

## Review Article

# The Role of Reactive Oxygen Species in the Pathogenesis of Alzheimer's Disease, Parkinson's Disease, and Huntington's Disease: A Mini Review

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Neurodegenerative diseases affect not only the life quality of aging populations, but also their life spans. All forms of neurodegenerative diseases have a massive impact on the elderly. The major threat of these brain diseases includes progressive loss of memory, Alzheimer's disease (AD), impairments in the movement, Parkinson's disease (PD), and the inability to walk, talk, and think, Huntington's disease (HD). Oxidative stress and mitochondrial dysfunction are highlighted as a central feature of brain degenerative diseases. Oxidative stress, a condition that occurs due to imbalance in oxidant and antioxidant status, has been known to play a vital role in the pathophysiology of neurodegenerative diseases including AD, PD, and HD. A large number of studies have utilized oxidative stress biomarkers to investigate the severity of these neurodegenerative diseases and medications are available, but these only treat the symptoms. In traditional medicine, a large number of medicinal plants have been used to treat the symptoms of these neurodegenerative diseases. Extensive studies scientifically validated the beneficial effect of natural products against neurodegenerative diseases using suitable animal models. This short review focuses the role of oxidative stress in the pathogenesis of AD, PD, and HD and the protective efficacy of natural products against these diseases.

## 1. Introduction

Neurodegenerative diseases were believed to be incurable and debilitating conditions, which primarily affected the neurons in the human brain resulting in the loss of nerve structure and function and ultimately leading to the death of nerve cells [1]. The major characteristic features of neurodegenerative diseases include ataxias (impairment in movement) and dementia (decline in memory). The three main types of neurodegenerative diseases that affect the life quality and life span of the elderly include Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) [2, 3].

## 2. Alzheimer's Disease

Alzheimer's disease (AD) is one of the most common neurodegenerative disorders affecting the elderly population worldwide [4]. The specific pathological lesions that were noticed in AD include deposition of amyloid beta protein, neuronal and/or synaptic loss, and brain atrophy in specific brain areas [5]. Both the neocortex and hippocampus are affected and brain plaques and tangles are the major features of AD. AD symptoms usually start with mild confusion and amnesia and end with a dramatic personality change. AD destroys memory and other important mental functions.

Other signs of AD include finding the right words, vision/spatial issues, and impaired reasoning or judgment [6]. Worldwide, around 16 million people are affected by AD and over four million Americans are currently affected, a figure that may rise further due to the increase in the life span [7]. This age-related, progressive, neurodegenerative disorder is the fourth leading cause of death in developed nations and accounts for 70% of dementia in the elderly population [8]. It has been suggested the incidence of AD could double every five years beyond the age of 65 [9]. Currently available medications only treat the symptoms of neurodegenerative diseases.

### 3. Oxidative Stress and Alzheimer's Disease

The etiology of AD is multifactorial. Both genetic and environmental factors are regarded as a risk factor of AD [9, 10]. Free radicals are chemical species with an unpaired electron and are formed during both physiological and pathological processes. Although reactive oxygen species (ROS) play a pivotal role in several cellular and signaling pathways at physiological concentrations (cell cycle regulation, phagocytosis, and enzyme activation), excessive generation of ROS leads to several harmful effects including DNA, lipid, and protein damage [11–14]. ROS are, however, scavenged by defence mechanisms, known as enzymatic and nonenzymatic antioxidants. An imbalance in this oxidant-antioxidant status could determine the extent of cell damage. Oxidative damage due to ROS has been implicated in the pathogenesis of neurodegenerative diseases, cancer, diabetes, and aging [15].

Mitochondrial dysfunction and enhanced apoptosis accompanied by a poor antioxidant status are the mechanisms for AD pathogenesis. Extensive studies pointed out the role of superoxide anion, hydroxyl radical, hydrogen peroxide, and nitric oxide in the oxidative stress mediated neurodegeneration in AD [16, 17]. Microglia activation due to neuronal lesions generates excessive superoxide radicals [18]. Higher metabolic demand and the postmitotic nature of glial cells and neurons make them more susceptible to oxidative stress. The low rate of brain regeneration and insufficient antioxidant potential in the brain further favors oxidative stress [19]. Mitochondrial autophagy serves as a major source of ROS production [20].

A $\beta$ (1-42) has been recognized as a key factor in the neurodegeneration in AD patients and it mediates its harmful effect via inducing oxidative stress in the brain [21–23]. A positive association has been shown between the amyloid plaque and the lipid peroxidation markers such as 4-hydroxynonenal and malondialdehyde [24]. Elevated lipid peroxidation and insufficient enzymatic and nonenzymatic antioxidants were shown in the peripheral tissues of AD patients [25, 26]. A large number of studies have shown an elevated level of lipid peroxidation marker in the brain of AD patients, especially in the region of the temporal lobe [27–29]. An increased level of 4-hydroxynonenal, the byproduct of oxidative stress, has been reported as well [30, 31]. Iron-induced oxidative stress, as evidenced by iron accumulation in the brain of AD, is responsible for neurodegeneration in patients diagnosed with AD [32]. Profound studies explored iron accumulation

in the brain of AD patients and found that, as a transition metal, it is capable of generating hydroxyl radical through the Fenton reaction [33, 34].  $\beta$ -Amyloid could elevate oxidative stress mainly by binding with iron [35]. The neuronal death occurs due to reactive oxygen species mediated changes in the neuronal lipid molecules, which includes alterations in the membrane, fluidity, rigidity, permeability, and transport [36]. It has been noticed that the entorhinal cortex and CA1 region of the hippocampus are the two major susceptible cerebral regions to oxidative stress [37]. Mitochondrial damage in AD could lead to excessive generation of ROS and lowered ATP production [38, 39]. Vitamin E, the major lipid-soluble nonenzymatic antioxidant, inhibits oxidative damage induced by A $\beta$ (1-42) [40]. Diminished levels of reduced glutathione in astrocytes have been reported [41]. Melo et al. [42] suggested that addition of antioxidants inhibited the activity of acetylcholine esterase in the neuronal culture. Also, superoxide dismutase activity was shown to have increased in the CA1 regions of hippocampus and amygdala [43]. The causes of oxidative stress in AD are given in Figure 1.

### 4. Natural Products and Alzheimer's Disease

Medicinal plants serve as a good source for the treatment of several illnesses, including neurodegenerative diseases, diabetes mellitus, and cancer [44, 45]. A large number of therapeutic medicines recommended worldwide for several diseases have been identified from medicinal plants. Indian traditional medicine has recommended several medicinal plants for the treatment of neurodegenerative diseases. In traditional medicine, several plants have been used to treat the symptoms of neurodegenerative diseases. A large number of studies scientifically validated the beneficial effects of natural products in the treatment of AD using suitable animal models [46, 47].

Veerendra Kumar and Gupta [48] explored the neuroprotective effect of aqueous extract of *Centella asiatica* in a streptozotocin model of AD in rats. They suggested that *Centella asiatica* reduced the oxidative stress as well. Dhanasekaran et al. [49] pointed out the neuroprotective role of *Centella asiatica* in B6C3-Tg(APP<sub>swe</sub>, PSEN1dE9)85 Dbo/J (PSAPP) mice. They concluded that the antioxidant role of *Centella asiatica* modulated the amyloid pathology in PSAPP mice. Clementi et al. [50] suggested that *Aloe arborescens* exerted a significant neuroprotective effect in IMR-32 cells via reducing the oxidative stress in the cells. Gong et al. [51] suggested the lotus seed pod *Proanthocyanidins* was a promising candidate for the treatment of AD as it exhibited a significant protective effect against cognitive impairment and brain aging induced by D-galactose. Turgut et al. [52] proposed oxidative stress reduction as a major mechanism for the neuroprotective effect of *Capparis spinosa L.* in D-galactose-induced cognitive impairment. Yu et al. [53] demonstrated the neuroprotective role of rutin against amylin-induced neurocytotoxicity in neuronal cells and concluded that the antioxidant property of rutin might have played a role in the protection of neuronal cells. Mairuae et al. [54] showed the in vitro neuroprotective effect of okra in SH-SY5Y cells and suggested that the antioxidant effect of okra was responsible

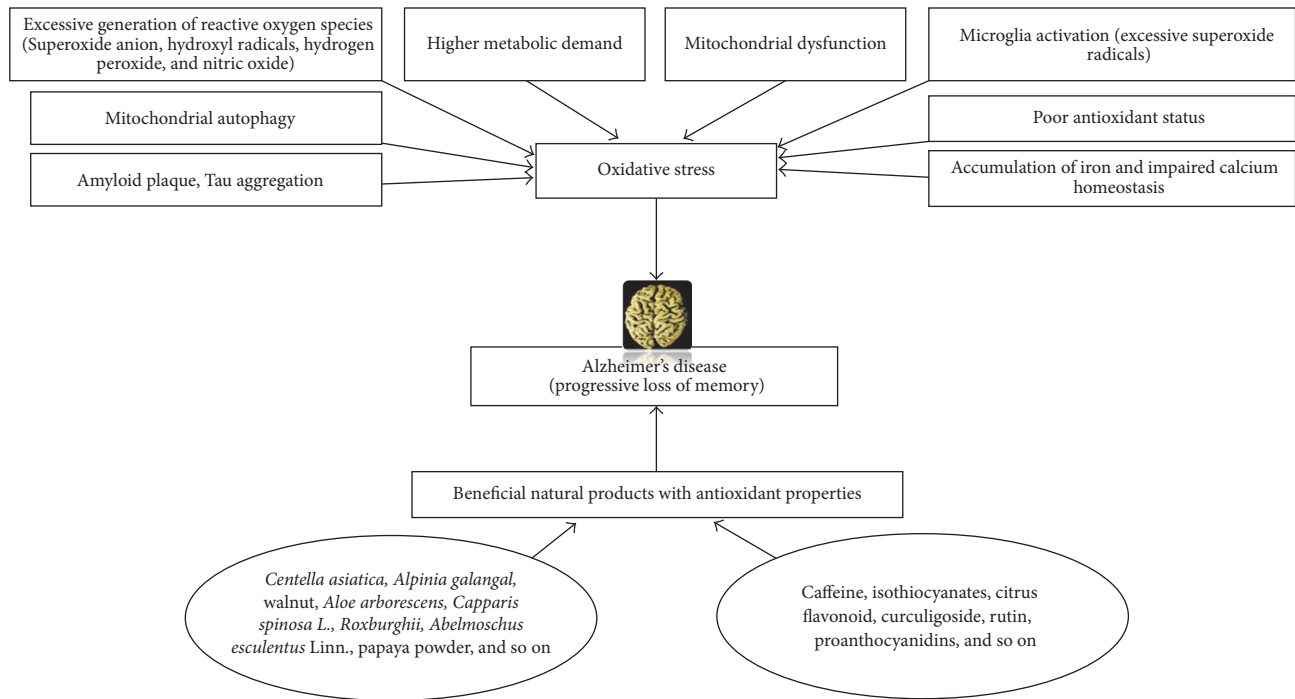


FIGURE 1: The causes of oxidative stress in Alzheimer's disease.

for the protective role. Uddin et al. [55] pointed out that the potent phenolic antioxidants present in the *Vanda roxburghii* could be responsible for the inhibition of the activation of acetylcholinesterase and butyrylcholinesterase. Barbagallo et al. [56] suggested that fermented papaya powder counteracted the excessive generation of reactive oxygen species in patients diagnosed with AD. Lu et al. [57] explored the protective role of *Rhubarb* extract against irradiation-induced apoptotic neuronal cell death and excessive ROS generation.

Giacoppo et al. [58] revealed the neuroprotective effect of isothiocyanates by highlighting their antioxidant potential as a major mechanism. Zhao et al. [59] demonstrated the neuroprotective effect of curculigoside on memory impairment in APP/PS1 mutated transgenic mice. They suggested that its antioxidant character played a major role. Muthaiyah et al. [60] reported that walnut extract has the ability to counteract amyloid beta peptide-induced oxidative stress in PC12 cells. Hartman et al. [61] pointed out that the antioxidant polyphenolic substances of pomegranate juice reduced amyloid load and improved behavior in an AD mouse. Subash et al. [62] suggested that dietary supplementation of dates and figs improved cognitive and behavioral deficit via maintaining oxidant-antioxidant balances in APPsw/Tg 2576 transgenic AD mice. Nakajima et al. [63] suggested that nobiletin significantly reduced oxidative stress and improved the cognitive impairment in a 3XTg-AD mouse model. Sun et al. [64] proposed antioxidant potential of saponin as one of the mechanisms involved in neuroprotection. Prasanthi et al. [65] showed that caffeine reduced the oxidative stress and improved the cognitive deficits induced by cholesterol-enriched diet in rabbit hippocampus. Boyd-Kimball et al. [66] reported that glutathione upregulation protected neuron

against oxidative stress and neurotoxicity induced by A(1-42) in the AD affected brain. Hanish Singh et al. [67] reported that ethanolic extract of *Alpinia galangal* improved the antioxidant status and inhibited the acetylcholine esterase activity in AD mice. Our research group from Oman reported the beneficial effects of natural products including pomegranate and figs on AD transgenic mice models [62, 68–77].

## 5. Parkinson's Disease

Parkinson's disease (PD), the most common neurodegenerative disease of the elderly, is characterized by progressive loss of muscle control. Premature death often results due to complications such as movement impairment-related injuries or pneumonia [78, 79]. PD is predominant at the 6th decade of life and men are 1.5 to 2 times more likely to contract the disease than women [80]. Head trauma, illness, or exposure to environmental toxins is identified as a risk factor. This neurodegenerative disorder is characterized by tremor, rigidity, bradykinesia, and impairment in balance [81]. PD also causes cognitive, psychiatric, autonomic, and sensory disturbances. Cognitive impairments are common in a large fraction of patients with PD at initial diagnosis and afflict a majority of patients as the disease progresses. The secondary manifestation includes anxiety, insecurity, stress, confusion, memory loss, constipation, depression, difficulty in swallowing and excessive salivation, diminished sense of smell, increased sweating, erectile dysfunction, skin problems, and a monotone voice [82, 83].

The pathology of PD is characterized by the gradual and selective loss of dopaminergic neurons in the substantia nigra pars compacta. Imbalance in dopamine metabolism

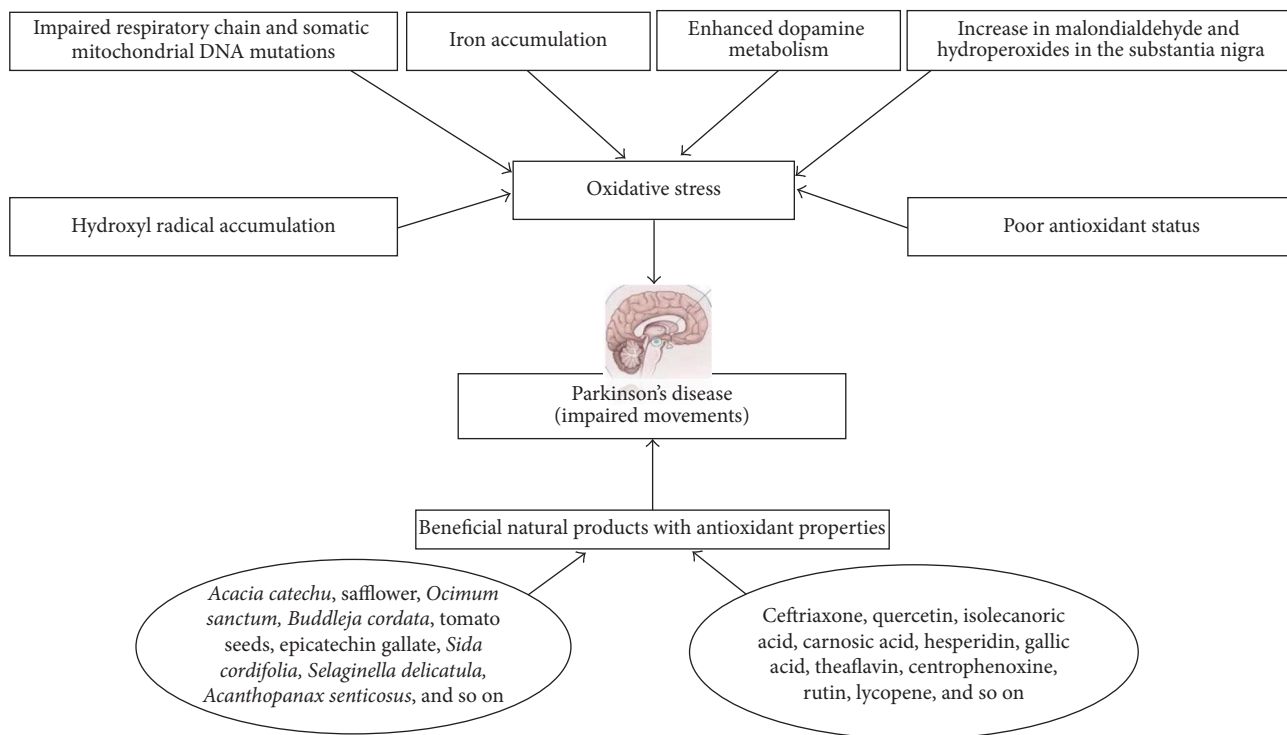


FIGURE 2: The causes of oxidative stress in Parkinson's disease.

due to oxidative stress has been recognised as a contributor to this disease [84]. The major pathological findings include the presence of Lewy bodies in the substantia nigra and loss of nerve cells in the portions of its ventral tier [85]. The treatment modality for PD involves either enhancing the activities of dopaminergic neuron activity or inhibiting the cholinergic effects to the stratum. While there is no cure for PD, medications provide dramatic relief from the symptoms. Recent advancement in medical and surgical treatment options has enormously improved the quality and length of life for patients with PD [86]. Worldwide, it is the second most common neurological disease and affects around 1.5 million Americans [87]. It has been pointed out that PD may double over the next 25 years in the United States and more than double in the developing nations of Asia and South America [88]. Research has indicated that 80% of the untreated PD patients die within 10 to 14 years after the onset of the disease [89].

## 6. Oxidative Stress and Parkinson's Disease

The brain utilizes around 20% of the basal oxygen from the total oxygen supplied to the human body. ROS mediated oxidative DNA damage is one of the prominent features in PD [90]. Several studies have reported impaired respiratory chain and somatic mitochondrial DNA mutations in the brain of patients with PD, which suggests the extensive role of oxidative metabolism in PD [91]. Enhanced dopamine metabolism in the brain of patients with PD could account for the accumulation of toxic radicals such as hydroxyl in the brain [92]. Iron accumulation in the neurons in the redox

active form plays a crucial role in pathogenesis of this disease [93]. Accumulation of iron has been reported in the substantia nigra in patients diagnosed with PD, which suggests the critical role of iron-induced lipid peroxidation in pathogenesis of PD [94–96]. The accumulation of lipid peroxidation byproducts has been reported in the serum and cerebral spinal fluid of patients with PD [97] while an increase in malondialdehyde and hydroperoxides has been reported in the substantia nigra of patients diagnosed with PD [98, 99].

Elevated levels of malondialdehyde, thiobarbituric acid reactive substance, and 4-hydroxy-2,3-nonenal have been reported in the substantia nigra and stratum of PD brains [100, 101]. A twofold increase in protein oxidation has been shown in the substantia nigra of PD patients compared to healthy subjects [102]. Accumulation of hydroxyl radical due to lowered glutathione content in the brain has been reported in PD patients [103]. Lowered activities of antioxidant enzymes and nonenzymatic antioxidants could be responsible for the progression of PD [104, 105]. Reduced glutathione and increased oxidized glutathione levels have been reported in PD patients while lowered glutathione content in the substantia nigra, due to neuronal loss, has been reported in patients with PD [106–109]. Decreased activity of glutathione peroxidase and a decline in glutathione content have been reported in the brain of PD patients and reduced glutathione content was found to be decreased in both human and experimental models of PD [110–112]. Lowered GSH content was reported in the substantia nigra and corpus striatum of PD patients [113]. The causes of oxidative stress in Parkinson's disease are given in Figure 2.

## 7. Natural Products and Parkinson's Disease

Extensive studies scientifically explored the protective effect of natural products against Parkinson's disease using suitable animal models. Weng et al. [114] reported that ceftriaxone prevented the loss of neuronal activity and decreased the neurogenesis in the brain of PD rats. Sharma et al. [115] suggested that administration of quercetin attenuated the neuronal death and reduced the oxidative stress in aluminium-induced neurodegeneration in the rat hippocampus. Saha et al. [116] explored the antineurogenic and antioxidant potential of *Acacia catechu* leaf extract using in vitro studies. Ren et al. [117] reported that safflower flavonoid extract could be used as the herbal therapy for PD treatment. De Pedro et al. [118] explored the in vitro protective effect of isolecanoric acid against the PD development. Wu et al. [119] investigated the neuroprotective effect of carnosic acid against 6-hydroxydopamine induced neurotoxicity. They concluded that the antioxidant and antiapoptotic potential of carnosic acid could play a protective role in the prevention of neurodegeneration. Siddique et al. [120] demonstrated the neuroprotective effect of *Ocimum sanctum* leaf extract in the transgenic *Drosophila* model of PD. Antunes et al. [121] suggested that hesperidin attenuated 6-hydroxydopamine induced oxidative stress in aged mice. Pérez-Barrón et al. [122] explored the antioxidant and neuroprotective effect of *Buddleja cordata* methanolic extract in the 1-methyl-4-phenylpyridinium induced PD rat model. Beppe et al. [123] suggested that the aqueous extract of *Albizia adianthifolia* leaves possesses antioxidant potential, which was responsible for the memory-enhancing activities in the rodent model of PD.

Gokul and Muralidhara [124] reported that tomato seeds alleviated motor abnormality, oxidative impairments, and neurotoxicity in a chronic ROT model of neurotoxicity in mice. Siddique et al. [125] reported that epicatechin gallate dietary supplementation reduced the oxidative stress and apoptosis in the brain of transgenic *Drosophila* model of PD. Khurana and Gajbhiye [126] showed the ameliorative effect of *Sida cordifolia* against rotenone-induced oxidative stress and neurochemical and behavioral alterations in a rat model of PD. Chandran and Muralidhara [127] showed the neuroprotective effect of aqueous extract of *Selaginella delicatula* in a chronic ROT exposure model of neurotoxicity in mice. They suggested that the neuroprotective property of *Selaginella delicatula* is largely attributed to the antioxidant properties. Prakash et al. [128] demonstrated the neuroprotective role of *Withania somnifera* root extract in parkinsonism mice. They suggested that *Withania somnifera* extract improved the behavioral, anatomical, and biochemical deformities. Mansouri et al. [129] suggested that the neuroprotective effect of oral gallic acid is due to the enhancement of cerebral antioxidant defense against oxidative stress induced by 6-hydroxydopamine in rats. Shalavadi et al. [130] suggested that the neuroprotective effect of the methanolic extract of *Stereospermum suaveolens* DC could be attributed to its antioxidant potential in 6-OHDA induced PD rats. Liu et al. [131] explored the neuroprotective effect of *Acanthopanax senticosus* in PD. Anandhan et al. [132] suggested that the neuroprotective effect of theaflavin may be due to its antioxidative

and antiapoptotic activities in chronic MPTP/probenecid induced PD. Some of our research group members reported the beneficial effects of natural products on PD animals [133–137].

Ahmad et al. [138] pointed out that the antioxidant efficacy of sesame seed oil is responsible for the neuroprotective effect in 6-hydroxydopamine induced neurotoxicity in mice. Martins et al. [139] demonstrated the protective effect of *Melissa officinalis* in manganese-induced oxidative stress in chronically exposed mice. They concluded that the antioxidant potential of this plant is responsible for the neuroprotective effect. Hritcu et al. [140] pointed out that the methanolic extract of *Hibiscus asper* leaves exerted neuroprotective activity through antioxidant and antiapoptotic activities in PD model. Ranpariya et al. [141] suggested that the antioxidant potential of *Matricaria recutita* could be largely attributed to its neuroprotective activity against fluoride-induced stress in rats. Wang et al. [142] suggested that the free radical scavenging activity of resveratrol protected the abnormal rotational behavior and the loss and apoptosis of nigral cells in Parkinsonian rats. Verma and Nehru [143] demonstrated the antioxidant effect of centrophoxine against rotenone-induced oxidative stress in PD rodent. Kaur et al. [144] demonstrated the beneficial effect of lycopene in rotenone-induced model of PD. They suggested that the therapeutic potential of lycopene is attributed to its antioxidant efficacy. Khan et al. [145] pointed out that rutin can protect dopaminergic neurons from oxidative stress in a PD rat. Essa et al. [146] suggested that walnut partially reversed MPTP-induced neurodegeneration in a mouse model of PD. They suggested that the antioxidant role of walnut might have played a neuroprotective role. Jahromi et al. [147] suggested that the antioxidants present in the *Decalepis hamiltonii* roots attenuated neuromotor deficits in transgenic *Drosophila* model of PD.

Tseng et al. [148] showed the protective effect of *Liuwei Dihuang* in Parkinson's toxin-induced dopaminergic neurodegeneration. Guo et al. [149] suggested that tetramethylpyrazine nitron rescued dopaminergic neurons by reducing ROS and increasing cellular antioxidative defense capability in the animal models of PD. Sudati et al. [150] concluded that *Valeriana officinalis* improved the antioxidant defence mechanism in the rotenone-induced toxicity in *Drosophila melanogaster*. Pasban-Aliabadi et al. [151] suggested that the protective effect of olive (*Olea europaea* L.) leaf extract in the 6-hydroxydopamine-induced PC12 cell apoptosis is due to their antioxidative and antiapoptotic properties. Kim et al. [152] explored the neuroprotective role of *Rhus verniciflua* in rotenone model of PD via its antioxidant efficacy. Li and Pu [153] reported that kaempferol inhibited MPTP induced oxidative stress in the mouse model of PD. Liang et al. [154] pointed out that tenuigenin exhibited potent neuroprotective effect through antioxidant potential in a SH-SY5Y cell model with 6-OHDA-induced injury. Hu et al. [155] showed that the ginseng attenuated (MPP(+)) induced cytotoxicity in SH-SY5Y cells through its antioxidant potential. Choi et al. [156] suggested that *Polygalae Radix*, through its antioxidant and antiapoptotic efficacy, inhibited the neuronal death in PD models. Sengupta

et al. [157] reported that the hydroxyl scavenging potential of *Hyoscyamus niger* seeds is responsible for its neuroprotective effect.

An et al. [158] reported that *Acanthopanax senticosus* prevented the MPP<sup>+</sup> induced damage in PC12 cells by reducing the levels of MDA, which suggested its antioxidant potential. Kim et al. [159] pointed out that Chunghyuldan exhibited neuroprotective effect against ROS-mediated neuronal cell death in PD model. Lee et al. [160] suggested that Cyperi rhizome exhibited the neuroprotective effects through antioxidant and antiapoptotic activities in an in vitro PD model. Shu et al. [161] suggested that the neuroprotective effect of *Chuanxiong Chatiao* may be associated with its potent antioxidant efficacy in MPTP-induced Parkinson's mice. Shim et al. [162] suggested that *Uncaria rhynchophylla* exhibited neuroprotective effect through antioxidative and antiapoptotic activities in PD models. Sankar et al. [163] suggested that *Withania somnifera* root extract exhibited potent neuroprotective effect by mitigating MPTP-induced oxidative stress in PD mice. Ahmad et al. [164] showed the neuroprotective effect of *Delphinium denudatum* via its antioxidant property in PD rats. Ahmad et al. [165] reported that *Nardostachys jatamansi* attenuated 6-hydroxydopamine-induced parkinsonism in rats via antilipid peroxidative potential. Zhang et al. [166] explored the neuroprotective effect of *Forsythia suspensa* with antioxidant property in an experimental model of rotenone-induced neurotoxicity. Lu et al. [167] suggested that resveratrol showed a neuroprotective effect in MPTP-induced parkinsonism through free radical scavenging potential. A large number of experimental studies on neurodegenerative diseases highlighted curcumin as a potent neuroprotective agent [168]. Braidy et al. [137] explored the neuroprotective effect of pomegranate extract in MPTP induced oxidative stress in human primary neurons.

## 8. Huntington's Disease

Huntington's disease (HD) is a devastating familial and inherited disease characterized by the progressive loss of brain and muscle function. It occurs due to the genetically programmed degeneration of neurons, which causes uncontrolled movements, loss of intellectual abilities, and emotional disturbances. HD is caused by a CAG trinucleotide expansion in exon 1 of the Huntingtin (HTT) gene, which is located on chromosome 4 (4p63) [169]. Healthy individuals have 6–35 CAG repeats, and affected individuals have more than 36 repeats. The accumulation of mutant Huntingtin proteins contains a long polyglutamine region which causes neuronal death and the degeneration of neuronal networks within the brain. The pathological changes in the cerebral cortex and striatum elicit the development of chorea and cognitive impairments and lead to premature death. There is a 50% chance that children will inherit HD from HD affected parents. Men and women are equally affected by HD which appears during 4th to 5th decade of life. The symptoms usually appear between the ages of 35 and 55. However, the age of onset and its progression varies from person to person [170]. The clinical course of HD typically progresses over 10 to 20 years from a presymptomatic state to complete disability

and death. The early symptoms includes tumbling, lack of focus, concentration and movement problems, clumsiness, lapses in short-term memory, and depression. As the disease progresses, difficulty in speech, weight loss, feeding problems, swallowing difficulties, uncontrollable movements of the face, and itching and stumbling are the major symptoms. It has been estimated that around 6000 and 30,000 people are affected by HD in UK and USA, respectively [171].

## 9. Oxidative Stress and Huntington's Disease

The exact cause of neuronal death in HD is unknown. However, oxidative stress may play an important role. The two major factors that make the brain more prone to oxidative damage are higher lipid concentrations and high energy requirement [172]. Compelling data supports a critical role for oxidative stress in the pathogenesis of HD, a disorder caused by polyglutamine expansion in Huntingtin (Htt). mHTT proteins serve as the source of reactive oxygen species (ROS), due to a significant amount of oxidized proteins in partially purified mHTT aggregates [173]. Though oxidative damage is not much reported in the early stages of HD, it is proposed as one of the major mechanisms in HD as it progresses [174].

Elevated oxidative stress plays a critical role in the late stage of HD pathogenesis. Impairment in the electron transport chain and mitochondrial dysfunction are the major mechanisms involved in the ROS mediated etiopathogenesis of HD [175, 176]. Dysfunction in the oxidative phosphorylation components has been documented in the brain tissues of HD patients [177]. HD patients showed an increased level of oxidative stress markers accompanied by a decrease in antioxidant status compared to healthy subjects [178]. ROS mediated oxidative damage to mitochondria has been postulated as a reasonable mechanism for the defect in glucose metabolism in the brain tissue of symptomatic HD patients [179]. A positive correlation between plasma lipid peroxidation byproduct and the severity of disease in patients with HD has been shown [180]. Enhanced lipid peroxidation has been reported in patients with severe symptoms of HD [178, 181]. An increase in the plasma lipid peroxidation accompanied by reduced glutathione content has been reported in HD patients [182]. The extensive oxidative DNA damage has been reported in a HD mouse model [183, 184]. Enhanced oxidative stress and a decline in nonenzymatic antioxidants have been reported in the peripheral blood of HD patients [185]. Stoy et al. [186] reported that abnormal tryptophan metabolism with enhanced oxidative stress could be responsible for brain dysfunction in HD. Duran et al. [187] reported that symptomatic HD patients are more prone to oxidative stress than asymptomatic HD patients. The causes of oxidative stress in HD are given in Figure 3.

## 10. Natural Products and Huntington's Disease

Researches utilized suitable experimental models to scientifically validate the protective efficacy of natural products against HD. Oliveira et al. [188] suggested that the protective

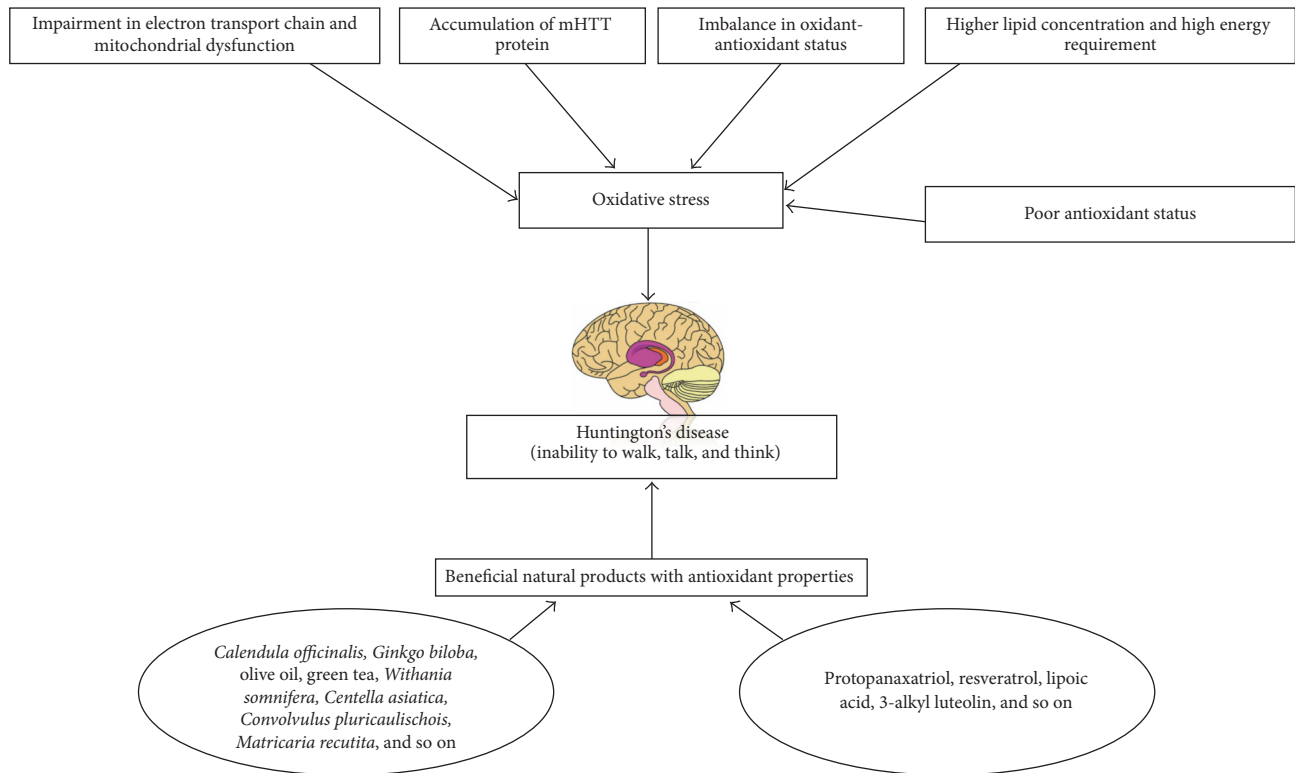


FIGURE 3: The causes of oxidative stress in Huntington's disease.

effect of *luteolin* derivatives on Huntington's mouse striatal cells is due to its antioxidant potential. Shivasharan et al. [189] showed the protective efficacy of *Calendula officinalis* flowers in 3-nitropropionic acid-induced HD in rats. They concluded that the anti-inflammatory and antioxidant potential of *Calendula officinalis* might have played a neuroprotective role. Mahdy et al. [190] explored the beneficial effect of *Ginkgo biloba* extract on 3-nitropropionic acid-induced neurobehavioral changes and striatal lesions. They concluded that the antioxidant and antiapoptotic potential of *Ginkgo biloba* extract might be responsible for the neuroprotective role. Tasset et al. [191] reported that olive oil reduced oxidative damage in 3-nitropropionic acid-induced HD in rats. They concluded that extravirgin olive oil and hydroxytyrosol served as a powerful brain antioxidant. Sagredo et al. [192] provided preclinical evidence for the neuroprotective effect of phytocannabinoid-based medicines in HD. Gao et al. [193] investigated the neuroprotective effect of protopanaxatriol against 3-nitropropionic acid-induced oxidative stress in experimental HD. Túnez et al. [194] showed the protective effect of melatonin in 3-nitropropionic acid-induced oxidative stress in synaptosomes in rat with HD. They concluded that melatonin modified the neural response to 3-nitropropionic acid with the antioxidative mechanism.

Rocha-González et al. [195] reported the neuroprotective role of resveratrol against HD. Andreassen et al. [196] suggested that lipoic acid, as an antioxidant, has the potential to improve the survival of transgenic mouse models of HD. Ehrnhoefer et al. [197] pointed out that green tea (-)-epigallocatechin gallate prevented the early events of HD

pathogenesis such as Huntington's misfolding. Denny Joseph and Muralidhara [198] suggested that fish oil in combination with quercetin provided better neuroprotection against 3-nitropropionic acid-induced HD. Fu et al. [199] suggested that trans-( $\epsilon$ )- $\epsilon$ -Viniferin could be considered as a promising candidate to treat HD, since it increased mitochondrial sirtuin 3 (SIRT3) and activated the AMP-activated protein kinase. Huang et al. [200] explored the neuroprotective role of N(6)-(4-hydroxybenzyl) adenine riboside against experimental HD. Ranpariya et al. [201] showed the neuroprotective effect of *German chamomile* against aluminium fluoride-induced oxidative stress in rats. P. Kumar and A. Kumar [202] explored the neuroprotective effect of *Withania somnifera* root extract against 3-nitropropionic acid-induced HD. They suggested that neuroprotective actions of *Withania somnifera* are mediated via its antioxidant activity. Shinomol and Muralidhara [203] reported that the prophylactic neuroprotective property of *Centella asiatica* could be related to the enhancement of GSH, thiols, and antioxidant machinery in the brain regions of 3-nitropropionic acid-induced HD prepubertal mice. Kaur et al. [204] suggested that *Convolvulus pluricaulis* exhibited a potent neuroprotective effect by accelerating the brain antioxidant defence mechanisms in 3-nitropropionic acid treated rats. Al-Sabahi et al. [205] reported the benefit of pomegranate seed oil on 3-NP induced HD.

## 11. Conclusion

Neurodegenerative diseases impose a significant health burden not only to the affected patients, but also to their families

and society. The incidences of these life threatening disorders are rapidly increasing in aged populations worldwide. Although several mechanisms have been postulated for the pathogenesis of neurodegenerative diseases, oxidative stress and mitochondrial dysfunctions are pointed out as a major mechanism. At present, medications are only available to treat the symptoms of neurodegenerative diseases. Several in vivo and in vitro studies have documented the protective role of various natural products or synthetic entities in the prevention of neurodegenerative diseases. However, the solution for these neurodegenerative diseases has not yet been found. Thus, researches are warranted to investigate the nontoxic active constituents found in natural resources which could correct the biochemical, metabolic, and behavioral abnormalities that occur in neurodegenerative diseases.

## 12. Opinion of the Authors

This review highlights the crucial role of oxidative stress in the pathogenesis of various neurodegenerative diseases. Based on the literature researched for this paper, it is clear that oxidative stress mediates its adverse effects either directly, causing neuronal damage, or by inducing the harmful effects of neurotoxicants. This review also explores the beneficial effects of various natural products against neurodegenerative diseases.

While many reports have focused on the role of protective efficacy of natural products against oxidative stress-induced neurodegenerative diseases, as yet, there have been no effective treatment solutions reported for these diseases. This indicates that the antioxidants alone are not sufficient to treat neurodegenerative diseases. Thus, intense research should be undertaken to investigate, or identify, the novel compounds that could be used to counteract the oxidative stress pathogenesis and for a better therapeutic agent for the treatment of neurodegenerative diseases.

## 13. Literature Search Strategy

For this study, an intense literature search on neurodegenerative diseases (AD, PD, and HD) was mainly done through PubMed articles published from 1982 to 2016. The articles were then scrutinized and the most relevant selected to write this review. We have also referred to previous review articles on neurodegenerative diseases and the references cited were also considered. The key words used to search the relevant articles included neurodegenerative diseases, Alzheimer's disease, Parkinson's disease, Huntington's disease, Reactive Oxygen Species, antioxidants, medicinal plants, and so forth.

## Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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