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Significance of Antioxidants in the Treatment and Prevention of Neurodegenerative Diseases

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ABSTRACT

Neurodegenerative diseases are ailments that disturb the brain, precisely the neurons. The utmost mutual indicators include failures in stability, inhalation, movement, reflexes, motor skills or heartbeat activity. These can be prevented using ordinary antioxidants, like vitamins E and C, flavonoids, and polyphenols compounds. Antioxidants show a substantial effect in human's health since they can ameliorate aging by fighting free radicals. Precisely Vitamin C can serve as a commanding antioxidant in reducing the consequence of oxidative injury triggered by pollutants, anxiety and poor diets amongst others. Thereby reducing the long-term risk of neurodegenerative diseases. Currently, neurodegenerative diseases have no cure, but they can be managed. This diseases management reduces the symptoms so as to sustain the value of life. Management with natural antioxidants such as polyphenols through diet or dietary supplements with lots of benefits have become an attractive alternative. The present knowledge on antioxidant in the treatment of neurodegenerative disorders and future bearings will be discussed and also assess the value for antioxidants as neuroprotective.

Keywords: Neurodegenerative diseases; vitamins; antioxidants; Neuroprotectives; Alzheimer's disease; Parkinson's disease.

INTRODUCTION

As earlier reported, neurodegenerative diseases (NDD) are multifactorial conditions characterized by aberrant protein dynamics with defective protein degradation and aggregation, oxidative stress (OS), free radical development, impaired cell energy transformation and power house dysfunction [1]. They are activated to a limited extent by oxidative and nitrosative stress (OS and NO) and furthermore supported by the production of inflammatory cytokine [2-9] and the particular cause of the destructive ROS/RNS and the influenced target structures extends between the neuronal pathologies [10]. Since metabolic disarrays underlying any single disease can also indirectly give rise to an oxidative microenvironment [11, 12], antioxidant and anti-inflammatory drugs have been suggested in the treatment of various neurodegenerative conditions [13]. Cell reinforcements are used on a significant scale to acquire as well as safeguard ideal wellbeing. While there is no uncertainty that the correct harmony among endogenous and exogenous cell antioxidant capacity is fundamental to life, the therapeutic intensity of this agents has regularly been misrepresented. The utilization in the treatment of human disease states (most especially neurodegenerative diseases, cardiovascular diseases, and cancer) have not been as fruitful as envisioned because of intrinsic pharmacokinetic or pharmacodynamic impediments.

Excess antioxidant ingestion often result in risks to initiate diseases as opposed disease prevention. These antioxidants may present certain negative effects if not strictly administered or in combination with other medications. Certain vitamins have also been proposed to present pro-oxidant impacts under certain conditions and increased doses [14, 15].

The possible curative use of antioxidants in free radical-related diseases prompted the theory of their utilization to reduce or turn around side effects related to neurodegenerative diseases. Such impact could be initiated through inhibition of proinflammatory cytokines activity and the subsequent oxidative damage [16-20]. However, studies demonstrated that excess of certain nutrients could set into motion oxidation phenomena and, therefore, cell damage [21, 22]. Therefore, it is of importance that before initiating antioxidant remedy into standard medicine, noteworthy progress in essential cell biology, pharmacology, and clinical bioanalysis are needed. Antioxidant properties of plant-derived foods protect membranes from ROS moderated DNA damage which could result in transformation and subsequent diseases. Natural antioxidant molecules have been proposed as another form of management/treatment of age-related

neurological diseases. Different types of antioxidant molecules and antioxidant vitamins may contribute to this prevention. Therefore, the significance of antioxidants as neuroprotective will be evaluated in some neurodegenerative diseases. There are still several gaps in the comprehension of the basis of oxidative damage in neurodegenerative disorders; notwithstanding, it is progressively acknowledged that numerous diseases share common pathways of oxidative stress-related damage, and all things considered, noteworthy advancement will be made in the structural design and implementation of viable therapeutic systems in the nearest future [23].

Antioxidants and Free radicals

Free radicals are regarded as atoms or molecules comprising one or more single electrons. Biologically important radicals are triggered atoms or groups of atoms with an odd (unpaired) number of electrons. They are continually created during normal physiological metabolism in tissues. Under standard conditions, the impacts of ROS/RNS are countered by the antioxidant defenses in the body, which contributed to the dietary intake of key nutrients (e.g. vitamins and trace minerals). Since reactive radicals can be alleviated by the help of antioxidants, they have the ability to sustain the integrity of cells (structurally and functionally). Therefore, they are vital to the defense system in plants, animals as well as humans.

Oxidative stress and damage

Although oxidative stress may not be deduced basically by estimating **only a fraction of the delicate balance that majorly exists between the generation of reactive oxygen species and damage limitation by the antioxidant system,** it is a phenomenon that produces an imbalance between reactive oxygen species and antioxidants in a biological system. These play a crucial role in pathophysiology of ND [24]. Since the brain is rich in polyunsaturated fatty acid, have increased metabolic activity and utilizes high oxygen together with moderately restricted capacity to battle with oxidative stress, it is prone to oxidative stress damage [25]. Waldbaum and Patel (26) confirmed that reactive oxygen species act as secondary messengers in many intracellular signaling pathways and as mediators of inflammation and oxidative damage. Free radicals can assault polyunsaturated unsaturated fatty acid and initiate lipid peroxidation thereby making the brain a potential target for the onset and pathogenesis of several neurological diseases through oxygen radical generation to cause damage [27, 28]. Aside from the fact that ROS can adversely affect biological molecules, their reactions with these biomolecules also generate additional reactive oxygen species resulting in cellular damage.

The hereditary material of the mitochondrial show vulnerability to a limited extent because of its closeness to the site of most uncontrolled ROS generation, and in light of the low level of repair occurrence [29-31].

Neurodegenerative diseases (NDD)

The basic highlights of NDDs of the central nervous system (CNS) are mitochondria dysfunction and inflammation of the neuron [32]. These conditions accumulate ROS and nitrogen species leading to oxidative stress which further initiate neuronal damage and subsequent inflammation resulting in progressive death of neurons. Neurodegeneration, therefore, is the loss of both structure and function in neurons. Numerous NDDs have been associated with neurodegeneration of the neurons. The neurological results of neurodegeneration in patients can have adverse impacts on mental and physical functioning. The genesis of most cases of common neurodegenerative diseases are unclear [33]. Examples of some NDDs include Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington disease, Friedreich's ataxia, and spinal muscular atrophy (figure 1).

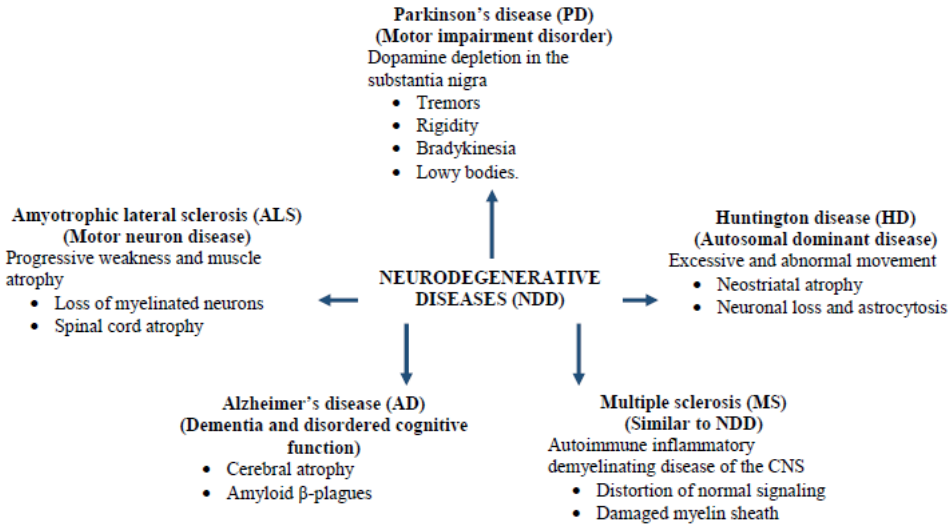

Figure 1: Schematic overview of common neurodegenerative disorders

Developmental stages of Neurodegenerative diseases (NDDs)

This section explains briefly the three development stages of NDDs and the symptoms that appear at each stage.

1. **Retrogenesis:** The beginning of NDDs is the malfunctioning of the cholinergic system of the basal forebrain, which promotes to the Entorhinal Cortex and the Hippocampus that are accountable for the short and the long-term memory. These modify the brain which usually starts 10-20 years in advance and the first visible sign of NDDs is forgetfulness or some problems in short-term memory [34]. Symptoms may include enhanced memory loss, difficulties in acknowledging the family members, in the ability to dress up alone and also gait problems. The disease with its progression starts affecting the cerebral cortex resulting in the form of a further decrease in cognitive power. This stage is linked with the clinical diagnosis of NDDs in patients which include confusing among familiar places, losing decision power, misplacing valuable things, mood and personality changes, childish actions in office, increased anxiety, and loss of spontaneity and sense of initiatives. Additional atrophy in the selected segment of the cerebral cortex results in the form of serious problems with language, sensory neurons, and reasoning. Patients show a serious attitude towards wandering and agitation [35].

2. **Cognitive Dysfunction:** There is a connection between neuro-degeneration and toxic proteins. This is accompanied with increasing pathological neurofibrillary plaques and tangles in the entorhinal cortex (EC), caudate, substantia nigra. These proteins play a pathogenic role in the progression of NDDs which leads to neurons degeneration and cognitive dysfunction. The Entorhinal Cortex (EC) is that part of the brain which gets affected due to Alzheimer's. It has been documented that in order to keep the memory alive the communication between the Entorhinal Cortex (EC) and the hippocampus is very vital and any difficulty between these two regions disrupts the circuit and leads towards memory disorder and memory damage. It is concluded that EC is the main hub which is more vulnerable to NDDs and these diseases propagate with the network of neurons [36].

3. **Gait Abnormality:** Predicting a disturbance in gait activity indicates a disturbance in cognitive functions. A term has been proposed, "Last-in-First-out" which refers to the phenomenon in which the neural circuits mature late in the developmental life cycle are more vulnerable to neuro-degeneration and this concept helps in early prediction of any kind of dementia (neurodegenerative diseases) stated that a strong gait pattern needs input not only from the neurological system linked to motor and sensory neurons but also from cortical processes for instance to judge, plan and a spatial awareness [37]. Disturbances in cognitive function have a direct link with higher level gait disturbances and it is one of the major symptoms of brain syndrome [38].

Mitochondrial dysfunction

The mitochondrion receives most acknowledgment for its role in generating energy for cells in the body and they are known as the *powerhouse*. Incredibly, the mitochondria in our cells have also generated a significant amount of attention from researchers the most recent decade for its role in numerous other life processes [39-41]. Mitochondrial diseases are attributed to either hereditary or mutations in mitochondria DNA or nuclear DNA which lead to modified proteins or mitochondria RNAs. Issues with mitochondrial function, nonetheless, may only influence certain tissues as a result of factors occurring amid growth and development yet unknown. Notwithstanding when tissue-specific isoforms of mitochondrial proteins are put into consideration, it is difficult to clarify the variable patterns of influenced organ frameworks in the mitochondrial disease syndromes. Because brain and muscle cells require a significant amount of energy, they contain high density of mitochondria to support their energy requirements. When there is a dysfunction in mitochondria, they as well present poor function. Symptoms of mitochondria dysfunction include; developmental delay or regression, Seizures, intellectual disability, impairment (social, hearing and language), neuropsychiatric symptoms, and general weakness [42]. Recent studies suggest that mitochondrial dysfunction might be crucial in a wide range of health conditions such as Parkinson's disease, bipolar disorder, schizophrenia, autism, depression, diabetes, asthma, chronic fatigue syndrome, Alzheimer's disease, an assortment of gastrointestinal diseases [43-45]. Numerous triggers can lead to mitochondrial dysfunction resulting into the symptoms of NDD. Some of the triggers include; genetic variations, shortages of essential vitamins and minerals in the diet foreign substances, drugs certain bacteria and viruses and stress [46]. Loss of function in mitochondria is predisposed to several signs including frequent weakness, visual impairment and other commonly encountered signs of hardened illnesses. Judging from the structure and functions of the powerhouse, depletion of function arises from the inability to maintain the transmembrane potential and electrical signals of its inner membrane. This then affect the flow of electron and/or metabolic reaction/pathways. Resulting in energy reduction energy [47-50].

Mitochondrial dysfunction is characterized by aging, and essentially, of all chronic diseases including NDDs [51-55]. One of the outcomes of mitochondria dysfunction relating to the electron transport process is the creation of ROS, produced as a metabolite of oxidative phosphorylation. The fundamental origin of ROS and the related reactive nitrogen species (RNS) are mitochondria, and these free radicals have the ability to damage biomolecules [56-58]. However, antioxidants and superoxide dismutase enzymes (SOD) have the ability to inhibit the actions of ROS/RNS [59, 60]. Reactions of the electron transport chain can also initiate uncoupling proteins, which could result in a leak of protons back across the proton gradient of the inner membrane of the mitochondrial into the matrix [61, 62]. This leak results in decreased energy generation (figure 2) with excess oxygen consumption [60].

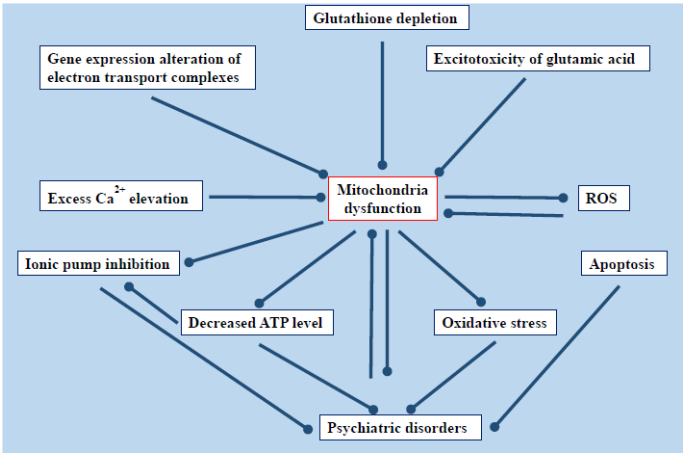

Figure 2: Consequences of Mitochondria dysfunction

Neurons fundamentally rely on mitochondrial capacities for long-distance flow of mitochondria to the synapse, isolation, and removal of faulty mitochondria from synaptic sites and metabolic demands that require high energy flow yields and regularly connected with the generation of ROS. Consistent build-up of ROS prompts oxidative damage and hindered proteostasis within mitochondrial compartments [63-65]. This in turn altered the balance of mitochondria dynamics leading to pathogenesis (figure 3). This is the basis of the mechanism by which mitochondria dysfunction causes neurodegenerative diseases.

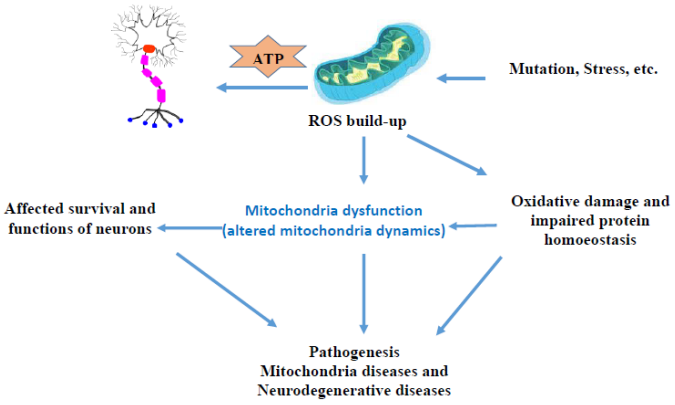

Figure 3: Mechanism of mitochondria dysfunction and in Neurodegenerative diseases

Several studies have pointed out the involvement of mitochondrial dysfunction alongside its stressors in NDDs most especially in Parkinson's disease and relative disorders [63, 66-69]. Mitochondrial dysfunction is a powerful cause of degeneration compared to oxidative damage in a number of Parkinson's and related disease model [70]. Mitochondrial stressors as lately reviewed, cause Parkinson's disease but concluded that more information is essential to effectively comprehend the function in Parkinson's disease pathogenesis [71]. Any antioxidant most especially plant-based antioxidant that can target mitochondria will be a perfect treatment for neurodegenerative diseases. Numerous studies are in progress most especially the potentiation of energy production, scavenging reactive oxygen species as well as preventing oxidative damage [72]. Also, it was reported that

antioxidant treatments can prevent or slow down disease progression in experimental animals of NDDs [73].

Alzheimer's Disease

AD is the commonest recognized NDDs [74]. Successful discovery in medicine have extended the average lifespan, resulting in an aging population. Because AD and most NDDs are diseases of aging, the prevalence is presumed to continue to increase in the future and the disorder has been suggested to affect 1 in 85 people in the world by 2050 (figure 4) [75].

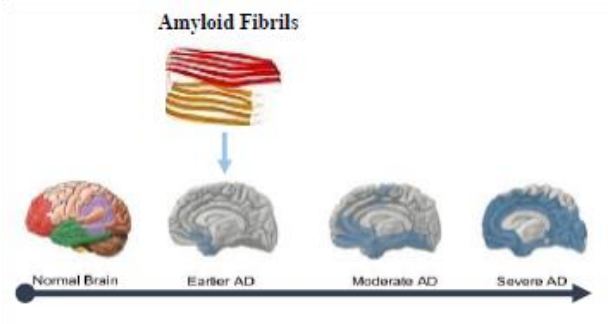

Figure 4: Time-dependent AD progression

Alzheimer disorders are distinctly described by progressive cognitive degeneration, and pathologically by the presence of senile plaques (amyloid-β peptide (Aβ)) and neurofibrillary tangles composed of hyperphosphorylated tau (figure 5). Around 5–10% of cases are familial, occurring in an early-onset, autosomal-dominant pattern. These proteins (amyloid precursor protein, presenilins 1 and 2) are related to the familiar cases of AD. [63, 76]. The risk factors of AD include environmental and genetic factors. Apolipoprotein E gene has been related to the prevalence of non-familial, sporadic Alzheimer's. APOE ε4 allele augments the predisposition for AD disease with less than 50% while ε2 and ε3 alleles have been labeled to convene a safeguard for the neurodegenerative disorder [77]. Furthermore, research based on genome-wide association reported that 19 candidate genes can trigger the onset of late on AD [78]. Since researcher has reported that mitochondrial dysfunction and oxidative damage occur in the AD brain before the onset of Aβ pathology, there is a need to exploit neuroprotective antioxidants to keep ROS is check thereby moderating oxidative stress and preventing oxidative neuron damage in AD.

Parkinson's disease

PD, ranked second most common NDD succeeding AD, is described clinically by progressive rigidity, bradykinesia, and tremor, and by loss of pigmented neurons in the substantia nigra in the midbrain and the presences of Lewy bodies pathologically [63, 79]. Globally as at 2006, over 4 million people of an average age of 60 years are living with PD and this incidence is higher in male compared to female [80, 81]. The lower effect in females is may be probably due to higher estrogen concentration [82]. Several pieces of evidence from post-mortem research demonstrated that multiple processes are associated with apoptosis or necrosis, including oxidative stress, mitochondrial dysfunction, neuroinflammation, excitotoxicity and accumulation of misfolded proteins due to proteasomal and autophagic disorders [83].

Huntington's disease or Huntington's chorea (HD)

It is a progressive neurodegenerative (autosomal dominant) disease located in the basal ganglia characterized by choreiform movement, dystonia, dementia, psychiatric problem, and dilation of the ventricle (decrease in brain size). This disease is linked with the unstable expansion of a trinucleotide cytosine, adenine, guanine (CAG) repeats in the Huntington gene [84, 85]. Glutamine (Q) encoded from this CAG repeat is expressed in the HTT protein as a Poly-Q stretch near its N-terminal [86]. Ordinarily, healthy individuals accept less than 26 CAG repeats in their HTT gene resulting in normal HTT functioning in vesicle trafficking and endocytosis. However, individuals with more than 36 repeats express mutant HTT (mHTT) protein are attributed to genetic changes such as mutation [87]. These misfolded and aberrant mHTT protein are not able to carry out its normal synaptic and pro-survival roles [88]. The unique trait of the disease includes cleavage and aggregation formation of misfolded mHTT in the nucleus of cell, cytoplasm, and neurites [84, 89]. Interestingly, despite the established connection of the function of ROS and oxidative stress in Huntington disease, trials attempting to treat the disease using classic antioxidants have largely been ineffective [90].

Amyotrophic lateral sclerosis (ALS) or Lou Gehrig's disease

ALS also was known as motor neuron disease is characterized by progressive loss of motor neurons in the anterior horn of the spinal cord [91]. ALS is classified as sporadic or familial depending on the involvement of inherited genetic element. Since the onset of sporadic ALS is yet a mystery, isolation of genes responsible for this disease and other factors remain elusive [92]. In familial ALS, about 20% of the cases resulted from mutations in SOD1 [93]. The functions of SOD1 are diverse and include scavenging excessive superoxide radical thereby modulating cellular respiration, energy metabolism, and posttranslational modification [94]. ALS disorders can be deadly when delayed leads to wasting of respiratory and motor neurons [95].

Antioxidant production in plant

The main energy production and sites of ROS generated within plant cells are mitochondria and chloroplasts. These organelles help to maintain a defined balance between energy functions and control of the production of ROS. Peroxisomes are also considered as the other crucial site of ROS production such as hydrogen peroxide (H_2O_2), superoxide ($O_2^{\bullet -}$) and nitric oxide($NO^{\bullet}$) in plant cells. This organelle contains basic enzymatic constituents like catalase and flavin oxidizes [96]. The ROS generated in plant cells (photosystem I, II, peroxisome and mitochondria (Electron transport chain)) in form of electron leaks and react with O_2 yielding $O_2^{\bullet -}$ and this is converted to hydroxyl radical and finally to hydrogen peroxide [97, 98]. Also in a similar fashion, reactive nitrogen species (nitric acid radical and peroxynitrite) are also formed in all these organelles mentioned above [99]. The final example of free radical (reactive sulfur species) is derived from sulfur-containing amino acid (thiols) by reaction with reactive oxygen species [100]. Since free radicals function as a signaling molecule, they are said to be genetically initiated [101, 102]. However, accumulation of ROS are also sometimes harmful to biomolecules. Plant has some devised steps to reduce/avoid the effect of the aforementioned free radicals through complex enzymatic and non-enzymatic defense systems. The four major enzymatic systems used to reduce the radicals' effect are SOD, catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR) while the low and high molecular weight antioxidants/metabolites are the non-enzymatic systems (figure 5) [103]. The proposed reasons for the accumulation of these low and high molecular weight antioxidants can be explained in two ways: (1) the hereditary composition of plants grants them with a natural capacity to produce several types of phytochemicals to play out their typical physiological roles and additionally shield them from microbial pathogens and herbivorous animals. (2) The production of reductant phytochemicals could be the regular inclination of plants to react to ecological pressure and other adverse conditions [104].

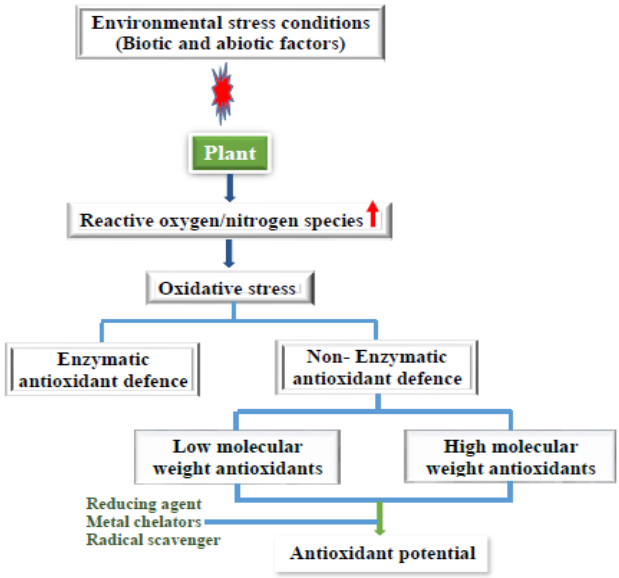

Figure 5: Antioxidant machinery in plant

Classification and mode of action of Antioxidants

Antioxidant can be classified as the first, second and third line of defense respectively (figure 5 and 6). Superoxide dismutase, glutathione reductase, glutathione peroxidase, catalase and some minerals including selenium, copper, manganese and zinc are regarded as the first line of defense. Superoxide dismutase react by quenching superoxide, glutathione reductase act as a scavenger for hydroxyl radicals, singlet oxygen, and numerous electrophiles (convert GSSG to 2GSH), glutathione peroxidase (selenium-containing enzyme) catalyzes the reduction of hydrogen peroxide and lipid hydroperoxides to H_2O using glutathione as substrate, catalase act by converting hydrogen peroxide to water. Alpha-tocopherol and selenium are involved in the scavenging of peroxides from the cell membrane and cytosol respectively. Copper act through the cytosolic superoxide dismutase. Zinc is essential for different functions in the body and thus exert its role through zinc-containing enzymes such as alcohol dehydrogenase, cytosolic superoxide dismutase, alkaline phosphatase, and carbonic anhydrase. The second line defense is Glutathione, vitamin E, Vitamin C, uric acid, albumin, carotenoids, flavonoids. Beta-carotene is an excellent scavenger of singlet oxygen. Vit C act synergistically with Vit E to donate hydrogen atoms and also interacts directly with radicals. Glutathione scavenges free radicals and various lipid hydroperoxides and also detoxify many pollutants such as ozone, NO_2 and free radicals in the respiratory tract. Vitamin E scavenges peroxyl radicals in lipid peroxidation which is responsible for protecting polyunsaturated fatty acids in the cell membrane. Phenolic compounds like flavonoids present in plants inhibit lipid peroxidation and lipoxygenases. The third line antioxidants are a complex group of enzymes for repair of damaged biomolecules such as protein, DNA and lipids. These enzymes (proteases, lipases, transferase, DNA repair enzymes etc) repair the damage and reconstitute damaged cell membrane.

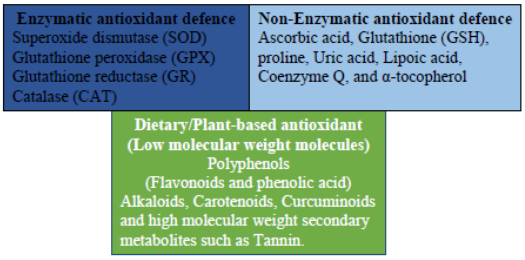

Figure 6: The antioxidant mechanism of the human cell.

Endogenous antioxidant defenses (enzymes and non-enzymatic low molecular weight molecules). Important antioxidants are majorly ingested through the diet such as plants.

The significance of Plant-based antioxidants

Antioxidants derived from plant are natural products with radical-scavenging capacity or reducing properties. Because of their powerful preventive and therapeutic activities, they attract attention from both pharmacologists and physicians. The maintenance of redox homeostasis is crucial in health and in the prevention of diseases. Oxidative stress is generated by unbalance between reactive oxygen/nitrogen species and antioxidants. Excess of ROS leads to degradation of biomolecules could lead to cells damage oxidatively and in a consequence to overexpression of oncogenes, mutagens formation, induction of atherogenic activity, or inflammation [105]. Diseases such as cancer, diabetes, disorders in the immune system and most especially NDDs are majorly initiated by several condition such as oxidative stress. Sources rich in antioxidants include fruits and vegetables from plant. These plant-based antioxidants have been reported to donate protons thereby reducing reactive oxygen species and preventing oxidative stress in human health. Antioxidant have several mode of actions. Example of some of these are scavenging, termination of lipid peroxidation, or metals chelation. Although the properties, including structural and functional properties of antioxidants have been elucidated, some important aspects still require careful consideration and additional investigations. More studies of the therapeutic roles of the antioxidant in the prevention or maintenance of cellular integrities are encouraged alongside with the exact concentrations and treatment efficacies. Moreover, the biological potentials of some natural compounds are still yet to be uncovered. Commonly known antioxidants, as well as those newly discovered, are promising for their vital role in the use to prevent and/or in the treatment of neurodegenerative disorders. 66% of the world's plant species have therapeutic significance, and practically these have phenomenal antioxidant benefits [106]. Antioxidants derived from plant are broadly distributed in foods and more specifically, medicinal plants. Flavonoids and provitamins such as vit A, exerts various biological effects on biological system. These biological effects are anti-inflammatory, anti-aging, anti-atherosclerosis, anticancer and neuroprotective. Successful extraction and subsequent bioactive isolation followed by proper evaluation of antioxidants from food and medicinal plants are crucial to investigate the potential of antioxidant sources and advance the application in functional foods, pharmaceuticals, and food additives. Exogenous antioxidants have the ability to prevent the damage induced through oxidative stress by preventing the activation of oxidative reactions, acting as scavengers, quenchers of singlet oxygen and reducing agents [107]. Antioxidants essentially slow down the oxidation of biomolecules even at a small concentration. The major sources of these antioxidants from plant and foods are mainly vegetables, herbs, spices and mushrooms [108-119]. In addition, the industries processing agricultural by-products are equally good sources of natural antioxidants [120]. These natural antioxidants from plant materials are mainly polyphenols (phenolic acids, flavonoids, anthocyanins, lignans, and stilbenes), carotenoids (xanthophylls and carotenes) and vitamins (vitamin E and C) [107, 121]. Generally, these natural antioxidants, especially polyphenols and pro-vitamin A, exhibit a wide range of biological effects, such as anti-inflammatory, antibacterial, antiviral, anti-aging, and anticancer [122-131]. Alam *et al* (132) reported that approximately 19 *in vitro* and 10 *in vivo* methods are used for the assessment and evaluation of antioxidant activity of plant samples. Extracts from plants have showed potent antioxidant activity in numerous in vitro assays. This can be attributed to the plant's innate ability to synthesize non-enzymatic antioxidants such as ascorbic acid and glutathione, as well as secondary metabolites such as phenolic compounds [104].

The aforementioned plant antioxidants have been exploited as therapeutics for human diseases most especially neurodegenerative diseases. Adewale *et al* (133) evaluated the *in vitro* antioxidant potentials of *Solanum macrocarpon* leaves in rat brain and concluded

that the leave extract possesses a powerful antioxidant activity and can offer good protection against oxidative damage to body cells, especially liver and brain. The protective effect of *Crassocephalum rubens* leaves has also been deduced to offer protection on some body tissues [134]. The HPLC-DAD fingerprinting analysis, activity of *Blighia sapida* and its inhibition of cholinergic enzymes have been reported to play a huge role in the treatment of Alzheimer's Disease [135]. Serrano *et al* (136) also discussed the biological effect of tannins as a neuroprotective compound. curcumin has also been studied as a neuroprotective against the MPTP-induced neurodegeneration [137]. Other studies have also confirmed the neuroprotective effect of curcumin [18, 138-148]. Ayurveda, a traditional medicine in India and in several other south Asian countries is also another neuroprotective potent plant in the treatment of neurodegenerative diseases [149-155].

In the system of therapeutic medicinal herbs, several medicinal plants have shown promising therapeutic effects in Neuropsychopharmacology: *Allium sativum, Bacopa monnierae, Centella asiatica, Celastrus paniculatus, Nicotiana tabaccum, Withania somnifera, Ricinus communis, Salvia officinalis, Acorus calmus, Curcuma longa, Terminalia chebula, Crocus sativus, Enhydra fluctuans, Valeriana wallichii, Glycyrrhiza glabra* etc. [156]. Other significant neuroprotective pants exploited for their potent treatment against NDDs such as AD, PD, multiple sclerosis, and amyotrophic lateral sclerosis include *Nardostachys jatamansi* [157, 158], *Semecarpus anacardium* [159], *Corydalis* spp, *Ruta graveolens, Lavandula angustifolia, Rosmarinus officinalis, Petroselinum crispum* and *Mentha spicata* [160]. The major effects of antioxidant to scavenge radical, inhibit cell death and or serve as neuroprotective through specialized mechanisms (figure 7).

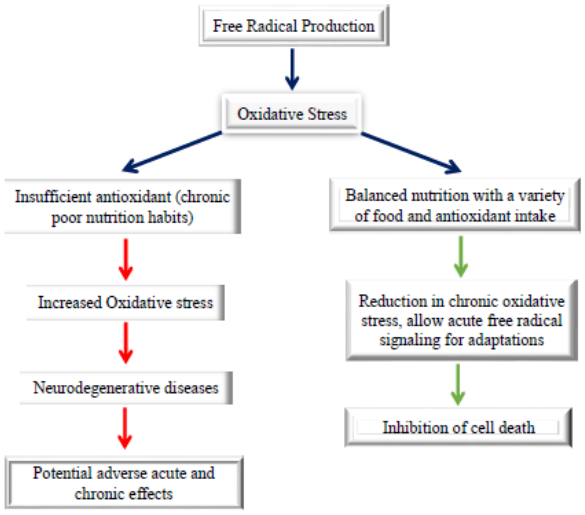

Figure 7: Role of Antioxidant in Neurodegenerative Disease

CONCLUSION

Knowledge of NDDs has advanced progressively in the last few decades, and the field holds incredible promise for further understanding and the cure for these diverse diseases. Since the treatments of these diseases with synthetic compounds in clinical trials have proven difficult due to their toxicity and ability to cause other diseases such as cancer, treatments with natural antioxidants such as polyphenols through diet or dietary supplements have become an attractive alternative against oxidative damage of neuronal cells that play a vital role in the origin of NDD. Antioxidants in plants have been reported to reduce the risk of several major diseases including cardiovascular diseases, cancers as well as NDDs. Also, Restorative methodologies that will address both the oxidative and inflammatory pathways in the neuropathogenesis of age-related neurodegeneration are earnestly required as well as the improvements in targeting and drug delivery such as Nano-particles will powerfully enhance the bioavailability and assist in the development of therapeutics effectively. More mitochondria-targeting antioxidants should as well be exploited as therapeutic agents in treatments for neurodegenerative disease. Also, the consumption of plant-based foods may reduce the risk for some of the diseases caused by neuronal dysfunction. On a whole, more insight is needed for potential future therapeutic strategies of NDD.

Authors' contributions

AOF, BOA, and IA conceived the concept, design, and first draft of the study. AOF, OAO AND BEO helped with the constitution of the images, AOF and MAO contributed to the revision and critical intellectual contents. All authors contributed significantly. All authors read and approved the final manuscript

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Competing interests

The authors declare that they have no competing interests.

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Consent for publication

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