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Divulging the Intricacies of Crosstalk Between NF-Kb and Nrf2-Keap1 Pathway in Neurological Complications of COVID-19

Ranjana Bhandari[1] · Garima Khanna[1] · Dhriti Kaushik[1] · Anurag Kuhad[1]

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Abstract

The severity of COVID-19 infection is surging day by day. With the cases increasing daily, it is becoming more and more essential to understand the pathogenic mechanisms underlying the severity of the disease. It is now well known that the infection manifests itself primarily as respiratory, but the involvement of the other organ systems has now been documented in many studies. SARS-CoV-2 can invade the nervous system by a multitude of proposed mechanisms that have been discussed in this review. NF-κB and Nrf2 are transcription factors that regulate genes responsible for inflammatory and anti-oxidant response respectively. Specific focus in this review has been given to NF-κB and Nrf2 pathways that are involved in the cytokine storm and oxidative stress that are the hallmarks of COVID-19. As the immune injury is an important mechanism of neuro-invasion and neuroinflammation, there is the possible involvement of these two pathways in the neurological complications. The crosstalk mechanisms of these signaling pathways have also been discussed. Immuno-modulators both synthetic and natural are promising candidates in catering to the pathologies targeted in the aforementioned pathways.

Keywords COVID-19 · Neuropathogenesis · NF-κB · Nrf2 · Oxidative stress

Introduction

In December 2019, several cases presenting pneumonia came up in Wuhan, China. The samples were taken from the lower respiratory tract and the organism was identified as a novel coronavirus [1]. After the analysis of the genome of the causative organism, it was identified to be SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) [2, 3]. COVID-19 received the status of a pandemic on March 11, 2020, by WHO [4]. Since its first reported case in Wuhan, China in December 2019, the disease has come a long way, with the number of cases and the number of deaths surging daily. The primary manifestations of COVID-19 are known to be respiratory, but several pieces of evidence suggest the involvement of the nervous system too, which results in a range of neurological complications [5, 6]. Several studies have established the incidence of neurological complications, both related to CNS (central nervous system) and PNS (peripheral nervous system) that have been quoted further in the article. These can be seen in the form of impaired consciousness, headache, dizziness, paraesthesia, encephalitis, infectious toxic encephalopathy, acute cerebrovascular diseases, and many others. These are more prevalent in patients in severe stages of infection [7, 8]. Cognitive dysfunction and memory loss have been reported in very few studies. A retrospective study on 50 hospitalized patients in Chicago revealed 24% of patients with short-term memory loss and 13 patients presented cognitive impairment [9]. Another study in the UK also reported COVID-19 patients with altered mental status having neurocognitive dysfunction such as new-onset psychosis, neurocognitive (dementia-like) syndrome, and an affective disorder apart from other neurological complications such as ischaemic stroke, intracerebral hemorrhage, CNS vasculitis, encephalopathy, and encephalitis [10]. Potential mechanisms of neuroinvasion have also been proposed, though there is still lesser clarity on them. The entry of the virus into the brain can be mediated by endothelial cells of BBB (blood–brain barrier) or epithelial cells of the blood–CSF barrier or through the inflammatory cells produced in the cytokine storm during COVID-19 infection. Retrograde axonal transport through the olfactory, enteric nervous system, and the respiratory

✉ Ranjana Bhandari
akb10in@yahoo.co.uk

✉ Anurag Kuhad
anurag_pu@yahoo.com; anurag.kuhad@pu.ac.in

[1] Pharmacology Research Laboratory, University Institute of Pharmaceutical Sciences, UGC-Centre of Advanced Study, Panjab University, Chandigarh 160 014, India

system could be the other possible routes of brain infection. The increasing evidence shows that it might be possible for the SARS-Cov2 virus to gain access to the cardiorespiratory center of the medulla oblongata in the brain through a synapse-connected route after invading peripheral nerve terminals such as mechanoreceptors and chemoreceptors present in the lungs and lower respiratory airways.

Blood circulation is another route that facilitates the entry of the viral particles and the inflammatory mediators into the brain [11]. Another mechanism is attributed to be injury through hypoxia that causes brain swelling, cerebral vasodilation, headache due to ischemia, and obstruction of cerebral blood flow which may worsen if hypoxia goes untreated and may result in coma or stroke [7]. The detailed mechanisms, with a specific focus on NF-κB and Nrf2 pathway, have been discussed in this review.

The release of a large number of cytokines in SARS-CoV-2 infection has now been well documented in various studies. In a study in Wuhan, higher levels of IL-2, IL-10, IL-7, TNF-α, and other inflammatory markers were found in the ICU patients than the non-ICU patients admitted for COVID-19 [12]. Another similar study on 452 patients, out of which 286 were severe cases, elevated levels of inflammatory cytokines, and biomarkers related to infection were found in severely infected patients. T-cells, monocytes, basophils, and eosinophils had a lower count [13]. Increased levels of C-reactive protein, D-dimer, ferritin, IL-6, IL-10, IL-2R, TNF-α, and markedly reduced levels of T-lymphocytes, CD8 + T cells, and CD4 + T cells were found in the severe cases of COVID-19 in another study [14]. The pathway for this hyper inflammation has been demonstrated to be through NF-κB by some studies. In a study on 48 Korean subjects, the genes that are involved in the NF-κB signaling pathway were found to be upregulated, along with increased levels of cytokines and inflammatory markers, showcasing the involvement of this pathway in the hyperinflammatory response in patients with COVID-19 [15]. NF-κB (nuclear factor κB) is a family consisting of inducible transcription factors that regulate the genes involved in immune and inflammatory responses. These normally exist in the cytoplasm in a sequestered form by inhibitory proteins that include the IκB family and some other related proteins. The most prominent member of the IκB family is IκBα. Phosphorylation of IκB during inflammation leads to the release of NF-κB. Thus, NF-κB activation is a hallmark of inflammatory diseases [16].

Nrf2 (nuclear factor erythroid 2 related factor-2) is a transcription factor that forms the genes coding for various enzymes that protect the cells from oxidative or electrophilic stress. It also transcriptionally represses inflammatory genes that regulate the inflammatory response. Normally, Nrf2 exists in bound form in the cytoplasm with its inhibitor, Keap1. When the cell is under stress, electrophile or ROS (reactive oxygen species) generation leads to dissociation of Nrf2-Keap1 complex and Nrf2 migrates into the nucleus to stimulate the transcription of a multitude of genes that are involved in redox homeostasis and anti-oxidant response [17]. Biopsies in COVID-19 patients have revealed that genes associated with Nrf2 anti-oxidant response were suppressed in these patients. Also, in vitro experiments showcased that the Nrf2 inducible proteins expression was also downregulated that tells the suppression of this pathway in COVID-19 patients [18]. A study on Nrf2 activator showed that it downregulated 36 genes that encode cytokines resulting in a decrease in the cytokine storm in COVID-19 [19].

All the above studies point to the involvement of Nrf2 and NF-κB in the pathogenesis of COVID-19. Since one of the mechanisms of neurological complications is through immune injury by the cytokines, the involvement of these signaling pathways in these complications can be well attributed. A study on transgenic mice also revealed that when the Nrf2 pathway was activated, it suppressed oxidative stress and improved the cognitive function of mice. When the pathway was blocked, it resulted in oxidative injury and a decrease in the viability of neurons [20]. As this pathway is reported to be downregulated in COVID-19 patients, this could be one of the possible causes of cognitive decline. The detailed signaling of both these pathways as well as their involvement in the neurological invasion of SARS-CoV-2 has been discussed. The potential mechanisms of crosstalk between these two pathways have also been viewed upon. Immuno-modulators both synthetic and natural which can modulate the Nrf2-Keap1 pathway or can inhibit NF-KB hence, affecting crosstalk are promising candidates in catering to the pathologies targeted in the aforementioned pathways. The compilation of promising candidates which can be explored as a therapeutic against COVID-19 has also been discussed.

Structure of SARS-CoV-2

SARS-CoV-2 is a beta-coronavirus that has single-stranded positive-sense RNA. It belongs to the family *Coronaviridae* and has a diameter between 80 and 220 nm [1]. SARS-CoV-2 has four main structural proteins—small envelopes (E) glycoprotein, spike (S) glycoprotein, nucleocapsid (N) protein, membrane (M) glycoprotein, and some other accessory proteins. M glycoprotein is the most abundant that spans the membrane 3 times. The N protein binds to nucleic acid material and plays a role in the viral replication cycle and is also involved in the cellular response elicited by the host cells to the infection. The S-glycoprotein weighs about 150 kDa. It is a transmembrane protein that is present in the form of spikes on the viral outer surface. This is only responsible for binding to the host cell receptors, ACE2. Some accessory proteins like HE (hemagglutinin esterase), 4a/b, and 3a/b protein are involved in virus replication and maintenance of the genome

[21, 22]. The spike glycoprotein is responsible for binding to the host cell receptors, ACE2 as well as to the CD147 receptor (also called basigin or EMMPRIN). CD147 is a transmembrane glycoprotein that belongs to the immunoglobulin superfamily and shows increased expression in the case of tumors or inflammatory processes [23]. It was recently demonstrated in a study that SARS-CoV-2 binds to CD147 receptors, apart from ACE2. A direct interaction was reported between the spike glycoprotein and CD147 by the finding that blocking of this receptor inhibited the viral replication [24]. To date, there has been an entire focus on the entry of SARS-COV-2 into the host cell via ACE2 receptors which are expressed at very low protein levels in the olfactory as well as respiratory epithelial cells. Hence, it was observed that there is a possibility that cofactors are required to facilitate virus–host cell interactions in cells with low ACE2 expression. Moreover, ACE2 is not present in most neurons despite increasing reports of neurological symptoms being common in COVID-19 patients. Hence, it supports the hypothesis that ACE2 is not the sole entry point for SARS-COV-2. Scientific literature has indicated that the SARS-CoV-2 spike protein can also bind to the b1b2 domain of the neuropilin-1 receptor (NRP-1). NRP1 receptor is present in the human respiratory and olfactory epithelium and it was observed that olfactory epithelium of patients infected with COVID-19 had enhanced expression of NRP1. NRP1 significantly potentiated infectivity of SARS-CoV-2 virus as observed from the pathological analysis of olfactory epithelium obtained from autopsy reports of COVID-19 patients[25, 26]. Another research report by Moutal et al. [27] reinforced the involvement of NRP1 for entry of SARS-COV-2 into the host cell. Since, both the spike protein of SARS-COV-2 and vascular endothelial growth factor-A (VEGF-A) bind to NRP-1, they tested weather VEGF-A/NRP-1 signaling was blocked by spike protein. It was observed that VEGF-A-triggered sensory neuron firing was blocked by spike protein as well as NRP-1 inhibitor substantiating the involvement of NRP1 in facilitating entry and infectivity of COVID-19 Fig. 1.

Symptoms of SARS-CoV-2 Infection

COVID-19 primarily spreads through the respiratory droplets from an infected person. The primary manifestations of COVID-19 include fever, fatigue, and dry cough. Out of 138 patients in a study, 26.1% of patients progressed to complications like ARDS (acute respiratory distress syndrome), arrhythmia, and shock. Most of these patients were old and had co-morbidities existing already [28]. Another study showed fever, cough, and shortness of breath among the major symptoms while a lesser percentage had muscle ache, confusion, sore throat, headache, rhinorrhea, diarrhea, chest pain, and nausea-vomiting. Seventeen percent of patients developed ARDS [29].

Apart from these respiratory symptoms, several studies have shown that patients exhibit neurological symptoms as well. A systematic review presented the main CNS complications to be an ischaemic stroke, acute myelitis, encephalomyelitis, and intracranial hemorrhage. The PNS complications were mainly GBS (Guillain-Barre syndrome) and Bell's palsy, while rhabdomyolysis was the main skeletal muscle manifestation [30]. In a UK-wide surveillance study on 153 patients, 62% had cerebrovascular events (ischaemic stroke, 74%; cerebral vasculitis, 1%; intracerebral hemorrhage, 12%; other cerebrovascular events, 13%); 31% showed altered mental status (encephalitis, 18%; unspecified

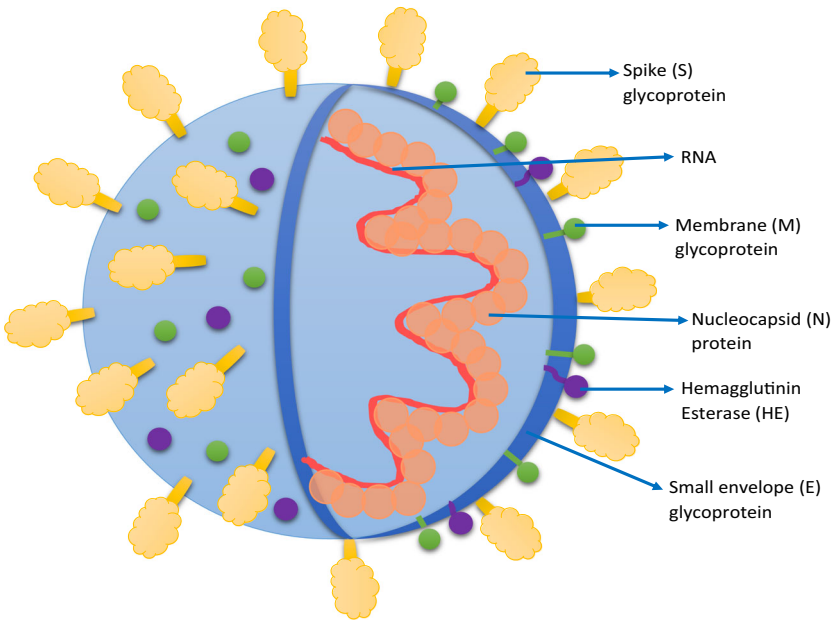

Fig. 1 Structure of SARS-CoV-2

encephalopathy, 23%; neuropsychiatric disorders, 59% including psychosis, 43%; neurocognitive disorder,26% and other psychiatric disorders, 36%); 5% showed peripheral disorders (GBS, 67%; other peripheral disorders, 23%); and 2% had other neurological disorders [10].

In another study on 214 subjects, 36.4% had neurological findings out of which 24.8% were CNS related and 8.9% were PNS-related. The CNS-related were dizziness in 16.8%, impaired consciousness in 7.5%, headache in 13.1%, acute cerebrovascular diseases in 2.5%, epilepsy in 0.5%, ataxia in 0.5% of the patients. The PNS-related findings were hypogeusia in 5.6%, hyposmia in 5.1%, and neuralgia in 2.3% of the patients [8]. The patients in France also showed neurological features with 84% of 58 patients showing neurological complications. Fifteen out of 45 patients showed cognitive impairment following discharge from ICU, mainly characterized by disorientation, inattention, and poor response to commands [31]. In another case study of four critical COVID-19 patients admitted in ICU, cognitive impairment was identified after discharge, mainly manifesting as a frontal syndrome and memory deficit. But this was soon remitted after immunoglobulin therapy for 5 days [32]. In another study on 71 hospitalized COVID-19 patients diagnosed with delirium in course of their hospitalization, 42% of them had lower cognitive scores in a telephonic interview 4 weeks after discharge [33].

MRI brain findings in 126 patients also showed acute or subacute infarcts in 32 cases, microhemorrhages in 14 cases, leukoencephalopathy in 17 cases, hypoxic ischemic encephalopathy in 1 case, leptomeningeal enhancement in 14 cases among the other findings [34]. Out of 59 patients in another study, 33.9% of them reported taste of olfactory disorders. Dysgeusia was reported in 8.5%, ageusia in 1.7%, and hyposmia in 5.1% of the patients. Mixed taste and olfactory disorders were also reported in 18.6% of the patients including dysgeusia and hyposmia in 3.4%; dysgeusia and anosmia in 3.4%; ageusia and hyposmia in 3.4%; ageusia and anosmia in 8.5% of the patients [35].

Epidemiology

With the appearance of the first case in Wuhan in December 2019, SARS-CoV-2 has spread to all the regions with many countries being severely affected. According to WHO, 37 million cases and over 1 million deaths were reported globally as of October 11 with 67,000 new deaths and 7 million new cases added to the list by November 24, 2020, making the number to 57.8 million reported cases and over 1.3 million reported deaths globally [36]. According to the Weekly Epidemiological Update by WHO issued on December 22, 2020, 75 million cases and 1.6 million deaths were reported since the pandemic start on December 20. USA, Brazil, Turkey, Russian Federation, and India were the five countries that reported the highest case numbers in which the USA, Brazil, and Russian Federation experienced a 14%, 8%, and less than 1% increase in cases respectively while Turkey and India experienced 11% and 18% decrease respectively in the case numbers [37]. As of February 13, 2021, 107,838,255 confirmed cases and 2,373,398 deaths were reported globally. The Americas region reported the highest confirmed cases while Western Pacific Region had the lowest number. Country-wise, the USA, India, and Brazil are the three leading countries in terms of confirmed cases [38]. Figure 2 shows the situation in numbers as of February 13, 2021.

Some studies have shown a higher prevalence of COVID-19 infection in men than in women. A meta-analysis of 57 studies that included 221,195 participants in total found the pooled prevalence in men to be 55.00 that indicated men were more susceptible to the infection. This analysis attributed this difference due to the higher incidence of smoking and alcohol consumption among men [39]. Another case series analysis on 43 patients revealed that the deceased rate is more in men as compared to women. Out of 37 patients who died due to the infection, 70.3% were males while 29.7% were females. The number of deceased men was 2.4 times that of deceased women [40]. This could be attributed to the fact that the X chromosome displays a higher

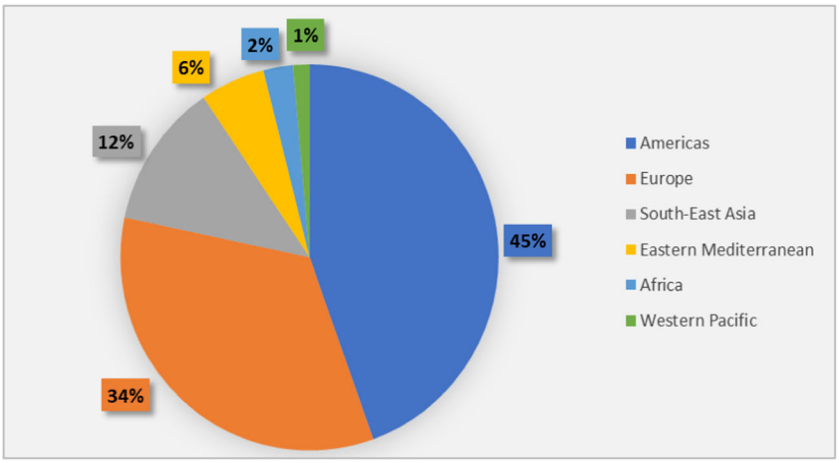

Fig. 2 Percentage of confirmed COVID-19 cases in WHO Regions as of February 13, 2020

number of immune-related genes that make the innate and adaptive immune responses stronger in women than in men [41]. The transmission of the virus is from human-to-human, mainly via respiratory droplets through sneezing, coughing, or direct contact with the infected person [42]. The droplets can also infect the surfaces and transmission may also occur by touching these surfaces and then touching your mouth or nose with the same hands. The incubation period generally varies between 2 and 14 days [43]. The basic reproduction number, R0, was also estimated for SARS-CoV-2 in several studies. A range of 1.4–6.49 was estimated initially. After this, an analysis multitude of studies estimated the average R0 value to be 3.28 and a median value of 2.79. Hence, 2–3 was found to be a reliable range that points to the transmission from human-to-human. Super-spreaders have the potential to infect more than 100 people [42].

Pathogenesis

Several studies have claimed that the ACE2 receptor is the one through which SARS-CoV-2 gains entry into the host cell [44, 45]. ACE2 has been found to show its expression on the alveolar epithelial cells of the lungs and in enterocytes in the small intestine. ACE2 receptors are expressed in both Types I and Type II alveolar cells. They are also present in the oral and nasal mucosa and nasopharynx. In the brain, ACE2 expression was found in endothelium and vascular smooth muscle cells [46]. ACE2 expression in the brain is lower than in other organs. The outer surface of SARS-CoV-2 houses the transmembrane spike(S) glycoproteins that are believed to mediate the entry of the virus into the host cell. S1 and S2 are the two subunits of S-glycoprotein. The S1 subunit has the RBD (receptor-binding domain) that binds directly to PD (peptidase domain) of the ACE2 receptors. The S2 subunit plays its role in membrane fusion of viral and host cell membranes [44]. After the binding of SARS-CoV-2 to ACE2 receptors, there occurs proteolytic cleavage by TMPRSS2 protease. In this, first of all, priming occurs at S1/S2 cleavage site that stabilizes the S2 subunit. Then, a second cleavage occurs that activates S-glycoprotein by conformational changes, and viral and host cell membranes fuse. After this, the viral contents are released into the host cells which starts the viral replication. The N protein present in the virus is responsible for binding to the new genomic RNA and integration to the endoplasmic reticulum (ER) is facilitated by the M protein. These nucleocapsids are enclosed in the membrane of ER and transported to the lumen and then to the cell membrane by the Golgi vesicles. Via exocytosis, these viral particles reach the extracellular space and invade the surrounding epithelial cells. This is the stage of community spread of the virus [47]. Figure 3 represents the pathogenesis of COVID-19.

The respiratory pathogenesis starts with the binding of SARS-CoV-2 to ACE2 receptors in the nasal epithelium where it undergoes propagation and local replication. This generates a limited immune response and highly infectious individuals, although the viral load is low. In the next stage, the virus migrates to the upper respiratory tract with the appearance of clinical symptoms like fever, dry cough, and malaise. The infected cells generate a greater immune response by the release of CXCL-10 (C-X-C motif chemokine ligand 10) and interferons-β and λ. From here, in about one-fifth of the patients, the infection progresses to the lower respiratory tract. Pulmonary infiltrates are developed and a range of cytokines and inflammatory markers are released including interleukins-1, 6, 8 120, 12, TNF-α, MCP-1 (monocyte chemoattractant protein) among others. These chemokines attract the neutrophils, CD8 and CD4 T cells, and their sequestration in the lung tissue begins that manifests as lung injury. Both Type I and Type II alveolar cells are infected, severe scarring, and fibrosis occur leading to diffuse alveolar damage that finally manifests as ARDS (acute respiratory distress syndrome) [47, 48].

Various routes of brain invasion of SARS-CoV-2 have also been proposed. The viral particles or the inflammatory mediators released can directly reach the brain by disrupting the tight junctions of the blood–brain barrier. Also, the sluggish blood circulation may facilitate spike protein binding with ACE2 receptors on the capillary epithelium [11]. The neuronal pathway could be by retrograde axonal transport through the respiratory, olfactory, and enteric nervous systems. From the nasal cells, the virus can reach directly to the brain via the olfactory bulbs and travel to the thalamus and brainstem causing neuroinflammation and demyelinating reactions. Cardiorespiratory function occurs in parts of the brainstem. Therefore, front-line workers may be treating respiratory effects of COVID-19 with methods such as ventilators, which may be ineffective if the respiratory areas are affected with COVID-19 [49, 50]. Invasion of peripheral nerve terminals in the respiratory system may also provide the virus access to the CNS through the synapse. Similarly, the sympathetic afferent neurons in the ENS (enteric nervous system) may also be an entry point of the virus to the CNS when it infects the gastrointestinal tract [11]. Another mechanism could be a hypoxic injury that leads to anaerobic metabolism in brain cell mitochondria which causes accumulation of acidic compounds that can cause brain swelling, cerebral vasodilation, ischaemic stroke, obstruction of cerebral blood flow, etc. Immune injury through local cytokine production can be another mechanism as it increases the permeability of the blood–brain barrier [7]. Patients with the cerebrovascular disease also showed a higher inflammatory response in a study, which points to the possibility that hyper inflammation leads to a high coagulation state that increases incidences of stroke [51]. Binding to ACE2 receptors also leads to increased blood pressure that increases the chances of cerebral hemorrhage [7]. Mechanisms involved in cognitive decline are not yet fully clear but can be attributed to direct infection of the nervous system, the systemic hyper

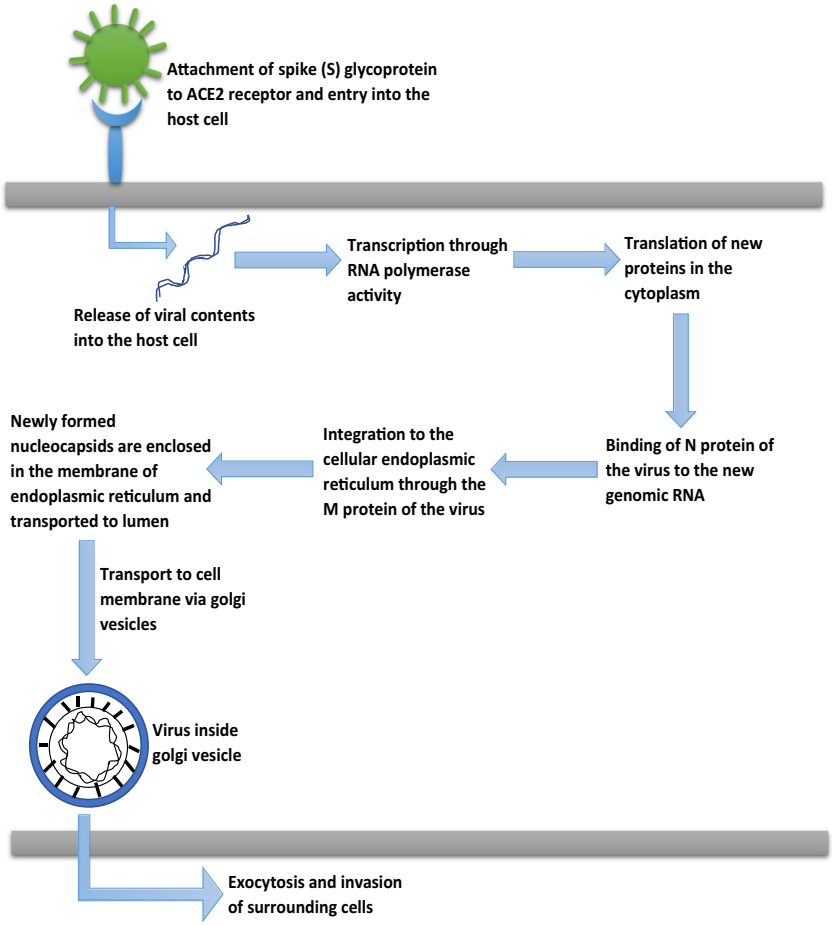

Fig. 3 Pathophysiology of COVID-19

inflammatory response, acute respiratory distress syndrome (ARDS), invasive ventilation, and sedation or side effects of the drugs used for COVID-19 [52]. Figure 4 depicts the various possible routes of neuro-invasion of SARS-CoV-2.

Neurological Complications and Their Possible Mechanisms

Headache

Several studies have reported headache as to be the common initial symptom in COVID-19 patients [8, 29]. The pain was mostly reported in the tempo-parietal region or anteriorly towards the forehead. The first suggested mechanism was the direct invasion of the virus on the trigeminal nerve endings present in the nasal cavity. Secondly, trigeminovascular activation may occur via ACE2 receptors present on the endothelial cells that may also lead to a headache. Thirdly, the cytokines and pro-inflammatory mediators released during COVID-19 may also trigger perivascular trigeminal nerve endings that may also be the cause of headache [53].

Cerebrovascular Events

Elevated levels of Interleukins (IL-6, IL-7), C-reactive protein (CRP), and other inflammatory markers due to the hyperinflammatory response in COVID-19 make the already existing atherosclerotic plaque more rupture susceptible [54]. Another mechanism can be the depletion of ACE2 by the virus as it binds to these receptors that may cause an imbalance in RAS (renin-angiotensin system) and result in ischaemic events [55]. This ACE2 downregulation may also cause vasoconstriction which leads to cerebral autoregulation dysfunction. This manifests as an increase in blood pressure and can cause rupturing of arteries resulting in hemorrhage [56].

Demyelinating Diseases

A systematic review analyzed that acute encephalomyelitis was reported in four patients while acute myelitis was reported in five patients [57]. The proposed mechanism was myelitis was secondary immunogenic overreaction after COVID-19 infection. Cytokines released in COVID-19 might explain the involvement of the spinal cord in this disease [58].

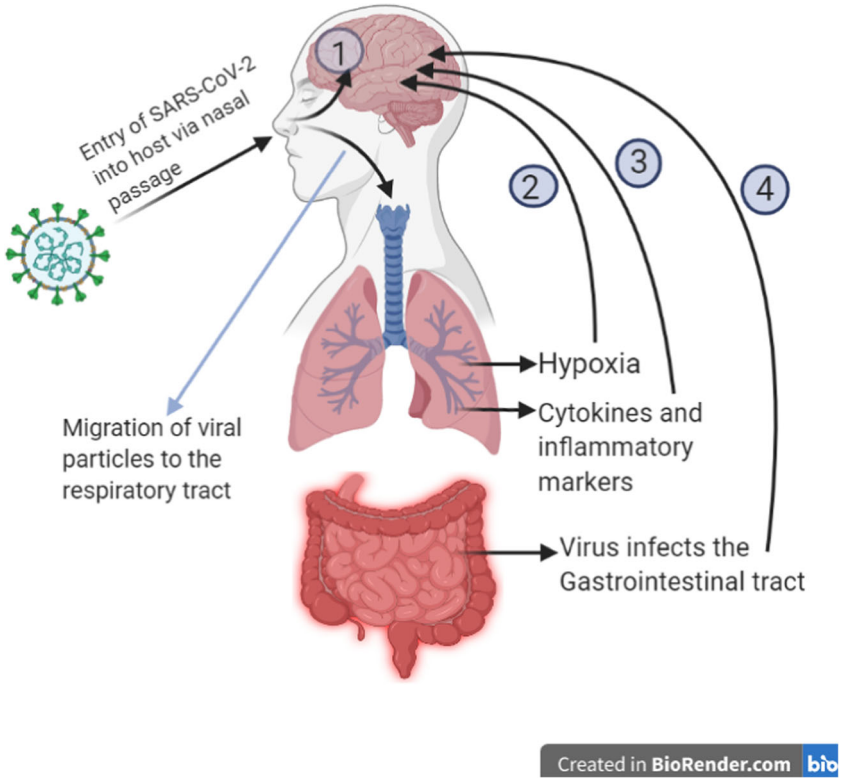

Fig. 4 Various proposed routes of neuro-invasion of SARS-CoV-2 after it entered into the host cells. 1- Migration of viral particles directly into the brain from the nasal passage via olfactory bulb, 2- hypoxia due to lung injury causes anaerobic respiration in the brain cells mitochondria leading to accumulation of acidic compounds that causes brain swelling, ischemia, and obstruction in cerebral blood flow, 3- cytokines and inflammatory markers released during the cytokine storm travel to the blood–brain barrier and increase its permeability, thus infiltrating into the brain, 4- virus infects the gastrointestinal tract and travels to the CNS via sympathetic afferent neurons in the enteric nervous system

Encephalitis

SARS-CoV-2 RNA was detected in the cerebrospinal fluid of a patient diagnosed with encephalitis [59]. Two potential mechanisms are suggested for encephalitis, the first one being through the olfactory and trigeminal nerve endings that results in central infiltration of SARS-CoV-2. Another reason could be an invasion by pro-inflammatory cytokines that increase the permeability of the blood-brain barrier and reach the central nervous system [57].

Encephalopathy

Confusion to delirium progressing to stupor and coma can be the manifestations of altered sensorium in COVID-19 patients in severe stages [60]. Diffuse white matter T2 hyperintensity and restricted diffusion were reported in some COVID-19 patients who were critically ill. Although the exact cause is still not known, it is proposed to be due to delayed post-hypoxic leukoencephalopathy. Leukoencephalopathy is proposed to occur after about 10–14 days following hypoxia that can also lead to oligodendroglial cell death and demyelination. Other etiologies could be the direct cerebral infection, post-infectious demyelination, and sepsis-associated encephalopathy [61]. Acute necrotizing encephalopathy (ANE) reported is proposed to be due to the cytokine storm associated with SARS-CoV-2. An intense surge in the levels of pro-inflammatory cytokines causes damage to the blood–brain barrier by increasing its permeability that can cause edema and necrosis [62].

Seizures

The viral infection in the CNS and the subsequent activation of inflammatory pathways in the brain lowers the seizure threshold and can facilitate epileptogenesis [63]. Local cortical irritation due to the accumulation of various inflammatory markers in the brain can also lead to seizures. Viral encephalitis as well as direct viral invasion of CNS can be the other causes of seizures [57, 64]. Critically ill patients presenting with electrolyte or metabolic imbalances, hypoxia, and inflammatory processes can also experience seizures or an abnormal EEG [65].

Cognitive Decline and Memory Loss

As discussed earlier in the article, few studies have reported short-term memory loss and neurocognitive disorder following COVID-19 infection. Majorly proposed mechanism of neurodegeneration is chronic systemic inflammation [52]. A study established the correlation of inflammatory factors and levels of C-reactive protein (CRP) in the patients that exhibited cognitive dysfunction. This study was done around 2–3 weeks after infection; hence, the assessment was short term. Further long-term studies are still required to establish proper evidence of inflammation-induced cognitive decline. It also

demonstrated a significant correlation between changes in attention and CRP levels when the patients were admitted for COVID-19 [66].

Guillain-Barre Syndrome

Molecular mimicry is the likely mechanism of GBS in which the pathogen has epitopes similar to peripheral nerve components. The host immune system produces antibodies to fight against the viral infection. These cross-react and bind to peripheral nerves that results in neuronal dysfunction [57, 67].

Loss of Smell and Taste

These are some of the first manifestations of COVID-19. The most proposed mechanism for these is that SARS-CoV-2 binds to ACE2 receptors in the olfactory epithelium and enters the neuronal cells spreading to the olfactory bulb via the olfactory nerve that leads to loss of sense of smell [60]. The frequency of loss of smell is high. Out of those reporting chemosensory impairment, 65% had a subsequent positive PCR for Covid-19 [68].

Neuromuscular Junction and Skeletal Muscle Abnormalities

Myalgia, general muscle pain, and fatigue are common symptoms of COVID-19. Muscle injury was noted, especially more in severe cases of COVID-19 [8]. Majorly proposed risk factors are acute respiratory distress syndrome (ARDS), sepsis, and systemic inflammatory response. As the ACE2 receptor is also present on muscle cells, the virus can directly invade the cells and cause muscle injury. The hyperinflammatory cytokine storm could also lead to immune-mediated muscle damage [69, 70].

Neurological Complications and Their Pathology Associated with NF-κB and Nrf2 Pathways

NF-κB Pathway and COVID-19

The NF-κB (nuclear factor κ-light-chain-enhancer of activated B cells) transcription factor family is a pleiotropic regulator of many cellular signaling pathways which provide mechanisms for stimuli that link to inflammation. It influences the growth of axons and dendrites originating right from the earliest stages of neuron establishment [71]. A lipopolysaccharide receptor complex is formed by toll-like receptors and the adaptor proteins present in the extracellular matrix. The signal pathway leads to activation of NF-κB. The blood–brain barrier prevents the entrance of immunogenic cells into the central nervous system [72]. The stimulated cells will be regulated by not only the canonical but also non-canonical NF-κB pathways. Besides neurons, NF-κB transcription factors are abundant in glial cells and cerebral blood vessels, and the diverse functions of NF-κB also regulate the inflammatory reaction around the neuronal environment. NF-κB transcription factors are abundant in the brain and exhibit diverse functions [73]. The pathogenesis of COVID-19 is similar to earlier discovered viral disorders namely cytomegalovirus, MERS, and varicella. Similarly, COVID-19 can cause activation of the NF-κB pathway which ultimately may lead to stroke or neuropathy associated with thromboembolism in the brain. The heightened immune response specially, the cytokine storm is characterized by an elevation in IL-6, IL-10, IFN-γ, and TNF-α in the granulocyte colony–stimulating factor [74]. The genetic induction of innate and adaptive immunogenic cells is influenced by NF-κB. Deregulated activation leads to activated T-cells in association with autoimmune inflammation and inflammasome release [75]. In a preclinical study, NF-κB influenced the regulation of various proinflammatory mediating chemicals. When inhibitors of NF-κB like parthenolide were administered, a reduced infection was seen. The NF-κB transcription is unmasked by the degradation of IκB which is phosphorylated by protein kinases activated by mitogens [76]. The upregulated proinflammatory genes result in excessive cytokine and reactive oxygen species which cause cerebellar damage and neuropathogenic dysregulation associated with neurotransmitters [77].

Nrf-2 and COVID-19

Nrf2 belongs to the basic leucine transcription factor and influences oxidative stress by expressing antioxidant genes [78]. Nrf2 remains situated in the cytoplasm wherein it binds with keap1, which is a known inhibitor of Nrf2. When reactive oxygen species emerge, the Keap1-Nrf2 complex gets dissociated and as a result, Nrf2 migrates towards the nucleus leading to stimulation of target genes eliciting an antioxidant action whose activation enforces protection from inflammation [17]. Upregulation in expressing Phase 1 and 2 drug-metabolizing enzymes in addition to the mitochondrial pathways is also a characteristic of this pathway. The upregulated target genes include glutathione S-transferase, catalase, heme oxygenase 1, and superoxide dismutase. These protect neuron function from oxidative degradation. All primary factors including oxidative degradation, inflammatory upregulation, and dysfunctional mitochondria contribute to aging of brain which exposes patients at a risk of neurodegenerative diseases. Nrf2 can prove to be beneficial in case of COVID-19 infections due to it's attractive efficacy against such pathologies [79]. To eradicate stress induced by oxidative species, Nrf2 is released, stabilized, and translocated. Nrf2 acts as an on-off switch and produces endogenous antioxidative relief. Several kinases like phosphoinositol-3 kinase, protein kinases, and pancreas enriched kinase also act as regulators of Nrf2 activity [80]. Mitogen-activated protein

kinases are enzymes that contain protein kinases regulated extracellularly. They catalyze the phosphorylated reactions on the amino acid serine, threonine residues which reside right next to the proline amino acid. The mitogen-activated protein kinase pathway works in response to oxidative stress and has been implied in the induction of the Nrf2 pathway [81]. The signals are mediated by the extracellular regulated kinase and mitogen activated kinases which culminate in upregulation of glutamate cysteine ligase modulatory subunit gene, influencing nuclear translocation of Nrf2. While Nrf2 and Keap1 are not directly targeted, the mitogen-activated kinases are directly involved in the translocation of Nrf2 into the nucleus [82].

Crosstalk Between NF-κB and Nrf2 Pathways

After the virus replicates inside the host, the innate immunogenic response causes activation of many inflammatory mediators namely macrophages and dendritic cells to fight against cytokines and reactive oxygen species. The reactive oxygen species and inflammatory cytokines damage erythrocytes releasing heme and free ion. Respiratory burst generates superoxide radicals and hydrogen peroxide which ultimately, cause oxidative stress. The cytokine storm is a consequence of the upregulates cytokine expression through the NF-κB pathway. This storm is responsible for severe damage to the tissue [83].

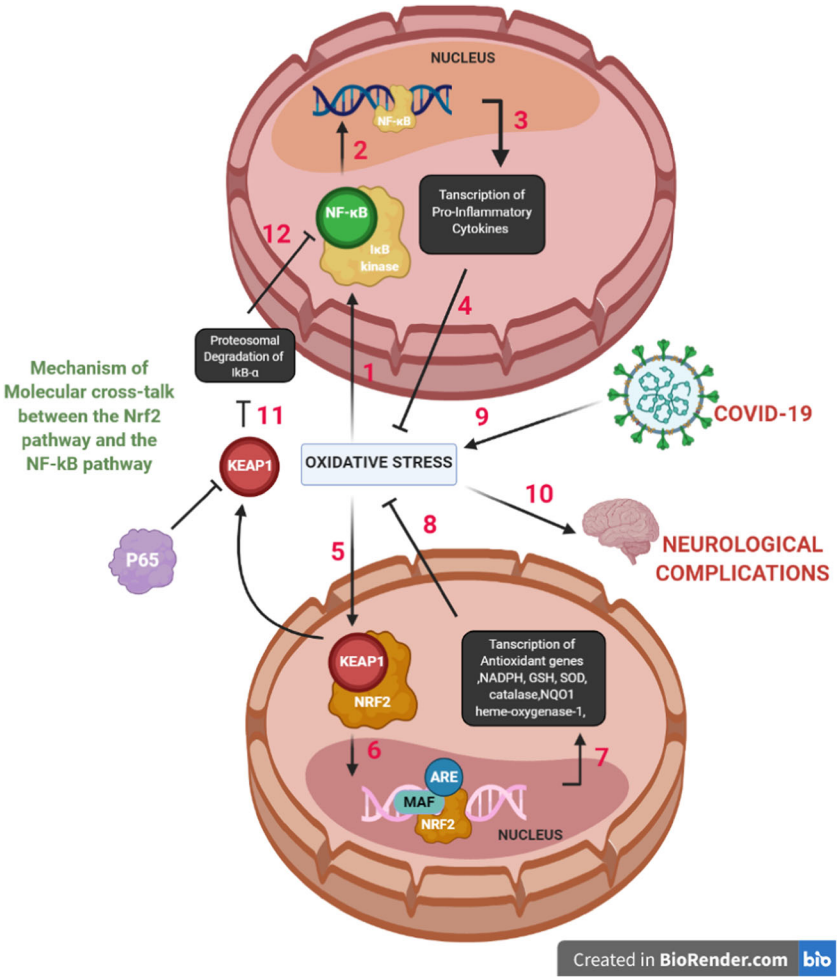

Fig. 5 Crosstalk between NF-κB and Nrf2 pathways mediated by COVID-19 infection leading to neurological complications. (1) Enhanced oxidative stress/cytokine storm leads to activation of IKβ kinase, which causes phosphorylation of IkB-α, an NF-kB inhibitor, and results in proteasomal degradation of IkB-α. (2) NF-kB binds to its region, p65 subunit after migrating into the nucleus. p65 is an inhibitor of KEAP1. (3) This results in transcription of pro-inflammatory cytokines and other genes such as TNF-α, Il-β, Il-6, iNOS, COX-2. (4) The NF-kB pathway and its contributing pro-inflammatory cytokines aggravate the oxidative state. (5) Oxidative stress leads to the activation of the Nrf2 signaling pathway resulting in dissociation of Nrf2 from its inhibitor Keap1. (6) It then causes translocation of Nrf2 to the nucleus and associates with Maf protein and antioxidant response element (ARE). (7) Transcription of antioxidant genes and phase II enzymes such as NADPH, GSH, SOD, catalase, heme-oxygenase-1, and NQO1 occurs which inhibits ROS. (8) Overall, the genetic interventions and consequent transcription show positive implications of Nrf2 pathway in reducing oxidative stress. (9) COVID-19 infection induces oxidative stress. (10) Oxidative stress drives neurological complications. (11) Free Keap1 prevents degradation of IkB-α. (12) Inhibition of the NF-kB pathway

In a study that induced scratch injury in astrocytes, it was found that this injury caused upregulation of NF-κB activity that resulted in overexpression of IL-6, IL-1β, TNF-α, and MMP9 (matrix metallopeptidase 9-gelatinase that aggravates inflammation process). This overexpression was found to be more aggravated in Nrf2 knockout astrocytes than the wild-type resulting in more astrocyte death [84]. In another experiment, Nrf2-deficient mice showed greater pro-inflammatory gene expression on TNF-α stimulation. NF-κB activation after LPS (lipopolysaccharide) activation was also found to be high in the lungs, MEFs (mouse embryonic fibroblasts), and peritoneal macrophages of Nrf2 deficient mice. These also showed higher IKK Kinase activity in response to TNF-α or LPS [85]. These studies point to the possible interplay between Nrf2 and NF-κB. It is proposed that these pathways exert an inhibitory effect on each other at the transcription level. The crosstalk can be both ways-Nrf2 inhibition of NF-κB and vice versa.

Nrf2 produces a multitude of antioxidant and cytoprotective enzymes in response to oxidative stress [86]. One of them, HO-1 (hemoxygenase-1), is involved in the metabolism of heme by acting as a catalyst in the cleavage of porphyrin ring in heme into

Table 1 A summary of agents targeting the crosstalk between the Nrf2 and NF-κB pathway

Drug	Classification	Action	Reference
Dexamethasone	Nrf-2 agonist glucocorticoid	Enhanced IκB expression, NF-κB retained in the cellular cytoplasm.	[95]
*Remdesivir	Nrf-2 agonist	Reduced dsRNA	[96]
N-acetylcysteine	NF-κB antagonist, amino acid derivative	Downregulated phosphorylation of IκB	[97]
Dimethyl fumarate	NF-κB Antagonist, dimethyl ester of fumaric acid	Reduced inflammation through Nrf2-dependent and Nrf2-independent pathways	[17]
Epigallocatechin 3-gallate	Nrf-2 Agonist	Inhibited furin which is a protease enzyme that allows SARS-CoV-2 S protein's entry inside the cell	[17]
4-Octyl-itaconate	Nrf-2 agonist	Inhibited the release of pro-inflammatory cytokines	[98]
Omega 3 fatty acids	NF-κB antagonist, α-linolenic acid	Decreased inflammatory markers and increased antioxidant capacity	[99]
Soybean isoflavones	NF-κB antagonist, flavonoid	Increased brachial flow-mediated dilation, improved antioxidant markers	[79]
Carnosic Acid	NF-κB antagonist, diterpenoids	Reduced spine loss in dendrites, improved memory and learning	[100]
Curcumin	Nrf-2 agonist, diarylheptanoid,	Antioxidant effect by activated Nrf2 pathway and i nduced expression of target genes, such as HO-1 and NQO1	[101]
Resveratrol	Nrf-2 agonist, Natural polyphenol	Stimulated the Nrf2 signaling by blockage of Keap1.	[102]
Bardoxolone methyl	Nrf-2 agonist, semisynthetic triterpenoid	Protection of cells and tissues from oxidative stress by increased NRF2 transcription	[103]
Sulfasalazine	NF-κB antagonist, disease-modifying anti-rheumatic drugs	Interfered with IκBα phosphorylation, inhibited NF-κB activation	[104]
Mesalamine	Nrf-2 agonist, disease-modifying antirheumatic drugs	Inhibiting posttranslational modifications	[104]
Thiophenacetamide	NF-κB antagonist, thiophenes	Specifically bound to the p65 subunit of the NF-κB and inhibited DNA and NF-κB binding	[105]
Garlic	Nrf-2 agonist	Activated Nrf2-antioxidant response element (ARE) pathway.	[106]
Quercetin	NF-κB antagonist, flavonoid	Inhibited macrophage inflammatory protein 2, TNF-induced interferon-gamma-inducible protein	[107]
Ocimum sanctum	NF-κB antagonist	Inhibited gene expression of cytokines, IL-6, TNF-α, MIP-1α, MCP-1	[108]
Hydroxycinnamic acid	NF-κB antagonist	Inhibited DNA-binding of NF-κB	[104]
Niclosamide	Nrf-2 agonist	AMPK-mediated phosphorylated of p62	[109]
Lycopene	NF-κB antagonist	Inhibitor of kappa B phosphorylation	[110]
β-Carotene	NF-κB antagonist	Scavenges reactive oxygen species	[111]
Ritonavir	NF-κB antagonist	Decreases Akt phosphorylation	[112]
Chalcone	Nrf-2 agonist	Induce expression of the Nrf2-dependent enzymes	[113]
Ginseng	Nrf-2 agonist	Increases Nrf2 protein expression	[114]
Fenofibrate	Nrf-2 agonist	Activates Nrf2 through p62-dependent Keap1 degradation	[115]

*Although the on-going clinical trials are yet to provide any conclusive evidence in favor of remdesivir. Furthermore, the clinical investigation is desired to substantiate the plausible use of remdesivir as a therapy for COVID-19. US-FDA issued emergency use authorization (FDA) on May 1, 2020

carbon monoxide, Fe2+, and biliverdin that converts into bilirubin [87]. A study showed that overexpression of HO-1 in the endothelial cells inhibited TNF-α-induced proinflammatory adhesion molecule expression (E-selectin and VCAM-1 (vascular cell adhesion protein 1)). This inhibition was found to be at mRNA level by interfering with the rate of transcription [88]. This represents one way of the crosstalk that the Nrf2 pathway inhibits NF-κB pathway activation by increasing HO-1 expression, thus reducing the cytokine release. Oxidative stress also causes IKK (IκB kinase) activation that further phosphorylates IκB which is the inhibitor of NF-κB and causes polyubiquitination mediated proteasomal degradation that releases NF-κB. It migrates to the nucleus and leads to the transcription of inflammatory genes. Nrf2 pathway inhibits degradation of IκB-α that leads to its stabilization and inhibition of NF-κB-mediated transcription. Hence, the release of pro-inflammatory cytokines is inhibited [86].

NF-κB can also regulate Nrf2 mediated ARE (antioxidant response element) expression. ARE is the site of the genome for the action of Nrf2. p65, that is the canonical NF-κB subunit can exert an inhibitory effect on the gene expression through ARE [87]. CBP (CREB binding protein)–p300 complex is the transcriptional co-activator of Nrf2 that has intrinsic histone acetyltransferase activity. This causes histone acetylation and loosens the chromatin structure, thus DNA is exposed for transcriptional activity [87]. A study showed that NF-κB/p65 antagonizes the Nrf2-ARE pathway by reducing ARE gene transcription, decrease in CBP, and enhancing the recruitment of HDAC3 (histone deacetylase 3) to the ARE region [89]. This strengthens the view that NF-κB activation suppresses the Nrf2 pathway in case of enhanced oxidative stress or cytokine storm

Keap1, with which Nrf2 exists in bound form in the cytoplasm, has been found to negatively regulate IKKβ. HSP90 (heat shock protein 90) is a chaperone protein that assists in protein folding. It has been observed that Keap1 prevents the binding of HSP90 to IKKβ which is the trigger for its autophagic degradation. Also, Keap1 reduces IKKβ phosphorylation by concealing those residues that bind with the phosphate groups. The result of this entire interaction is that IκB-α is stabilized because IKKβ is not phosphorylated that, as a result, reduces NF-κB signaling [87, 90]. Figure 5 represents crosstalk between NF-κB and Nrf2 pathways mediated by COVID-19 infection leading to neurological complications.

Patients with pre-existing auto-immune disorder susceptibility are at grave risk for COVID-19. Due to the administration of immunosuppressant for mitigating the virus, the interest in auto-immunity is implied [91]. The dysfunctional regulatory T cells have been regarded as the cause of many autoimmune disorders. When Nrf2 is systemically activated by Keap1 (Kelch-like ECH-associated protein 1), tissue inflammation is enhanced. On the other hand, its knockdown reduces T cell and cytokine production. Nrf2 induction can mitigate the regulatory T cell dysfunction and alleviate autoimmune disorders especially, in the case of COVID-19 where the latter is further stressed upon [92]. NF-κB has a role in promoting inflammation in autoimmune attacks as well as mediating immunogenic tolerance. It promotes the formation of regulatory T cells and plays a role in deleting self-reacting T cells situated in the thymus. The NF-κB thus lies centrally in preserving immune homeostasis and prevention of autoimmunity caused in COVID-19 [93].

Various Modulators with Action on NF-κB and Nrf2 Pathways

COVID-19 is characterized by a cytokine storm due to the attack on the patient's immune cells. The mainstay of treatment is the use of anti-viral agents. Immunomodulatory agents both synthetic and herbal can be pertinent in catering and

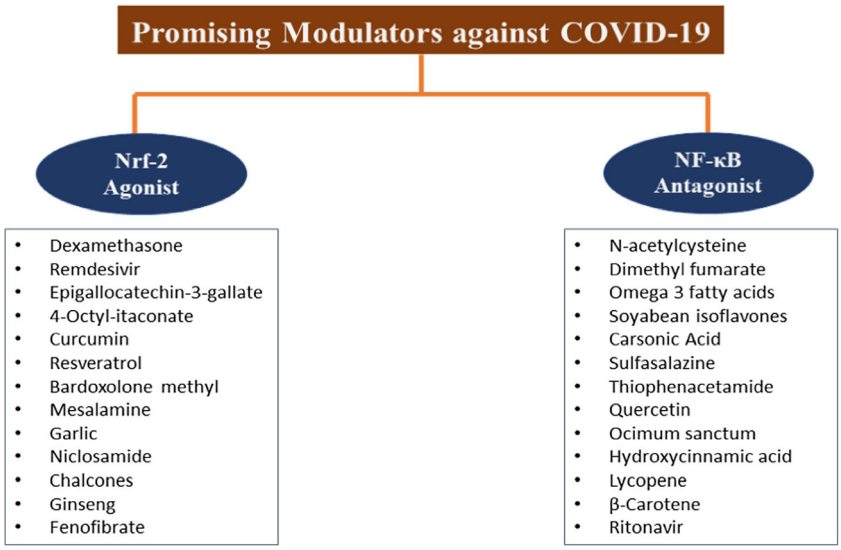

Fig. 6 Promising modulating agents against COVID-19

resolving the serious effects of the attack of the virus. These immunomodulatory agents act in synergism with the pre-existing approaches and act as adjunctive therapy or prophylaxis [94]. The Nrf2 and NF-κB pathway are involved in the development and progress of inflammatory pathology in COVID-19. Consequently, immunomodulators targeting the crosstalk between these key signaling pathways offer an innovative approach in tackling this deadly pandemic and present a ray of shine in tackling COVID-19 associated neurological complications. Table 1 presents a comprehensive summary of agents targeting the crosstalk between the Nrf2 and NF-κB pathways. Figure 6 presents promising modulating agents against COVID-19.

Perspectives and Conclusion

COVID-19 received the status of a pandemic on March 11, 2020, by WHO. Since its first case in Wuhan, China in December 2019, the disease has come a long way, with the number of cases and the number of deaths surging daily. Oxidative stress and inflammatory cytokine storm are key characteristics of the pathology concerning this deadly virus. Many studies discussed point the substantial body of evidence hinting at severe neurological complications in patients. Various drugs have been repurposed to cater to the emergent need for therapeutics. The development and early approval of vaccines have been fast-tracked all around the globe. While the citizens of the globe await an efficacious vaccine, there is a dire need for innovative therapeutic approaches to cater to this deadly disorder. Crosstalk between both, NF-κB and Nrf2 signaling pathway lies at the center of neurological complications in COVID-19 patients. Immuno-modulators both synthetic and natural can be promising candidates in catering to the pathologies targeted in the aforementioned pathways. Immunomodulatory agents act in synergism with the pre-existing approaches and act as adjunctive therapy or prophylaxis and outstand existing approaches by specifically targeting the oxidative stress and consequently, eradicating and undermining the pathology leading to severe neurological disorders.

Data Availability of Data and Material It's a review article. Hence, all the material has been provided.

Authors' Contributions RB & AK conceived and designed the article. GK & DK did the literature search using various databases. RB, GK, and DK wrote the manuscript. AK approved and revised the final draft.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Consent to Publication All authors have agreed upon the final version of the article before submission and their consent has been sought.

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