Nanotechnology for Neurological Disorders after Long COVID Syndrome

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Long-term neurological complications, persisting in patients who cannot fully recover several months after severe SARS-CoV-2 coronavirus infection, are referred to as neurological sequelae of the long COVID syndrome. Among the numerous clinical post-acute COVID-19 symptoms, neurological and psychiatric manifestations comprise prolonged fatigue, “brain fog”, memory deficits, headache, ageusia, anosmia, myalgias, cognitive impairments, anxiety, and depression lasting several months. Considering that neurons are highly vulnerable to inflammatory and oxidative stress damages following the overproduction of reactive oxygen species (ROS), neuroinflammation and oxidative stress have been suggested to dominate the pathophysiological mechanisms of the long COVID syndrome. It is emphasized that mitochondrial dysfunction and oxidative stress damages are crucial for the pathogenesis of neurodegenerative disorders. Importantly, antioxidant therapies have the potential to slow down and prevent disease progression. However, many antioxidant compounds display low bioavailability, instability, and transport to targeted tissues, limiting their clinical applications. Various nanocarrier types, e.g., liposomes, cubosomes, solid lipid nanoparticles, micelles, dendrimers, carbon-based nanostructures, nanoceria, and other inorganic nanoparticles, can be employed to enhance antioxidant bioavailability. Here, the potential of phytochemical antioxidants and other neuroprotective agents (curcumin, quercetin, vitamins C, E and D, melatonin, rosmarinic acid, N-acetylcysteine, and Ginkgo Biloba derivatives) in therapeutic strategies for neuroregeneration is highlighted. A particular focus is given to the beneficial role of nanoparticle-mediated drug-delivery systems in addressing the challenges of antioxidants for managing and preventing neurological disorders as factors of long COVID sequelae.

Keywords: antioxidant-delivery nanosystems ; lipid nanocarriers ; oxidative stress ; neuroinflammation ; neurodegeneration ; neurological long COVID-19

1. Introduction

Management of post-acute coronavirus SARS-CoV-2 infection presents current concerns for society as the global pandemic has massively affected health, the economy, education, and employment since the outbreak of COVID-19 in 2019 [1][2][3][4]. Several reports affirmed that many patients who survived COVID-19 illness continue to exhibit neurological COVID symptoms and fail to revert to their regular daily routines [3][4][5]. Such a post-COVID-19 condition has been classified as "long COVID", "long-haul COVID", "post-acute COVID syndrome", "chronic COVID", and post-acute sequelae of SARS-CoV-2 (PASC)[5][6][7][8][9][10][11][12]. The National Institute of Health (NIH) has pointed out the most common symptoms associated with long COVID, like headaches, depression, anosmia, cognitive impairments, shortness of breath, "brain fog," fever, and gastrointestinal symptoms [8][6]. More severe cases include Myalgic Encephalitis/Chronic Fatigue Syndrome (ME/CFS) and stroke, indicating that the neurological symptoms are the core aspects of long COVID [9][10][11][12][13][14].

The SARS-CoV-2 virus invades the CNS by binding to the angiotensin-converting enzyme-2 (ACE2) receptor, which is widely distributed in the epithelial cells of lungs and the endothelial cells of the blood-brain barrier (BBB) [9]. The neuroinvasive potential of the coronavirus is revealed by the provoked neuroinflammation and neuronal demyelination of the CNS, cellular apoptosis, metabolic imbalances, various coagulopathies and endotheliopathies that induce hypoxic-ischemic neuronal injury or blood-brain barrier dysfunction [1][5][8][9].

There is still no cure for the neurological sequelae of COVID-19. During acute COVID-19, patients have been treated with corticosteroids, antibiotics, and antiviral drugs [1]. Antioxidants are attracting scientific interest in the therapy and prevention of COVID-induced neuronal damage [15]. Examples of antioxidants include vitamins C, E, and D, curcumin, quercetin, melatonin and rosmarinic acid [16][17][18][19][20]. These molecules have advantages in counteracting the oxidative

stress effects by scavenging ROS, combating the cytokine storm, and providing neuroprotection. Antioxidants with poor bioavailability and low water solubility have limited therapeutic usage [21][22]. To solve these challenges, nanomedicine-based delivery systems; lipid-based nanoparticles, polymeric particles and other nanostructured assemblies are gaining much attention as a promising field for drug delivery and a valuable tool for future medicine [23][24][25][26]. Given that they can enhance pharmacokinetics, it is feasible to obtain proper targeting and lower toxicity of medicinal compounds [26].

2. Nanodelivery systems for development of antioxidant-based nanomedicines against the neurological sequelae of SARS-CoV-2

Nanomedicine-based therapies against neurological sequelae of long COVID will require developing nanoscale delivery systems for the efficient use of antioxidants. In terms of drug delivery, antioxidants display several limitations, including (i) low permeability into the CNS due to the presence of physiological barriers such as the BBB or the spinal–blood barrier (SBB) [27]; (ii) low bioavailability associated with insolubility or instability [28]; (iii) chemical and physical barriers in the gut such as the acidic pH of the stomach, intestinal mucosal lining, and selectively permeable membranes of enterocytes [29], and (iv) rapid metabolism [30]. Significant efforts have been made to improve the efficacy of antioxidant agents using various drug delivery approaches.

2.1. Organic nanovectors

Antioxidants such as polyphenols have shown a capacity to interfere with various stages of the coronavirus entry as well as inhibitory activities against viral components, rendering them potentially suitable to counteract the SARS-CoV-2 infection [31]. Computational studies have indicated that flavonoids, which are a class of polyphenols including quercetin, baicalin, luteolin, hesperetin, gallocatechin gallate (GCG), epigallocatechin gallate (EGCG), naringenin, cyanidin, genistein, kaempferol, luteolin-7-glucoside, apigenin-7-glucoside, catechin, taxifolin and rutin can exert inhibitory activity against SARS-CoV-2 by binding to essential proteins involved in the coronavirus infective cycle such as Mpro, PLpro, 3CLpro and NTPase/helicase [32][33][34][35][36].Debnath and colleagues demonstrated that nanoquercetin could exhibit anti-amyloidogenic activity at lower quercetin concentrations, thereby preventing polyglutamine aggregation in a cell model of Huntington's disease [37].

Moreover, Ravikiran *et al*. have reported that 4-hydroxyisophthalic acid (4-HIA), encapsulated PLGA-NPs significantly decreased the cytotoxicity of H_2O_2 in PC12 cells when compared to non-encapsulated 4-HIA.Yang *et al*. demonstrated the beneficial effect of PLGA-PEG-Fucoxanthin nanoparticles in improving cognitive performance and transport through the CNS [38]. In an animal model of AD, resveratrol-loaded NPs have decreased the levels of matrix metalloproteinase-9 (MMP-9) in cerebrospinal fluid, highlighting that resveratrol limits brain permeability, infiltration of leukocytes, and other inflammatory agents. Resveratrol presents therapeutic interest because it modulates neuroinflammation and induces adaptive immunity [39].

2.2. Inorganic based antioxidant nanomaterials

Another class of nanoparticles that have produced fascinating outcomes as nano-antioxidants, able to mimic CAT and SOD activity, is platinum-based nanomaterials. In the research of Takamiya *et al*. Pt nanoparticles were utilized as a preventative approach to lessen the effects of an ischemic stroke and to repair any damage, while maintaining the structure and neurological capabilities of the neurovascular unit (NVU) in a mouse model of cerebral infarction [40]. Mu *et al*. developed a trimetallic (triM) nanozyme with a multienzyme-mimetic activity that functioned as an effective scavenger of ROS and RNS in brain traumatic injuries [41].

Furthermore, Yttrium oxide nanoparticles (Y_2O_3) have been reported as a neuroprotector in HT-22 mouse hippocampal neuronal cells, in a rat model of lead-induced neuronal damage, and in an *in vivo* model of photo degeneration [42].Several carbon-based nanomaterials, including fullerene, graphene, carbon nanotubes, and carbon clusters, have been investigated as antioxidants and as possible treatments for some CNS disorders [43]. 2D carbon-based nanomaterials have also demonstrated antioxidant properties, as exhibited in the work by Qiu *et al*. which used electron paramagnetic resonance spectroscopy (EPR) to examine graphene's capability to scavenge ROS and found that graphene oxide was able to do so for both OH and O_2 radicals [44].

2.3. Antioxidant enzymes

Regarding antioxidant enzymes, the ability of the combination (t-PA + nano-SOD/CAT) to stimulate the migration of stem/progenitor cells from the subventricular zone and circulation, and thus to promote neurogenesis, has been recently emphasized. The inhibition of edema formation has suggested the protection of the BBB from reperfusion injury in a thromboembolic rat stroke model [45]. Another study has reported a significant reduction of mitochondrial ROS activities,

increased mitochondrial membrane potential, reduced calcium levels, and also higher adenosine triphosphate ATP content after intravenous administration of nano-SOD/CAT, 6-hr following injury in a rat severe contusion model of spinal cord injury (SCI), thus protecting cell apoptosis and further degeneration [46].

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