REVIEW ARTICLE

A Review on Antioxidants as Therapeutic in Use of Oxidative Stress and Neurodegenerative Disease

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ABSTRACT

Normal aerobic cellular metabolism, therefore, generates free radicals. An instinctive antioxidant device of the frame performs an influential function inside any damage due to free radicals' prevention by the body's antioxidant mechanism. Conversely, an imbalanced process of antioxidants, overconsumption, or assimilation of loose militants as of the environment to the dwelling device ensuing in neurodegenerative sicknesses, reasons neural cells to travel through purposeful or sensory loss. Moreover, numerous different environmental or genetic factors, oxidative stress (OS) are the primary motives for the atom assault on neural cells that contribute a ruinous function to neurodegeneration. Although oxygen is additionally a should, imbalanced antioxidants and extra reactive oxygen species (ROS) outcomes in quite a few continual problems like cancer, diabetes, coronary heart sicknesses, and neurodegenerative sicknesses similar to Alzheimer's disease (AD), Parkinson's disease (PD), aging, also plenty more and lots of varied neural problems. Recently, several antioxidants are being hired upon as resounding healing towards dementia that reversing age-associated declines in neurocognitive performances and excessive neuronal loss, as they will prevent oxidative pressure via way of means of neutralizing loose radicals. Diet is a chief supply of antioxidants and plant natural flavonoids, are catching interest to be an advert supply of phytonutrients at this time. Here, we review how *Caenorhabditis elegans* has been utilized for understood oxidative stress and neurodegenerative diseases therapeutic. Specifically, we will discuss the mechanisms that lead to free radicals that disrupted the antioxidant system and the pharmacological therapy that has been in use for a long time, and novel therapies in an oxidative stress consequence.

Keywords: Antioxidants, Neurodegenerative disease, Oxidative stress, Plant flavonoids, Toxicity, ROS.

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INTRODUCTION

Free radicals are molecules or atoms using unpaired electrons that remain highly unstable and dynamic towards compound responses with different molecules. Free radicals have a significant role within the beginning of life and biotic evolution, exit valuable effects on the entities. Oxygen radicals are engaged with numerous biochemical activities of cells like signal transduction, gene transcription. Electromagnetic radiation from imitation atmosphere like pollutants such as metals, pesticides, herbicides, fungicides, etc. generated free radicals are continuously exposed to humans. Natural assets such as radon, cosmic emission, just as cell digestion systems (respirational rupture, enzymatic activity) likewise enhance free fanatics to the surrounding area.[1] They arise from three elements as nitrogen, sulfur, and oxygen consequently generating reactive nitrogen species (RNS), reactive sulfur species (RSS), and reactive oxygen species (ROS). The hydroperoxyl radical (HO_2^-), nitric oxide (NO), hydroxyl radical ($OH^•$), superoxide anion ($O_2^{-•}$), and other species like singlet oxygen ($^1O_2$), peroxynitrite ($ONOO^-$), hydrogen peroxide (H_2O_2), and hypochlorous acid (HOCl) are generated by ROS (free radicals). Nitric oxide (NO) reacting with ROS originated RNS. The reaction of ROS with thiols is simply formed RSS. The atmospheric invigorated by oxygen constantly produces superoxide from Cells. For the neutralizing oxidative damage from superoxide, evolved Antioxidant's resistance systems alongside aerobic digestion.[2] Oxygen-derived free radicals ($OH^•$ and $O_2^{-•}$) and other ROS (hydrogen peroxide, nitric oxide, peroxynitrite, and hypochlorous acid), as side-effects through various physiological and biochemical processes and are delivered inside the body, fundamentally because of aerobic metabolism. Simultaneously, antioxidants, such as vitamin C, vitamin A, vitamin E, glutathione, and plant flavanoids help to control the oxidative stress by neutralizing free radicals.

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Additionally, some antioxidant enzymes, such as glutathione reductase, glutathione peroxidase, catalase, and superoxide dismutase, exert synergistic activities in expelling free radicals. Numerous prolonged diseases such as diabetics, cancer, rheumatoid arthritis, cardiovascular diseases, myocardial infarction, atherosclerosis, aging, chronic inflammation, and other neurodegenerative diseases in human being caused by the excessive production of free extremists which impairment macromolecules, (DNA, proteins lipids) (Figure 1).[2]

Due to high oxygen consumption and low antioxidant defenses, the brain is susceptible to neuronal damage and free radicals. Phyto-compounds are categorized as exogenous (natural or synthetic) or else endogenous compounds, both answerable for the exclusion of scavenging ROS, free radicals, or their originators, for catalysis of ROS generation binds metal ions., and preventing the development of ROS.[10] The two main groups, non-enzymatic and enzymatic are part of the natural antioxidant system. Various enzymes like glutathione peroxidase, superoxide dismutase (SOD) as well as catalase alongside various associate enzymes, categorizing as enzymatic antioxidants. Activism antioxidants, which are exceedingly important in resistance against Oxidative stress, which categorizing as non-enzymatic antioxidants.[3] Several studies have been done for evaluating oxidative stress but there are limitations. So, we need frequent research to prevent oxidative stress and focused our attention on natural antioxidants for reducing oxidative stress by the removal of ROS.[3] Many scientific studies suggested that various natural antioxidants like flavonoids such as quercetin, kaempferol, trolox, hesperidin, eugenol, isothymusin, and naringin, etc. have antioxidants, anti-inflammatory, anti-stress, anti-oxidative, immunomodulatory and anti-cancerous properties and neuroprotective effects of these compounds in contradiction of oxidative stress thru DAF-16 in *C. elegans* has increased lifespan also reported.[4] Dietary antioxidants like vitamin C, vitamin, and plant flavonoids can inactivate free radicals to protect against neurodegenerative diseases associated with oxidative stress.

ANTIOXIDANT

Antioxidants square measure a substance that inhibits the reaction, it's a chemical process that produces free radicals, particularly one accustomed to counteract the deterioration of keep food merchandise. Antioxidants square measure categorized as exogenous or endogenous compounds, more exogenous antioxidants divide into 2 teams natural and artificial, each in charge of the exclusion of free radicals, or their precursors and scavenging of ROS.[5] Supported their activity, they'll be classified into 2 major teams, protein and non-enzymatic. Protein antioxidants square measure contained varied numbers of enzymes like enzymes, peroxidase likewise as an enzyme (SOD) aboard some supporting enzymes. Non-enzymatic antioxidants embrace tocopherol, A, C, flavonoids, carotenoids, glutathione, plant polyphenols, and direct-acting antioxidants, that square measure very necessary in resistance against aerophilic stress (Figure 2).[6]

Why the Necessity of Antioxidants?

Many scientific studies suggested that many antioxidants like flavonoids such as quercetin, kaempferol, hesperidin, naringin, trolox, eugenol, etc. possess anti-stress, anti-oxidative, anti-ulcer, anticancerous and therosclerotic, antitumor, anti-inflammatory, antimutagenic, anticarcinogenic, antiviral, neuroprotective, and antibacterial activities towards greater or lesser magnitude.[7] Prolonged oxidative stress associated with the development and progression of many chronic disorders heart disease, diabetes, cancer, and neurodegenerative diseases also its obstacles which are frequently conveyed via loss of antioxidant defense system or a significant production of free radicals.[7] Much use of antioxidant in daily diet has been testified to a reduced threat of many diseases like cancer, cardiovascular diseases, diabetes, and other aging-allied diseases here is substantial contention in this extent (Figure 3).[8]

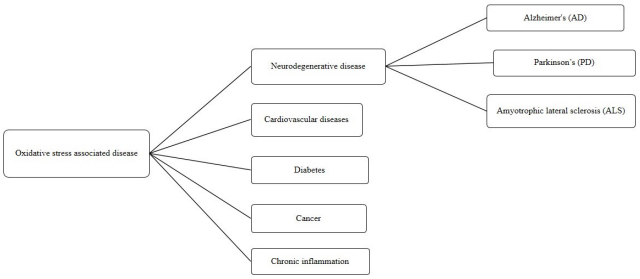

Figure 1: Oxidative stress play in important role in etiology of various disorders.

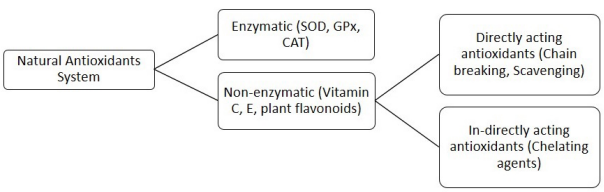

Figure 2: Classification of phytonutrients.

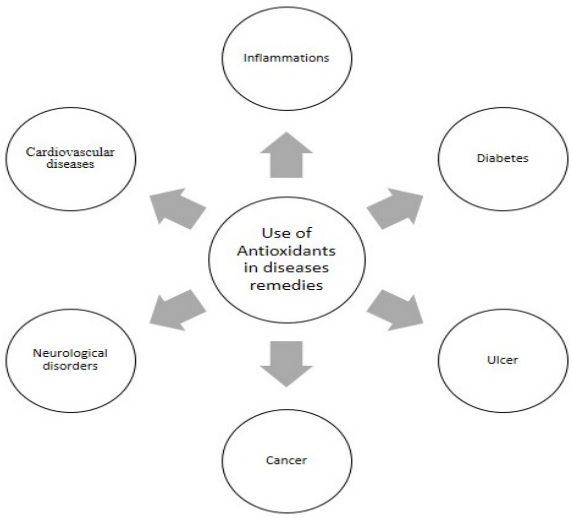

Figure 3: Applications of antioxidants in disease remedies.

The main defense system to protect organisms from increasing ROS by antioxidant enzymes like glutathione peroxidase (GSH-Px), catalase (CAT), superoxide dismutase (SOD).[2] However, they cause alteration in DNA, contribute to carcinogenic processes and oxidative damages if ungoverned. In many experiments and studies infer that antioxidant modulate the a etiopathogenesis of chronic infection and, are essential to scavenge and avert the formation of ROS. Evidence proved that DNA damage is increased when there is antioxidants deficiency in the intake and advised that use an antioxidant in our daily diet are protective for us.[9]

Where the Antioxidants can be Found?

The four main endogenous sources found in organisms that oxidants produced by cells.

(1) Normal aerobic respiration O_2, H_2O_2, and OH^- as a derivative of oxygen production by mitochondria consume oxygen
(2) Nitric oxide (NO), O_2^-, H_2O_2 and OCl are oxidative burst by phagocytosis in Bacteria/virus-infected cells.
(3) In the beginning, a by-product of fatty acid (H2O2) and peroxisome produces other lipids molecular degradation, degraded by catalase at the end. Suggestion recommends that certain circumstances courtesy escape of a number of the hydrogen peroxide from digression, subsequently let loose into alternative parts of the cell and increasing aerobic stress resulting in DNA harm.[9]
(4) Defensive adverse from natural harmful substances in or from plants, the key supply of dietetic toxins by one of the primary defense system animal Cytochrome P450 enzymes. Even these enzymes area unit protecting contrary to acute harmful effects from extraneous substances, nevertheless, they'll produce some aerobic consequences that harm DNA.[10]

Several antioxidants are found in the diet of the human that important for both vegetarians as well as non-vegetarian. β-carotene, coenzyme Q, and Vitamins C and E square measure the foremost noted antioxidants of diet, among these, vitamins E is found extravagantly in nutrition and vegetable oils.[6] It's a fat-soluble vitamin, absorbed within the intestines and convey within the extracellular fluid by conjugated protein, which may effectively stop macromolecule peroxidation of the semipermeable membrane.[5]

Plants are one of the most important sources of antioxidants. It (vegetables, medicative herbs, fruits) contains a huge form molecule of radical scavenging, like vitamins, nitrogen (N) compounds (betalains, alkaloids, amines, etc.), terpenoids (including carotenoids) phenoplast compounds (coumarins, flavonoids, stilbenes, quinons, phenolic acids, lignans, tannins, etc.), and some alternative secondary metabolites that are wealthy in antioxidants activity.[11]

The Protagonist of Oxidative Stress in Neurodegenerative Disorders

Oxidative stress is one in all the most causes of the aging method, significantly in organs demanding a high-energy supply like the center, brain, muscles, or liver. The brain is especially susceptible to aerobic stress and injury, as a result of its high chemical element intake, low inhibitor defenses. In consequence, it's not shocking the prominence of protective systems, together with inhibitor defenses, to keep up neuronic integrity and survival. Aerobic stress is taking part in a crucial role within the aging method and neurodegenerative diseases (ND).[12] Nerve cells from the brain and neural structure are nowhere to be found resulting in either one practical harm (ataxia) or sensual pathology (dementia) thanks to this condition. Mitochondrial dysfunctions and excite-toxicity and at last caspase-mediated cell death has been according as a pathological reason for aging, aerobic stress and neurodegenerative diseases like Alzheimer's (AD), Amyotrophic lateral induration (ALS), Parkinson's (PD).[13]

Oxidative Stress

Now these days, pesticides are more frequently used not only agriculture but also used in household activities. Continuously use of these pesticides leads to oxidative stress. Protein reaction associate degreed super molecule peroxidation square measure consequences of aerobic stress thanks to a difference between the general appearance of reactive element species and an organic system's capability to without delay detoxify the volatile intermediates or to healing the ensuing injury. Macromolecule reaction is that the valency alteration of a protein-induced either by indirect reactions with secondary by-products of aerobic stress or the direct responses with reactive element species (ROS). Super molecule peroxidation is that the method during which free extremists "steal" electrons from the fatty acid in the cell membrane, consequential, cell injury caused to the aerobic degradation of lipids.[14]

Free Radicals

A particle one or more highly reactive paramagnetic in their external covering called free radicals. It can be produced in cells by losing or accepting a single electron when oxygen act together with assured molecules.[7] They arise from three elements: sulfur, nitrogen, and oxygen consequently generating reactive reactive sulfur species (RSS) nitrogen species (RNS), and reactive oxygen species (ROS).

$$Fe_3^+ + O_2^{-\bullet} \rightarrow O_2 + Fe_2^+ \text{ (I)}$$

Fenton reaction:

$$Fe_2^+ + H_2O_2 \rightarrow OH^- + Fe3^+ + OH\bullet \text{ (II)}$$

Haber-Weiss reaction:

$$H_2O_2 + O_2^{-\bullet} \rightarrow O_2 + OH\bullet + OH- \text{ (combining both)}$$

Formation of free radicals: Fenton reaction, in this method, Iron (II) is changed by oxide to iron (III), forming a hydroxyl and a hydroxyl ion. In Haber-Weiss reaction: OH• (hydroxyl radicals) generated by H_2O_2 (hydrogen peroxide) and iron ions catalyze from superoxide (O2−•c).[2]

Significantly ROS levels are the primary causes of inflammation, oxidative damage in the cells, DNA, and protein, eventually leads to many prolonged diseases such as cardiovascular diseases, cancer, diabetics, aging, atherosclerosis, chronic inflammation, and other neurodegenerative diseases in human being. Under normal circumstances, free radicals are toxic to neuronal cells, have a proficient regulating coordina-

tion for oxygen and metal ion contact that leading to oxidative stress.

A number of Neurodegenerative Disorders (AD, ALS, and PD)

Alzheimer's sickness (AD) is that the commonest explanation for dementedness within aging, accounting for 60–70% of the cases of progressive psychological feature impairment. The explanation for presenile dementia is poorly understood however studies counsel that almost all affected neurons embody cholinergic and glutamatergic neurons within the hippocampus and therefore the isocortex regions of the brain. Clinically, the sickness is taken into account by the presence of gaga plaques (SPs) and neurofibrillary tangles (NFTs) within the brain of affected people. The most important constituents of SPs are venomous species of β-amyloid (Aβ) amide, whereas NFTs contain hyperphosphorylated and collective varieties of the microtubule-associated micromolecular tau.[1] Extracellular depositions of Aβ are one compulsive assurance of AD. The most abundant form under normal conditions is $A\beta_{1-40}$, followed by a smaller amount of $A\beta_{1-42}$, found at N-terminal have a tendency to aggregated into fibrils rapidly and deposited into plaques.[15]

Parkinson's disease (PD) is a common neurodegenerative disorder that leads to shaking, stiffness, and difficulty with walking, balance, and coordination. Both environmental and genetic factors are responsible for PD pathogenesis, which leads to the loss of neurons, including dopaminergic neurons in the substantia nigra pars compacta, Lewy bodies and Lewy neurites are the major hallmarks of PD.[11] As extremely toxin-free radicals square measure generated each through the metabolism of dopamine and its auto-oxidation that increased by exposure to environmental stressors leading to aerobic stress. Several PD-associated genes are known, as well as PINK1, SNCA, PARKIN, DJ-1, LRRK2, UCH-L1, and NURR1.[16]

Amyotrophic lateral sclerosis (ALS), is a progressive neuromuscular disorder associated with the death of motor neurons that control voluntary muscles, also known as motor neuron disease (MND) or Lou Gehrig's disease. ALS include the DNA/ RNA binding proteins FUS, and TDP-43 and C9ORF72.[17]

Characteristics of *C. elegans*

The neurodegenerative disease researchers have turned to a soil nematode, *Caenorhabditis elegans*. It is advantageous in modeling the learning and memory losses seen for the duration of the neurodegenerative disease due to its properties like the nematode *C. elegans* has a small transparent body (~1-mm) with a short life cycle (3 days) with high reproducible rate and also it has a short life span.[18] Adult hermaphrodite contains 302 neurons with a completely sequenced genome and it has 65% orthologous genes of human-related diseases with neurotransmitters and receptors.

C. elegans is a prevailing genetic model entity to study living processes such as development, cell division, oxidative stress resistance regulation, aging, and neurobiology as well as toxicological studies.[19] *C. elegans* has become a widespread model organism to investigating the positive aspects of natural metabolites and its products.

Antioxidant Therapy in Free Radicals Mediated Neurodegenerative Diseases and Prevention against Oxidative Stress

Oxidative stress is an associate degree imbalance of free radicals and antioxidants within the body, which might result in cells and tissue injury. Aerophilous stress happens naturally and plays a vital role within the aging method, long-run aerophilous stress contributes to a variety of chronic conditions like cancer, diabetes, ulcer, heart diseases and neurodegenerative disease by damage of cells, DNA and protein. Particularly oxidative damage in brain cells due to pesticides leads to neurodegenerative diseases[19] due to disturb reactive oxygen species and antioxidants.[8] Therefore, underneath traditional conditions, there's a balance between ROS formation and antioxidants. This equilibrium is discontinuous throughout many pathological situations within which the inhibitor defenses become meagerly, leading to aerobic stress usually resulting in caspase-mediated cell death, a mechanism employed by organisms to eliminate redundant or broken cells, and/or death.[13] Several naturally occurring antioxidants enzymes present in our body such as glutathione peroxidase, catalase (CAT), superoxide dismutase (SOD), glutathione S-transferase (GST), glutathione reductase, etc. to protect us from oxidative stress.[6] In the course of evolution, the organisms have established many mechanisms of safeguard against the vesicant paraphernalia of ROS in such some way that the complete quantity of pro-oxidants is in regulate. Many enzymatical activities found in our body naturally include glutathione peroxidase (GPx), superoxide dismutase (SOD), glutathione reductase (GR), and catalase (CAT) [2]. SOD is one of the first and most protecting mechanisms contrary to ROS and the conversion of $O_2^{-\bullet}$ to O_2 and H_2O_2, is converted into water and O_2 catalyzes by CAT and GPx. In *C. elegans*, one of the ROS protection mechanisms is conferred by DAF-16 via the c-Jun N-terminal Kinase (JNK) Pathway and the insulin/IGF-1 signaling (IIS) pathway, which regulates MnSOD gene expression (Figure 4).[20]

JNK and IIS pathways are well conserved across mammals and nematodes for investigating the process of aging and oxidative stress resistance regulation.[4]

The ILS pathway is concerned with extending lifetime by regulating the entry of transcription issue DAF-16 and warmth shock factor-1 (HSF-1) into the nucleus. Beginning with the receptor DAF-2. In contrast, in pressure, this pathway stimulates the de-phosphorylation of these factors, permitting their access into the nucleus as a result of they act as transcription factors, which changed the level of cellular energy metabolism and gene expression of SOD-3 which in turn activates the stimulation of mitochondrial antioxidant defense system (Figure 5).[21]

The vast majority of antioxidants incorporate lipoic and ascorbic acid, flavonoids, polyphenols, and carotenoids are available in dietetic sources and, the cell themself amalgamates

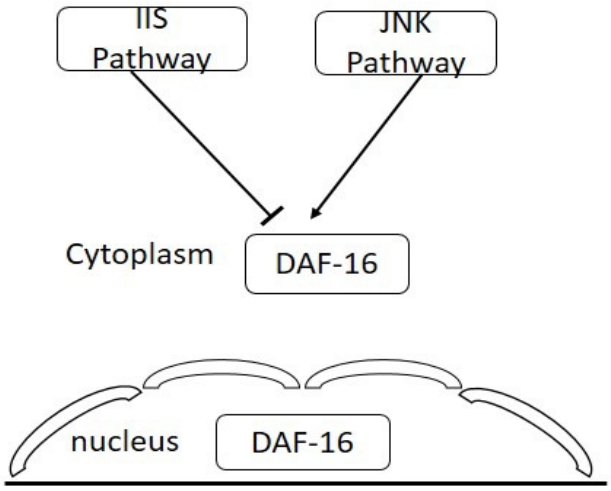

Figure 4: DAF-16 nucleus translocation thru JNK and IIS pathway.

an alternative of these molecules. By implication, acting antioxidants typically consist of chelating proxies and drag to redox elements to thwart free radical generation.

Dietetic Natural Flavonoids as Defensive Extent

There are several clinical evidences that dietetic or additional intake of natural flavonoids ameliorate effects on neurodegeneration. Dietetic consumption contains a variety of flavonoids, vitamins, and other food supplements that play a vital role in neuroprotection in a variety of neurological disorders like AD, PD, and ALS.[17] They act as therapeutic barriers to OS to inhibit oxidation of proteins, fatty acids peroxidation and avert the generation of ROS.

One of the important revolutionary therapeutic aspects that vaccination against different types of neuronal disorders can normalize aerophilous stress to keep neuronal cells. A promising example is an AD that inhibits plaque establishment and consequent neuron inflammation by β-amyloid vaccination. It may possibly be a therapeutic approach for other neural conditions lead by oxidative stress PD, ALS.

Other Dietary Supplementary as Antioxidant Therapy; Preventing Neurodegenerative Diseases associated with Oxidative Stress and Aging

Oxidative stress hypothesis in neurodegenerative diseases concluded that free radicals are convoluted in the pathogenesis of neuron loss directly or indirectly. Accordingly, there must be therapeutic treatment for oxidative stress. Several synthetic and natural products have been suggested for neuroprotection to combat the perilous effects of oxidative stress. Natural products like green tea, EGCG, coffee extract, Cocoa peptide,[22] curcumin, royal jelly, *Cistanche deserticola*, and orange extracts extends the lifespan and stress resistance properties and reconnoitered the allied regulatory mechanism and heightens its resistance to oxidative stress via a daf-16/FOXO- mediated proteostasis to tolerate β amyloid toxicity in *C. elegans.*[20] A synthetic product like Metformin, Gengnianchun (GNC), a traditional Chinese medicine

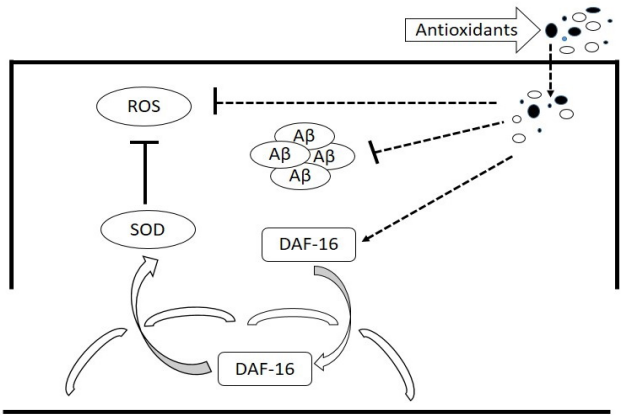

Figure 5: Systematic representation of antioxidant defense system.

(TCM), rBTI,[23] brazilin, ApoE,[24] DhHP-6,[25] MCCP,[20] and phosphatidylcholine[21] are potential drug candidate that efficiently protects against ROS-mediated and age-related diseases, β-amyloid peptide (Aβ) toxicity,[25] increases lifespan and stress resistance to oxidative stress via a daf-16/FOXO in *C. elegans.*[21] Therefore, the molecular machines concerning oxidative stress in aging and neurodegeneration, it may help to identify new approaches for improving public health and prolonging lifespan for understanding the neuroprotective effect of these antioxidants. After knowing various protective effects of these antioxidants, concluded that these antioxidants may help to explain its neuroprotective role in addition to minimizing oxidative stress by reducing the production of free radicals.

Concluding Interpretations and Future Directions

Various current research on neurodegenerative diseases concluding that environmental and genetic mutation plays a ruinous protagonist in catalyzing in vivo chemical reactions that cause neural death and aerobic stress. Pesticide's area unit crucial cofactors to hold out various chemical action accelerator reactions in cell signaling and cellular metabolism. Every alteration in DNA due to pesticides within the brain resulting in free radical-refereed neurotic variations in neurons and oxidative stress. Completely Different neurologic disorders resulting in psychological feature operate in AD, PD, and ALS due to oxidative stress fluctuations in structural parts and neural proteins, and neuroinflammation. Since in this review, oxidative stress has been identified as a principal pathological explanation for neurodegeneration, antioxidants area unit planned as therapeutic choices to conflict the free radical generation and preservation. The employment of antioxidants in ND cure and hindrance as a one compound or an additional combination with medicine targeting alternative pathogenetic mechanisms is also a source and effective means of serving to ND patients and rising the standard of their life span. Besides, we have given an account of antioxidants on neuronal inflammation by in oxidative stress and challenges in designing therapeutic antioxidants for free radical scavenging.

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