Hindawi
Oxidative Medicine and Cellular Longevity
Volume 2020, Article ID 4356386, 27 pages
https://doi.org/10.1155/2020/4356386

Review Article

Oxidative Stress-Mediated Blood-Brain Barrier (BBB) Disruption in Neurological Diseases

Ke Song,[1] Yuanyuan Li,[1] Hanlai Zhang,[1] Na An,[1,2] Yufei Wei,[1] Liqin Wang,[1] Chao Tian,[1] Mengchen Yuan,[1] Yikun Sun,[1] Yanwei Xing,[2] and Yonghong Gao[1]

[1]*Key Laboratory of Chinese Internal Medicine of Ministry of Education and Beijing, Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine, 100700 Beijing, China*
[2]*Guang'an Men Hospital, China Academy of Chinese Medical Sciences, 100053 Beijing, China*

Correspondence should be addressed to Yanwei Xing; xingyanwei12345@163.com and Yonghong Gao; gaoyh7088@163.com

Received 27 March 2020; Revised 25 May 2020; Accepted 3 June 2020; Published 3 July 2020

Guest Editor: Juan Francisco Santibañez

The blood-brain barrier (BBB), as a crucial gate of brain-blood molecular exchange, is involved in the pathogenesis of multiple neurological diseases. Oxidative stress is caused by an imbalance between the production of reactive oxygen species (ROS) and the scavenger system. Since oxidative stress plays a significant role in the production and maintenance of the BBB, the cerebrovascular system is especially vulnerable to it. The pathways that initiate BBB dysfunction include, but are not limited to, mitochondrial dysfunction, excitotoxicity, iron metabolism, cytokines, pyroptosis, and necroptosis, all converging on the generation of ROS. Interestingly, ROS also provide common triggers that directly regulate BBB damage, parameters including tight junction (TJ) modifications, transporters, matrix metalloproteinase (MMP) activation, inflammatory responses, and autophagy. We will discuss the role of oxidative stress-mediated BBB disruption in neurological diseases, such as hemorrhagic stroke, ischemic stroke (IS), Alzheimer's disease (AD), Parkinson's disease (PD), traumatic brain injury (TBI), amyotrophic lateral sclerosis (ALS), and cerebral small vessel disease (CSVD). This review will also discuss the latest clinical evidence of potential biomarkers and antioxidant drugs towards oxidative stress in neurological diseases. A deeper understanding of how oxidative stress damages BBB may open up more therapeutic options for the treatment of neurological diseases.

1. Introduction

BBB is a highly complex and dynamic structure composed mainly of brain microvascular endothelial cells (BMVECs), astrocytes, pericytes, and basement membrane, which plays a causative role in regulating central nervous system (CNS) homeostasis [1]. The BBB is selectively permeable to certain substances thereby preventing toxins and other macromolecules in the blood from reaching the brain. A variety of pathological factors can cause the destruction of the BBB, including oxidative stress, neuroinflammation, immune cells, and various pathogens [2, 3]. These pathological factors interact with each other, induce MMP activation, reduce tight connections between cerebrovascular endothelial cells, and degrade basement membranes all culminating to an increase in BBB permeability paving way for large molecules and harmful substances to reach brain tissue causing damage [4, 5].

Oxidative stress refers to a pathological state that produces a variety of toxic effects on cells due to the excessive accumulation of ROS and their related metabolites [6]. Accumulating evidence strongly suggests that ROS are the core factor of acute brain injury and also participate in the tissue repair in the long-lasting neurological recover time. After several minutes to several hours of cerebral ischemia or reperfusion, ROS were produced in large quantities, and they continued to rise within a few days until they gradually returned to normal around 20 days [7]. Further studies show that ROS produced by ischemia can activate hypoxia-inducible factor-1 (HIF) and downstream pathways, such as the Notch pathway, Wnt pathway, and hypoxia-induced growth factor changes, which are closely related to neural

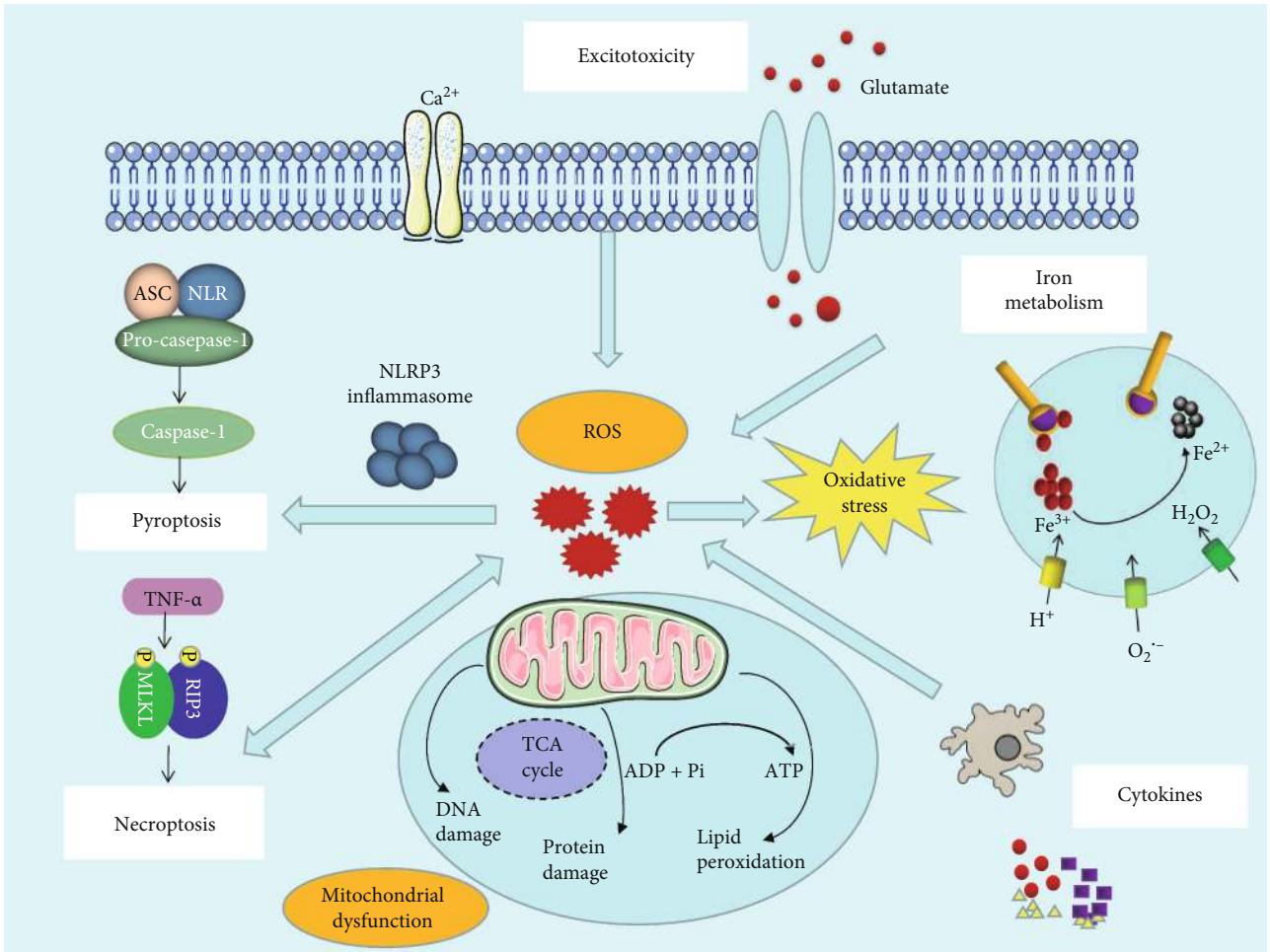

Figure 1: Schematic diagram of common pathological mechanisms that trigger oxidative stress. Primary mechanisms: (A) Formation of ROS. They are the main biomarkers of oxidative stress. A variety of enzymes including superoxide anion (O^{2-}), hydrogen peroxide (H_2O_2), nitric oxide (NO), and glutathione peroxidase (GPx) all belong to a group of molecules called ROS. (B) Mitochondrial dysfunction. ROS are mainly derived from oxidative phosphorylation (OXPHOS) occurring in the mitochondria. Secondary mechanisms: (C) Excitotoxicity. This occurs mainly through the excessive release of glutamate and the influx of Ca^{2+} to cause calcium overload in neurons, leading to the production of ROS. (D) Iron metabolism. When the amount of iron exceeds the cell's detoxification systems, the iron content increases, especially the ferrous (Fe^{2+}) content, and will promote the conversion of H_2O_2 to IOH through the Fenton reaction leading to an amplification of oxidative stress. (E) Cytokines. Inflammatory cells can release harmful compounds or cytokines, exacerbating oxidative stress. (F) Pyroptosis. ROS generation triggers the NLRP3 inflammasome to induce cell pyrolysis. (G) Necroptosis. The accumulation of intracellular ROS can cause necroptosis. In turn, TNF-induced necroptosis could also lead to ROS generation. Abbreviations: TCA cycle: tricarboxylic acid cycle; NLRP3: NLR pyrin domain-containing 3; RIP3: receptor-interacting protein 3; MLKL: mixed lineage kinase domain-like pseudokinase.

stem cell differentiation and migration in the long-lasting neurological recover time [8, 9]. Therefore, oxidative stress is extremely important in neurological diseases.

Increasing evidence shows that oxidative stress plays an essential role in the induction of BBB changes [10, 11]. ROS-related pathways that trigger BBB dysfunction include excitotoxicity, mitochondrial dysfunction, giant cell/microglial activation, extracellular transport, TJ modification, and MMP activation. This review will focus on the effects of oxidative stress-mediated BBB disruption in various neurological diseases with the goal of exposing novel therapeutic targets that can be exploited to treat neurological diseases in the future.

2. Molecular Mechanisms Involved in the Initiation of Oxidative Stress

At present, accumulating experimental and clinical evidence shows that oxidative stress plays a causative role in neurological diseases. The main primary mechanisms leading to the triggering of oxidative stress involve the formation of ROS and mitochondrial dysfunction, and the secondary mechanisms include excitotoxicity, iron metabolism, cytokines, pyroptosis, and necroptosis (Figure 1).

2.1. Formation of ROS. ROS are active substances produced when oxidative stress is imbalanced. Several important

molecules are involved in neurological diseases including nicotinamide adenine dinucleotide (NADPH), nitric oxide synthase (NOS), xanthine oxidase (XO), glutathione peroxidase (GPx), and catalase (CAT). Examples of ROS include superoxide ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), peroxynitrite ($ONOO^-$), nitric oxide (NO), and hydroxyl radicals ($^{\bullet}OH$). All of these are unstable molecules that destroy cellular lipids and proteins, thereby activating intracellular ROS production [12]. Excessive amounts of ROS generation may be a critical factor contributing to oxidative stress in the pathogenesis of neurological diseases [13].

After excessive stimulation, NADPH and the electron transport chain will cause excessive production of ROS. NADPH is used as an electron donor to transfer electrons through the cell membrane, reducing molecular oxygen (O_2) to ROS [14]. NOX1 (NADPH oxidase 1) and NOX2 are the main sources of ROS in the pathophysiology of neurological diseases such as stroke [15], AD [16], and PD [17]. Thus, NOX-mediated oxidative stress has been identified as a primary contributor to BBB damage in neurological diseases [18, 19].

NOS is divided into inducible (iNOS), endothelial (eNOS), and neuronal (nNOS) [20]. NOS has four groups with redox-active structures, which can transfer electrons to O_2, and single electrons reduce O_2 to O_2^-, convert normal NOS into ROS ion-producing enzymes, and promote ROS production. Sustained oxidative stress results in NOS-mediated uncoupling of O_2. O_2^- is produced at the expense of NO. NO production from iNOS enzyme activation is a major factor in oxidative stress response. NO can dramatically affect the host's defense ability against various pathogens, but excessive production of NO may be detrimental and can cause neurological diseases [21, 22]. NOS activation leads to an increase in NO production [23]. NO and $ONOO^-$ may increase the permeability of the BBB by affecting TJ proteins or via the cyclic guanosine monophosphate-(cGMP-) protein kinase G (PKG) pathway [24, 25].

XO can activate xanthine dehydrogenase (XDH) through proteolysis to produce ROS during brain ischemia/reperfusion (I/R) [26, 27]. Although XDH mainly functions to produce hypoxanthine and xanthine to produce urate under normoxic conditions, XO promotes ROS production to induce brain damage under hypoxic conditions. Therefore, inhibition of XO has great advantages in reducing ROS production and protecting mitochondria from oxidative damage.

2.2. Mitochondrial Dysfunction. Mitochondria were identified as the center of the "free radical theory of aging," because they are not only the major source of ROS but also the major generators of energy in cells [28]. ROS are mainly derived from OXPHOS occurring in the mitochondria. Indeed, mitochondria producing ATP require cells to consume approximately 85% of O_2. Mitochondrial complex IV uses electrons derived from FADH2 or NADH to reduce O_2 to H_2O in the respiratory chain. The electron transport chain (ETC) activity will inevitably produce O_2^- [29]. The mitochondria are not only the major site of intracellular ROS production but are also the main target organelle of ROS-induced injury. The slower electron transfer of the mitochondrial respiratory chain results in increased ROS production and serious damage to the antioxidant system [30]. In addition, mitochondria are susceptible to nitrosation induced by $ONOO^-$ and NO·[31]. The latter can deleteriously alter the activities of enzymes such as Cyt-C oxidase and NAD dehydrogenase [32]. Furthermore, ROS-mediated ETC complex I, II, and III Fe-S center failure and the tricarboxylic acid cycle aconite lead to mitochondrial uncoupling [33]. The effects of reactive species on mitochondria and their metabolic processes ultimately lead to elevated levels of ROS, resulting in oxidation of DNA, mitochondrial proteins, and lipids [34, 35].

2.3. Mechanisms Responsible for ROS-Mediated Oxidative Secondary Damage

2.3.1. Excitotoxicity. Excitotoxicity refers to an abundance of excitatory amino acids (such as glutamic acid or excitatory toxins), which can lead to pathological responses through increased ROS and amino acid production. Glutamate is the core molecule in many neurological diseases [36–38]. It mainly promotes ROS generation in two ways. On the one hand, excessive release of glutamic acid leads to excessive activation of NMDARs and increased Ca^{2+} influx, resulting in calcium overload in neurons and disturbances in intracellular Ca^{2+} homeostasis that can lead to free radical production through multiple pathways. On the other hand, glutamate uncouples oxidative phosphorylation leading to increased Na^+ influx, enhances the activity of Na^+ and K^+-ATPase on the membrane, and consumes a large amount of energy, which in turn enhances mitochondrial respiratory function and promotes ROS production [39]. There is evidence that ROS are also involved in non-NMDA receptor-mediated glutamate neurotoxicity. Free radicals can inhibit glutamine synthetase, promote the release of glutamic acid, and inhibit glutamate reuptake. This leads to high concentrations of glutamic acid in the extracellular fluid exacerbating excitotoxicity [40]. That is, glutamate excitatory neurotoxicity is accompanied by ROS production, and ROS can intensify the excitotoxicity of glutamate through multiple pathways. In addition to inducing oxidative stress, excitotoxicity can aggravate BBB disruption by disrupting astrocyte function [41]. NO pathways can lead to mitochondrial disorders and increased BBB permeability following excitotoxicity [42, 43].

2.3.2. Iron metabolism. As an essential trace element of the human body, iron can be used as a catalyst in ROS production [44]. High iron levels in pathologically relevant brain regions and iron-mediated oxidative stress are the main factors involved in various neurological diseases [45–47]. When the amount of iron exceeds the cell's detoxification systems, the iron content, especially Fe^{2+}, increases and facilitates the conversion of H_2O_2 to IOH through the Fenton reaction. This promotes a preferable conversion rate in the Haber-Weiss cycle, resulting in the amplification of oxidative stress [48]. Ferritin, an iron storage protein, can act as a scavenger and a donor of free iron, a source of $^{\bullet}OH^-$. After the BBB is destroyed, the accumulated ferritin and free iron in brain capillary endothelial cells enter the penumbra together with

plasma ferritin. Iron-dependent oxidative stress in the penumbra can cause nervous system deterioration [49]. The imbalance of iron leads to the accumulation of free iron and the overload of iron in the brain, thus increasing ROS production. In this respect, excessive iron content in the brain has been reported in Huntington's disease (HD), PD, and AD [50, 51].

2.3.3. Cytokines. Inflammation is an interaction between the immune system and damaged tissues, which restores homeostasis through complex signaling pathways [52]. Inflammatory cells such as macrophages and neutrophils, immune factors, and chemokines can release harmful compounds or cytokines, thereby exacerbating oxidative stress to metabolically impair neurons, thus playing a critical role in neurological diseases. The signs of an inflammatory response include leukocyte infiltration and astrocyte and microglial activation [53]. After an injury, neutrophils, as a part of the inflammatory response, are recruited to the BBB [54]. In the process of inflammation, activated neutrophils are the main source of ROS, and enzymes such as NOX can catalyze ROS production [55]. The resulting ROS may negatively affect the integrity of the BBB through TJ protein modification or expression of inflammatory mediators [56]. Microglial phenotypes are also important for redox stability. After a cerebral infarction, NOX and NOS enzymes are activated, resulting in a sharp rise in ROS and RNS levels [57]. Under these conditions, ROS and RNS act as second messengers capable of regulating gene expression by inhibiting target phosphatases or inducing target kinases [58, 59]. Among these targets, nuclear factor-kappa B (NF-κB) in activated B cells is particularly sensitive to ROS and is essential for the acquisition of the proinflammatory M1 polarization.

2.3.4. Pyroptosis. Pyroptosis is a highly specific type of inflammatory programmed cell death different from necrosis or apoptosis, which was discovered recently. Accumulating research unveiled that pyroptosis plays a magnificent role in neurological diseases. Astrocytes induce the activation and proliferation of microglia, producing a large number of inflammatory mediators in the CNS. These inflammatory mediators can activate endothelial cells to produce a variety of tissue factors, increase excitatory amino acid toxicity, and promote the release of NO and ROS, thereby destroying intracellular lipids, proteins, and nucleic acids and triggering a variety of inflammatory cell signaling pathways, such as NF-κB and signal transducers and activators of transcription 3 (STAT3). These factors could induce caspase-1-independent pyroptosis downstream of noncanonical NLRP3 inflammasome activators, expand a cascade of inflammatory response, and aggravate neurological diseases [60, 61]. Studies have shown that ROS generation after cerebral I/R injury can destroy phagocytic cells and promote their rupture. The rupture may also trigger the NLRP3 inflammasome, and the rupture of lysosomes may damage cell integrity and activate the NLRP3 inflammasome signaling pathway to induce cell pyrolysis [62]. In addition, ROS are also an important factor in the regulation of NLRP3 inflammasome activation in TBI [63, 64]. They could be detected in neurons, astrocytes, and microglia in an injured brain, which contribute to inducing inflammatory response and neuronal death, as well as aggravating the neurological outcome [65, 66].

2.3.5. Necroptosis. Programmed necrosis (necroptosis) is a newly identified mechanism of regulated cell death combining features of both apoptosis and necrosis, which can be activated by several stimuli including oxidative stress, infection, inflammation, and activation of toll-like and cell death receptors [67–69]. Necroptosis has crucial functions in development and tissue homeostasis, yet emerging evidence has implicated this pathway in the development of several pathological conditions including various neurological diseases [70–72]. The accumulation of intracellular ROS can modify proteins, glucose, lipids, and nucleic acids in cells and tissues to cause dysfunction and cell death [73]. In turn, necroptosis could be activated by activating important metabolic enzymes including glycogen phosphorylase, glutamate ammonia ligase, and glutamate dehydrogenase 1; RIP3/RIP-like protein kinase 3 (RIPK3)/MLKL regulates tumor necrosis factor- (TNF-) induced ROS production [74]. Therefore, the participation of oxidative stress induced necroptosis as a common mediator of various neuronal demise. Pharmacological inhibition of necroptosis prevents mitochondrial dysfunction, oxidative injury, energetic failure, and dopaminergic neuronal loss in PD models [75]. Further studies demonstrated that upon TNF-induced necroptosis, the necrosome complex can translocate to the mitochondria and activate the pyruvate dehydrogenase and upregulate glycolysis and aerobic respiration leading to ROS generation [76].

3. Pathogenesis of Oxidative Stress-Mediated BBB Disruption

The BBB is a heterogeneous structure of the vasculature which is more susceptible to oxidative stress and neurovascular uncoupling damage in a specific region. Oxidative stress plays a pivotal role in the changes in the BBB. Oxidative stress can damage a variety of cells such as BMVECs, pericytes, and astrocytes, destroying the BBB. To some extent, as a result of vicious circles generated at molecular levels, it is difficult to separate or clearly indicate the cause and the effect of oxidative stress on BBB. A detailed description of the various pathological mechanisms of oxidative stress-mediated BBB disruption has been provided in the schematic illustration (Figure 2).

3.1. Tight Junctions. Tight junctions act as molecular gatekeepers of the paracellular space by mainly blocking water-soluble molecules, ions, blood-borne toxins, drugs, and pathogens from permeating the BBB channels [77]. The TJ chain of the brain endothelium consists of intact membrane proteins (claudins, obliteratin, and connecting adhesion molecules (jams)) [78], which are involved in intercellular contacts and interaction with cytosolic scaffolds ZO protein and actin cytoskeleton [79] and related proteins, including VE-cadherin [80], protein kinase [81], small GTPase [82], and heterotrimeric G protein [83]. Several lines of evidence indicate that TJ proteins are critical for the maintenance of BBB integrity.

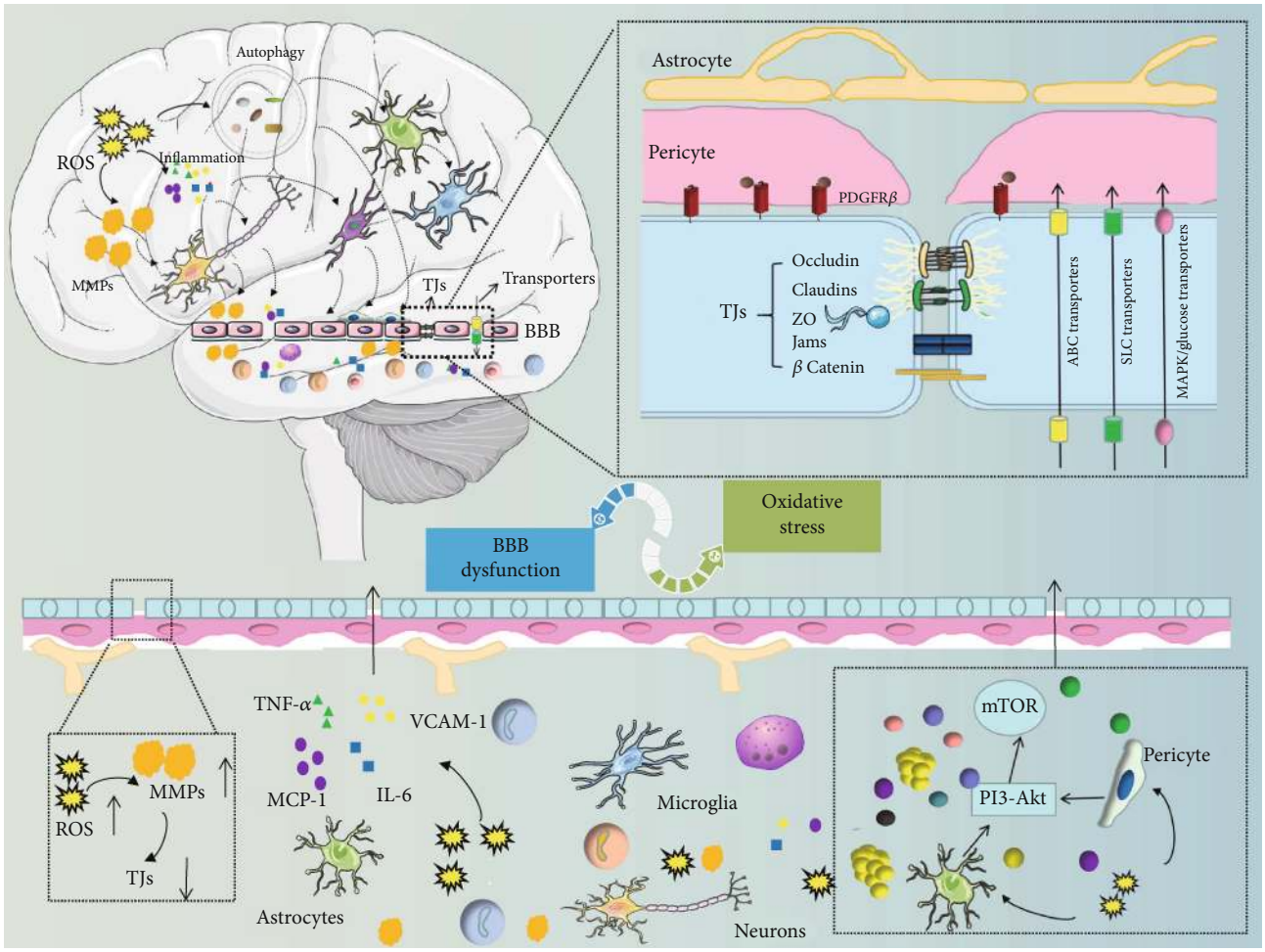

Figure 2: Schematic illustration of the main pathological mechanisms of oxidative stress-mediated BBB disruption. BBB is a highly complex and dynamic structure composed mainly of BMVECs, astrocytes, pericytes, and basement membrane. Oxidative stress can damage a variety of cells, such as BMVECs, astrocytes, and pericytes, and structures such as tight junctions (TJs) and basement membranes leading to the destruction of the BBB. (A) Many soluble carrier (SLC) transporters expressed in BMVECs allow substances such as peptides, amino acids, and glucose to selectively cross the BBB. ATP-binding cassette (ABC) transporters work by releasing toxic substances and drugs into the blood preventing them from entering the brain. (B) ROS can directly or indirectly promote MMP protein expression and can cause an increase in inflammatory factor levels, leading to BBB leakage possibly through degradation of TJ proteins and basement membrane proteins. (C) Tight junctions include TJ-related proteins such as occludin, claudin-5, and ZO-1. (D) Oxidative stress causes BBB disruption through induced lysosomal dysfunction, autophagy of the hippocampus, pericytes, and astrocytes, which may be involved in activating the AKT/mTOR signaling pathway. Abbreviations: IL-6: interleukin-6; MCP-1: monocyte chemoattractant protein-1; VCAM-1: vascular cell adhesion molecule-1; ZO: zonula occludens.

Pericytes and astrocytes associate with endothelial cells to mediate the formation of TJs essential to the function of the BBB. It has been reported that pericytes induce the synthesis of TJ proteins such as occludin, claudin-1, ZO-1, and ZO-2 by releasing proangiogenic protein factors, suggesting that the interaction between pericytes and endothelial cells can maintain the integrity of BBB [84]. Another type of cell that interacts with pericytes is astrocytes. Astrocytes regulate the integrity of TJs through signaling pathways such as WNT [85]. In vitro studies indicate that astrocytes can regulate TJ tightness and polarized distribution of transporters at the endothelial level [86]. Therefore, any changes in these proteins will affect the permeability of the BBB.

Occludin is the main structural protein of the TJs, and its expression level can represent the structural state of the BBB; for example, lower levels of occludin can signify BBB damage [87]. Experimental data showed that the expression and post-translational modification (phosphorylation) of occludin are tightly regulated, and its levels of expression reflect changes in BBB permeability [88]. Claudin protein may act as a regulatory target of the BBB and can alter the selective opening of tight junctions. The production of ROS can regulate the expression of claudin-5, increase the leakage of solute, and affect the BBB integrity [89–91]. Similarly, AMP-activated protein kinase (AMPK) activation was shown to reduce the expression of occludin and improve the functions of the BBB impaired by LPS through suppression of NADPH oxidase-derived ROS in mice [92]. The JAM subtype regulates cell bypass permeability of the BBB, especially in immune cells (i.e., neutrophils and monocytes/macrophages)

[93]. Malfunctioning of BMVECs of the BBB can be directly caused by the absence of JAM proteins in the TJs [94]. In addition to claudin and occludin, ROS can also change the permeability of the BBB by affecting the distribution of ZO protein. Exposure to hydrogen peroxide led to the redistribution of ZO-1 from the TJ_S to the cytosol, resulting in decreased transepithelial electric resistance (TEER) and increased BBB permeability [95]. That is, the expression, phosphorylation, and distribution of TJ proteins are important factors affecting BBB permeability. Therefore, any change of these parameters caused by ROS may compromise the integrity of the BBB. Increasing evidence suggests that there is a correlation between BBB disruption, oxidative stress, alteration of TJ complexes, and the progression of various neurological diseases [96, 97].

3.2. Transporters. Transporters, an important component of maintaining the strength of the BBB, can protect the CNS from exposure to circulating chemicals by regulating the exchange between the CNS and blood and controlling the ability of many endogenous and exogenous substances through pores [98]. These transporters mainly include ABC and SLC transporters. Among these, ABC transporters are the most important involved in limiting the permeability of several toxins and therapeutic agents [99]. In particular, ABCB1 (P-gp), ABCC (MRPs), and ABCG2 (BCRP) as exogenous efflux pumps driven by ATP participate in the extrusion of drugs from cells, thus limiting the delivery of small-molecule drugs to the brain [100]. Oxidative stress-induced signaling pathways that affect the expression of ABC transporters may be essential regulators in the pathogenesis and treatment of CNS diseases. After detoxification by binding to molecules like glutathione (GSH), glucuronic acid, and sulfate, toxic compounds can then be extruded by ABC transporters.

As discussed above, ROS participate in cytotoxicity and play a pivotal role in the signal transduction of multiple transcription factors, such as HIF-1, NF-κB, and nuclear factor E2-related factor 2 (Nrf2) [101]. In turn, these transcription factors could regulate the expression of ABC transporters. NF-κB activation is associated with the overexpression of P-gp in the brain caused by epilepsy [102]. Nrf2 is a cell sensor of oxidative stress. It was found that with the activation of oxidative stress, the expression levels of Nrf2 and the activity of P-gp, Mrp2, and Bcrp increased in the BBB [103]. Strikingly, reactive astrocytes display an increased expression of P-gp and Mrp1 in multiple sclerosis (MS) lesions [104].

Compared with ABC transporters, SLC transporters act as the "metabolic gate" of cells and mediate the transport of various necessary metabolites and nutrients, including glucose, neurotransmitters, inorganic/metal ions, and amino acids [105]. Of the known SLC transporters that transport drugs across the BBB, the most common target transporters are members of the SLC21A/SLCO family, which includes organic anion transporters (human and rodent Oatps). OATP/Oatp is the prototype transporter of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (i.e., statins), which has antioxidant and neuroprotective functions that could be of great advantage in neurological diseases [106, 107].

In addition to ABC and SLC transporters, ROS can also change BBB permeability by modulating AMPK. AMPK has been reliably confirmed to target transporters, including glucose transporter types 1 and 4 (i.e., GLUT-1 and GLUT-4), K^+, and Cl^- channels in the epithelium [108, 109] and Na-K-Cl (NKCC2) cotransporters [110]. AMPK is also known to be involved in critical cell stress signaling responses in the BBB [111]. The interaction between pericytes and astrocytes is essential for maintaining BBB integrity and AMPK protein kinase activity and influencing the expression of glucose transporters GLUT-1 and GLUT-4 and glucose uptake [112].

3.3. Matrix Metalloproteinases. Zinc-containing proteolytic matrix metalloproteinases (MMPs) can degrade the extracellular matrix and the epithelial basement membrane thus affecting the integrity of the BBB [113]. Endothelial cells, basement membranes, and TJs are essential for the normal functioning of the BBB. In turn, any disruptive changes in the BBB can compromise its integrity leading to neurological disease progression [114]. It has been suggested that inhibiting MMPs prevents the digestion of basement membrane proteins and TJs thus preventing BBB compromise [115]. Therefore, MMP activity is the key mediator of BBB permeability [116, 117]. ROS directly downregulate TJs and indirectly activate MMPs that promote the opening of the BBB [118, 119]. Oxidative stress-induced activation of MMPs and aquaporin leads to the loosening of the perivascular units and vasculature, promotes vascular or cellular fluid edema, enhances BBB leakage, and leads to neuroinflammatory progression [120–122]. The structural changes of pericytes and astrocytes increase the permeability of BBB, which leads to the entry of microbial pathogens into the brain, the accumulation of neurotoxic substances, and the induction of oxidative stress [123]. In addition, oxidative stress can activate the secretion of MMP-9 and other factors by pericytes and astrocytes, degrade the basement membrane, change the expression and distribution of TJ proteins, and aggravate the damage of BBB [124].

3.4. Inflammation. Excessive oxidative damage occurs when inflammatory cells release large amounts of ROS at the inflammatory site. Beyond that, increased intracellular ROS levels accelerate the proinflammatory response. ROS activate a variety of redox-sensitive transcription factors and are involved in the inflammatory response, leading to BBB damage. NF-κB, as a major regulator of the inflammatory response, is mainly activated in a redox-dependent manner. Activation of NF-κB by ROS can increase intercellular adhesion molecule-1 (ICAM-1) and VCAM-1 expression [125]. The activation of the Ca^{2+} signaling pathway by ICAM-1 can lead to changes in the cytoskeleton in BMVECs, leading to BBB damage [126]. Macrophage/microglial activation appears to be an early stage of injury, and before BBB breakdown, inhibition of its activation prevents BBB dysfunction [127]. Activated macrophages/microglia can induce the expression of cytokines (i.e., TNF-α and Egr-1), leading to

BBB destruction [128, 129]. Release of IL-1β in astrocytes leads to immune cell recruitment, BBB destruction, edema, and loss of neurons [130]. MCP-1 from astrocytes and microglia can attract microglia to sites of injury and stimulate monocyte migration through the BBB [131]. Crosstalk among BMVECs, pericytes, and astrocytes occurs through soluble factors, including cytokines [132]. Oxidative stress leads to the death of pericytes and further destruction of BBB. Pericytes can mediate inflammatory cascades and white matter damage and eventually increase nerve damage [133]. TGF-β, IL-6, glial cell line-derived neurotrophic factor, and basic fibroblast growth factor released by astrocytes can change the barrier characteristics of BMVECs. In contrast, leukemia inhibitory factors released by BMVECs can induce astroglial differentiation, further aggravating BBB injury [134].

3.5. Autophagy. Autophagy is a cellular degradation pathway that transports damaged, denatured, or senescent proteins and damaged organelles to the lysosome for digestion and degradation. Therefore, under physiological and pathological conditions, the autophagy pathway can be critical for neuronal homeostasis and can play the role of a local housekeeper [135]. Some recent findings suggested that oxidative stress caused BBB disorders through induced lysosomal dysfunction, autophagy activation in the hippocampus, pericytes, and astrocytes [136–138]. In in vivo and in vitro subarachnoid hemorrhage (SAH) models, mTOR inhibition has a potent protective effect on neuronal damage after SAH by reducing excessive mitochondrial fission [139]. Studies have found that oxidative stress induces damage to the frontal cortex and hippocampal neurons. The mechanism for this damage may involve the activation of the AKT/mTOR signaling pathway to regulate autophagy and inhibit neuronal apoptosis [140]. Studies have found that in astrocytes exposed to H_2O_2, 2-(2-benzofuranyl)-2-imidazoline (2-BFI) can exert cytoprotective effects by enhancing lysosomal stability under conditions of oxidative stress [141]. A study indicated that autophagy was activated during starvation and protected the endothelial barrier integrity by scavenging ROS and inhibiting the redistribution of claudin-5 [89]. A novel mechanism of autophagy disturbance secondary to nitrosative stress-induced tyrosine nitration of transient receptor potential M2 (TRPM2) during pericyte injury both in vitro and in vivo has been revealed [142]. A prolonged oxidative stress in astrocytes inhibits LC3 lipidation and impairs autophagosome formation and autophagic flux, despite concomitant activation of several proautophagic signals [143]. ROS can induce autophagy under conditions of oxidative stress, and autophagy can reduce the damage caused by oxidative stress. Therefore, both ROS and autophagy can jointly maintain the stability of the intracellular environment and the structural and functional integrity of brain cells and the BBB [144, 145].

4. Oxidative Stress-Mediated BBB Disruption in Neurological Diseases

Recent researches have suggested that oxidative stress-mediated BBB disruption is an important process in various neurological diseases, including IS, hemorrhagic stroke, TBI, AD, PD, ALS, and CSVD (Table 1).

4.1. Ischemic Stroke. Ischemic stroke is a destructive cerebrovascular disease that has become the leading cause of long-term disability and the fourth leading cause of death worldwide [173]. Oxidative stress plays a critical role in I/R-induced brain injury [174, 175]. Various mechanisms in the body can trigger oxidative stress, including mitochondrial dysfunction, excitatory toxins, and glutamate release, and defects in the antioxidant system, and enzymes and phagocytes can activate oxidative stress [176, 177]. Mitochondria are both important intracellular organelles for energy metabolism organelles, the main intracellular source of ROS [178], and important targets for I/R injury [179, 180]. During cerebral ischemia, inflammatory factors, oxidative stress, and calcium overload stimulate the mitochondria, causing them to produce large amounts of ROS, thereby initiating the mitochondrial necrosis program and causing cell death. In addition, macrophages, endothelial cells, and other immune cells produce large amounts of ROS during the cerebral ischemia phase [181], which in turn induce the expression of NF-κB, NOS, and proinflammatory factors, triggering the upregulation of vascular endothelial cell adhesion molecules and causing BBB permeability.

The occurrence of ischemic stroke and subsequent reperfusion reduces the integrity of the BBB and increases cell permeability, causing brain edema [182]. Inflammatory factors can directly damage neurons by permeating the compromised BBB, aggravating I/R injury [183]. Importantly, I/R injury involves changes in endothelial barrier function and recruitment of immune cells, both of which are conducive to oxidative stress and the BBB disruption. Using experimental models of cerebral ischemia, abundant evidence indicates that molecules such as NOX, NOS, or GPx can reduce oxidative stress and protect the BBB and brain from I/R injury [184, 185]. Recent research showed that stanniocalcin-1 attenuates I/R injury by reducing oxidative stress and BBB permeability [186]. Dihydrocapsaicin downregulated ROS, NOX2, NOX4, NF-κB, and MMP-9 levels to reduce oxidative stress and increase TJ protein expression, thereby protecting the BBB and brain from I/R injury [147].

4.2. Hemorrhagic Stroke. When compared with ischemic stroke, hemorrhagic stroke is more detrimental, with higher mortality and morbidity [187]. The pathophysiological processes of cerebral injury after intracranial hemorrhage (ICH) can be divided into primary mechanical injury and secondary brain injury, involving oxidative stress, BBB disruption, excitotoxicity, neuroinflammation, and neuronal apoptosis [188, 189]. Increasing evidence suggests that oxidative stress plays a role in the pathological process of ICH and in the important stages of the pathophysiological response to ICH [190]. Multiple pathways can induce ROS production after ICH, the two main pathways. First, blood cell breakdown products such as hemoglobin, ionized iron, and thrombin can induce free radical generation [191]. Increased extracellular iron levels during ischemia can lead to excessive activation of glutamate receptors, thereby promoting iron

Table 1: Oxidative stress-mediated BBB disruption in neurological diseases.

Diseases	Model	Targets: Oxidative stress	Targets: BBB	Pathways	Mechanisms	Ref
IS	MCAO, rat	MDA, GSH, and NADPH	ZO-1 and occludin	REK	Oxidative stress and tight junctions	[146]
	MCAO, rat	NOX2, NOX4, ROS, MDA, GPx, and NO	Occludin, MMP-9, Nrf2, and Nqo1	MAPK	MMP, oxidative stress, and inflammatory response	[147]
	OGD/R, BMVECs	ROS	ZO-1 and claudin-5	PI3K/Akt/Nrf2	Oxidative stress	[148]
	MCAO, rat; OGD/R, primary cortical neurons	NO, MDA, and ROS	IL-6 and TNF-α	NF-κB	Neuroinflammation and oxidative stress	[149]
	MCAO, rat; OGD/R, BMVECs	ROS	ZO-1	mTOR	Cell autophagy and oxidative stress	[150]
Hemorrhagic stroke	Autologous blood injection, rat	ROS	ATP, Bcl-2, Bax, caspase-3, and caspase-9	DJ-1/Akt/IKK/NF-κB	Apoptosis, oxidative stress, and inflammatory response	[151]
	Collagenase injection, rat	ROS, GSH-px, and SOD	ZO-1 and occludin	MAPK	Oxidative stress	[152]
	LPS-activated, microglia	ROS, NOX2, and NOX4	CD86, Arg1, CD206, IL-1α, IL-1β, TNF-α, and FeSO4	Not mentioned	Oxidative stress, inflammatory response, and iron metabolism	[153]
	Autologous blood injection, rat; OxyHb, primary rat cortical neurons	ROS, NOX1, and NOX2	TNF-α, MMP-9, NQO1, Bcl-2, Bax, caspase-3, CD14, CD68, γ-H2AX, and XRCC1	HO-1	Oxidative stress, apoptosis, inflammation, mitochondria injury, and DNA damage	[154]
TBI	Free fall brain trauma, rat	ROS, SOD, and 4-HNE	MMP-9, ZO-1, and occludin	JNK	MMP inhibition and oxidative stress	[155]
	A cryogenic injury, mice; biaxial stretch SI, BMVECs	ROS	GFAP, IL-6, IL-β, and ICAM-1	Nrf2/HO-1 and NF-κB	Oxidative stress and inflammatory response	[156]
	Controlled cortical, mice	SOD, CAT, and GSH	TNF-α, NLRP3, caspase-1, IL-1β, and IL-6	AMPK and Nrf2	Oxidative stress, inflammation, and apoptosis	[157]
	Controlled cortical, mice	SOD, GPx, and MDA	NQO1 and Bax	Nrf2-ARE	Oxidative stress and apoptosis	[158]
AD	Neuronal damage, neurons	ROS, 4HNE, H_2O_2, SOD, MDA, and GPx4	MMP	Nrf2/HO-1	MMP inhibition and oxidative stress	[159]
	H_2O_2-induced N2a, SH-SY5Y cells	ROS	Fe^{2+} and Fe^{3+}	Nrf2/HO-1	Iron metabolism and oxidative stress	[160]
	Injection of D-galactose and Aβ25-35-ibotenic acid, rats	SOD, MDA, and GSH-Px	5-HT, methionine, glutamine, and tryptophan	AMPK-SIRT	Oxidative stress and energy metabolism	[161]
	H_2O_2-induced, PC12 cells	ROS	Caspase-3, MMP	ASK1-JNK/MAPK	MMP inhibition, apoptosis, and oxidative stress	[162]
	Aβ-induced, rats and SH-SY5Y cells	ROS	TXNIP	Not mentioned	Oxidative stress	[163]
PD	People, blood	ROS	P-gp	Not mentioned	Oxidative stress	[164]
	H_2O_2-induced, rat and PC12 cells	SOD and catalase	Caspase-3 and Hsp-70	Nrf2/HO-1	Oxidative stress and apoptosis	[165]

Table 1: Continued.

Diseases	Model	Targets: Oxidative stress	Targets: BBB	Pathways	Mechanisms	Ref
	6-OHDA-treated, mice	DA, ROS, and SOD	IL-1β and TNF-α	PI3K/AKT and IKK/IκBα/NF-κB	Neuronal inflammation and oxidative stress	[166]
	6-OHDA-induced, mice and SH-SY5Y cells	ROS and GSH	Caspase-3, Bax, and Bcl-2	Nrf2/HO-1	Oxidative stress and apoptosis	[167]
	MPTP-induced, mice and PC12 cells	ROS	Mitochondrial membrane potential and caspase-3	ROS/JNK	Oxidative stress and apoptosis	[168]
ALS	hSOD1-linked, Drosophila and NSC-34 cells	GSH and GCLC	HSP70	Nrf2/STAT3	Oxidative stress	[169]
	SOD1 mutation, B6SJL-Tg 1Gur/J mice	COX, LDH, thiol groups, and lipid dienes	Cav-1, respiratory capacity rate, and cholesterol	Not mentioned	Mitochondrial bioenergetics and oxidative stress	[170]
CSVD	Spontaneously hypertensive, rat	SOD, GSH, MDA, and CAT	IL-6, TNF-α, IL-1β, Bcl-2, caspase-3, and VEGF	STAT3/VEGF	Oxidative stress and inflammatory response	[171]
	Spontaneously hypertensive, rat	SOD, GSH, MDA, and CAT	TNF-α, IL-6, IL-1β, MCP-1, and COX-2	Not mentioned	Oxidative stress and inflammatory response	[172]

Abbreviations: OGD/R: oxygen-glucose deprivation/reperfusion; MCAO: middle cerebral artery occlusion; OxyHb: Oxygen hemoglobin; SI: stretch injury; SH-SY5Y: human neuroblastoma cells; 4HNE: 4-hydroxynonenal; DA: dopamine; GCLC: glutamate-cysteine ligase catalytic; Bcl-2: B cell lymphoma-2; Bax: Bcl-2-associated X protein; Arg1: arginase 1; XRCC1: X-ray repair crosscomplementing gene 1; GFAP: glial fibrillary acidic protein; NQO1: NAD(P)H:quinone oxidoreductase; 5-HT: 5-hydroxytryptamine; TXNIP: thioredoxin-interacting protein; VEGF: vascular endothelial growth factor; Hsp-70: heat shock protein 70; Cav-1: caveolin-1; COX-2: cyclooxygenase-2; JNK: c-Jun N-terminal kinase; MAPK: mitogen-activated protein kinase; HO-1: heme oxygenase-1; SIRT: sirtuin; ASK1: apoptosis signal-regulating kinase 1; PKC: protein kinase C.

uptake in neurons and subsequent excessive production of membrane peroxides [192]. Experimental results show that deposition of free iron can trigger oxidative stress, leading to nerve damage, cytotoxicity, and poor outcomes after thrombolytic therapy following an acute stroke [193, 194]. In addition, the use of nonspecific ROS scavengers and NADPH oxidase inhibitors can reduce ROS production and neurotoxicity, improve cerebral vascular function, and reduced cerebral amyloid angiopathy-related microhemorrhages [153, 195]. Also, infiltration of macrophages, excessive microglial activation, and neutrophils releasing large amounts of ROS, NO, and the activation of a series of cascades mediate direct and indirect neuronal damage and promote neuronal apoptosis, astrocyte necrosis, and cerebral edema after ICH [196, 197]. These overlapping mechanisms interact to cause BBB disruption, loss of neurons, and glial hyperplasia leading to permanent neurological deficits [198, 199]. Therefore, ROS and BBB play a key role in brain injury after a hemorrhagic stroke.

ROS can trigger multiple interconnected molecular and cellular pathways involved in BBB disruption after ICH. Studies in animal models have shown that ROS can also upregulate MMP-9 expression, degrade TJ proteins, and activate microglia, leading to BBB disruption following ICH [200, 201]. There is also emerging evidence that ROS are maintained at a stable level via a stable ROS production balance and a balance of mitochondrial oxidative phosphorylation and antioxidant mechanisms [202]. A recent study showed that the overexpression of E3 ubiquitin ligase ring finger protein 34 in mice exacerbates ICH-induced neurological deficits and brain injury, hematoma volume, and BBB disruption by facilitating mitochondrial dysfunction-mediated oxidative stress [203]. More importantly, the presence of multiple inflammatory mediators such as IL-6 and lipopolysaccharides has been noted after ICH. These can induce the production of ROS, activate microglia and astrocytes, and disrupt the BBB causing brain edema [204, 205]. Thus, oxidative stress and BBB disruption are also pivotal in the underlying pathological process of ICH.

4.3. Traumatic Brain Injury (TBI). TBI is the main cause of mortality and morbidity in children and young adults [206, 207], and it is currently estimated to be the third largest cause of global disease burden [208, 209]. Accumulating evidence strongly suggests that oxidative stress is a major threat in the development of TBI [210]. Besides, it has been reported that biomarkers of oxidative stress accumulate in patients with TBI [211].

ROS production may lead to lipid peroxidation, protein crosslinking, DNA breakage, mitochondrial electron transport chain damage, and disruption of the structure and function of brain cells [212]. Lipid peroxidation, a sequence of

oxidative stress in TBI, also triggers the formation of aldehyde byproducts including propenal (acrolein) and 4-HNE from neurotoxic reactions. These byproducts aggravate the production of ROS/RNS, mitochondrial dysfunction, and BBB dysfunction and permeability. Finally, aldehyde byproduct accumulation will lead to intracellular Ca^{2+} overload leading to the activation of proteolytic degradation of neuronal cytoskeletal proteins [213, 214]. NOX is the main source of ROS after TBI [215]. A recent study has confirmed that the deletion of NOX4 decreases the severity of TBI [216]. The absence of NOX2 can reduce the expression of M1-like markers in microglia/macrophages which initiate damage of the cerebral cortex [217]. Studies have indicated that ICAM-1 can increase markers of oxidative stress, promote microglial transformation into the activated phenotype, promote BBB permeability, and increase the neuropathological index [218]. Increasing exposure of endothelial cells to ROS can increase the function of contraction and adhesion molecules, resulting in functional impairment of the BBB [219]. Impairment of pericyte-endothelium crosstalk results in BBB disruption following TBI [10].

In TBI, MMPs, ROS, and inflammatory cytokines including TNF-α, IL-1β, and TGF-β are activated [220]. ROS promote blood vessel and cellular edema through oxidative stress-induced MMP activation and aquaporin release and increase the BBB permeability, leading to the progression of neuroinflammation [122]. Ultimately, similar to the destruction of the BBB in TBI, circulating neutrophils, macrophages, and lymphocytes are recruited to the injured sites to further exacerbate the inflammatory response. In the early stage of TBI, the brain parenchyma upregulates the expression of leukocyte adhesion molecules on brain endothelial cells [221]. Leukocytes can further damage the BBB by secreting cytokines and chemokines, promoting ROS generation, and hydrolyzing proteases, in addition to other mechanisms [222].

4.4. Alzheimer's Disease (AD). AD is a multifactorial neurological disease, characterized by the formation, aggregation, and accumulation of amyloid-beta (Aβ). As mentioned above, oxidative stress can cause BBB dysfunction through neurotoxicity, mitochondrial dysfunction, heavy metal deposition, etc. In turn, the BBB can also trigger oxidative stress and neuroinflammation, enhance the activity of secretases, and finally promote the generation of Aβ. With gradual accumulation of Aβ in the brain and the presence of oxidative stress, BBB dysfunction may become a vicious circle, leading to cognitive impairment and dementia.

Studies have shown that Aβ-induced oxidative imbalance is related to elevated levels of byproducts of protein oxidation, lipid peroxidation, and DNA/RNA oxidation levels [223–225]. Also, oxidative stress is a crucial determinant of Aβ accumulation, triggering mitochondrial dysfunction and apoptosis [226, 227]. Studies have shown that damaged mitochondria can produce ROS and other active substances, which can lead to abnormal phosphorylation of tau protein [228–230]. The latest progress in the study of the gene expression profile of an AD brain shows that the production of brain insulin and insulin signal transduction are significantly impaired, indicating that an AD brain shows the characteristics of a diabetic brain; that is, brain insulin depletion can lead to the initiation of mitochondrial dysfunction and increase oxidative stress and the sensitivity to brain insulin [231].

In a recent study, the mouse microglial cell line BV2 was used to establish the H_2O_2-mediated oxidative stress injury model of cells, which led to MMP-9 degradation, apoptosis, and BBB destruction [232]. The expression of nNOS was increased in astrocytes around β-amyloid plaques in humans [233]. Other teams also reported increased expression of eNOS and iNOS in the neurofibrils, suggesting that the production of NO and peroxynitrite by reactive astrocytes plays a critical role in the pathogenesis of AD [234, 235]. Since oxidative stress/nitration stress and NO production by active astrocytes and microglia in neurofibrillary tangles are markers of AD, even in the early stages, targeting ROS production as a therapy could be potentially important for curbing disease progression.

4.5. Parkinson's Disease (PD). PD is characterized by selective damage of dense dopaminergic (DA) neurons in the substantia nigra and the loss of DA levels in the striatum nigra in the brain [236]. Accumulating evidence strongly suggests that ROS are crucial determinants leading to the loss of DA neurons in a PD brain, low GSH, mitochondrial dysfunction, neuroinflammation, and disorders of metal metabolism [237]. In addition, there are several polyunsaturated fatty acids in the brain that can undergo lipid peroxidation under conditions of oxidative stress releasing toxic products [238]. Similarly, evidence of elevated ROS levels in the brains of PD patients includes the occurrence of lipid, protein, and DNA oxidation as documented in numerous studies [239, 240].

Although most of the DA released at the end of the synapse is reabsorbed by DA neurons, astrocytes may reabsorb some dopamine. Astrocytes play an active and key role in the development of PD, and they mediate the survival and function of neurons [241]. A recent study has indicated that dopamine-induced activation of the pentose phosphate pathway in astrocytes reduces oxidative stress and exerts a neuroprotective role in PD [242]. Oxidative- or ROS-induced molecules, such as α-synuclein, neuromelanin, and active MMP-3, from damaged substantia nigra dopaminergic neurons trigger microglial activation. The active form of MMP-3 is increased in response to oxidative stress in dopaminergic cells. MMP-3 leads to the activation of microglia, thus producing RNS and ROS [243]. It was found that MMP-3 induced by oxidative stress can also result in BBB degradation and neutrophil infiltration, further resulting in neuroinflammation [244].

4.6. Amyotrophic Lateral Sclerosis (ALS). ALS is one of the most devastating neurological diseases. Autopsy and laboratory studies in ALS have shown that oxidative stress plays a critical role in motor neuron degeneration and astrocyte dysfunction [245, 246]. Increased oxidative stress biomarkers in cerebrospinal fluid, plasma, and urine indicated abnormal oxidative stress outside of the CNS [247]. Recent studies suggest that oxidative stress is part of the neuroinflammatory

response and may be triggered by a combination of mitochondrial dysfunction and pathophysiological activation of astrocytes and microglia in G93A-SOD1 rats and mice [248]. Considerable experimental evidence suggests that ROS generation in motor neurons in response to excitotoxic activation can induce oxidative damage of glutamate transport in surrounding astrocytes, leading to excitatory stress expansion and, thereby, triggering the development of ALS [249, 250]. The end of the stellate cells lining the BBB is rich in two proteins, aquaporin 4 (AQP4) and inward rectifying potassium channels (Kir) [251]. Both channels are important for maintaining a functional BBB astrocyte lining. Studies have found that the ability of astrocytes to maintain water and potassium homeostasis is hindered in the ALS model. The imbalance in homeostasis affects the BBB, disrupts the microenvironment of neurons, and causes neuronal dysfunction and death [252]. A recent study has indicated that the pivotal mechanism that promotes the pathogenesis of ALS, which involves the Ets-2 transcription factor of the Bts-xL gene, protects glial cells from oxidative stress [253].

4.7. Cerebral Small Vessel Disease (CSVD). CSVD refers to a variety of clinical manifestations such as hypertension, acute stroke, and cognitive dysfunction caused by pathological changes in the cerebral microcirculation (including small blood vessels or microvessels) [254, 255]. The pathogenesis of cerebral microangiopathies involved endothelial dysfunction, BBB disruption, oxidative stress, amyloid deposition, and decreased blood perfusion [256, 257].

Among these mechanisms, BBB disruption and oxidative stress are considered to be important pathophysiological mechanisms of CSVD [258, 259]. BBB injury, as an early feature of CSVD, involves vascular endothelial dysfunction, TJ destruction, and degradation of the extracellular matrix [260]. Increased BBB permeability plays a critical role in normal aging, dementia, white matter, lacunar infarction, and CSVD. Aging and hypertension have a synergistic effect on aggravating BBB injury, which will eventually promote oxidative stress in brain tissues [261]. For example, the expression of NO was increased compromising areas of the BBB. Peripheral cytopathy leads to disruption of the BBB and microvascular disruption as well. The mechanism leading to this disruption may be related to the end of astrocytes detached from the brain microvessels, the leakage of plasma proteins, and the decreased expression of endothelium adhesion connexin [262]. In addition to endothelial cell injury, the decrease in pericyte coverage in aged hypertension mice further reduces the integrity of the BBB [263]. Ischemic injury induces increased expression of MMPs, which impairs BBB integrity by changing the structure of TJ proteins and pericyte damage [264, 265]. A study found that white matter damage, cognitive damage, brain atrophy, TJ protein expression, and microglial proliferation were downregulated in a mouse model of persistent cerebral hypoperfusion. These indicated that impaired BBB plays a role in the pathogenesis of CSVD [266].

Excessive ROS are generated during tissue injury, triggering neuron edema and release of excitatory transmitters, which activate excitatory toxic cascades leading to the activation of inflammatory cells, exacerbating focal neurovascular injury [267]. Endothelial dysfunction may be caused by oxidative stress and inflammation. Conditions such as hypertension, diabetes, hypercysteineemia, smoking, and infection produce large amounts of ROS [268, 269]. In hypercholesterolemic apolipoprotein E gene-knockout mice, NOX2 knockout can block the production of ROS and damage of the cerebral vasodilation [270]. Similarly, the absence of NOX2 can prevent obesity-induced cerebral small blood vessel dysfunction [271]. The cerebrovascular network is one of the main goals of the process of local oxidative stress. Local oxidative stress can trigger damage to the vasculature and changes in BBB and blood flow and can promote changes in neurodegeneration in brain tissues [272]. A recent study indicated that salvianolic acid B ameliorated oxidative stress and neurocyte apoptosis, attenuated BBB disruption, and restored cognitive deficits and angiogenesis in a rat model of CSVD via the STAT3/VEGF signaling pathway [171]. Oxidative stress is involved in disrupting microvascular integrity, loss of integrin, and leakage of plasma proteins, which collectively destroy the integrity of the BBB [273].

5. ROS Can Affect the Integrity of the BBB via Mechanisms Interconnecting Multiple Organ Systems

In addition to the main factors described earlier that ROS can cause BBB disruption, recent studies also show that ROS can affect the BBB via mechanisms interconnecting multiple organ systems (Figure 3).

5.1. Microflora Gut-Brain Axis. With the recognition of a two-way communication system between the gut and brain, there is evidence that the "microbiota gut-brain axis" plays a major role in neurological diseases [274, 275]. The microflora gut-brain axis is considered a two-way neuroendocrine system and plays a pivotal role in oxidative stress response. Dietary ingestion of antioxidants, such as probiotics [276], prebiotics, and polyphenol [277], can influence gut microbiota composition, thereby contributing to the integrity of the BBB. *Megasphaera massiliensis* MRx0029 has antioxidant effects on differentiated SH-SY5Y neuroblastoma cells [275]. Chronic stress-induced gut dysfunction exacerbates intestinal hyperpermeability and disruption of TJ proteins such as ZO-1, occludin, and claudin-1 in a rotenone-induced mouse model of PD [278]. Alpha-synuclein (α-syn) deposition and related neurodegeneration in the intestinal nervous system can increase intestinal permeability, local inflammation, and oxidative stress, causing constipation in patients with PD. It is believed that chronic low-grade inflammation in the gut is the trigger factor for BBB leakage, activation of immune cells, and CNS inflammation [279].

5.2. Myocardial I/R Injury. Circulatory damage due to acute myocardial infarction and reperfusion injury can also interfere with systemic blood flow [280, 281]. Therefore, when myocardial I/R injury occurs, several important organs, including the brain, are also affected [282, 283]. Importantly, myocardial I/R injury may lead to the onset of oxidative

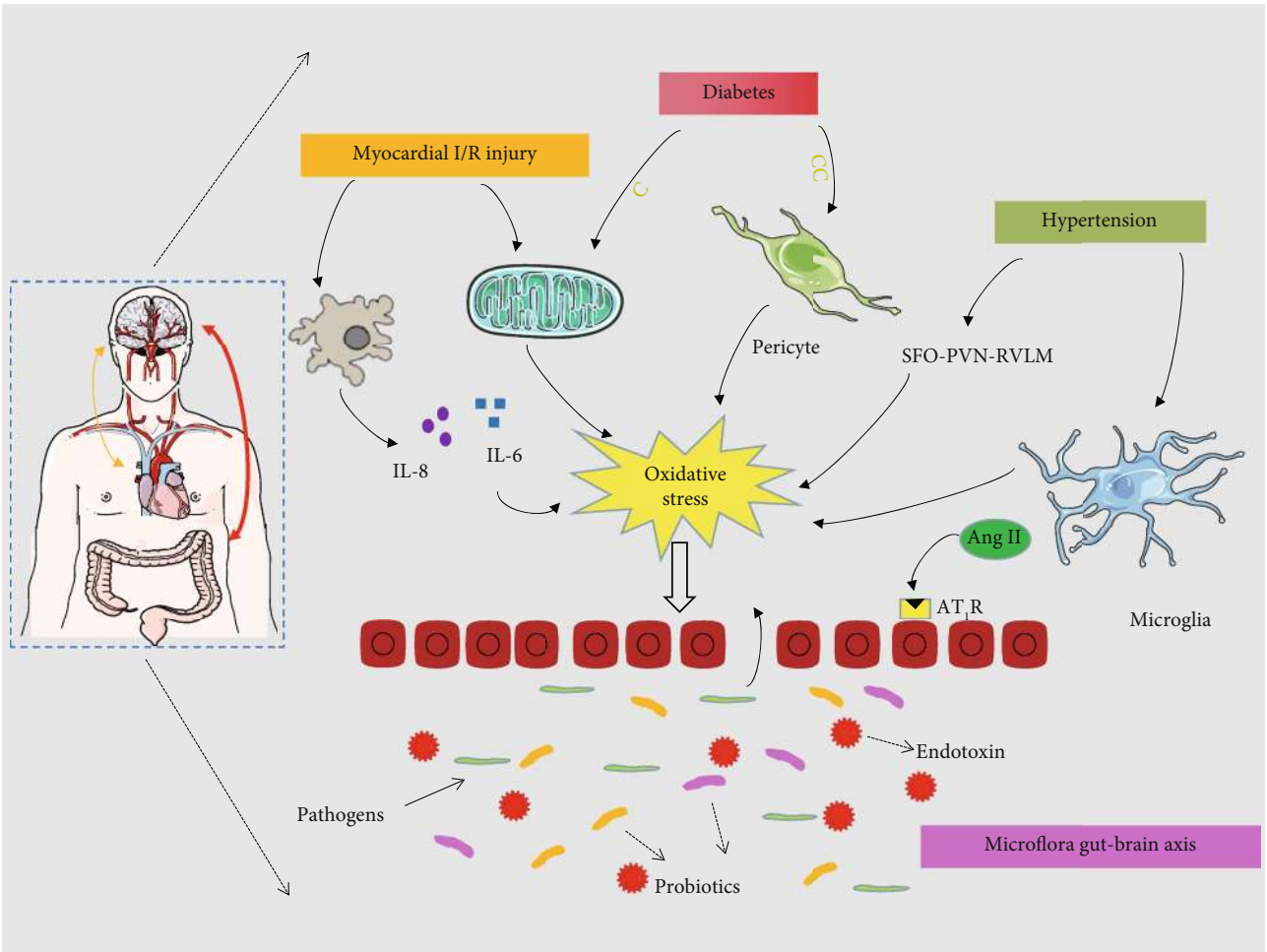

Figure 3: Schematic illustration of how ROS can affect the BBB via mechanisms interconnecting multiple organ systems. (A) Microflora gut-brain axis. Probiotics and pathogens can affect the composition of the intestinal flora and, thus, affect the integrity of BBB. (B) Myocardial I/R injury. It causes oxidative stress in the brain through mitochondrial dysfunction and inflammation, leading to BBB dysfunction. (C) Hypertension. Endothelial dysfunction, microglial activation, Ang II-mediated pathways, and the subfornical organ-paraventricular nucleus of the hypothalamus-rostral ventrolateral medulla pathway (SFO-PVN-RVLM pathway) may contribute to ROS production leading to the destruction of the BBB during hypertension. (D) Diabetes. Increased mitochondrial oxidative stress can be caused by hyperglycemia. This induces peripheral blood cell loss and is a prerequisite for BBB destruction.

stress in the brain, BBB dysfunction, mitochondrial swelling, brain cell apoptosis, and brain death [284]. Recent studies have also confirmed that myocardial I/R injury causes BBB decomposition, increased oxidative stress, and mitochondrial disruption [285]. In addition to myocardial I/R injury, neurological abnormalities after cardiac surgery are very common. Neurological complications after cardiac surgery are one of the most serious complications [286]. Glial cell injury with the two CSF markers (S-100B and GFAP) increased respectively by 35% and 25%, and IL-6 and IL-8 increased by 3.5 and 12 times, respectively, in 10 patients who underwent aortic valve replacement, indicating that cardiac surgery with cardiopulmonary bypass can lead to brain inflammation, glial cell damage, and BBB disruption [287].

5.3. Hypertension. Hypertension carries the highest risk for cardiovascular and cerebrovascular diseases [288, 289]. Damage to target organs, such as the heart, brain, kidney, and peripheral blood vessels, caused by uncontrolled hypertension affects the structure and function of these important organs [290]. In recent years, numerous studies have shown that hypertension is the most important cerebrovascular risk factor [291, 292]. The main mechanisms involved in hypertension-induced organ damage include endothelial cell activation, platelet activation, renin-angiotensin system activation, and oxidative stress. Endothelial dysfunction occurring under conditions of uncontrolled hypertension may be a potential underlying factor leading to vascular inflammation and BBB destruction [293].

Ang II-mediated proinflammatory effect is now widely recognized as a key mechanism for promoting excitatory hypertension in sensory nerves, and growing evidence supports that microglia are the key cellular targets that mediate the proinflammatory effect of central Ang II [294, 295]. Besides, recent studies also support that this mechanism contributes to the destruction of the BBB in hypertensive states

Table 2: Potential biomarkers towards oxidative stress in neurological diseases.

Biomarkers	Diseases	Sources	Methods	Ref
NcRNAs				
miR-27b	AIS	Rat striatum and PC12 cells	qRT-PCR	[313]
miR-210	IS	Ischemic penumbra regions of the right cerebral cortex	qRT-PCR	[314]
miR-186	AD	Hippocampal neuronal cells	qRT-PCR	[315]
lncRNA SOX21-AS1	AD	Hippocampal neuronal cells	qRT-PCR	[316]
Exosomes				
α-SYN and DJ-1	PD	CSF and plasma	Differential centrifugation	[319]
CTRP9	Stroke	Plasma	ELISA	[320]
Uric acid	AIS	Serum	Bayer technician	[322]
F2-isoprostanes	AIS and AD	Plasma, serum, urine, saliva, and cerebrospinal fluid	GC-MS, LC-MS, and HPLC	[325, 326]

Table 3: Antioxidant drugs towards oxidative stress in neurological diseases.

Antioxidant drugs	Targets	Clinical use	Ref
Edaravone	ROS, MDA, SOD, Nrf2/HO-1, GFAP, and TJs	AIS and ALS	[327, 328]
N-Acetylcysteine	Nrf2/HO-1, GSH, SOD, MDA, TAS, vitamin A, vitamin C, and vitamin E	PD, ALS, AD, and TBI	[334, 351–354]
Minocycline	GSH, MDA, NO, iNOS, eNOS, DPPH, MMP-9, MAP2, GFAP, CD11b, and Iba1	IS and AIS	[355–357]
Metformin	ROS, SOD, MDA, GSH, CAT, 8-iso-$PGF_{2\alpha}$, glutathione, glutamate, catalase, Nrf2/HO-1, and AMPK/mTOR	TBI, AD, and acute stroke	[339, 340, 342]
Fingolimod	NO, iNOS, cNOS, tNOS, SOD, MDA, GSH, and GSH-Px	RRMS and stroke	[358–360]
Idebenone	MDA, NO, GSH, and CAT	AD and HD	[361–363]
Dimethyl fumarate	SOD, MDA, GSH, GPx, NADPH, GFAP, Iba1, and Nrf2/HO-1	RRMS and stroke	[364, 365]

[296]. Ang II-mediated ROS production in the SFO-PVN-RVLM pathway is also considered to be a key factor in the sympathetic excitability of hypertension [297]. In this sense, in addition to the release of various proinflammatory cytokines, activated microglia also produce and release ROS [298]. Besides, studies have shown that hypertension can aggravate cerebrovascular oxidative stress caused by mild craniocerebral injury through the protective effect of the mitochondrial-targeted antioxidant peptide SS-31 [299]. Renovascular hypertension also significantly increases brain AT1R and oxidative stress in the brain and plasma [300].

5.4. Diabetes. Recent evidence has demonstrated that diabetes is a potential cause of neuropsychiatric disorders such as stroke [301], cerebral microangiopathy [302], diabetes-related cognitive decline [303], and BBB disruption [304]. Diabetes-related cognitive decline is characterized by impaired cognitive function and neurochemical and structural abnormalities, mainly involving neuronal damage caused by glucose-driven oxidative stress [305, 306]. In diabetes, increased mitochondrial oxidative stress is a mechanism for hyperglycemia-induced pericyte loss as a prerequisite causing BBB disruption [307]. It was shown that decreased GSH and SOD and elevated HNE in tissues of the early brain of diabetic mice, as well as a decreased number of late pericytes, led to BBB disruption [308]. Studies have shown that neurons and glial cells in different brain regions (such as the hypothalamus, lateral amygdala, and cerebral cortex) of diabetic rats promote the expression of iNOS, IKK, IKB, and NF-κB, while also inhibiting the expression of microglial CD11b and astrocyte GFAP [309]. Glycosylation of methylglyoxal with amino acids can generate superoxide radical anions [310]. Therefore, methylglyoxal damage to proteins can be mediated by oxidative stress generated by ROS, which may cause protein carbonyl formation [311]. Increased methylglyoxal and decreased GSH in diabetes lead to increased BBB permeability and increased I/R damage in the brain of mice [312].

6. Clinical Approaches towards Oxidative Stress in Neurological Diseases

Numerous studies have been conducted on various antioxidant agents. We here discuss the latest clinical evidence of potential biomarkers (Table 2) in neurological diseases such as noncoding RNAs (ncRNAs), exosomes, C1q and tumor necrosis factor-related protein 9 (CTRP9), uric acid, and F2-isoprostanes, and antioxidant drugs (Table 3) have been extensively investigated, such as edaravone, N-acetylcysteine (NAC), minocycline, metformin, fingolimod, idebenone, and dimethyl fumarate (DMF). They may provide more strategies for the treatment of neurological diseases.

6.1. Potential Biomarkers. ncRNAs are a class of functional RNAs that regulate gene expression in a posttranscriptional manner. ncRNAs, including microRNAs, long noncoding

RNAs (lncRNAs), and circular RNAs (circRNAs), can be used as diagnostic biomarkers and are emerging as novel therapeutic targets for neurological diseases. The study by Xu and colleagues showed that the inhibition of miR-27b could alleviate brain injury and upregulate the expression of Nrf2, Hmox1, SOD1, and Nqo1 after ICH via the Nrf2/ARE pathway [313]. Knockdown of miR-210 attenuated neuronal death and the antioxidant stress response effects of vagus nerve stimulation in the cortex following transient MCAO [314]. Recently, a study has defined the potential role of miR-186 as an inhibitor of AD development by downregulation of IL2 through the suppression of the JAK-STAT signaling pathway [315]. lncRNA SOX21-AS1 acted on oxidative stress-induced neuronal injury in AD mice via the Wnt signaling pathway by targeting FZD3/5 and may be a novel biomarker for enhanced AD treatment [316]. Accumulating evidence suggests that secreted exosomes may serve as vehicles for the transport of a wide range of proteins and immune markers, thereby potentially initiating or exacerbating pathogenic processes by fusing with recipient cells, including neurons [317, 318]. Since oxidative stress and mitochondrial dysfunction influence the underlying mechanisms of misfolded α-syn aggregation [319], biomarkers such as DJ-1 (oxidative stress sensor) and α-syn have the potential as clinical tools for early and accurate diagnosis of PD.

CTRP9 is a novel cytoprotective cytokine with antioxidant effects, which is highly expressed in brain tissue. It has been reported that high concentration of CTRP9 can reduce the risk of cerebral infarction and is an independent protective factor for cerebral infarction [320]. Uric acid is a potent water-soluble antioxidant that targets free radicals caused by oxidative damage, including hydroxyl radicals and superoxide [321]. In a prospective study involving 881 consecutive patients, uric acid levels were inversely associated with the extent of neurological deficits on admission and the final infarct volume on CT/MRI scans [322]. F2-isoprostanes (F2-isoP) are widely considered accurate and reliable biomarkers of oxidative damage that can be measured in plasma, serum, urine, saliva, and cerebrospinal fluid [323]. F2-isoP are measured in nanomolar units and are accurately analyzed using analytical platforms such as high-performance liquid chromatography (HPLC), gas chromatography-mass spectrometry (GC-MS), and light chromatography-mass spectrometry (LC-MS). F2-isoP have been studied among individuals with various neurological conditions such as acute ischemic stroke (AIS) and PD [324]. Elevated hyperacute plasma F2-isoP concentrations independently predict the occurrence of infarct growth and infarct growth volume in patients with AIS [325]. Measuring plasma F2-isoP might be helpful in the acute setting to stratify patients with AIS for relative severity of ischemic injury and expected progression.

6.2. Antioxidant Drugs. Edaravone, a new antioxidant and hydroxyl radical scavenger, is the novel scavenger for clinical use, mainly for nervous system diseases [327, 328]. In vitro and in vivo data of edaravone suggests that it may possess broad free radical scavenging activity and protect neurons, glia, and vascular endothelial cells against oxidative stress [329]. It was found that the neuroprotective effect of edaravone on hippocampal oxidative stress and cognitive impairment may be related to the enhancement of the antioxidant defense system through activation of the ERK/Nrf2/HO-1 signaling pathway [330]. Similarly, edaravone has been shown to exert a neuroprotective effect through its ability to suppress astrocyte activation and markedly decrease MDA levels and increase SOD levels in stroke events [331]. Edaravone was also found to ameliorate such an oxidative damage by t-PA with protecting outer layers of BBB (in vivo) and tight junctions (in vitro) [332].

NAC, a well-known antioxidant, is a prescription product for treating cystic fibrosis and acetaminophen overdose and is also widely available as a dietary supplement. It was found that the antioxidant defense mechanisms of NAC mainly include directly scavenging free radicals and enhancing the activation of Nrf2 [333]. Long-term oral administration of NAC in patients with PD substantially increased the levels of GSH and thus inhibits oxidative stress [334]. Brain cortex GSH, total antioxidant status (TAS), vitamin A, vitamin C, and vitamin E values were improved by NAC treatments in TBI-induced rats [335].

Minocycline is a semisynthetic derivative of the tetracycline group of antibiotics that is capable of crossing the BBB, which exerts the neuroprotective effect by anti-inflammatory and antioxidative stress. Patients with AIS who received oral minocycline combined with tPA had a significantly better thrombolytic effect by inhibiting the activity of MMP-9 [336]. Minocycline can downregulate the expression of iNOS and upregulate the expression of eNOS in vascular dementia, which restrains oxidative stress to protect neural function [337]. The present study showed that minocycline treatment can activate astrocytes and microglia, attenuate oxidative stress, increase GSH levels, decrease the content of MDA and nitrite, and reduce neuronal degeneration [338].

Other common drugs for the treatment of type 2 diabetes, such as metformin, a biguanide drug, may also benefit TBI, AD, and stroke patients [339–341]. Metformin can improve the neurological function and oxidative stress status of acute stroke patients with type 2 diabetes, and its mechanism may be related to the AMPK/mTOR signaling pathway and oxidative stress [342]. Pretreatment with metformin could activate Nrf2 antioxidant pathways and enhance the level of glutathione and catalase activities through induction of AMPK after transient global cerebral ischemia [343]. It has been reported that metformin plays a neuroprotective role by inhibiting the level of MDA and 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$) induced by ICH [344].

In addition to the main antioxidants mentioned above, fingolimod, idebenone, and DMF have a better clinical value in neurological diseases. Fingolimod is an oral sphingosine-1-phosphate receptor analog used to treat relapsing-remitting MS (RRMS). The neuroprotective effect of flavonoids against focal cerebral I/R injury in rats may be associated with the decreased production of oxidative stress targets including NO, tNOS, iNOS, and cNOS [345]. Idebenone is a short-chain benzoquinone that is structurally related to coenzyme Q10 (ubiquinone) and is a potent antioxidant and electron carrier [346]. It was approved in Japan in

1986 for the treatment of AD and other cognitive disorders [347]. Pretreatment with idebenone on pilocarpine could induce changes in MDA, GSH, NO, and CAT content in rat hippocampus tissue [348]. DMF is the first line of disease-modifying therapies for patients who have got RRMS. Its antioxidant mechanism has been confirmed to attenuate ROS overproduction, promote Nrf2/HO-1 pathway activation, increase reactivity of astrocytes and microglia, increase the content of SOD and GSH, and decrease MDA level for the treatment of MS or other demyelinating diseases [349, 350]. Future studies should include more RCTs to confirm the clinical efficacy of these treatments.

7. Conclusion

In summary, substantial evidence exists that implicates the role of oxidative stress and BBB disruption in the pathogenesis of neurological diseases. A variety of pathological factors can cause BBB compromise, mainly increasing BBB permeability. Also, direct insults on endothelial cells and the BBB can affect other components of the neurovascular unit, namely, peripheral cells, astrocytes, and basement membrane, further aggravating BBB damage and dysfunction. In neurological diseases, disruption of the integrity of the BBB is usually the first pathological change that occurs before clinical symptoms appear. The tight connection, inflammation, and degradation of MMP caused by oxidative stress are often accompanied by the opening of the BBB, which eventually leads to neuronal dysfunction, neuroinflammation, and neurodegeneration. Studying the relevance of oxidative stress to the development and outcome of neurological diseases and protecting the BBB in the early stages of diseases will help limit disease progression and improve clinical prognosis. Future research could be directed to examine the importance of redox imbalances in the pathogenesis of neurological diseases to reveal chelating agents that can be used to curb the progression of neurological diseases.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgments

This work was supported by grants from the National Natural Science Foundation of China (No. 81673899) and the National Key R&D Program of China (No. 2018YFC1705005).

References

[1] A. K. Reinhold and H. L. Rittner, "Barrier function in the peripheral and central nervous system-a review," *Pflügers Archiv - European Journal of Physiology*, vol. 469, no. 1, pp. 123–134, 2017.

[2] P. Majerova, A. Michalicova, M. Cente et al., "Trafficking of immune cells across the blood-brain barrier is modulated by neurofibrillary pathology in tauopathies," *PLoS One*, vol. 14, no. 5, article e0217216, 2019.

[3] P. Van Dyken and B. Lacoste, "Impact of metabolic syndrome on neuroinflammation and the blood-brain barrier," *Frontiers in Neuroscience*, vol. 12, 2018.

[4] D. N. Doll, H. Hu, J. Sun, S. E. Lewis, J. W. Simpkins, and X. Ren, "Mitochondrial Crisis in Cerebrovascular Endothelial Cells Opens the Blood–Brain Barrier," *Stroke*, vol. 46, no. 6, pp. 1681–1689, 2015.

[5] W. Qin, J. Li, R. Zhu et al., "Melatonin protects blood-brain barrier integrity and permeability by inhibiting matrix metalloproteinase-9 via the NOTCH3/NF-κB pathway," *Aging*, vol. 11, no. 23, pp. 11391–11415, 2019.

[6] V. Chiurchiù, A. Orlacchio, and M. Maccarrone, "Is modulation of oxidative stress an answer? The state of the art of redox therapeutic actions in neurodegenerative diseases," *Oxidative Medicine and Cellular Longevity*, vol. 2016, Article ID 7909380, 11 pages, 2016.

[7] H. L. A. Vieira, P. M. Alves, and A. Vercelli, "Modulation of neuronal stem cell differentiation by hypoxia and reactive oxygen species," *Progress in Neurobiology*, vol. 93, no. 3, pp. 444–455, 2011.

[8] Y. M. Chang, W. Y. Chi, T. Y. Lai et al., "Dilong: Role in Peripheral Nerve Regeneration," *Evidence-Based Complementary and Alternative Medicine*, vol. 2011, Article ID 380809, 9 pages, 2011.

[9] L. A. Cunningham, K. Candelario, and L. Li, "Roles for HIF-1α in neural stem cell function and the regenerative response to stroke," *Behavioural Brain Research*, vol. 227, no. 2, pp. 410–417, 2012.

[10] S. Bhowmick, V. D'Mello, D. Caruso, A. Wallerstein, and P. M. Abdul-Muneer, "Impairment of pericyte-endothelium crosstalk leads to blood-brain barrier dysfunction following traumatic brain injury," *Experimental Neurology*, vol. 317, pp. 260–270, 2019.

[11] N. Kakaroubas, S. Brennan, M. Keon, and N. K. Saksena, "Pathomechanisms of Blood-Brain Barrier Disruption in ALS," *Neuroscience Journal*, vol. 2019, Article ID 2537698, 16 pages, 2019.

[12] L. Zuo, T. Zhou, B. K. Pannell, A. C. Ziegler, and T. M. Best, "Biological and physiological role of reactive oxygen species–the good, the bad and the ugly," *Acta Physiologica*, vol. 214, no. 3, pp. 329–348, 2015.

[13] P. H. Chan, J. W. Schmidley, R. A. Fishman, and S. M. Longar, "Brain injury, edema, and vascular permeability changes induced by oxygen-derived free radicals," *Neurology*, vol. 34, no. 3, pp. 315–320, 1984.

[14] N. Sinha and P. Dabla, "Oxidative Stress and Antioxidants in Hypertension–A Current Review," *Current Hypertension Reviews*, vol. 11, no. 2, pp. 132–142, 2015.

[15] P. W. M. Kleikers, K. Wingler, J. J. R. Hermans et al., "NADPH oxidases as a source of oxidative stress and molecular target in ischemia/reperfusion injury," *Journal of Molecular Medicine*, vol. 90, no. 12, pp. 1391–1406, 2012.

[16] Y. Yao, J.-. Z. Huang, L. Chen, Y. Chen, and X. Li, "In vivo and in vitro studies on the roles of p38 mitogen-activated protein kinase and NADPH-cytochrome P450 reductase in Alzheimer's disease," *Experimental and Therapeutic Medicine*, vol. 14, no. 5, pp. 4755–4760, 2017.

[17] K. Belarbi, E. Cuvelier, A. Destée, B. Gressier, and M. C. Chartier-Harlin, "NADPH oxidases in Parkinson's disease: a systematic review," *Molecular Neurodegeneration*, vol. 12, no. 1, 2017.

[18] T. Kahles, P. Luedike, M. Endres et al., "NADPH Oxidase Plays a Central Role in Blood-Brain Barrier Damage in Experimental Stroke," *Stroke*, vol. 38, no. 11, pp. 3000–3006, 2007.

[19] A. Tarafdar and G. Pula, "The Role of NADPH Oxidases and Oxidative Stress in Neurodegenerative Disorders," *International Journal of Molecular Sciences*, vol. 19, no. 12, p. 3824, 2018.

[20] P. Hendrix, P. M. Foreman, M. R. Harrigan et al., "Endothelial Nitric Oxide Synthase Polymorphism Is Associated with Delayed Cerebral Ischemia Following Aneurysmal Subarachnoid Hemorrhage," *World Neurosurgery*, vol. 101, pp. 514–519, 2017.

[21] R. Mathew, N. Y. T. Fan, N. Yuan, P. N. Chander, M. H. Gewitz, and C. T. Stier Jr., "Inhibition of NOS enhances pulmonary vascular changes in stroke-prone spontaneously hypertensive rats," *American Journal of Physiology-Lung Cellular and Molecular Physiology*, vol. 278, no. 1, pp. L81–L89, 2000.

[22] O. Romero Kräuchi and A. M. Verger Bennasar, "Protective measures against cerebral ischemia following subarachnoid hemorrhage: Part 1," *Revista Española de Anestesiología y Reanimación*, vol. 58, no. 4, pp. 230–235, 2011.

[23] H. H. H. W. Schmidt, J. S. Pollock, M. Nakane, U. Förstermann, and F. Murad, "Ca^{2+}calmodulin-regulated nitric oxide synthases," *Cell Calcium*, vol. 13, no. 6-7, pp. 427–434, 1992.

[24] Y. Yuan, H. J. Granger, D. C. Zawieja, D. V. DeFily, and W. M. Chilian, "Histamine increases venular permeability via a phospholipase C-NO synthase-guanylate cyclase cascade," *American Journal of Physiology-Heart and Circulatory Physiology*, vol. 264, no. 5, pp. H1734–H1739, 1993.

[25] J. Haorah, B. Knipe, J. Leibhart, A. Ghorpade, and Y. Persidsky, "Alcohol-induced oxidative stress in brain endothelial cells causes blood-brain barrier dysfunction," *Journal of Leukocyte Biology*, vol. 78, no. 6, pp. 1223–1232, 2005.

[26] V. J. Thannickal and B. L. Fanburg, "Activation of an H_2O_2-generating NADH oxidase in human lung fibroblasts by transforming growth factor beta 1," *Journal of Biological Chemistry*, vol. 270, no. 51, pp. 30334–30338, 1995.

[27] J. M. McCord and R. S. Roy, "The pathophysiology of superoxide: roles in inflammation and ischemia," *Canadian Journal of Physiology and Pharmacology*, vol. 60, no. 11, pp. 1346–1352, 1982.

[28] D. Harman, "Aging: A Theory Based on Free Radical and Radiation Chemistry," *Journal of Gerontology*, vol. 11, no. 3, pp. 298–300, 1956.

[29] P. Jezek and L. Hlavatá, "Mitochondria in homeostasis of reactive oxygen species in cell, tissues, and organism," *The International Journal of Biochemistry & Cell Biology*, vol. 37, no. 12, pp. 2478–2503, 2005.

[30] D. B. Zorov, M. Juhaszova, and S. J. Sollott, "Mitochondrial Reactive Oxygen Species (ROS) and ROS-Induced ROS Release," *Physiological Reviews*, vol. 94, no. 3, pp. 909–950, 2014.

[31] K. Sas, H. Robotka, J. Toldi, and L. Vécsei, "Mitochondria, metabolic disturbances, oxidative stress and the kynurenine system, with focus on neurodegenerative disorders," *Journal of the Neurological Sciences*, vol. 257, no. 1-2, pp. 221–239, 2007.

[32] A. C. Andreazza, L. Shao, J. F. Wang, and L. T. Young, "Mitochondrial Complex I Activity and Oxidative Damage to Mitochondrial Proteins in the Prefrontal Cortex of Patients With Bipolar Disorder," *Archives of General Psychiatry*, vol. 67, no. 4, pp. 360–368, 2010.

[33] D. Ghezzi and M. Zeviani, "Assembly Factors of Human Mitochondrial Respiratory Chain Complexes: Physiology and Pathophysiology," *Advances in Experimental Medicine and Biology*, vol. 748, pp. 65–106, 2012.

[34] M. T. Islam, "Oxidative stress and mitochondrial dysfunction-linked neurodegenerative disorders," *Neurological Research*, vol. 39, no. 1, pp. 73–82, 2017.

[35] G. Cenini, A. Lloret, and R. Cascella, "Oxidative Stress in Neurodegenerative Diseases: From a Mitochondrial Point of View," *Oxidative Medicine and Cellular Longevity*, vol. 2019, Article ID 2105607, 18 pages, 2019.

[36] Y. Y. Hu, L. Li, X. H. Xian et al., "GLT-1 Upregulation as a Potential Therapeutic Target for Ischemic Brain Injury," *Current Pharmaceutical Design*, vol. 23, no. 33, pp. 5045–5055, 2017.

[37] W. Bai, W. L. Zhu, Y. L. Ning et al., "Dramatic increases in blood glutamate concentrations are closely related to traumatic brain injury-induced acute lung injury," *Scientific Reports*, vol. 7, no. 1, p. 5380, 2017.

[38] F. M. Ribeiro, L. B. Vieira, R. G. W. Pires, R. P. Olmo, and S. S. G. Ferguson, "Metabotropic glutamate receptors and neurodegenerative diseases," *Pharmacological Research*, vol. 115, pp. 179–191, 2017.

[39] S. Piccirillo, P. Castaldo, M. L. Macrì, S. Amoroso, and S. Magi, "Glutamate as a potential "survival factor" in an in vitro model of neuronal hypoxia/reoxygenation injury: leading role of the Na^+/Ca^{2+} exchanger," *Cell Death & Disease*, vol. 9, no. 7, 2018.

[40] Y.-Y. Yin, W.-P. Li, H.-L. Gong, F.-F. Zhu, W.-Z. Li, and G.-C. Wu, "Protective Effect of Astragaloside on Focal Cerebral Ischemia/Reperfusion Injury in Rats," *The American Journal of Chinese Medicine*, vol. 38, no. 3, pp. 517–527, 2012.

[41] M. Yudkoff, "Interactions in the Metabolism of Glutamate and the Branched-Chain Amino Acids and Ketoacids in the CNS," *Neurochemical Research*, vol. 42, no. 1, pp. 10–18, 2017.

[42] H. H. C. Cederberg, N. C. Uhd, and B. Brodin, "Glutamate Efflux at the Blood-Brain Barrier: Cellular Mechanisms and Potential Clinical Relevance," *Archives of Medical Research*, vol. 45, no. 8, pp. 639–645, 2014.

[43] W. Manucha, "Disfunción mitocondrial asociada a las vías del óxido nítrico en la neurotoxicidad por glutamato," *Clínica e Investigación en Arteriosclerosis*, vol. 29, no. 2, pp. 92–97, 2017.

[44] M. S. Runge, K. Molnar, and N. R. Madamanchi, ""Old" Hearts and Arteries: The Role of Oxidative Stress," *Transactions of the American Clinical and Climatological Association*, vol. 121, pp. 52–58, 2010.

[45] D. Berg and M. B. H. Youdim, "Role of Iron in Neurodegenerative Disorders," *Topics in Magnetic Resonance Imaging*, vol. 17, no. 1, pp. 5–17, 2006.

[46] C. Garza-Lombó, Y. Posadas, L. Quintanar, M. E. Gonsebatt, and R. Franco, "Neurotoxicity Linked to Dysfunctional Metal Ion Homeostasis and Xenobiotic Metal Exposure: Redox Signaling and Oxidative Stress," *Antioxidants & Redox Signaling*, vol. 28, no. 18, pp. 1669–1703, 2018.

[47] B. G. Trist, D. J. Hare, and K. L. Double, "A Proposed Mechanism for Neurodegeneration in Movement Disorders Characterized by Metal Dyshomeostasis and Oxidative Stress," *Cell Chemical Biology*, vol. 25, no. 7, pp. 807–816, 2018.

[48] J. Sripetchwandee, N. Pipatpiboon, N. Chattipakorn, and S. Chattipakorn, "Combined Therapy of Iron Chelator and Antioxidant Completely Restores Brain Dysfunction Induced by Iron Toxicity," *PLoS One*, vol. 9, no. 1, article e85115, 2014.

[49] T. Carbonell and R. Rama, "Iron, Oxidative Stress and Early Neurological Deterioration in Ischemic Stroke," *Current Medicinal Chemistry*, vol. 14, no. 8, pp. 857–874, 2007.

[50] G. Morris, M. Berk, A. F. Carvalho, M. Maes, A. J. Walker, and B. K. Puri, "Why should neuroscientists worry about iron? The emerging role of ferroptosis in the pathophysiology of neuroprogressive diseases," *Behavioural Brain Research*, vol. 341, pp. 154–175, 2018.

[51] R. M. Uranga and G. A. Salvador, "Unraveling the Burden of Iron in Neurodegeneration: Intersections with Amyloid Beta Peptide Pathology," *Oxidative Medicine and Cellular Longevity*, vol. 2018, Article ID 2850341, 12 pages, 2018.

[52] K. P. Devi, D. S. Malar, S. F. Nabavi et al., "Kaempferol and inflammation: From chemistry to medicine," *Pharmacological Research*, vol. 99, pp. 1–10, 2015.

[53] M. M. Zaleska, M. L. T. Mercado, J. Chavez, G. Z. Feuerstein, M. N. Pangalos, and A. Wood, "The development of stroke therapeutics: promising mechanisms and translational challenges," *Neuropharmacology*, vol. 56, no. 2, pp. 329–341, 2009.

[54] S. L. Joice, F. Mydeen, P. O. Couraud et al., "Modulation of blood-brain barrier permeability by neutrophils: in vitro and in vivo studies," *Brain Research*, vol. 1298, pp. 13–23, 2009.

[55] J. V. Bannister, P. Bellavite, A. Davoli, P. J. Thornalley, and F. Rossi, "The generation of hydroxyl radicals following superoxide production by neutrophil NADPH oxidase," *FEBS Letters*, vol. 150, no. 2, pp. 300–302, 1982.

[56] L. Morgan, B. Shah, L. E. Rivers et al., "Inflammation and dephosphorylation of the tight junction protein occludin in an experimental model of multiple sclerosis," *Neuroscience*, vol. 147, no. 3, pp. 664–673, 2007.

[57] L. Qin and F. T. Crews, "NADPH oxidase and reactive oxygen species contribute to alcohol-induced microglial activation and neurodegeneration," *Journal of Neuroinflammation*, vol. 9, no. 1, 2012.

[58] V. Waetzig, K. Czeloth, U. Hidding et al., "c-Jun N-terminal kinases (JNKs) mediate pro-inflammatory actions of microglia," *Glia*, vol. 50, no. 3, pp. 235–246, 2005.

[59] Y. Zhou, E. A. Ling, and S. T. Dheen, "Dexamethasone suppresses monocyte chemoattractant protein-1 production via mitogen activated protein kinase phosphatase-1 dependent inhibition of Jun N-terminal kinase and p38 mitogen-activated protein kinase in activated rat microglia," *Journal of Neurochemistry*, vol. 102, no. 3, pp. 667–678, 2007.

[60] J. R. Caso, M. A. Moro, P. Lorenzo, I. Lizasoain, and J. C. Leza, "Involvement of IL-1β in acute stress-induced worsening of cerebral ischaemia in rats," *European Neuropsychopharmacology*, vol. 17, no. 9, pp. 600–607, 2007.

[61] J. L. Yang, S. Mukda, and S. D. Chen, "Diverse roles of mitochondria in ischemic stroke," *Redox Biology*, vol. 16, pp. 263–275, 2018.

[62] K. L. Rock, E. Latz, F. Ontiveros, and H. Kono, "The Sterile Inflammatory Response," *Annual Review of Immunology*, vol. 28, no. 1, pp. 321–342, 2010.

[63] L. Minutoli, D. Puzzolo, M. Rinaldi et al., "ROS-Mediated NLRP3 Inflammasome Activation in Brain, Heart, Kidney, and Testis Ischemia/Reperfusion Injury," *Oxidative Medicine and Cellular Longevity*, vol. 2016, Article ID 2183026, 10 pages, 2016.

[64] K. Mortezaee, N. Khanlarkhani, C. Beyer, and A. Zendedel, "Inflammasome: Its role in traumatic brain and spinal cord injury," *Journal of Cellular Physiology*, vol. 233, no. 7, pp. 5160–5169, 2018.

[65] W. Liu, Y. Chen, J. Meng et al., "Ablation of caspase-1 protects against TBI-induced pyroptosis in vitro and in vivo," *Journal of Neuroinflammation*, vol. 15, no. 1, 2018.

[66] S. W. Lee, S. Gajavelli, M. S. Spurlock et al., "Microglial Inflammasome Activation in Penetrating Ballistic-Like Brain Injury," *Journal of Neurotrauma*, vol. 35, no. 14, pp. 1681–1693, 2018.

[67] X. Xia, L. Lei, S. Wang, J. Hu, and G. Zhang, "Necroptosis and its role in infectious diseases," *Apoptosis*, vol. 25, no. 3-4, pp. 169–178, 2020.

[68] M. K. Khoury, K. Gupta, S. R. Franco, and B. Liu, "Necroptosis in the pathophysiology of disease," *The American Journal of Pathology*, vol. 190, no. 2, pp. 272–285, 2020.

[69] T. Molnár, A. Mázló, V. Tslaf, A. G. Szöllősi, G. Emri, and G. Koncz, "Current translational potential and underlying molecular mechanisms of necroptosis," *Cell Death & Disease*, vol. 10, no. 11, 2019.

[70] M. E. Choi, D. R. Price, S. W. Ryter, and A. M. K. Choi, "Necroptosis: a crucial pathogenic mediator of human disease," *JCI Insight*, vol. 4, no. 15, 2019.

[71] Y. Wang, L. Guo, J. Wang, W. Shi, Z. Xia, and B. Li, "Necrostatin-1 ameliorates the pathogenesis of experimental autoimmune encephalomyelitis by suppressing apoptosis and necroptosis of oligodendrocyte precursor cells," *Experimental and Therapeutic Medicine*, vol. 18, no. 5, pp. 4113–4119, 2019.

[72] N. Salvadores and F. A. Court, "The necroptosis pathway and its role in age-related neurodegenerative diseases: will it open up new therapeutic avenues in the next decade?," *Expert Opinion on Therapeutic Targets*, pp. 1–15, 2020.

[73] T. Kalogeris, C. P. Baines, M. Krenz, and R. J. Korthuis, "Ischemia/Reperfusion," *Comprehensive Physiology*, vol. 7, no. 1, pp. 113–170, 2016.

[74] D. W. Zhang, J. Shao, J. Lin et al., "RIP3, an Energy Metabolism Regulator That Switches TNF-Induced Cell Death from Apoptosis to Necrosis," *Science*, vol. 325, no. 5938, pp. 332–336, 2009.

[75] A. Iannielli, S. Bido, L. Folladori et al., "Pharmacological Inhibition of Necroptosis Protects from Dopaminergic Neuronal Cell Death in Parkinson's Disease Models," *Cell Reports*, vol. 22, no. 8, pp. 2066–2079, 2018.

[76] Z. Yang, Y. Wang, Y. Zhang et al., "RIP3 targets pyruvate dehydrogenase complex to increase aerobic respiration in TNF-induced necroptosis," *Nature Cell Biology*, vol. 20, no. 2, pp. 186–197, 2018.

[77] H. Bauer and A. Traweger, "Tight Junctions of the Blood-Brain Barrier – A Molecular Gatekeeper," *CNS & Neurological Disorders - Drug Targets*, vol. 15, no. 9, pp. 1016–1029, 2016.

[78] R. F. Haseloff, S. Dithmer, L. Winkler, H. Wolburg, and I. E. Blasig, "Transmembrane proteins of the tight junctions at the blood-brain barrier: structural and functional aspects," *Seminars in Cell & Developmental Biology*, vol. 38, pp. 16–25, 2015.

[79] Y. Xue, J. T. He, K. K. Zhang, L. J. Chen, Q. Wang, and X. L. Xie, "Methamphetamine reduces expressions of tight junction proteins, rearranges F-actin cytoskeleton and increases the blood brain barrier permeability via the RhoA/ROCK-dependent pathway," *Biochemical and Biophysical Research Communications*, vol. 509, no. 2, pp. 395–401, 2019.

[80] Z. Redzic, "Molecular biology of the blood-brain and the blood-cerebrospinal fluid barriers: similarities and differences," *Fluids and Barriers of the CNS*, vol. 8, no. 1, 2011.

[81] A. Jong, C. H. Wu, N. V. Prasadarao et al., "Invasion of Cryptococcus neoformans into human brain microvascular endothelial cells requires protein kinase C-alpha activation," *Cellular Microbiology*, vol. 10, no. 9, pp. 1854–1865, 2008.

[82] A. W. Vorbrodt and D. H. Dobrogowska, "Molecular anatomy of intercellular junctions in brain endothelial and epithelial barriers: electron microscopist's view," *Brain Research Reviews*, vol. 42, no. 3, pp. 221–242, 2003.

[83] A. C. Luissint, C. Federici, F. Guillonneau et al., "Guanine Nucleotide-Binding Protein Gαi2: A New Partner of Claudin-5 that Regulates Tight Junction Integrity in Human Brain Endothelial Cells," *Journal of Cerebral Blood Flow & Metabolism*, vol. 32, no. 5, pp. 860–873, 2012.

[84] R. Daneman, L. Zhou, A. A. Kebede, and B. A. Barres, "Pericytes are required for blood-brain barrier integrity during embryogenesis," *Nature*, vol. 468, no. 7323, pp. 562–566, 2010.

[85] S. Liebner, C. J. Czupalla, and H. Wolburg, "Current concepts of blood-brain barrier development," *The International Journal of Developmental Biology*, vol. 55, no. 4-5, pp. 467–476, 2011.

[86] J. Correale and A. Villa, "Cellular Elements of the Blood-Brain Barrier," *Neurochemical Research*, vol. 34, no. 12, pp. 2067–2077, 2009.

[87] M. Ueno, "Molecular Anatomy of the Brain Endothelial Barrier: An Overview of the Distributional Features," *Current Medicinal Chemistry*, vol. 14, no. 11, pp. 1199–1206, 2007.

[88] H. Xu, Y. Liu, D. Wang, and Z. Zhang, "Shenmai injection maintains blood-brain barrier integrity following focal cerebral ischemia via modulating the expression and trafficking of occludin in lipid rafts," *Journal of Ethnopharmacology*, vol. 237, pp. 55–63, 2019.

[89] Z. Yang, C. Huang, Y. Wu, B. Chen, W. Zhang, and J. Zhang, "Autophagy protects the blood-brain barrier through regulating the dynamic of claudin-5 in short-term starvation," *Frontiers in Physiology*, vol. 10, 2019.

[90] F. J. Irudayanathan, N. Wang, X. Wang, and S. Nangia, "Architecture of the paracellular channels formed by claudins of the blood–brain barrier tight junctions," *Annals of the New York Academy of Sciences*, vol. 1405, no. 1, pp. 131–146, 2017.

[91] W. Jia, R. Lu, T. A. Martin, and W. G. Jiang, "The role of claudin-5 in blood-brain barrier (BBB) and brain metastases (Review)," *Molecular Medicine Reports*, vol. 9, no. 3, pp. 779–785, 2014.

[92] H. Y. Yu, Y. B. Cai, and Z. Liu, "Activation of AMPK improves lipopolysaccharide-induced dysfunction of the blood–brain barrier in mice," *Brain Injury*, vol. 29, no. 6, pp. 777–784, 2015.

[93] N. Sladojevic, S. M. Stamatovic, R. F. Keep et al., "Inhibition of junctional adhesion molecule-A/LFA interaction attenuates leukocyte trafficking and inflammation in brain ischemia/reperfusion injury," *Neurobiology of Disease*, vol. 67, pp. 57–70, 2014.

[94] X. S. Wang, H. L. Fang, Y. Chen et al., "Idazoxan reduces blood-brain barrier damage during experimental autoimmune encephalomyelitis in mouse," *European Journal of Pharmacology*, vol. 736, pp. 70–76, 2014.

[95] S. M. Seok, J. M. Kim, T. Y. Park, E. J. Baik, and S. H. Lee, "Fructose-$_1$,6-bisphosphate ameliorates lipopolysaccharide-induced dysfunction of blood-brain barrier," *Archives of Pharmacal Research*, vol. 36, no. 9, pp. 1149–1159, 2013.

[96] J. J. Lochhead, P. T. Ronaldson, and T. P. Davis, "Hypoxic Stress and Inflammatory Pain Disrupt Blood-Brain Barrier Tight Junctions: Implications for Drug Delivery to the Central Nervous System," *The AAPS Journal*, vol. 19, no. 4, pp. 910–920, 2017.

[97] A. C. Luissint, C. Artus, F. Glacial, K. Ganeshamoorthy, and P. O. Couraud, "Tight junctions at the blood brain barrier: physiological architecture and disease-associated dysregulation," *Fluids and Barriers of the CNS*, vol. 9, no. 1, 2012.

[98] L. Sanchez-Covarrubias, L. M. Slosky, B. J. Thompson, T. P. Davis, and P. T. Ronaldson, "Transporters at CNS Barrier Sites: Obstacles or Opportunities for Drug Delivery?," *Current Pharmaceutical Design*, vol. 20, no. 10, pp. 1422–1449, 2014.

[99] D. S. Miller, "Regulation of ABC transporters at the blood-brain barrier," *Clinical Pharmacology & Therapeutics*, vol. 97, no. 4, pp. 395–403, 2015.

[100] A. Mahringer and G. Fricker, "ABC transporters at the blood-brain barrier," *Expert Opinion on Drug Metabolism & Toxicology*, vol. 12, no. 5, pp. 499–508, 2016.

[101] A. M. Johnston, L. Pirola, and E. Van Obberghen, "Molecular mechanisms of insulin receptor substrate protein-mediated modulation of insulin signalling," *FEBS Letters*, vol. 546, no. 1, pp. 32–36, 2003.

[102] N. Yu, Q. Di, H. Liu et al., "Nuclear Factor-Kappa B Activity Regulates Brain Expression of P-Glycoprotein in the Kainic Acid-Induced Seizure Rats," *Mediators of Inflammation*, vol. 2011, Article ID 670613, 10 pages, 2011.

[103] X. Wang, C. R. Campos, J. C. Peart et al., "Nrf2 Upregulates ATP Binding Cassette Transporter Expression and Activity at the Blood–Brain and Blood–Spinal Cord Barriers," *Journal of Neuroscience*, vol. 34, no. 25, pp. 8585–8593, 2014.

[104] G. Kooij, M. R. Mizee, J. van Horssen et al., "Adenosine triphosphate-binding cassette transporters mediate chemokine (C-C motif) ligand 2 secretion from reactive astrocytes: relevance to multiple sclerosis pathogenesis," *Brain*, vol. 134, no. 2, pp. 555–570, 2011.

[105] Y. Zhang, Y. Zhang, K. Sun, Z. Meng, and L. Chen, "The SLC transporter in nutrient and metabolic sensing, regulation, and drug development," *Journal of Molecular Cell Biology*, vol. 11, no. 1, pp. 1–13, 2019.

[106] E. Barone, G. Cenini, F. di Domenico et al., "Long-term high-dose atorvastatin decreases brain oxidative and nitrosative stress in a preclinical model of Alzheimer disease: a novel mechanism of action," *Pharmacological Research*, vol. 63, no. 3, pp. 172–180, 2011.

[107] D. A. Butterfield, E. Barone, and C. Mancuso, "Cholesterol-independent neuroprotective and neurotoxic activities of statins: perspectives for statin use in Alzheimer disease and other age-related neurodegenerative disorders," *Pharmacological Research*, vol. 64, no. 3, pp. 180–186, 2011.

[108] K. R. Hallows, G. P. Kobinger, J. M. Wilson, L. A. Witters, and J. K. Foskett, "Physiological modulation of CFTR activity by AMP-activated protein kinase in polarized T84 cells," *American Journal of Physiology-Cell Physiology*, vol. 284, no. 5, pp. C1297–C1308, 2003.

[109] H. Klein, L. Garneau, N. T. N. Trinh et al., "Inhibition of the KCa3.1 channels by AMP-activated protein kinase in human airway epithelial cells," *American Journal of Physiology-Cell Physiology*, vol. 296, no. 2, pp. C285–C295, 2009.

[110] S. A. Fraser, I. Gimenez, N. Cook et al., "Regulation of the renal-specific Na+–K+–2Cl– co-transporter NKCC2 by AMP-activated protein kinase (AMPK)," *Biochemical Journal*, vol. 405, no. 1, pp. 85–93, 2007.

[111] S. Prasad, R. K. Sajja, M. A. Kaisar et al., "Role of Nrf2 and protective effects of Metformin against tobacco smoke-induced cerebrovascular toxicity," *Redox Biology*, vol. 12, pp. 58–69, 2017.

[112] V. Castro, M. Skowronska, J. Lombardi et al., "Occludin regulates glucose uptake and ATP production in pericytes by influencing AMP-activated protein kinase activity," *Journal of Cerebral Blood Flow & Metabolism*, vol. 38, no. 2, pp. 317–332, 2017.

[113] S. M. Reinhard, K. Razak, and I. M. Ethell, "A delicate balance: role of MMP-9 in brain development and pathophysiology of neurodevelopmental disorders," *Frontiers in Cellular Neuroscience*, vol. 9, 2015.

[114] S. Rivera, L. García-González, M. Khrestchatisky, and K. Baranger, "Metalloproteinases and their tissue inhibitors in Alzheimer's disease and other neurodegenerative disorders," *Cellular and Molecular Life Sciences*, vol. 76, no. 16, pp. 3167–3191, 2019.

[115] A. Trivedi, L. J. Noble-Haeusslein, J. M. Levine, A. D. Santucci, T. M. Reeves, and L. L. Phillips, "Matrix metalloproteinase signals following neurotrauma are right on cue," *Cellular and Molecular Life Sciences*, vol. 76, no. 16, pp. 3141–3156, 2019.

[116] S. Feng, J. Cen, Y. Huang et al., "Matrix metalloproteinase-2 and -9 secreted by leukemic cells increase the permeability of blood-brain barrier by disrupting tight junction proteins," *PLoS One*, vol. 6, no. 8, article e20599, 2011.

[117] M. Lischper, S. Beuck, G. Thanabalasundaram, C. Pieper, and H. J. Galla, "Metalloproteinase mediated occludin cleavage in the cerebral microcapillary endothelium under pathological conditions," *Brain Research*, vol. 1326, pp. 114–127, 2010.

[118] J. Haorah, S. H. Ramirez, K. Schall, D. Smith, R. Pandya, and Y. Persidsky, "Oxidative stress activates protein tyrosine kinase and matrix metalloproteinases leading to blood-brain barrier dysfunction," *Journal of Neurochemistry*, vol. 101, no. 2, pp. 566–576, 2007.

[119] Z. Yang, R. Fan, P. Sun et al., "Rhubarb attenuates cerebral edema via inhibition of the extracellular signal-regulated kinase pathway following traumatic brain injury in rats," *Pharmacognosy Magazine*, vol. 14, no. 53, pp. 134–139, 2018.

[120] P. M. Abdul-Muneer, N. Chandra, and J. Haorah, "Interactions of oxidative stress and neurovascular inflammation in the pathogenesis of traumatic brain injury," *Molecular Neurobiology*, vol. 51, no. 3, pp. 966–979, 2015.

[121] P. M. Abdul-Muneer, H. Schuetz, F. Wang et al., "Induction of oxidative and nitrosative damage leads to cerebrovascular inflammation in an animal model of mild traumatic brain injury induced by primary blast," *Free Radical Biology and Medicine*, vol. 60, pp. 282–291, 2013.

[122] T. Higashida, C. W. Kreipke, J. A. Rafols et al., "The role of hypoxia-inducible factor-1α, aquaporin-4, and matrix metalloproteinase-9 in blood-brain barrier disruption and brain edema after traumatic brain injury," *Journal of Neurosurgery*, vol. 114, no. 1, pp. 92–101, 2011.

[123] M. D. Sweeney, A. P. Sagare, and B. V. Zlokovic, "Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders," *Nature Reviews Neurology*, vol. 14, no. 3, pp. 133–150, 2018.

[124] A. C. C. da Fonseca, D. Matias, C. Garcia et al., "The impact of microglial activation on blood-brain barrier in brain diseases," *Frontiers in Cellular Neuroscience*, vol. 8, 2014.

[125] S. R. Kim, Y. H. Bae, S. K. Bae et al., "Visfatin enhances ICAM-1 and VCAM-1 expression through ROS-dependent NF-κB activation in endothelial cells," *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research*, vol. 1783, no. 5, pp. 886–895, 2008.

[126] S. Etienne-Manneville, J. B. Manneville, P. Adamson, B. Wilbourn, J. Greenwood, and P. O. Couraud, "ICAM-1-Coupled Cytoskeletal Rearrangements and Transendothelial Lymphocyte Migration Involve Intracellular Calcium Signaling in Brain Endothelial Cell Lines," *The Journal of Immunology*, vol. 165, no. 6, pp. 3375–3383, 2000.

[127] A. Prat, K. Biernacki, K. Wosik, and J. P. Antel, "Glial cell influence on the human blood-brain barrier," *Glia*, vol. 36, no. 2, pp. 145–155, 2001.

[128] K. Färber, G. Cheung, D. Mitchell et al., "C1q, the recognition subcomponent of the classical pathway of complement, drives microglial activation," *Journal of Neuroscience Research*, vol. 87, no. 3, pp. 644–652, 2009.

[129] N. J. Lynch, C. L. Willis, C. C. Nolan et al., "Microglial activation and increased synthesis of complement component C1q precedes blood-brain barrier dysfunction in rats," *Molecular Immunology*, vol. 40, no. 10, pp. 709–716, 2004.

[130] J. P. de Rivero Vaccari, W. D. Dietrich, and R. W. Keane, "ctivation and Regulation of Cellular Inflammasomes: Gaps in Our Knowledge for Central Nervous System Injury," *Journal of Cerebral Blood Flow & Metabolism*, vol. 34, no. 3, pp. 369–375, 2014.

[131] G. Yang, Y. Meng, W. Li et al., "Neuronal MCP-1 Mediates Microglia Recruitment and Neurodegeneration Induced by the Mild Impairment of Oxidative Metabolism," *Brain Pathology*, vol. 21, no. 3, pp. 279–297, 2011.

[132] W. A. Banks, A. Kovac, and Y. Morofuji, "Neurovascular unit crosstalk: pericytes and astrocytes modify cytokine secretion patterns of brain endothelial cells," *Journal of Cerebral Blood Flow & Metabolism*, vol. 38, no. 6, pp. 1104–1118, 2017.

[133] L. Lue, S. Yan, D. Stern, and D. Walker, "Preventing Activation of Receptor for Advanced Glycation Endproducts in Alzheimers Disease," *Current Drug Target -CNS & Neurological Disorders*, vol. 4, no. 3, pp. 249–266, 2005.

[134] J. I. Alvarez, T. Katayama, and A. Prat, "Glial influence on the blood brain barrier," *Glia*, vol. 61, no. 12, pp. 1939–1958, 2013.

[135] J. A. Lee, "Neuronal Autophagy: A Housekeeper or a Fighter in Neuronal Cell Survival?," *Experimental Neurobiology*, vol. 21, no. 1, pp. 1–8, 2012.

[136] X. Tan, S. Azad, and X. Ji, "Hypoxic Preconditioning Protects SH-SY5Y Cell against Oxidative Stress through Activation of Autophagy," *Cell Transplantation*, vol. 27, no. 12, pp. 1753–1762, 2018.

[137] W. Wang, S. M. Luo, J. Y. Ma, W. Shen, and S. Yin, "Cytotoxicity and DNA Damage Caused from Diazinon Exposure by Inhibiting the PI3K-AKT Pathway in Porcine Ovarian Granulosa Cells," *Journal of Agricultural and Food Chemistry*, vol. 67, no. 1, pp. 19–31, 2018.

[138] X. Zhu, K. Shen, Y. Bai et al., "NADPH oxidase activation is required for pentylenetetrazole kindling-induced hippocampal autophagy," *Free Radical Biology and Medicine*, vol. 94, pp. 230–242, 2016.

[139] Y. Li, P. Wu, J. Dai et al., "Inhibition of mTOR Alleviates Early Brain Injury After Subarachnoid Hemorrhage Via Relieving Excessive Mitochondrial Fission," *Cellular and Molecular Neurobiology*, vol. 40, no. 4, pp. 629–642, 2020.

[140] N. Wang, J. He, C. Pan et al., "Resveratrol Activates Autophagy via the AKT/mTOR Signaling Pathway to Improve Cognitive Dysfunction in Rats With Chronic Cerebral Hypoperfusion," *Frontiers in Neuroscience*, vol. 13, 2019.

[141] D. H. Choi, J. H. Yun, and J. Lee, "Protective effect of the imidazoline I2 receptor agonist 2-BFI on oxidative cytotoxicity in astrocytes," *Biochemical and Biophysical Research Communications*, vol. 503, no. 4, pp. 3011–3016, 2018.

[142] Q. Jiang, Y. Gao, C. Wang et al., "Nitration of TRPM2 as a Molecular Switch Induces Autophagy During Brain Pericyte Injury," *Antioxidants & Redox Signaling*, vol. 27, no. 16, pp. 1297–1316, 2017.

[143] E. Janda, A. Lascala, C. Carresi et al., "Parkinsonian toxin-induced oxidative stress inhibits basal autophagy in astrocytes via NQO2/quinone oxidoreductase 2: Implications for neuroprotection," *Autophagy*, vol. 11, no. 7, pp. 1063–1080, 2015.

[144] Y. Yin, G. Sun, E. Li, K. Kiselyov, and D. Sun, "ER stress and impaired autophagy flux in neuronal degeneration and brain injury," *Ageing Research Reviews*, vol. 34, pp. 3–14, 2017.

[145] A. K. Singh, S. Singh, V. K. Tripathi, A. Bissoyi, G. Garg, and S. I. Rizvi, "Rapamycin Confers Neuroprotection Against Aging-Induced Oxidative Stress, Mitochondrial Dysfunction, and Neurodegeneration in Old Rats Through Activation of Autophagy," *Rejuvenation Research*, vol. 22, no. 1, pp. 60–70, 2019.

[146] H. Xiao, M. Deng, B. Yang, Z. Hu, and J. Tang, "Pretreatment with 17β-Estradiol Attenuates Cerebral Ischemia-Induced Blood-Brain Barrier Disruption in Aged Rats: Involvement of Antioxidant Signaling," *Neuroendocrinology*, vol. 106, no. 1, pp. 20–29, 2017.

[147] A. Janyou, P. Wicha, J. Jittiwat, A. Suksamrarn, C. Tocharus, and J. Tocharus, "Dihydrocapsaicin Attenuates Blood Brain Barrier and Cerebral Damage in Focal Cerebral Ischemia/Reperfusion via Oxidative Stress and Inflammatory," *Scientific Reports*, vol. 7, no. 1, article 10556, 2017.

[148] S. Hu, Y. Wu, B. Zhao et al., "Panax notoginseng Saponins Protect Cerebral Microvascular Endothelial Cells against Oxygen-Glucose Deprivation/Reperfusion-Induced Barrier Dysfunction via Activation of PI3K/Akt/Nrf2 Antioxidant Signaling Pathway," *Molecules*, vol. 23, no. 11, 2018.

[149] D. D. Zhang, M. J. Zou, Y. T. Zhang et al., "A novel IL-1RA-PEP fusion protein with enhanced brain penetration ameliorates cerebral ischemia-reperfusion injury by inhibition of oxidative stress and neuroinflammation," *Experimental Neurology*, vol. 297, pp. 1–13, 2017.

[150] H. Li, A. Gao, D. Feng et al., "Evaluation of the Protective Potential of Brain Microvascular Endothelial Cell Autophagy on Blood–Brain Barrier Integrity During Experimental Cerebral Ischemia–Reperfusion Injury," *Translational Stroke Research*, vol. 5, no. 5, pp. 618–626, 2014.

[151] W. Xu, T. Li, L. Gao et al., "Sodium Benzoate Attenuates Secondary Brain Injury by Inhibiting Neuronal Apoptosis and Reducing Mitochondria-Mediated Oxidative Stress in a Rat Model of Intracerebral Hemorrhage: Possible Involvement of DJ-1/Akt/IKK/NFκB Pathway," *Frontiers in Molecular Neuroscience*, vol. 12, 2019.

[152] J. Shi, G. Wu, X. Zou, and K. Jiang, "Oleuropein protects intracerebral hemorrhage-induced disruption of blood-brain barrier through alleviation of oxidative stress," *Pharmacological Reports*, vol. 69, no. 6, pp. 1206–1212, 2017.

[153] Y. J. Yauger, S. Bermudez, K. E. Moritz, E. Glaser, B. Stoica, and K. R. Byrnes, "Iron accentuated reactive oxygen species release by NADPH oxidase in activated microglia contributes to oxidative stress in vitro," *Journal of Neuroinflammation*, vol. 16, no. 1, 2019.

[154] Z. Wang, F. Zhou, Y. Dou et al., "Melatonin Alleviates Intracerebral Hemorrhage-Induced Secondary Brain Injury in Rats via Suppressing Apoptosis, Inflammation, Oxidative Stress, DNA Damage, and Mitochondria Injury," *Translational Stroke Research*, vol. 9, no. 1, pp. 74–91, 2018.

[155] L. Lu, M. Wang, F. Yuan, X. Wei, and W. Li, "Roles of elevated 20-HETE in the breakdown of blood brain barrier and the severity of brain edema in experimental traumatic Brain Injury," *Molecular Medicine Reports*, vol. 17, no. 5, pp. 7339–7345, 2018.

[156] Y. L. Liu, Z. M. Xu, G. Y. Yang et al., "Sesamin alleviates blood-brain barrier disruption in mice with experimental traumatic brain injury," *Acta Pharmacologica Sinica*, vol. 38, no. 11, pp. 1445–1455, 2017.

[157] Z. M. Liu, Q. X. Chen, Z. B. Chen et al., "RIP3 deficiency protects against traumatic brain injury (TBI) through suppressing oxidative stress, inflammation and apoptosis: dependent on AMPK pathway," *Biochemical and Biophysical Research Communications*, vol. 499, no. 2, pp. 112–119, 2018.

[158] J. Zhou, H. Wang, R. Shen et al., "Mitochondrial-targeted antioxidant MitoQ provides neuroprotection and reduces neuronal apoptosis in experimental traumatic brain injury possibly via the Nrf2-ARE pathway," *American Journal of Translational Research*, vol. 10, no. 6, pp. 1887–1899, 2018.

[159] K. Murphy, K. Llewellyn, S. Wakser et al., "Mini-GAGR, an intranasally applied polysaccharide, activates the neuronal Nrf2-mediated antioxidant defense system," *Journal of Biological Chemistry*, vol. 293, no. 47, pp. 18242–18269, 2018.

[160] N. Sajjad, A. Wani, A. Sharma et al., "Artemisia amygdalina upregulates Nrf2 and protects neurons against oxidative stress in Alzheimer disease," *Cellular and Molecular Neurobiology*, vol. 39, no. 3, pp. 387–399, 2019.

[161] X. Gu, H. Zhao, J. Zhou et al., "Effects of Huang-Lian-Jie-Du Decoction on Oxidative Stress and AMPK-SIRT1 Pathway in Alzheimer's Disease Rat," *Evidence-Based Complementary and Alternative Medicine*, vol. 2020, 12 pages, 2020.

[162] L.-M. Zhang, R.-R. Zhen, C. Gu et al., "Chinese medicine Di-Huang-Yi-Zhi protects PC12 cells from H2O2-induced apoptosis by regulating ROS-ASK1-JNK/p38 MAPK signaling,"

BMC Complementary Medicine and Therapies, vol. 20, no. 1, p. 54, 2020.

[163] Q. Pan, K. Guo, Y. Li, and Q. Tu, "Role of TXNIP-mediated oxidative stress in delaying Alzheimer's disease by estrogen," *Zhong Nan Da Xue Xue Bao Yi Xue Ban*, vol. 44, no. 12, pp. 1360–1366, 2019.

[164] C. Funke, A. S. Soehn, J. Tomiuk, O. Riess, and D. Berg, "Genetic analysis of coding SNPs in blood-brain barrier transporter MDR1 in European Parkinson's disease patients," *Journal of Neural Transmission*, vol. 116, no. 4, pp. 443–450, 2009.

[165] N. Ansari, F. Khodagholi, and M. Amini, "2-Ethoxy-4,5-diphenyl-1,3-oxazine-6-one activates the Nrf2/HO-1 axis and protects against oxidative stress-induced neuronal death," *European Journal of Pharmacology*, vol. 658, no. 2-3, pp. 84–90, 2011.

[166] T. Yan, Y. Sun, G. Gong et al., "The neuroprotective effect of schisandrol A on 6-OHDA-induced PD mice may be related to PI3K/AKT and IKK/IκBα/NF-κB pathway," *Experimental Gerontology*, vol. 128, p. 110743, 2019.

[167] J. Ren, L. Yuan, W. Wang et al., "Tricetin protects against 6-OHDA-induced neurotoxicity in Parkinson's disease model by activating Nrf2/HO-1 signaling pathway and preventing mitochondria- dependent apoptosis pathway," *Toxicology and Applied Pharmacology*, vol. 378, p. 114617, 2019.

[168] H. Chen, J. Xu, Y. Lv et al., "Proanthocyanidins exert a neuroprotective effect via ROS/JNK signaling in MPTP-induced Parkinson's disease models invitro and invivo," *Molecular Medicine Reports*, vol. 18, pp. 4913–4921, 2018.

[169] C. Zhang, W. Liang, H. Wang et al., "γ-Oryzanol mitigates oxidative stress and prevents mutant SOD1-Related neurotoxicity in _Drosophila_ and cell models of amyotrophic lateral sclerosis," *Neuropharmacology*, vol. 160, p. 107777, 2019.

[170] D. J. Flis, K. Dzik, J. J. Kaczor et al., "Swim training modulates skeletal muscle energy metabolism, oxidative stress, and mitochondrial cholesterol content in amyotrophic lateral sclerosis mice," *Oxidative Medicine and Cellular Longevity*, vol. 2018, 12 pages, 2018.

[171] W. Wang and W. Hu, "Salvianolic acidï¿½B recovers cognitive deficits and angiogenesis in a cerebral small vessel disease rat model via the STAT3/VEGF signaling pathway," *Molecular Medicine Reports*, vol. 17, pp. 3146–3151, 2017.

[172] D. Guan, Y. Li, X. Peng, H. Zhao, Y. Mao, and Y. Cui, "Thymoquinone protects against cerebral small vessel disease: role of antioxidant and anti-inflammatory activities," *Journal of biological regulators and homeostatic agents*, vol. 32, no. 2, pp. 225–231, 2018.

[173] G. Mukundan and D. J. Seidenwurm, "Economic and societal aspects of stroke management," *Neuroimaging Clinics of North America*, vol. 28, no. 4, pp. 683–689, 2018.

[174] R. L. Jayaraj, S. Azimullah, R. Beiram, F. Y. Jalal, and G. A. Rosenberg, "Neuroinflammation: friend and foe for ischemic stroke," *Journal of Neuroinflammation*, vol. 16, no. 1, p. 142, 2019.

[175] J. Yang, J. Qi, B. Xiu, B. Yang, C. Niu, and H. Yang, "Reactive oxygen species play a biphasic role in brain ischemia," *Journal of Investigative Surgery*, vol. 32, no. 2, pp. 97–102, 2017.

[176] M.-S. Sun, H. Jin, X. Sun et al., "Free radical damage in ischemia-reperfusion injury: an obstacle in acute ischemic stroke after revascularization therapy," *Oxidative Medicine and Cellular Longevity*, vol. 2018, 17 pages, 2018.

[177] V. Singh, P. Krishan, and R. Shri, "Improvement of memory and neurological deficit with Ocimum basilicum L. extract after ischemia reperfusion induced cerebral injury in mice," *Metabolic Brain Disease*, vol. 33, no. 4, pp. 1111–1120, 2018.

[178] D. W. Busija and P. V. Katakam, "Mitochondrial mechanisms in cerebral vascular control: shared signaling pathways with preconditioning," *Journal of Vascular Research*, vol. 51, no. 3, pp. 175–189, 2014.

[179] X.-Y. Zhao, M.-H. Lu, D.-J. Yuan et al., "Mitochondrial dysfunction in neural injury," *Frontiers in Neuroscience*, vol. 13, 2019.

[180] K. Niizuma, H. Yoshioka, H. Chen et al., "Mitochondrial and apoptotic neuronal death signaling pathways in cerebral ischemia," *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, vol. 1802, no. 1, pp. 92–99, 2010.

[181] S. Liu, D. Adewole, L. Yu et al., "Rutin attenuates inflammatory responses induced by lipopolysaccharide in an in vitro mouse muscle cell (C2C12) model," *Poultry Science*, vol. 98, no. 7, pp. 2756–2764, 2019.

[182] N. Sadeghian, J. Shadman, A. Moradi, M. Ghasem Golmohammadi, and H. Panahpour, "Calcitriol protects the Blood-Brain Barrier integrity against ischemic stroke and reduces vasogenic brain edema via antioxidant and antiapoptotic actions in rats," *Brain Research Bulletin*, vol. 150, pp. 281–289, 2019.

[183] C. Yang, K. E. Hawkins, S. Doré, and E. Candelario-Jalil, "Neuroinflammatory mechanisms of blood-brain barrier damage in ischemic stroke," *American Journal of Physiology-Cell Physiology*, vol. 316, no. 2, pp. C135–C153, 2019.

[184] Z. Li, J. Yulei, J. Yaqing et al., "Protective effects of tetramethylpyrazine analogue Z-11 on cerebral ischemia reperfusion injury," *European Journal of Pharmacology*, vol. 844, pp. 156–164, 2019.

[185] L. Liu, M. G. Kelly, E. L. Wierzbicki, I. C. Escober-Nario, M. K. Vollmer, and S. Doré, "Nrf2 plays an essential role in long-term brain damage and neuroprotection of Korean red ginseng in a permanent cerebral ischemia model," *Antioxidants*, vol. 8, no. 8, p. 273, 2019.

[186] S. Bonfante, A. Della Giustina, L. G. Danielski et al., "Stanniocalcin-1 ameliorates cerebral ischemia by decrease oxidative stress and blood brain barrier permeability," *Microvascular Research*, vol. 128, p. 103956, 2020.

[187] C. J. J. van Asch, M. J. A. Luitse, G. J. E. Rinkel, I. van der Tweel, A. Algra, and C. J. M. Klijn, "Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis," *The Lancet Neurology*, vol. 9, no. 2, pp. 167–176, 2010.

[188] C. Delcourt, S. Sato, S. Zhang et al., "Intracerebral hemorrhage location and outcome among INTERACT2 participants," *Neurology*, vol. 88, no. 15, pp. 1408–1414, 2017.

[189] T. Y. Wu, G. Sharma, D. Strbian et al., "Natural history of perihematomal edema and impact on outcome after intracerebral hemorrhage," *Stroke*, vol. 48, no. 4, pp. 873–879, 2017.

[190] J. Aronowski and X. Zhao, "Molecular pathophysiology of cerebral hemorrhage: secondary brain injury," *Stroke*, vol. 42, no. 6, pp. 1781–1786, 2011.

[191] N. DeGregorio-Rocasolano, O. Martí-Sistac, and T. Gasull, "Deciphering the iron side of stroke: neurodegeneration at

the crossroads between iron dyshomeostasis, excitotoxicity, and ferroptosis," *Frontiers in Neuroscience*, vol. 13, 2019.

[192] A. V. Alekseenko, T. V. Waseem, and S. V. Fedorovich-Ferritin, a protein containing iron nanoparticles, induces reactive oxygen species formation and inhibits glutamate uptake in rat brain synaptosomes," *Brain Research*, vol. 1241, pp. 193–200, 2008.

[193] M. Millan, T. Sobrino, M. Castellanos et al., "Increased body iron stores are associated with poor outcome after thrombolytic treatment in acute stroke," *Stroke*, vol. 38, no. 1, pp. 90–95, 2007.

[194] S. Azimipour, S. Ghaedi, Z. Mehrabi et al., "Heme degradation and iron release of hemoglobin and oxidative stress of lymphocyte cells in the presence of silica nanoparticles," *International Journal of Biological Macromolecules*, vol. 118, pp. 800–807, 2018.

[195] B. H. Han, M.-l. Zhou, A. W. Johnson et al., "Contribution of reactive oxygen species to cerebral amyloid angiopathy, vasomotor dysfunction, and microhemorrhage in aged Tg2576 mice," *Proceedings of the National Academy of Sciences*, vol. 112, no. 8, pp. E881–E890, 2015.

[196] B. Y. Hwang, G. Appelboom, A. Ayer et al., "Advances in neuroprotective strategies: potential therapies for intracerebral hemorrhage," *Cerebrovascular Diseases*, vol. 31, no. 3, pp. 211–222, 2011.

[197] Y. P. Yu, X. L. Chi, and L. J. Liu, "A hypothesis: hydrogen sulfide might be neuroprotective against subarachnoid hemorrhage induced brain injury," *The Scientific World Journal*, vol. 2014, 9 pages, 2014.

[198] M. Valko, H. Morris, and M. T. Cronin, "Metals, toxicity and oxidative stress," *Current Medicinal Chemistry*, vol. 12, no. 10, pp. 1161–1208, 2005.

[199] X. Zhao and J. Aronowski, "Nrf2 to pre-condition the brain against injury caused by products of hemolysis after ICH," *Translational Stroke Research*, vol. 4, no. 1, pp. 71–75, 2013.

[200] D. Wang, K. Liu, H. Wake, K. Teshigawara, S. Mori, and M. Nishibori, "Anti-high mobility group box-1 (HMGB1) antibody inhibits hemorrhage-induced brain injury and improved neurological deficits in rats," *Scientific Reports*, vol. 7, no. 1, 2017.

[201] Y. Zhou, Y. Wang, J. Wang, R. Anne Stetler, and Q. W. Yang, "Inflammation in intracerebral hemorrhage: from mechanisms to clinical translation," *Progress in Neurobiology*, vol. 115, pp. 25–44, 2014.

[202] J. Qu, W. Chen, R. Hu, and H. Feng, "The injury and therapy of reactive oxygen species in intracerebral hemorrhage looking at mitochondria," *Oxidative Medicine and Cellular Longevity*, vol. 2016, 9 pages, 2016.

[203] X. Qu, N. Wang, W. Chen, M. Qi, Y. Xue, and W. Cheng, "RNF34 overexpression exacerbates neurological deficits and brain injury in a mouse model of intracerebral hemorrhage by potentiating mitochondrial dysfunction-mediated oxidative stress," *Scientific Reports*, vol. 9, no. 1, 2019.

[204] D. Vela, "Hepcidin, an emerging and important player in brain iron homeostasis," *Journal of Translational Medicine*, vol. 16, no. 1, p. 25, 2018.

[205] J. Ma, F.-L. Zhang, G. Zhou, Y.-X. Bao, Y. Shen, and Z.-M. Qian, "Different Characteristics of Hepcidin Expression in IL-6+/+ and IL-6−/− Neurons and Astrocytes Treated with Lipopolysaccharides," *Neurochemical Research*, vol. 43, no. 8, pp. 1624–1630, 2018.

[206] A. Colantonio, R. Croxford, S. Farooq, A. Laporte, and P. C. Coyte, "Trends in hospitalization associated with traumatic brain injury in a publicly insured population, 1992-2002," *The Journal of Trauma: Injury, Infection, and Critical Care*, vol. 66, no. 1, pp. 179–183, 2009.

[207] A. I. R. Maas, N. Stocchetti, and R. Bullock, "Moderate and severe traumatic brain injury in adults," *The Lancet Neurology*, vol. 7, no. 8, pp. 728–741, 2008.

[208] V. L. Feigin, A. Theadom, S. Barker-Collo et al., "Incidence of traumatic brain injury in New Zealand: a population-based study," *The Lancet Neurology*, vol. 12, no. 1, pp. 53–64, 2013.

[209] The Lancet Neurology, "Traumatic brain injury: time to end the silence," *The Lancet Neurology*, vol. 9, no. 4, p. 331, 2010.

[210] N. Khatri, M. Thakur, V. Pareek, S. Kumar, S. Sharma, and A. K. Datusalia, "Oxidative stress: major threat in traumatic brain injury," *CNS & Neurological Disorders - Drug Targets*, vol. 17, no. 9, pp. 689–695, 2018.

[211] G. W. Hergenroeder, J. B. Redell, A. N. Moore, and P. K. Dash, "Biomarkers in the clinical diagnosis and management of traumatic brain injury," *Molecular Diagnosis & Therapy*, vol. 12, no. 6, pp. 345–358, 2008.

[212] C. Cornelius, R. Crupi, V. Calabrese et al., "Traumatic brain injury: oxidative stress and neuroprotection," *Antioxidants & Redox Signaling*, vol. 19, no. 8, pp. 836–853, 2013.

[213] K. Mertsch, I. Blasig, and T. Grune, "4-Hydroxynonenal impairs the permeability of an in vitro rat blood-brain barrier," *Neuroscience Letters*, vol. 314, no. 3, pp. 135–138, 2001.

[214] R. Vagnozzi, A. Marmarou, B. Tavazzi et al., "Changes of cerebral energy metabolism and lipid peroxidation in rats leading to mitochondrial dysfunction after diffuse brain injury," *Journal of Neurotrauma*, vol. 16, no. 10, pp. 903–913, 1999.

[215] M. W. Ma, J. Wang, K. M. Dhandapani, R. Wang, and D. W. Brann, "NADPH oxidases in traumatic brain injury - Promising therapeutic targets?," *Redox Biology*, vol. 16, pp. 285–293, 2018.

[216] M. W. Ma, J. Wang, K. M. Dhandapani, and D. W. Brann, "Deletion of NADPH oxidase 4 reduces severity of traumatic brain injury," *Free Radical Biology and Medicine*, vol. 117, pp. 66–75, 2018.

[217] A. Kumar, J. P. Barrett, D. M. Alvarez-Croda, B. A. Stoica, A. I. Faden, and D. J. Loane, "NOX2 drives M1-like microglial/macrophage activation and neurodegeneration following experimental traumatic brain injury," *Brain, Behavior, and Immunity*, vol. 58, pp. 291–309, 2016.

[218] E. M. Lutton, R. Razmpour, A. M. Andrews et al., "Acute administration of catalase targeted to ICAM-1 attenuates neuropathology in experimental traumatic brain injury," *Scientific Reports*, vol. 7, no. 1, p. 3846, 2017.

[219] A. Pajoohesh-Ganji and K. R. Byrnes, "Novel neuroinflammatory targets in the chronically injured spinal cord," *Neurotherapeutics*, vol. 8, no. 2, pp. 195–205, 2011.

[220] H. Zhang, Z.-W. Wang, H.-B. Wu et al., "Transforming growth factor-β1 induces matrix metalloproteinase-9 expression in rat vascular smooth muscle cells via ROS-dependent ERK-NF-κB pathways," *Molecular and Cellular Biochemistry*, vol. 375, pp. 11–21, 2012.

[221] R. A. Worthylake and K. Burridge, "Leukocyte transendothelial migration: orchestrating the underlying molecular machinery," *Current Opinion in Cell Biology*, vol. 13, no. 5, pp. 569–577, 2001.

[222] E. A. Winkler, D. Minter, J. K. Yue, and G. T. ManleyCerebral edema in traumatic brain injury: pathophysiology and prospective therapeutic targets," *Neurosurgery Clinics of North America*, vol. 27, no. 4, pp. 473–488, 2016.

[223] D. A. Butterfield and D. Boyd-Kimball, "Oxidative stress, amyloid-β peptide, and altered key molecular pathways in the pathogenesis and progression of Alzheimer's disease," *Journal of Alzheimer's Disease*, vol. 62, no. 3, pp. 1345–1367, 2018.

[224] Y. Zhao and B. Zhao, "Oxidative Stress and the Pathogenesis of Alzheimer's Disease," *Oxidative Medicine and Cellular Longevity*, vol. 2013, Article ID 316523, 10 pages, 2013.

[225] X. Wang, W. Wang, L. Li, G. Perry, H.-g. Lee, and X. Zhu, "Oxidative stress and mitochondrial dysfunction in Alzheimer's disease," *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, vol. 1842, no. 8, pp. 1240–1247, 2014.

[226] D. Zádori, G. Veres, L. Szalárdy, P. Klivényi, and L. Vécsei, "Alzheimer's disease: recent concepts on the relation of mitochondrial disturbances, excitotoxicity, neuroinflammation, and kynurenines," *Journal of Alzheimer's Disease*, vol. 62, no. 2, pp. 523–547, 2018.

[227] T. Jiang, Q. Sun, and S. Chen, "Oxidative stress: a major pathogenesis and potential therapeutic target of antioxidative agents in Parkinson's disease and Alzheimer's disease," *Progress in Neurobiology*, vol. 147, pp. 1–19, 2016.

[228] P. Picone, D. Nuzzo, L. Caruana, V. Scafidi, and M. Di Carlo, "Mitochondrial Dysfunction: Different Routes to Alzheimer's Disease Therapy," *Oxidative Medicine and Cellular Longevity*, vol. 2014, Article ID 780179, 11 pages, 2014.

[229] K. L. Schulz, A. Eckert, V. Rhein et al., "A new link to mitochondrial impairment in tauopathies," *Molecular Neurobiology*, vol. 46, no. 1, pp. 205–216, 2012.

[230] T. O. Tobore, "On the central role of mitochondria dysfunction and oxidative stress in Alzheimer's disease," *Neurological Sciences*, vol. 40, no. 8, pp. 1527–1540, 2019.

[231] Y. Nakabeppu, "Molecular pathophysiology of insulin depletion, mitochondrial dysfunction, and oxidative stress in Alzheimer's disease brain," *Advances in Experimental Medicine and Biology*, vol. 1128, pp. 27–44, 2019.

[232] Y.-W. Tang, C.-J. Shi, H.-L. Yang et al., "Synthesis and evaluation of isoprenylation-resveratrol dimer derivatives against Alzheimer's disease," *European Journal of Medicinal Chemistry*, vol. 163, pp. 307–319, 2019.

[233] G. Šimić, P. J. Lucassen, Ž. Krsnik et al., "nNOS expression in reactive astrocytes correlates with increased cell death related DNA damage in the hippocampus and entorhinal cortex in Alzheimer's disease," *Experimental Neurology*, vol. 165, no. 1, pp. 12–26, 2000.

[234] H. J. Lüth, M. Holzer, U. Gärtner, M. Staufenbiel, and T. Arendt, "Expression of endothelial and inducible NOS-isoforms is increased in Alzheimer's disease, in APP23 transgenic mice and after experimental brain lesion in rat: evidence for an induction by amyloid pathology," *Brain Research*, vol. 913, no. 1, pp. 57–67, 2001.

[235] H. J. Lüth, G. Münch, and T. Arendt, "Aberrant expression of NOS isoforms in Alzheimer's disease is structurally related to nitrotyrosine formation," *Brain Research*, vol. 953, no. 1-2, pp. 135–143, 2002.

[236] V. Dias, E. Junn, and M. M. Mouradian, "The role of oxidative stress in Parkinson's disease," *Journal of Parkinson's Disease*, vol. 3, no. 4, pp. 461–491, 2013.

[237] P. Jenner and C. W. Olanow, "The pathogenesis of cell death in Parkinson's disease," *Neurology*, vol. 66, Issue 10, Supplement 4, pp. S24–S36, 2006.

[238] X. Liu, N. Yamada, W. Maruyama, and T. Osawa, "Formation of dopamine adducts derived from brain polyunsaturated fatty acids: mechanism for Parkinson disease," *Journal of Biological Chemistry*, vol. 283, no. 50, pp. 34887–34895, 2008.

[239] M. A. Ortiz-Ortiz, J. M. Morán, J. M. Bravosanpedro et al., "Curcumin enhances paraquat-induced apoptosis of N27 mesencephalic cells via the generation of reactive oxygen species," *Neurotoxicology*, vol. 30, no. 6, pp. 1008–1018, 2009.

[240] G. D. Zeevalk, R. Razmpour, and L. P. Bernard, "Glutathione and Parkinson's disease: Is this the elephant in the room?," *Biomedicine & Pharmacotherapy*, vol. 62, no. 4, pp. 236–249, 2008.

[241] P. M. Rappold and K. Tieu, "Astrocytes and therapeutics for Parkinson's disease," *Neurotherapeutics*, vol. 7, no. 4, pp. 413–423, 2010.

[242] K. Mashima, S. Takahashi, K. Minami et al., "Neuroprotective role of astroglia in Parkinson disease by reducing oxidative stress through dopamine-induced activation of pentose-phosphate pathway," *ASN Neuro*, vol. 10, p. 175909141877556, 2018.

[243] D. H. Choi, J. H. Kim, J. H. Seo, J. Lee, W. S. Choi, and Y. S. Kim, "Matrix metalloproteinase-3 causes dopaminergic neuronal death through Nox1-regenerated oxidative stress," *PLoS ONE*, vol. 9, no. 12, p. e115954, 2014.

[244] D. H. Choi, O. Hwang, K. H. Lee, J. Lee, M. F. Beal, and Y. S. Kim, "DJ-1 cleavage by matrix metalloproteinase 3 mediates oxidative stress-induced dopaminergic cell death," *Antioxidants & Redox Signaling*, vol. 14, no. 11, pp. 2137–2150, 2011.

[245] L. Chico, M. Modena, A. L. Gerfo et al., "Cross-talk between pathogenic mechanisms in neurodegeneration: the role of oxidative stress in amyotrophic lateral sclerosis," *Archives Italiennes de Biologie*, vol. 155, no. 4, pp. 131–141, 2017.

[246] Y. Ohta, E. Nomura, J. Shang et al., "Enhanced oxidative stress and the treatment by edaravone in mice model of amyotrophic lateral sclerosis," *Journal of Neuroscience Research*, vol. 97, no. 5, pp. 607–619, 2019.

[247] Z. Wang, Z. Bai, X. Qin, and Y. Cheng, "Aberrations in oxidative stress markers in amyotrophic lateral sclerosis: a systematic review and meta-analysis," *Oxidative Medicine and Cellular Longevity*, vol. 2019, Article ID 1712323, 9 pages, 2019.

[248] K. Hensley, M. Mhatre, S. Mou et al., "On the relation of oxidative stress to neuroinflammation: lessons learned from the G93A-SOD1 mouse model of amyotrophic lateral sclerosis," *Antioxidants & Redox Signaling*, vol. 8, no. 11-12, pp. 2075–2087, 2006.

[249] T. Dal-Cim, G. G. Poluceno, D. Lanznaster, K. A. de Oliveira, C. B. Nedel, and C. I. Tasca, "Guanosine prevents oxidative damage and glutamate uptake impairment induced by oxygen/glucose deprivation in cortical astrocyte cultures: involvement of A1 and A2A adenosine receptors and PI3K, MEK, and PKC pathways," *Purinergic Signalling*, vol. 15, no. 4, pp. 465–476, 2019.

[250] F. Martorana, M. Foti, A. Virtuoso et al., "Differential modulation of NF-κB in neurons and astrocytes underlies neuroprotection and antigliosis activity of natural antioxidant molecules," *Oxidative Medicine and Cellular Longevity*, vol. 2019, Article ID 8056904, 16 pages, 2019.

[251] S. Zou, Y. L. Lan, H. Wang, B. Zhang, and Y. G. Sun, "The potential roles of aquaporin 4 in amyotrophic lateral sclerosis," *Neurological Sciences*, vol. 40, no. 8, pp. 1541–1549, 2019.

[252] D. Bataveljić, L. Nikolić, M. Milosević, N. Todorović, and P. R. Andjus, "Changes in the astrocytic aquaporin-4 and inwardly rectifying potassium channel expression in the brain of the amyotrophic lateral sclerosis SOD1(G93A) rat model," *Glia*, vol. 60, no. 12, pp. 1991–2003, 2012.

[253] J. Lee, M. Kannagi, R. J. Ferrante, N. W. Kowall, and H. Ryu, "Activation of Ets-2 by oxidative stress induces Bcl-xL expression and accounts for glial survival in amyotrophic lateral sclerosis," *The FASEB Journal*, vol. 23, no. 6, pp. 1739–1749, 2009.

[254] H.-M. Kwon, M. J. Lynn, T. N. Turan et al., "Frequency, risk factors, and outcome of coexistent small vessel disease and intracranial arterial stenosis: results from the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial," *JAMA Neurology*, vol. 73, no. 1, pp. 36–42, 2016.

[255] F. Arba, T. Quinn, G. J. Hankey et al., "Cerebral small vessel disease, medial temporal lobe atrophy and cognitive status in patients with ischaemic stroke and transient ischaemic attack," *European Journal of Neurology*, vol. 24, no. 2, pp. 276–282, 2017.

[256] P. Benjamin, A. J. Lawrence, C. Lambert et al., "Strategic lacunes and their relationship to cognitive impairment in cerebral small vessel disease," *NeuroImage: Clinical*, vol. 4, pp. 828–837, 2014.

[257] W. Swardfager, D. Yu, G. Scola et al., "Peripheral lipid oxidative stress markers are related to vascular risk factors and subcortical small vessel disease," *Neurobiology of Aging*, vol. 59, pp. 91–97, 2017.

[258] A. H. Hainsworth and M. J. Fisher, "A dysfunctional blood-brain barrier and cerebral small vessel disease," *Neurology*, vol. 88, no. 5, pp. 420-421, 2017.

[259] C. Grochowski, J. Litak, P. Kamieniak, and R. Maciejewski, "Oxidative stress in cerebral small vessel disease. Role of reactive species," *Free Radical Research*, vol. 52, no. 1, pp. 1–13, 2018.

[260] J. M. Wardlaw, "Blood-brain barrier and cerebral small vessel disease," *Journal of the Neurological Sciences*, vol. 299, no. 1-2, pp. 66–71, 2010.

[261] X. L. Ma, F. Gao, A. H. Nelson et al., "Oxidative inactivation of nitric oxide and endothelial dysfunction in stroke-prone spontaneous hypertensive rats," *The Journal of Pharmacology and Expiremental Therapeutics*, vol. 298, no. 3, 2001.

[262] M. Ghosh, M. Balbi, F. Hellal, M. Dichgans, U. Lindauer, and N. Plesnila, "Pericytes are involved in the pathogenesis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy," *Annals of Neurology*, vol. 78, no. 6, pp. 887–900, 2015.

[263] P. Toth, Z. Tucsek, D. Sosnowska et al., "Age-related autoregulatory dysfunction and cerebromicrovascular injury in mice with angiotensin II-induced hypertension," *Journal of Cerebral Blood Flow & Metabolism*, vol. 33, no. 11, pp. 1732–1742, 2013.

[264] S. E. Lakhan, A. Kirchgessner, D. Tepper, and A. Leonard, "Matrix metalloproteinases and blood-brain barrier disruption in acute ischemic stroke," *Frontiers in Neurology*, vol. 4, 2013.

[265] M. M. A. Almutairi, C. Gong, Y. G. Xu, Y. Chang, and H. Shi, "Factors controlling permeability of the blood-brain barrier," *Cellular and Molecular Life Sciences*, vol. 73, no. 1, pp. 57–77, 2016.

[266] P. R. Holland, J. L. Searcy, N. Salvadores et al., "Gliovascular disruption and cognitive deficits in a mouse model with features of small vessel disease," *Journal Cerebral Blood Flow & Metabolism*, vol. 35, no. 6, pp. 1005–1014, 2015.

[267] G. Gudiño-Cabrera, M. E. Ureña-Guerrero, M. C. Rivera-Cervantes, A. I. Feria-Velasco, and C. Beas-Zárate, "Excitotoxicity Triggered by Neonatal Monosodium Glutamate Treatment and Blood- Brain Barrier Function," *Archives of Medical Research*, vol. 45, no. 8, pp. 653–659, 2014.

[268] M. Blanco, M. Rodríguez-Yáñez, T. Sobrino, R. Leira, and J. Castillo, "Platelets, inflammation, and atherothrombotic neurovascular disease: the role of endothelial dysfunction," *Cerebrovascular Diseases*, vol. 20, no. 2, pp. 32–39, 2005.

[269] H. Girouard, L. Park, J. Anrather, P. Zhou, and C. Iadecola, "Angiotensin II attenuates endothelium-dependent responses in the cerebral microcirculation through nox-2-derived radicals," *Arteriosclerosis Thrombosis and Vascular Biology*, vol. 26, no. 4, pp. 826–832, 2006.

[270] A. A. Miller, T. M. De Silva, C. P. Judkins, H. Diep, G. R. Drummond, and C. G. Sobey, "Augmented superoxide production by Nox2-containing NADPH oxidase causes cerebral artery dysfunction during hypercholesterolemia," *Stroke*, vol. 41, no. 4, pp. 784–789, 2010.

[271] C. M. Lynch, D. A. Kinzenbaw, X. Chen et al., "Nox2-derived superoxide contributes to cerebral vascular dysfunction in diet-induced obesity," *Stroke*, vol. 44, no. 11, pp. 3195–3201, 2013.

[272] L. Nanetti, R. Taffi, A. Vignini et al., "Reactive oxygen species plasmatic levels in ischemic stroke," *Molecular and Cellular Biochemistry*, vol. 303, no. 1-2, pp. 19–25, 2007.

[273] I. Kwon, E. H. Kim, G. J. del Zoppo, and J. H. Heo, "Ultrastructural and temporal changes of the microvascular basement membrane and astrocyte interface following focal cerebral ischemia," *Journal of Neuroscience Research*, vol. 87, no. 3, pp. 668–676, 2009.

[274] Y. Xu, H. Zhou, and Q. Zhu, "The impact of microbiota-gut-brain axis on diabetic cognition impairment," *Frontiers in Aging Neuroscience*, vol. 9, 2017.

[275] S. Ahmed, A. Busetti, P. Fotiadou et al., "In vitro characterization of gut microbiota-derived bacterial strains with neuroprotective properties," *Frontiers in Cellular Neuroscience*, vol. 13, p. 402, 2019.

[276] N. Xu, W. Fan, X. Zhou et al., "Probiotics decrease depressive behaviors induced by constipation via activating the AKT signaling pathway," *Metabolic Brain Disease*, vol. 33, no. 5, pp. 1625–1633, 2018.

[277] S. Filosa, F. Di Meo, and S. Crispi, "Polyphenols-gut microbiota interplay and brain neuromodulation," *Neural Regeneration Research*, vol. 13, no. 12, pp. 2055–2059, 2018.

[278] H. B. Dodiya, C. B. Forsyth, R. M. Voigt et al., "Chronic stress-induced gut dysfunction exacerbates Parkinson's disease phenotype and pathology in a rotenone-induced mouse model of Parkinson's disease," *Neurobiology of Disease*, vol. 135, article 104352, 2020.

[279] A. T. Nair, V. Ramachandran, N. M. Joghee, S. Antony, and G. Ramalingam, "Gut microbiota dysfunction as reliable non-invasive early diagnostic biomarkers in the

pathophysiology of Parkinson's disease: a critical review," *Journal of Neurogastroenterology and Motility.*, vol. 24, no. 1, pp. 30–42, 2018.

[280] L. M. Buja, "Myocardial ischemia and reperfusion injury," *Cardiovascular Pathology*, vol. 14, no. 4, pp. 170–175, 2005.

[281] K. Iwakura, H. Ito, S. Takiuchi et al., "Alternation in the coronary blood flow velocity pattern in patients with no reflow and reperfused acute myocardial infarction," *Circulation*, vol. 94, no. 6, pp. 1269–1275, 1996.

[282] D. J. Hausenloy and D. M. Yellon, "Myocardial ischemia-reperfusion injury: a neglected therapeutic target," *Journal of Clinical Investigation*, vol. 123, no. 1, pp. 92–100, 2013.

[283] T. H. Sanderson, C. A. Reynolds, R. Kumar, K. Przyklenk, and M. Hüttemann, "Molecular mechanisms of ischemia-reperfusion injury in brain: pivotal role of the mitochondrial membrane potential in reactive oxygen species generation," *Molecular Neurobiology*, vol. 47, no. 1, pp. 9–23, 2013.

[284] M. Nour, F. Scalzo, and D. S. Liebeskind, "Ischemia-reperfusion injury in stroke," *Interventional Neurology*, vol. 1, no. 3-4, pp. 185–199, 2012.

[285] S. Kumfu, S. T. Charununtakorn, T. Jaiwongkam, N. Chattipakorn, and S. C. Chattipakorn, "Humanin prevents brain mitochondrial dysfunction in a cardiac ischaemia-reperfusion injury model," *Experimental Physiology*, vol. 101, no. 6, pp. 697–707, 2016.

[286] A. Hendy and R. Hall, "Cardiac surgery and the blood-brain barrier," *Anesthesiology Clinics*, vol. 37, no. 4, pp. 787–800, 2019.

[287] B. Reinsfelt, S. E. Ricksten, H. Zetterberg, K. Blennow, J. Fredén-Lindqvist, and A. Westerlind, "Cerebrospinal fluid markers of brain injury, inflammation, and blood-brain barrier dysfunction in cardiac surgery," *The Annals of Thoracic Surgery*, vol. 94, no. 2, pp. 549–555, 2012.

[288] P. L. Yu, C. Wang, W. Li, and F. X. Zhang, "Visfatin level and the risk of hypertension and cerebrovascular accident: a systematic review and meta-analysis," *Hormone and Metabolic Research*, vol. 51, no. 4, pp. 220–229, 2019.

[289] M. Paquette, S. Bernard, G. Paré, and A. Baass, "Triglycerides, hypertension, and smoking predict cardiovascular disease in dysbetalipoproteinemia," *Journal of Clinical Lipidology*, vol. 14, no. 1, pp. 46–52, 2020.

[290] E. E. Nishi, V. R. Almeida, F. G. Amaral et al., "Melatonin attenuates renal sympathetic overactivity and reactive oxygen species in the brain in neurogenic hypertension," *Hypertension Research*, vol. 42, no. 11, pp. 1683–1691, 2019.

[291] N. Tanahashi, "Hypertension associated with cerebrovascular disease," *Nihon Rinsho*, vol. 73, no. 11, pp. 1864–1870, 2015.

[292] T. Iyonaga, K. Shinohara, T. Mastuura, Y. Hirooka, and H. Tsutsui, "Brain perivascular macrophages contribute to the development of hypertension in stroke-prone spontaneously hypertensive rats via sympathetic activation," *Hypertension Research*, vol. 43, no. 2, pp. 99–110, 2020.

[293] P. W. Pires, C. M. Dams Ramos, N. Matin, and A. M. Dorrance, "The effects of hypertension on the cerebral circulation," *American Journal of Physiology Heart Circulatory Physiology*, vol. 304, no. 12, pp. H1598–H1614, 2013.

[294] R. Kunze and H. H. Marti, "Angioneurins - key regulators of blood-brain barrier integrity during hypoxic and ischemic brain injury," *Progress in Neurobiology*, vol. 178, article 101611, 2019.

[295] V. C. Biancardi and J. E. Stern, "Compromised blood-brain barrier permeability: novel mechanism by which circulating angiotensin II signals to sympathoexcitatory centres during hypertension," *The Journal of Physiology*, vol. 594, no. 6, pp. 1591–1600, 2016.

[296] V. C. Biancardi, S. J. Son, S. Ahmadi, J. A. Filosa, and J. E. Stern, "Circulating angiotensin II gains access to the hypothalamus and brain stem during hypertension via breakdown of the blood-brain barrier," *Hypertension*, vol. 63, no. 3, pp. 572–579, 2014.

[297] V. A. Braga, I. A. Medeiros, T. P. Ribeiro, M. S. França-Silva, M. S. Botelho-Ono, and D. D. Guimarães, "Angiotensin-II-induced reactive oxygen species along the SFO-PVN-RVLM pathway: implications in neurogenic hypertension," *Brazilian Journal of Medical and Biology Research*, vol. 44, no. 9, pp. 871–876, 2011.

[298] K. Saijo and C. K. Glass, "Microglial cell origin and phenotypes in health and disease," *Nature Reviews Immunology*, vol. 11, no. 11, pp. 775–787, 2011.

[299] A. Czigler, L. Toth, N. Szarka et al., "Hypertension exacerbates cerebrovascular oxidative stress induced by mild traumatic brain injury: protective effects of the mitochondria-targeted antioxidative peptide SS-31," *Journal of Neurotrauma*, vol. 36, no. 23, pp. 3309–3315, 2019.

[300] V. Boshra and A. M. Abbas, "Effects of peripherally and centrally applied ghrelin on the oxidative stress induced by renin angiotensin system in a rat model of renovascular hypertension," *Journal of Basic and Clinical Physiology and Pharmacology*, vol. 28, no. 4, pp. 347–354, 2017.

[301] N. Shi, J. He, Q. Guo, T. Liu, and J. Han, "Liraglutide protects against diabetes mellitus complicated with focal cerebral ischemic injury by activating mitochondrial ATP-sensitive potassium channels," *Neuroreport*, vol. 30, no. 7, pp. 479–484, 2019.

[302] Y. Li, K. W. Zeng, and X. M. Wang, "Cerebral microangiopathy of diabetes," *Zhongguo Zhong Yao Za Zhi*, vol. 42, no. 12, pp. 2247–2253, 2017.

[303] M. Ahmadi, Z. Rajaei, M. A. Hadjzadeh, H. Nemati, and M. Hosseini, "Crocin improves spatial learning and memory deficits in the Morris water maze via attenuating cortical oxidative damage in diabetic rats," *Neurosciene Letters*, vol. 642, pp. 1–6, 2017.

[304] J. K. Ferris, S. Peters, K. E. Brown, K. Tourigny, and L. A. Boyd, "Type-2 diabetes mellitus reduces cortical thickness and decreases oxidative metabolism in sensorimotor regions after stroke," *Journal of Cerebral Blood Flow & Metabolism*, vol. 38, no. 5, pp. 823–834, 2017.

[305] M. Muriach, M. Flores-Bellver, F. J. Romero, and J. M. Barcia, "Diabetes and the brain: oxidative stress, inflammation, and autophagy," *Oxidative Medicine and Cellular Longevity*, vol. 2014, 9 pages, 2014.

[306] A. Arcambal, J. Taïlé, P. Rondeau, W. Viranaïcken, O. Meilhac, and M. P. Gonthier, "Hyperglycemia modulates redox, inflammatory and vasoactive markers through specific signaling pathways in cerebral endothelial cells: insights on insulin protective action," *Free Radical Biology and Medicine*, vol. 130, pp. 59–70, 2019.

[307] A. Katychev, X. Wang, A. Duffy, and P. Dore-Duffy, "Glucocorticoid-induced apoptosis in CNS microvascular pericytes," *Developmental Neuroscience*, vol. 25, no. 6, pp. 436–446, 2004.

[308] T. O. Price, V. Eranki, W. A. Banks, N. Ercal, and G. N. Shah, "Topiramate treatment protects blood-brain barrier pericytes

from hyperglycemia-induced oxidative damage in diabetic mice," *Endocrinology*, vol. 153, no. 1, pp. 362–372, 2012.

[309] R. Richa, A. K. Yadawa, and C. M. Chaturvedi, "Hyperglycemia and high nitric oxide level induced oxidative stress in the brain and molecular alteration in the neurons and glial cells of laboratory mouse, _Mus musculus_," *Neurochemistry International*, vol. 104, pp. 64–79, 2017.

[310] S.-O. Kang, "Free radicals generated during the glycation reaction of amino acids by Methylglyoxal," *Journal of Biological Chemistry*, vol. 270, no. 47, pp. 28228–28233, 1995.

[311] I. Dalle-Donne, D. Giustarini, R. Colombo, R. Rossi, and A. Milzani, "Protein carbonylation in human diseases," *Trends in Molecular Medicine*, vol. 9, no. 4, pp. 169–176, 2003.

[312] B. Wang, T. Y. Aw, and K. Y. Stokes, "The protection conferred against ischemia-reperfusion injury in the diabetic brain by N-acetylcysteine is associated with decreased dicarbonyl stress," *Free Radical Biology and Medicine*, vol. 96, pp. 89–98, 2016.

[313] W. Xu, F. Li, Z. Liu et al., "MicroRNA-27b inhibition promotes Nrf2/ARE pathway activation and alleviates intracerebral hemorrhage-induced brain injury," *Oncotarget*, vol. 8, no. 41, pp. 70669–70684, 2017.

[314] Y. Jiang, L. Li, X. Tan, B. Liu, Y. Zhang, and C. Li, "miR-210 mediates vagus nerve stimulation-induced antioxidant stress and anti-apoptosis reactions following cerebral ischemia/-reperfusion injury in rats," *Journal of neurochemistry*, vol. 134, no. 1, pp. 173–181, 2015.

[315] D. M. Wu, X. Wen, Y. J. Wang et al., "Effect of microRNA-186 on oxidative stress injury of neuron by targeting interleukin 2 through the Janus kinase-signal transducer and activator of transcription pathway in a rat model of Alzheimer's disease," *Journal of cellular physiology*, vol. 233, no. 12, pp. 9488–9502, 2018.

[316] L. Zhang, Y. Fang, X. Cheng, Y. J. Lian, and H. L. Xu, "Silencing of long noncoding RNA SOX21-AS1 relieves neuronal oxidative stress injury in mice with Alzheimer's disease by upregulating FZD3/5 via the Wnt signaling pathway," *Molecular neurobiology*, vol. 56, no. 5, pp. 3522–3537, 2019.

[317] L. Barile and G. Vassalli, "Exosomes: therapy delivery tools and biomarkers of diseases," *Pharmacology & therapeutics*, vol. 174, pp. 63–78, 2017.

[318] S. Vanherle, M. Haidar, J. Irobi, J. F. J. Bogie, and J. J. A. Hendriks, "Extracellular vesicle-associated lipids in central nervous system disorders," *Advanced drug delivery reviews*, 2020.

[319] A. Picca, F. Guerra, R. Calvani et al., "Mitochondrial-derived vesicles as candidate biomarkers in Parkinson's disease: rationale, design and methods of the EXosomes in PArkiNson Disease (EXPAND) study," *International journal of molecular sciences*, vol. 20, no. 10, p. 2373, 2019.

[320] J. L. Dai, R. Li, H. T. Liu, W. M. Jian, and L. Q. Hu, "The clinical significance of serum C1q tumor necrosis factor-related protein-9 (CTRP9) in patients with cerebral infarction," *Zhonghua nei ke za zhi*, vol. 58, no. 6, pp. 449–452, 2019.

[321] K. Kikuchi, K. Setoyama, E. Tanaka et al., "Uric acid enhances alteplase-mediated thrombolysis as an antioxidant," *Scientific reports*, vol. 8, no. 1, p. 15844, 2018.

[322] A. Chamorro, V. Obach, A. Cervera, M. Revilla, R. Deulofeu, and J. H. Aponte, "Prognostic significance of uric acid serum concentration in patients with acute ischemic stroke," *Stroke*, vol. 33, no. 4, pp. 1048–1052, 2002.

[323] R. C. S. Seet, C.-Y. J. Lee, B. P. L. Chan et al., "Oxidative damage in ischemic stroke revealed using multiple biomarkers," *Stroke*, vol. 42, no. 8, pp. 2326–2329, 2011.

[324] R. C. Seet, C. Y. Lee, E. C. Lim et al., "Oxidative damage in Parkinson disease: measurement using accurate biomarkers," *Free radical biology & medicine*, vol. 48, no. 4, pp. 560–566, 2010.

[325] S. Lorenzano, N. S. Rost, M. Khan et al., "Oxidative stress biomarkers of brain Damage," *Stroke*, vol. 49, no. 3, pp. 630–637, 2018.

[326] S. Lorenzano, N. S. Rost, M. Khan et al., "Early molecular oxidative stress biomarkers of ischemic penumbra in acute stroke," *Neurology*, vol. 93, no. 13, pp. e1288–e1298, 2019.

[327] B. J. Distad and M. D. Weiss, "Edaravone for amyotrophic lateral sclerosis: more evidence for long-term benefit," *Muscle & nerve*, vol. 61, no. 2, pp. 129-130, 2020.

[328] Z. Sun, Q. Xu, G. Gao, M. Zhao, and C. Sun, "Clinical observation in edaravone treatment for acute cerebral infarction," *Nigerian journal of clinical practice*, vol. 22, no. 10, pp. 1324–1327, 2019.

[329] S. Kobayashi, S. Fukuma, T. Ikenoue, S. Fukuhara, S. Kobayashi, and on behalf of the Japan Stroke Data Bank, "Effect of edaravone on neurological symptoms in real-world patients with acute ischemic stroke," *Stroke*, vol. 50, no. 7, pp. 1805–1811, 2019.

[330] D. Zhang, Y. Xiao, P. Lv et al., "Edaravone attenuates oxidative stress induced by chronic cerebral hypoperfusion injury: role of ERK/Nrf2/HO-1 signaling pathway," *Neurological research*, vol. 40, no. 1, pp. 1–10, 2017.

[331] L. Jiao, J. Zhang, Z. Li, H. Liu, Y. Chen, and S. Xu, "Edaravone alleviates delayed neuronal death and long-dated cognitive dysfunction of hippocampus after transient focal ischemia in Wistar rat brains," *Neuroscience*, vol. 182, pp. 177–183, 2011.

[332] V. Lukic-Panin, K. Deguchi, T. Yamashita et al., "Free radical scavenger edaravone administration protects against tissue plasminogen activator induced oxidative stress and blood brain barrier damage," *Current neurovascular research*, vol. 7, no. 4, pp. 319–329, 2010.

[333] Y. Zhou, H. D. Wang, X. M. Zhou, J. Fang, L. Zhu, and K. Ding, "N-Acetylcysteine amide provides neuroprotection via Nrf2-ARE pathway in a mouse model of traumatic brain injury," *Drug design, development and therapy*, vol. Volume 12, pp. 4117–4127, 2018.

[334] D. A. Monti, G. Zabrecky, D. Kremens et al., "N-Acetyl cysteine is associated with dopaminergic improvement in Parkinson's disease," *Clinical pharmacology and therapeutics*, vol. 106, no. 4, pp. 884–890, 2019.

[335] N. Senol, M. Nazıroğlu, and V. Yürüker, "N-Acetylcysteine and selenium modulate oxidative stress, antioxidant vitamin and cytokine values in traumatic brain injury-induced rats," *Neurochemical research*, vol. 39, no. 4, pp. 685–692, 2014.

[336] J. A. Switzer, D. C. Hess, A. Ergul et al., "Matrix metalloproteinase-9 in an exploratory trial of intravenous minocycline for acute ischemic stroke," *Stroke*, vol. 42, no. 9, pp. 2633–2635, 2011.

[337] Z. Y. Cai, Y. Yan, S. Q. Sun et al., "Minocycline attenuates cognitive impairment and restrains oxidative stress in the hippocampus of rats with chronic cerebral hypoperfusion," *Neuroscience bulletin*, vol. 24, no. 5, pp. 305–313, 2008.

[338] D. K. Verma, D. K. Singh, S. Gupta et al., "Minocycline diminishes the rotenone induced neurotoxicity and glial activation via suppression of apoptosis, nitrite levels and oxidative stress," *Neurotoxicology*, vol. 65, pp. 9–21, 2018.

[339] A. Taheri, M. Emami, E. Asadipour et al., "A randomized controlled trial on the efficacy, safety, and pharmacokinetics of metformin in severe traumatic brain injury," *Journal of neurology*, vol. 266, no. 8, pp. 1988–1997, 2019.

[340] A. M. Koenig, D. Mechanic-Hamilton, S. X. Xie et al., "Effects of the insulin sensitizer metformin in Alzheimer disease: pilot data from a randomized placebo-controlled crossover study," *Alzheimer disease and associated disorders*, vol. 31, no. 2, pp. 107–113, 2017.

[341] E. Osei, S. Fonville, A. A. M. Zandbergen et al., "Metformin and sitAgliptin in patients with impAired glucose tolerance and a recent TIA or minor ischemic Stroke (MAAS): study protocol for a randomized controlled trial," *Trials*, vol. 16, no. 1, 2015.

[342] M. Zhao, X. W. Li, D. Z. Chen et al., "Neuro-protective role of metformin in patients with acute stroke and type 2 diabetes mellitus via AMPK/mammalian target of rapamycin (mTOR) signaling pathway and oxidative stress," *Medical science monitor*, vol. 25, pp. 2186–2194, 2019.

[343] G. Ashabi, L. Khalaj, F. Khodagholi, M. Goudarzvand, and A. Sarkaki, "Pre-treatment with metformin activates Nrf2 antioxidant pathways and inhibits inflammatory responses through induction of AMPK after transient global cerebral ischemia," *Metabolic brain disease*, vol. 30, no. 3, pp. 747–754, 2015.

[344] B. Qi, L. Hu, L. Zhu et al., "Metformin attenuates neurological deficit after intracerebral hemorrhage by inhibiting apoptosis, oxidative stress and neuroinflammation in rats," *Neurochemical research*, vol. 42, no. 10, pp. 2912–2920, 2017.

[345] X. Fang, Y. Li, J. Qiao, Y. Guo, and M. Miao, "Neuroprotective effect of total flavonoids from Ilex pubescens against focal cerebral ischemia/reperfusion injury in rats," *Molecular medicine reports*, vol. 16, no. 5, pp. 7439–7449, 2017.

[346] J. B. Schulz, N. A. Prospero, and K. Fischbeck, "Clinical experience with high-dose idebenone in Friedreich ataxia," *Journal of neurology*, vol. 256, no. S1, Supplement 1, pp. 42–45, 2009.

[347] T. Meier and G. Buyse, "Idebenone: an emerging therapy for Friedreich ataxia," *Journal of neurology*, vol. 256, no. S1, Supplement 1, pp. 25–30, 2009.

[348] M. A. E. Ahmed, "Neuroprotective effects of idebenone against pilocarpine-induced seizures: modulation of antioxidant status, DNA damage and Na(+), K (+)-ATPase activity in rat hippocampus," *Neurochemical research*, vol. 39, no. 2, pp. 394–402, 2014.

[349] Y. Yao, W. Miao, Z. Liu et al., "Dimethyl fumarate and monomethyl fumarate promote post-ischemic recovery in mice," *Translational stroke research*, vol. 7, no. 6, pp. 535–547, 2016.

[350] S. Gopal, A. Mikulskis, R. Gold, R. J. Fox, K. T. Dawson, and L. Amaravadi, "Evidence of activation of the Nrf2 pathway in multiple sclerosis patients treated with delayed-release dimethyl fumarate in the Phase 3 DEFINE and CONFIRM studies," *Multiple sclerosis : clinical and laboratory research*, vol. 23, no. 14, pp. 1875–1883, 2017.

[351] L. D. Coles, P. J. Tuite, G. Öz et al., "Repeated-dose oral N-acetylcysteine in Parkinson's disease: pharmacokinetics and effect on brain glutathione and oxidative stress," *Journal of clinical pharmacology*, vol. 58, no. 2, pp. 158–167, 2018.

[352] E. S. Louwerse, G. J. Weverling, P. M. M. Bossuyt, F. E. P. Meyjes, and J. M. B. V. de Jong, "Randomized, double-blind, controlled trial of acetylcysteine in amyotrophic lateral sclerosis," *Archives of neurology*, vol. 52, no. 6, pp. 559–564, 1995.

[353] F. T. Hagos, P. E. Empey, P. Wang et al., "Exploratory application of neuropharmacometabolomics in severe childhood traumatic brain injury," *Critical care medicine*, vol. 46, no. 9, pp. 1471–1479, 2018.

[354] P. I. Moreira, P. L. R. Harris, X. Zhu et al., "Lipoic acid and N-acetyl cysteine decrease mitochondrial-related oxidative stress in Alzheimer disease patient fibroblasts," *Journal of Alzheimer's disease : JAD*, vol. 12, no. 2, pp. 195–206, 2007.

[355] M. R. Amiri-Nikpour, S. Nazarbaghi, M. Hamdi-Holasou, and Y. Rezaei, "An open-label evaluator-blinded clinical study of minocycline neuroprotection in ischemic stroke: gender-dependent effect," *Acta neurologica Scandinavica*, vol. 131, no. 1, pp. 45–50, 2015.

[356] E. Kohler, D. A. Prentice, T. R. Bates et al., "Intravenous minocycline in acute Stroke," *Stroke*, vol. 44, no. 9, pp. 2493–2499, 2013.

[357] M. V. Padma Srivastava, A. Bhasin, R. Bhatia et al., "Efficacy of minocycline in acute ischemic stroke: a single-blinded, placebo-controlled trial," *Neurology India*, vol. 60, no. 1, pp. 23–28, 2012.

[358] Y. Fu, J. Hao, N. Zhang et al., "Fingolimod for the treatment of intracerebral hemorrhage: a 2-arm proof-of-concept study," *JAMA neurology*, vol. 71, no. 9, pp. 1092–1101, 2014.

[359] C. C. Leonardo and S. Doré, "Dietary flavonoids are neuroprotective through Nrf2-coordinated induction of endogenous cytoprotective proteins," *Nutritional neuroscience*, vol. 14, no. 5, pp. 226–236, 2013.

[360] A. Cassidy, E. B. Rimm, E. J. O'Reilly et al., "Dietary flavonoids and risk of stroke in women," *Stroke*, vol. 43, no. 4, pp. 946–951, 2012.

[361] N. G. Ranen, C. E. Peyser, J. T. Coyle et al., "A controlled trial of idebenone in Huntington's disease," *Movement disorders*, vol. 11, no. 5, pp. 549–554, 1996.

[362] K. V. Voronkova and M. N. Meleshkov, "Noben (idebenone) in the treatment of dementia and memory impairment without dementia," *Zhurnal nevrologii i psikhiatrii imeni S.S. Korsakova*, vol. 108, no. 4, pp. 27–32, 2008.

[363] U. Senin, L. Parnetti, G. Barbagallo-Sangiorgi et al., "Idebenone in senile dementia of Alzheimer type: a multicentre study," *Archives of gerontology and geriatrics*, vol. 15, no. 3, pp. 249–260, 1992.

[364] D. Sałacińska, A. Pogoda, J. Żółkiewicz, and A. Stępień, "Effectiveness of dimethyl fumarate as first line therapy in MS patients - one center real life observation study," *Polski merkuriusz lekarski : organ Polskiego Towarzystwa Lekarskiego*, vol. 47, no. 282, pp. 221–225, 2019.

[365] T. Saida, T. Yamamura, T. Kondo et al., "A randomized placebo-controlled trial of delayed-release dimethyl fumarate in patients with relapsing-remitting multiple sclerosis from East Asia and other countries," *BMC neurology*, vol. 19, no. 1, p. 5, 2019.