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A review on neurodegenerative diseases associated with oxidative stress and mitochondria

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***Abstract*---**Alzheimer's disease, Parkinson's disease, and other neurological diseases afflict people of all ages. Neuronal loss and cognitive dysfunction are common symptoms of these disorders. Overproduction of reactive oxygen species has been demonstrated to aggravate disease progression in previous investigations (ROS).

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Because of the large quantities of polyunsaturated fatty acids in their membranes and their fast oxygen consumption rate, neurons are especially susceptible to oxidative damage. The molecular aetiology of neurodegeneration produced by changes in redox balance has not yet been established. New antioxidants have shown considerable potential in modifying disease characteristics. For the treatment of Alzheimer's disease and other neurodegenerative illnesses such as Parkinson's disease, ALS and spinocerebellar ataxia and Huntington's disease, antioxidant-based therapies are examined extensively in the literature.

***Keywords*---**neurodegenerative disorders, oxidative stress, Parkinson's, Alzheimer's, Huntington.

Introduction

The gradual loss of brain cells and neurons is a hallmark of neurodegenerative illnesses, resulting in diminished motor or cognitive function. The most common neurodegenerative disorders are ALS, HD, PD, and PD/Spinocerebellar Ataxia (SCA). These illnesses are more common among the elderly. Alzheimer's disease (AD), which is currently the sixth biggest cause of mortality in the United States, illustrates this phenomenon. Parkinson's disease (PD) is the second most common neurological illness in the elderly, affecting between 1% and 2% of the population (Patel & Chu, 2011; Pillar, Moisseiev, Sokolovska, & Grzybowski, 2020). The development of neurodegenerative illnesses has been linked to reactive oxygen species (ROS) (ROS). Inflammation, cell survival, and stressor responses are all assumed to be part of cytokines' impact on illnesses such as cardiovascular disease, muscular dysfunction, allergies, and cancer, among many others. ROS are thought to be the root cause of oxidative stress (OS), characterised by an unbalanced ratio of pro-oxidant to antioxidant enzymes in the body (Valluri et al., 2021; Vyas, Mathur, Patel, & Patel, 2017). OS is often raised in the brains of persons with neurodegenerative disorders. Many diseases' pathogeneses remain a mystery, but new research shows ROS may play an important role (Pope, Land, & Heales, 2008; Praticò, 2008).

The involvement of ROS in neurodegenerative disease has been the subject of several investigations, and some promising findings have emerged. If we blame ROS, their oxidative damage and interactions with mitochondria are likely to speed up the course of neurodegenerative disorders. This makes neurons especially sensitive to oxidative damage because of the high quantity of polyunsaturated fatty acids found in their membranes, the speed at which they consume oxygen, and the lack of antioxidant protection. Endogenous antioxidants modulate the amount of ROS produced by mitochondria, NADPH oxidase (Nox), and xanthine oxidase (XO) in healthy people (Preissler et al., 2016; Ray, Martinez, Berkowitz, Caldwell, & Caldwell, 2014). However, if there is inflammation in the brain or aberrant mitochondrial activity, the redox equilibrium may be disrupted. Protein misfolding may have a role in several neurodegenerative diseases, including Alzheimer's and Parkinson's. Inflammation in the brain begins when these changed proteins clump together, resulting in a significant release of ROS and OS (Muchakayala et al., 2022; Subramanian et al.,

2022). Neurodegenerative diseases are closely associated with mitochondrial dysfunction and abnormal ROS generation. In HD, mitochondria may be damaged, and ROS levels may rise due to mHTT directly interacting with mitochondria. By adjusting ROS levels, it is possible to slow the course of neurodegenerative disorders and alleviate associated symptoms (Figure 1).

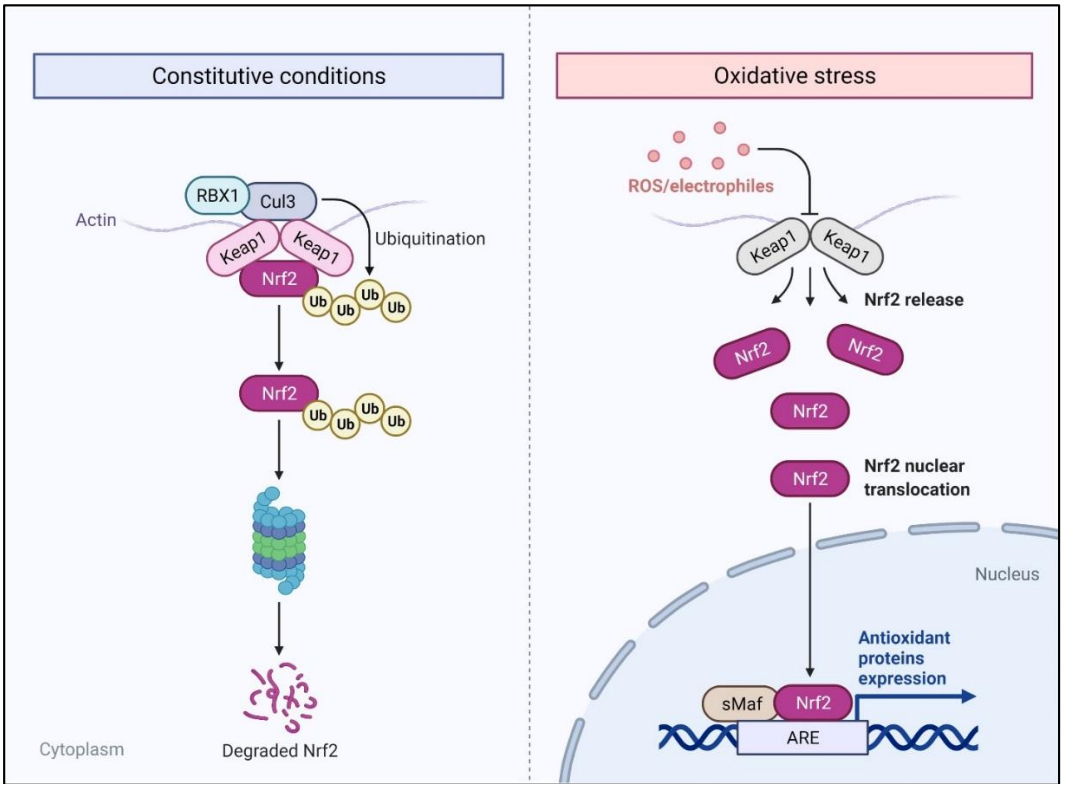

Figure 1: Nrf2 and Keap 1 pathway and oxidative stress

Even though glutathione (GSH), vitamin C, and vitamin E have been tested for their ability to treat neurodegenerative symptoms, inconsistent findings have been reported from these molecules (Mathur & Vyas, 2013). A two-year course of vitamin E therapy, for example, has been demonstrated to slow the progression of functional deterioration in people with mild Alzheimer's disease (Agostinho, Cunha, & Oliveira, 2010; Anderson & Maes, 2014).

Taking vitamin E supplements early in life has reduced the risk of developing Parkinson's disease (PD). According to Pappert and colleagues ' research, patients with Parkinson's disease who received vitamin E supplements for five months had no change in their ventricular cerebrospinal fluid vitamin E levels. The blood-brain barrier and the fast degradation of antioxidants may restrict the ability to provide antioxidants orally. Antioxidants, such as Ferrostatin-1 (Fer-1) and other compounds, may help alleviate symptoms of neurodegenerative disease. Research on the effects of antioxidant therapy should consider the patient's current state of illness, the antioxidant delivery method, and dosage. As far as we know, the molecular causes of neurodegeneration are unknown. More research into ROS

and neurodegenerative illnesses may lead to more effective treatments. However, ROS's crucial function in Alzheimer's disease, Parkinson's disease, and hysteria have not yet been extensively investigated systematically (Azadzoi, Golabek, Radisavljevic, Yalla, & Siroky, 2010; Azadzoi, Yalla, & Siroky, 2007).

As a consequence, the earliest feasible inspection must be undertaken. Neurodegenerative disease research at the forefront has been the focus of this essay. Research on ROS and antioxidant treatment in neurodegenerative illnesses was the focus of our study. Model disorders like this may be helpful in future research aimed at developing new therapeutics for neurodegenerative diseases (Barsukova, Bourdette, & Forte, 2011; Botella et al., 2004).

Alzheimer's disease and oxidative stress are linked (AD)

Alzheimer's disease (AD), the most common neurological disorder, is characterised by declines in behaviour, cognition, and everyday activities. Extracellular formation of amyloid-beta plaque and tau neurofibrillary tangles are two of Alzheimer's disease's most essential components (NFT). An excess of Ca2+ in the cytoplasm may be caused by the presence of A plaques in the ER. ROS can develop within cells when the cytosolic Ca2+ level rises [34]. In Alzheimer's disease (AD), ROS overproduction is connected to the accumulation and deposition of A. ROS misregulation, decreased ATP generation, altered Ca2+ homeostasis, and excitotoxicity is all possible side effects of mitochondrial malfunction. If any or all of these changes are present, Alzheimer's disease progression may be affected (Brown, 2005; Butterfield, 2003; Butterfield & Boyd-Kimball, 2004) (Figure 2).

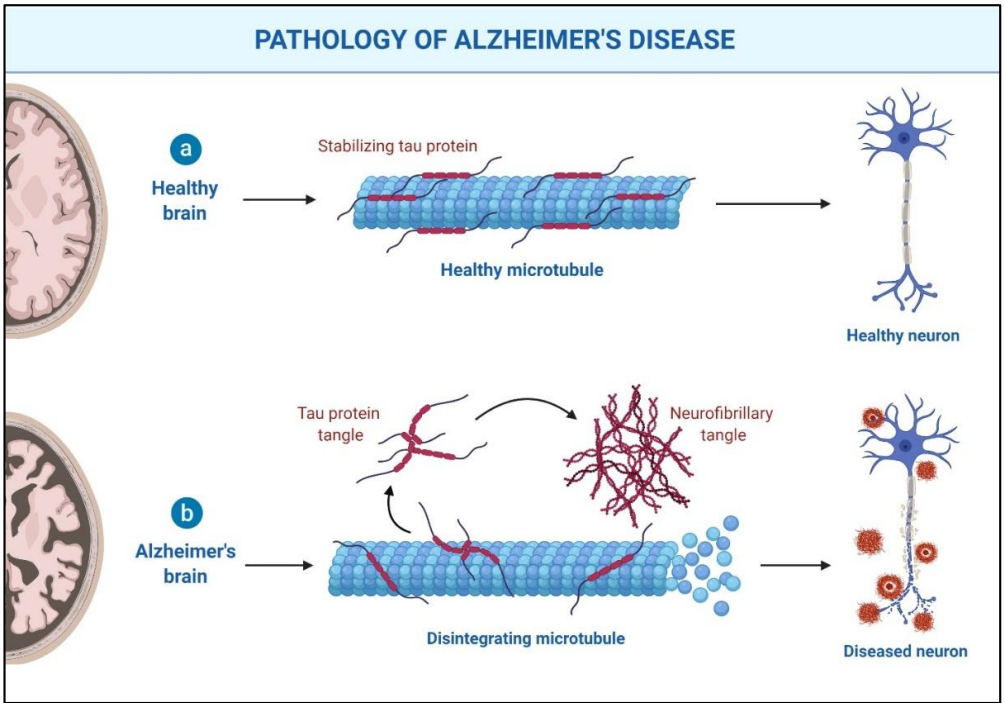

Figure 2: Pathophysiology of Alzheimer

N-methyl-D-aspartate receptors may be overexcited in AD patients, as shown by their OS severity (NMDARs). When NMDARs are triggered, a large amount of ROS and reactive nitrogen species are found to be neurotoxic and may result in brain death (RNS). Stress-activated protein kinase pathways may use ROS as a mediator. Tau hyperphosphorylation and activation of these pathways have been linked to A-induced cell death. The activation of NADPH oxidase by A proteins may also directly lead to the production of free radicals. p38 Tau hyperphosphorylation is caused by the activation of mitogen-activated protein kinase (MAPK) by A. (MAPK). Intracellular NFT development may be caused by an aberrant buildup of hyperphosphorylated tau proteins (Cabezas et al., 2019; Carrì et al., 2001). In yet another approach, A's involvement in regulating cell apoptosis has been uncovered. By increasing the activity of the calcineurin enzyme, A activates the Bcl-2-associated death promoters and causes mitochondrial leakage. In addition, caspases, which are directly linked to A., may be responsible for neurons' death. Neurotransmitter A production increases due to events such as ageing, inflammation and environmental stress (e.g., redox-active metals). As the population ages, older people are more likely to get Alzheimer's disease (AD). These factors contribute to Alzheimer's disease's development via inflammation: ROS, cytokines, and cellular damage. Microglia get activated as soon as A is injected into the body. Activation of microglia results in proinflammatory cytokines, which in turn causes neuronal injury and death. Toxic and radioactive pollutants in the environment may be a possible cause of OS. Excessive iron deposits may promote ROS generation, for example (Carrí, Ferri, Cozzolino, Calabrese, & Rotilio, 2003; Cassagnes et al., 2018). Because A may create free radicals when combined with metal ions, Methionine 35 is essential in these processes. The antioxidative property may be due to its structural similarity with the enzyme superoxide dismutase (SOD), which scientists discovered. There has been speculation that adding Cu2+ and Zn2+ might reduce ROS production and metal-catalyzed A deposition. Therapy for Alzheimer's disease aims to lower oligomer and phosphorylated tau levels, minimise OS, and modulate epigenetic alterations (AD). These are the most critical issues that need attention. Alzheimer's disease is typically treated using anti-inflammatory, neuroprotective, and antioxidant drugs (AD). Medical therapeutics that target ROS-mediated cascades like JNK and NF-B have shown promising outcomes in studies in vitro and animals. For the best results, antioxidants must be utilised to maximise their bioavailability (i.e. absorption and distribution). Neuroprotective therapies based on ROS can be beneficial in the fight against Alzheimer's disease (Chen et al., 2008; Chico et al., 2017). Nuclear factor erythroid 2-related factor 2 (Nrf2) is renowned for its function in protecting oxidative stress (OS). The binding of Nrf2 may coordinate antioxidant genes to ARE, which may aid in oxidative detoxification. Adoptive Nrf2 gene transfer was reported to protect against A deposition in AD-symptomatic transgenic rats, while the Nrf2-ARE pathways were reduced. Using endogenous antioxidant transcriptional reprogramming may significantly impact Alzheimer's disease symptoms (AD). Alzheimer's disease has shown promise in treatments including Ayurveda, Chinese medicine, metal ion chelators, and histone deacetylase inhibitors (AD) (Contestabile, 2001; Crews & Nixon, 2009; D'Amico, Factor-Litvak, Santella, & Mitsumoto, 2013).

Reactive Oxygen Species (ROS) and Huntington's Disease

Because of an unstable increase in CAG repeats, the HTT gene has been associated with a progressive neurological disorder in HD. CAG repeats in exon1 of the HTT gene are increased, which results in a mutation that makes an HTT protein product more vulnerable to aggregation. A buildup of mHTT aggregates in the brain may indicate a problem with protein quality control and transcription. These changes may cause HD's abnormal motor and cognitive deficits. A cure or substantial slowing of the disease's course has not yet been found for HD patients (Dasuri, Zhang, & Keller, 2013; De Chiara et al., 2012). A common HD mutation, mHTT, causes cytoplasmic plaque and neuronal nuclear inclusions in HD. In addition, antioxidant enzyme levels and striatal mitochondrial concentrations are reduced by mHTT, which lowers the expression of peroxisome proliferator-activated receptor-coactivator-1. Studies to treat the disease with conventional antioxidants have failed, although the well-known link between HD and OS is worth noting. They're particularly interested in how HD impacts the brain's energy level. Compared to the control group, HD patients eat less glucose and have lower lactate levels. An increase in lactate levels has been linked to the overexpression of glucose transporter 3 (GLUT)-3, which inhibits glucose absorption (S. Deng et al., 2021; Y. Deng et al., 2015). The bulk of ATP is produced during electron transport chain activity via the production of protons.
Mitochondrial dysfunction has been linked to mHtt deficiency. As indicated by electron microscopy, anomalies in mitochondrial calcium may be traced back to mHtt's N-terminal; according to Panov et al. MHT also has a more direct effect on the respiratory complex II. Both an increase in ROS and a reduction in ATP generation may be attributed to mitochondrial electron transport. When it was first postulated that mitochondrial damage in HD was caused by OS inhibiting GPD catalysis, it was a long time ago that the specific mechanism that has been described for this damage was first put forth (GAPDH). The inactive GAPDH (iGAPDH) clings to damaged mitochondria and works as a signalling molecule to encourage the defective mitochondria to die via lysosome engulfment (Dias-Santagata, Fulga, Duttaroy, & Feany, 2007; Fatokun, Stone, & Smith, 2008). When IGAPDH is attached to the mitochondrial outer membrane by IGAPDH, its breakdown is slowed down because of the lengthy polypeptide chain of mitochondrial HTT. Due to a shortage of lysosomes, cells that express mHtt die of oxidative stress. Positive feedback loops between ROS and mitochondrial changes in the brain's striatum and cortex may be responsible for a rise in OS and neuronal death. HD advancement has been linked to mitochondrial changes and ROS overproduction, although it's not clear which starts first in the disease development process (Gupta, Pathak, et al., 2020; Gupta, Singh, et al., 2020).

Studies have indicated that increased oxidative indicators are linked to long-term neurological damage. A study used HD-related biomarkers such as NSE and 8-hydroxy-2-deoxyguanosine (OHdG) concentrations to determine the benefits of neurorehabilitation exercise. SOD1 is a possible indicator of neuronal oxidative damage in HD, and patients exhibited much higher levels than healthy controls, suggesting a compensatory response. Although SOD1 has been proposed as an oxidative biomarker in HD, conflicting results have been obtained about SOD1 concentrations and activity in the disease (Gibson & Zhang, 2002; Gil & Rego,

2008; Go, Kim, Yang, & Choe, 2017; Gonsette, 2008a; Prasher et al., 2020; Samuel et al., 2019).

Neurorehabilitation reduced NSE and 8-OHdG levels significantly, while SOD1 levels remained high, suggesting that SOD1 may play a role in scavenging free radicals. Physical exercise is recommended for people with HD to improve redox homeostasis and delay or stop the disease's development. Biomarkers such as TBARS, 3-nitrotyrosine, protein carbonyls, and protein carbonyls are also employed in HD model systems (Gonsette, 2008b; Gorman, McGowan, O'Neill, & Cotter, 1996).

According to research, F2-isoprostane levels are greater in those with HD and Alzheimer's disease (F2-IsoP). Since OS is crucial in HD patients, it may be possible to measure F2-IsoPs. In the early phases of HD development, F2-IsoP levels and controls may be identical. You must keep this in mind. Keep in mind that oxidative biomarker changes might be caused by various things, such as ageing or sickness. The oxidative changes levels may not provide enough information to establish whether these modifications are the consequence of cell death or if they are linked to the development of diseases. A clearer picture of the link between operating systems and hard drives has emerged. Still, We need reliable biomarkers to understand better how OS functions in neurodegenerative disorders and to find HD therapeutic options (Haddadi, Eyvari-Brooshghalan, Nayebi, Sabahi, & Ahmadi, 2020; Higgins et al., 2010; Hinerfeld et al., 2004; Kazmi et al., 2021; Mehta et al., 2019).

Parkinson's disease and oxidative stress (PD)

Parkinson's disease is characterised by the death of dopaminergic brain neurons and is the second most common neurodegenerative illness in the United States. The frequency of Parkinson's disease (PD) grows from 1% to 4% between 85 and 89. Dopaminergic neuron death has been linked to an accumulation of reactive oxygen species (ROS) or other free radicals in the body. Excess ROS generation may be caused by inflammation and mitochondrial malfunction. To keep neurons healthy, redox-sensitive signalling proteins must be kept in balance. The mitochondria in neurons and glia are the brain's principal source of reactive oxygen species (ROS) (Hood, Jenkins, Milatovic, Rongzhu, & Aschner, 2010; Jenner, 2003; Jia et al., 2012). It is thought that neuroinflammation, dopamine breakdown, mitochondrial dysfunction, age-related decline in GSH, and elevated iron or Ca2+ levels are all contributing factors to free radical production in Parkinson's disease patients. When Parkinson's disease (PD) patients are exposed to chemicals, neurotoxins, or dopamine, their production of reactive oxygen species (ROS) may rise. Pesticide exposure has been linked to Parkinson's disease (PD). The degeneration of dopaminergic neurons has been linked to the production of ROS. Dopaminergic neurons are more vulnerable to injury if they are strongly pigmented. This has been linked to neuromelanin in recent investigations (Kazmi, Afzal, Gupta, & Anwar, 2012; Koppenhöfer et al., 2015; Koutsilieri, Scheller, Tribl, & Riederer, 2002; Krishna, Dubey, Singhvi, Gupta, & Kesharwani, 2021).

The formation of neuromelanin seems to be linked to ROS-induced dopamine auto-oxidation. The ROS produced by neurodegeneration damages proteins and alters lipid membranes, which may lead to OS. Free radicals are produced in the respiratory chain as a result of mitochondrial malfunction. Parkinson's disease and mitochondrial complex I impairment have been linked by researchers. Because of the unusually high rate of neuronal apoptosis in PD, the complex I deficiency is most likely to be to fault (cell death). PTEN-inducible putative kinase 1 mutations have been linked to this problem (PINK1). To keep mitochondria's membrane potential constant and resist OS, the PINK1 protein is present in all human tissues (Kwakye et al., 2019; Lahiri & Greig, 2004). Parkinson's disease is linked to a PINK1 gene defect (PD). Mutations in other proteins, such as parkin, synuclein, and leucine-rich repeat kinase 2 (LRK2), as well as the PINK1 gene itself, are considered to increase Parkinson's disease (PD) (LRRK2). These mutations raise the possibility of OS and ROS formation in part because of mitochondrial dysfunction. PD may be caused by mutations in parkin, a protein that regulates the synthesis of neurotoxic proteins through ubiquitination and reduces ROS (Lee et al., 2016; Luca, Luca, & Calandra, 2013). Because of this, the functions of mitochondrial complex I are hampered, resulting in mitochondrial disease. Proteasomal dysfunction and synuclein buildup in Parkinson's disease may both be caused by overexpression of translation and posttranslational proteins. Dopamine-induced reactive oxygen species (ROS) aggravate Parkinson's disease-related neurodegeneration (PD) (Gupta et al., 2017; Maciejczyk, Żebrowska, & Chabowski, 2019; Meejuru, Somavarapu, Danduga, Nissankara Roa, & Kola, 2021; Sachdeva, Sachdeva, Arora, Redhu, & Gupta, 2013; Singh et al., 2020).

ROS-related pathways play an important role in the development of Parkinson's disease (PD), even though there is currently no treatment for PD. Dopaminergic neurons may benefit from a wide range of neuroprotective therapies. Antioxidants and fruits have been shown to be effective in counteracting the harmful effects of free radicals. Vitamin C, E, and GSH may be recycled in the body by antioxidant lipoic acid (LA). LA produces GSH and increases lipid peroxide depletion to protect neurons against OS and OS-induced mitochondrial dysfunction. In an animal research, therapy with LA increased ATP efficiency and motor coordination (Melo et al., 2019; Milbourn et al., 2017; Miller & Sadeh, 2014). Los Angeles lowered lipid peroxidation in the brains of Parkinson's disease rats given rotenone and enhanced their motor function as a result. Studies on the neuroprotective properties of vitamin C, docosahexaenoic acid, and ginkgo biloba have all been conducted, but no conclusive evidence has been found to support these beliefs. In developing novel therapies for Parkinson's disease, the failures of antioxidant medicines should serve as a warning lesson (Gupta et al., 2021; Gupta et al., 2018; Mishra et al., 2015; Miyata et al., 2008; Moreira et al., 2005).

Summary and future prespective

Antioxidant therapy has been investigated in the area of neurodegenerative illnesses, but the results have been inconsistent. It's possible that the problem stems from using the wrong dose, timing, or length of treatment. Novel antioxidants may have an impact on disease characteristics. The antioxidant Fer-1 has been proven to be effective in preventing neuronal cell death in HD and PD

and is one of many such antioxidants. Because they work both upstream and downstream of OS, antioxidants protect this delicate redox equilibrium. Antioxidant effects can be achieved by inhibiting ROS accumulation, as well as lipid and protein oxidation. Antioxidant vitamins C and E, which are present in many foods, may help minimise the toxicity of oxoradicals. It's a good idea to eat more fat in order to reduce your body's oxidative stress. Antioxidant treatment is helpful after OS because it reduces brain inflammation and reduces the detrimental consequences of mutant protein aggregation. A number of studies have shown that Ginkgo biloba, a Chinese plant with powerful antioxidant qualities, may aid Alzheimer's patients with cognitive deficits.

More than one ROS type is likely to have a role in the onset of illness. Antioxidant defence mechanisms inside the biological system regulate ROS generation. In the absence of adequate exogenous antioxidants to battle OS caused by pathophysiological circumstances, the body's oxidative potential may become imbalanced. Neurodegenerative disorders may be prevented by using a mixture of antioxidants. The appropriate timing, dosage, and duration of antioxidant therapy must yet be discovered in order to get the best results.

The function of ROS in neurodegenerative diseases such as Alzheimer's, Huntington's, and Parkinson's was examined in our study. Those who consume more omega-3 fatty acids have a decreased chance of getting neurological diseases such as Alzheimer's disease (OS). Studies demonstrate that ROS is created in a variety of ways and serves a variety of functions as illness progresses. One of the most prevalent causes of long-term neurodegenerative illness is mitochondrial malfunction. Antioxidants have been studied extensively to see whether they may slow the progression of neurodegenerative diseases. In spite of promising results, neuroprotective effectiveness has yet to be shown conclusively. Antioxidant treatments for many neurodegenerative diseases will need more ROS research.

Conflict of interest:
There is no conflict of interest, the authors declare.

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