

RESEARCH ARTICLE

Unifying Mechanism for Multiple Sclerosis and Amyotrophic Lateral Sclerosis: Reactive Oxygen Species, Oxidative Stress, and Antioxidants

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Abstract

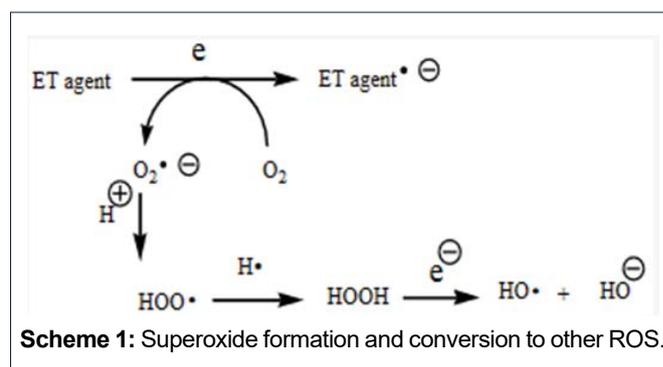
Multiple Sclerosis (MS) and Amyotrophic Lateral Sclerosis (ALS) are neurological diseases whose symptoms are described. Evidence is presented for involvement of harmful reactive oxygen species (ROS) and oxidative stress (OS) with beneficial effects by antioxidants (AO). Details of action mode for AOs and ROS-OS are presented. Mechanistic similarity exists with other brain illnesses, such as Alzheimer's disease (AD), Parkinson's disease (PD), and Schizophrenia (SCZ). Other factors are involved in a multifaceted manner.

Keywords: ALS, MS, Radicals, Oxidative Stress, Reactive Oxygen Species, Antioxidants, Electron Transfer

Abbreviations: ROS: Reactive Oxygen Species; OS: Oxidative Stress; AO: Antioxidant; ALS: Amyotrophic Lateral Sclerosis and MS: Multiple Sclerosis

Introduction

Multiple Sclerosis (MS) and Amyotrophic Lateral Sclerosis (ALS) fit into the unifying mechanism which has been widely applied as set forth in the Kovacic and Somanathan's 2017 [1] article involving electron transfer (ET), reactive oxygen species (ROS), and oxidative stress (OS). This unifying mechanism argues that the preponderance of bioactive substances, usually as the metabolites, incorporate ET functionalities. We believe these ET metabolites play an important role in physiological responses. The main group include quinones (or phenolic precursors), metal complexes (or complexors), aromatic nitro compounds (or reduced hydroxylamine and nitroso derivatives), and conjugated imines (or iminium species). Resultant redox cycling is illustrated in Scheme 1. In vivo redox cycling with oxygen can occur, giving rise to oxidative stress (OS) through generation of reactive oxygen species (ROS), such as hydrogen peroxide, hydroperoxides, alkyl peroxides, and diverse radicals (hydroxyl, alkoxy, hydroperoxy, and superoxide) (Scheme 1). Cellular and mitochondrial enzymes can also perform catalytically in the reduction of O₂. In some cases ET results in involvement with normal electrical effects (e.g. neurochemistry). Generally, active entities possessing ET groups display reduction potentials in the physiologically responsive range [2]. Hence, ET in vivo can occur resulting in production of ROS which can be beneficial in cell signaling at low concentrations, but produce toxic results at high levels. Electron donors consist of phenols, N-heterocycles or disulfides in proteins which produce relatively stable radical



cations. ET, ROS, and OS have been increasingly implicated in the mode of action of drugs and toxins, e.g. anticancer drugs [3], carcinogens [4], cardiovascular toxins [5], toxins [6], autotoxins [7], and various other categories [8]. ROS and OS play roles in schizophrenia (SCZ), Alzheimer's (AD), and Parkinson's disease (PD). Various sources, including oxidase, serve as generators of ROS-OS, such as mitochondria, NADPH, cytochromes P450, monoamines, ET metal complexes, G72 gene, and microglia in the brain. Diverse types of AO exert a positive influence [9]. In addition to the above, there is a plethora of experimental evidence supporting the theoretical framework. This evidence includes generation of the common ROS, lipid peroxidation, degradation products of oxidation, depletion of AOs, effect of exogenous AOs, and DNA oxidation and cleavage products, as well as electrochemical data [1]. This comprehensive, unifying mechanism is consistent with

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the frequent observation that many ET substances display a variety of activities (e.g. multiple-drug properties), as well as toxic effects. It is necessary to recognize the importance of the multifaceted nature of physiological action. In addition to ET-ROS-OS-AO, other factors are at play: cell signaling, mitochondria, receptor binding and enzyme inhibition [10]. The literature addresses the basic aspects of these items: cell signaling [11], mitochondria [6], and receptor binding [12]. Related articles deal with the role of AOs in decreasing ROS-OS. Phenolics and phenolic derivatives are the predominant AOs involved, followed by disulfides, thiols, and others. There is a relationship to AD [13] and PD [14] in which phenolics and derivatives are the principal AOs. MS is a neurological disorder in which immune cells damage the central nervous system (CNS), brain and spinal cord [15]. Present are inflammatory demyelinating lesions in the CNS. Common symptoms include impairment of vision; slurred speech, limb weakness; sensory, intellect, and organ impairment. Lesions can occur in various parts of the body. Other symptoms include fatigue, pain, tingling, imbalance, tremor, spasticity and sexual dysfunction [16]. ALS is a fatal neurodegenerative disease that produces atrophy [17]. There are two forms, namely sporadic and familial, sporadic being the most common form. ALS, also called Lou Gehrig's disease, causes degeneration of motor neurons that control muscle movement [18]. Symptoms include muscle weakness and wasting (atrophy), muscle twitching and stiffness, slowed speech, difficulty breathing and swallowing, changes in gait and eventual loss of ability to walk, and sudden involuntary bursts of laughter or crying [17].

DISCUSSION

Multiple Sclerosis

Even as late as 2017, questions are being raised concerning the clinical efficacy of AO treatment in MS, AD, PD, and HD [19]. Despite promising *in vitro* and preclinical *in vivo* results, the clinical outcome of the AO studies is marginal and most clinical trials of AOs have been disappointing. Various reasons were offered, including time parameters, doses, differences in delivery systems, and problems with blood-brain barrier. Better compounds are needed to counter OS. The main players in OS are discussed in addition to the potential of AO. MS generates inflammation and neural degeneration which relate to ROS and OS. Apoptosis is related to ROS [20]. Medical therapies have been proposed to control the pathology and symptoms of the brain disease. Studies were performed on the therapeutic effect of the AO lipoic acid (LA) [Figure 1] on humans and rodents afflicted with the disease. Since ROS and OS are known to play a role in MS, LA was investigated as an AO. LA was shown to exert protective effects including decrease in OS and prevention of apoptosis. There is also reduction of redox signaling [21]. LA is reduced to the thiol which is a more powerful AO [21]. OS plays a major role in MS and inflammation. Khalili et.al's 2013 [22] case study of the AO lipoic acid demonstrated improvement among MS patients. The results suggest that LA improves serum total AO capacity among MS patients. The mechanism of action

is addressed in another reference [21]. ROS play important roles in cell signaling in homeostasis that can produce harm in excess, which can be alleviated by *in vivo* or AO therapy [23]. Other functions of AOs include vascular regulation and control of hypoxia. The review addresses mechanisms of oxidative damage and involvement in neurodegenerative illness, such as MS, AD, PD, and others. Neurodegenerative disorders, such as MS, are known to be under continuous OS. N-Acetyl cysteine has the potential of providing AO therapy [24]. The AO exerted a beneficial effect on OS generated by H_2O_2 . OS is associated with various brain disorders, such as MS and PD. Morroniside [Figure 2] is an AO derived from a Chinese herb [25]. H_2O_2 , which increases apoptosis, enhances ROS formation and lipid peroxidation which was alleviated by the AO. The AO also prevents oxidative damage to neuroblastoma cells by decreasing ROS generation. The natural drug may be beneficial in treatment and prevention of neural brain illness. Oligodendrocytes (ODD) insult is a major factor in MS [26]. ODD is quite sensitive to ROS. Protandim, an herbal supplement, which contains 5 herbal ingredients: Milk Thistle, Bacopa, Green Tea, Turmeric, Ashwagandha, induces AOs protecting against OS and preventing cell death induced by ROS. Evidence is presented for widespread oxidation by RNS in MS [27]. Neurons are proven to suffer from oxidative damage of RNA done by ROS. 8-Hydroxyguanosine (8-OHG) served as the marker for oxidative insult. The abundance of 8-OHG indicated extensive oxidative damage. Dihydroasparagusic acid (DHA) [Figure 3], a dithiol plant component, is able to

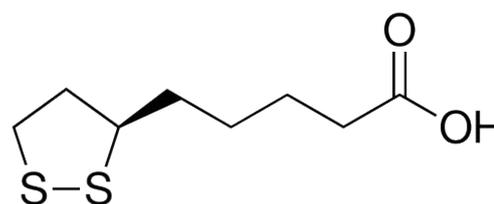


Figure 1: Lipoic Acid.

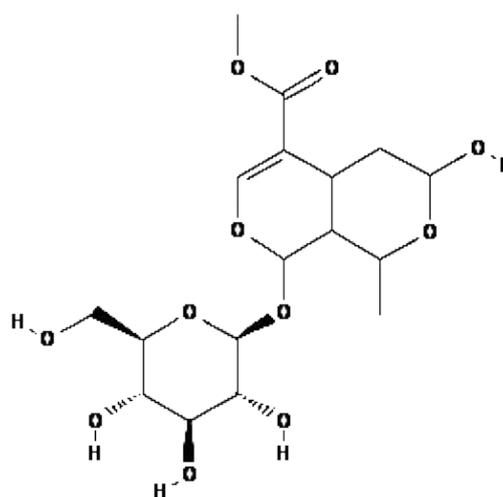


Figure 2: Morroniside.

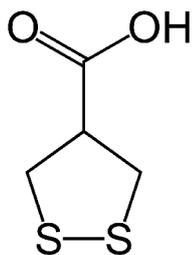


Figure 3: Dihydroasparagusic acid.

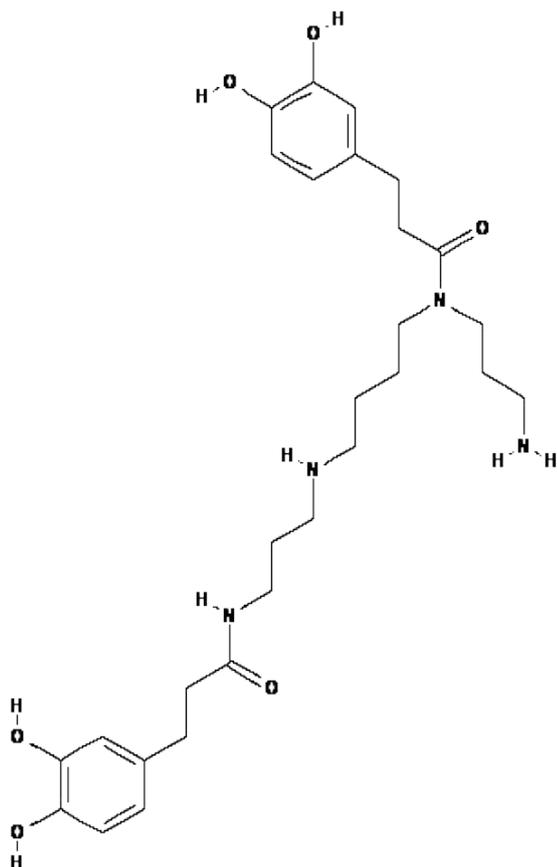


Figure 4: Kukoamine B.

coordinate toxic metals, which may be adversely involved in brain damage, e.g. MS, AD and PD [28]. Thiols are present as AOs in other biomolecules, such as glutathione (GSH). DHA greatly reduced the concentration of ROS. Evidence indicates effective counteraction to oxidative reactions and inflammation. Gene polymorphism is an important factor in MS. Repair systems and AOs may restore OS/AO balance in a favorable direction [29]. OS is known to play an important adverse role in MS. OS is involved in brain disease, including MS, AD, and PD [30]. Kukoamine B (KuB) [Figure 4] treatment prior to H_2O_2 exposure increases AO enzyme activity of superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH), with decrease in OS-ROS. KuB may prevent neurodegenerative diseases produced by OS. Since MS subjects are different in tyrosine phosphates 1 (SHP-1) [31]. AO treatment of SHP-1 deficient oligodendrocytes (ODD)

reversed pathological change. SHP-1 depleted cells produce larger amounts of ROS. Routes associated with different SHP-1 relate to susceptibility to inflammatory disease related to ROS. This investigation reinforces the involvement of OS in MS using saliva [32]. In patients with MS, higher levels of OS and lower AO concentrations were observed. A report deals with OS, which is related to neurodegeneration in MS [33]. Inflammation involves ROS and reactive nitrogen species (RNS). Levels of ROS, MDA, GSH, and total AO were determined. A prior article which deals with inflammation and ROS is relevant [34]. Depletion of AOs is associated with cell disorders and cytotoxicity, such as OS and MS. Measuring the amount of AOs in foods, preservatives, and cosmetics is important [35]. The sensing was carried out by use of gold Nano clusters. A study indicates that milder MS is related to OS. Coenzyme Q10 was lower in patients [36]. Apoptosis induced by OS is a vital aspect of MS. Astragaloside IV (ASI) [Figure 5], a natural product, decreased in ROS and inflammation, as well as decrease in ROS after H_2O_2 treatment [37]. There was prevention of adverse symptoms by OS and of ROS. ASI might be useful for therapy or prevention of MS. The aim of the report is to treat the role of OS in relation to MS [38]. One effect of OS and ROS is involvement of lipid peroxidation which is characterized by the production of isoprostanes, dimalonealdehyde, and 4-hydroxynonenal. Paraonase-1 (PON-1), a gene, plays an important role in counteracting the harmful peroxidation. The enzyme PON-1 is bound to lipoproteins. The nuclear factor (erythroid-derived 2)-like 2 (Nrf2) and DG-1 protein are unregulated in MS involving inflammation. Involved in a harmful manner are ROS-OS, along with a positive effect by AOs, as demonstrated in other reports [39]. Data point to axonal damage by ROS-OS in MS (40). AO defense systems are weakened in the central nervous system (CNS) which is quite susceptible to damage by OS. Modulation of immune response might be a means of MS treatment. AO enzymes, including SOD and

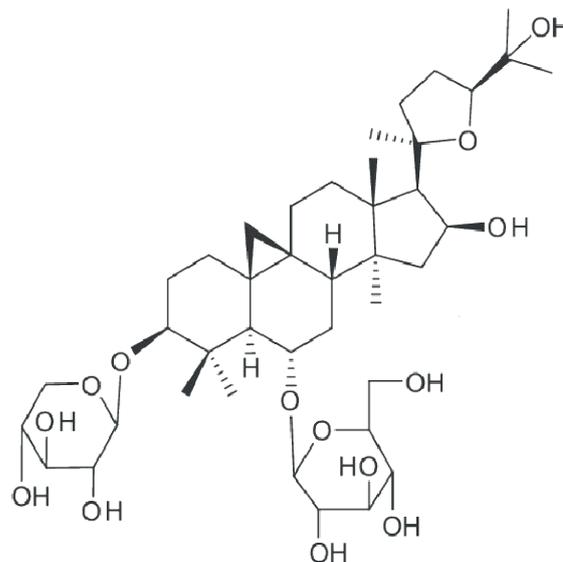


Figure 5: Astragaloside IV.

catalase (CAT), are unregulated in MS lesions [39]. OS can be counteracted by the endogenous AO enzymes. Increased AO enzyme generation may comprise a defense mechanism to ROS damage. A novel AO thiol compound, involving N-acetylcysteine amide (AD4) [Figure 6] increases GSH levels and diminishes OS in disorders, such as MS, AD, and PD [24]. The review discussed therapeutic effects and other aspects of endogenous AO enzymes involving MS [41]. The target is ROS-OS in various neurological disorders.

Amyotrophic Lateral Sclerosis

Free radicals and OS have been linked to neurodegenerative disease, e.g. ALS, AD, PD, and HD. Scavengers of ROS play an alleviating role. Bikaverin [Figure 7], a natural product, was able to protect against OS and apoptosis [42]. Treatment with the drug lessens mitochondrial and plasma damage, as well as replenishing AO enzymes which were depleted by H_2O_2 . The cellular damage, induced by H_2O_2 was restored by bikaverin which shows promise in prevention of neurodegeneration. The human enzyme CBR is a neuroprotective, based on detoxification of toxic aldehydes derived from lipid peroxidation, against OS, with increase in cell survival [43]. The enzyme is a major factor in the control of OS in brain illness, e.g. ALS, AD, and PD. Superoxide dismutase (SOD1) is quite susceptible to adverse protective modifications involving ROS [44]. These modifications occur in ALS leading to insoluble aggregates and cytotoxicity. The molecular mechanism and implications of OS in SOD1 induced toxicity were examined. Oxidative damage may highly destabilize SOD1. Also, SOD1 stability decreases when

expanded by OS. In addition, OS mutations of the SOD1 gene may be an added factor. A mitochondrial peroxide theory was proposed for aging and OS illnesses, such as ALS, AD, PD, and others [45]. AO systems act against OS. Superoxide, an important aspect of ROS generation, plays a central role in brain illnesses. Reaction with NO produces peroxynitrite, an additional significant oxidant. This theory is related to our unifying theme of ET-ROS-OS-AO (see intro). ALS involves loss of Moto neurons and decline in synaptic function. OS, an important factor in ALS, affects the presynaptic transmitter. Nerve terminals are damaged by ROS. Initial dysfunction is followed by inflammatory agents. Since OS is involved, AO therapy appears promising, accompanied by anti-inflammatory treatment [46]. In a review, ALS patients show pathology involving OS and reduction in AO proteins [47]. An overview is presented involving ROS leading to oxidative damage. There is interaction between redox homeostasis and neurodegeneration. AO genes serve as key protective proteins in coping with toxicity involving OS. Selective proteins may be useful for treatment of these brain illnesses. Galantamine [Figure 8] and derivatives exhibit AO properties and inhibitory activity against acetyl cholinesterase [48]. It scavenges ROS, thereby decreasing oxidative neuronal damage in brain illnesses, including ALS, AD, PD, and HD. Galantamine provides neuroprotection against various neurotoxic agents, including H_2O_2 and oxygen. The drug may comprise a novel therapy for brain disease. OS, involved with ALS, AD, and PD, is part of perturbed redox circuitry. Dysfunction of AO enzymes can lead to excess ROS. Important redox enzymes are involved in redox status. The review deals with ROS production, basic chemistry and detoxification in addition to redox processes in neurodegeneration [49]. The review deals with the various forms and sources of OS in the brain, including their roles in regulation [50]. Protein synthesis and degradation play a role in OS. Our knowledge is enhanced as to how OS is successfully managed. These findings are treated in relation to a variety of brain illnesses, including ALS, AD, and PD. Coenzyme Q10 (COQ10) [Figure 9], which possesses AO properties, is used in the treatment of mitochondrial disorders.

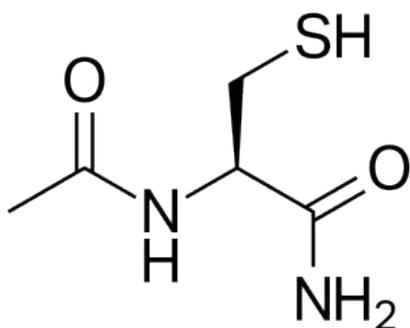


Figure 6: N-acetylcysteine amide.

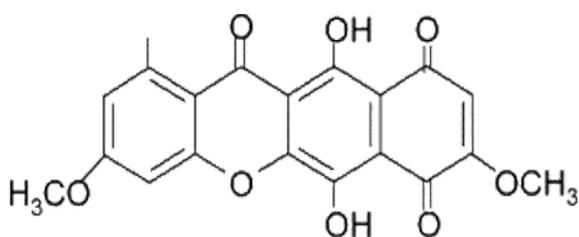


Figure 7: Bikaverin.

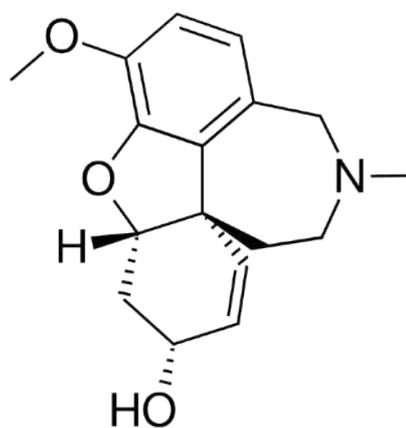
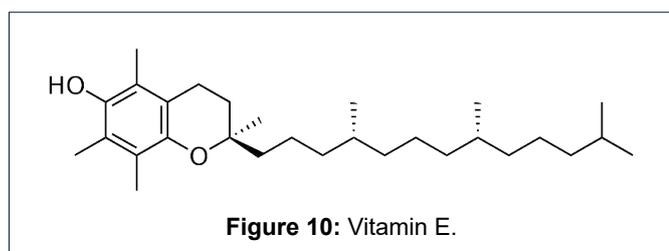
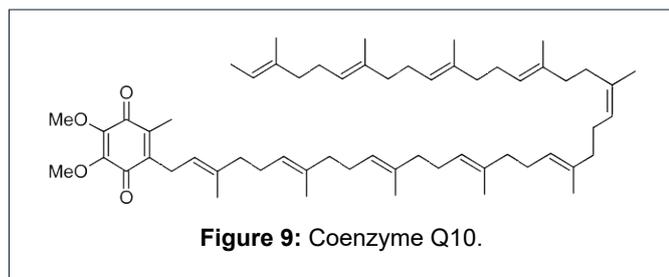


Figure 8: Galantamine.

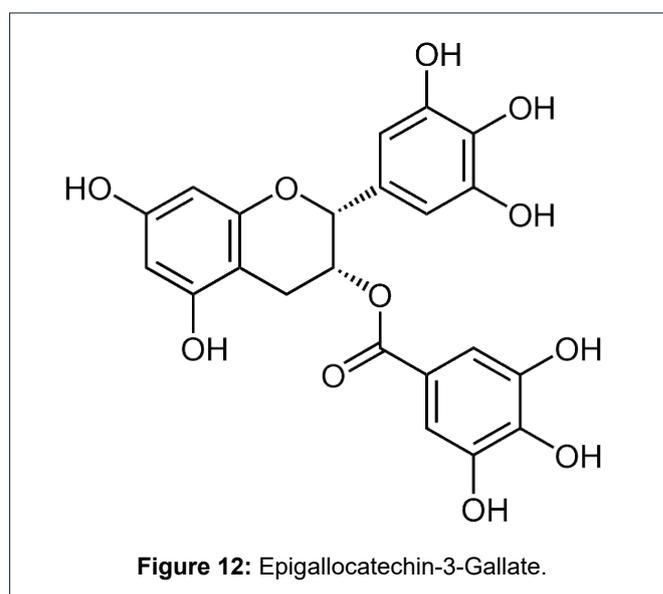
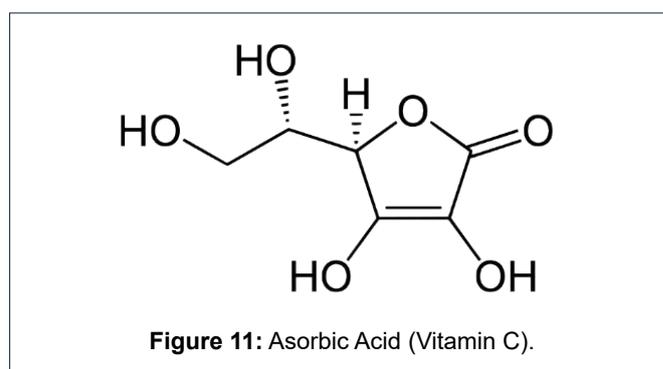


These diseases are linked to increase in ROS. The AO may also be useful in treatment of other illnesses, namely ALS, AD, PD, and HD. The review addresses the link between these disorders and OS. Also, therapeutic use of COQ10 is discussed [51]. Recent studies with vitamin E [Figure 10] supplementation were linked to lower rates of ALS [52]. Controversial earlier studies showed that AOs did not lessen OS and in some cases OS was worse. The situation was rationalized in a recent article [22]. The AO was found to decrease generation of ROS by mitochondria. Heavy metals, such as Cu, are found to play a significant adverse effect in neurodegenerative diseases, such as ALS, AD, and PD [53]. The toxic effect involves ROS-OS and is reduced by AOs. A study involving ALS showed marked impairment of GSH peroxidase activity [54]. The report involves AO enzymes in relation to involvement of OS. A lessened activity of enzymes was noted. Lipid peroxidation appreciably increased in patients with ALS [55]. Free radicals are involved with decrease of ROS by AOs, such as SOD, CAT, and GSH enzymes. The study points to adverse involvement of OS [55]. Novel nanomaterials were examined as therapy for neurodegenerative diseases, such as ALS, AD, PD, and stroke [56]. The materials tested include fullerene, which act as AOs for elimination of ROS-OS. The problem of crossing the blood-brain barrier is addressed.

Multiple Sclerosis and Amyotrophic Lateral Sclerosis

A review deals with involvement of ascorbic acid (AA) (Vitamin C) [Figure 11] in neurodegenerative diseases, including MS, ALS, AD, PD and Huntington's disease [57]. In the brain, AA scavenges ROS. This is important since redox imbalances comprise significant mechanisms in these brain diseases. Important action involves AO defense by decreasing OS and decreasing generation of protein aggregates which may be involved in reduction of cognitive and mental impairments. Brain diseases, such as MS, ALS, AD, PD, and Huntington's disease involve harmful loss of neurons. OS, which plays a vital role in these conditions, results from an

imbalance in oxidant and AO levels in favor of oxidant [58]. Evidence is presented that links apoptosis signal regulating kinase 1 (ASK1) with pathogenesis of several brain diseases. ASK1 may be a therapy for prevention or treatment of brain diseases. Prior research provides support for the thesis that excess ROS play multifaceted roles in development of MS, Neuron cells are particularly susceptible to OS due to reaction with unsaturated fatty acids and insufficient presence of AOs [59]. Evidence supports application of novel AOs as a primary means of alleviating this illness and should be a focus for further research. The role of ROS is addressed in relation to MS, AD, PD, ALS, and D with emphasis on AO therapy. The pathology appears similar in ALS, AD, PD, and HD with apoptosis importantly involved, These illnesses have been associated with OS and imbalance in redox in favor of oxidation. MS and related illnesses have been linked to ROS and NO. An overview is discussed based on OS and apoptosis [60]. Other prior studies have dealt with the beneficial effect of AOs in alleviating the harmful effects of OS in AD, PD, and schizophrenia (SCZ) [9]. In contrast, in this report, many drugs in the class are known to act by generation of lethal OS in the affected cells (61). This mechanism has also been proposed for treatment of other illnesses [13, 14]. Systemic sclerosis (SSc) is associated with OS. The AO epigallocatechin-3-gallate (EGCG) [Figure 12] was capable of reducing adverse ROS in the condition [62]. EGCG may be beneficial in therapeutic



use in reduction of OS. Systemic sclerosis involves arterial hypertension as a major factor [63]. As in the case of MS and ALS, OS plays a major role arising from ROS. Evidence indicates that therapy based on AO species should be beneficial. Ocrevus (or Ocrelizumab) is a very recent MS drug. Ocrevus, a humanized monoclonal antibody that selectively depletes CD20-expressing B cells, in the primary progressive form of the disease [64]. MS and Guillain-Barre (GBS) are not the same; however, they do have many similarities since they are both autoimmune diseases. Most significantly, GBS damages the peripheral nervous system, while MS damages the central nervous system (brain and spinal cord). However, in a 2010 study Ghabaee et.al found a decrease in serum AO for MS and GBS [65]. An imbalance between AO and malondialdehyde (MDA) levels was noted for both illnesses. A structure activity relationship article deals with phenolics in AD and PD [66] which appears relevant to the present report.

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