

## Review Article

# Rutin as a Potent Antioxidant: Implications for Neurodegenerative Disorders

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A wide range of neurodegenerative diseases (NDs), including Alzheimer's disease, Parkinson's disease, Huntington's disease, and prion diseases, share common mechanisms such as neuronal loss, apoptosis, mitochondrial dysfunction, oxidative stress, and inflammation. Intervention strategies using plant-derived bioactive compounds have been offered as a form of treatment for these debilitating conditions, as there are currently no remedies to prevent, reverse, or halt the progression of neuronal loss. Rutin, a glycoside of the flavonoid quercetin, is found in many plants and fruits, especially buckwheat, apricots, cherries, grapes, grapefruit, plums, and oranges. Pharmacological studies have reported the beneficial effects of rutin in many disease conditions, and its therapeutic potential in several models of NDs has created considerable excitement. Here, we have summarized the current knowledge on the neuroprotective mechanisms of rutin in various experimental models of NDs. The mechanisms of action reviewed in this article include reduction of proinflammatory cytokines, improved antioxidant enzyme activities, activation of the mitogen-activated protein kinase cascade, downregulation of mRNA expression of PD-linked and proapoptotic genes, upregulation of the ion transport and antiapoptotic genes, and restoration of the activities of mitochondrial complex enzymes. Taken together, these findings suggest that rutin may be a promising neuroprotective compound for the treatment of NDs.

## 1. Introduction

Neurodegenerative diseases (NDs) are regarded as an age-related group of chronic and untreatable conditions which constitutes a major threat to human health [1]. They are becoming increasingly prevalent, due to a significant increase in the size of elderly populations worldwide [2]. NDs represent the fourth highest source of disease burden in high-income countries, in terms of economic cost for society [3]. NDs are characterized by the gradual and progressive loss of neurons and diverse clinical features such as memory and cognitive impairments and others affecting a person's ability to move, speak, and breathe [4–6]. Some overlapping

pathways recognized in the pathogenicity of NDs include free radical formation and oxidative stress, protein misfolding and aggregation, metal dyshomeostasis, phosphorylation impairment, and mitochondrial dysfunction [7] (Figure 1).

Oxidative stress has been shown by many studies to be a crucial player in the development and progression of NDs [8]. Oxidative stress is defined as the disturbance in balance between prooxidant and antioxidant levels and results from an imbalance between the production of reactive oxygen species (ROS) and the biological system's ability to detoxify the reactive intermediates [8]. ROS play important roles in mediating cellular activities [9, 10]; however, due to their reactivity, high amounts of ROS

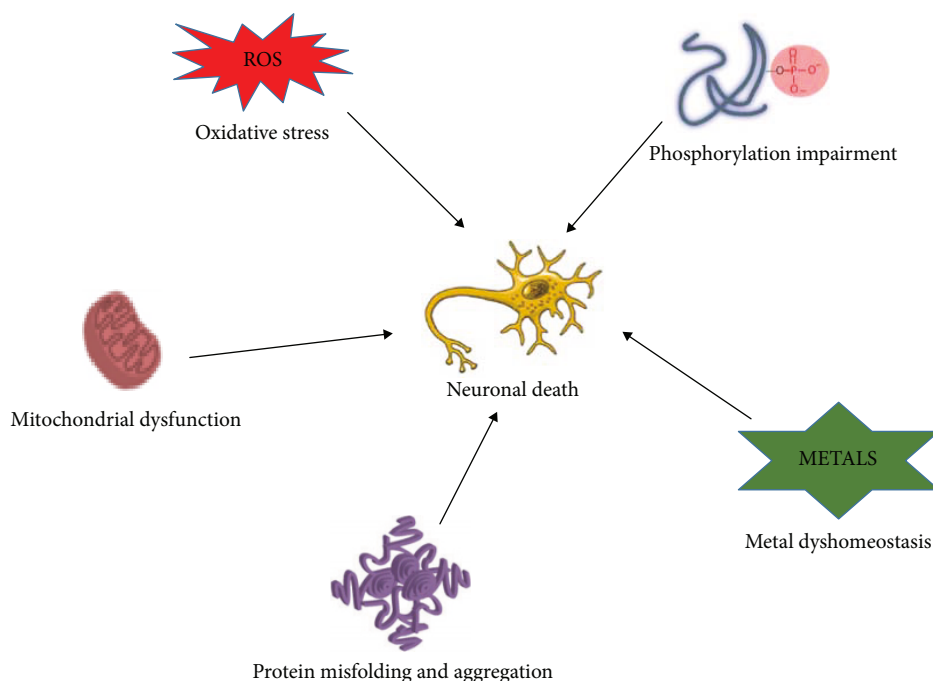


FIGURE 1: Various processes shown to be dysregulated in neurodegenerative disorders.

can cause cell death or oxidative stress [11]. While it is still unclear whether ROS is the triggering factor for NDs, they are likely to aggravate disease progression through oxidative damage and effects on mitochondria.

In view of the important roles of oxidative stress in NDs, the manipulation of ROS levels may be an encouraging treatment option to delay neurodegeneration and attenuate associated symptoms. Presently, there is no potent treatment for NDs and the available drugs are mainly focused on symptoms though with many adverse effects and limited ability to prevent disease progression [12].

Accordingly, medicinal plants such as *Hypericum perforatum* possessing antioxidant properties have been studied for their potential to attenuate neurodegenerative symptoms [13–16]. For instance, previous reports show that extracts of *H. perforatum* significantly attenuated oxidative stress by reducing lipid peroxidation [17], reducing oxidation of the mitochondrial lipid membrane [18], preserving the activities of antioxidant enzymes [19], and consequently preventing neurotoxicity in experimental models of NDs. As a result of these findings amongst others, Sánchez-Reus et al. proposed standardized extracts of *H. perforatum* as a possible treatment for elderly patients showing signs of NDs associated with elevated oxidative stress [19]. Although reports show that treatments involving *H. perforatum* are generally safe, minor adverse effects have been reported; they include dizziness, allergic reactions, restlessness, gastrointestinal symptoms, dryness of the mouth, and lethargy [20–22].

Similarly, there is currently an increase in the usage of natural compounds/products as potential neuroprotective agents. Examples include, curcumin, bilobalide, chitosan, and apigenin, all known to have potent protective effects on neurons [23–28]. Recently, bioflavonoids have found use in

the healthcare system owing to their wide range of biological activities, low cost, and significantly high safety margins [29]. Rutin (3,3',4',5,7-pentahydroxyflavone-3-rhamnoglucoside, Figure 2) also called sophorin, rutoside, and quercetin-3-rutinoside is a polyphenolic bioflavonoid, largely extracted from natural sources such as oranges, lemons, grapes, limes, berries, and peaches [30, 31]. Rutin is a vital nutritional component of plants [32] and its name originates from the plant *Ruta graveolens*, which also contains rutin [33]. Chemically, it is a glycoside comprising of flavonol aglycone quercetin along with disaccharide rutinose [33]. Some studies suggest that rutin has a potential protective role in NDs due to its beneficial effects as a potent antioxidant [34, 35]. Hence, this review presents an outline of the scientific literature regarding the potential neuroprotective role of rutin in NDs.

**1.1. Oxidative Stress and Reactive Oxygen Species.** Oxygen is essential for all multicellular life but in excess, it is potentially hazardous. ROS is formed when cells exposed to oxygen continuously generate oxygen free radicals. Endogenous free radicals are generated from inflammation, mental stress, immune cell activation, excessive exercise, infection, ischemia, cancer, and aging while exogenous free radicals are produced from air and water pollution, radiation, alcohol, cooking (smoked meat, used oil, and fat), heavy or transition metals, cigarette smoke, and industrial solvents [36–38]. The main source of endogenous ROS production is the mitochondria but it can also occur in other organelles [39]. ROS include free radicals (superoxide,  $\cdot\text{O}_2^-$ ), hydroxyl radical ( $\cdot\text{OH}$ ), or nonradicals (hydrogen peroxide,  $\text{H}_2\text{O}_2$ ).  $\cdot\text{O}_2^-$  is proposed to play a crucial role in ROS production and  $\cdot\text{OH}$  is recognized as the most reactive ROS that are primarily liable for the toxic effects of ROS [40].

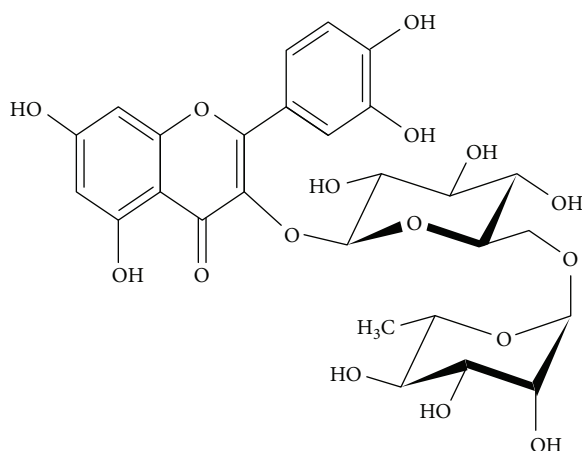


FIGURE 2: Diagram showing the chemical structure of rutin.

Cellular levels of ROS may be decreased through the defence mechanisms of small-molecule antioxidants and antioxidant enzymes [41].  $\cdot\text{O}_2^-$  is reduced by superoxide dismutases (SOD) into the more stable form of  $\text{H}_2\text{O}_2$ .  $\text{H}_2\text{O}_2$  may produce highly reactive hydroxyl radicals  $\cdot\text{OH}$  and can be reduced to  $\text{H}_2\text{O}$  and  $\text{O}_2$  by catalase (CAT), glutathione peroxidase (GPx), and other peroxidases [42, 43]. The cellular antioxidant glutathione (GSH) is involved in two types of reactions. First of all, in its reduced form, GSH nonenzymatically reacts with  $\cdot\text{O}_2^-$  and  $\cdot\text{OH}$  for the elimination of ROS [41, 44]. Next, GSH serves as the electron contributor for the reduction of peroxides in the GPx reaction [45]. When GSH reacts with ROS, it is oxidized (GSSG) and produces glutathione disulfide (the last product of GPx reactions). GSH can be further restored from glutathione disulfide by the reaction with glutathione reductase through a transfer of electrons from NADPH to glutathione disulfide [46]. Numerous studies have stated that GSH is involved in impeding apoptotic cell death and DNA damage in cells following oxidative stress [47, 48]. Hence, cellular antioxidants and antioxidant enzymes work together to prevent the accumulation of damaging ROS in the cell. Dysregulation of their functions is an indication of altered oxidative states, which may contribute to cell death.

The harmful effects of ROS include damage of DNA or RNA, oxidation of amino acids in proteins, oxidative deactivation of particular enzymes by oxidation of cofactors, and oxidations of polyunsaturated fatty acids in lipids (lipid peroxidation). The uninterrupted attack of protein by ROS forms protein carbonyls and nitrites, such that monitoring of their levels provides an additional measure of the effect of oxidative stress [49]. Lipid peroxidation results in the generation of lipid peroxidation products such as malondialdehyde (MDA) and thiobarbituric acid reactive substances (TBARS) [50]. Assay of TBARS measures MDA present in the sample and MDA generated from lipid hydroperoxides. An increase in free radicals is directly proportional to overproduction of MDA and is therefore a commonly used marker of oxidative stress and antioxidant status [50].

## 2. Link between Oxidative Stress and Neurodegenerative Disorders

The pathogenesis of NDs is a complex interplay between genetic and nongenetic factors [51]. Generally, nongenetic/sporadic forms represent the majority of these cases. There are a number of NDs, but for the purposes of this review, we will focus on Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and human prion diseases (PrDs) [1, 12].

AD is the most common ND and it primarily affects middle- to old-aged individuals, nearly one in four individuals over the age of 85 [52]. AD has various etiological factors including genetic and environmental factors [52, 53]. It is characterized by neuronal loss and atrophy in the neocortex, hippocampus, amygdala, and basal forebrain [54, 55]. Its pathophysiological hallmarks include depositions in the forms of senile plaques, extracellular  $\beta$ -amyloid ( $A\beta$ ) protein, and intracellular deposits of the microtubule-linked protein tau as neurofibrillary tangles in the AD brains leading to dementia [56].

A common pathological feature in AD is the oxidation of nucleic acids, proteins, and lipids in neurons [57]. ROS interacts with polyunsaturated fatty acids in the neurons, leading to high levels of lipid peroxidation [58]. Increased levels of oxidative stress biomarkers (carbonyls, MDA, and 3-nitrotyrosine) in the blood [59, 60] and changes in the activities of antioxidant enzymes (SOD and CAT) reflect oxidative stress in the brain [61, 62].

The underlying mechanisms (Figure 3) proposed for the initiation of oxidative stress in AD include  $A\beta$  accumulation [63, 64], hyperphosphorylated tau [65, 66], inflammation [67, 68], mitochondrial dysfunction [64, 69], and metal accumulation [70, 71].

To date, there is no treatment that can cure AD, but there are available symptomatic drug treatments consisting mostly of cholinesterase inhibitors such as donepezil, rivastigmine, and galantamine [72]. Others include memantine [73, 74], a N-methyl-D-aspartate receptor antagonist approved by the US Food and Drug Administration (FDA), and a combination of memantine with donepezil [75].

PD is characterized by chronic degeneration of dopaminergic neurons in the substantia nigra pars compacta of the midbrain [76]. This in turn results in the depletion of dopamine neurotransmitter production, which leads to motor deficits such as symptomatic rigidity, bradykinesia, postural instability, and resting tremor [77]. The cause of dopaminergic neuronal cell death in PD remains unidentified, but several factors such as oxidative stress may contribute to this degeneration and have been closely linked to other sections of neurodegenerative processes, such as  $\alpha$ -synuclein, inflammation, and cell death [78–81].

Oxidative stress is believed to be a fundamental mechanism leading to cellular dysfunction in both idiopathic and familial forms of PD. An increase in protein oxidation has been detected in the substantia nigra of PD patients compared to healthy individuals [82]. Accordingly, the substantia nigra of PD patients reveals decreased levels of GSH and higher levels of oxidized proteins, DNA, and lipids [83, 84].

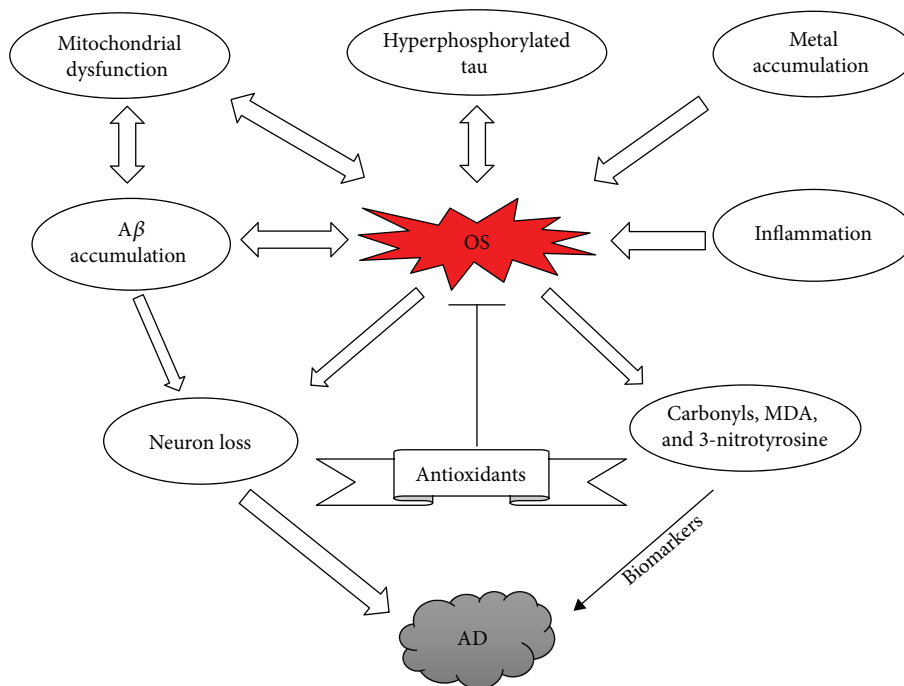


FIGURE 3: Schematic diagram showing the role of oxidative stress (OS) in Alzheimer's disease.

The accumulation of lipid peroxidation by-products has been reported in the serum and cerebral spinal fluid of PD patients while higher levels of MDA and TBARS have been reported in the substantia nigra and stratum of PD brains [85–87].

Various mechanisms for the generation of ROS in PD include mitochondrial dysfunction, metabolism of dopamine, iron, aging, calcium, and neuroinflammation [88]. PD causing genes such as *SNCA*, *DJ-1*, *LRRK2*, *PINK1*, and *PARK2* also affect in complex ways leading to aggravation of ROS production and vulnerability to oxidative stress [88]. In addition, homeostatic processes such as mitophagy and the ubiquitin-proteasome system are affected by oxidative stress [88]. The interaction amongst these numerous mechanisms are thought to contribute to neurodegeneration in PD (Figure 4).

The primary treatment for symptomatic patients and the most effective pharmacologic agent for PD is levodopa [89, 90]. It is reported that levodopa is mostly effective at controlling rigidity and bradykinesia [89]; however, postural reflex, gait disturbance, and speech are less likely to respond. Levodopa is combined with carbidopa, because carbidopa blocks dopa decarboxylase thereby preventing peripheral conversion of levodopa to dopamine. Additionally, its combination with levodopa reduces the peripheral adverse effects of dopamine (e.g., nausea and hypotension) and increases cerebral levodopa bioavailability. Treatment with monoamine oxidase-B (MAO-B) inhibitors, amantadine (Symmetrel), or anticholinergics may modestly improve mild symptoms; nevertheless, most patients need a dopamine agonist or levodopa [91]. Furthermore, advances in brain imaging and neurosurgical techniques has highlighted surgical treatment for this disorder. In an evidence-based review, it is reported that deep brain stimulation of the subthalamic nucleus effectively improves motor function and reduces dyskinesia and motor fluctuations [90, 92].

HD is characterized by motor, cognitive, and behavioral dysfunction [93] and demonstrates an autosomal dominant mode of inheritance [94]. It is characterized by a remarkable specificity of neuronal loss and the regions most affected are the striatum, where there is usually 50–60% loss of cross-sectional area from the caudate nucleus and the putamen in advanced stages of the disease [95]. HD is linked with a triad of symptoms which includes cognitive deterioration, movement disorders, and psychiatric disturbances [95]. These signs begin subtly, most frequently between the ages of 35 to 50, but the age of onset can differ from early childhood until old age. The disease is relentlessly progressive and is deemed to be fatal 15–20 years after the onset of symptoms [95]. Classical features of HD are disturbances of motor function which include chorea (unintentional brief movements that tends to flow between body regions) and progressive deficiency of coordination of voluntary movements [95–98].

Convincing data supports a critical role for oxidative stress in the pathogenesis of HD [99–101] (Figure 5). Mutant huntingtin proteins (MTPs) serve as the source of ROS, owing to a substantial amount of oxidized proteins in partially purified MTP aggregates [99]. It is proposed that elevated oxidative stress is a major mechanism in the late stages of HD pathogenesis. [100]. Another mechanism involved in ROS-mediated HD pathogenesis is the impairment of the electron transport chain and mitochondrial dysfunction [102, 103]. Defects in oxidative phosphorylation have been detected in the brain tissues of HD patients [104], and enhanced lipid peroxidation accompanied by reduced GSH content has been reported in patients with severe symptoms of HD [101, 105, 106]. Substantial oxidative DNA damage has also been reported in HD mouse models [107, 108].

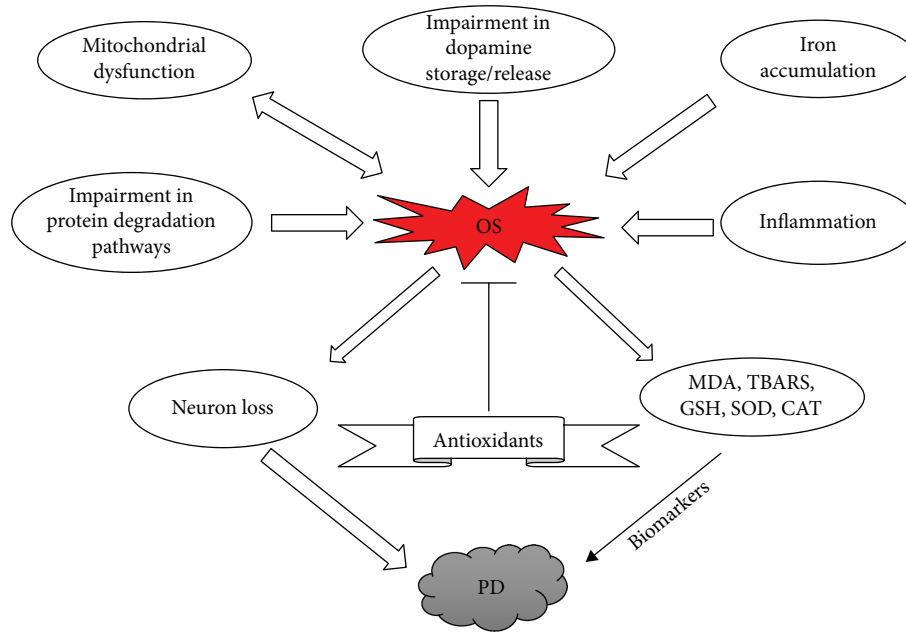


FIGURE 4: Schematic diagram showing the role of oxidative stress in Parkinson's disease.

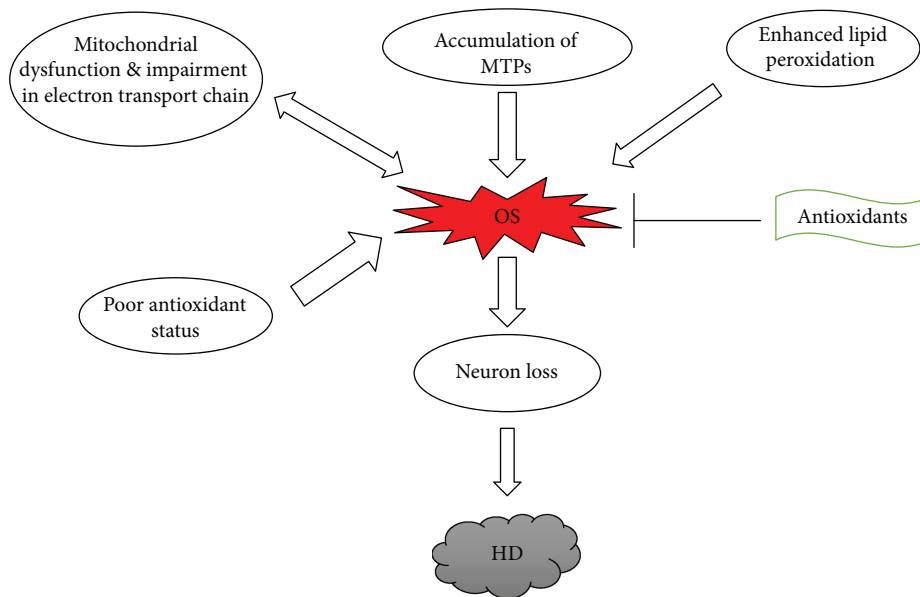


FIGURE 5: Schematic diagram showing the involvement of oxidative stress in Huntington's disease.

There are no existing treatments to alter the course of HD, but symptomatic therapies and education are effective tools used by clinicians in addressing patients and families affected by HD. Several drugs and surgical procedures have been assessed in HD for their effectiveness in subduing chorea. These include dopamine-depleting agents, agonists and antagonists, deep brain stimulation, benzodiazepines, fetal cell transplantation, acetylcholinesterase inhibitors, glutamate antagonists, antiseizure prescriptions, lithium, and cannabinoids [94, 109, 110]. Tetrabenazine is the only FDA-approved drug for HD designated for the treatment of chorea linked with HD [111, 112]. Other promising drugs shown in controlled trials to considerably lessen chorea in HD patients

include amantadine [113], olanzapine [114, 115], quetiapine [116, 117], and aripiprazole [118, 119].

PrDs are related to a variety of clinical presentations and have attracted vast research awareness for many years not only due to their distinctive composition and properties but also because of their effect on public health [120–122]. Examples of PrDs include Gerstmann Sträussler-Scheinker syndrome, Creutzfeldt-Jakob disease (CJD), kuru, and fatal familial insomnia while animal PrDs include scrapie and bovine spongiform encephalopathy [123].

According to the “protein-only” hypothesis [124, 125], host-encoded cellular prion protein (PrP<sup>C</sup>) is converted to a different structural isoform which is known as PrP<sup>Sc</sup>



[120–122, 126]. It is widely regarded as the infectious agent which can duplicate itself with high conformity by enlisting endogenous PrP<sup>C</sup> and that the modification between these isoforms lies strictly in its state of aggregation and its monomer conformation [120, 127]. Microscopic examination of the brains of patients with PrDs typically shows characteristic histopathologic alterations, comprising of neuronal degeneration, and vacuolation, which gives the cerebral grey matter a spongiform appearance, and a reactive increase of astroglial cells [125, 128].

Various lines of evidence have recognized markers of oxidative stress in the brains of rodents with prion disease [129, 130] (Figure 6). Immunohistochemical studies in the brains of scrapie-infected mice have revealed the presence of lipid oxidation markers, nitrotyrosine (a marker of peroxynitrite production), and heme-oxygenase-1 (an enzyme leading to the development of antioxidant molecules), suggesting that oxidative stress might be one mechanism of neuronal loss [131, 132]. There are also indications for mitochondrial damage induced by oxidative stress in cells from brains of scrapie-infected mice and hamsters [133, 134]. Furthermore, a study by Kim et al. suggested that iron-induced oxidative stress might be a key mechanism of neuronal loss in scrapie [135].

Unfortunately, there is presently no effective treatment or disease-modifying therapy for PrDs. The search for treatments is primarily hindered by inadequate understanding of prion disease pathogenesis. However, identified drugs which show some effectiveness in treating prion diseases in *in vitro* and *in vivo* systems include quinacrine and pentosan polysulfate [136]. These compounds have been used as compassionate therapy in CJD patients; however, no therapeutic value was observed [137, 138]. Other treatment options attempted for PrDs that have had limited success include immunotherapy and vaccination [139].

### 3. General Uses of Rutin

Rutin has been shown to have an extensive array of pharmacological applications due to its numerous properties including antioxidant, anti-inflammatory, cardiovascular, neuroprotective, antidiabetic, and anticancer activities [140, 141].

Over the years, various mechanisms have been found to be responsible for its antioxidant activities in both *in vitro* and *in vivo* models. Firstly, it was reported that its chemical structure can directly scavenge ROS [142]. Secondly, it increases the production of GSH and cellular oxidative defence systems are believed to be upregulated by an increased expression of numerous antioxidant enzymes such as CAT and SOD [143–145]. Thirdly, rutin inhibits xanthine oxidase which is involved in generating ROS [146]. From the aforementioned, the optimism generated by the therapeutic potential of rutin in many health conditions in which oxidative stress is an underlying cause is understandable [34, 143, 147, 148]. The rest of this review will summarize the main findings of the neuroprotective effects of rutin in various experimental models of NDs. The various *in vitro* and *in vivo* studies are summarized in Tables 1 and 2, respectively.

#### 3.1. Studies of Rutin in AD

**3.1.1. Toxins Used to Generate Models of AD.** Several lines of evidence indicate that A $\beta$  peptides are the key factors in AD pathogenesis [149–151]. A $\beta$  peptide, produced from amyloid precursor protein (APP), is a very important part of amyloid plaques and has been described to be neurotoxic [152]. It is hypothesized that an anomaly in the proteolytic processing of the APP leads to an increase in the generation of A $\beta$  peptides (such as A $\beta$ <sub>40–42</sub> and A $\beta$ <sub>25–35</sub>) which in turn leads to the buildup of A $\beta$ , a key event in the pathogenesis of AD [153, 154]. A $\beta$  may also induce oxidative stress by causing mitochondria dysfunction which results in increased ROS and decreased levels of antioxidants such as GSH and the activity of antioxidant enzymes such as SOD, GPx, and CAT [155]. A $\beta$ -induced ROS production is believed to aid A $\beta$  production and accumulation, thereby quickening the progression of AD [68, 156]. Additionally, A $\beta$  induces nitric oxide (NO) generation by upregulating the expression of nitric oxide synthase (iNOS) [157, 158] which plays a fundamental role in the series of events leading to cell death [159].

**3.1.2. In Vitro Studies.** A $\beta$  accumulation is a key feature of AD, and rutin has been shown to decrease and reverse A $\beta$ <sub>25–35</sub> fibril formation *in vitro* indicating that its action might be connected to their free radical scavenger activity and might subdue neurotoxicity [153]. Furthermore, in a different study [155], rutin acted as a multifunctional agent by inhibiting A $\beta$  aggregation and cytotoxicity, preventing mitochondrial damage, reducing production of MDA, ROS, NO, GSSG, iNOS, and proinflammatory cytokines, and increasing CAT, SOD, GSH, and GPx levels. Yu et al. demonstrated the ability of rutin to inhibit amylin-induced neurocytotoxicity and enhance antioxidant enzyme activities in the SH-SY5Y cells [35]. Treatment of human neuroblastoma SH-SY5Y cells with rutin-loaded nanoparticles conferred protective effects on A $\beta$ -induced cytotoxicity, decreased levels of NO, and ROS [160]. In a related activity, rutin modulated the generation of proinflammatory cytokines by reducing TNF- $\alpha$  and interleukin- (IL-) 1 $\beta$  generation in A $\beta$ <sub>40–42</sub>-treated BV-2 cells [155]. Bispo da Silva et al. established that rutin treatment was not toxic to microglial cells and induced a dose-dependent increase in microglial proliferation, decreasing the mRNA levels of *TNF*, *IL-1b*, *IL-6*, and *iNOS*; reduced production of IL-6, TNF, and NO; increased production of the M2 regulatory cytokine IL-10 and arginase; and significantly inhibited the LPS-induced expression of *PTGS2*, *IL-18*, and *TGF $\beta$*  [161].

**3.1.3. In Vivo Studies.** Several studies have utilized animal models as a preclinical tool to evaluate the neuroprotective potential of bioactive compounds such as edaravone and vitamin D3 in AD [162, 163]. In a study, Xu et al. [164] showed that following oral administration of rutin at a daily dose of 100 mg/kg for six weeks, rutin attenuated memory deficits in APP<sup>swe</sup>/PS1<sup>dE9</sup> transgenic mice, reduced oligomeric A $\beta$  level as well as downregulated microgliosis and astrocytosis, and reduced IL-1 and IL-6 levels in the brain. In an interesting and similar study by Hu et al., intravenous

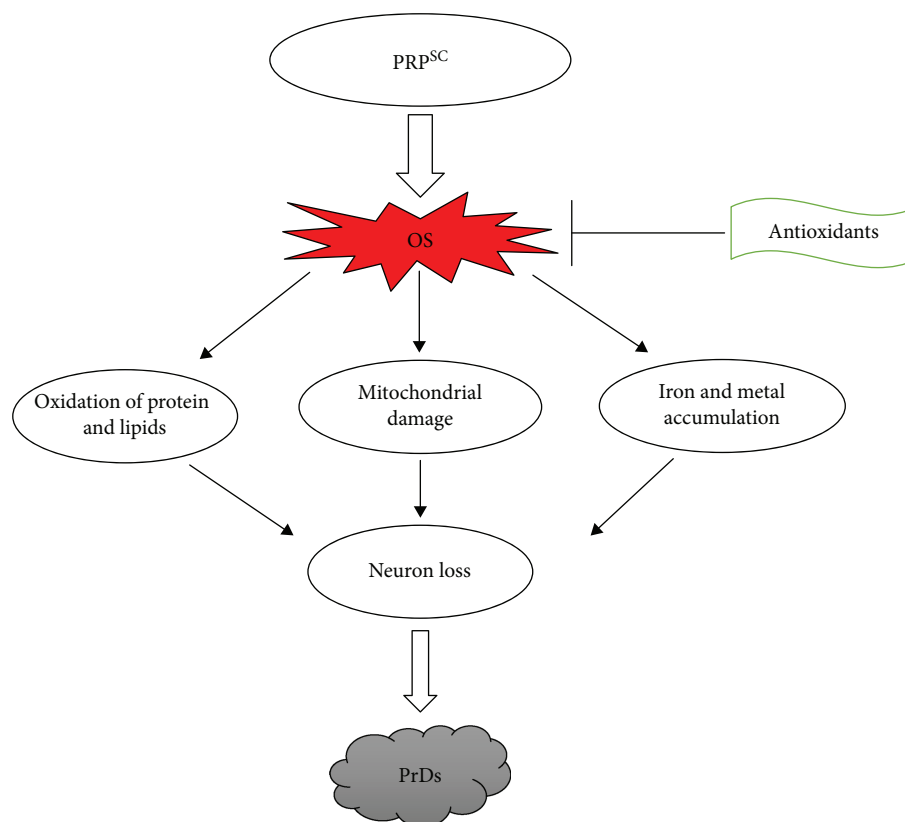


FIGURE 6: Schematic diagram showing the involvement of oxidative stress in prion diseases.

TABLE 1: Summary of the protective effects of rutin in *in vitro* models of neurodegeneration.

Toxin used in cellular model	Disorder	Key findings	Reference
$A\beta_{25-35}$ -treated SH-SY5Y neuroblastoma cells and $A\beta_{25-35}$ -treated APP695-transfected SH-SY5Y (APP <sup>swe</sup> ) cells	AD	$\downarrow A\beta$ fibrils, $\downarrow \beta$ -secretase enzyme (BACE), $\downarrow$ ROS, $\uparrow$ GSH, $\downarrow$ lipid peroxidation	[153]
$A\beta_{42}$ -treated SH-SY5Y and BV-2 cells	AD	$\downarrow$ ROS, $\downarrow$ NO, $\downarrow$ GSSG, $\downarrow$ MDA, $\downarrow$ iNOS, $\downarrow$ MMP, $\uparrow$ GSH/GSSG ratio, $\uparrow$ SOD, CAT, and GPx, $\downarrow$ TNF- $\alpha$ , $\downarrow$ IL-1 $\beta$	[155]
Amylin-treated SH-SY5Y neuroblastoma cells	AD	$\uparrow$ cell viability, $\downarrow$ ROS, $\downarrow$ NO, $\downarrow$ GSSG, $\downarrow$ MDA and $\downarrow$ TNF- $\alpha$ and $\downarrow$ IL-1 $\beta$ , $\uparrow$ GSH/GSSG ratio, $\uparrow$ SOD, $\uparrow$ CAT, $\uparrow$ GPx, $\downarrow$ iNOS	[35]
6-OHDA-treated PC-12 cells	PD	$\uparrow$ cell viability, $\uparrow$ 6-OHDA-induced reduction in SOD, CAT, GPx, and GSH, $\downarrow$ lipid peroxidation	[147]
6-OHDA-treated PC-12 cells	PD	$\uparrow$ 6-OHDA-induced reduction in SOD, CAT, GPx, and GSH. $\downarrow$ lipid peroxidation, $\downarrow$ MDA	[184]
6-OHDA-treated PC-12 cells	PD	$\downarrow$ Park2, $\downarrow$ UCHL1, $\downarrow$ DJ-1, $\downarrow$ Casp3, $\downarrow$ Casp7, $\uparrow$ TH, $\uparrow$ NSF, $\uparrow$ Opa1	[185]
Prion peptide-treated HT22 cells	PrD	$\downarrow$ ROS, $\downarrow$ NO, $\downarrow$ apoptosis, $\downarrow$ Fas, $\downarrow$ Fas-L	[210]

6-OHDA: 6-hydroxydopamine; CAT: catalase; Fas L: Fas ligand; GPx: glutathione peroxidase; GSH: reduced glutathione; GSSG: glutathione disulfide; IL-10; interleukin 10; IL-6: interleukin 6; IL-8: interleukin 8; IL-1 $\beta$ : interleukin 1 beta; iNOS: inducible nitric oxide synthase; MDA: malondialdehyde; MMP: mitochondrial membrane potential; NSF: N-ethylmaleimide-sensitive factor; Opa1: optic atrophy 1; ROS: reactive oxygen species; SOD: superoxide dismutase; TH: tyrosine hydroxylase; TNF- $\alpha$ : tumor necrosis factor- $\alpha$ .

administration of Congo red/rutin magnetic nanoparticles (MNPs) resulted in rescue of memory deficits and amelioration of neurologic changes in the brains of APP<sup>swe</sup>/PS1<sup>dE9</sup> transgenic mice [160]. Cheng et al. showed that rutin and exercise enhanced high-fat diet-induced cognitive defects in

mice [165]. Rutin's ability to alleviate impaired cognition and memory in  $A\beta_{25-35}$ -induced mouse model of AD was demonstrated by Choi et al. in 2015 [166].

Most recently, Ramalingayya et al. [167] demonstrated that pretreatment with rutin inhibited doxorubicin- (DOX-)

TABLE 2: Summary of the protective effects of rutin in *in vivo* models of neurodegeneration.

Toxin used in animal model	Disorder	Key findings	Reference
Doxorubicin- (DOX-) treated neuroblastoma cells (IMR32) and doxorubicin-induced cognitive dysfunction in Wistar rats	AD	↓ apoptosis, ↓ ROS, ↓ episodic memory deficit, ↓ TNF- $\alpha$ , ↑ DOX-induced reduction of catalase, GSH, and SOD	[167]
Microglial cells obtained from the cortex of Wistar newborn rats	AD	↓ TNF, ↓ IL-1b, ↓ IL-6, ↓ iNOS, ↑ IL-10, ↑ arginase, ↓ PTGS2, ↓ IL-18, ↓ TGF $\beta$	[161]
** APPswe/PS1dE9 transgenic mice	AD	↑ memory, ↑ SOD, ↑ GSH/GSSG ratio, ↓ GSSG, ↓ MDA, ↓ IL-1, ↓ IL-6	[164]
High-fat diet-induced obese (DIO) cognitively impaired C57BL/6J mice	AD	↓ cognitive defects	[165]
Scopolamine-treated Wistar rats	AD	↑ recognition, ↑ discriminative indices	[168]
A $\beta_{25-35}$ -infused mouse model	AD	↓ impaired cognition, ↑ memory, ↓ NO, ↓ lipid peroxidation	[166]
Beta-amyloid-induced neurotoxic rats	AD	↑ ERK1, ↑ CREB, ↑ BDNF, ↑ memory retrieval, ↓ MDA	[171]
Intracerebroventricular streptozotocin- (ICV-STZ-) infused rats	AD	↓ TBARS, ↓ nitrite level, ↓ poly ADP-ribosyl polymerase, ↑ GSH, ↓ lipid peroxidation, ↓ cognitive deficits, ↓ COX-2, ↓ GFAP, ↓ IL-8, ↓ iNOS, ↓ NF- $\kappa$ B	[172]
Scopolamine-induced zebrafish	AD	↓ amnesia	[173]
Intrastratial injection of 6-OHDA in rats	PD	↓ 6-OHDA-induced increase in rotations, ↓ deficits in locomotor activity, ↓ motor coordination, ↑ antioxidant levels, ↑ DA, ↑ dopaminergic D2 receptors	[78]
Haloperidol-treated rats	PD	↓ catalepsy, ↓ akinesia, ↑ locomotor activity, ↑ GSH, ↑ SOD, ↓ TBARS	[77]
3-Nitropropionic (3-NP) acid-treated rats	HD	Improved 3-NP-induced behavioral alterations; restored activities of mitochondrial complex enzymes	[199]
3-Nitropropionic (3-NP) acid-treated rats	HD	Restored biochemical, behavioral, and cellular alterations	[200]
3-Nitropropionic (3-NP) acid-treated rats	HD	↑ body weight, ↑ locomotor activities, ↑ memory, ↑ antioxidant levels, ↓ lipid peroxides, ↓ nitrite, ↓ GFAP, ↓ AchE	[201]

\*\*Rutin loaded magnetic nanoparticles were used in this experiment; 6-OHDA: 6-hydroxydopamine; AchE: acetylcholine esterase; BDNF: brain-derived neurotrophic factor; CAT: catalase; CREB: cAMP response element binding protein; DA: dopamine; doxorubicin: DOX; ERK1: extracellular signal-regulated kinase 1; GFAP: glial fibrillary acidic protein; GPx: glutathione peroxidase; GSH: reduced glutathione; GSSG: glutathione disulfide; IL-10: interleukin 10; IL-6: interleukin 6; IL-8: interleukin 8; IL-1b: interleukin 1 beta; iNOS: inducible nitric oxide synthase; MDA: *malondialdehyde*; MMP: mitochondrial membrane potential; NF- $\kappa$ B: nuclear factor-kappaB; NSF: N-ethylmaleimide-sensitive factor; PTGS2: prostaglandin-endoperoxide synthase 2; ROS: reactive oxygen species; SOD: superoxide dismutase; TBARS: thiobarbituric acid reactive substances; TGF $\beta$ : transforming growth factor beta; TH: tyrosine hydroxylase; TNF- $\alpha$ : tumor necrosis factor- $\alpha$ .

induced ROS generation and increased DOX-induced reduction of CAT, GSH, and SOD levels in Wistar rats. Other findings include prevention of DOX-induced cell cycle and morphological changes, reduction of DOX-induced apoptosis, prevention of DOX-induced episodic-like memory deficit, prevention of rise in TNF- $\alpha$  levels, and reversal of myelosuppressive effect of DOX [167]. In a similar AD study by Ramalingayya et al. [168], rutin dose dependently improved recognition and discriminative indices in time-induced long-term as well as scopolamine-induced short-term episodic memory deficit AD models without disturbing locomotor activity. Moghbelinejad et al. demonstrated that rutin significantly increased extracellular signal-regulated protein kinase 1 (ERK1), cAMP response element-binding protein (CREB), and brain-derived neurotrophic factor (BDNF) gene expression in the hippocampus of rats. Studies show that the mitogen-activated protein kinase (MAPK) cascade that includes ERK1/2 and CREB is involved in neural plasticity and survival [169]. Long-lasting changes in synaptic plasticity

and memory are the resultant effects arising from the activation the MAPK cascade [169]. BDNF affects the survival and function of neurons in the CNS and is essential for normal synaptic connection formation during growth and for learning and memory in adults [170]. They also found rutin to significantly increase memory retrieval while significantly lowering MDA levels in the hippocampus [171].

In a different type of AD model, Javed et al. showed that rutin significantly reduced intracerebroventricular streptozotocin- (ICV-STZ-) induced increase in TBARS, poly ADP-ribosyl polymerase, and nitrite in the hippocampus of rats. Rutin also significantly increased levels of GSH, GPx, glutathione reductase (GR), and CAT [172]. Furthermore, rutin also significantly improved cognitive deficits, attenuating STZ-induced inflammation by decreasing the expression of interleukin-8 (IL-8), glial fibrillary acidic protein (GFAP), cyclooxygenase-2 (COX-2), nuclear factor- $\kappa$ B, inducible iNOS, and reduced histological abnormalities in the hippocampus [172]. In a different model of AD using zebrafish,



Richetti et al. were able to show that rutin did not affect zebrafish general locomotor activity and prevented scopolamine-induced amnesia [173].

The various studies highlighted in this section demonstrates the neuroprotective capability of rutin in ameliorating the adverse effects of neurodegeneration as well as cognitive impairments associated with AD in various animal models.

### 3.2. Studies of Rutin in PD

**3.2.1. Toxins Used to Generate Models of PD.** Over the years, neurotoxins used to induce dopaminergic neurodegeneration include 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 1,1-dimethyl-4,4-bipyridinium (paraquat) and rotenone [174, 175]. Seemingly, all of these toxins provoke the formation of ROS. 6-OHDA is known to be taken up by dopaminergic neurons through the dopamine transporter [174, 176]. In the neurons, oxidized molecules of 6-OHDA produces free radicals that hinders mitochondrial complex I and produces  $\cdot\text{O}_2^-$  and  $\cdot\text{OH}$  which becomes toxic to dopaminergic neurons and induces microglial activation. Rotenone and MPTP are known for their ease of use in animals and their similar ability to potently inhibit complex I. After its systemic administration, MPTP swiftly crosses the blood brain barrier [175].

Once in the brain, MPTP is converted in the astrocytes by monoamine oxidase B (MAO-B) to 1-methyl-4-phenylpyridinium (MPP<sup>+</sup>) and is thereafter released into the extracellular space [175, 177, 178]. Once inside dopaminergic neurons, MPP<sup>+</sup> accumulates in mitochondria and impairs mitochondrial respiration by impeding complex I in the electron transport chain, which induces the production of ROS [177, 179]. Rotenone is also very lipophilic and is circulated evenly throughout the brain after crossing the BBB [174, 180]. Paraquat, an herbicide, has a very close structural similarity to MPP<sup>+</sup> and has been proposed to be a risk factor for PD [181]. A neurobehavioral syndrome characterized by reduced ambulatory activity, a decline in striatal dopamine nerve terminal density, and a significant decrease in substantia nigra dopaminergic neurons have all been associated and linked to effects from systemic administration of paraquat [182]. Experimental evidence show that paraquat crosses the BBB to cause damage to the dopamine neurons in the substantia nigra, like MPP<sup>+</sup> [182]. In addition, sustained exposure to paraquat results in a marked accrual of  $\alpha$ -synuclein-like aggregates in neurons of the substantia nigra pars compacta in mice [183].

**3.2.2. In Vitro Studies.** PD has been modelled *in vitro* through the specific neurotoxic effect of the 6-OHDA on dopaminergic neurons. Neurotoxicity triggered by 6-OHDA was attenuated by rutin treatment in PC12 cells where a significant dose-dependent cytoprotective activity was detected in rutin-pretreated cells [147]. Rutin activated antioxidant enzymes including SOD, CAT, GPx, and GSH when compared to cells incubated with 6-OHDA alone in conjunction with a significantly reduced lipid peroxidation activity [147, 184]. In 2015, Magalingam et al. reported that pretreatment with rutin in PC12 cells downregulated the mRNA expression of PD-linked genes (*PARK2*, *UCHL1*, and *DJ-1*) and

proapoptotic (*Casp3* and *Casp7*) genes which were upregulated in the 6-OHDA-treated PC12 cells [185]. The study showed that rutin upregulated the *TH* gene which is essential in dopamine biosynthesis and further upregulated the ion transport and antiapoptotic genes (*NSF* and *Opa1*) [185].

In a different model of PD, rutin pretreatment prevented rotenone-induced loss of SH-SY5Y cells, inhibited rotenone-induced ROS formation, and suppressed elevation of calcium [34]. Rutin attenuated rotenone-induced reduction of mitochondrial membrane potential and activation of the JNK and p38 MAPK pathways, reversed changes of Bcl-2 and Bax levels, and inhibited apoptosis and caspase-9/3 activation [34].

**3.2.3. In Vivo Studies.** In one of the very few and earliest studies documenting the neuroprotective effects of rutin in *in vivo* models, oral administration of rutin significantly protected against 6-OHDA-induced increase in rotations, deficits in locomotor activity and motor coordination in male Wistar rats [78]. Immunohistochemical and histopathological findings in the substantia nigra showed that rutin protected neurons from toxic effects of 6-OHDA [78]. In a different model of PD, Sharma et al. [77] showed that rutin played an important role in attenuating behavioral, biochemical, and histological parameters after haloperidol administration in rats and further confirmed the protective effects of rutin.

These *in vivo* and *in vitro* studies exhibit the potential of rutin as a neuroprotector and suggest a role for this compound in the prevention and reversal of degenerative diseases such as PD.

### 3.3. Studies of Rutin in HD

**3.3.1. Toxins Used to Generate Models of HD.** Animal models of HD have provided understanding into disease pathology, and previous studies of HD used toxin-induced models to study excitotoxicity-induced cell death and mitochondrial impairment, both mechanisms of HD degeneration. These models, based on quinolinic acid (QA) and 3-nitropropionic acid (3-NP), are still often used in HD studies [186]. QA is experimentally administered straight to the striatum because it is incapable of crossing the BBB [187]. Its key features include striatal neurodegeneration in rats [188, 189], mice [190], and primates [191, 192] in a strikingly similar pattern to that seen in human HD. Its advantages as a HD model includes its ease of use in more complex animals, its influences on cognitive function, numerous resemblances between pathology observed in the HD brain, and its mode of cell death that mimics the mechanism of neuronal death seen in HD brains [193–195]. 3-NP is known to irreversibly inhibit the mitochondrial enzyme succinate dehydrogenase [196, 197]. Its major advantage is that it mimics cell death seen in the HD brain through a combination of apoptosis and necrosis [186]. Instantly after administration of 3-NP, there is a surge of necrotic cell death followed by gradual apoptosis [198]. 3-NP crosses the blood-brain barrier and can be administered systemically to mice, rats, and nonhuman primates [186].

**3.3.2. In Vivo Studies.** In a pioneering work on HD with rutin in 3-NP-treated rats, Suganya and Sumathi reported that oral

administration of rutin (25 mg/kg and 50 mg/kg) significantly decreased protein oxidation and improved endogenous antioxidant defence system. Furthermore, rutin improved 3-NP-induced behavioral alterations and restored the activities of mitochondrial complex enzymes (I, II, IV, and V) when compared to the 3-NP-induced group [199].

In 2016, Suganya and Sumathi again reported that oral administration of rutin (25 mg/kg body weight) to Wistar rats increased the levels of nonenzymatic antioxidants (vitamin C and E) when compared to a reduction in the 3-NP-induced group. In addition, rutin protected against 3-NP-induced reduction in motor activities, muscle coordination, and activities of adenosine triphosphatases (ATPases) [200].

Most recently, Suganya and Sumathi showed that rutin restored 3-NP-induced reduction of body weight, locomotor activities, memory, and antioxidants levels. They further stated that rutin ameliorated 3-NP-induced striatal damage by reducing levels of lipid peroxides, nitrite, GFAP, and activity of acetylcholine esterase [201].

Although these few *in vivo* studies offer concrete evidence for the therapeutic potential of rutin, there exists a critical need to further elucidate and provide more evidence for the therapeutic potential of rutin in *in vitro* models of HD.

### 3.4. Studies of Rutin in PrD

**3.4.1. Toxins Used to Generate Models of PrD.** The prion protein peptide 106–126 (PrP (106–126)) has frequently been used as a model system to study prion-induced neurodegeneration [202, 203]. This peptide induces neurotoxicity in neuronal cells owing to its amyloidogenic properties both *in vivo* and *in vitro* [204]. One of the major advantages of PrP (106–126) is that it is comparable to PrP<sup>Sc</sup> in numerous respects and at the same time is more soluble and easy to deploy for cell culture experiments [205]. PrP (106–126) is rich in  $\beta$ -sheet structure, increases the membrane microviscosity of neurons and astrocytes [206], and forms aggregates that are proteinase K-resistant and detergent-insoluble [204, 207, 208]. PrP (106–126) weakens liposomes and induces liposome fusion [209].

**3.4.2. In Vitro Studies.** In a pioneering study [210], the authors studied the neurotoxicity of PrP (106–126) in the HT22 hippocampal cell line and assessed the neuronal protection provided by rutin against the toxic effects of PrP (106–126). Rutin treatment blocked PrP- (106–126-) mediated increases in ROS production and NO release and delayed the decrease of neurotrophic factors that resulted from PrP accumulation. In addition, rutin mitigated PrP- (106–126-) associated mitochondrial apoptotic events by hindering mitochondrial permeability transition and caspase-3 activity and blocking expression of the apoptotic signals (Bax and PARP) in conjunction with a significantly reduced expression of the death receptor Fas and its ligand Fas-L [210].

There are currently no *in vivo* studies on the therapeutic potential of rutin in PrP models. Consequently, there is a dire need to further elucidate and provide more evidence for the

therapeutic potential of rutin in more *in vitro* and *in vivo* models of PrD.

## 4. Future Perspectives and Conclusion

Numerous *in vitro* (Table 1) and *in vivo* (Table 2) studies have demonstrated the ability of rutin to ameliorate various neurodegenerative processes that trigger AD, PD, HD, and PrDs. The ability of rutin to exert its neuroprotective effects in different models of NDs could be ascribed to its antioxidant as well as antiapoptotic and anti-inflammatory activities. In addition, rutin's activation of BDNF and the MAPK cascade (ERK1/2 and CREB) signifies its involvement in plasticity and survival of neurons in the CNS.

The benchmark for authenticating rutin's neuroprotective properties is clinical trials in humans. A few clinical trials have been conducted to examine the effect of a compound from the rutin family, O-( $\beta$ -hydroxyethyl)-rutosides (HRs) in venous disease patients with diabetes treated for a prolonged period of time [211]. HRs is obtained by substituting rutin hydroxyl groups with O- $\beta$ -hydroxyethyl groups. Human clinical trials with rutin (in the form of HRs) have shown that it is safe and well tolerated [211]. The lack of clinical trials exploring the efficacy of rutin in NDs is of concern. This may be due to lack of sufficient data on animal models in the various NDs.

As a flavonol among similar flavonoids, rutin's low bioavailability [212] owing to high metabolism, poor absorption, and rapid excretion generally makes its prospective use as a therapeutic agent restricted. Further studies to improve its bioavailability and investigations into its protective activities in more models of NDs (most especially PrDs and motor neuron disease) would provide a solid foundation for its use in clinical trials. Rutin's ability to offer neuroprotection against pathological insult offers hope in its utilization and development as a safe and effective neurotherapeutic agent.

## Conflicts of Interest

The authors have no conflict of interests to declare.

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## References

- [1] A. D. Gitler, P. Dhillon, and J. Shorter, "Neurodegenerative disease: models, mechanisms, and a new hope," *Disease Models & Mechanisms*, vol. 10, no. 5, pp. 499–502, 2017.
- [2] J. V. Hindle, "Ageing, neurodegeneration and Parkinson's disease," *Age and Ageing*, vol. 39, no. 2, pp. 156–161, 2010.
- [3] WHO, *Global Burden of Disease*, World Health Organization, Geneva, Switzerland, 2004.
- [4] G. G. Kovacs, "Current concepts of neurodegenerative diseases," *European Medical Journal Neurology*, vol. 2, no. 1, pp. 78–86, 2014.

- [5] D. Aarsland, K. Bronnick, J. P. Larsen, O. B. Tysnes, G. Alves, and For the Norwegian ParkWest Study Group, "Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest study," *Neurology*, vol. 72, no. 13, pp. 1121–1126, 2009.
- [6] G. J. Canter, "Speech characteristics of patients with Parkinson's disease: I. Intensity, pitch, and duration," *Journal of Speech and Hearing Disorders*, vol. 28, no. 3, p. 221, 1963.
- [7] S. Sheikh, Safia, E. Haque, and S. S. Mir, "Neurodegenerative diseases: multifactorial conformational diseases and their therapeutic interventions," *Journal of Neurodegenerative Diseases*, vol. 2013, Article ID 563481, 8 pages, 2013.
- [8] X. Chen, C. Guo, and J. Kong, "Oxidative stress in neurodegenerative diseases," *Neural Regeneration Research*, vol. 7, no. 5, pp. 376–385, 2012.
- [9] G. H. Kim, J. E. Kim, S. J. Rhie, and S. Yoon, "The role of oxidative stress in neurodegenerative diseases," *Experimental Neurobiology*, vol. 24, no. 4, pp. 325–340, 2015.
- [10] B. Uttara, A. Singh, P. Zamboni, and R. Mahajan, "Oxidative stress and neurodegenerative diseases: a review of upstream and downstream antioxidant therapeutic options," *Current Neuropharmacology*, vol. 7, no. 1, pp. 65–74, 2009.
- [11] Z. Liu, T. Zhou, A. C. Ziegler, P. Dimitrion, and L. Zuo, "Oxidative stress in neurodegenerative diseases: from molecular mechanisms to clinical applications," *Oxidative Medicine and Cellular Longevity*, vol. 2017, Article ID 2525967, 11 pages, 2017.
- [12] S. Cirmi, N. Ferlazzo, G. Lombardo et al., "Neurodegenerative diseases: might citrus flavonoids play a protective role?," *Molecules*, vol. 21, no. 10, p. 1312, 2016.
- [13] Z. Kiasalari, T. Baluchnejadmojarad, and M. Roghani, "*Hypericum perforatum* hydroalcoholic extract mitigates motor dysfunction and is neuroprotective in intrastriatal 6-Hydroxydopamine rat model of Parkinson's disease," *Cellular and Molecular Neurobiology*, vol. 36, no. 4, pp. 521–530, 2016.
- [14] A. I. Oliveira, C. Pinho, B. Sarmiento, and A. C. P. Dias, "Neuroprotective activity of *Hypericum perforatum* and its major components," *Frontiers in Plant Science*, vol. 7, p. 1004, 2016.
- [15] A. E. Khalifa, "Neural monoaminergic mediation of the effect of St. John's wort extract on prepulse inhibition of the acoustic startle response in rats," *Journal of Psychopharmacology*, vol. 19, no. 5, pp. 467–472, 2005.
- [16] B. Kraus, H. Wolff, J. Heilmann, and E. F. Elstner, "Influence of *Hypericum perforatum* extract and its single compounds on amyloid- $\beta$  mediated toxicity in microglial cells," *Life Sciences*, vol. 81, no. 11, pp. 884–894, 2007.
- [17] B. A. Silva, A. C. P. Dias, F. Ferreres, J. O. Malva, and C. R. Oliveira, "Neuroprotective effect of *H. perforatum* extracts on  $\beta$ -amyloid-induced neurotoxicity," *Neurotoxicity Research*, vol. 6, no. 2, pp. 119–130, 2004.
- [18] B. Silva, P. J. Oliveira, A. Dias, and J. O. Malva, "Quercetin, kaempferol and biapigenin from *hypericum perforatum* are neuroprotective against excitotoxic insults," *Neurotoxicity Research*, vol. 13, no. 3–4, pp. 265–279, 2008.
- [19] M. I. Sánchez-Reus, M. A. Gómez del Río, I. Iglesias, M. Elorza, K. Slowing, and J. Benedí, "Standardized *Hypericum perforatum* reduces oxidative stress and increases gene expression of antioxidant enzymes on rotenone-exposed rats," *Neuropharmacology*, vol. 52, no. 2, pp. 606–616, 2007.
- [20] J. Barnes, L. A. Anderson, and J. D. Phillipson, "St John's wort (*Hypericum perforatum* L.): a review of its chemistry, pharmacology and clinical properties," *Journal of Pharmacy and Pharmacology*, vol. 53, no. 5, pp. 583–600, 2001.
- [21] J. M. Greeson, B. Sanford, and D. A. Monti, "St. John's wort (*Hypericum perforatum*): a review of the current pharmacological, toxicological, and clinical literature," *Psychopharmacology*, vol. 153, no. 4, pp. 402–414, 2001.
- [22] E. Ernst, J. I. Rand, J. Barnes, and C. Stevinson, "Adverse effects profile of the herbal antidepressant St. John's wort (*Hypericum perforatum* L.)," *European Journal of Clinical Pharmacology*, vol. 54, no. 8, pp. 589–594, 1998.
- [23] F. Khodagholi, B. Eftekharzadeh, N. Maghsoudi, and P. F. Rezaei, "Chitosan prevents oxidative stress-induced amyloid  $\beta$  formation and cytotoxicity in NT2 neurons: involvement of transcription factors Nrf2 and NF- $\kappa$ B," *Molecular and Cellular Biochemistry*, vol. 337, no. 1–2, pp. 39–51, 2010.
- [24] A. Y. Choi, J. H. Choi, J. Y. Lee et al., "Apigenin protects HT22 murine hippocampal neuronal cells against endoplasmic reticulum stress-induced apoptosis," *Neurochemistry International*, vol. 57, no. 2, pp. 143–152, 2010.
- [25] L.-J. Zhou and X.-Z. Zhu, "Reactive oxygen species-induced apoptosis in PC12 cells and protective effect of bilobalide," *Journal of Pharmacology and Experimental Therapeutics*, vol. 293, no. 3, pp. 982–988, 2000.
- [26] M. Sano, C. Ernesto, R. G. Thomas et al., "A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease," *New England Journal of Medicine*, vol. 336, no. 17, pp. 1216–1222, 1997.
- [27] C. Van der Merwe, H. C. Van Dyk, L. Engelbrecht et al., "Curcumin rescues a PINK1 knock down SH-SY5Y cellular model of Parkinson's disease from mitochondrial dysfunction and cell death," *Molecular Neurobiology*, vol. 54, no. 4, pp. 2752–2762, 2017.
- [28] P. Janhom and P. Dharmasaroja, "Neuroprotective effects of alpha-mangostin on MPP<sup>+</sup>-induced apoptotic cell death in neuroblastoma SH-SY5Y cells," *Journal of Toxicology*, vol. 2015, Article ID 919058, 11 pages, 2015.
- [29] S. Sharma, A. Ali, J. Ali, J. K. Sahni, and S. Baboota, "Rutin: therapeutic potential and recent advances in drug delivery," *Expert Opinion on Investigational Drugs*, vol. 22, no. 8, pp. 1063–1079, 2013.
- [30] S. Kreft, M. Knapp, and I. Kreft, "Extraction of rutin from buckwheat (*Fagopyrum esculentum* Moench) seeds and determination by capillary electrophoresis," *Journal of Agricultural and Food Chemistry*, vol. 47, no. 11, pp. 4649–4652, 1999.
- [31] W.-Y. Huang, H.-C. Zhang, W.-X. Liu, and C.-Y. Li, "Survey of antioxidant capacity and phenolic composition of blueberry, blackberry, and strawberry in Nanjing," *Journal of Zhejiang University Science B*, vol. 13, no. 2, pp. 94–102, 2012.
- [32] J. B. Harborne, "Nature, distribution and function of plant flavonoids," *Progress in Clinical and Biological Research*, vol. 213, pp. 15–24, 1986.
- [33] A. Ganeshpurkar and A. K. Saluja, "The pharmacological potential of rutin," *Saudi Pharmaceutical Journal*, vol. 25, no. 2, pp. 149–164, 2017.
- [34] S.-E. Park, K. Sapkota, J.-H. Choi et al., "Rutin from *Dendropanax moribifera* Leveille protects human dopaminergic cells against rotenone induced cell injury through inhibiting JNK



- and p38 MAPK signaling,” *Neurochemical Research*, vol. 39, no. 4, pp. 707–718, 2014.
- [35] X.-L. Yu, Y.-N. Li, H. Zhang et al., “Rutin inhibits amylin-induced neurocytotoxicity and oxidative stress,” *Food & Function*, vol. 6, no. 10, pp. 3296–3306, 2015.
- [36] I. Young and J. Woodside, “Antioxidants in health and disease,” *Journal of Clinical Pathology*, vol. 54, no. 3, pp. 176–186, 2001.
- [37] M. Valko, C. J. Rhodes, J. Moncol, M. Izakovic, and M. Mazur, “Free radicals, metals and antioxidants in oxidative stress-induced cancer,” *Chemico-Biological Interactions*, vol. 160, no. 1, pp. 1–40, 2006.
- [38] M. Valko, H. Morris, and M. Cronin, “Metals, toxicity and oxidative stress,” *Current Medicinal Chemistry*, vol. 12, no. 10, pp. 1161–1208, 2005.
- [39] R. S. Balaban, S. Nemoto, and T. Finkel, “Mitochondria, oxidants, and aging,” *Cell*, vol. 120, no. 4, pp. 483–495, 2005.
- [40] S. Bolisetty and E. Jaimes, “Mitochondria and reactive oxygen species: physiology and pathophysiology,” *International Journal of Molecular Sciences*, vol. 14, no. 3, pp. 6306–6344, 2013.
- [41] S. Gandhi and A. Y. Abramov, “Mechanism of oxidative stress in neurodegeneration,” *Oxidative Medicine and Cellular Longevity*, vol. 2012, Article ID 428010, 11 pages, 2012.
- [42] D. A. Patten, M. Germain, M. A. Kelly, and R. S. Slack, “Reactive oxygen species: stuck in the middle of neurodegeneration,” *Journal of Alzheimer's Disease*, vol. 20, no. s2, pp. S357–S367, 2010.
- [43] P. Song and M. H. Zou, “Roles of reactive oxygen species in physiology and pathology,” in *Atherosclerosis: Risks, Mechanisms, and Therapies*, pp. 379–392, John Wiley & Sons, Inc, Hoboken, NJ, USA, 2015.
- [44] R. Dringen, J. M. Gutterer, and J. Hirrlinger, “Glutathione metabolism in brain,” *The FEBS Journal*, vol. 267, no. 16, pp. 4912–4916, 2000.
- [45] R. Dringen, “Metabolism and functions of glutathione in brain,” *Progress in Neurobiology*, vol. 62, no. 6, pp. 649–671, 2000.
- [46] R. Dringen and J. Hirrlinger, “Glutathione pathways in the brain,” *Biological Chemistry*, vol. 384, no. 4, pp. 505–516, 2003.
- [47] A. Y. Abramov, A. Scorziello, and M. R. Duchon, “Three distinct mechanisms generate oxygen free radicals in neurons and contribute to cell death during anoxia and reoxygenation,” *Journal of Neuroscience*, vol. 27, no. 5, pp. 1129–1138, 2007.
- [48] C. E. Presnell, G. Bhatti, L. S. Numan et al., “Computational insights into the role of glutathione in oxidative stress,” *Current Neurovascular Research*, vol. 10, no. 2, pp. 185–194, 2013.
- [49] A. F. Francisco, P. M. de Abreu Vieira, J. M. Arantes et al., “Increase of reactive oxygen species by desferrioxamine during experimental Chagas' disease,” *Redox Report*, vol. 15, no. 4, pp. 185–190, 2010.
- [50] S. Gawel, M. Wardas, E. Niedworok, and P. Wardas, “Malondialdehyde (MDA) as a lipid peroxidation marker,” *Wiadomości Lekarskie*, vol. 57, no. 9–10, pp. 453–455, 2004.
- [51] C. Ramassamy, “Emerging role of polyphenolic compounds in the treatment of neurodegenerative diseases: a review of their intracellular targets,” *European Journal of Pharmacology*, vol. 545, no. 1, pp. 51–64, 2006.
- [52] R. N. Kalara, G. E. Maestre, R. Arizaga et al., “Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors,” *The Lancet Neurology*, vol. 7, no. 9, pp. 812–826, 2008.
- [53] Y. Feng and X. Wang, “Antioxidant therapies for Alzheimer's disease,” *Oxidative Medicine and Cellular Longevity*, vol. 2012, Article ID 472932, 17 pages, 2012.
- [54] C. Pennanen, M. Kivipelto, S. Tuomainen et al., “Hippocampus and entorhinal cortex in mild cognitive impairment and early AD,” *Neurobiology of Aging*, vol. 25, no. 3, pp. 303–310, 2004.
- [55] D. P. Devanand, G. Pradhaban, X. Liu et al., “Hippocampal and entorhinal atrophy in mild cognitive impairment: prediction of Alzheimer disease,” *Neurology*, vol. 68, no. 11, pp. 828–836, 2007.
- [56] G. G. Glenner and C. W. Wong, “Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein,” *Biochemical and Biophysical Research Communications*, vol. 120, no. 3, pp. 885–890, 1984.
- [57] D. Praticò, “Oxidative stress hypothesis in Alzheimer's disease: a reappraisal,” *Trends in Pharmacological Sciences*, vol. 29, no. 12, pp. 609–615, 2008.
- [58] Z. Chen and C. Zhong, “Oxidative stress in Alzheimer's disease,” *Neuroscience Bulletin*, vol. 30, no. 2, pp. 271–281, 2014.
- [59] M. F. Beal, “Oxidatively modified proteins in aging and disease,” *Free Radical Biology & Medicine*, vol. 32, no. 9, pp. 797–803, 2002.
- [60] D. A. Butterfield and J. Kanski, “Brain protein oxidation in age-related neurodegenerative disorders that are associated with aggregated proteins,” *Mechanisms of Ageing and Development*, vol. 122, no. 9, pp. 945–962, 2001.
- [61] L. L. Torres, N. B. Quaglio, G. T. de Souza et al., “Peripheral oxidative stress biomarkers in mild cognitive impairment and Alzheimer's disease,” *Journal of Alzheimer's Disease*, vol. 26, no. 1, pp. 59–68, 2011.
- [62] D. L. Marcus, C. Thomas, C. Rodriguez et al., “Increased peroxidation and reduced antioxidant enzyme activity in Alzheimer's disease,” *Experimental Neurology*, vol. 150, no. 1, pp. 40–44, 1998.
- [63] 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.
- [64] M. H. Yan, X. Wang, and X. Zhu, “Mitochondrial defects and oxidative stress in Alzheimer disease and Parkinson disease,” *Free Radical Biology & Medicine*, vol. 62, pp. 90–101, 2013.
- [65] D. Dias-Santagata, T. A. Fulga, A. Duttaroy, and M. B. Feany, “Oxidative stress mediates tau-induced neurodegeneration in *Drosophila*,” *The Journal of Clinical Investigation*, vol. 117, no. 1, pp. 236–245, 2007.
- [66] K. Stamer, R. Vogel, E. Thies, E. Mandelkow, and E.-M. Mandelkow, “Tau blocks traffic of organelles, neurofilaments, and APP vesicles in neurons and enhances oxidative stress,” *The Journal of Cell Biology*, vol. 156, no. 6, pp. 1051–1063, 2002.
- [67] G. Candore, M. Bulati, C. Caruso et al., “Inflammation, cytokines, immune response, apolipoprotein E, cholesterol, and oxidative stress in Alzheimer disease: therapeutic implications,” *Rejuvenation Research*, vol. 13, no. 2-3, pp. 301–313, 2010.

- [68] Y.-J. Lee, S. B. Han, S. Y. Nam, K. W. Oh, and J. T. Hong, "Inflammation and Alzheimer's disease," *Archives of Pharmacological Research*, vol. 33, no. 10, pp. 1539–1556, 2010.
- [69] A. Federico, E. Cardaioli, P. Da Pozzo, P. Formichi, G. N. Gallus, and E. Radi, "Mitochondria, oxidative stress and neurodegeneration," *Journal of the Neurological Sciences*, vol. 322, no. 1-2, pp. 254–262, 2012.
- [70] S. Ayton, P. Lei, and A. I. Bush, "Metallostasis in Alzheimer's disease," *Free Radical Biology & Medicine*, vol. 62, pp. 76–89, 2013.
- [71] M. A. Greenough, J. Camakaris, and A. I. Bush, "Metal dys-homeostasis and oxidative stress in Alzheimer's disease," *Neurochemistry International*, vol. 62, no. 5, pp. 540–555, 2013.
- [72] Y. Hong-Qi, S. Zhi-Kun, and C. Sheng-Di, "Current advances in the treatment of Alzheimer's disease: focused on considerations targeting A $\beta$  and tau," *Translational Neurodegeneration*, vol. 1, no. 1, p. 21, 2012.
- [73] M. O. Chohan and K. Iqbal, "From tau to toxicity: emerging roles of NMDA receptor in Alzheimer's disease," *Journal of Alzheimer's Disease*, vol. 10, no. 1, pp. 81–87, 2006.
- [74] E. R. Peskind, S. G. Potkin, N. Pomara et al., "Memantine treatment in mild to moderate Alzheimer disease: a 24-week randomized, controlled trial," *The American Journal of Geriatric Psychiatry*, vol. 14, no. 8, pp. 704–715, 2006.
- [75] K. Matsuzono, N. Hishikawa, Y. Ohta et al., "Combination therapy of cholinesterase inhibitor (donepezil or galantamine) plus memantine in the Okayama Memantine Study," *Journal of Alzheimer's Disease*, vol. 45, no. 3, pp. 771–780, 2015.
- [76] E. A. Mazzio, F. Close, and K. F. A. Soliman, "The biochemical and cellular basis for nutraceutical strategies to attenuate neurodegeneration in Parkinson's disease," *International Journal of Molecular Sciences*, vol. 12, no. 1, pp. 506–569, 2011.
- [77] S. Sharma, J. K. Narang, J. Ali, and S. Baboota, "Synergistic antioxidant action of vitamin E and rutin SNEDDS in ameliorating oxidative stress in a Parkinson's disease model," *Nanotechnology*, vol. 27, no. 37, article 375101, 2016.
- [78] M. Moshahid Khan, S. S. Raza, H. Javed et al., "Rutin protects dopaminergic neurons from oxidative stress in an animal model of Parkinson's disease," *Neurotoxicity Research*, vol. 22, no. 1, pp. 1–15, 2012.
- [79] P. Jenner, "Oxidative stress in Parkinson's disease," *Annals of Neurology*, vol. 53, Supplement S3, pp. S26–S38, 2003.
- [80] H.-M. Gao, P. T. Kotzbauer, K. Uryu, S. Leight, J. Q. Trojanowski, and V. M.-Y. Lee, "Neuroinflammation and oxidation/nitration of  $\alpha$ -synuclein linked to dopaminergic neurodegeneration," *Journal of Neuroscience*, vol. 28, no. 30, pp. 7687–7698, 2008.
- [81] E. C. Hirsch and S. Hunot, "Neuroinflammation in Parkinson's disease: a target for neuroprotection?," *The Lancet Neurology*, vol. 8, no. 4, pp. 382–397, 2009.
- [82] Y. Ihara, M. Chuda, S. Kuroda, and T. Hayabara, "Hydroxyl radical and superoxide dismutase in blood of patients with Parkinson's disease: relationship to clinical data," *Journal of the Neurological Sciences*, vol. 170, no. 2, pp. 90–95, 1999.
- [83] J. L. Cadet and C. Brannock, "Invited review free radicals and the pathobiology of brain dopamine systems," *Neurochemistry International*, vol. 32, no. 2, pp. 117–131, 1998.
- [84] S. Manoharan, G. J. Guillemin, R. S. Abiramasundari, M. M. Essa, M. Akbar, and M. D. Akbar, "The role of reactive oxygen species in the pathogenesis of Alzheimer's disease, Parkinson's disease, and Huntington's disease: a mini review," *Oxidative Medicine and Cellular Longevity*, vol. 2016, Article ID 8590578, 15 pages, 2016.
- [85] B. A. Faucheux, M. E. Martin, C. Beaumont, J. J. Hauw, Y. Agid, and E. C. Hirsch, "Neuromelanin associated redox-active iron is increased in the substantia nigra of patients with Parkinson's disease," *Journal of Neurochemistry*, vol. 86, no. 5, pp. 1142–1148, 2003.
- [86] A. Yoritaka, N. Hattori, K. Uchida, M. Tanaka, E. R. Stadtman, and Y. Mizuno, "Immunohistochemical detection of 4-hydroxynonenal protein adducts in Parkinson disease," *Proceedings of the National Academy of Sciences*, vol. 93, no. 7, pp. 2696–2701, 1996.
- [87] E. Floor and M. G. Wetzal, "Increased protein oxidation in human substantia nigra pars compacta in comparison with basal ganglia and prefrontal cortex measured with an improved dinitrophenylhydrazine assay," *Journal of Neurochemistry*, vol. 70, no. 1, pp. 268–275, 1998.
- [88] 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.
- [89] J. M. Miyasaki, W. Martin, O. Suchowersky, W. J. Weiner, and A. E. Lang, "Practice parameter: initiation of treatment for Parkinson's disease: an evidence-based review: report of the quality standards subcommittee of the American Academy of Neurology," *Neurology*, vol. 58, no. 1, pp. 11–17, 2002.
- [90] C. G. Goetz, W. Poewe, O. Rascol, and C. Sampaio, "Evidence-based medical review update: pharmacological and surgical treatments of Parkinson's disease: 2001 to 2004," *Movement Disorders*, vol. 20, no. 5, pp. 523–539, 2005.
- [91] S. S. Rao, L. A. Hofmann, and A. Shakil, "Parkinson's disease: diagnosis and treatment," *American Family Physician*, vol. 74, no. 12, pp. 2046–2054, 2006.
- [92] R. Pahwa, S. A. Factor, K. E. Lyons et al., "Practice parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): [RETIRED]," *Neurology*, vol. 66, no. 7, pp. 983–995, 2006.
- [93] O. R. Adam and J. Jankovic, "Symptomatic treatment of Huntington disease," *Neurotherapeutics*, vol. 5, no. 2, pp. 181–197, 2008.
- [94] C. Pidgeon and H. Rickards, "The pathophysiology and pharmacological treatment of Huntington disease," *Behavioural Neurology*, vol. 26, no. 4, pp. 253 pages, 2013.
- [95] D. Rubinsztein, "The molecular pathology of Huntingtons disease (HD)," *Current Medicinal Chemistry - Immunology, Endocrine & Metabolic Agents*, vol. 3, no. 4, pp. 329–340, 2003.
- [96] J. Brandt, M. E. Strauss, J. Larus, B. Jensen, S. E. Folstein, and M. F. Folstein, "Clinical correlates of dementia and disability in Huntington's disease," *Journal of Clinical Neuropsychology*, vol. 6, no. 4, pp. 401–412, 1984.
- [97] S. E. Folstein, M. H. Abbott, G. A. Chase, B. A. Jensen, and M. F. Folstein, "The association of affective disorder with Huntington's disease in a case series and in families," *Psychological Medicine*, vol. 13, no. 3, pp. 537–542, 1983.
- [98] S. Frank, "Treatment of Huntington's disease," *Neurotherapeutics*, vol. 11, no. 1, pp. 153–160, 2014.



- [99] B. Rotblat, A. L. Southwell, D. E. Ehrnhoefer et al., "HACE1 reduces oxidative stress and mutant Huntingtin toxicity by promoting the NRF2 response," *Proceedings of the National Academy of Sciences*, vol. 111, no. 8, pp. 3032–3037, 2014.
- [100] A. Johri and M. F. Beal, "Antioxidants in Huntington's disease," *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, vol. 1822, no. 5, pp. 664–674, 2012.
- [101] C.-M. Chen, Y. R. Wu, M. L. Cheng et al., "Increased oxidative damage and mitochondrial abnormalities in the peripheral blood of Huntington's disease patients," *Biochemical and Biophysical Research Communications*, vol. 359, no. 2, pp. 335–340, 2007.
- [102] E. Trushina and C. T. McMurray, "Oxidative stress and mitochondrial dysfunction in neurodegenerative diseases," *Neuroscience*, vol. 145, no. 4, pp. 1233–1248, 2007.
- [103] L. M. Sayre, G. Perry, and M. A. Smith, "Oxidative stress and neurotoxicity," *Chemical Research in Toxicology*, vol. 21, no. 1, pp. 172–188, 2008.
- [104] D.-H. Lee, R. Gold, and R. A. Linker, "Mechanisms of oxidative damage in multiple sclerosis and neurodegenerative diseases: therapeutic modulation via fumaric acid esters," *International Journal of Molecular Sciences*, vol. 13, no. 12, pp. 11783–11803, 2012.
- [105] I. Túnez, F. Sánchez-López, E. Agüera, R. Fernández-Bolaños, F. M. Sánchez, and I. Tasset-Cuevas, "Important role of oxidative stress biomarkers in Huntington's disease," *Journal of Medicinal Chemistry*, vol. 54, no. 15, pp. 5602–5606, 2011.
- [106] N. Klepac, M. Relja, R. Klepac, S. Hećimović, T. Babić, and V. Trkulja, "Oxidative stress parameters in plasma of Huntington's disease patients, asymptomatic Huntington's disease gene carriers and healthy subjects," *Journal of Neurology*, vol. 254, no. 12, pp. 1676–1683, 2007.
- [107] A.-V. Goula, B. R. Berquist, D. M. Wilson, V. C. Wheeler, Y. Trottier, and K. Merienne, "Stoichiometry of base excision repair proteins correlates with increased somatic CAG instability in striatum over cerebellum in Huntington's disease transgenic mice," *PLoS Genetics*, vol. 5, no. 12, article e1000749, 2009.
- [108] S. E. Browne, A. C. Bowling, U. Macgarvey et al., "Oxidative damage and metabolic dysfunction in Huntington's disease: selective vulnerability of the basal ganglia," *Annals of Neurology*, vol. 41, no. 5, pp. 646–653, 1997.
- [109] M. J. Armstrong, J. M. Miyasaki, and American Academy of Neurology, "Evidence-based guideline: pharmacologic treatment of chorea in Huntington disease: report of the guideline development subcommittee of the American Academy of Neurology," *Neurology*, vol. 79, no. 6, pp. 597–603, 2012.
- [110] S. P. Bagchi, "Differential interactions of phencyclidine with tetrabenazine and reserpine affecting intraneuronal dopamine," *Biochemical Pharmacology*, vol. 32, no. 19, pp. 2851–2856, 1983.
- [111] N. Kaur, P. Kumar, S. Jamwal, R. Deshmukh, and V. Gauttam, "Tetrabenazine: spotlight on drug review," *Annals of Neurosciences*, vol. 23, no. 3, pp. 176–185, 2016.
- [112] V. Shen, K. Clarence-Smith, C. Hunter, and J. Jankovic, "Safety and efficacy of tetrabenazine and use of concomitant medications during long-term, open-label treatment of chorea associated with Huntington's and other diseases," *Tremor and Other Hyperkinetic Movements*, vol. 3, 2013.
- [113] C. Lucetti, G. Gambaccini, S. Bernardini et al., "Amantadine in Huntington's disease: open-label video-blinded study," *Neurological Sciences*, vol. 23, Supplement 2, pp. s83–s84, 2002.
- [114] R. M. Bonelli, F. A. Mahnert, and G. Niederwieser, "Olanzapine for Huntington's disease: an open label study," *Clinical Neuropharmacology*, vol. 25, no. 5, pp. 263–265, 2002.
- [115] H. C. Dipple, "The use of olanzapine for movement disorder in Huntington's disease: a first case report," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 67, no. 1, pp. 123–124, 1999.
- [116] M. Alpay and W. J. Koroshetz, "Quetiapine in the treatment of behavioral disturbances in patients with Huntington's disease," *Psychosomatics*, vol. 47, no. 1, pp. 70–72, 2006.
- [117] R. M. Bonelli and G. Niederwieser, "Quetiapine in Huntington's disease: a first case report," *Journal of Neurology*, vol. 249, no. 8, pp. 1114–1115, 2002.
- [118] A. Ciammola, J. Sassone, N. Mencacci et al., "Aripiprazole in the treatment of Huntington's disease: a case series," *Neuropsychiatric Disease and Treatment*, vol. 5, pp. 1–4, 2008.
- [119] L. Brusa, A. Orlacchio, V. Moschella, C. Iani, G. Bernardi, and N. B. Mercuri, "Treatment of the symptoms of Huntington's disease: preliminary results comparing aripiprazole and tetrabenazine," *Movement Disorders*, vol. 24, no. 1, pp. 126–129, 2009.
- [120] J. Collinge, "Prion diseases of humans and animals: their causes and molecular basis," *Annual Review of Neuroscience*, vol. 24, no. 1, pp. 519–550, 2001.
- [121] J. Collinge and A. R. Clarke, "A general model of prion strains and their pathogenicity," *Science*, vol. 318, no. 5852, pp. 930–936, 2007.
- [122] S. B. Prusiner, "Prions," *Proceedings of the National Academy of Sciences*, vol. 95, no. 23, pp. 13363–13383, 1998.
- [123] D. R. Brown, "Neurodegeneration and oxidative stress: prion disease results from loss of antioxidant defence," *Folia Neuro-pathologica*, vol. 43, no. 4, pp. 229–243, 2005.
- [124] J. S. Griffith, "Nature of the scrapie agent: self-replication and scrapie," *Nature*, vol. 215, no. 5105, pp. 1043–1044, 1967.
- [125] J. D. F. Wadsworth and J. Collinge, "Molecular pathology of human prion disease," *Acta Neuropathologica*, vol. 121, no. 1, pp. 69–77, 2011.
- [126] W. K. Surewicz and M. I. Apostol, "Prion protein and its conformational conversion: a structural perspective," in *Prion Proteins*, pp. 135–167, Springer, Berlin, Heidelberg, 2011.
- [127] S. B. Prusiner, "A unifying role for prions in neurodegenerative diseases," *Science*, vol. 336, no. 6088, pp. 1511–1513, 2012.
- [128] H. Budka, A. Aguzzi, P. Brown et al., "Neuropathological diagnostic criteria for Creutzfeldt-Jakob disease (CJD) and other human spongiform encephalopathies (prion diseases)," *Brain Pathology*, vol. 5, no. 4, pp. 459–466, 1995.
- [129] L. Westergard, H. M. Christensen, and D. A. Harris, "The cellular prion protein (PrP<sup>C</sup>): its physiological function and role in disease," *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, vol. 1772, no. 6, pp. 629–644, 2007.
- [130] S. Basu, M. L. Mohan, X. Luo, B. Kundu, Q. Kong, and N. Singh, "Modulation of proteinase K-resistant prion protein in cells and infectious brain homogenate by redox iron: implications for prion replication and disease pathogenesis," *Molecular Biology of the Cell*, vol. 18, no. 9, pp. 3302–3312, 2007.

- [131] M. Guentchev, T. Voigtländer, C. Haberler, M. H. Groschup, and H. Budka, "Evidence for oxidative stress in experimental prion disease," *Neurobiology of Disease*, vol. 7, no. 4, pp. 270–273, 2000.
- [132] Z. Guan, M. Söderberg, P. Sindelar, S. B. Prusiner, K. Kristensson, and G. Dallner, "Lipid composition in scrapie-infected mouse brain: prion infection increases the levels of dolichyl phosphate and ubiquinone," *Journal of Neurochemistry*, vol. 66, no. 1, pp. 277–285, 1996.
- [133] S.-I. Choi, W.-K. Ju, E.-K. Choi et al., "Mitochondrial dysfunction induced by oxidative stress in the brains of hamsters infected with the 263 K scrapie agent," *Acta Neuropathologica*, vol. 96, no. 3, pp. 279–286, 1998.
- [134] D. W. Lee, H. O. Sohn, H. B. Lim et al., "Alteration of free radical metabolism in the brain of mice infected with scrapie agent," *Free Radical Research*, vol. 30, no. 6, pp. 499–507, 1999.
- [135] N.-H. Kim, S.-J. Park, J.-K. Jin et al., "Increased ferric iron content and iron-induced oxidative stress in the brains of scrapie-infected mice," *Brain Research*, vol. 884, no. 1-2, pp. 98–103, 2000.
- [136] C. R. Trevitt and J. Collinge, "A systematic review of prion therapeutics in experimental models," *Brain*, vol. 129, no. 9, pp. 2241–2265, 2006.
- [137] S. Haik, J. P. Brandel, D. Salomon et al., "Compassionate use of quinacrine in Creutzfeldt–Jakob disease fails to show significant effects," *Neurology*, vol. 63, no. 12, pp. 2413–2415, 2004.
- [138] I. R. Whittle, R. S. G. Knight, and R. G. Will, "Unsuccessful intraventricular pentosan polysulphate treatment of variant Creutzfeldt–Jakob disease," *Acta Neurochirurgica*, vol. 148, no. 6, pp. 677–679, 2006.
- [139] L. Li, S. Napper, and N. R. Cashman, "Immunotherapy for prion diseases: opportunities and obstacles," *Immunotherapy*, vol. 2, no. 2, pp. 269–282, 2010.
- [140] N. A. Al-Dhabi, M. V. Arasu, C. H. Park, and S. U. Park, "An up-to-date review of rutin and its biological and pharmacological activities," *EXCLI Journal*, vol. 14, pp. 59–63, 2015.
- [141] A. A. Perk, I. Shatynska-Mytsyk, Y. C. Gerçek et al., "Rutin mediated targeting of signaling machinery in cancer cells," *Cancer Cell International*, vol. 14, no. 1, p. 124, 2014.
- [142] Y. Hanasaki, S. Ogawa, and S. Fukui, "The correlation between active oxygens scavenging and antioxidative effects of flavonoids," *Free Radical Biology & Medicine*, vol. 16, no. 6, pp. 845–850, 1994.
- [143] M. M. Al-Enazi, "Protective effects of combined therapy of rutin with silymarin on experimentally-induced diabetic neuropathy in rats," *Pharmacology & Pharmacy*, vol. 5, no. 9, pp. 876–889, 2014.
- [144] F. M. Kandemir, M. Ozkaraca, B. A. Yildirim et al., "Rutin attenuates gentamicin-induced renal damage by reducing oxidative stress, inflammation, apoptosis, and autophagy in rats," *Renal Failure*, vol. 37, no. 3, pp. 518–525, 2015.
- [145] M. M. Ahmed and N. I. Zaki, "Assessment the ameliorative effect of pomegranate and rutin on chlorpyrifos-ethyl-induced oxidative stress in rats," *Nature and Science*, vol. 7, no. 10, pp. 49–61, 2009.
- [146] D. A. Kostić, D. S. Dimitrijević, G. S. Stojanović, I. R. Palić, A. S. Đorđević, and J. D. Ickovski, "Xanthine oxidase: isolation, assays of activity, and inhibition," *Journal of Chemistry*, vol. 2015, Article ID 294858, 8 pages, 2015.
- [147] K. B. Magalingam, A. Radhakrishnan, and N. Haleagrahara, "Rutin, a bioflavonoid antioxidant protects rat pheochromocytoma (PC-12) cells against 6-hydroxydopamine (6-OHDA)-induced neurotoxicity," *International Journal of Molecular Medicine*, vol. 32, no. 1, pp. 235–240, 2013.
- [148] Y. B. Wang, Z. M. Ge, W. Q. Kang, Z. X. Lian, J. Yao, and C. Y. Zhou, "Rutin alleviates diabetic cardiomyopathy in a rat model of type 2 diabetes," *Experimental and Therapeutic Medicine*, vol. 9, no. 2, pp. 451–455, 2015.
- [149] C. L. Joachim and D. J. Selkoe, "The seminal role of  $\beta$ -amyloid in the pathogenesis of Alzheimer disease," *Alzheimer Disease & Associated Disorders*, vol. 6, no. 1, pp. 7–34, 1992.
- [150] W. Cerpa, M. Dinamarca, and N. Inestrosa, "Structure-function implications in Alzheimers disease: effect of  $A\beta$  oligomers at central synapses," *Current Alzheimer Research*, vol. 5, no. 3, pp. 233–243, 2008.
- [151] J. E. Simpson, P. G. Ince, G. Lace et al., "Astrocyte phenotype in relation to Alzheimer-type pathology in the ageing brain," *Neurobiology of Aging*, vol. 31, no. 4, pp. 578–590, 2010.
- [152] T. Kihara, S. Shimohama, H. Sawada et al., " $\alpha 7$  nicotinic receptor transduces signals to phosphatidylinositol 3-kinase to block a  $\beta$ -amyloid-induced neurotoxicity," *Journal of Biological Chemistry*, vol. 276, no. 17, pp. 13541–13546, 2001.
- [153] K. Jiménez-Aliaga, P. Bermejo-Bescós, J. Benedí, and S. Martín-Aragón, "Quercetin and rutin exhibit anti-amyloidogenic and fibril-disaggregating effects in vitro and potent antioxidant activity in APP<sup>swe</sup> cells," *Life Sciences*, vol. 89, no. 25-26, pp. 939–945, 2011.
- [154] M. Domínguez-Prieto, A. Velasco, L. Vega, A. Taberero, and J. M. Medina, "Aberrant co-localization of synaptic proteins promoted by Alzheimer's disease amyloid- $\beta$  peptides: protective effect of human serum albumin," *Journal of Alzheimer's Disease*, vol. 55, no. 1, pp. 171–182, 2017.
- [155] S.-w. Wang, Y.-J. Wang, Y.-j. Su et al., "Rutin inhibits  $\beta$ -amyloid aggregation and cytotoxicity, attenuates oxidative stress, and decreases the production of nitric oxide and proinflammatory cytokines," *NeuroToxicology*, vol. 33, no. 3, pp. 482–490, 2012.
- [156] A. Kern and C. Behl, "The unsolved relationship of brain aging and late-onset Alzheimer disease," *Biochimica et Biophysica Acta (BBA) - General Subjects*, vol. 1790, no. 10, pp. 1124–1132, 2009.
- [157] K. T. Akama, C. Albanese, R. G. Pestell, and L. J. Van Eldik, "Amyloid  $\beta$ -peptide stimulates nitric oxide production in astrocytes through an NF $\kappa$ B-dependent mechanism," *Proceedings of the National Academy of Sciences*, vol. 95, no. 10, pp. 5795–5800, 1998.
- [158] Q. Wang, M. J. Rowan, and R. Anwyl, " $\beta$ -amyloid-mediated inhibition of NMDA receptor-dependent long-term potentiation induction involves activation of microglia and stimulation of inducible nitric oxide synthase and superoxide," *Journal of Neuroscience*, vol. 24, no. 27, pp. 6049–6056, 2004.
- [159] T.-C. Huang, K.-T. Lu, Y.-Y. P. Wo, Y.-J. Wu, and Y.-L. Yang, "Resveratrol protects rats from  $A\beta$ -induced neurotoxicity by the reduction of iNOS expression and lipid peroxidation," *PLoS One*, vol. 6, no. 12, article e29102, 2011.
- [160] B. Hu, F. Dai, Z. Fan, G. Ma, Q. Tang, and X. Zhang, "Nanotheranostics: Congo red/rutin-MNPs with enhanced magnetic resonance imaging and H<sub>2</sub>O<sub>2</sub>-responsive therapy of Alzheimer's disease in APP<sup>swe</sup>/PS1<sup>dE9</sup> transgenic mice," *Advanced Materials*, vol. 27, no. 37, pp. 5499–5505, 2015.

- [161] A. Bispo da Silva, P. L. Cerqueira Coelho, J. Alves Oliveira Amparo et al., "The flavonoid rutin modulates microglial/macrophage activation to a CD150/CD206 M2 phenotype," *Chemico-Biological Interactions*, vol. 274, pp. 89–99, 2017.
- [162] A. R. Mohamed, G. Y. Soliman, C. A. Ismail, and H. F. Manna, "Neuroprotective role of vitamin D3 in colchicine-induced Alzheimer's disease in rats," *Alexandria Journal of Medicine*, vol. 51, no. 2, pp. 127–136, 2015.
- [163] S. Zhou, G. Yu, L. Chi et al., "Neuroprotective effects of edaravone on cognitive deficit, oxidative stress and tau hyperphosphorylation induced by intracerebroventricular streptozotocin in rats," *NeuroToxicology*, vol. 38, pp. 136–145, 2013.
- [164] P. Xu, S. Wang, X. Yu et al., "Rutin improves spatial memory in Alzheimer's disease transgenic mice by reducing A $\beta$  oligomer level and attenuating oxidative stress and neuroinflammation," *Behavioural Brain Research*, vol. 264, pp. 173–180, 2014.
- [165] J. Cheng, L. Chen, S. Han, L. Qin, N. Chen, and Z. Wan, "Treadmill running and rutin reverse high fat diet induced cognitive impairment in diet induced obese mice," *The Journal of Nutrition, Health & Aging*, vol. 20, no. 5, pp. 503–508, 2016.
- [166] J. Y. Choi, J. M. Lee, D. G. Lee et al., "The *n*-butanol fraction and rutin from tartary buckwheat improve cognition and memory in an in vivo model of amyloid- $\beta$ -induced Alzheimer's disease," *Journal of Medicinal Food*, vol. 18, no. 6, pp. 631–641, 2015.
- [167] G. V. Ramalingayya, S. P. Cheruku, P. Nayak et al., "Rutin protects against neuronal damage in vitro and ameliorates doxorubicin-induced memory deficits in vivo in Wistar rats," *Drug Design, Development and Therapy*, vol. 11, pp. 1011–1026, 2017.
- [168] G. V. Ramalingayya, M. Nampoothiri, P. G. Nayak et al., "Naringin and rutin alleviates episodic memory deficits in two differentially challenged object recognition tasks," *Pharmacognosy Magazine*, vol. 12, no. 45, p. 63, 2016.
- [169] J. P. E. Spencer, "Flavonoids: modulators of brain function?," *British Journal of Nutrition*, vol. 99, E-S1, pp. ES60–ES77, 2008.
- [170] K. Thomas and A. Davies, "Neurotrophins: a ticket to ride for BDNF," *Current Biology*, vol. 15, no. 7, pp. R262–R264, 2005.
- [171] S. Moghbelinejad, M. Nassiri-Asl, T. Naserpour Farivar et al., "Rutin activates the MAPK pathway and BDNF gene expression on beta-amyloid induced neurotoxicity in rats," *Toxicology Letters*, vol. 224, no. 1, pp. 108–113, 2014.
- [172] H. Javed, M. M. Khan, A. Ahmad et al., "Rutin prevents cognitive impairments by ameliorating oxidative stress and neuroinflammation in rat model of sporadic dementia of Alzheimer type," *Neuroscience*, vol. 210, pp. 340–352, 2012.
- [173] S. K. Richetti, M. Blank, K. M. Capiotti et al., "Quercetin and rutin prevent scopolamine-induced memory impairment in zebrafish," *Behavioural Brain Research*, vol. 217, no. 1, pp. 10–15, 2011.
- [174] J. Bové, D. Prou, C. Perier, and S. Przedborski, "Toxin-induced models of Parkinson's disease," *NeuroRX*, vol. 2, no. 3, pp. 484–494, 2005.
- [175] S. Hisahara and S. Shimohama, "Toxin-induced and genetic animal models of Parkinson's disease," *Parkinson's Disease*, vol. 2011, Article ID 951709, 14 pages, 2011.
- [176] A. Schober, "Classic toxin-induced animal models of Parkinson's disease: 6-OHDA and MPTP," *Cell and Tissue Research*, vol. 318, no. 1, pp. 215–224, 2004.
- [177] W. Nicklas, I. Vyas, and R. E. Heikkila, "Inhibition of NADH-linked oxidation in brain mitochondria by 1-methyl-4-phenyl-pyridine, a metabolite of the neurotoxin, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine," *Life Sciences*, vol. 36, no. 26, pp. 2503–2508, 1985.
- [178] S. Przedborski and M. Vila, "The 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model," *Annals of the New York Academy of Sciences*, vol. 991, no. 1, pp. 189–198, 2003.
- [179] R. Ramsay and T. Singer, "Energy-dependent uptake of *N*-methyl-4-phenylpyridinium, the neurotoxic metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, by mitochondria," *Journal of Biological Chemistry*, vol. 261, no. 17, pp. 7585–7587, 1986.
- [180] V. N. Uversky, "Neurotoxicant-induced animal models of Parkinson's disease: understanding the role of rotenone, maneb and paraquat in neurodegeneration," *Cell and Tissue Research*, vol. 318, no. 1, pp. 225–241, 2004.
- [181] D. Di Monte, M. S. Sandy, G. Ekström, and M. T. Smith, "Comparative studies on the mechanisms of paraquat and 1-methyl-4-phenylpyridine (MPP<sup>+</sup>) cytotoxicity," *Biochemical and Biophysical Research Communications*, vol. 137, no. 1, pp. 303–309, 1986.
- [182] A. I. Brooks, C. A. Chadwick, H. A. Gelbard, D. A. Cory-Slechta, and H. J. Federoff, "Paraquat elicited neurobehavioral syndrome caused by dopaminergic neuron loss," *Brain Research*, vol. 823, no. 1–2, pp. 1–10, 1999.
- [183] A. B. Manning-Bog, A. L. McCormack, J. Li, V. N. Uversky, A. L. Fink, and D. A. di Monte, "The herbicide paraquat causes up-regulation and aggregation of  $\alpha$ -synuclein in mice," *Journal of Biological Chemistry*, vol. 277, no. 3, pp. 1641–1644, 2002.
- [184] K. B. Magalingam, A. Radhakrishnan, and N. Haleagrahara, "Protective effects of quercetin glycosides, rutin, and isoquercitrin against 6-hydroxydopamine (6-OHDA)-induced neurotoxicity in rat pheochromocytoma (PC-12) cells," *International Journal of Immunopathology and Pharmacology*, vol. 29, no. 1, pp. 30–39, 2016.
- [185] K. B. Magalingam, A. Radhakrishnan, P. Ramdas, and N. Haleagrahara, "Quercetin glycosides induced neuroprotection by changes in the gene expression in a cellular model of Parkinson's disease," *Journal of Molecular Neuroscience*, vol. 55, no. 3, pp. 609–617, 2015.
- [186] S. Ramaswamy, J. L. McBride, and J. H. Kordower, "Animal models of Huntington's disease," *ILAR Journal*, vol. 48, no. 4, pp. 356–373, 2007.
- [187] A. C. Foster, L. P. Miller, W. H. Oldendorf, and R. Schwarcz, "Studies on the disposition of quinolinic acid after intracerebral or systemic administration in the rat," *Experimental Neurology*, vol. 84, no. 2, pp. 428–440, 1984.
- [188] Y. M. Bordelon, M. F. Chesselet, D. Nelson, F. Welsh, and M. Ercińska, "Energetic dysfunction in quinolinic acid-lesioned rat striatum," *Journal of Neurochemistry*, vol. 69, no. 4, pp. 1629–1639, 1997.
- [189] C. A. J. Ribeiro, V. Grando, C. S. Dutra Filho, C. M. D. Wannmacher, and M. Wajner, "Evidence that quinolinic acid severely impairs energy metabolism through activation of NMDA receptors in striatum from developing rats,"



- Journal of Neurochemistry*, vol. 99, no. 6, pp. 1531–1542, 2006.
- [190] J. P. McLin, L. M. Thompson, and O. Steward, “Differential susceptibility to striatal neurodegeneration induced by quinolinic acid and kainate in inbred, outbred and hybrid mouse strains,” *European Journal of Neuroscience*, vol. 24, no. 11, pp. 3134–3140, 2006.
- [191] D. F. Emerich, C. G. Thanos, M. Goddard et al., “Extensive neuroprotection by choroid plexus transplants in excitotoxin lesioned monkeys,” *Neurobiology of Disease*, vol. 23, no. 2, pp. 471–480, 2006.
- [192] A. L. Kendall, F. David, G. Rayment, E. M. Torres, L. E. Annett, and S. B. Dunnett, “The influence of excitotoxic basal ganglia lesions on motor performance in the common marmoset,” *Brain*, vol. 123, no. 7, pp. 1442–1458, 2000.
- [193] M. F. Beal, R. Ferrante, K. Swartz, and N. Kowall, “Chronic quinolinic acid lesions in rats closely resemble Huntington’s disease,” *Journal of Neuroscience*, vol. 11, no. 6, pp. 1649–1659, 1991.
- [194] R. J. Ferrante, N. W. Kowall, P. B. Cipolloni, E. Storey, and M. F. Beal, “Excitotoxin lesions in primates as a model for Huntington’s disease: histopathologic and neurochemical characterization,” *Experimental Neurology*, vol. 119, no. 1, pp. 46–71, 1993.
- [195] R. C. Roberts, A. Ahn, K. J. Swartz, M. F. Beal, and M. DiFiglia, “Intrastriatal injections of quinolinic acid or kainic acid: differential patterns of cell survival and the effects of data analysis on outcome,” *Experimental Neurology*, vol. 124, no. 2, pp. 274–282, 1993.
- [196] T. A. Alston, L. Mela, and H. J. Bright, “3-Nitropropionate, the toxic substance of *Indigofera*, is a suicide inactivator of succinate dehydrogenase,” *Proceedings of the National Academy of Sciences*, vol. 74, no. 9, pp. 3767–3771, 1977.
- [197] C. J. Coles, D. E. Edmondson, and T. P. Singer, “Inactivation of succinate dehydrogenase by 3-nitropropionate,” *Journal of Biological Chemistry*, vol. 254, no. 12, pp. 5161–5167, 1979.
- [198] Z. Pang and J. W. Geddes, “Mechanisms of cell death induced by the mitochondrial toxin 3-nitropropionic acid: acute excitotoxic necrosis and delayed apoptosis,” *Journal of Neuroscience*, vol. 17, no. 9, pp. 3064–3073, 1997.
- [199] S. N. Suganya and T. Sumathi, “Rutin attenuates 3-nitropropionic acid induced behavioural alterations and mitochondrial dysfunction in the striatum of rat brain,” *World Journal of Pharmacy and Pharmaceutical Sciences*, vol. 4, pp. 1080–1092, 2014.
- [200] S. N. Suganya and T. Sumathi, “Rutin a dietary flavonoid protects against altered neurobehavioral, membrane bound enzymes and striatal damage induced by 3-nitropropionic acid in male Wistar rats,” *International Journal of Pharmacognosy and Phytochemical Research*, vol. 8, no. 7, pp. 1191–1199, 2016.
- [201] S. N. Suganya and T. Sumathi, “Effect of rutin against a mitochondrial toxin, 3-nitropropionic acid induced biochemical, behavioral and histological alterations—a pilot study on Huntington’s disease model in rats,” *Metabolic Brain Disease*, vol. 32, no. 2, pp. 471–481, 2017.
- [202] V. Della-Bianca, F. Rossi, U. Armato et al., “Neurotrophin p75 receptor is involved in neuronal damage by prion peptide-(106–126),” *Journal of Biological Chemistry*, vol. 276, no. 42, pp. 38929–38933, 2001.
- [203] M. Pérez, A. I. Rojo, F. Wandosell, J. Díaz-Nido, and J. Avila, “Prion peptide induces neuronal cell death through a pathway involving glycogen synthase kinase 3,” *Biochemical Journal*, vol. 372, no. 1, pp. 129–136, 2003.
- [204] M. Ettaiche, R. Pichot, J.-P. Vincent, and J. Chabry, “In vivo cytotoxicity of the prion protein fragment 106–126,” *Journal of Biological Chemistry*, vol. 275, no. 47, pp. 36487–36490, 2000.
- [205] Y. Gu, H. Fujioka, R. S. Mishra, R. Li, and N. Singh, “Prion peptide 106–126 modulates the aggregation of cellular prion protein and induces the synthesis of potentially neurotoxic transmembrane PrP,” *Journal of Biological Chemistry*, vol. 277, no. 3, pp. 2275–2286, 2002.
- [206] L. Diomedea, S. Sozzani, W. Luini et al., “Activation effects of a prion protein fragment [PrP-(106-126)] on human leucocytes,” *Biochemical Journal*, vol. 320, no. 2, pp. 563–570, 1996.
- [207] D. L. Rymer and T. A. Good, “The role of prion peptide structure and aggregation in toxicity and membrane binding,” *Journal of Neurochemistry*, vol. 75, no. 6, pp. 2536–2545, 2000.
- [208] D. R. Brown, “PrPSc-like prion protein peptide inhibits the function of cellular prion protein,” *Biochemical Journal*, vol. 352, no. 2, pp. 511–518, 2000.
- [209] I. Dupiereux, W. Zorzi, L. Lins et al., “Interaction of the 106–126 prion peptide with lipid membranes and potential implication for neurotoxicity,” *Biochemical and Biophysical Research Communications*, vol. 331, no. 4, pp. 894–901, 2005.
- [210] J.-Y. Na, S. Kim, K. Song, and J. Kwon, “Rutin alleviates prion peptide-induced cell death through inhibiting apoptotic pathway activation in dopaminergic neuronal cells,” *Cellular and Molecular Neurobiology*, vol. 34, no. 7, pp. 1071–1079, 2014.
- [211] S. Stuard, M. R. Cesarone, G. Belcaro et al., “Five-year treatment of chronic venous insufficiency with O-( $\beta$ -hydroxyethyl)-rutosides: safety aspects,” *International Journal of Angiology*, vol. 17, no. 3, pp. 143–148, 2008.
- [212] J. Maciej, C. T. Schäff, E. Kanitz et al., “Bioavailability of the flavonol quercetin in neonatal calves after oral administration of quercetin aglycone or rutin,” *Journal of Dairy Science*, vol. 98, no. 6, pp. 3906–3917, 2015.



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