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Chapter

COVID-19 and Its Impact on Onset and Progression of Parkinson's and Cognitive Dysfunction

Swapan Kumar Chatterjee, Snigdha Saha and Shahin Muhammed T.K.

Abstract

In the COVID-19 pandemic, neurological complications have emerged as a significant cause of morbidity and mortality. A wide range of neurological manifestations ranging from cognitive or memory disturbances, headache, loss of smell or taste, confusion, and disabling strokes have been reported during and post COVID conditions. The COVID-19 virus can utilize two possible pathways for invasion into the brain, either through retrograde axonal transport (olfactory route) or by crossing the blood-brain barrier (BBB). Furthermore, the production of SARS-CoV-2-associated cytokines, such as interleukin (IL)-6, IL-17, IL-1b, and tumor necrosis factor (TNF), is able to disrupt the BBB. The neuroinvasive nature of SARS-CoV-2 has a more severe impact on patients with preexisting neurological manifestations such as Parkinson's disease (PD). Pathological features of PD include selective loss of dopaminergic neurons in the substantia nigra pars compacta and aggregation of α-syn proteins present in neurons. Interaction between SARS-COV-2 infection and α-synuclein might have long-term implications on the onset of Parkinsonism by the formation of toxic protein clumps called amyloid fibrils—a hallmark of Parkinson's. Molecular modeling is an emerging tool to predict potential inhibitors against the enzyme α-synuclein in neurodegenerative diseases by using plant bioactive molecules.

Keywords: neurotropism, neuroinflammation, cytokine storm, ACE-2, Parkinson's, α-synuclein amyloid fibrils, molecular modeling, COVID-19

1. Introduction

Since the onset of pandemics, our world has witnessed over 500 million confirmed cases of COVID-19 and over 15 million related (direct and indirect) deaths till date [1]. With the progression of the disease, severe and more complex processes like acute respiratory distress syndrome, cytokine storm, and NETosis may develop [2, 3]. This is the tip of the iceberg. Our knowledge about the disease manifestation is increasing day by day. A wide spectrum of illnesses vary from a simple cold and fever to multisystemic diseases. It has been reported that a hypercoagulable state, damage of renal tubule cells, and heart muscles are also associated with the development of COVID 19 [4–6].

Besides respiratory insufficiency, neurological complications like seizures, loss of consciousness, encephalitis, Guillain-Barre syndrome, acute necrotizing, hemophagocytic lymphohistiocytosis, acute ischemic cerebrovascular syndrome, anosmia, or ageusia as well as neuropsychiatric symptoms like headaches, nausea, dizziness, hallucinations, and depression have emerged as a significant cause for COVID-related morbidity and mortality [6–8]. Of note, these damages may significantly increase the incidence rate of other neurodegenerative diseases and foster dementia (**Figure 1**) [8].

Over the past few decades, different novel viral epidemics, such as influenza, Middle Eastern respiratory syndrome (MERS), and severe acute respiratory syndrome (SARS) have appeared, with the aid of zoonosis [9]. So far, various studies have been done to establish the link between viral infections and neurodegeneration disease. The most eminent of them is the 1918 influenza pandemic (Spanish flu) which coexisted with an increased rate of encephalitis lethargica, followed by postencephalitic Parkinsonism [10]. In recent times, multiple studies have indicated a possible relation between onset and/or worsening progression of PD and viral infections. Although the detailed mechanism of viral infections–induced neurodegeneration is still unclear, the role of the immune system or the direct effect of zoonosis cannot be overruled. Neurodegenerative diseases like PD and Alzheimer's disease (AD) are

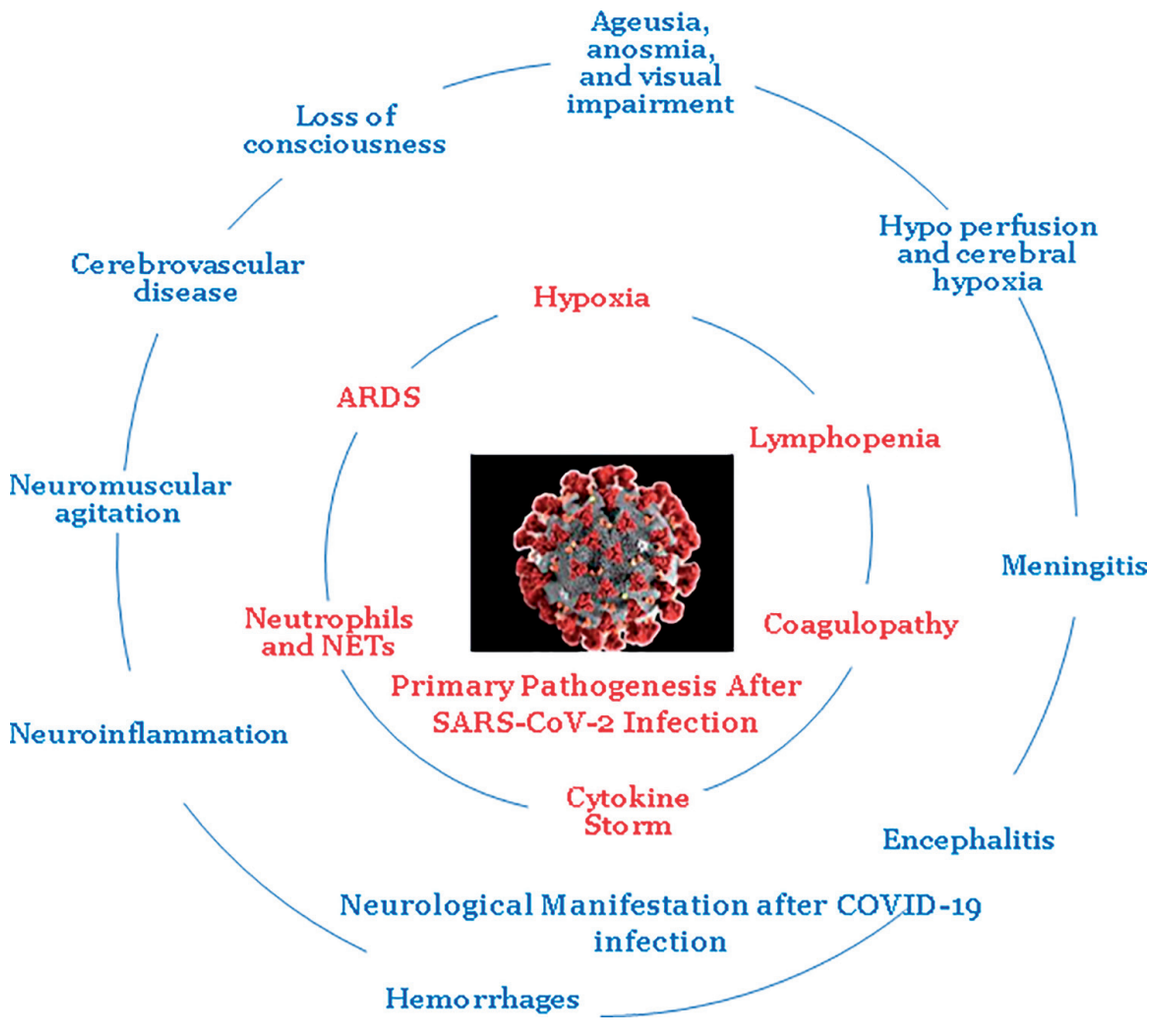

Figure 1.
Schematic representation of COVID-19-related symptoms. Primary pathogenesis associated with COVID-19 are shown in inner circle (in red). The outer circle (in blue) depicts the neurological manifestation related to COVID-19.

mainly protein aggregation diseases in which specific proteins, such as α-synuclein (α-Syn) in PD and tau and Aβ peptide in AD aggregate together to form amyloids. Once triggered, the aggregation process begins to spread from cell to cell and continues to form and deposit amyloids that in turn hamper the brain function [9–11]. A detailed study on molecular pathogenesis of the acute and delayed neurological manifestations and establishment of the link between SARS-CoV-2 infections and the development of PD will be helpful to design the new therapeutic approach.

2. Brain expression of SARS-CoV-2 receptor and molecular pathogenesis

The beta-coronaviruses are large enveloped non-segmented positive-sense RNA viruses. Like its related family members MERS-CoV (exploits dipeptidyl peptidase 4), and SARS-CoV-1, SARS-CoV-2 utilizes its specific proteins, in particular, Spike (S) protein, to bind to a number of host proteins (virus receptors) that assist in its entry [12]. Distributions of host receptors on various tissues are generally believed to decide the virus tropisms within the host cell. For an efficient host cell entry similar to SARS-CoV-1, SARS-CoV-2 uses angiotensin converting enzyme-2 (ACE2) type 1 transmembrane receptors as the major docking receptor followed by proteolytic processing of the spike protein by transmembrane protease serine 2 (TMPRSS2) [13]. Targeting of different cell types by the viral protein has been partially attributed to the distribution ACE2 receptors on the endothelial and epithelial cells of the respiratory system, as well as on immune cells. Along with that, expression of ACE2 is widely found in lung parenchyma, vasculature, heart, kidney, and the gastrointestinal tract [14, 15]. Expression of ACE2 receptors is widespread within brain structures, such as the central nervous system, in human brain vessels, pericytes and smooth muscle cells in the vascular wall, hypothalamus, and visual tracts, which are associated with the various neurological symptoms in coronavirus disease 2019 (COVID-19) infection [10, 11, 14]. However, data mining study of human brain single-nuclear RNA sequencing (RNA-seq) data has also found the expression of ACE2 receptors in the choroid plexus and neocortical neurons, in less amount [16]. Even presence of non-canonical SARS-CoV-2 receptors in other brain cell types makes them vulnerable to the virus.

Interaction with viral S protein and ACE2 receptors on the vascular endothelial cells leads to disruption of the blood-brain barrier, resulting in consequent cerebral edema and microhemorrhages. In addition to this, SARS-CoV-2 may expend direct neuronal damage due to the affinity of the spike S1 protein toward ACE2 receptors expressed on neurons. In short, the virus can utilize two possible pathways for invasion into the brain, either through retrograde axonal transport (olfactory route) or by crossing the blood-brain barrier [17]. Furthermore, production of SARS-CoV-2-associated cytokines, such as interleukin (IL)-6, IL-17, IL-1b, and tumor necrosis factor (TNF), are able to disrupt the BBB [18] and could facilitate the viral entry. Even in some studies SARS-CoV-2 has been predicted to induce infection in cerebral endothelial cells as well as inflammation in peripheral vessels [19], but direct evidence has not been far provided. Co-morbidity factors like cardiovascular risk factors and/or pre-existing neurological diseases could alone or in combination with cytokines intensify the rate of BBB permeability [18]. Nonetheless, viruses are able to enter the brain by carried by infected immune cells that also act as a reservoir [20]. Neutrophils T cells and Monocytes, may traffic into the brain through the vasculature, whereas the meninges and the choroid plexus [21], could be considered as entry points for infected immune cells. In COVID-19 loss of smell is considered a frequent

neurological manifestation that is consistent with infection of the olfactory system. The internalization of the virus in nerve terminals by endocytosis, transportation retrogradely, and spread trans-synaptically to other regions of brain, has been studied in other coronaviruses [22]. Detection of ACE2and TMPRSS2 in the nasal mucosa at both RNA and protein levels increases the chance of involvement of olfactory neurons in viral transmission. The hypothalamus could contribute to the dysregulation of the immune cells. In COVID-19, upregulation of cytokines like IL-6, IL-1b, and TNF act as the activators of the hypothalamic-pituitary-adrenocortical (HPA) axis. This HPA axis acts as the center of the systemic immune activity regulation and is activated by BBB dysfunction and neurovascular inflammation [23].

However, apart from ACE2, SARS-CoV-2 can utilize neuropilin-1 (NRP1) and basigin (BSG; CD147) as docking receptors, whereas a variety of proteases such as cathepsin B and L,TMPRSS11A/B, and furin (FURIN) have been shown to promote viral cell entry as well as replication within the host cell [24–26]. Exposure of brain tissue to COVID-19-related injuries like hypercoagulable states, inflammation, hypoxia, immune response (cytokine storm), or dyselectrolytemia is thought to play the main role in the cerebral pathomechanism of viral damage and cause all the neurodegenerative conditions like AD and PD [27].

3. Molecular link between COVID-19 and Parkinson's

Parkinson's disease (PD) is a neurodegenerative disorder, defined as α-synucleinopathy that affects 1% of the population aged above 60 years with an annual incidence of 15 per 100,000 populations. It is a disorder of the central nervous system (progressive loss of dopamine neurons) that mainly affects the motor system, particularly, the nigrostriatal pathway. Therefore, the major PD symptoms include tremor, bradykinesia/akinesia, rigidity, and postural instability. The clinical manifestations of PD also include non-motor symptoms (NMS) such as dementia, anxiety, depression, fatigue, and others [28]. The major pathological features of PD include selective loss of dopaminergic neurons in the substantia nigra pars compacta and aggregation of protein (called Lewy neurites and Lewy bodies) consisting mainly of α-syn proteins present in neurons [29, 30].

Alpha-synuclein (α-syn), is a small protein (forms an α-helix-rich tetramer) that comprises of 140 amino acids, and the human *SNCA* gene encodes them. Expression of α-syn takes place in the central nervous system (CNS) and is mainly localized in synapses and nuclei. Although the exact function of α-syn is not clearly explained yet, various studies have shown that maintaining synaptic plasticity, vesicle trafficking, and interaction with synaptic vesicles as well as physiological regulation of vesicle recycling is regulated by α-syn [30–32]. The major biological function of α-syn is employed through the non-amyloid-beta component (NAC), N-terminal, and C-terminal domains. The KTKEGV motif is present in the N-terminus that maintains tetramerization of α-syn, and mutations in this motif lead to neurotoxicity. NAC is a highly hydrophobic domain and was first identified in patients with AD. It forms a β-sheet structure for α-syn aggregation. The C-terminus of α-syn is a proline-rich region domain that helps in interaction with other proteins [30, 33]. Misfolded or unfolded α-syn protein forms fibrillar aggregates that generate insoluble inclusions in the affected neurons and glial cells. Aggregated α-syn can induce other pathological features, such as mitochondrial dysfunction, dysregulation of calcium homeostasis, endoplasmic reticulum (ER) stress, neuroinflammation, Golgi fragmentation,

lysosomal dysfunction, and impaired protein quality control that lead to neuronal toxicity [30, 33–35]. The non-neuronal cells present in the brain are called Gila cells that play a critical role in maintenance of the neuronal system. Glia cells are comprised of microglia, astrocytes, and oligodendrocytes in the CNS. The glial cells comprise a majority of brain cells, and they regulate neurogenesis and synaptogenesis. Furthermore, glial cells influence the development and function of brain-blood barrier (BBB) by interactions with endothelial cells and neurons to protect the brain from pathogenic attacks [30, 33]. Although the major function of astrocytes and microglia involves the immune response but under pathological conditions, they seem to be activated by specific stimuli. Upon activation, microglia and astrocytes can release pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), IL-2, IL-4, interleukin-6 (IL-6), and also causes reduced levels of neurotrophins, like nerve growth factor and brain-derived neurotrophic factor (BDNF) that lead to the reactive oxidative stress (ROS) production followed by BBB dysfunction. Intercellular crosstalk between these factors induces neuronal cell death and engenders neurodegenerative diseases such as AD or PD [30, 33, 36].

In patients with PD/parkinsonism, the COVID-19 pandemic has had an indirect and negative impact that might be explained by the dopamine-dependent adaptation hypothesis. Due to the pandemic, there is a change in daily life and routine; therefore, flexibility in cognitive (and motor) functions is required to adapt to such changes. Even pharmacodynamic effects, social isolation, stress, and anxiety as well as prolonged immobility have detrimental effects on motor and non-motor symptoms and quality of life in PD. In patients with PD, damage to nigrostriatal dopamine neurons results in lower cognitive as well as motor neuron flexibility. Such patients often experience confusion and increased psychological stress, which can lead to the worsening of parkinsonism symptoms as well as mental illnesses such as anxiety and depression [37]. The development of permanent or transient Parkinsonism followed by a viral might occur through different mechanisms:

1. Damage to structural and functional basal ganglia mainly involving the substantia nigra pars compacta and nigrostriatal dopaminergic projection;

2. Extensive inflammation including hypoxic brain injury within the context of an encephalopathy;

3. Unmasking hidden non-symptomatic Parkinson's disease; or

4. A series of processes that might be triggered by a viral infection that result in Parkinson's disease development over the long term in individuals with genetic susceptibility.

There are fundamental clinical and anatomopathological differences present in each of these instances [37, 38].

The onset of transient parkinsonism has been associated with many viral infections including West Nile Virus, Japanese Encephalitis, Western Equine virus, Coxsackie virus, Epstein Barr virus, HIV, and currently SARS- CoV-2. Expression of high level ACE2 receptor on the midbrain dopamine neurons could facilitate entry of SARS-CoV-2 that can alter the expression of alpha-synuclein [39–41]. Since elevated alpha-synuclein levels can promote aggregation of the protein, this could predispose an infected patient to PD down the line. Various experimental models also suggest that SARS-CoV-2 may interact with different proteins in age-related pathways (lipid

metabolism, proteostasis, mitochondrial function, and stress responses) [37, 40]. Dysfunction of these pathways could lead to alpha-synuclein aggregation and selective neurodegeneration. Even elevated cytokines (the primary mediators of inflammation in SARS-CoV-2) can accelerate the neurodegeneration in PD [41]. Studies revealed that the release of cytokines may activate the resident immune cells in the CNS. Activation of immune cells leads to their infiltration including activated T cells and microglia from the periphery that may kill neurons, astrocytes, and vascular cell types. Elevated levels of pro-inflammatory cytokines, such as TNF and IL-1beta, are also associated with increased risk of PD [41].

A current study has established the possible mechanism of triggering PD followed by COVID-19 infection. Virus-initiated amyloid-formation of α-synuclein acts as the main cell-toxic agent in the death of dopamine-producing neurons in the brain. By interacting with amyloidogenic regions with nucleocapsid protein (that encapsulates the RNA genome inside the virus), SARS-COV-2 speeds up the formation of amyloid fibrils. In the context of Alzheimer's disease, it has been speculated that amyloid fibrils are formed as an immune response to an infection, and neutralizing pathogens. A similar mechanism may play a role in progression of PD. In a current study, test tube experiments have shown that SARS-CoV-2 spike protein (S-protein) has no effect on α-synuclein aggregation, whereas SARS-CoV-2 nucleocapsid protein (N-protein) considerably speeds up the aggregation process That results in formation of multiprotein complexes and eventually amyloid fibrils that disturb the α-synuclein proteostasis and increase the rate of cell death (**Figure 2**) [42, 43].

As the cases of PD rises sharply in the older age group, particularly in those over the age of 80 years, a personalized approach to the clinical management of PD patients affected by COVID-19 is need of the hour. In addition, disturbance of α-synuclein proteostasis might be considered the first step toward nucleation of

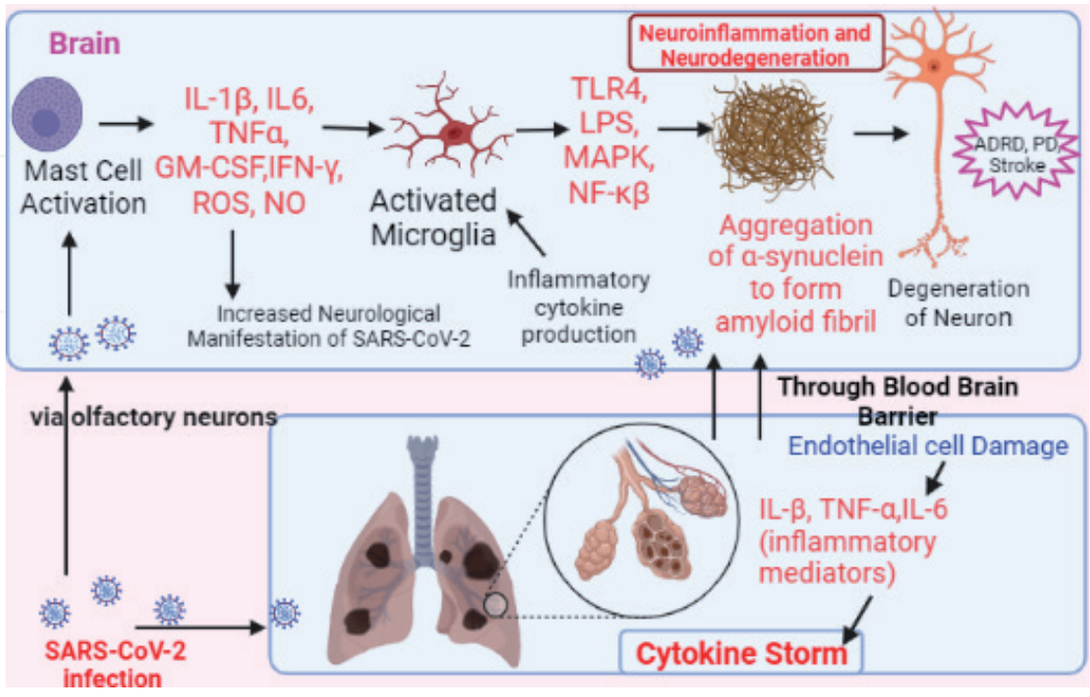

Figure 2.
Schematic representation of neuroinflammation and neurodegeneration due to SARS-CoV-2 infection. A immunological crosstalk between different organs. Created with BioRender.com.

fibrils. Direct interaction between the N-protein of SARS-CoV-2 and α-synuclein establishes a molecular link between virus infections and Parkinsonism. This piece of puzzle thus suggests that SARS-CoV-2 infections may have prolonged implications and consider N-protein as an attractive alternative target in designing novel vaccination strategies.

4. Targeted therapies for Parkinson's disease

Till date, no specific curative therapy is available for PD. There are two main approaches such as protective therapy and symptomatic therapy that have been practiced for the treatment of PD. Under symptomatic therapy, anticholinergic agents and some dopamine analogs help to restore the dopamine levels and result in improvement of the movement disabilities. Though, anticholinergic agents cause some serious effects on central nervous system such as cognitive impairment and hallucination along with constipation and dryness of mouth. In the field of PD management Levodopa brought a revolution by improving quality of life, parkinsonian symptoms, and normalizing life expectancy [44]. Other recent dopaminergic therapies, such as monoamine oxidase B inhibitors, dopamine agonists, catechol-O-methyltransferase inhibitors, and other unique formulations of levodopa, have also been developed to address parkinsonian symptoms [44, 45]. Continuous duodenal infusion of levodopa/carbidopa intestinal gel and apomorphine subcutaneous pumps are used to overcome the levodopa shortcomings. On the other hand, as PD pathogenesis mainly deals with oxidative damage, protective therapy that has free radical scavenging properties helps to reduce the side effects of drugs. Selegiline, bromocriptine, ropinirole, pramipexole, and vitamin E fall under this category [46].

Moreover, deep brain stimulation (DBS) is considered a very useful approach for patients with motor complications [47]. All these therapies have been of great value in the PD symptoms management in patients who are not responsive to medication. Currently, development of PD treatments majorly depends upon development and application of biomarkers that will help to improve the target engagement, disease state, safety, and disease outcome [48]. The development of new genetic editing technologies can open the possibility to correct mutated genes and regulatory DNA in the monogenic forms of PD [49–51]. Several methods of gene delivery that include use of viral vectors and CRISPR as well as the process of genome editing have been developed to manage PD symptoms. Currently, clinical trials of Gene therapy in PD have tried to focus on 4 main targeted approaches such as restoring dopamine synthesis, neuroprotection, genetic neuromodulation, and addressing disease-specific pathogenic variants [52].

To prevent the neurodegeneration of dopaminergic neurons by the overexpression of neurotrophic factors (NTF) is considered as a powerful strategy in PD management. The delivery of these factors, such as the glial cell line-derived neurotrophic factor (GDNF), neurotrophic factor (NF), cerebral dopamine neurotrophic factor (CDNF), neurturin (NRTN), and growth/differentiation factor 5 (GDF5) by the use of recombinant viral vectors to enable long-term expression might open a new way in PD management [53].

Even experimental studies have shown that down-regulation of α-syn levels by gene silencing with RNA interference (RNAi) can be beneficial in the normalizing expression of α-syn and improving motor function, though balance is important to avoid nigrostriatal neurotoxicity caused by excess downregulation. At epigenetic

level, DNA methylation at SNCA intron1 acts as a regulator of the α-syn transcription, and thus it can consider a target for tight control of α-syn expression. In recent times, active immunization approaches are involved to develop vaccines targeting either the N or C-terminal of α-syn or its aggregation forms. Extensive clinical trials on these advanced techniques are required to prove their efficacy against PD symptoms [54].

4.1 In silico studies and prediction of therapeutic drug

In the absence of extensive experimental and pharmacological studies, none of the drug candidates are recommended for human use. Molecular docking or in silico studies is the answer to the problem with good potential tool in drug development. Molecular docking is an early guidance tool in contemporary drug discovery that minimizes not only time but also resource. In some cases, scientific data shows that the prediction results based on in silico studies are comparable with in vitro and in vivo results [55]. Molecular docking studies depend upon on joining of a particular ligand to a receptor region, providing information about orientation, conformation, and organization at the receptor site [55]. Nowadays, studies using computational chemistry have been done to predict potential inhibitors for neurodegenerative diseases from flavonoid derivatives [39]. During the pandemics or for the disease like PD or AD alternative food-based medicine or the flavonoids or bioactive compounds from the plant can be considered as the good alternatives. Development of the drug from the plant bioactive compound depends upon a great deal of in silico molecular docking investigation.

In silico studies, involving Parkinson's disease and anti-inflammatory activity of novel bioactive compounds such as quercetin, epigallocatechin gallate (EGCG), and acacetin have been done to predict inhibitory activities against the enzyme α-synuclein. According to other studies involving flavonoids including morin, naringenin, taxifolin, esculatin, daidzein, genistein, scopoletin, galangin, and silbinin have proven their inhibitory effect against lipoxygenase enzyme. Moreover, data using karanjin against several protein targets in relation to AD and PD have shown their efficiency in management of PD. Ligand-based-virtual screening together with structure-based virtual screening (docking) can be done to prove the efficiency of plant-based bioactive compounds, like alkaloids or flavonoids as inhibitors of PD- or AD-related proteins [56–58].

4.2 Treatment of Parkinson's disease and its impact on SARS-CoV-2 infection

Till now, no specific medicine is available to treat the SARS-CoV-2 infection. Nowadays, drug repurposing by the in silico studies is an essential technique for quick identification of frontline weapons to combat COVID-19. Antiviral and other life-saving drugs are trying to repurpose for the treatment of COVID-19 as SARS-CoV-2 replication shows a variety of clinical symptoms. Some of them are investigated to block different steps of host tropism such as transmembrane serine protease 2 (TMPRSS2), and/or viral entrance through the ACE2 receptor, viral membrane fusion, endocytosis, the activity of the SARS-CoV-2-3-chymotrypsin-like protease, etc. Treatment options for various diseases linked with COVID-19 such as obesity, sleep apnea, Parkinson's disease, and Alzheimer's disease have markedly changed during the pandemic. FDA-approved drug levodopa is mainly involved in alteration in dopamine synthetic pathways but studies have shown its involvement in the pathophysiology of SARS-CoV-2. DDC inhibitors act upon *DDC* and also *ACE2*, the gene encoding, the main receptor to SARS-CoV2. On the other hand, dopamine agonists

are found to have detrimental effects on patients with PD symptoms and positive for the COVID-19. As per a study, a small number of COVID-19-positive PD patients were prescribed to take amantadine but did not manifest symptoms of the disease. Furthermore, COMT inhibitors like entacapone have shown potential effects against the virus SARS-CoV-2, when interactome analysis of potential drug repurposing studies was done [59, 60].

5. Conclusion

Since the beginning of the pandemics, SARS-CoV-2 has become one of the main research interests, especially due to high mortality rates among different populations and its catastrophic impact on global healthcare as well as socio-economic condition. Like other members of the Coronaviridae family, SARS-CoV-2 also has neurotropic properties. The harmful effects of the virus seem to exert either in a direct manner—by spreading through gastrointestinal nervous and/or olfactory pathways, or by evoking an inflammatory response. Along with the inflammatory response, the pathophysiology of COVID-19 also involves the complement and the coagulation systems. These triad systems interact with each other and show detrimental effects like appearance of the cytokine storm in ARDS. This leads to multisystem failure, especially in the case of disseminated intravascular coagulation disorders. In both cases – prodromal PD and COVID-19 induced PD. Parkinsonism is majorly associated with motor dysfunction, the hyposmia and hypogeusia. The cytoplasmic alpha-synuclein accumulation is associated with neurodegeneration in the nigrostriatal system of PD-affected patients [6, 8].

As SARS-CoV-2 may have a trigger for blood-brain barrier impairment and gain direct access to brain regions, the N-protein of the virus may play a major role in PD pathogenesis. Interaction between viral N-protein and alpha-synuclein promotes formation of amyloid fibril and hallmark of Parkinson's. There is a broad spectrum of COVID-19-related symptoms, perhaps associated with either pre-existing conditions or the presence of T cells that are reactive to previous coronavirus infections or in part of viral entry points. The neurological manifestations may be involved with capillaries inflammation, hypoxemia, the blood-brain barrier, and thrombosis that act as triggers for seizures or ischemic or hemorrhagic strokes. Production of pro-inflammatory cytokines and chemokines by activated microglia, astrocytes, or mitochondrial dysfunction in glial cells is considered as a major contributor to neuroinflammation. The crosstalk between these contributors may induce α-syn accumulation mediated neurodegeneration in α-synucleinopathies. This crosstalk mechanism may be considered a favorable target for α-synucleinopathy-associated neurodegenerative disease treatment [17, 18, 24]. Due to various impeding factors, such as limited understanding of the neurodegeneration mechanisms in PD, the heterogeneity of the pathology, absence of reliable biomarkers to diagnose the pathology, and the lack of adequate animal models, the development of effective preventive or curative therapies for PD has become extremely challenging. Though some medicine and therapy are available for the management of PD, they have severe detrimental effects on the central nervous system. Molecular docking or in silico studies are good potential tools in drug development for repurposing the drug or identification of new plant-based bioactive with potential neuroprotective activity. Shortly, by using this technology it will be possible to develop broad-spectrum, novel drugs active against not only a larger array of coronavirus but also will be the ultimate treatment strategy for circulating and emerging COVID-related neurological manifestations.

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