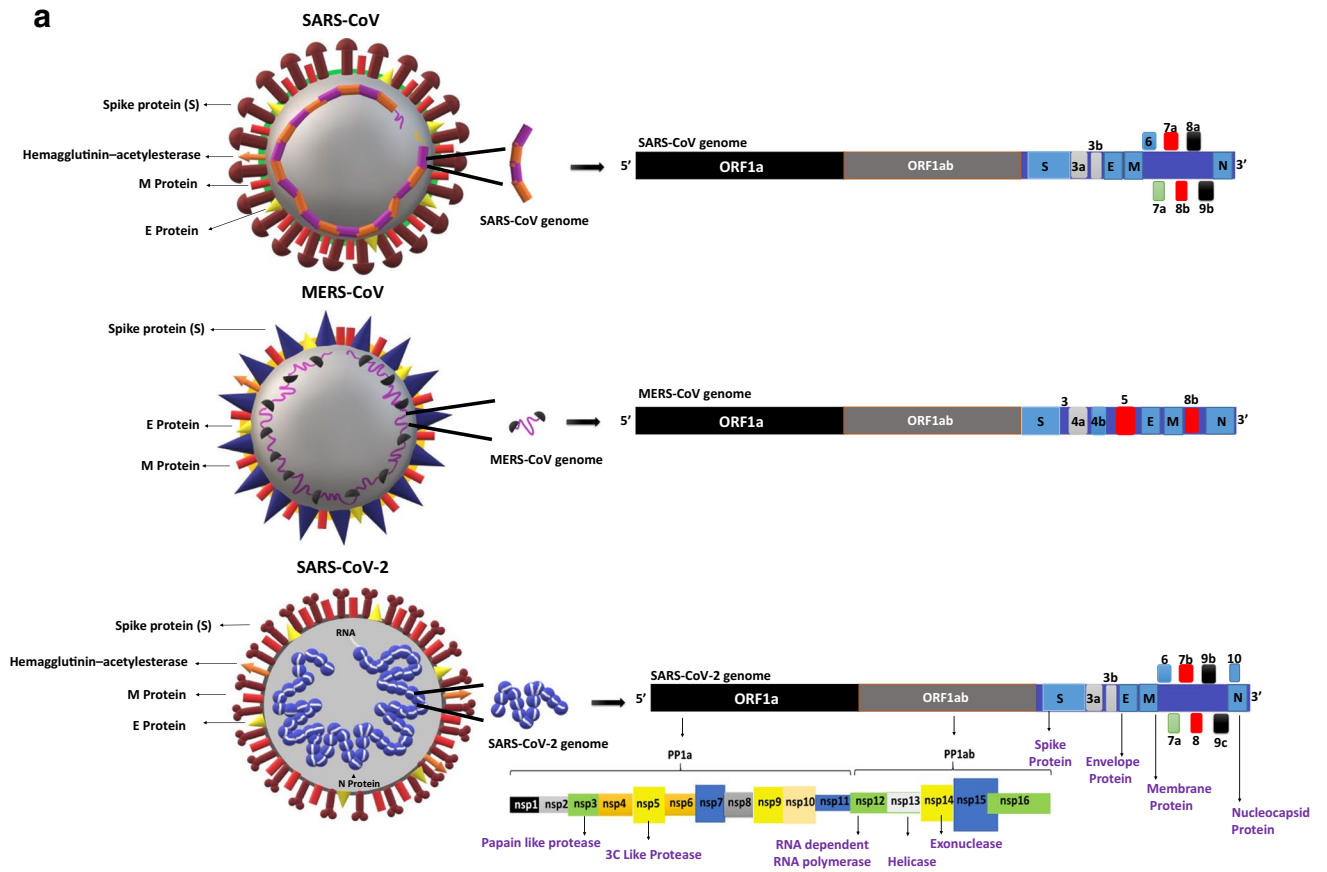


Fig. 1 Genome organization of coronaviruses and variations in their mode of entry into human cells: **a** Structural representation and genome organization of SARS-CoV, MERS-CoV, and SARS-CoV-2: SARS-CoV-2 genome encodes four major proteins viz., spike (S) protein, the nucleocapsid (N) protein, the membrane (M) protein, and the envelope (E) protein. Total six open reading frames (ORFs), ORF3a, ORF6, ORF7a, ORF7b, ORF8, ORF10, and the polyprotein ORF1ab encodes several enzymatic proteins for the effective viral invasion of the host cells. **b** Host cell receptors and replication mechanism of SARS-CoV, MERS-CoV, and SARS-CoV-2: the spike protein of the CoVs interacts with receptors on the host cell to make its entry. ACE-2 serves as a receptor for SARS-CoV and SARS-CoV-2. DC-SIGN and L-SIGN serve as co-receptors for SARS-CoV. DPP4 serves as a receptor for MERS-CoV. CoVs replicate in the host causing cellular damage leading to further complications

deletion (D) of a 287 bp Alu repeat sequence in intron 16 of the ACE gene [63]. Further studies are needed to assess ACE gene polymorphism in COVID-19 patients in the ongoing clinical trials using ACE-2 inhibitors and angiotensin II receptor blockers therapy.

ACE-2 is expressed in many other organs, hence, SARS-CoV-2 is likely to enter tissues and organs through ACE-2 binding, causing multiple organ damage including kidney injury, cardiac injury, liver dysfunction, and cerebral damage [41, 64–66] (Fig. 3). The current understanding of the pathogenic mechanisms of SARS-CoV-2 binding to ACE-2 in the brain, liver, kidney, and heart are poorly described, hence, further studies are warranted.

Addressing this gap, recent studies have shown that in the brain, ACE-2 is expressed in glial cells and neurons,

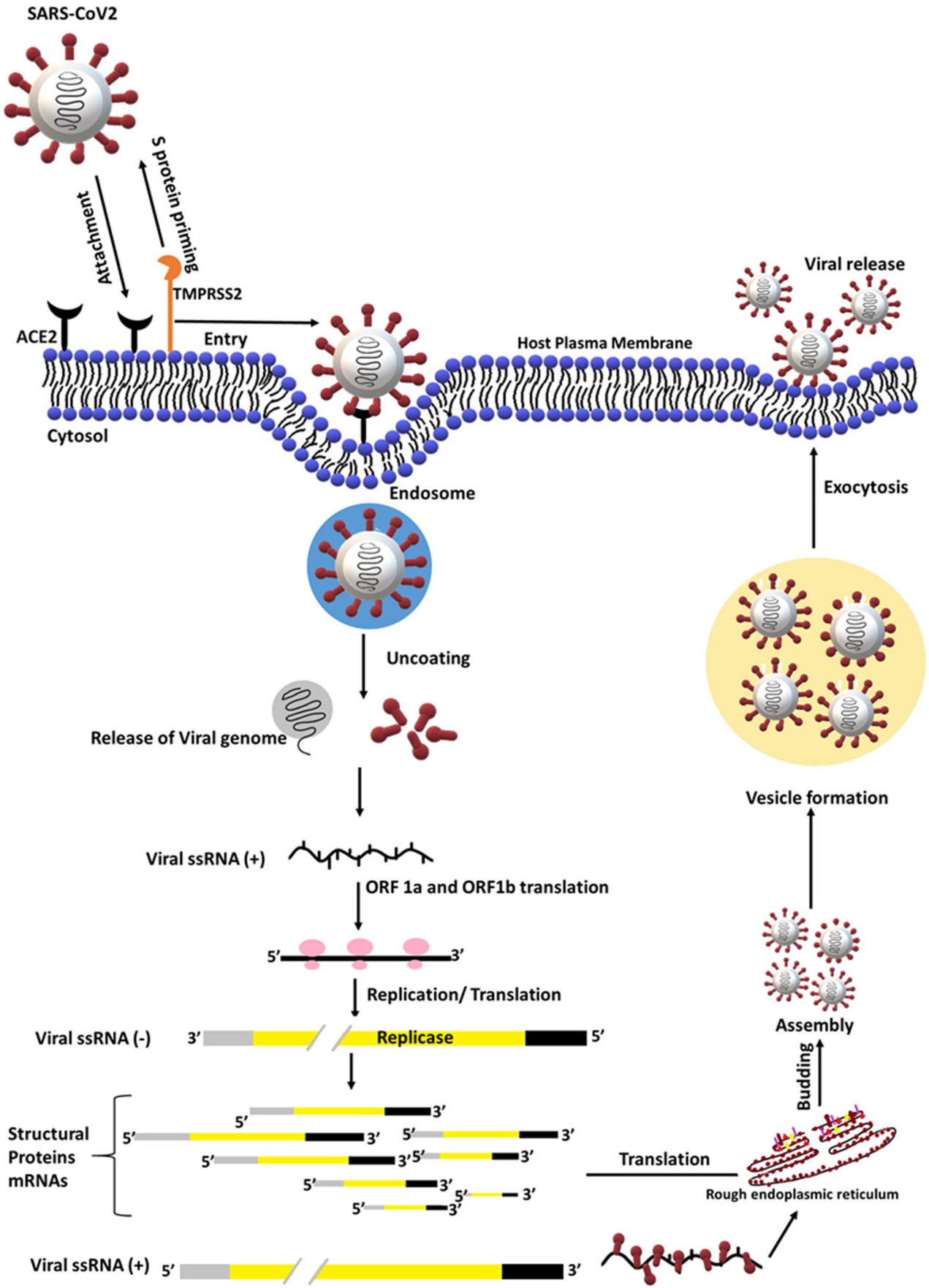
suggesting the neurotrophic potential of SARS-CoV-2, entering through circulation or an upper nasal transcribrial route causing cerebral damage [64]. More research studies are required to elucidate the specific mechanisms behind neuronal damage mediated by SARS-CoV-2 infection (Fig. 3).

In addition to the brain, ACE-2 is expressed in hepatocytes of the liver, and bile duct cells consequently invoke damage to the liver [67]. Moderate microvascular steatosis, mild lobular, and portal activity were observed in biopsies of COVID-19 individuals [65]. Nevertheless, a mechanism underlying the liver dysfunction needs to be explored further, as the injuries could be caused by SARS-CoV-2 infection or antiviral drugs used during the treatment [65]. For example, several recent studies have shown that the antiviral drugs lopinavir/ritonavir causes injury to the liver [68]. Addressing this aspect will help to develop better strategies for mitigating SARS-CoV-2-induced liver damage (Fig. 3).

The kidney is another organ with elevated ACE-2 expression. The renal tubular cells are known to express high levels of ACE-2 [69]; however, no research evidence has been reported for the SARS-CoV-2 invoked kidney injury. In a statistical survey of 1099 COVID-19 patients, 0.5% reported acute kidney injury with a severity rate of 83.3%. In some COVID-19 patients, SARS-CoV-2 was detected in the urine [69]. Additional studies are immediately warranted to test whether SARS-CoV-2 infections cause kidney damage, if so, the mechanisms involved in such cellular damage. Further, it is currently unknown whether urine collected from

Table 1 Therapeutic strategies to target ACE-2 receptor and S-protein interaction in SARS-CoV-2 infection

Type	Target	Description
Synthetic compounds		
RS504393	ACE-2 and S-protein of SARS-CoV-2	Treated for lung injury and bronchial wall thickening [20]
KT185	S-protein of SARS-CoV-2	Anti-inflammatory [21]
TNP	ACE-2	Tyrosine kinase inhibitor [22, 23]
GNF-5	ACE-2	Kinase inhibitor [24]
GR127935 hydrochloride hydrate	ACE-2	Vasoconstriction monitoring [25]
Eptifibatide acetate	ACE-2	Protects lung injury and inflammation [26]
Monoclonal antibody		
47D11	Entry of SARS-CoV-2	Human antibody specific to SARS-CoV-2 [27]
Antiviral agents		
HrsACE-2	ACE-2	Recombinant protein [28]
CR3022	S-protein	Neutralizing antibody [29]
Umifenovir (Arbidol)	Endocytosis	Membrane fusion inhibitor [30, 31]
EK1C4	Endocytosis	Pan-coronavirus fusion inhibitor [32]
Camostat mesilate	TMPRSS2	Serine protease inhibitor [33, 34]
Nafamostat	TMPRSS2	Serine protease inhibitor [30, 35]
Bromhexine hydrochloride	TMPRSS2	Mucolytic drug [36]
PAI-1	TMPRSS2	Serine protease inhibitor [37]
Chloroquine	Cell fusion/virus	Drug for autoimmune disease [38]



◀**Fig. 2** Interaction of SARS-CoV-2 with ACE-2 receptors in lungs: the lysosomal proteases, such as elastase, and cell surface proteases TMPRSS2 could induce activation of SARS-CoV-2 S-protein for membrane fusion through ACE-2 receptors, which consequently causes lung tropism through endosome formation, multiple virion replication, and exocytosis

COVID-19 patients could also be used to detect SARS-CoV-2. Establishing methods to detect SARS-CoV-2 in urine will help in minimizing the distress caused due to nasal/throat sample collection (Fig. 3).

In the case of heart, SARS-CoV-2 follows the mechanisms similar to SARS-CoV to trigger cardiovascular complications [70]. ACE-2 expressed in cardiomyocytes is capable of interacting with SARS-CoV and fosters the extensive levels of Ang-II, consequently promoting cardiovascular abnormalities [70]. But it is currently unknown whether SARS-CoV-2 can also directly infect cardiomyocytes.

ACE-2 expression is also detected in exocrine glands and islets of the pancreas. ACE-2 expression in the pancreas is slightly higher compared to the lungs, indicating the possibility of binding of SARS-CoV-2 to ACE-2 in the pancreas, causing severe pancreatic injury [71].

Studies have reported coagulation and fibrinolysis in COVID-19 patients, which is due to the activation of host defense mechanisms to limit the spread of the virus upon infection [72]. The initial phase of viral infection triggers a systemic inflammatory response characterized by an elevated level of cytokine activity and generation of thrombin and fibrinogen [72]. This response induces the expression of tissue factors, which initiate the coagulation. The measurement of coagulation and fibrinolysis factors in bronchoalveolar lavage (BAL) fluid showed elevated thrombin levels and the suppression of fibrinolysis, indicating the pathogenesis of respiratory distress. Furthermore, massive endothelial cell apoptosis, which is caused by vascular endothelial damage upon SARS-CoV-2 infection contributes to procoagulant changes in COVID-19 [72]. Recent studies have shown thrombocytopenia in COVID-19 patients, but the mechanism of SARS-CoV-2 involvement is still unclear [73] (Fig. 3).

Cytokine Storm

Innate- and acquired-immunity mediated antiviral responses triggered by recognizing pathogen-associated molecular patterns (PAMPs) and induced antigen-specific adaptive immunity are the key defense systems that protect the host organisms from devastating effects of infections [74, 75]. The response to viral infections depends on the release of cytokines, chemokines, leukotrienes, proteases, reactive oxygen species, and the rate of viral clearance [76]. The balance between the antagonistic signals and cellular reactions

influences the immune response to pathogens by preventing damage to host tissues. As a result, the activated immune system returns to a resting state and prevents the damage, which is otherwise caused by continuously activated host immune reactions [76]. Excessive synthesis of cytokines in response to viral infections results in an acute and severe systemic inflammatory response known as “cytokine storm,” which causes multi-organ damage [76]. Studies have shown that IL-6 and IL-17 are predictive of disease severity and correlate with respiratory failure [77]. Potential therapeutic strategies targeting IL-17 alone or in combination with IL-6 for COVID-19 are currently under investigation. Tocilizumab, which targets IL-6, is currently approved by the United States Food and Drug Administration (US-FDA) for treating COVID-19 patients [78].

SARS-CoV-2-Induced Neurological Complications

The SARS-CoV-2 primarily affects pulmonary, cardio-, and renal functions [79]. However, recently it has been reported that SARS-CoV-2 can cause secondary complications on other systems as well [79]. Neurological complications are one such set of complications that require more attention to develop novel therapeutic modalities. Frequently, SARS-CoV-2 infections-induced neurological disorders are combined with either pre-existing metabolic abnormalities such as diabetes, other infections, or chronic- to acute inflammatory episodes of the nervous system [80]. However, it is currently not clear whether all COVID-19 patients develop neurological complications or only a portion is prone. Therefore, it is important to know the signs and features of susceptible individuals who are at risk for developing neurological infections.

Routes of SARS-CoV-2 Entry into the Nervous System

The SARS-CoV-2 virus, which enters the bloodstream can spread into the central and peripheral nervous systems (PNS) via retrograde axonal transport or by infecting the pericytes and astrocytes, which are the central part of the blood–brain barrier (BBB) [81]. Neuro-invasion of SARS-CoV-2 may also be mediated through the olfactory nerve or infection of vascular endothelium or by infected leukocyte migration across the BBB. Once the virus enters CNS through the conceded BBB, the SARS-CoV-2 can be distributed along the neurotransmission or hematogenous pathways that include serotonergic dorsal raphe system and Virchow-Robin spaces, respectively. The neuro-invasive potential of SARS-CoV-2 predominantly relies on the medullary structures interacting with the brain stem, accompanied by the respiratory system. This could be one of

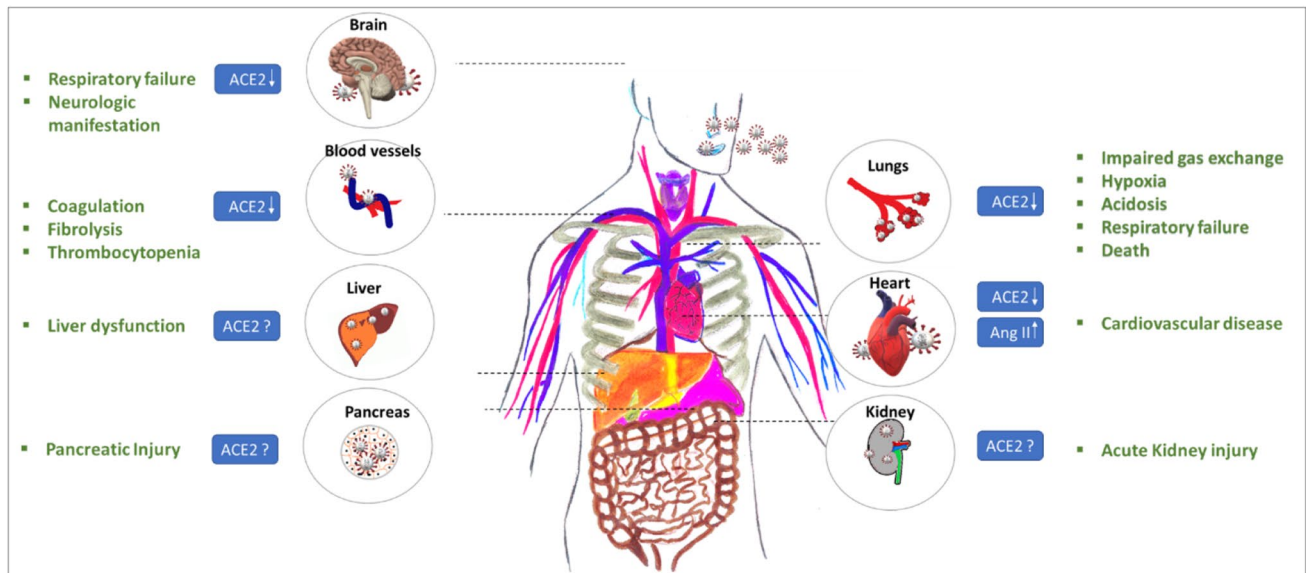


Fig. 3 Multiple organ dysfunctions induced by the interaction of SARS-CoV-2 with host cell ACE-2 receptors. The figure represents multi-organ dysfunction which is characterized by acute kidney

injury, respiratory failure, liver failure, neurological complications, and cardiovascular disease upon SARS-CoV-2 infection

the conducive factors responsible for the high incidence of respiratory failures in COVID-19 patients [81].

The neurological effects of COVID-19 are due to either direct viral entry or indirect infection into the CNS [82, 83]. Epidemiological studies have shown that the latency of 1-week gap between the initial infection and severe infection for COVID-19 patients provides space sufficient for potential viral entry into the CNS [84]. Neurotropism activity is commonly detected in coronaviruses; neuro-invasive properties are well documented in SARS-CoV, MERS-CoV, HCoV-229E, and HCoV-OC43 [85–87]. Further, the spike protein of SARS-CoV-2 alters the blood–brain barrier (BBB) function, which provides an additional mechanism of potential CNS entry [88]. The conserved viral structure and genetic similarity of SARS-CoV-2 with SARS-CoV provide further evidence that the virus can enter into the CNS [89, 90].

Kanberg et al. reported CNS damage in COVID-19 patients by measuring the variations in serological biomarkers. For instance, elevated plasma glial fibrillary acidic protein (GFAP) and neurofilament light chain (NfL), which are the markers of astrocytic and neuronal injury, were reported in 47 COVID-19 patients [91]. The authors of this study demonstrated a significant increase in GFAP and NfL in 18 patients with severe COVID-19; however, GFAP levels were reported to decrease upon treatment follow-up. But a continuous increase in NfL level was reported throughout the treatment. Similar to severe COVID-19 cases, an increase in the levels of plasma GFAP was also reported even in 9 patients with moderate COVID-19 [91]. But no treatment follow-up status is reported in this study. This phenomenon is evident

in astrocytes' early involvement and delayed axonal injury in the CNS due to COVID-19 infection [91].

Coolen et al. have provided evidence of central nervous system involvement in COVID-19 patients [92]. Authors of this study have performed magnetic resonance imaging (MRI) on COVID-19 patients within 24 h of death and showed parenchymal abnormalities, including white matter changes, posterior reversible encephalopathy syndrome, and hemorrhage in four individuals [92]. This could be due to the breakdown of the BBB and COVID-19 based endothelial abnormalities, irrespective of SARS-CoV-2 virus infection in endothelial cells. The study also showed an indication of olfactory bulb unevenness and anosmia in four other patients [92]. A study conducted in Strasbourg, France, on the neurological function of 58 COVID-19 patients with acute respiratory distress syndrome (ARDS) admitted into the intensive care unit (ICU) was assessed and showed neurological abnormalities in the 8/58 patients (~ 14%) during admission to the ICU. However, 67% (39/58) patients exhibited profound neurological signs while 69% (40/58) of patients exhibited agitation after the withdrawal of sedation or a neuromuscular blocker. Also, approximately 45% (26/58) of patients were characterized by a state of confusion, while 67% (39/58) of patients reported exhibiting corticospinal tract signs. Serendipitously 13 patients (22.41%) exhibited encephalopathic features followed by leptomeningeal enhancement in (8/13) patients and bilateral frontotemporal hypoperfusion (11/13) in MRI scans. Follow-up clinical studies were performed on 45 patients in which 15 patients

typically exhibited dysexecutive syndrome followed by the presence of inattention, disorientation, alterations in movements, and responses [93]. A research study on 214 COVID-19 patients from Wuhan, China, delineated severe SARS-CoV-2 infection in 41.1% (88/214) patients. The remaining had non-severe infection (58.9%; 126/214); among them 36.4% (78/214) of patients had orchestrated distinct neurologic signs due to damage to sensory neurons that consequently foster defects in sensations of olfaction and gustation and invoke neuropathic pain, seizures, and strokes [83]. Furthermore, these defects were more evident in COVID-19 patients across the world [83].

Based on the symptoms, neurological manifestations underlying the COVID-19 were segregated into skeletal, muscular injury indexes, and CNS indexes [94]. Among these neurological manifestations, acute cerebrovascular disease, headache, dizziness, ataxia, defects in consciousness, and seizures were reported as critical ones. For instance, the SARS-CoV-2 infection invoked alterations in the peripheral nervous system (PNS) as indicated by nerve pain, impaired taste, smell, or vision [6]. Results of this study showed that 78/214 patients exhibited neurological abnormalities exhibiting symptoms related to CNS dysfunction, skeletal muscle injury, and defects in PNS function [83]. All these neurological symptoms were predominantly reported in older patients [60 years or above], who had existing co-morbid conditions viz., hypertension, diabetes, chronic malignancy, and cerebrovascular diseases [95–98].

A plethora of recent research reports depicted that the ACE-2 receptor extensively plays a crucial role in SARS-CoV-2 virus entry into the host body. This protein is also widely reported in CNS, predominantly in the brainstem and subfornical organ, paraventricular nucleus, nucleus of the tractus solitarius, and the rostral ventrolateral medulla regions [99]. These regions of the brain are known to control cardiovascular functions [99]. ACE-2 expression is also reported in neurons and astrocytes [99]. Li et al. deciphered that COVID-19 infection could induce changes in gut microbial composition and invoke neuropathogenesis which confers neuropsychiatric symptoms through the gut-brain axis [100].

Initial studies using RT-PCR depicted the extensive ACE-2 expression in the brain [101], but ACE-2 immunoreactivity was typically reported in the brain endothelial and smooth muscle cells [102]. The expression of ACE-2 in glial cells [99, 103] concludes that brain tissue could be a potential target for SARS-CoV-2. SARS-CoV-2 RNA was evident during CNS infection indicating the possibility of direct infection of CNS by SARS-CoV-2.

The COVID-19 patients with meningitis exhibit seizures, hippocampal atrophy, and pan-paranasal sinusitis [104]. A recent case study showed the existence of SARS-CoV-2 virus in the CNS of a 56-year-old encephalitis patient who

had reported mitigation of consciousness. These findings in COVID-19 patients are in line with past reports with HCoV-OC43 infected patients [105]. Likewise, SARS-CoV was observed in CSF from SARS patients with persistent epilepsy [106]. A retrospective study of COVID-19 patients showed acute ischemic stroke, cerebral venous sinus thrombosis, and cerebral hemorrhage [83]. Hence, it was concluded that the SARS-CoV-2 exhibits a capacity to bypass the respiratory tract and the capability to confer infection in other tissues, which could be a critical feature of the SARS-CoV-2 virus.

SARS-CoV-2 and a Robust Mitochondrial System and Immune-Competency Rely on Hormesis

Recent studies have shown the ability of SARS-CoV-2 to impair autophagy and block mitophagy [107]. This effect is similar to SARS-CoV, which is capable of mitochondrial fusion, impairs mitophagy, and induces cell death [108, 109]. Studies are currently investigating the SARS-CoV-2-induced modulation of mitochondrial- and immune system changes by unraveling the modulation of the viral-mediated inflammasome. Irisin, a muscle-derived hormone, is reported to protect mitochondria and ischemia/reperfusion injury in the lung during exercise [110]. But it is unknown whether SARS-CoV-2-induced mitochondrial dysfunctions are mediated by irisin modulation. Furthermore, studies have demonstrated that irisin could facilitate changes in the genes in adipocytes that are affected by SARS-CoV-2 and neutralize the ROS in macrophages thereby display antioxidant and anti-inflammatory properties [111, 112]. Since mitochondria play an important role in immune response, and several viruses can modulate mitochondrial function, it is presumed that SARS-CoV-2-induced effects could also be mediated through the dysregulation of mitochondrial function [109]. The altered mitochondrial function might be a variant process, which occurs in SARS-CoV-2-mediated pathophysiology [113]. Several immune cells possess mitochondria and are now embraced by the “immunometabolism concept” [114, 115]. However, age and lifestyle are two crucial factors that determine susceptibility to the virus based on hormetic-like preconditioning [115]. Any “virus-induced exogenous hormetic stimuli” could be mitigated by the recurrent physical activity consequently decreasing the viral-mediated mitochondrial stress [116–118]. Preconditioning signal through hormone-like irisin by the physical activity is leading to cellular protection via hormesis, which is an important redox-dependent anti-inflammatory and anti-oxidant-associated mechanism [113]. Thus, mitochondrial hijacking and hormetic-like preconditioning through SARS-CoV-2 could be considered as a significant factor in the pathophysiology of neuroinflammation [113].

SARS-CoV-2 is reported to enhance aerobic glycolysis (Warburg shift) to promote replication, which is a strategic tactic used by many viruses (similar to cancer cells) via metabolic reprogramming [119]. For instance, melatonin can impair this metabolic reprogramming mediated by SARS-CoV-2, hence, melatonin could be considered as the powerful antioxidant which can protect mitochondria [120, 121]. This kind of divergent SARS-CoV-2 signaling should be unraveled in neuronal cells by studying the melatonin-induced mitochondrial antioxidant system [121]. Several viruses including SARS-CoV-2 can modulate mitochondrial bioenergetics and redox function in both immune systems and acquire the capability of infecting other cells to enhance their replication, which consequently fosters viral-mediated pathophysiology due to extensive oxidative stress [121]. Hormetic dose–response of novel anti-viral molecules may provide the central underpinning of neuroprotective responses against viral infections. The study of hormetic dose-responses is crucial to illustrate the cellular defense pathways including sirtuin and Nrf-2 related signaling cascades about SARS-CoV-2-induced neuronal diseases [122]. Furthermore, it is crucial to unravel the underlying viral-mediated pathophysiology as SARS-CoV-2 may modulate the functions of neuronal mitochondria to generate oxidative stress. As mitochondria-mediated aging is associated with dysregulated metabolism and requires novel therapeutic modalities viz., mitochondrial anti-oxidants and anti-inflammatory molecules are likely to correct these dysregulated metabolic and physiological processes before the administration of vaccines against SARS-CoV-2-induced neuropathology [123]. “Hydroxytyrosol (HT)-rich aqueous olive pulp extract (HIDROX®)” has been reported to mitigate SARS-CoV-2-induced pathophysiology by inducing potent virucidal activity [124]. Hydroxytyrosol (HT) and oleuropein aglycone (OLE) are two potential molecules reported being beneficial to mitigate the pathophysiology of neurodegeneration [124]. Hormesis and anti-oxidant nature, which enhances the activity of proteasome and phase II detoxifying enzymes, are potential mechanisms of action by which these pharmacological molecules work against SARS-CoV-2-induced neuropathophysiology [125, 126]. In addition to the above therapies, the vaccinomics approach might be useful to mitigate the complications accelerated with immunosenescence factors against SARS-CoV-2 in the infected individuals over 65 years of age [123, 127]. Additional studies are warranted to prove the role of vaccinomics-based approaches for reducing the complications of SARS-CoV-2 infections.

Mechanism of Infection of Central Nervous System (CNS) and Peripheral Nervous System (PNS) by SARS-CoV-2

Extensive scientific evidence now proved that COVID-19 can cause many neurological complications [128]. Also, neurological complications have attracted widespread

attention among researchers to delineate the short- and long-term impact on population health during COVID-19 infections [129]. Yet, in-depth studies are required to ascertain the underlying mechanisms/pathways involved in the COVID-19 induced neuronal complications.

Indirect Entry

SARS-CoV-2 may enter the nervous tissue through retrograde and anterograde transport along with peripheral nerves [130]. Existing data showed that SARS-CoV-2 can infect the olfactory bulb through TMPRSS2 and ACE-2 receptors [131, 132]. Once infected, the transfer of virus may occur through extracellular vesicles (EVs) in the olfactory ensheathing cells (OECs), independent of the ACE-2 receptors. In addition to the olfactory nerve, the virus can migrate via the trigeminal and vagus nerves [130].

SARS-CoV-2 may invade the nervous tissue through the ACE-2 or TMPRSS2 receptors. Since, ACE-2 receptors are also expressed on the membrane of the spinal cord, the virus may invade the spinal cord through its binding to the ACE-2 receptors on the surface of peripheral neurons. The virus can penetrate the cribriform plate located closely to the olfactory bulb and the olfactory epithelium (OE), thereby enters the CNS system indirectly. Anosmia or hyposmia are considered as novel complications of COVID-19 patients to confirm this route of infection [133].

COVID-19 induced neural infection is accompanied by the uptake of the virus into the ciliated dendrites/soma [134]. The virus could effectively enter via anterograde axonal machinery transport along the olfactory nerve [134]. Moreover, the virus can also infect and cross non-neuronal olfactory epithelium cells and directly enter the CSF around the olfactory nerve bundles [135]. ACE-2 and TMPRSS2 receptors of these cells could propagate the infection in elderly individuals, which may be considered as the higher risk of SARS-CoV-2 accumulation in OE cells [135] (Fig. 4).

Direct Pathway

Even though it is now confirmed that SARS-CoV-2 infection leads to neurological complications, the direct entry of the SARS-CoV-2 into the nervous system and its exact microinvasion are yet to be unraveled. For instance, the virus may directly confer invasion of brain tissues as indicated by the presence of nucleic acid materials in both CSF and brain tissue [130]. This kind of viremia occurred through a direct pathway likely to provoke virus transcytosis across the endothelial cells of the blood–brain barrier (BBB) of the brain or the virus infection across the epithelial cells of

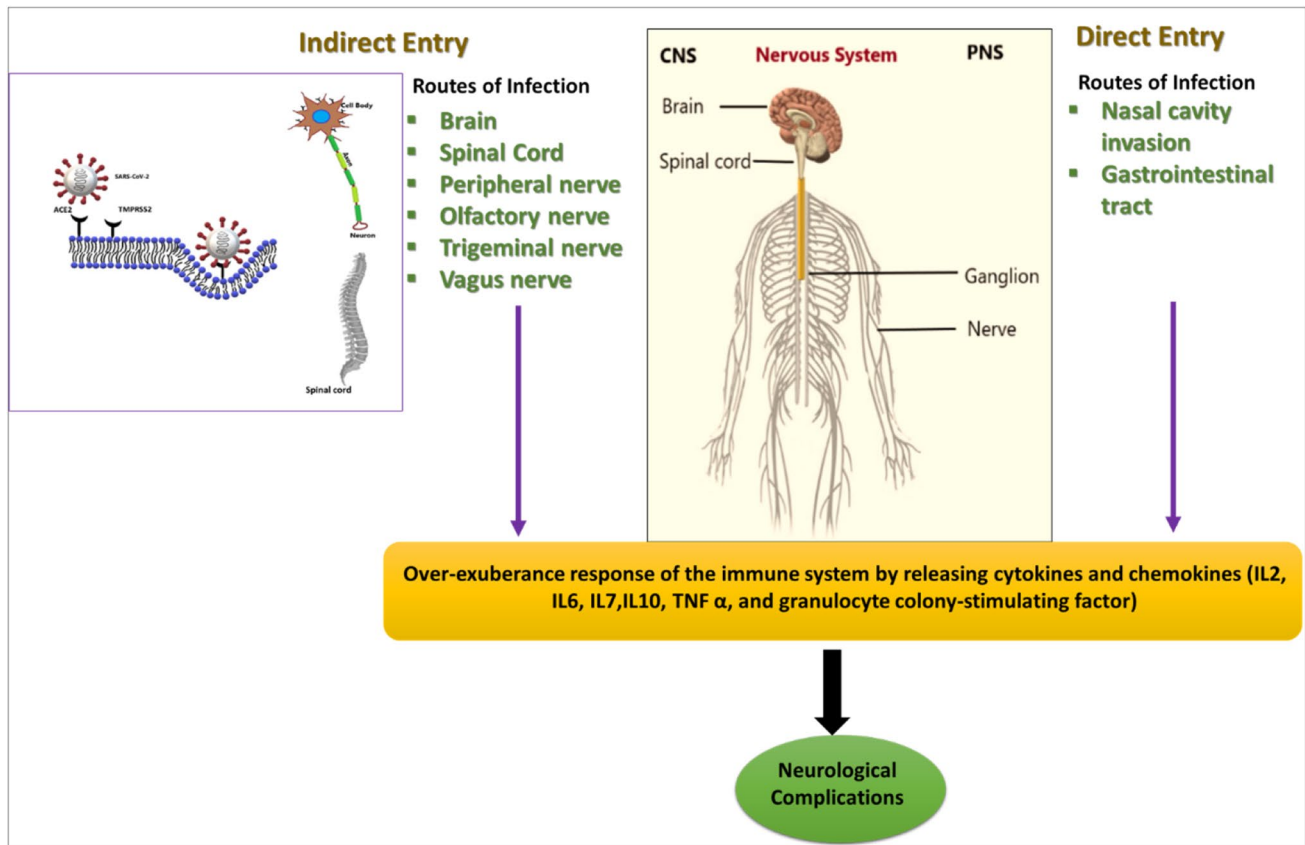


Fig. 4 Overview of SARS-CoV-2 entry in the nervous system. SARS-CoV-2 virus is reported to infect CNS and PNS by direct and indirect pathways. This results in the generation of cytokines and

chemokines by elevating the immune response and causing severe neurological complications

the blood-cerebrospinal fluid barrier (BCSFB) in the choroid plexus (CP) of brain ventricles. Besides, the leukocytes may also act as a vector to transport the virus across the BBB [136, 137]. The Braak hypothesis says that an invasive neuro-virus could enter the CNS through the nasal cavity and the gastrointestinal tract [138] (Fig. 4).

COVID-19 Induced Neuroinflammation

One of the significant neuropathological mechanisms of SARS-CoV-2 infection is the induction of a hyperinflammatory state in infected individuals [66]. The over-exuberance response of the immune system could foster the generation of cytokines and chemokines viz., interleukins 2, 6, 7, and 10, TNF α , and granulocyte colony-stimulating factor (GCSF) [139]. These cytokines and chemokines provoke extensive activation of neuroinflammatory cascades and drive neuronal hyperexcitability via glutamate receptor activation followed by induction of seizures [140, 141]. An inflammatory theory of SARS-CoV-2 infection was also supported by the steroid response of COVID-19 patients comorbid with severe encephalitis [142].

Over-exuberance response of the immune system in SARS-COV-2 infection may cause inflammatory injury and brain edema, which consequently induce defects in consciousness [143]. Inflammatory and immunologic responses further amplify the cytokine storm [144]. Intracranial cytokine storm potentially confers BBB breakdown and leading to the migration of leukocytes. During this condition, the virus is failed to exhibit the potential of direct invasion or para-infectious demyelination [130].

It has been reported that COVID-19 patients experience defects in gustation (sense of taste) and olfaction due to direct damage to the olfactory bulb leading to inflammation in the nasal cavity. This inflammation blocks binding of odorants to the olfactory receptors thereby affect the olfactory responses [145]. Regeneration and repair of damaged neurons during COVID-19 take a longer time within the olfactory bulb [145]. Similarly, COVID-19 led to the dysfunction of taste buds thereby cause ageusia (loss of taste function of the tongue) [146]. In acute phases of this infection, the loss of olfaction could be due to nasal inflammation and mucosal edema. These symptoms may persist for months to years due to extensive olfactory insult triggered by the virus [145].

Impact of COVID-19 on Neurological Disorders

COVID-19 pandemic exhibited numerous short-term and long-term adverse effects on a large group of elderly people with neurological disorders and neurodegenerative diseases [147]. For instance, Parkinson's disease (PD) is one of the devastating neurological diseases, which occurs due to the defects in the mesolimbic system of basal ganglia [148]. PD patients infected with COVID-19 exhibit adverse effects that include motor symptoms, such as tremors, freezing of gait, or dyskinesias [149], and diminished dopaminergic medication efficacy [150–152]. Thus, the COVID-19 pathophysiology and alteration in the dopamine synthesis pathway have been hypothesized. Recent reports have demonstrated the co-expression of dopa decarboxylase (DDC), a significant enzyme of both dopamine and synthetic serotonin pathways, and ACE-2 receptor [153]. SARS-CoV-2 binding with ACE-2 has been reported to invoke a downregulation of ACE-2 [154]. The possible functional connection between ACE-2 and DDC indicates the alterations in dopamine synthesis, which further confer PD-related complications [153]. An imbalance in dopamine levels can worsen the severity of PD. In addition to the impact of COVID-19 on PD patients, the virus may invoke sporadic PD during infection. For instance, ACE-2 is reported to be involved in co-regulating the dopa decarboxylase (DDC) during dopamine synthesis; any SARS-CoV-2-induced downregulation of ACE-2 expression would invoke alterations in both serotonin and dopamine pathways, which are significant pathways involved in PD pathophysiology [53, 153]. Hence, it is hypothesized that the SARS-CoV-2 can effectively induce alterations in dopamine during defective expression of ACE-2 and DDC [153].

Multiple sclerosis (MS) is another neurological complication reported to be worsened by SARS-CoV-2 infection. The mortality/morbidity risk was reported to be relatively low with disease-modifying therapies (DMTs) in the MS patients suffering from COVID-19 infection. Furthermore, the intake of immunomodulatory drugs in these patients could invoke low pulmonary capacity, which further enhances the risk of COVID-19 related pneumonia [155]. Hence, the decision to avoid the intake of DMTs in COVID-19 patients comorbid with MS relies upon several miscellaneous factors viz., immunomodulation, and disease severity. Complications of COVID-19 infection are much higher due to the over-reaction of the immune system to the SARS-CoV-2. However, further studies are warranted to decipher the molecular pathways to be targeted to mitigate the complications. Furthermore, the establishment of appropriate preclinical animal models would help in developing better therapeutic agents for combating COVID-19 induced complications in individuals suffering from MS [156–158].

SARS-CoV-2 infection may also invoke a severe neurodegeneration process, which could reduce the overall survival of COVID-19 patients with Alzheimer's disease (AD) [130]. But, currently, no evidence suggests a correlation between COVID-19 and AD development [159]. One of the key factors responsible for AD induction is the accumulation of amyloid-beta plaques (A β plaques) in the brain [160, 161]. A β is produced from the enzymatic processing of amyloid precursor protein (APP). An intriguing relation between viral infections and A β has been delineated by several researchers and the data supports that A β is an antimicrobial peptide (AMP) [162]. The whole-brain homogenates obtained from AD patients compared to the age-matched non-AD samples suggested a strong correlation between AMP action and A β levels [162]. However, the extensive anti-microbial activity of A β was ablated in the models of immune depletion of AD brain homogenates, who were subjected to treatment with anti-A β antibodies. Transient infection with SARS-CoV-2 virus could either initiate or accelerate A β accumulation inside the brain and cause AD [159]. Further, a positive inflammatory response was stimulated through transient viral infection inside the CNS, which may foster the abnormal self-perpetuating innate immune responses due to the severe cerebral A β stagnation [159]. Neuroinflammation is another early characteristic of AD. CNS tropism of the virus across brain tissues expressing ACE-2 can induce ACE-2 expression, which may enhance the risk of virus invasion and activate molecular processes that invoke neurodegeneration [159]. However, these molecular mechanisms in SARS-CoV-2 infection are yet to be unraveled to delineate the viral-induced alterations in neurodegeneration.

SARS-CoV-2-Associated Neurological Diseases

Guillain–Barré Syndrome (GBS) and SARS-CoV-2

Guillain–Barré syndrome (GBS) is an inflammatory polyradiculo-neuropathy and it is associated with several viral infections [163]. The incidence of GBS is considered to be the most significant aspect in the SARS-CoV-2 infected patients as GBS could confer respiratory failure, which is the most devastating complication observed with SARS-CoV-2 infection [164]. The other disease complications of GBS are flaccid paralysis, sensory abnormalities, and autonomic dysfunction due to autoimmune-mediated pathophysiology [165].

GBS in a COVID-19 patient was first reported in Wuhan, China, where demyelination of motor and sensory nerves was detected with a prolonged distal latency [166]. It is caused due to the cross-reaction of antibodies produced by the host against the viral infection, binding to peripheral nerves causing neuronal dysfunction [167].

Reports suggested symptoms like facial and limb paresis (a muscular weakness caused due to nerve damage), paresthesia, and immune-inflammatory responses were evident in SARS-CoV-2-mediated neuronal pathophysiology in GBS patients [168]. For instance, a variant of GBS Miller Fisher syndrome and polycranial neuritis was reported by Gutiérrez-Ortiz et al. [169]. Albumin cytologic dissociation was observed in the CSF after few days of COVID-19 infection in the individuals with Miller Fisher syndrome and polycranial neuritis [169]. Few reports suggested that the demyelination of multiple peripheral nerves might be another reason associated with SARS-CoV-2 that may induce deteriorating conditions of the patients with GBS [170]; however, extensive research studies are required to elucidate this pathophysiology vividly to develop counteracting therapeutic modalities [171].

Encephalomyelitis and SARS-CoV-2

Acute disseminated encephalomyelitis (ADEM) is one of the reported diseases generated through the central infiltration of SARS-CoV-2 components in the olfactory and trigeminal nerve endings [172]. Patients diagnosed with ADEM associated with SARS-CoV-2 infection suffer from weakness and numbness in the limbs and few urinary disorders; however, to date, the complete pathophysiology is not investigated. The complete CSF analysis in these patients has been reported with xanthochromia with high protein and glucose [172].

Myalgia and Neuromuscular Junction Damage

Myalgia, referred to as the general muscle pain accompanied by the presence of fatigue, is worsened in SARS-CoV-2

infected individuals due to chronic muscle injury [173]. Myalgic symptoms are due to respiratory complications invoked via acute respiratory distress syndrome (ARDS) and inflammatory-cytokine storm-induced via SARS-CoV-2 pathophysiology through muscle cell ACE-2 receptors [173]. Another evident chronic effect is the immune-mediated muscle damage due to inflammatory cytokine responses in these patients [174, 175] (Table 2).

SARS-CoV-2 and Animal Models of Neuronal Damage

Animal studies on SARS-CoV-2 can deliver key information on the pathophysiology of CNS [159]. For instance, mice, hamsters, ferret, and non-human primate models were already in use to examine the effects of virulence in vivo [176]. Transgenic models of mice expressing the human ACE-2 (hACE-2) gene, which is the receptor for SARS-CoV-2 in humans, are one such animal model to study the role of viral infection on neuronal damage.

Potential treatment strategies include pre-treatment with pan-coronavirus fusion inhibitors like EK1 peptide (an amino acid modified OC43-HR2P) and TMPRSS2 inhibitors like Camostat mesylate, Nafamostat mesylate should be tested for the efficacy in these animal models before considering for further assessment. The neural tissues of animal models are beneficial to examine the SARS-CoV-2-induced modulation in ACE-2 [33, 177, 178]. Dysregulation of RAS systems in COVID-19 infection contributes to ischemic brain injury through small-vessel hypoperfusion and arterial atherothrombosis [179]. Molecular mechanisms regulating these processes can be deciphered using mice models of SARS-CoV-2 infection.

Table 2 List of neurological disorders due to SARS-CoV-2 infection

Neurological diseases	Disease—clinical manifestations	SARS-CoV-2-induced clinical manifestations	References
Parkinson's disease (PD)	Tremors, dyskinesia	Chronic defects in the mesolimbic system of basal ganglia mainly in the dopaminergic neurons; enhanced neurodegeneration	[148, 149]
Alzheimer's disease (AD)	Cognitive decline and memory loss	Enhanced accumulation of amyloid-beta plaques in the brain; enhanced neurodegeneration	[130]
Multiple sclerosis	Severe lymphopenia, optic neuritis	Extensive demyelination	[155]
Guillain-Barré syndrome (GBS)	Progressive flaccid paralysis, dyssynergia, areflexia	Severe autonomic dysfunction, respiratory failure, demyelination through immune response in the peripheral nervous system (PNS)	[163, 165, 166]
Miller Fisher syndrome	Diplopia, balance disturbances, and areflexia	Chronic demyelination of cranial and facial nerves	[169]
Acute disseminated encephalomyelitis (ADEM)	Encephalopathy, transverse myelitis, weakness, numbness of the limbs, and urinary disorders	Immune-mediated inflammatory demyelination affecting the white matter of brain and spinal cord	[172]

SARS-CoV and Models for CNS Research

Accumulating evidence has demonstrated the presence of coronaviruses in the autopsies isolated from CNS of patients suffering from MS, PD, and AD. Experimental studies have shown that human CoVs can easily infect neurons, glial cells viz., astrocytes, and microglia in primary cultures as well as immortalized human microglial cells [180]. This suggests that SARS-CoV-2 may use the brain as a reservoir, which potentially favors the development of neurodegenerative diseases [181]. Therefore, there is a need to analyze the effect of SARS-CoV-2 infection on CNS.

SARS-CoV and CNS Cell Lines

The existing data, which is available from research on SARS-CoV, showed approximately 78% nucleotide homology with SARS-CoV-2. However, there are no specific neural cell lines developed to study the models of SARS-CoV-2 [182]. Currently neural progenitor cells, neurons, and microglia cells (obtained from human induced pluripotent stem cells (iPSCs)) are being used to ascertain the *in vitro* studies of SARS-CoV-2 viral infections and the impact of infection on cellular metabolism and various signaling cascades involved in cellular survival [182–184]. However, few other studies have used neurotropic human coronaviruses and neural cell lines such as human oligodendrogloma cell line HOG and rat glial tumor cell line C6. These cell lines are sensitive to SARS-CoV-2 infection and help to decipher the underlying virulence mechanisms through which the virus attacks the human CNS [185–187]. Even though both cell lines are reported to be sensitive to SARS-CoV infection, it was mentioned that viral replication is very low in cell lines such as Vero E6 and Caco-2 [188]. Miscellaneous neural cell lines viz., “human H4 brain neuroglioma cells, LA-N-5 human neuroblastoma cells, CHME-5 human fetal microglia cells, and U-373 MG and U-87 MG astrocytic cells” were also used for studying the infection ability of the HCoV-229E and HCoV-OC43 in the CNS [189–193]. Cultures of human primary neurons, glial cells such as astrocytes, oligodendrocytes, and microglia could also be used to study the virulence of the above viruses. Further studies are warranted to test the suitability of these neural cell lines to conduct experiments using SARS-CoV-2.

SARS-CoV-2 and Models of Brain Organoids

Organoids are the miniaturized, simplified, three-dimensional versions of an organ developed *in vitro* [194]. Organoids represent the cellular structure and functioning of a particular organ [195, 196]. The implementation of

organoids could foster researchers to develop and ascertain the complex physiological or pathological processes in an *in vivo* system. SARS-CoV-2 infection, tropism, and potential treatments were examined in human organoids of the lung, liver, intestine, blood vessels, and kidney [196–198]. Currently, human brain organoids are being developed to study the pathophysiological aspects associated with SARS-CoV-2-induced alterations in the brain [198, 199]. These organoids are useful to study the early stages of neuronal development during COVID-19 infection.

SARS-CoV-2 infect mature cortical neurons that are present in brain organoids [182]. Besides, the neurodegenerative effects observed in SARS-CoV-2 infected cells are due to cellular death and hyperphosphorylation, followed by the mislocation of Tau protein. These changes were more evident in tauopathies or AD [182]. However, there is no productive viral replication observed in these cells during the initial phase of infection, which would support the hypothesis that the CNS can be considered as a long-term reservoir for the virus [181]. In contrast, Bullen et al. delineated overaccumulation of viral particles across neurons in brain organoid models between 6 and 72 h after SARS-CoV-2 infection [200]. This is indicating that an active replication was more evident during the initial phase of viral infection. Furthermore, the viral particles were noticed significantly across the neuronal soma as well as in neurites. Mesci et al. [201] have successfully implemented the brain organoid model to assess whether the SARS-CoV-2 could be able to infect neurons, NPCs, and other cortical neurons to foster the cell death accompanied by the failure of excitatory synapses. Also, the above work was examined for Sofosbuvir's efficiency, which is an FDA-approved brain-penetrant antiviral drug for (+) ss RNA viruses, as a part of therapeutic modality during SARS-CoV-2 infection [202]. This study has concluded that Sofosbuvir could reinstate the altered synaptogenesis and mitigate neural cell death induced by viral accumulation in these brain organoids. Another study reported that SARS-CoV-2 exhibits neuro-invasive property in human brain organoids, typically in NPCs and mature cortical neurons [183]. These cells are exemplified by the hypermetabolic state where the viral particles undergo accumulation across the endoplasmic reticulum-like structures. From these evidences, it is now confirmed that SARS-CoV-2 has the capability to utilize neural cell machinery to replicate in the cells. Furthermore, hypoxia, as well as extensive neuronal death, was more evident across the infected brain tissues with high-density SARS-CoV-2, suggesting that SARS-CoV-2 could foster bystander cell death [203]. This study also concluded that IgG antibodies generated against SARS-CoV-2 in the CSF of COVID-19 patients could confer blockade of SARS-CoV-2 infection in brain organoids [183]. Thus, these studies reported that SARS-CoV-2 could infect neural cells and invoke neurological complications

with devastating adverse effects. In conclusion results of these studies depicted the immense potential of the usage of human brain organoids for the study of the SARS-CoV-2 effects in the CNS.

MHV-CoV Infection in Mice and Neural Complications

Mouse hepatitis virus (MHV) is a β CoV, which has no risk to humans but typically presents a similarity with other viruses from the same family viz., SARS-CoV, MERS-CoV, and SARS-CoV-2. Furthermore, this virus can cross CNS and invoke white matter lesions; hence this model could be proposed as a viral model of demyelinating disease [204, 205]. MHV can undergo replication in white matter, hence, is a useful model for the study of coronavirus-induced CNS infection. Neurotropic strains of MHV-CoV were previously reported to be implicated to cause acute and chronic demyelinating disease mediated by neuroinflammation [206, 207]. Based on the inoculation route and the MHV-CoV strain, it is now feasible to predict and identify the CNS region that was significantly affected. Inoculation with experimental MHV-A59 neurotropic strains could invoke an acute meningoencephalitis followed by the occurrence of subacute, chronic inflammatory demyelination in both brain and spinal cord [208]. Virus translocation from the initial site of inoculation in the brain to the spinal cord is caused by the transit of virus particles in neural and glial cells and mechanisms that involve the fusion of lipid membranes, probably during the virus internalization step [209]. Intranasal and intracranial inoculation of JHM-CoV induces similar symptoms in BALB/c mice to those caused by MHV-A59. After intranasal inoculation of mice, MHV-CoV accesses the CNS through the olfactory nerve and propagates from the olfactory system to limbic system structures and their connections with the brainstem [210].

In order to study the immune system role in demyelination induction caused by MHV infection, Wang et al. [211] treated infected animals with gamma radiation to cause immunosuppression and, subsequently, reconstituted immunity by transferring cells from other

immunocompetent animals. The results concluded that demyelination was prevented by radiation and was reinstated again when the immunity was restored, indicating that immunity is directly involved in the demyelination process. Moreover, CD4 and CD8 T cells have been observed to play a critical role in developing the demyelinating process, with T cells being the most important for this process [212, 213]; MHV offers a unique model for studying host defense-mediated demyelination during chronic viral infection and acute phase of viral infection (for instance, SARS-CoV-2) [214].

COVID-19 and Impact on Neurodevelopment

The global COVID-19 pandemic raised concern for pregnant women regarding the outcomes of SARS-CoV-2 infections, as this viral infection may invoke potential fetal defects viz., long-term neurodevelopmental impacts [215]. There are three primary considerations for a developing fetus:

- Vertical transmission of the disease from the mother
- The prenatal effects of maternal systemic infection on the fetus
- The possible effects on placental functioning and consequent pregnancy outcomes [179]

The presence of ACE-2 receptors in the placenta suggests the potential risk of getting SARS-CoV-2 transmission. In addition to vertical transmission, the maternal infection may invoke neurodevelopmental alterations during fetal development. However, the SARS-CoV-2-induced neurodevelopmental alterations should be unraveled fully to understand the infection-induced pathophysiology in early pregnancy [216]. For instance, this infection could foster the incidence of cytokine storm accompanied by the modulation of maternal immune systems and generate a cascade of cytokines and chemokines (TNF- α , IL-6) and other immune alterations that may be transmitted to the fetus. Subsequently, the critically ill pregnant women with viral infection could be at a higher risk of placental hypoxia, compromising fetal oxygen supply

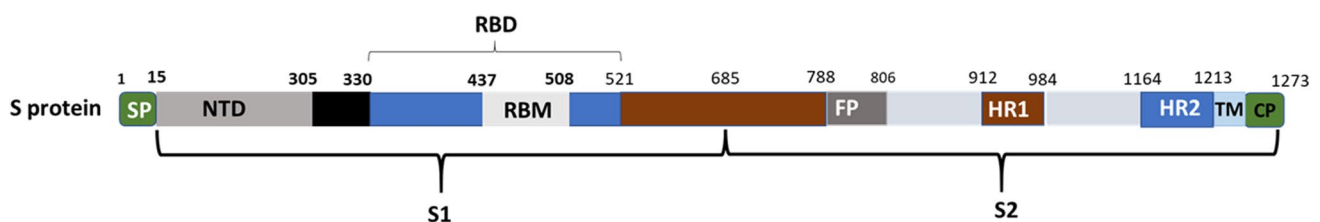


Fig. 5 Structural motifs of S-protein: the S-protein of SARS-CoV-2 is composed of S1 and S2 subunits. Whereas the S1 domain is composed of N-terminal domain (NTD), receptor-binding domain (RBD),

receptor-binding motif (RBM), the S2 domain is composed of fusion peptide, heptad repeat 1 (HR1), heptad repeat 2 (HR2), transmembrane domain (TM), and a cytoplasmic domain (CP)

consequently invoke defects in regional growth and brain development [217–219]. Thus, the impact of COVID-19 on pregnancy remains undetermined in terms of neurological complications in both mother and newborn. Even though reports suggested critical illness and maternal death in few cases, to date, no evidences are reported indicating pregnancy as one of the risk factors for acquiring COVID-19.

Proteins of Virus- and Host-Origin Involved in the Pathogenesis

S-Protein

S-protein is one of the viral proteins, which consists of a large ectodomain, a single-pass transmembrane anchor, and a short intracellular tail (Fig. 5) [220]. Ectodomain consists of two subunits: viz., S1 (receptor-binding subunit) and S2 (membrane fusion subunit), serving as primary targets for human inventions. S1 and S2 subunits are highly conserved with 70% and 99% similarity with bat SARS-CoV and human SARS-CoV, respectively [1, 221]. S1 functional domains include the N-terminal domain (NTD), receptor-binding domain (RBD), and receptor-binding motif (RBM) (Fig. 5). S2 has a fusion peptide, heptad repeat 1 (HR1),

heptad repeat 2 (HR2), transmembrane domain (TM), and a cytoplasmic domain (CP) (Fig. 5) [2, 59, 220]. Electron microscopy studies revealed that the spike appears as a clove-shaped trimer with three S1 heads and a trimeric S2 stalk [222–225]. The receptor-binding subunit interacts efficiently with various host receptors and facilitates the virus attachment on the host cell surface. The membrane fusion subunit fuses the host and viral membrane, mediating the entry of the virus into the host cells [226].

ACE-2 receptor is the binding partner of SARS-CoV-2's S-protein [2, 59]. Studies have reported and confirmed the existence of cross-reaction, by amino-acid sequence analysis of S1 subunit revealing 77% similarity of SARS-CoV-2 to SARS-CoV [29, 227, 228], while S2 subunit of SARS-CoV-2 was highly conserved and shared 99% homology with human SARS-CoV [1].

The difference in RBD of SARS-CoV and SARS-CoV-2 was that SARS-CoV specific ACE-2 binding neutralizing antibodies (m96, CR3014) failed to bind with the S-protein of SARS-CoV-2 [29]. Analysis of RBD of SARS-CoV and SARS-CoV-2 showed the presence of arginine (R426) in SARS-CoV RBD compared to asparagine (N439) in SARS-CoV-2, which leads to a significant decrease in the strong polar interactions [229]. Similarly, a replacement of valine (V404 in SARS-CoV) by lysine (K417 in SARS-CoV-2) on

Table 3 List of US-FDA approved vaccines under clinical trials

Vaccine name	Type of vaccine	Current stage of the clinical trial	Efficacy	Dosing regimen	Type of administration	Manufacturer of the vaccine
Comirnaty/tozinameran/BNT162b2	mRNA vaccine	Phases 2, 3	95%	2 doses, 3 weeks apart	Muscle injection	Pfizer and BioNTech
mRNA-1273	mRNA vaccine	Phase 3	94.5%	2 doses, 4 weeks apart	Muscle injection	Moderna
Sputnik V/Gam-Covid-Vac	Viral vector (Ad26, Ad5)	Phase 3	91.6%	2 doses, 3 weeks apart	Muscle injection	Gamaleya Research Institute
AZD1222/Covishield	Viral vector (ChAd0×1)	Phases 2, 3	82.4%	2 doses	Muscle injection	University of Oxford and AstraZeneca
Convidecia/Ad5-nCoV	Viral vector (Ad5)	Phase 3	Unknown	Single dose	Muscle injection	CanSino Biologics
EpiVacCorona	Protein subunit	Phase 3	Unknown	2 doses, 3 weeks apart	Muscle injection	Vector Institute
BBIBP-CorV	Inactivated	Phase 3	79.34%	2 doses, 3 weeks apart	Muscle injection	Sinopharm and Beijing Institute of Biological Products
CoronaVac	Inactivated	Phase 3	50.38%	2 doses, 2 weeks apart	Muscle injection	Sinovac Biotech
Covaxin	Inactivated	Phase 3	Unknown	2 doses, 4 weeks apart	Unknown	Indian Council of Medical Research, National Institute of Virology and Bharat Biotech
Name not announced	Inactivated	Phase 3	Unknown	Unknown	Unknown	Sinopharm and Wuhan Institute of Biological Products

$\beta 6$ formed an extra salt bridge with D30 on ACE-2 [228]. The structural changes in the RBM modulate the hACE-2-binding ridge into a more compact one, which facilitates better interaction with N-terminal hACE-2, making SARS-CoV-2 a more favorable binding partner [230] (Fig. 5).

TMPRSS2

TMPRSS2 is a cellular serine protease, which [57, 231, 232] plays a significant role in the entry of coronaviruses such as SARS-CoV and MERS-CoV into host cells [233, 234]. Several investigators have confirmed that TMPRSS2 causes S-protein priming for SARS-CoV-2 entry into primary target cells and enables the spreading of the virus in the infected host [33, 56, 235, 236]. Thus, TMPRSS2 is an attractive drug target for blocking the initial step of SARS-CoV-2 infection to avoid multiorgan dysfunction. However, the above intricate structure of S-protein interaction with TMPRSS2 is a challenging aspect for virologists to develop suitable therapeutic interventions against SARS-CoV-2.

Targeting COVID-19 Using Vaccines

As of 3 April 2021, 83 vaccine candidates are currently in clinical trials on humans and 77 vaccine candidates are under investigation in animals. Among which 48 are in phase I, 33 in phase II, and 23 in phase III evaluation (Table 3, Fig. 6). Some of the vaccine candidates are currently in phase III clinical trials and the clinical data is supportive of large-scale manufacturing in several industrial production units worldwide with complete FDA approval [237].

The current COVID-19 vaccine candidates are antibody and/or T cell immune response promoting agents [237]. For instance, the protein-based vaccines are safe and induce immune responses through the adjuvants used along with the vaccine. Mainly, the S-protein, which is composed of S1 RBD, RBD-Fc, and N-terminal regions, could exert immune protection in several in vivo and nonhuman primate models [238–242]. Furthermore, the subunit vaccines could invoke immune responses in the host through one or more antigens in the presence of a suitable adjuvant. However, the immunization through subunit vaccine in animal models is capable of inducing fusion of S1 RBD with IgG1 FC portion consequently actuate generation of highly potent antibodies to foster neutralization of SARS-CoV [243, 244]. The clinical models of SARS-CoV-2 are yet to be examined for subunit vaccine as there is a very minimal success with clinical efficacy in animal models.

Ozonation of Vaccine

Systemic ozone therapy (OT) could be referred to as the potential approach useful in SARS-CoV-2 [245]. OT can be

beneficial for the effective clinical management of complications secondary to SARS-CoV-2 [245]. OT improves oxygenation and exerts protection against lung fibrosis [246] and renal failure [247]. Furthermore, this therapy can stabilize the plasma levels in viral-infected patients by improving hepatic protein synthesis [248]. It could also exert a cytoprotective effect by preventing oxidative damage to the heart [249, 250], liver [251, 252], and renal tissues [253]. Systemic OT has the capacity to modulate the expression of the NF- κ B/Nrf2 pathway and IL-6/IL-1 β pathway consequently foster cytoprotection by blocking viral replication [245]. Previously, hormetic responses and oxidative preconditioning have been examined experimentally to the chronic oxidative stress during OT [254]. However, the hormetic responses of ozone were delineated vividly. For instance, a high dose of ozone can modulate gene transcription of pro-inflammatory cytokines and inflammatory cytokines while inducing a negative regulation of type I IFN in response to viral infection pathways [255]. Despite OT has no significant effect to kill the virus but it has the ability to modulate oxidative stress and inflammatory cytokines; hence OT could be considered as a complementary proposed treatment in COVID-19 patients. Exemplarily, the global vaccine preparation against HIV involves the prolonged and controlled exposure of plasma to a “precise dose of ozone” [245]. Similarly, therapeutic human albumin and ozonated ethyl oleate are predominantly mixed to enhance the absorption and boost the immune function through the vaccine [248, 256, 257]. This kind of ozonation of the vaccine approach towards the preparation of the COVID-19 vaccine can enhance the “oxidation of free viral components” thereby improves the efficacy.

Viral Vector-Based Vaccines.

These vaccines could promote the delivery of one or more antigens coded through a modified viral vector [258]. This technology promotes the delivery of antigens into the host cells and fosters the generation of both humoral and cell-based immune responses against viral pathogen [244, 259, 260]. The efficacy of viral vectors is yet to be examined against SARS-CoV and SARS-CoV-2. Previous reports delineated the efficacy of the modified vaccinia Ankara (MVA) vector, a live attenuated vector-based vaccine that encodes S-protein [261]. It induces a potent neutralizing antibody in mice, rabbits, and monkeys [262]. Immunization of mice models using recombinant adenovirus has been shown to induce neutralizing antibodies in serum and CD8+ T cells of lungs [263–266].

DNA vaccines consist of plasmid DNA molecules, which encode for immunogens and proven to be more effective than mRNA vaccines for stability and easy delivery [267]. However, their implications are constrained by the risk of

Fig. 6 List of vaccines in various stages of clinical trials: current SARS-CoV-2 vaccine candidates targeting various biomolecules of the virus. Viral biomolecules targeting vaccine candidates include DNA-based vaccines, inactivated virus, live attenuated virus, non-replicating viral vector, protein subunit, replicating viral vector, RNA-based, and virus-like particle-based vaccines



getting mutations by integrating with the host genome [267, 268]. The passive transfer of sera from immunized mice with DNA that encodes the S-domain of MERS-CoV has been shown to protect naïve mice infected with MERS-CoV [269]. Another study showed that DNA encoding S1 and S-proteins invoke the generation of cross-neutralizing antibodies towards multiple MERS-CoV strains originated from

humans and camels [270]. Furthermore, the immunization of mice with S-protein encoding DNA has been conducive to the generation of CD4 + and CD8 + T cells specific peptides, which consequently enhanced the extensive cytokine expression [271]. In the case of pseudotyped lentiviral vector-based DNA, the vaccine-induced potent neutralizing antibodies in SARS-CoV consequently invoked S-protein-specific

CD4+ and CD8+ T cell immune responses in immunized volunteers [272]. A summary of the ongoing DNA/subunit/protein-based vaccine trials are provided in Table 2. However, the implications of these vaccine models in SARS-CoV-2 are constrained by the antibody-dependent enhancement (ADEs) and Th2-immunopathology.

Successful Phase II COVAXIN (Bharat Biotech)

BBV152 (COVAXIN) is a whole-virion β -propiolactone-inactivated SARS-CoV-2 vaccine investigated and formulated along with a toll-like receptor 7/8 agonist (imidazoquinoline molecule) to foster Th-1 immune responses through the intramuscular route of administration [273, 274]. A double-blind, multicenter, and randomized controlled phase I trial was conducted across 11 hospitals in India by Bharat Biotech. Further, this study assessed the safety and immunogenicity of BBV152 (ClinicalTrials.gov NCT04471519) assessment of safety and immunogenicity of BBV152 [275]. However, additional studies are required to ascertain the cell-mediated responses.

Covishield is another vaccine developed by Serum Institute of India (SII) in collaboration with Oxford-AstraZeneca, UK, and Bharat Biotech. This vaccine was approved by the Drugs Controller General of India (DCGI) recently for emergency usage through the intramuscular route of administration in SARS-CoV-2 infected patients in India (DCGI, India).

Vaccine-Induced Neurological Complications

To date, 665 million vaccine doses have been administered worldwide. Several recent reports suggest that the COVID-19 vaccination has no- or minimal risk to the neurological system [171, 276]. However, mild side effects such as dizziness, headache, pain, muscle spasms, myalgia, and paresthesias were reported in the clinical trials of the vaccines during phase III study [276]. For instance, AZD1222 adenoviral vector vaccine administration during phase III trial in two patients was reported with neurological complications. Upon detailed investigation, it was concluded that one patient exhibited multiple sclerosis, which was undiagnosed at the time of vaccination, and the later reports concluded that the other factors might be contributing to this side effect [277–279]. Subsequently, these reports delineated that this vaccine had no neurological side effects and the study was resumed, with approvals in India, Argentina, and the UK [277]. In an mRNA vaccine trial, 7 out of 37,000 participants developed Bell's palsy (a temporary weakness or paralysis of the muscles in the face); US-FDA concluded that the rate of the disease was not higher than expected in the population [280]. A vaccine candidate developed by Johnson & Johnson has been reported with GBS in two patients in the phase III trial. Among them,

one participant was vaccinated and the other was a placebo, suggesting that there was no association between GBS and COVID-19 infection [281]. A case study by Waheed et al. reported the first case of GBS after 2 weeks of the first dose of Pfizer COVID-19 vaccine (mRNA vaccine) [171]. In rare case, the vaccine administration that was associated with tremor, diplopia (simultaneous perception of two images of a single object), tinnitus (experience of ringing or other noises in one or both the ears), dysphonia (abnormal voice), seizures, and reactivation of herpes zoster has been reported [276]. To date, 17 cases of stroke, 32 cases of GBS, 190 cases of Bell's palsy, and 6 cases of encephalomyelitis have been reported in the "Vaccine Adverse Event Reporting System database" [276]. However, there is no significant report that suggests a higher rate of neurological complications with COVID-19 vaccination [276].

Conclusions

Infection with SARS-CoV-2, the culprit for the COVID-19 pandemic, has caused several health complications, including the disturbances associated with the neurological system and cognition-related behavioral changes. Fundamental molecular mechanisms that triggered these alterations are reported to be inflammation, induction of cell death, and poor cell-to-cell communications. However, further studies are warranted to address and further confirm (a) whether SARS-CoV-2 can directly enter the neuronal cells? If so, what is the route of entry? (b) The pathogenic responses triggered in infected cells? (c) Why only certain COVID-19 patients develop neurological complications? Moreover, (d) is there any association between age group and susceptibility to COVID-19 induced neurological damage? Further, it is also unknown whether the vaccines that the FDA approves could also extend protection to prevent the entry of SARS-CoV-2 into neuronal cells. Addressing these queries would likely provide clues and mechanisms that can be considered for developing better treatment agents and protection strategies from SARS-CoV-2 infections.

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Author Contribution Medha Karnik (MK), Narasimha M. Beeraka (NMB), Chinnappa A. Uthaiiah (CAU), SubbaRao V. Madhunapantula (SVM), Suma M. Nataraj (SMN), Anjali Devi S. Bettadapura (ASB), and Gjumrakch Aliev (GA) conceptualized and designed the study. MK and NMB contributed equally to this work. MK, NMB, and CAU performed the literature analysis and wrote the original manuscript draft. MK, NMB, and SVM revised and improved the final draft. All authors have reviewed and approved the manuscript before submission.

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Declarations

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