Chapter

A Review on Natural Antioxidants

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Abstract

Free radicals and related species have attracted a great deal of attention in recent years. Oxidative stress has been considered a major contributory factor to the diseases. They are mainly derived from oxygen (reactive oxygen species (ROS)) and nitrogen (reactive nitrogen species (RNS)) and are generated in our body by various endogenous systems and exposure to different physicochemical conditions or pathophysiological states. Free radical damage to protein can result in loss of enzyme activity. There are epidemiological evidences correlating higher intake of components/foods with antioxidant abilities to lower incidence of various human morbidities or mortalities. The sources and origin of antioxidants which include fruits and vegetables, meats, poultry, and fish were treated in this study. The classification and characteristics of antioxidant, its measurements and level in food and free radicals, were also documented. The chemistry of antioxidants which includes chain reactions, molecular structures, food antioxidants and reaction mechanisms, biochemical activity, therapeutic properties, and future choice of antioxidants was reported in this review.

Keywords: antioxidants, free radicals, oxidative stress

1. Introduction

Plants such as shrubs, herbs, or trees in parts or in whole were used in the treatment and management of various diseases, and disorders can be dated long back. Natural phytochemicals present at low levels in fruits, vegetables, herbs, and spices offer many health benefits, but these compounds may not be effective or safe when consumed at higher dose [1]. The presence of free radicals in biological materials was discovered less than 50 years ago [2].

Pollutants, ionizing radiation or UV light, smoking, exposure of biological systems to xenobiotics, and development of certain pathological conditions lead to oxidative stress, thereby increases production of oxy radicals [3]. Cell damage caused by free radicals appears to be a major contributor in aging and degenerative diseases such as cancer, cardiovascular disease, cataracts, rheumatoid arthritis, and brain dysfunction. Free radicals have been implicated in the pathogenesis of at least 50 diseases. Fortunately, free radical formation is controlled naturally by various beneficial compounds and antioxidants, and its availability is limited that this damage can become cumulative and debilitating. Antioxidants are capable of stabilizing, deactivating, or scavenging free radicals before they attack cells.

Reactive species	Symbol	Half-life (in seconds)	Reactivity/remarks
Reactive oxygen species			
Superoxide	$O_2^{\bullet}$	10^{-6} s	Generated in mitochondria, in cardiovascular system, and others

Hydroxyl radicle	$^{*}OH$	10^{-9} s	Very highly reactive, generated during iron overload and such conditions in our body
Hydrogen peroxide	H_2O_2	Stable	Formed in our body by a large number of reactions and yields potent species like. OH
Peroxyl radical	ROO*	S	Reactive and formed from lipids, proteins, DNA, sugars, etc. during oxidative damage
Organic hydroxide	ROOH	Stable	Reactive with transient metal ions to yield reactive species
Singlet oxygen	$^{1}O_2$	10^{-6} s	Highly reactive, formed during photosensitization and chemical reactions
Ozone	O_3	S	Present as an atmospheric pollutant can react with various molecules
Reactive nitrogen species			
Nitric oxide	NO*	S	Neurotransmitter and blood pressure regulator can yield potent oxidants during pathological status
Peroxy nitrile	$ONOO^-$	10^{-3} s	Formed from nitric oxide and superoxide and highly reactive
Peroxynitrous acid	ONOOH	Fairly stable	Protonated from of $ONOO^-$
Nitrogen dioxide	NO_2	S	Formed during atmospheric pollution

Antioxidants can be defined as substances whose presence in relatively low concentrations significantly inhibits the role of oxidation of the targets. Due to continuous generation of partially reduced forms of oxygen by constitutive metabolic pathways, a number of protective antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSHPx), glutathione reductase (GSHRx), glutathione-S-transferase (GST), and nonenzymatic antioxidants, have involved to deal with toxic species. Oxidation is a chemical reaction that transfers electrons from a substance to an oxidizing agent. Oxidation reactions can produce free radicals, which start chain reactions that damage cells. Antioxidants terminate these chain reactions by removing free radical intermediates and inhibit other oxidation reactions by being oxidized themselves. Antioxidants are often reducing agents such as thiols, ascorbic acid, or polyphenols.

1.1 Sources and origin of antioxidants

Antioxidants are abundant in fruits and vegetables, as well as in other foods including nuts, grains, and some meats, poultry, and fish. β-Carotene is found in many foods, including sweet potatoes, carrots, cantaloupe, squash, apricots, pumpkin, and mangoes. Lutein, best known for its association with healthy eyes, is abundant in green, leafy vegetables such as collard greens, spinach, and kale. Lycopene is a potent antioxidant found in tomatoes, watermelon, guava, papaya, apricots, pink grapefruit, blood oranges, and other foods. Estimates suggest 85% of American dietary intake of lycopene comes from tomatoes and tomato products [4].

1.1.1 Types of antioxidants

Antioxidants are grouped into two:

1. Primary or natural antioxidants

2. Secondary or synthetic antioxidants

1.1.1.1 Primary or natural antioxidants

They are the chain breaking antioxidants which react with lipid radicals and convert them into more stable products. They are mainly phenolic in structures and include the following [5]:

1. Antioxidant minerals: These are cofactor of antioxidants enzymes. Their absence will definitely affect metabolism of many macromolecules such as carbohydrates. Examples include selenium, copper, iron, etc.

2. Antioxidant vitamins: They are needed for most body metabolic functions. They include vitamin C, vitamin E, and vitamin B.

3. Phytochemicals: These are phenolic compounds that are neither vitamins nor minerals. These include:

Flavonoids: These are phenolic compounds that give vegetables fruits, grains, seeds leaves, flowers, and bark their colors. Catechins are the most active antioxidants in green and black tea and sesamol. Carotenoids are fat soluble color in fruits and vegetables. Zeaxanthin is high in spinach and other dark greens.

1.1.1.2 Secondary or synthetic antioxidants

These are phenolic compounds that perform the function of capturing free radicals and stopping the chain reactions; the compound includes [5]:

1. Butylated hydroxyanisole (BHA)

2. Butylated hydroxytoluene (BHT)

3. Propyl gallate (PG) and metal chelating agent (EDTA)

4. Tertiary butylhydroquinone (TBHQ)

5. Nordihydroguaiaretic acid (NDGA).

2. Classification

- **Enzymatic antioxidants:**

  1. Primary antioxidants, for example, SOD, catalase, glutathione peroxidase

  2. Secondary enzymes, for example, glutathione reductase, glucose-6-phosphate dehydrogenase

- **Nonenzymatic antioxidants:**

  1. Minerals, for example, zinc, selenium

  2. Vitamins, for example, vitamin A, vitamin C, vitamin E

  3. Carotenoids, for example, β-carotene, lycopene, lutein, zeaxanthin

4. Low-molecular weight antioxidants, for example, glutathione, uric acid

5. Organosulfur compounds, for example, allium, allyl sulfide, indoles

6. Antioxidant cofactors

7. Polyphenols

2.1 Enzymatic antioxidants

2.1.1 Copper/zinc and manganese dependent

Superoxide dismutase (SOD): SOD is a group of endogenously produced metalloenzymes with various prosthetic groups present both in prokaryotes and eukaryotes [6]. Three main classes of them differ in their amino acid sequence structure and metallic factors as follows:

1. Cu-Zinc SOD in the cytoplasm with two sub-units and sensitivity to cyanide and hydrogen peroxide.

2. Mn SOD in the mitochondrial matrix and in prokaryotes and is insensitive to cyanide.

3. Fe SOD, usually found in prokaryotes and in the chloroplasts of some plants. It is not sensitive to cyanide but is inhibited by hydrogen peroxide.

4. Al SOD has recently reported [7].

Catalase: H_2O_2 is also metabolized by catalase (CAD), a heme protein with an extremely high turnover rate

$$2\,H_2O_2 \rightarrow 2\,H_2O + O_2$$

SOD protects from senescence, aging, ischemic tissue damage, lipid peroxidation, protein denaturation, and radiation damage.

Glutathione peroxidase: Glutathione carries out the reduction of H_2O_2 which is enzymatic reaction catalyzed by GPx, found in vacuole, cystol, and extracellular space. The enzyme has substrate specificity. Peroxidases are involved in (1) biotic and abiotic stresses, (2) lignin and suberin synthesis, and (3) disease and pathogen response [8].

$$2\,GSH + H_2O_2 \rightarrow GSSG + 2\,H_2O$$

Consequence of H_2O_2 accumulation in glucose-6-phosphate dehydrogenase deficiency due to malarial drug primaquine results in hemolytic anemia due to oxidative stress.

Glutathione reductase: Glutathione keeps cysteine thiol groups in the reduced state. If two thiol groups become oxidized, they can be reduced nonenzymatically by glutathione. GSSG is reduced by NADPH-dependent enzyme glutathione reductase.

$$GSSG + NADPH + H \rightarrow 2GSH + NADP^{+}$$

Glutathione-S-transferases: Through the action of this widely distributed enzyme, glutathione participates in detoxification of xenobiotics or foreign organic compounds.

Glutathione: Glutathione is a tripeptide that is present in high concentrations in most eukaryotic cells and reacts with free radicals. It directly quenches lipid peroxides. Vitamin C and glutathione work interactively [9].

2.2 Nonenzymatic antioxidants

These are biological molecules that can act as antioxidants by either quenching a free radical directly or indirectly by promoting a process responsible for radical scavenging indirectly [10].

a. **Selenium:** Selenium is a mineral and a component of antioxidant enzymes. Rice and wheat are the major dietary sources of selenium. The amount of selenium in soil, which varies by region, determines the amount of selenium in the foods grown in that soil. Animals that eat grains or plants grown in selenium-rich soil have higher levels of selenium in their muscle. Brazil nuts also contain large quantities of selenium.

b. **Transferrin:** Transferrin is a major iron transporting protein in the body. It is normally 20–30% loaded.

c. **Lactoferrin:** Lactoferrin is a milk protein similar to transferrin that helps in iron binding.

d. **Ceruloplasmin:** Ceruloplasmin catalyzes the oxidation of Fe^{++} to Fe^{+++}, while oxygen is reduced to water.

e. **Vitamin A:** Vitamin A is found in three main forms: retinol (vitamin A1), 3,4-didehydroretinol (vitamin A2), and 3-hydroxyretinol (vitamin A3). Foods rich in vitamin A include liver, sweet potatoes, carrots, milk, egg yolks, and mozzarella cheese.

f. **Vitamin C (ascorbic acid):** In the aqueous phase, ascorbic acid may reduce reactive oxygen metabolites directly, with the concurrent formation of dehydroascorbate and/or indirectly by the regeneration of tocopherol from the tocopherol radical [11]. Vitamin C can be found in high abundance in many fruits and vegetables and is also found in cereals, beef, poultry, and fish.

g. **Vitamin E:** Vitamin E, also known as alpha-tocopherol, is found in almonds and oils, including wheat germ, safflower, corn, and soybean oils, and is also found in mangoes, nuts, broccoli, and other foods [12]. It reacts with reactive oxygen metabolites, yielding lipid hydroperoxide, which can be removed by the activity of the phospholipase-GSPHx system.

h. **β-Carotene:** β-Carotene is a lipid-soluble precursor of vitamin A. It functions synergistically with tocopherol to prevent lipid peroxidation.

i. **Ubiquinol-10:** It is a reduced form of coenzyme Q10, present in lipoprotein at relatively low concentrations. It probably regenerates tocopherol from the tocopheroxyl radical and increases its antioxidant efficiency.

2.3 Plant-derived antioxidants

To protect the cells and organ systems of the body against ROS, humans have evolved a highly sophisticated and complex antioxidant protection system. It involves a variety of components, both endogenous in origin, that function interactively and synergistically to neutralize free radicals [13].

These components include:

Nutrient-derived antioxidants like ascorbic acid, tocopherols and carotenoids, and other low-molecular weight compounds such as GSH and lipoic acid.

Antioxidant enzymes, for example, SOD, GSHPx and GSH reductase, which catalyze free radical quenching reactions.

Metal-binding proteins such as ferritin, lactoferrin, albumin, and ceruloplasmin that sequester free iron and copper ions as these ions are capable of catalyzing oxidative reactions.

Numerous other antioxidant phytonutrients present in a wide variety of plant foods.

3. Antioxidant operation and mechanisms

The word antioxidant is used in a general sense to refer to any type of chemical agent which inhibits attack by oxygen or ozone [14]. As applied to vegetable oils, antioxidants are compounds which interrupt the oxidation process by preferentially reacting with the fat radical to form a stable radical which does not quickly react with oxygen [15]. Antioxidants function either by inhibiting the formation of free alkyl radicals in the initiation step or by interrupting the propagation of the free radical chain. In truncating the propagation step, the antioxidants function as hydrogen donors. Generally, the most popular antioxidants are hydroxyphenol compounds with various ring substitutions. The antioxidant radical is stabilized with its local electrons delocalized; hence antioxidant free radicals do not readily initiate other free radicals. They rather even react with lipid free radicals to form stable and complex compounds. In investigating phenolic antioxidants, it is found that their antioxidative capabilities bear a relationship to the number of phenol groups occupying 1,2 or 1,4 positions in an aromatic ring as well as to the volume and electronic characteristics of the ring substituents present [16]. In elucidating the mechanism of oxidative inhibition, it is generally established that antioxidants function as oxygen interceptors in the oxidative process thereby breaking the chain reaction that perpetuates the process [17]. The general scheme is presented below:

$$R + AH \rightarrow RH + A$$

$$RO + AH \rightarrow ROH + A$$

$$ROO + AH \rightarrow ROOH + A$$

$$R + A \rightarrow RA$$

$$RO + A \rightarrow ROA$$

$$ROO + A \rightarrow ROOA$$

$$\text{Antioxidant} + O_2 \rightarrow \text{Oxidized antioxidant}$$

Certain metallic ions such as copper and iron act as prooxidants, catalyzing the oxidation process. Such metal ions can be sequestered or chelated by certain organic acids. They effectively contribute to lower transition metal activity. Examples of such compounds are citric acid, phosphoric acid, and some of their derivatives.

4. Estimation of antioxidants

4.1 Conjugated diene assay

This method allows dynamic quantification of conjugated dienes as a result of initial PUFA (polyunsaturated fatty acids) oxidation by measuring UV absorbance at 234 nm. The principle of this assay is that during linoleic acid oxidation, the double bonds are converted into conjugated double bonds, which are characterized by a strong UV absorption at 234 nm. The activity is expressed in terms of inhibitory concentration (IC_{50}) [17, 18, 19].

4.2 DPPH method (1,1 diphenyl-2-picrylhydrazyl)

This most widely reported DPPH assay method is based on the reduction of methanolic solution of colored free radical DPPH by free radical scavenger. The procedure involves measurement of decrease in absorbance of DPPH at its absorption maxima of 516 nm, which is proportional to concentration of free radical scavenger added to DPPH reagent solution. The activity is expressed as effective concentration EC_{50} [20].

4.3 Superoxide radical scavenging activity

In vitro superoxide radical scavenging activity is measured by riboflavin/light/NBT (Nitro blue tetrazolium) reduction. NBT method is based on generation of superoxide radical by auto-oxidation of riboflavin in presence of light. The superoxide radical reduces NBT to a blue-colored formazan that can be measured at 560 nm. The capacity of extracts to inhibit the color to 50% is measured in terms of EC_{50}. Antioxidant activity of *Ailanthus*, flavonoids, and triphala has been reported in terms of superoxide radical scavenging activity. The superoxide radical can also be detected by oxidation of hydroxylamine, yielding nitrite which is measured colorimetric reaction [21, 22].

4.4 Hydroxyl radical scavenging activity

This method involves in the in vitro generation of hydroxyl radicals using Fe^{3+}/ascorbate/EDTA/H_2O_2 system using Fenton reaction. Scavenging of this hydroxyl radical in presence of antioxidant is measured. In one of the methods, the hydroxyl radicals formed by the oxidation is made to react with DMSO (dimethyl sulphoxide) to yield formaldehyde. Formaldehyde formed produces the intense yellow color with Nash reagent (2 M ammonium acetate with 0.05 M acetic acid and 0.02 M acetyl acetone in distilled water). The intensity of yellow color formed by

that reaction is measured at 412 nm spectrophotometrically against reagent blank. The activity is expressed as % hydroxyl radical scavengering [21].

4.5 Nitric oxide radical inhibition activity

Nitric oxide, because of its unpaired electron, is classified as a free radical and displays important reactivities with certain types of proteins and other free radicals. In vitro inhibition of nitric oxide radical is also a measure of antioxidant activity. This method is based on the inhibition of nitric oxide radical generated from sodium nitroprusside in buffer saline and measured by Griess reagent. In presence of scavengers, the absorbance of the chromophore is evaluated at 546 nm. The activity is expressed as % reduction of nitric oxide [21].

4.6 Reducing power method

This method is based on the principle of increase in the absorbance of the reaction mixture, which indicates increase in the antioxidant activity. In this method, antioxidant compound forms a colored complex with potassium ferricyanide, trichloroacetic acid, and ferric chloride, which is measured at 700 nm. Increase in absorbance of the reaction mixture indicates the reducing power of the samples [23].

4.7 Phosphomolybdenum method

A spectroscopic method for the quantitative determination of antioxidant capacity, through the formation of phosphomolybdenum complex. The assay is based on the reduction of Mo (VI) to Mo (V) by the sample and subsequent formation of a green phosphate Mo (V) complex at acidic pH [24].

4.8 Peroxynitrite radical scavenging activity

Peroxynitrite is now recognized by researchers as the culprit in many toxic reactions. Hence, an in vitro method for scavenging of peroxy radical has been developed to measure antioxidant activity. The scavenging activity is measured by monitoring the oxidation of dihydrorhodamine on a microplate fluorescence spectrophotometer at 485 nm [25].

4.9 ABTS (2,2-azino-bis(3-ethyl benzothiazoline-6-sulfonic acid) diammonium salt) method

This is a measure of antioxidant activity. It also permits to distinguish between additive and synergistic effects. The assay is based on interaction between antioxidant and ABTS+ radical cation which has a characteristic color showing maxima at 645, 734 and 815 nm [24–26].

4.10 DMPD (N,N-dimethyl-p-phenylenediamine dihydrochloride) method

This assay is based on the reduction of buffered solution of colored DMPD in acetate buffer and ferric chloride. The procedure involves measurement of decrease in absorbance of DMPD in presence of scavengers at its absorption maxima of 505 nm. The activity was expressed as percentage reduction of DMPD [24–27].

4.11 Oxygen radical absorbance capacity (ORAC)

ORAC is an exciting and revolutionary new test tube analysis that can be utilized to test "antioxidant power" of foods and other chemical substances. It calculates the ability of a product or chemical to protect against potentially damaging free radicals. This analytical procedure measures the ability of a substance to act as an antioxidant. The test is performed using Trolox (a water-soluble analog of vitamin E) as a standard to determine the Trolox equivalent (TE). The ORAC value is then calculated from the Trolox equivalent and expressed as ORAC units or value. From this assay it shows the higher the ORAC value, the greater the "antioxidant power." In automated ORAC assay B-phycoerythrin (b-PE) was used as a target free radical damage, AAPH as a peroxy radical generator and Trolox as a standard control. After addition of AAPH to the test solution, the fluorescence is recorded, and the antioxidant activity is expressed as Trolox equivalent [28].

4.12 β-Carotene linoleate model

This is one of the rapid methods to screen antioxidants, which is mainly based on the principle that linoleic acid, which is an unsaturated fatty acid, gets oxidized by "reactive oxygen species" (ROS) produced by oxygenated water. The products formed will initiate the β-carotene oxidation, which will lead to discoloration. Antioxidants decrease the extent of discoloration, which is measured at 434 nm, and the activity is measured [24].

4.13 TRAP method

This method is defined as total radical trapping antioxidant parameter. The fluorescence of R-phycoerythrin is quenched by ABAP (2,2′-azobis(2-amidinopropane) hydrochloride) as a radical generator. The antioxidative potential is evaluated by measuring the delay in decoloration [29].

4.14 Cytochrome c test

Superoxide anions were assayed spectrophotometrically by a cytochrome reduction method described by McCord [6]. Xanthine oxidase converts xanthine to uric acid and yields superoxide anions which directly reduce ferricytochrome c to ferrocytochrome c, having an absorbance change at 550 nm. [30].

4.15 Erythrocyte ghost system

This method involves isolation of erythrocyte ghost cells and the induction of lipid peroxidation using them and the induction of tetra-butyl hydroxy peroxide (t-BHP). Thiobarbituric acid reactive substance (TBARS) produced during the reaction is measured at 535 nm [31].

4.16 Microsomal lipid peroxidation or thiobarbituric acid (TBA) assay

TBA test involves isolation of microsomes from rat liver and induction of lipid peroxides with ferric ions leading to the production of small amount of malondialdehyde (MDA). TBA reacts with MDA to form a pink chromogen, which can be detected spectrophotometrically at 532 nm [32].

5. The potential role of antioxidants in disease

5.1 Oxidative stress and diseases

5.1.1 Nephrotic syndrome

The nephrotic syndrome (NS) is defined by heavy proteinuria (urine total protein excretion greater than 3.5 g/d or total protein-creatinine ratio greater than 3.5 g/g) due to abnormal increase of glomerular permeability and following hypoalbuminemia, hyperlipidemia, and edema. Peroxidation of lipid membranes raises the concentration of their by-product MDA and the consequent lowering of antioxidants as a result of consumption [33]. The combined therapy of antioxidants, minerals with B complex vitamins for treatment of imbalance oxidant/antioxidant status, hyperhomocyst(e)inemia, and deficiency of copper and zinc in nephrotic syndrome patients.

5.1.2 Oxidative stress and neurodegenerative diseases

The brain is exposed throughout life to OS, and certain diseases of the brain and nervous system are thought to involve free radical processes and oxidative damage, either as a primary cause or as a consequence of disease progression.

1. **Alzheimer's disease:** Alzheimer's disease (AD) is a progressive neuropsychiatric disorder of unknown etiology. It is characterized by neuronal degeneration and cognitive deterioration, especially in the elderly [34]. OS has been implicated in the pathogenesis of AD [35] by the finding of several characteristics, such as enhanced lipid peroxidation, in specific areas of the brain in postmortem studies [36]. Several investigators detected an increase in the activity of catalase, superoxide dismutase, glutathione peroxidase, and glutathione reductase in the hippocampus and amygdale.

2. **Cognitive dysfunction in the elderly:** Cognitive impairment is a common problem in the over 65-year age group, progressing to its most devastating form of clinical dementia, usually Alzheimer's dementia, in about 5% of this population [37]. Goodwin noted a correlation between memory function and vitamin C in the blood of healthy volunteers aged 60 or over [38]. Accordingly, Perry found a positive association of memory performance with β-carotene and vitamin C levels in plasma measured twice [39].

3. **Parkinson's disease:** Data from postmortem studies of brains from patients with Parkinson's disease (PD) suggest that OS plays an important role in neural degeneration of the pigmented dopaminergic neurons in the substantia nigra pars compacta (SNpc) [40]. One of the suggested causes of OS in the SNpc is the production of ROS during the normal metabolism of dopamine. In the human SNpc, the oxidation products of dopamine may polymerize to form neuromelanin, which may also be toxic [41, 42]. According to postmortem studies, the SNpc of PD patients shows a significant (60%) reduction in GSH and a moderate (29%) increase in oxidized glutathione (GSSG) levels [43, 44].

4. **Huntington's disease:** Huntington's disease is an autosomal neuronal disorder characterized as a movement disorder caused by repetition of a CAG trinucleotide sequences encoding for a polyglutamine tract at the N terminus of the gene encoding a protein named huntingtin [45]. Several postmortem studies showed increased iron levels in the striatum of patients with Huntington's disease [46].

5. **Amyotrophic lateral sclerosis (ALS):** ALS is characterized by a selective and progressive degeneration of the lower motor neurons in the spinal cord and the upper motor neurons in the cerebral cortex, usually beginning in midlife. OS may be involved in all types of ALS [47]. Levels of vitamin E and malondialdehyde (MDA), as a measure of lipid oxidation, increased over time in mutant CuZnSOD mice, as compared to controls [48].

6. **Schizophrenia and tardive dyskinesia:** The presence of excess levels of ROS has been described for both schizophrenia and neuroleptic-induced tardive dyskinesia [49]. The contribution of oxidative injury to the pathophysiology of schizophrenia is indicated by the increase in lipid peroxidation products in the plasma and CSF and the altered levels of both enzymatic and nonenzymatic antioxidants in chronic naive first-episode patients [50, 51].

7. **Chemically induced neurological disorders:** Several neurotoxic chemicals have been shown to elevate the cerebral rate of ROS production in experimental animals. These include methylmercuric chloride, cadmium, toluene, and other organic solvents [52, 53]. All of these agents are also capable of increasing intracellular levels of calcium ions [54].

8. **Brain aging:** Aging in mammalian species appears to be the result of normal developmental and metabolic processes responsible for graying of the hair, decreases in the rate of wound healing, and increases in susceptibility to disease and death. Studies have found evidence of oxidative damage to macromolecules (DNA, lipids, and proteins) especially in brains from elderly subjects, supporting the hypothesis that oxidative injury might directly cause the aging process [55–57].

5.1.3 Diabetes mellitus

Diabetes in humans is a disease associated with increased oxidative stress. The cause of this is not yet fully understood but is thought to include mitochondrial dysfunction, direct enzyme inhibition by hyperglycemia, auto-oxidation of glucose, and activation of NADPH oxidase. The oxidative stress manifests itself as elevated concentrations of lipid peroxidation products, erythrocyte fragility, and decreases in the antioxidant enzyme systems (CAT, GSH-PX, and SOD) [58–61].

5.1.4 Asthma

Feline asthma closely parallels human asthma, which is known to be associated with oxidative stress. Such cells generate ROS, which are involved in the pathophysiology of asthma [62, 63].

5.1.5 Atherosclerosis

It has been known that LDL can be oxidized by many kinds of oxidants by different mechanisms and pathways. Myeloperoxidase (MPO) secreted from phagocytes has been implicated in the pathogenesis of atherosclerosis. Reactive nitrogen species are another species, which may contribute in atherosclerosis. Nitric oxide (NO) is not a strong oxidant in itself, but it reacts rapidly with O_2 to give peroxynitrite, which oxidizes LDL to an atherogenic form [64].

5.1.6 Heart failure

Accumulating evidence suggests that reactive oxygen species (ROS) play an important role in the development and progression of heart failure, regardless of the etiology.

5.1.7 Hemorrhagic shock

Acute hemorrhagic shock causes decreases in the cardiac function and contractility and is associated with an increase in oxygen free radical (OFR) producing activity of PMN leukocytes [65].

5.1.8 Ischemia–reperfusion

Reactive oxygen-derived radicals and metabolites are known to play important roles in the pathogenesis of ischemia/reperfusion and anoxia/reoxygenation injury. Free radicals are induced by the reperfusion blood flow in addition the lack of oxygen (O_2) supply to the ischemic cell.

5.1.9 Lung disease

The large endothelial surface is constantly exposed to many atmospheric pollutants including tobacco smoke, fuel emissions, ozone, and nitrogen dioxide, and given the natural oxidizing nature of the atmosphere (e.g., 21% O_2), the lung is always at risk of oxidative injury [66].

5.1.10 Aging

The free radical theory of aging includes phenomenological measurements of age-associated oxidative stress, interspecies comparisons, dietary restriction, the manipulation of metabolic activity and oxygen tension, treatment with dietary and pharmacological antioxidants, in vitro senescence, classical and population genetics, molecular genetics, transgenic organisms, the study of human diseases of aging, epidemiological studies, and the ongoing elucidation of the role of active oxygen in biology [67].

5.1.11 Free radicals and cancer

One type of endogenous damage is that arising from intermediates of oxygen (dioxygen)-reduction oxygen free radicals, which attacks not only the bases but also the deoxyribosyl backbone of DNA. OFR are also known to attack other cellular components such as lipids, leaving behind reactive species that in turn can couple to DNA bases [68].

5.1.12 Inflammation

During phagocytosis, cells consume increased amount of oxygen, a process termed the respiratory burst. Activation results in increased NADPH production via the hexose monophosphate shunt, and the generation of O_2, H_2O_2, OH and hypochlorous acid (HOCI), hypoxanthine concentration, xanthine oxidase activity, and ROS production are increased in rheumatoid arthritis [69].

5.1.13 Ocular disease

Oxidative stress is implicated in age-related macular degeneration and cataracts by altering various cell types in the eye either photochemically or nonphotochemically [70]. Under the action of free radicals, the crystalline proteins in the lens can cross-link and aggregate, leading to the formation of cataract [71, 72].

5.1.14 Fetus

Oxidative stress is involved in many mechanisms in the development of fetal growth restriction and preeclampsia in prenatal medicine. Some reports indicate that blood levels of lipid peroxidation products (F2-isoprostanes, MDA) are elevated in preeclamptic pregnancy and intra-uterine growth retardation, and it has been suggested that ROS/RNS play a role in the etiology of these diseases [63, 73]. In pregnancies complicated by preeclampsia, increased expression of NADPH oxidase 1 and 5 isoforms which are the major enzymatic sources of superoxide in the placenta is seen [74].

S. no	Plant name	Family	Part used	Chemical constituents responsible for antioxidant activity	Reference(s)
1	*Amaranthus paniculatus*	Amaranthaceae	Leaf	Carotenoids, ascorbic acid, flavonoids, and phenolic acids	[75]
2	*Amaranthus gangeticus*	Amaranthaceae	Leaf	Carotenoids, ascorbic acid, flavonoids, and phenolic acids	[75]
3	*Amaranthus blitum*	Amaranthaceae	Leaf	Carotenoids, ascorbic acid, flavonoids, and phenolic acids	[75]
4	*Amaranthus spinosus*	Amaranthaceae	Leaf	Carotenoids, ascorbic acid, flavonoids, and phenolic acids	[75]
5	*Amaranthus viridis*	Amaranthaceae	Leaf	Carotenoids, ascorbic acid, flavonoids, and phenolic acids	[75]
6	*Coriandrum sativum*	Umbelliferae	Leaf, fruit	S-(+)-linalool, monoterpenes, hydrocarbons, namely, α-pinene, limonene, γ-terpinene, p-cymene, borneol, citronellol, camphor, geraniol, and geraniol acetate, heterocyclic components like pyrazine, pyridine, thiazole, furan and tetrahydrofuran derivatives, isocoumarins, coriandrin, dihydrocoriandrin, coriandrons A–E, flavonoids, pthalides, neochidilide, digustilide phenolic acids, and sterols	[76]
7	*Emblica officinalis*	Umbelliferae	Fruit, leaves	Vitamins, ascorbic acid, and phenolics are known as hydrophilic antioxidants, while carotenoids are known as lipophilic antioxidants	[76]
8	*Digera muricata* (L.)	Amaranthaceae	Leaf	Phenols, flavonoids, glycosides, tannins and terpenoids, and minimum for saponins	[76]
9	*Chenopodium album* L.	Amaranthaceae	Leaf	Alkaloids, apocarotenoids, flavonoids, phytoecdysteroids xyloside, limonene (23.2%), α-terpinyl acetate (13.7%), α-terpinene (12.3%), and cis-ascaridole (12.2%)	[77]

S. no	Plant name	Family	Part used	Chemical constituents responsible for antioxidant activity	Reference(s)
10	*Basella alba Linn*	Basellaceae	Leaf	Proteins, fat, vitamin A, vitamin C, vitamin E, vitamin K, vitamin B9 (folic acid), riboflavin, niacin, thiamine, and minerals such as calcium, magnesium, iron	[78]
11	*Basella rubra*	Basellaceae	Leaf	Calcium, iron, vitamins A, B, and C, saponins A, B, C, and D, oleanane-type triterpene oligoglycosides, spinacoside C, and momordins IIb and IIc, β-carotene, small amounts of α-carotenes, 4-coumaroyl, and feruloyl derivatives	[79–81]
12	*Physalis philadelphica*	Solanaeae	Leaf, fruit	2,3-Dihydro-3beta-methoxyixocarpalactone A, 2,3-dihydro-3beta-methoxyixocarpalactone B, 2,3-dihydroixocarpalactone B	[82]
13	*Rumex vesicarius*	Polygonaceae	Leaf	Minerals, protein and ascorbic acid, oxalic acid, tocopherol and lipids. Ca, Cu, Fe, Mg, K, Na, Zn, lipids, ascorbic acid, tocopherol	[83]
14	*Paederia foetida*	Rubiaceae	Leaves	B-Sitosterol, leupiol, methyl mercaptan, crystalline keto alcohol, paederolone, paederone, and hetasitosterol	[84]
15	*Solanum nigrum Linn*	Solanaceae	Leaf	Acetic acid, tartaric acid, malic acid and citric acid, solanine, alpha, beta gamma chaconines, and alpha, beta gamma solanines, solanine, beta-2-solamargine, solamargine, and degalactotigonin. Five non-saponins including p-hydroxybenzoic acid and 3-methoxy-4-hydroxybenzoic acid	[85]
16	*Trigonella foenum-gracecum Linn*	Leguminosae	Leaf	Amino acid, fatty acid, vitamins, saponins, folic acid, disogenin, gitogenin, neogitogenin, homorientinsaponaretin, neogigogenin, and trigogenin, 4,5[delta]-cadinene (27.6%), [á]-cadinol, palmitic acid, linoleic acid, oleic acid and stearic acid, hexanal, 2-methyl-2-butenal, 3-octen-2-one, flavonoids, polysaccharides, saponins, polysaccharides, trigonelline, choline, quercetin, galactomannan, polysaccharides	[86]
17	*Brassica oleracea* Capitata	Brassicaceae	Leaf	Glucosinolates and their derived products, flavonoids, and other phenolics, quercetin 3-O-sophoroside-7-O-glucoside, 3-p-coumaroylquinic acid, kaempferol-3-O-sophoroside-7-O-glucoside, kaempferol 3-O-(caffeoyl)-sophoroside-7-O-glucoside, sinapoyl glucoside acid, kaempferol 3-O-(sinapoyl)-sophoroside-7-O-glucoside, sinapic acid, 3 isomeric forms of 1,2-disinapoylgentiobiose, kaempferol 3-O-sophoroside-7-O-glucoside	[87]
18	*Moringa pterygosperma Gaertn*	Moringaceae	Leaf	4-(4'-*O*-Acetyl-α-L-rhamnopyranosyloxy) benzyl isothiocyanate, 4-(α-L-rhamnopyranosyloxy)benzyl isothiocyanate, niazimicin, pterygospermin, benzyl isothiocyanate, and 4-(α-L-rhamnopyranosyloxy)benzyl glucosinolate, carotenoids (including β-carotene or pro-vitamin A)	[88]

S. no	Plant name	Family	Part used	Chemical constituents responsible for antioxidant activity	Reference(s)
19	*Hibiscus cannabinus L*	Malvaceae	Leaf	Tannins, saponins, polyphenolics, alkaloids, lignans, essential oils, and steroids	[89]
20	*Sesbania grandiflora L*	*Fabaceae*	Leaf	Galactomannans, linoleic acid, β-sitosterol, and carbohydrates. Vitamin C, and calcium, iodine, pectin, saponins, aliphatic alcohol, leucocyanidin and cyanidin, oleanolic acid and its methyl ester and kaempferol-3-rutinoside, tannins and gum, sesbanimide	[90–92]
21	*Portulaca oleracea L*	Portulacaceae	Leaf	Omega-3 fatty acids, gallotannins, kaempferol, quercetin, apigenin, α-tocopherols, ascorbic acid and glutathione, free oxalic acids, β-carotene, omega-3 fatty acids, coumarins, flavonoids, monoterpene glycoside, and anthraquinone glycosides	[93–95]
22	*Murraya koenigii L*	Rutaceae	Leaf	Alkaloid, volatile oil, glycozoline, xanthotoxin, and sesquiterpine	[96–100]
23	*Celosia argentea*	Amaranthaceae	Leaf	Alkaloids, glycosides, flavonoids, saponins, tannins, carbohydrate and essential oils, steroids, carotenoids, and anthocyanins	[101]
24	*Boerhavia diffusa*	Nyctaginaceae	Leaf	Alkaloids, punarnavine, rotenoids (boeravinones A–F), amino acids, lignans (liriodendrons), ß-sitosterols and tetracosanoic, esacosanoic, stearic, and ursolic acids. Rotenoids known as boeravinones, punarnavoside, a phenolic glycoside, 11,12 C-methyl flavone liriodendrin and syringaresinolmono-β-D-glycoside, fatty acids and allantoin boerhavin and boerhavic acid, aegeline, aegelinine, rutin, sterol, tannins, flavonoids, quercetin, volatile oils, ß-sitosterols	[102–109]
25	*Eclipta alba*	Asteraceae	Leaf	Coumestans, alkaloids, flavonoids, glycosides, polyacetylenes, triterpenoids, and thiophenes. Phytosterol, P-amyrin, luteolin-7-glucoside, P-glucoside of phytosterol, a glucoside of a triterpenic acid and wedelolactone. Cystine, glutamic acid, phenylalanine, tyrosine and methionine, nicotine, and nicotinic acid	[110]
26	*Centella asiatica*	Apiaceae	Leaf	Asiaticoside carotene, ascorbic acid, phenols, madecassic acid	[111]
27	*Phyllanthus amarus*	Euphorbiaceae	Leaf	Alkaloids, astragalin, brevifolin, carboxylic acids, corilagin, cymene, ellagic acid, ellagitannins, gallocatechins, *geraniin*, hypophyllanthin, phyllanthin, lignans, lintetralins, lupeols, methyl salicylate, phyllanthine, phyllanthenol, phyllochrysine, phyltetralin, repandusinic acids, quercetin, quercetol, quercitrin, rutin, saponins, triacontanal, and tricontanol	[112]
28	*Hibiscus sabdariffa*	Malvaceae	Leaf	Ascorbic acid (vitamin C) and tocopherol (vitamin E), flavonoids, polyphenols	[83]

S. no	Plant name	Family	Part used	Chemical constituents responsible for antioxidant activity	Reference(s)
29	*Curcuma longa*	Zingiberaceae	Leaf	Ascorbic-acid rhizome,beta-carotene rhizome, caffeic-acid rhizome, curcumin rhizome, eugenol essential oil, p-coumaric-acid rhizome, protocatechuic acid leaf, syringic-acid leaf, vanillic acid in leaf, camphene, eugenol, curcumin	[113]
30	*Ocimum sanctum*	Labiatae	Leaf	Volatile oil, terpenoids, eugenol, thymol, estragole	[114]
31	*Basella alba*	Basellaceae	Leaf	High in vitamin A, vitamin C, Ca, Iron, phosphorus, vitamin B9 (folic acid), calcium, magnesium, flavonoids, polyphenols	[115]
32	*Mentha arvensis*	Labiatae	Leaf	Flavonoids, acacetin, chrysoeriol, diosmin, eriocitrin, hesperidin, luteolin, esperidoside, menthoside, methyl rosmarinate, rutin, tilianine, narirutin, and nodifloretin. Phenolic acids such as caffeic acid, lithospermic acid, rosmarinic acid, protocatechuic acid, protocatechuic aldehyde, phytosterols, β-sitosterol, and daucosterol; the anthraquinones aloe-emodin,emodin, chrysophanol, and tannins	
33	*Alternanthera sessilis*	Amaranthaceae	Leaf	Carotenoids, triterpene, saponins, flavonoids, steroids, stigmasterol, β-sitosterol, glycosides, protein and amino acids, campesterol, lupeol	[116]
34	*Rumex acetosa*	Polygonaceae	Leaf	Oxalates, including calcium oxalate and tannins; anthracene derivatives, emodin, rhein, quinoids, and flavonoids	[117]
35	*Spinacia oleracea*	Amaranthaceae	Leaf	Vitamin A (especially high in lutein), vitamin C, vitamin E, vitamin K, magnesium, manganese, folate, betaine, iron, vitamin B2, calcium, potassium, vitamin B6, folic acid, copper, protein, phosphorus, zinc, niacin, selenium, and omega-3 fatty acids. Recently, opioid peptides called rubiscolins have also been found in spinach. It is a source of folic acid	[117]
36	*Trianthema portulacastrum*	Aizoaceae		Tetraterpenoid 1 (trianthenol) flavonoid, 5,7-dihydroxy-6,8-dimethylchromone (leptorumol) Isoamericanin A	[118–121]
37	*Hibiscus sabdariffa*	Malvaceae	Leaf	Alkaloids, saponins, tannins, anthraquinones, cardiac glycosides, flavonoids and phlobatannins	[122]

6. Conclusion

The most important free radical in biological systems is radical derivatives of oxygen with the increasing acceptance of free radical as common place and important biochemical intermediate. Antioxidants are believed to play a very important role in the body defense system against reactive oxygen species (ROS), which are the harmful by-products generated during normal cell aerobic respiration. The imbalance between ROS and antioxidant defense system increases the oxidation

burden and leads to the damage of macromolecules such as carbohydrates or proteins, such processes of various diseases. To protect the cells and organ systems of the body against reactive oxygen species, humans have evolved a highly sophisticated and complex antioxidant protection system. Plants having vitamins (C, E, carotenoids, etc.), flavonoids (flavones, isoflavones, flavanones, anthocyanins, and catechins), polyphenols (ellagic acid, gallic acid, and tannins) possess remarkable antioxidant activity. Antioxidant activity is neither restricted to a particular part of plant nor the specific families. Current review reveals the different potential application of antioxidant/free radical manipulations in prevention or control of diseases. All plants discussed in this review exhibited significant, clinical, and pharmacological activity with fewer side effects.

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