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REVIEW ARTICLE

Exploring multifunctional antioxidants as potential agents for management of neurological disorders

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Abstract

Free radical or oxidative stress may be a fundamental mechanism underlying several human neurologic diseases. Therapy using free radical scavengers (antioxidants) has the potential to prevent, delay, or ameliorate many neurologic disorders. However, the biochemistry of oxidative pathobiology is complex, and optimum antioxidant therapeutic options may vary and need to be tailored to individual diseases. In vitro and animal model studies support the potential beneficial role of various antioxidant compounds in neurological disease. Antioxidants generally play an important role in reducing or preventing the cell damage and other changes which occur in the cells like mitochondrial dysfunction, DNA mutations, and lipid peroxidation in the cell membrane. Based on their mechanism of action, antioxidants can be used to treat various neurological disorders like Huntington's disease, Alzheimer's disease, and Parkinson's disease. Vitamin E has a scavenging action for reactive oxygen species (ROS) and also prevents the lipid peroxidation. Creatine generally reduces the mitochondrial dysfunction in Parkinson's disease (PD) patients. Various metal chelators are used in PD for the prevention of accumulation of the metals. Superoxidase dismutase (SOD), lipases, and proteases act as repair enzymes in patients with AD. Accordingly, the antioxidant defense system is found to be most useful for treating various neurological disorders.

Keywords Antioxidants · ROS · SOD · Neurodegenerative disorders · Vitamin E

Introduction

Antioxidants are referred to as those substances which can reduce or prevent the cellular damage generally caused by free radicals (Grewal et al. 2021; Bhattacharya et al., 2021a, b). They are also known as free radical scavengers. Free radicals are defined as molecular entities consisting of one or more unpaired electrons (Arya et al. (2021); Rahman (2021)). The free radicals may result in many cellular changes including DNA mutations, cell membrane lipid peroxidation, changes in the enzymatic activity, and even cell death (Birangane et al. 2011). Aerobic metabolism in the body results in the formation of oxygen free radicals such as hydroxyl radicals, superoxides and reactive oxygen species (ROS) (Rahman et al. (2020); Sharma et al. (2021); Bhattacharya et al. (2021a)). Oxidative damage to the biomolecules such as DNA, lipids, and proteins can be caused by the overproduction of free radicals. This may ultimately lead to the risk of many chronic diseases like rheumatoid arthritis, cancer, diabetes, neurological disorders, and atherosclerosis in humans (Akter et al. 2021; Rahman et al. 2020a). There are various neurological disorders based on the mechanism of oxidative injury or free radicals. Free radical scavengers are generally used for the prevention and delaying of neurological disorders (Sridevi et al. 2018). These generally include scavenging activity, metal chelation, or lipid peroxidation (Fadaka et al. 2019). The physiological defense mechanism of antioxidants against oxidative stress has been studied mainly by preventing the chain reactions which promote various diseases and by neutralizing the free radicals (Changa et al. 2018). All aerobic organisms are mainly liable

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to oxidative stress. Oxidative damage can mainly affect the vital organs like the brain and leads to its membrane peroxidation (Akter et al. 2021; Uddin et al. 2020); Tagde et al. 2021). Various antioxidants like pyrrolopyrimidine which can cross the blood-brain barrier (BBB) are generally preferred for the treatment of neurological disorders. These act by inhibiting lipid peroxidation (Delanty and Dichter 2000). Vitamin E and vitamin C when given in combination are proved to be effective in shoeing the free radical scavenging activity rather than giving them alone (Rahman et al. 2022). Other combination therapies include coenzyme Q_{10}, pyrrolopyrimidine, and deferoxamine for conditions like Parkinson's disease (Delanty and Dichter 2000). The multifunctional role of the antioxidants for managing neurological diseases have been significantly discussed and as multifunctional antioxidants and potential agents have been explored.

Oxidative stress and antioxidants

Oxidative stress is defined as a phenomenon that may arise due to an imbalance between the production of oxidants (reactive oxygen species) and their removal by a safe mechanism (Chowdhury et al. 2016). Oxidative stress may even lead to the enhancement of various disorders like ischemia/perfusion (Kašparová et al. 2005), diabetes, neurological disorders (Kabir et al. 2021), cancer, and asthma (Dut et al. 2008; Ercan et al. 2006; Fitzpatrick et al. 2009). Generally, all the biomolecular groups like lipids, DNA, and proteins are targeted by ROS. Hence, oxidative stress plays an important role in induced cellular damage and also in signal transduction (Al-Dalaen and Al-Qtaitat 2014). Antioxidants are said to be the first-line drugs for the treatment of oxidative stress (Adeola et al. 2021).

Antioxidants are those molecules that can counteract the effects of oxidants before they attack all the cells as described in Figure 1.

Types of antioxidants

There are different types of antioxidant systems involving enzymatic or non-enzymatic antioxidants (Figure 2) in human cells which work together and prevent the body from free radical damage (Al-Dalaen and Al-Qtaitat 2014).

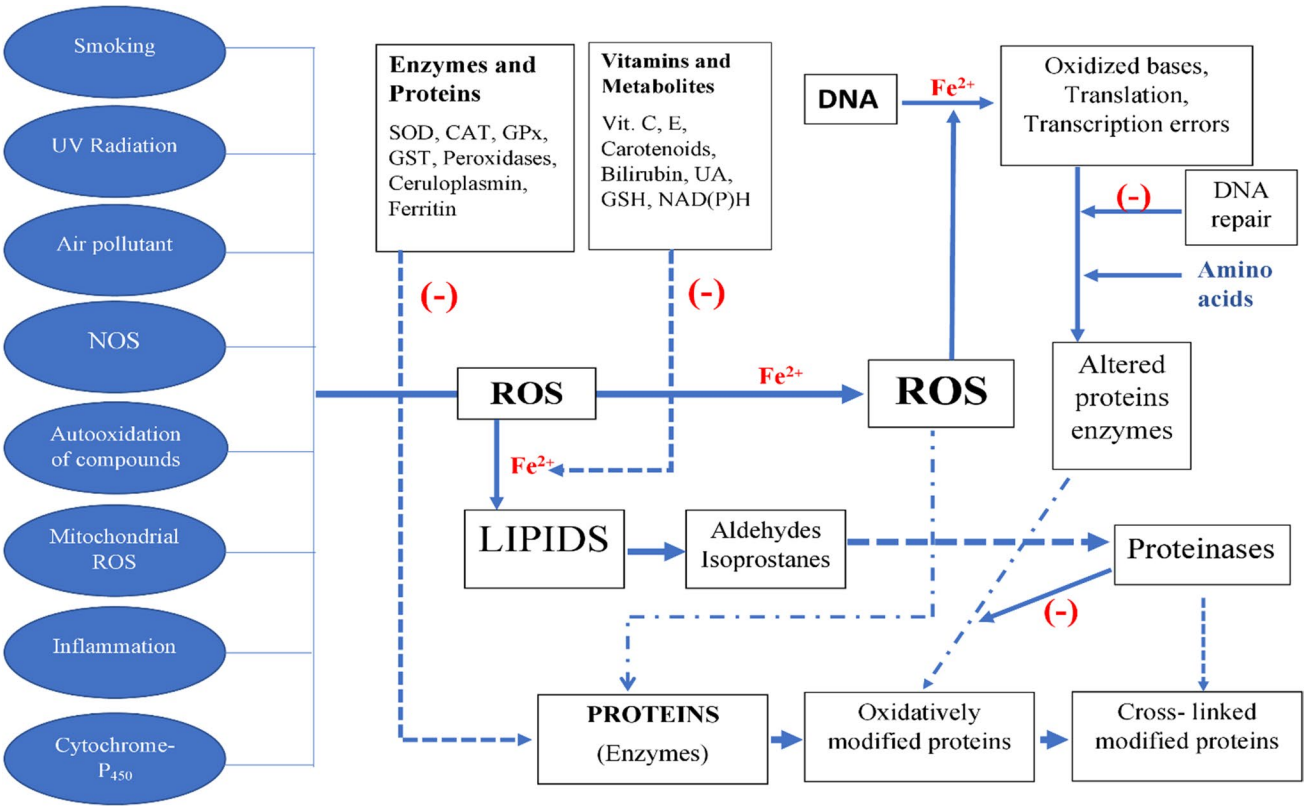


Fig. 1 Association between oxidants and antioxidants. There are various oxidants on which the antioxidants act having the ability to counterbalance the effect of oxidants before they attack the cell. The antioxidants work in collaboration with each other to protect the body against free radical damage (Said et al. 2014). Abbreviations: ROS, reactive oxygen species; SOD, superoxide dismutase; CAT, common antioxidant enzyme; GST, glutathione-s-transferase; NAD, nicotinamide adenine dinucleotide

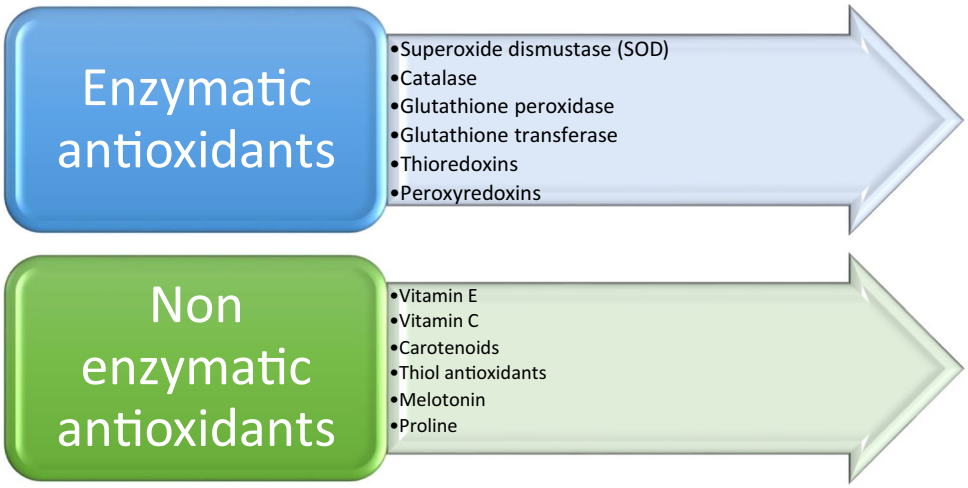


Fig. 2 Types of antioxidants (Said et al. 2014)

Enzymatic antioxidants

Enzymatic antioxidants comprise only a few proteins which include catalase, superoxide dismutase (SOD), glutathione, and some other supporting enzymes (Uttara et al. 2009). All these enzymes show significant antioxidant activity in the body, and they have specific reactions as shown in Table 1.

Superoxide dismutase (SOD) with a generalized existence acts by catalyzing the superoxide dismutation in the body. Hydrogen peroxide is produced as a by-product of this reaction. An improbable number of reactive oxidants like superoxide, hydrogen peroxide, and hydroxyl radicals are produced in the human body. Among these, the hydroxyl radical is believed to be the most powerful and acts by destroying the adjacent cells. There are three alternatives for SOD. The enzymes containing copper-zinc are normally found in the cytoplasm, manganese SOD is present in the mitochondria, and the third one is located extracellularly (Jeeva et al. 2015; Ramasarma 2007).

Catalase, another antioxidant enzyme, acts as a catalyst in converting hydrogen peroxide to water and oxygen. The actual amount of catalase cannot be determined because during the process of tissue manipulation, most of it is lost (Aly and Shahin 2010).

Glutathione generally occurs as two enzymes, i.e., glutathione peroxidase and glutathione reductase. Only the reduced form of glutathione shows the defense mechanism, whereas the oxidized form does not show any protective action. Reduced glutathione plays a key role in neutralizing the hydrogen peroxide which is produced inside the cell (Champe et al. 2004). Therefore, the repetitive reduction and oxidization of glutathione help in making it a free radical scavenger (Maritim et al. 2003).

Peroxidase enzyme (POD) is an oxidoreductase enzyme and is commonly found in plants and animals as well as in some microorganisms (Al-Aloosy et al. 2019; Dey et al. 1997). It stimulates the oxidation of many hydrogen donor substances like aromatic amines, hydroquinone, phenol compounds, hydroquinone amines, and gasoline derivatives in the presence of H_2O_2 (hydrogen peroxide) acting as hydrogen receiver (Ryan et al. 1994). Peroxidase acts as a plant defense enzyme against the oxidative stress characterized by the stimulation capability to convert hydrogen peroxide (H_2O_2) into water (H_2O) (Kawano 2003).

Non-enzymatic antioxidants

- Different types of antioxidants are used to treat oxidative stress or free radical damage. These comprise carot-

Table 1 Enzymatic antioxidants

S. no.	Name of scavengers	Abbreviation	Reaction	Reference
1	Catalase	CAT	$2\ H_2O_2 \rightarrow 2\ H_2O + O_2$	Birben et al. (2012); Kurutas (2015)
2	Superoxide dismutase	SOD	$2(O_2^-) + 2H^+ \rightarrow H_2O_2 + O_2$	Birben et al. (2012); Kurutas (2015)
3	Thioredoxin	TRX	Thioredoxin disulfide + adenosine monophosphate + sulfite = 5'-adenylyl sulfate + thioredoxin	Birben et al. (2012); Kurutas (2015)
4	Glutathione peroxidase	GTPx	$2GSH + ROOH \rightarrow GSSG + ROH + H_2O$	Birben et al. (2012); Kurutas (2015)
5	Glutathione transferase	GST	GSH + RX = R-S-GSH + HX	Birben et al. (2012); Kurutas (2015)

enoids, thiol antioxidants, vitamin C, vitamin E, etc. as shown in Table 2.

Vitamin E (α-tocopherol) is generally a fat-soluble vitamin. It is a potent membrane-bound antioxidant that is used by the cell (Hensley et al. 2004) for protecting from lipid peroxidation (Pryor 2000). α-Tocopherol gets converted to α-Tocopherol radical during the antioxidant reaction by donating liable hydrogen to a lipid or a lipid peroxyl radical (Kojo 2004).

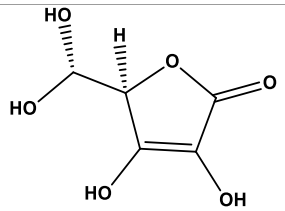
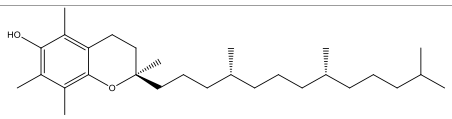
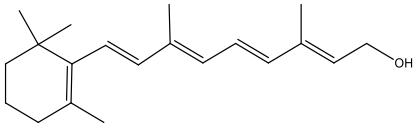
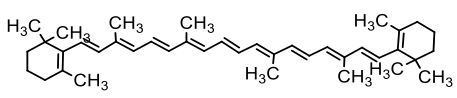
- *Vitamin C* (ascorbic acid) is generally water soluble, so it mainly acts in the damp environment of the body along with the enzymatic antioxidants. Vitamin C in cooperation with vitamin E helps in regenerating α-tocopherol from α-tocopherol radical in membranes and lipoproteins (Pryor 2000). It also plays a major role in protecting the protein thiol group against oxidation by raising the intracellular glutathione levels (Naziroğlu and Butterworth 2005).
- *Melatonin* is a neurohormone that is derived from tryptophan in the pineal gland. It mainly acts as a free radical scavenger in the metabolism of oxygen and hereby protects against the free radical damage caused to the membranes, proteins, and DNA (Rahimi et al. 2005).
- *Carotenoids* (β-carotene) are the colored pigments that are present in plants and microorganisms. It has been explained in some studies that a diet rich in carotenoids lowers the risk of age-related disorders (Rahman 2007). Carotenoids act as an antioxidant by delocalizing the unpaired electrons and quenching singlet oxygen without degradation (Mortensen et al. 2001).
- *Thiol antioxidants* are the compounds containing sulfur atom, which easily accommodate the single electron loss (Karoui et al. 1996). Thioredoxin (TRX) is a type of thiol antioxidant that generally shows ubiquitous and oxidoreductase activity in prokaryotic and mammalian cells. Another thiol-disulfide derivative is α-lipoic. It is fat and water soluble and distributed widely in the cytosol and cellular membranes of both prokaryotic and eukaryotic cells (Smith et al. 2004). The reduced form of lipoic acid is dihydrolipoic acid, and both forms act as a powerful antioxidant. They act as a free radical scavenger, chelate the metal ions, and repair the damage to the proteins caused due to oxidative stress (Navari-Izzo et al. 2002).

Proline is a type of amine acid that participates in protein synthesis. Proline keeps accumulating because of the inability of a plant to synthesize the proteins for the further demolition process. It has been characterized by an ability to reduce each hydroxyl (OH*) radical and single oxygen and also by inhibiting lipid oxidation (Trovato et al. 2008).

Sources of antioxidants

- Antioxidants can be obtained from various herbs and spices. Various analytical methods can be used for get-

Table 2 Non-enzymatic antioxidants

S.No.	The chemical name of Scavengers	Name of Scavengers	Structure	Reference
1	Ascorbic acid	Vitamin-C (5R)-[(1S)-1,2-Dihydroxyethyl]-3,4-dihydroxyfuran-2(5H)-one		(Birben et al., 2012)
2	α-Tocopherol	Vitamin- E		(Birben et al., 2012)
3	All-trans retinol 2	Vitamin-A		(Birben et al., 2012)
4	β- Carotene	Carotenoids		(Birben et al., 2012)

ting various antioxidants from different plants. Most commonly used tests for analysis include the following:

- FRAP (ferric reducing antioxidant power)
- CUPRAC (cupric reducing antioxidant capacity)
- DPPH (2,2-diphenyl-1-picrylhydrazyl)
- ABTS (2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid))
- ORAC (oxygen radical absorbance capacity)
- TRAP (total radical trapping antioxidant parameter)
- TEAC (Trolox equivalent antioxidant capacity)

Spices and herbs are the best sources of natural antioxidants because they contain the essential components which give an antioxidant effect to the food (Embuscado 2015; Table 3).

Other than spices and herbs, mushrooms and various other vegetables are also a rich source of antioxidants (Fadaka et al. 2019). Even the agricultural by-products processed by some industries prove to be a good source of naturally occurring antioxidants (Shahidi et al. 1992). The antioxidant activity of plants can be assessed and evaluated by performing various in vivo and in vitro techniques (Fadaka et al. 2019).

Antioxidants can also be prepared synthetically and are referred to as synthetic antioxidants. These do not occur in nature and are therefore added as preservatives to the food for preventing lipid oxidation (Shahidi et al. 1992). Synthetic antioxidants can be divided into primary antioxidants and secondary antioxidants. Primary antioxidants can be further categorized into the following:

- Natural: includes various phytoconstituents, e.g., flavonoids, phenolic acids, tocopherols, and carotenoids
- Endogenous: e.g., glutathione and lipoic acid
- Exogenous: can be derived from natural sources (vitamins, flavonoids, etc.) and also synthetically (gallates, butyl hydroxyanisole, etc.) (Litescu et al. 2011)

Mechanism of action of antioxidants

A low concentration of antioxidants present in the human body plays a key role in the reduction and prevention of oxidation of oxidizable substrates. Enzymatic and non-enzymatic antioxidants together form a complex system and work hand in hand to prevent free radical damage to cells and organs (Figure 3) (Kurutas 2015). These antioxidants can be produced by the body itself or can be taken from outside in the form of dietary supplements. Some supplements do not directly attack free radicals but act on endogenous systems to enhance the potency of endogenous antioxidants. Formation of chelation complex and elimination of free radicals are considered as two ideal characteristics to define the effectiveness of antioxidants. It should also have to interact with genes and should also be effective in both membrane and aqueous mediums. Well-being and systemic health are chiefly maintained by endogenous antioxidants which play a key role in maintaining flawless cellular functions (Kurutas 2015). Dietary supplements are required in some conditions such as nitrosative or oxidative stress where endogenous antioxidants may not be enough for prevention and control of oxidation. "Antioxidant network" is formed when various antioxidants work together to broaden their initial properties (Valko et al. 2007).

Enzymatic antioxidant mechanism of action

Optimal levels of ROS are maintained by various free radical scavenging enzymes through cell signaling mechanisms. Merely disproportion of ROS breakdown and ROS formation leads to the development of oxidative stress which can rattle cellular functions. Macromolecules of cells such as DNA, proteins, and lipids can be irreversibly damaged by elevated ROS levels which further can initiate carcinogenesis. Therefore, several enzymatic antioxidants play a major role in preventing and slowing down the oxidation of macromolecules through various defense mechanisms (Duarte and Lunec 2005). Certain enzymatic antioxidants such as catalases, SOD, and peroxidases act through various mechanisms to protect cells from damage and lysis (Valko et al. 2007). Enzymatic antioxidants act through various mechanisms such as inhibiting the production of free radicals, scavenging action, formation of less toxic substances from more toxic substances, inhibition of secondary toxic metabolites and inflammatory mediators' production, breaking chain propagation step of secondary oxidant reaction, reconstruction of damaged molecules, and strengthening endogenous antioxidants. All these mechanisms work together to protect the cell from damage (Figure 4) (Halliwell 2007).

Homeostasis of the majority of body cells is maintained by three primary classes of enzymatic antioxidants which are catalases, SOD, and glutathione peroxidases (GPx). Excessive signaling due to increased oxidative stress leads to the induction of these enzymes (Cheung et al. 2001). The conversion of superoxide radical into hydroperoxide is done by the scavenging action of the SOD (McCord and Fridovich 1969). Further reduction of lipid hydroperoxide, hydrogen peroxide, and other organic hydroperoxide is accomplished by GPx (Tappel et al. 1982). The cellular detoxification of cytotoxic and genotoxic compounds along with protection of tissue from oxidative damage is archived by a family of multifunction proteins which is formed by a group of detoxifying enzymes together represented as glutathione-S-transferases (GST) (Hayes and Pulford 1995; Mannervik et al. 1988; Pickett and Lu 1989). The detoxification of xenobiotics like drugs, pollutants, and carcinogens in human and animal and insecticide

Table 3 General summary of various herbs and spices having antioxidant compound (Embuscado 2015)

S. no.	Plant parts	Spices/herbs	Scientific names	Antioxidant compounds	Mode of action
1	Leaves	Green tea	*Camellia sinensis*	• Catechin called epigallocatechin-3-gallate (EGCG)	• Prevents cell damage
2	Leaves	Oregano	*Origanum vulgare*	• Rosmarinic acid • Caffeic acid • Protocatechuic acid • 2-caffeoyloxy-3-[2-(4-hydroxybenzyl)-4,5-dihydroxy] phenylpropionic acid • Flavonoids – apigenin, eriodyctiol, dihydroquercetin, dihydrokaempferol • Carvacrol, thymol	• Free radical scavenger
3	Root	Ginger	*Zingiber officinale*	• Gingerol • Shogaol • Zingerone	• Free radical scavenger
4	Flower bud	Clove	*Syzygium aromaticum*	• Phenolic acids (gallic acid) • Flavanol glucosides • Phenolic volatile oils (eugenol, acetyl eugenol) • Tannins	• Free radical scavenger • Metal chelator
5	Leaves	Thyme	*Thymus vulgaris*	• Phenolic acids (gallic acid, caffeic acid, rosmarinic acid) • Thymol • Phenolic diterpenes • Flavonoids	• Free radical scavenger
6	Root	Turmeric	*Curcuma longa*	• Curcumins • 4-hydroxycinnamoyl methane	• Free radical scavenger
7	Fruits	Black pepper	*Piper nigrum*	• Kaempferol • Rhamnetin • Quercetin	• Free radical scavenger
8	Berries	Chili pepper	*Capsicum frutescens*	• Capsaicin • Capsaicinol	• Free radical scavenger
9	Seed	Cumin	*Cuminum cyminum*	• Cuminal • Pinocarveol • γ-Terpinene • Linalool • Carotol • 1-methyl-2-(1-methylethyl) benzene	• Free radical scavenger • Metal chelator
10	Leaves	Sage	*Salvia officinalis*	• Carnosol • Carnosic acid • Rosmadial • Rosmanol • Methyl and ethyl esters of carnosol • Rosmarinic acid	• Free radical scavenger
11	Leaves	Rosemary	*Salvia rosmarinus*	• Carnosol • Carnosic acid • Rosmanol • Rosmadial • Diterpenes (epirosmanol, isorosmanol, rosmaridiphenol, rosmariquinone, rosmarinic acid)	• Scavenge superoxide radicals • Lipid antioxidant • Metal chelator

and herbicide resistance in insects and plants has also correlated these enzymes (Hayes et al. 1991). The inactivation of GPx and GST by hydroperoxides has been shown in certain studies (Pigeolet et al. 1990). Several studies have shown GPx activates are elevated by the number of the GST isoenzymes along with induction of breakdown of organic hydroperoxides into corresponding alcohols (Prohaska 1991; Mosialou et al. 1993). The breakdown of the superoxide ions into hydrogen and oxygen peroxidase is activated by superoxide dismutase (Zelko et al. 2002).

Mechanism of action of non-enzymatic antioxidants

Thiol is generally the first-line defense against oxidative stress as both protein-bound and non-protein-bound thiols act as cellular protective and a reducing agent through

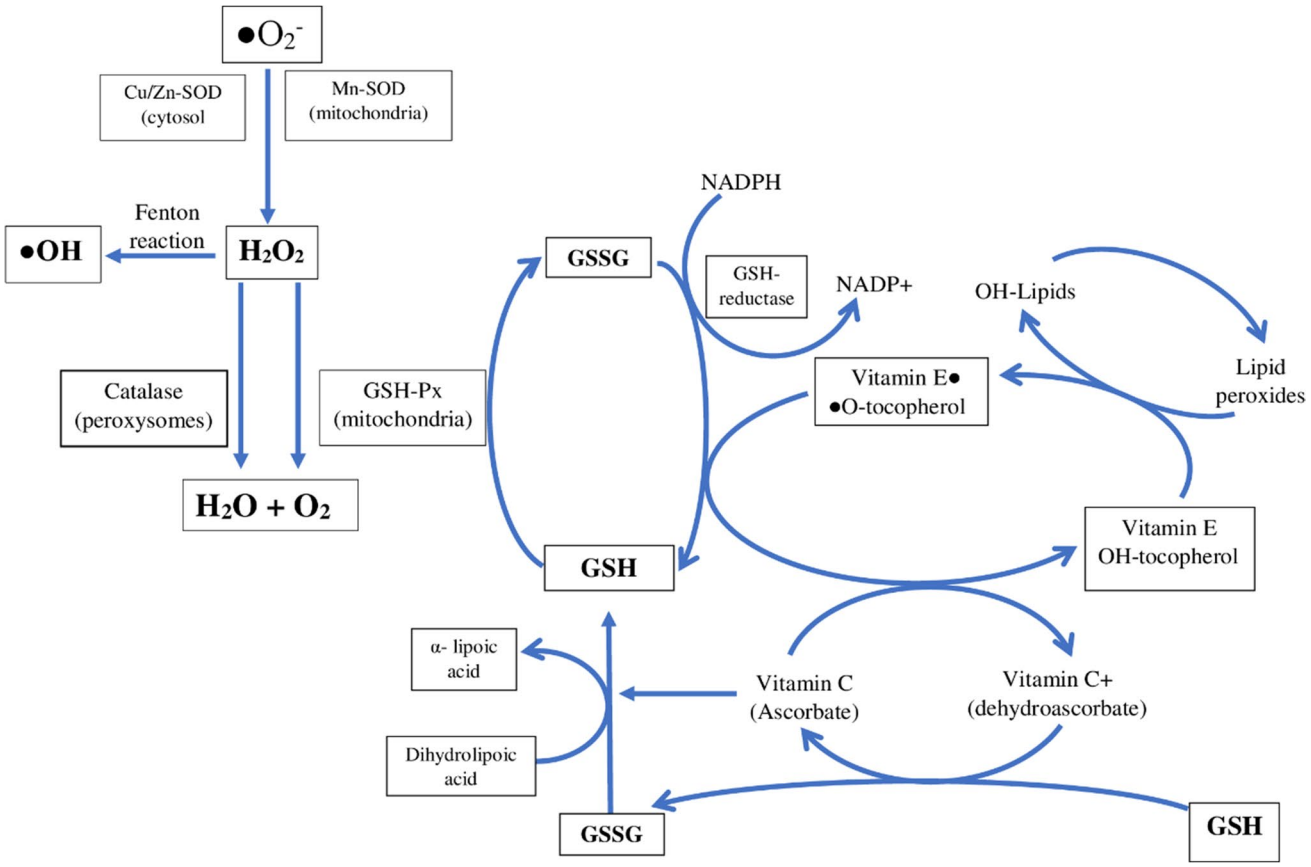


Fig. 3 Antioxidant defense system in the body. Enzymatic and non-enzymatic antioxidant systems working synergistically and together with each other to protect the cells and organ system of the body against free radical damage (Ergul 2016)

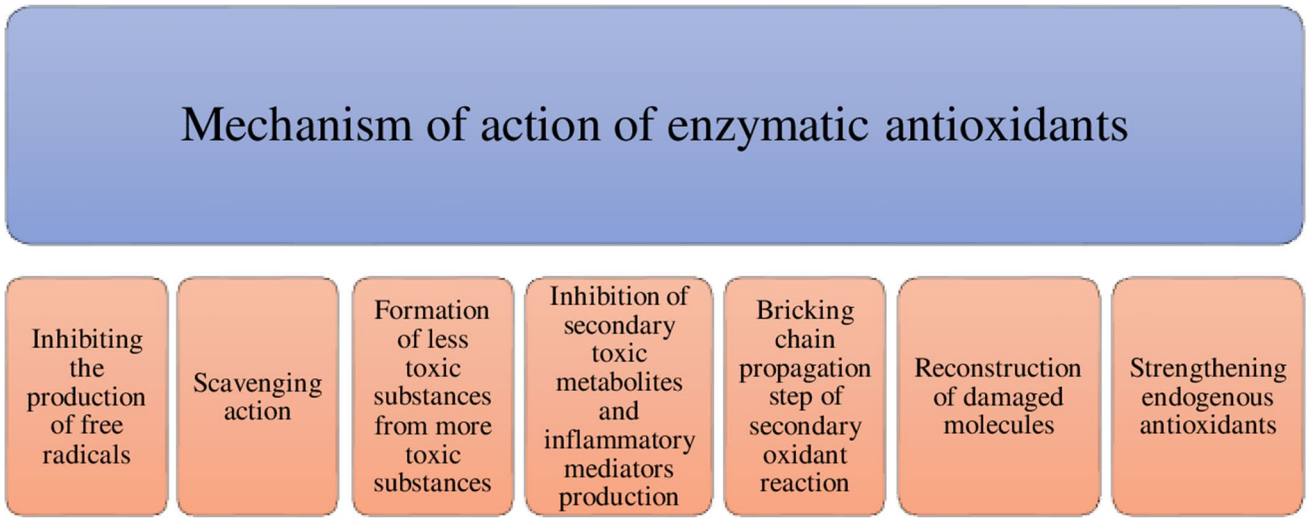


Fig. 4 Mode of action of enzymatic antioxidants. All the mechanisms occur simultaneously for protecting the cell damage (Adwas et al. 2019)

the –SH group against most of the inorganic pollutants (Mosialou et al. 1993). The increase in the synthesis of thiol levels may act as an adaptive mechanism to the oxidative stress; moreover, severe oxidative stress may also lead to reduced levels of thiol because of loss in the adaptive mechanism as shown in Figure 5.

A cellular antioxidant, glutathione helps to maintain the redox state in the cells (Ulusu and Tandoğan 2007). Ascorbic acid acts by reducing and neutralizing the reactive oxygen species (ROS) (Linster and Schaftingen 2007). Vitamin E removes the free radical intermediates and reacts with the lipid radical therefore protecting the cell membrane from oxidation (Sen et al. 2006). Beta-carotene protects against the free radical attack generally by removing singlet oxygen.

Antioxidants in neurological disorders

ROS toxicity to the neurons occurs in neurodegenerative disease as a result of protein misfolding. This can be well explained with the help of an example. The process of AB aggregation helps in the generation of ROS by activating NADPH-dependent oxidase (a pro-oxidative enzyme) (Behl et al. 1994) and reducing divalent metal ions like Fe^{2+} and Cu^{2+} (Lynch et al. 2000). This ROS accumulation leads to lipid peroxidation, and subsequently, cytotoxic 4-hydroxynonenal (HNE) is generated (Mark et al. 1995), and lipid peroxidation leads to the disturbance in the membrane organization and certain modifications in proteins and DNA (Morrow et al. 1999).

Neurological disorders may arise due to the loss of nerve cells from the spinal cord and brain further leading to ataxia (functional loss) or dementia (sensory dysfunction). Mitochondrial dysfunction further leading to apoptosis has been reported as a pathological reason for aging and various neurogenerative disorders like Parkinson's disease (PD), multiple sclerosis (MS), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS) (Mattson 2004) as shown in Figure 6. Various antioxidant therapies have been used for the treatment of such neurological diseases. Consumption of many dietary supplements, fruits, vegetables, various herbs, and spices may be used as antioxidant therapy and in repairing the damaged neuronal cells.

Parkinson's disease (PD)

Parkinson's disease is one of the most common types of neurodegenerative disease and can be clinically described by continuous rigidity, tremor, bradykinesia, and the loss of pigment neurons in substantia nigra generally in the midbrain and pathologically the presence of Lewy bodies (Lin and Beal 2006). It is generally characterized as a preferential death of dopaminergic neurons (Filograna et al. 2016). It has been observed that in 2006 approximately 4 million people of an average age of 60 years are dealing with Parkinson's disease in which the number of females

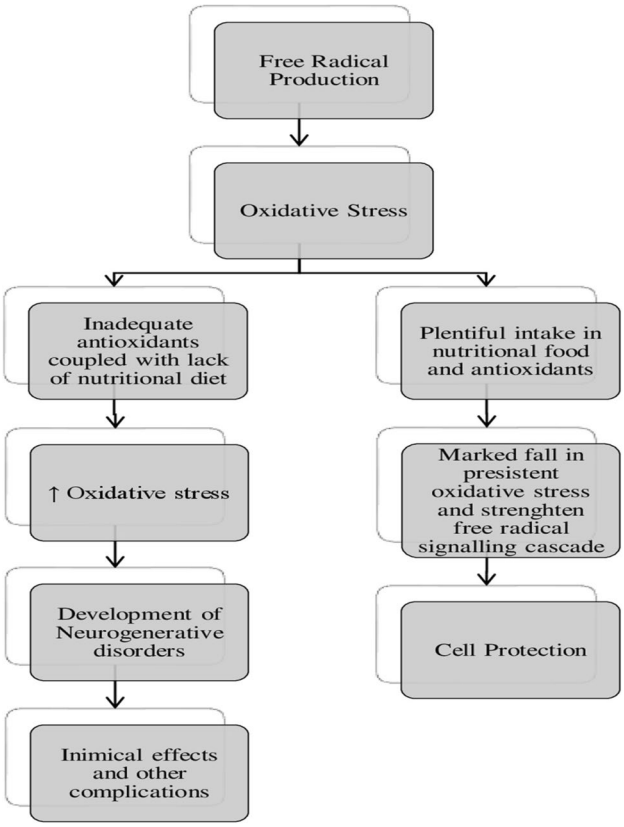


Fig. 5 Antioxidant role in neurodegenerative diseases (Adwas et al. 2019)

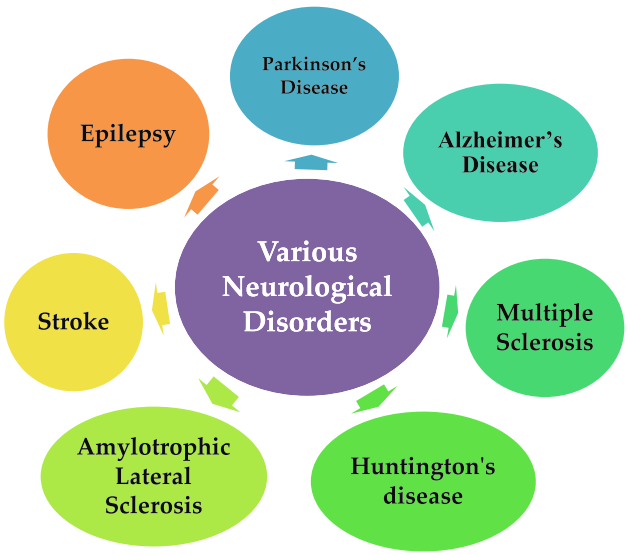


Fig. 6 Different types of neurological disease (Mattson 2004)

suffering from this disease is low than that of males (Bose and Beal 2016). The high estrogen concentration is the reason why mainly females are not affected by this disease (Hirsch et al. 2016). Post-mortem research showed various pieces of evidence which demonstrated that the multiple processes are mainly due to factors like mitochondrial dysfunction, oxidative stress, and neuroinflammation (Esteves et al. 2009).

The significant accumulation of iron in the SN of a PD patient provides additional support to the oxidative stress in DA neuron loss (Hirsch et al. 1991; Dexter et al. 1989; Sofic et al. 1988). There are various ways by which iron can generate oxidative stress, and its ability to take part in the Fenton reaction to produce the hydroxyl radicals is considered to be the most prominent of all (Bharath et al. 2002). Mitochondrial dysfunction is said to be a significant risk factor in Parkinson's disease. All these conditions like mitochondrial dysfunction and protein aggregation promote oxidative stress and contribute to a loss of neurons. These processes generally do not have a cascade relation but are correlated cyclically, oxidative stress being the major component of all. According to the central role of mitochondrial dysfunction and oxidative stress in causing PD, antioxidant therapy is considered a significant cure for PD. Various neurotoxin-based animal models are often raised in evaluating the therapeutic agent efficacy in PD. The sensory and motor impairment similar in PD patients can be observed in these animal models which experience a generation of DA neurons (Bové et al. 2005; Terzioglu and Galter 2008).

There are various antioxidants including vitamin C, vitamin E, creatine, iron chelators, and melatonin, which can be used against PD. "Vitamin E" basically acts as a scavenger for various reactive oxygen species and therefore inhibits lipid peroxidation. The vitamin E supplements given to the animal models of PD showed contradictory results. Still, the chemical trials were undergone in the same way. The results showed that administration of **vitamin E** reduced the disease progression in the patients (Fahn 1992).

The neuroprotective action of "Coenzyme Q_{10}" has been shown in various in vivo models of PD. Protection against MPTP-induced DA neural loss by CoQ_{10} was observed in various mice (Behl et al. 1994). These trials were even passed in monkeys (Horvath et al. 2003); further several clinical trials were conducted.

1. **Creatine**: These are strong pieces of evidence that suggest the antioxidant property of creatine. It generally possesses neuroprotective properties and helps in reducing mitochondrial dysfunction. It is used in in vitro models of neurodegenerative diseases like PD (Beal 2011).
2. **Iron chelators**: The accumulation of iron in SN of patients of PD can be treated by using iron chelators. Various preclinical studies have been successfully designed using iron chelators as a therapeutic agent (Weinreb et al. 2013).
3. **Melatonin**: In vivo studies relevantly showed the antioxidant properties of melatonin. The neuronal degeneration in the nigrostriatal pathway was prevented on the administration of melatonin in various MPTP-based mouse models of PD (Antolin et al. 2002). 6-OHDA animal model of PD also depicts its neuroprotective action (Dabbeni-Sala et al. 2001).

Alzheimer's disease (AD)

Alzheimer's disease (AD) is the most common neurological disorder which causes dementia frequently and affects middle- and old-aged people generally above 85 years. Alzheimer's disease must be distinguished from other factors of dementia which include Parkinson's disease with dementia, dementia with Lewy bodies, vascular dementia, reversible dementia, and frontotemporal dementia (Feng and Wang 2012; Castellani et al. 2010). Nearly 65–75% of all dementia cases are constituted in AD. The incidence of AD generally increases with age 65–69, 75–79, 80–84, 85, and older which has been estimated at 0.6%, 1.0%, 2.0%, 3.3%, and 8.4% (Hebert et al. 1995). There are various factors like germline mutations, genetic factors, lifestyle-related factors, environmental factors, and other health-related factors which cause oxidative stress in patients with AD (Gharib 2016). The AD patients are affected by oxidative stress at 4 stages proteins, nucleic acids, lipids, and enzymes (Sroka and Cisowski 2003). The increased levels of protein oxidation may be caused by the increased nitrative stress in patients with Alzheimer's disease (Pankuweit et al. 2004). AD is characterized by loss functions of neurons and synapses as well as by extracellular Aβ plaque accumulation. An imbalance in the reactive oxygen species (ROS) leads to oxidative stress, and antioxidants are used as a defense mechanism that removes ROS (Harman 1981). All the reactive oxygen species (ROS) and reactive nitrogen species (RNS) are believed to contribute to the pathogenesis of many neurological disorders in humans (Jung et al. 2009). Generally, the mitochondria are considered to be the center of the production of reactive oxygen species (ROS). Therefore, in Alzheimer's disease, damage in the mitochondria and their dysfunction can be seen (Castellani et al. 2002). Although there is no such drug that can completely protect the neurons, there are two approaches for treating Alzheimer's disease. One approach for the treatment is preventing the onset of disease, and the other is by treating the tertiary cognitive symptoms of the disease. Antioxidant therapy is considered to be an important therapeutic strategy for the treatment of Alzheimer's disease as described in Figure 7. It has been observed that various antioxidants like vitamin E, vitamin C, lipoic

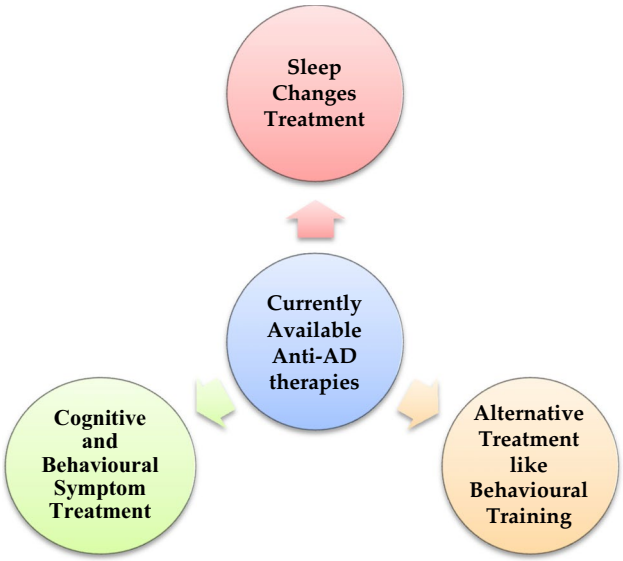


Fig. 7 Anti-AD therapies currently available (Bjelakovic et al. 2007)

acid, and β-carotene help in the breakdown of the intracellular and extracellular superoxide radicals.

Many anti-cholinesterase-based therapies provide symptomatic relief, and the development of novel interventions targeting oxidative stress has been considered as anti-AD therapy. Based on the mechanism of action, the antioxidant therapy for AD has been divided into 3 types:

- The metal chelators, glutathione peroxidase, and metal chelators are the preventive antioxidants.
- Vitamin E, vitamin C, and β-carotene are the free radical scavengers.
- Proteases, SOD enzymes, lipases, etc. are the repair enzymes.

Other antioxidants like melatonin, curcumin, α-lipoic acid, omega-3, and PUFA are generally non-specific (Sridevi et al. 2018).

Multiple sclerosis (MS)

Multiple sclerosis is typically a complex neurological disorder in pathophysiology in which various conditions like oxidative stress, disruption of the blood-brain barrier, demyelination, remyelination, and chronic inflammation can be observed. The block of impulse conduction and the permanent inflammation processes lead to axon demyelination. The pathogeneses of multiple sclerosis have not been exactly known, but they are characterized as an inflammatory demyelinating disease (Miller et al. 2013; Bielekova and Martin 2004; Ohl et al. 2016; Bendszus et al. 2013). Based on the clinical trials on MS in 1996, the National Multiple Sclerosis Society (NMSS) Advisory Board defined 4 clinical types of MS:

- Relapsing-remitting (RR)
- Secondary progressive (SP)
- Primary progressive (PP)
- Progressive relapsing (PR) (Lublin and Reingold 1996)

Oxidative stress is considered to be the major factor responsible not only for the cell damage in CNS aging and chronic inflammation but also in the vascular and neurological disorders involving all stages of MS. Generally, the ROS and RNS are found to be present in high amounts in the CNS of MS patients specifically in the brain cells including microglia, activated macrophages, and osteocytes. In oxidative stress, generally, the mitochondrial functioning is interrupted by altering the respiratory chain components (Nita and Grzybowski 2016).

In many studies, it has been observed that antioxidant therapy is the effective treatment for multiple sclerosis (MS) as shown in Table 4. There are various dietary supplements and other plant products which constitute the components having antioxidant properties. The antioxidants used in the MS treatment include vitamin D, melatonin, curcumin, omega-3-PUFAs, flavonoids, and β-glucan (Miller et al. 2019).

Huntington's disease

Huntington's disease is an acquired triplet repeat disease where Huntington's (Htt) protein's polyglutamine tract is dilated from below 30 to 200 residues of tandem glutamines (Walker 2007). This disease mainly objects to the cautious loss of medium spiny neurons of the caudate nucleus (Kamat et al. 2008). The Huntingtin (Htt) mutant persuades degeneration which involves gaining toxic functions and loss of neurotrophic functions (Leavitt et al. 2006). The prior preclinical studies of Huntington's disease, yet employed in present, were injected intrastriatal with the 3-nitropropionic acid (3NP) which is a mitochondrial complex-2 inhibitor (Beal et al. 1986; Brouillet et al. 2005). After the findings of the Htt mutant gene product as the genetic reason of human HD, mice were introduced which were transgenic, and 150 counts of polyglutamine expansion were expressed with the first axon of mHtt. R6 model is the most common model employed of these animals (Li et al. 2005). Transgenic models with mHtt occurred from yeast artificial chromosomes (YAC) become popular (Van-Raamsdonk et al. 2007) as models like knock-in expressed mHtt form along with regional specificity (Menalled et al. 2003). For HD models on animals, antioxidant trials have been organized. Flint Beal's group introduced the quinolinic acid model

Table 4 Antioxidant therapy is the effective treatment for multiple sclerosis

S. no.	Compounds	Basic role in MS	References
1	Resveratrol	• Triggered apoptosis in activated T cells in the spinal cord reduces the inflammatory response, therefore the reduction in pro-inflammatory mediators	Singh et al. (2007)
2	Vitamin A	• The expression of Foxp3 in PBMCs and TGF-β PBMCs is increased	Saboor-Yaraghi et al. (2015)
3	Catechins	• The plasma oxidized LDL is reduced by 18%	Inami et al. (2007)
4	Curcumin	• CNS inflammatory cell infiltration is decreased • Gene expression of TGF-β, interleukins, STAT3 in the spinal cord is suppressed • Phosphorylation of STAT3 in Jurkat T cells is inhibited • MBP-specific T cell responses are inhibited • Demyelination and CNS inflammation are decreased	Xie et al. (2009); Natarajan and Bright (2002)
5	Melatonin	• The concentration of MDA in erythrocytes is decreased, and that of SOD and GPx is increased	Rathnasamy et al. (2014)
6	β-Glucan	• The phagocytic activity and phagocytic index are increased • The level of triglyceride glucose concentration and total cholesterol is decreased	Salim et al. (2011)

of Huntington's disease and came into consideration that antioxidants like vitamin E, beta-carotene, or ascorbic acid did not protect against the quinolinic-induced striatal neurotoxicity (Beal et al. 1988). A productive therapeutic control was seen by NMDA receptor antagonists which have shown some benefits. After the investigations are done by the Beal group, it was found that mitochondrial enzyme cofactor lipoic acid and thiol antioxidant improved the survival in transgenic mouse models (Andreassen et al. 2001). In aged rats, 3NP-induced deficiency of stratum energy is provided by vitamin E plus coenzyme Q10, suggested by recent work (Kašparová et al. 2006). High doses of coenzyme Q10 increased the life span of R6/2 mice (Smith et al. 2006). The therapy which is done only with antioxidants may not be productive because damaging one part may not be enough to control the disease. Various methods of therapy may be needed to halt the disease. For example, potent antioxidants combined usage of N-methyl D-aspartate (NMDA) and non-NMDA receptor antagonists, apoptosis inhibitors, and calcium channel blockers which act centrally (Delanty and Dichter 2000). Two types of antioxidants are used in therapies for Huntington's disease, which are enzymatic and non-enzymatic antioxidants. Enzymatic antioxidants are those types that include defense mechanisms against free radicals. These mainly consist of catalase, superoxide dismutase, and glutathione peroxidase. On the other hand, non-enzymatic antioxidants include alpha-tocopherol which is also known as vitamin E, ascorbic acid also called vitamin C, retinoic acid, flavonoids, and carotenoids.

Alpha-tocopherol (vitamin E) therapeutic approach is that it is a lipid-soluble antioxidant, which helps in the prevention of oxidation from the cell membrane. It acts by a pathway called as glutathione peroxidase pathway (Miyamoto et al. 1989).

Creatinine is another antioxidant that plays a vital role in buffering of energy between the cells in co-occurrence with phosphocreatine; this antioxidant is efficacious in opposition to hydroxyl radicals, peroxynitrite, and superoxide.

Coenzyme Q10 is present on the membrane of mitochondria which helps in the reduction of singlet oxygens which further prevents oxidation of protein and mitochondrial bases. A combination of both coenzyme Q10 and creatine shows the productive result and is referred to as powerful antioxidants.

Lipoic acid is an important cofactor of the enzyme network of mitochondrion which results in pyruvate decarboxylation.

Melatonin is an antioxidant that is formed by the pineal gland inside the body. This particular antioxidant acts by showing scavenging activity by protecting lipids, proteins, DNA, and mitochondrion. It also results in the inhibition of NOS (Johri and Beal 2012).

A catalytic antioxidant that contains metals is known as **metalloporphyrin**. This antioxidant has a scavenging activity which means it scavenges reactive oxygen species (Petersén et al. 2000).

An antioxidant that is potent and is acquired exogenously is called **ascorbic acid** or vitamin C. This helps in oxidizing it to dehydroascorbic acid (Majewska and Bell 1990).

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is the disease in which degeneration of neurons occurs by a disturbance in the oxidative metabolism and also by the oxidative stress being expanded (Rosen et al. 1993; Beal et al. 1997). ALS undergoes pathogenesis in some particular forms where mutation occurs in the superoxide of the copper-zinc dismutase gene

(Delanty and Dichter 2000). ALS is also known as motor neuron disease which means that it is a fatal disorder and disabled excessively. Antioxidants are utilized for the treatment of amyotrophic lateral sclerosis – vitamin C, vitamin E, selenium, coenzyme Q10, and selegiline (Orrell et al. 2007). In this type of disease, skeletal muscles lost their functional ability resulting in having difficulty while walking, running, speaking, or working. This disease's course is variable but generally rapid with the norm period from the very first symptom to the symptom of disorders leading to death which occurs in about 3.5 years. Death usually occurs due to the failure of the respiratory tract (Mitchell et al. 1993). This disease particularly occurs in individuals who belong to ethnic origins. Females are less prominent to this disease whereas males are affected more by ALS. Mainly, this disease occurs in individuals between the age of 50 and 70 years (Sejvar et al. 2005). Amyotrophic lateral sclerosis has been caused by various unknown reasons, but some individuals acquire this disease due to inheritance. About 5 to 10% of people are affected due to family history. The main cause of this disease is the mutation of superoxide of copper-zinc dismutase gene which can occur in both rare or family cases (Rosen et al. 1993). This disease has recent treatment options which include "riluzole" which has a little beneficial effect in the decreasing of propagation of the disease and the survival rate is being increased (Miller et al. 2004). Death of neurons in this disease is occurred by accumulations of free radicals which resulted from oxidative stress (Bergeron et al. 1996). These free radicals are neutralized by the various enzymes which are part of antioxidants. Those antioxidant enzymes include catalase, superoxide dismutase, and glutathione peroxidase. Also, it is neutralized by nutrient antioxidants which are vitamin C, vitamin E, flavonoids, uric acid, taurine, and carotenes (Sardesai 1995). There are some biological agents which have antioxidant activity. For example, vitamin C and vitamin E are normally prescribed by the doctor to patients suffering from amyotrophic lateral sclerosis.

More often, medicaments which are antioxidants and are used in **amyotrophic lateral sclerosis** disease include the following:

- Ascorbic acid (vitamin C)
- Alpha-tocopherol (vitamin E)
- L-deprenyl (selegiline)
- N-acetylcysteine

Vitamin C: It is also known as ascorbic acid. This type of antioxidants mainly occurred naturally, and these are normally prescribed to take it through oral administration (Orrell et al. 2008).

Vitamin E: This is also known as alpha-tocopherol. This type of antioxidant is also a naturally occurring component. It is also recommended to take it through the oral route. After the oral administration, this particular antioxidant crosses the blood-brain barrier slightly (Halliwell 2001).

L-deprenyl: This type of antioxidant is also known as selegiline which is the type of antioxidant that is usually monoamine oxidase (Knoll 1989).

N-acetylcysteine: It is the antecedent of glutathione which is a natural antioxidant occurring intracellularly (Louwerse et al. 1995).

Stroke

Stroke disease arises from the interruption of blood flow in the cerebral part by cerebral artery occlusion. This results in the dysfunction of the cells or damage which is irreversible. The acute ischemic stroke is treated by reperfusion therapy along with recombinant tissue plasminogen activator (rt-PA) (Shirley et al. 2014). Acquired adult disability is caused by stroke disease (Murray et al. 2012). The only pharmacological invention approved for this thrombolytic disease is given intravenously rt-PA within the time of 4.5 h during the ischemic onset (Li et al. 2013). The therapeutic window of this intervention is about 2% to 5% of all the patients with stroke (Adeoye et al. 2011). Endogenous antioxidants which show a defense mechanism that balances are ROS which is being produced continuously. After the injury had taken place in the cerebral area, the free radical formation has been increased to a greater extent which results in the disequilibrium of redox in the antioxidant system which is endogenous: mechanisms of detoxification are basically inactivated, and overproduction of oxidants also occurred. There will be an increase in the level of ROS after the ischemia occurred in the cerebral area which would result in oxidative stress and injury of neurons. This would make the free radicals a target of therapeutic effect (Facchinetti et al. 1998).

Antioxidants work by three strategies:

1. Formation of free radicals is being inhibited.
2. Formation of free radicals is being scavenged.
3. Degradation of free radicals is being increased (Margaill et al. 2005).

Formation of free radicals is being inhibited

ROS promoting disease generation is done by various inhibitors of ROS generating enzymes. NADPH oxidases (NOXs) are the source of the production of ROS in cerebral reperfusion injury (Tang et al. 2007). The NADPH oxidase inhibition with apocynin which is a pharmacological agent

and is before the reperfusion (Genovese et al. 2011). I/R injury upregulation is shown by various homologues of NOX with NOX2 and NOX4 (McCann et al. 2008).

Formation of free radicals is being scavenged

Some compounds are developed which are capable of scavenging the free radicals which are used for the treatment of stroke in the cerebral area, whereas translation to the clinical trials from pre-clinical trials is being disappointing largely. One of those compounds is known as "tirilazad mesylate" which is an inhibitor of lipid peroxidation (Park and Hall 1994; Xue et al. 1992). The efficiency of this treatment was maximum when it was given before focal ischemia. This drug was given within the period of 6 h of the onset (Ranttas 1996). It was found that tirilazad metabolizes up to 60% in women more than that in men (Fleishaker et al. 1995).

Degradation of free radicals is increased

Oxidative stress is being reduced by rising levels of antioxidants in stroke. Glutathione peroxidase inhibitor is ebselen which is used in improving damage and neurological deficit (Namura et al. 2001; Imai et al. 2001). The antioxidant approach which is a novel approach is called gas inhalation. For example, inhaling hydrogen gas shows beneficial effects (Ohsawa et al. 2007).

Epilepsy

Epilepsy is a neurological disorder that is characterized by seizures. In this disease, neurodegeneration occurs due to oxidative stress, which is the propagating factor. In this disorder, disturbance of the antioxidant system balance has been noted, and reactive species production has been increased. If we treat the patient with antioxidants during the process of epilepsy, that could lead to reduced structural damages which are severe, also reducing epileptogenesis (Martinc et al. 2014).

Antioxidants used for the epilepsy are of two types:

- Endogenous antioxidants
- Exogenous antioxidants

Endogenous antioxidants: These antioxidants and those which are the result of metabolic them in the body. These antioxidants are alpha-lipoic acid, melatonin, and ubiquinone (Militão et al., 2010).

Alpha-lipoic acid: It is a cofactor that is crucial for the mitochondrial enzymes and also an important natural antioxidant (Maczurek et al. 2008). Pre-treatment with LA was done and resulted in decreasing content of nitrite as well as the level of lipid per oxidation (Bellissimo et al. 2001). It was demonstrated that LA treatment reduces oxidative metabolism in the brain, and it helps in preventing seizures triggered by pilocarpine (Mesulam et al. 2002).

Melatonin: A pineal hormone is called melatonin which functions to regulate the rhythm of circadium (Gupta et al. 2003). This antioxidant shows potent activity by scavenging the components like free radicals and hydroxyl (Mori et al. 2004). Melatonin was observed to suppress the epileptic seizures occurring in rats. Various protective functions have been shown by melatonin; therefore, it has been a neuroprotective agent (Mevissen and Ebert 1998).

Ubiquinone: This is a very potent antioxidant that is found to be highly reactive with ROS which results in the prevention of cell's free radicals which induces oxidative damage (Geromel et al. 2002). This antioxidant shows effects like neuroprotecting effects in epileptic models which are induced with pilocarpine. Ubiquinone is utilized as an effective antioxidant for epilepsy treatment for both the functions that are protecting against oxidative damage occurred to seizures and for reducing the severity of seizures (Tawfik 2011).

Exogenous antioxidants: These types of antioxidants are those which are taken from our diet by taking supplements or by having antioxidant-rich foods. These types of antioxidants are the following:

- Ascorbic acid (vitamin C)
- Curcumin
- Epigallocatechin (EGCG)
- N-acetylcysteine-thiol–containing compounds
- Resveratrol

Ascorbic acid: It is also known as a vitamin C antioxidant, which is a potent water-soluble antioxidant, which results in the reduction of oxidants which are harmful (Padayatty and Levine 2001). Ascorbic acid was noted to reduce their epileptic convulsions which are evoked by ferric chloride or by administration of penicillin (Yamamoto et al. 2002; Ayyıldız et al. 2006).

Curcumin: This antioxidant shows a great effect of scavenging ROS and RNS because it possesses anti-apoptotic properties and antioxidative properties. It is used as an add-on therapy that is found to improve cognitive functions as well as controlling seizures (Shin et al. 2007).

Epigallocatechin: Treatment with EGCG shows the results of decreasing the meantime of the seizure phase and has resulted in the arising time of latent period before tonic-clonic seizures. It might reduce oxidative stress (Xie et al. 2012).

N-acetylcysteine-thiol–containing compounds: Thiol-containing compounds are similar to the antioxidant glutathione. This function of antioxidant arises from thiol groups reducing function. It can reduce epileptogenesis (Rowles and Olsen 2012).

Resveratrol: It is an antioxidant compound that is aromatic. Its antioxidant activity arises from its ability to delocalize the electrons which are unpaired (Murias et al. 2005).

Other health benefits

Antioxidants play a vital role in providing health benefits to patients suffering from diseases other than those mentioned above. It shows beneficial effects in atherosclerosis which is an inflammatory disorder. In this type of disease, antioxidants that are useful for the treatment are of two types, that is, endogenous antioxidants and exogenous antioxidants. The endogenous antioxidants include glutathione, glutathione peroxidase, and catalase, whereas exogenous antioxidants include vitamin C, vitamin E, and polyphenols (Malekmohammad et al. 2019).

In cancer disease, oxidative stress is very much high in cancer cells than in normal cells. So, to reduce the oxidative stress within the body, antioxidants are being used. By the use of vitamins like vitamin C and vitamin E, the adverse effects of the disease can be reduced.

Antioxidants also play a vital role in cardiovascular diseases like heart failure, hypertrophy, cardiomyopathy, atherosclerosis, cardiac hypertrophy, cardiomyopathy, and ventricular modeling, reactive oxygen species is originated when the oxidative stress is in excess. In these types of diseases, normal physiology is not maintained due to the excess oxidative stress in the body. So, to reduce this type of oxidative stress, antioxidants are given as supplements which include coenzyme Q10, beta-carotene, resveratrol, and lycopene (Sridevi et al. 2018).

Ischemia reperfusion is the disease in which myocardium damage occurs. To treat this injury, myocardial antioxidants are used. Some of them are used as primary defense mechanisms, and some are used for the secondary role of attenuating the injury. The antioxidants which are used for primary defense function are known as catalase, glutathione peroxidase, and superoxide dismutase, whereas for secondary purposes, vitamin E may be used to attenuate the injury (Dhalla et al. 2000).

Conclusion

Oxidative stress and damage to the cellular components can be managed by using antioxidant therapy. Various antioxidants and their supplements are found to act against different neurological diseases. They have a great potential in treating various diseases like cancer, atherosclerosis, Parkinson's disease, epilepsy, stroke, and Alzheimer's disease. Therefore, the intake of dietary supplements containing antioxidants can help to recover from these types of diseases. Antioxidants like vitamin E, vitamin C, carotenoids, and melatonin help in preventing premature aging and in the treatment of various diseases. Vegetables, fruits, nuts, spices, and herbs are the rich sources of these antioxidants, and their proper consumption helps to prevent and treat many disorders by reducing oxidative stress and preventing cellular damage.

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