Chapter 4

Free Radicals and the Role of Plant Phytochemicals as Antioxidants Against Oxidative Stress-Related Diseases

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Additional information is available at the end of the chapter

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Abstract

Free radicals or reactive oxygen species (ROS) generated from various sources in the environment as well as from cellular processes in the body are of serious health challenges. Overwhelming levels of these free radicals disrupt the antioxidant defense system in the body thereby damaging cell membranes and cellular macromolecules such as proteins, lipids and nucleic acids leading to cell death or causing mutations leading to uncontrolled cell division. Once the cellular antioxidant system is disrupted and becomes deficient, oxidative stress emerges thereby promoting several diseases such as diabetes, arthrosclerosis, cancer, cardiovascular diseases, etc. Better management of oxidative stress requires antioxidants from external sources to supplement the body's antioxidant defense system. Because of their natural origin and therapeutic benefits, plants have been considered as a major source of antioxidants. Certain non-enzymatic plant phytochemicals such as glutathione, polyphenols, bioflavonoids, carotenoids, hydroxycinnamates as well as some vitamins have shown to possess antioxidant properties in vitro and in vivo. These plant phytochemicals are now been used in the prevention and management of oxidative stress-related diseases.

Keywords: free radicals, oxidative stress, reactive oxygen species (ROS), plants, phytochemicals, antioxidants, diseases

1. Introduction

Man as a living creature has always indulged himself into several activities to ensure his survival and well-being. In so doing, he has induced the production or release of various reactive substances or free radicals which are either consumed or inhaled. Also, certain physiological processes in the body generate free radicals or proxidants. These free radicals or reactive species, because of

their deficiency in electron and instability, attack electron rich centers such as lipid membranes, proteins and nucleic acids thereby damaging cells and tissues in the body. Eventual, the human body is adapted to remove these unstable molecules by a myriad of molecules including certain enzymes collectively known as antioxidants. This antioxidant defense system reduces the level of these free radicals in the body and maintains the homeostatic balance for proper functioning of the body. However, when these reactive species are overwhelming high in the body, it surpasses the capacity of the antioxidant defense system leading to a condition known as oxidative stress. This imbalance between antioxidant and proxidants is characteristic of certain disease conditions such as diabetes, atherosclerosis, cardiovascular diseases, cancer etc. One of the possible remedy for this condition is to supplement the endogenous antioxidant defense system with exogenous antioxidants. Plants have gained considerable interest in recent time in managing oxidative stress related diseases; firstly, because of their ethnopharmacological uses in managing diseases and secondly, due to their richness in phytochemicals which possess antioxidant properties. Hence, this chapter is aimed to give an overview of free radicals, their sources of origin and processes of generation in the environment and body. Also, it will highlight on the various mechanisms of free radical induced cellular damage and the associated diseases due to oxidative stress. The various mechanisms of the antioxidant defense system; both enzymatic and non-enzymatic antioxidants will be described as well as the contribution of plant phytochemicals as antioxidants. Emphasis will be laid on some plants and phytochemicals with antioxidant activities stating their mode of scavenging free radicals and prevention of oxidative stress-related diseases.

2. Free radicals

Free radicals are molecular species with unpaired electrons in their atomic orbital capable of independent existence. As such, these radicals are highly reactive and can either extract an electron from molecules or donate an electron to other molecules thus acting as a reductant or an oxidant. Though free radicals have high reactivity, most of them have a very short half-life of less than 10^{-6} s in biological systems [1]. Some oxygen species known as reactive oxygen species (ROS) are non-reactive in their natural state but are capable of generating free radicals.

The idea of free radicals began in chemistry around the beginning of the twentieth century, where chemists initially described them as intermediate organic and inorganic compounds with several suggested definitions. A clear understand of these radicals was then proposed based on the work of Daniel Gilbert and Rebecca Gersham in 1954 [2] in which these radicals were suggested to play important roles in biological environments but also responsible for certain deleterious processes in the cell. Thereafter by 1956, Herman Denham further suggested that these reactive species may play critical roles in physiological process particularly aging process [3]. This hypothesis on the theory of free-radical on aging, inspired numerous research and studies which significantly contributed to the understanding of radicals and other related species such as ROS, reactive nitrogen species (RNS) and non-radical reactive species [4].

2.1. Types of free radicals or reactive oxygen species

ROS are classified into two major categories of compounds which includes the free radicals and the non-reactive radicals. The free radical includes nitric oxide radical ($NO^{\bullet}$), hydroxyl

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radical ($OH^{\bullet}$), superoxide ion radical ($O^{\bullet}_2$), peroxyl ($ROO^{\bullet}$), alkoxyl radicals ($RO^{\bullet}$), and one form of singlet oxygen ($^1O_2$) as shown in **Table 1** [5]. These species are considered as free radicals since they contain at least one unpaired electron in the shells around the atomic nucleus which makes them unstable and therefore can easily donate or obtain another electron to attain stability. As such, they are highly reactive and capable of independent existence [6, 7]. On the other hand, the non-reactive radicals are a group of compounds which are not radicals but are extremely reactive or can easily be converted to reactive species. Examples of these substances include hypochlorous acid (HClO), hydrogen peroxide (H_2O_2), organic peroxides, aldehydes, ozone (O_3), and O_2 as shown in **Table 1**.

2.2. Sources of free radicals

As reviewed from Sultan [8], free radicals can originate either from the environment, physiological processes or endogenous sources.

External sources: Certain organic compounds in the atmosphere can react non-enzymatically with oxygen to generate free radicals. Also, reactions initiated by ionizing radiations in the environment can generate free radicals. Thus, some external sources of free radicals include environmental pollutant, cigarette smoke, alcohol, radiations, ozone, ultraviolet light, pesticides, anesthetic, certain drugs, industrial solvents etc.

Endogenous sources: This includes processes in living organisms that necessitates enzymatic reactions to generate free radicals. These include reactions involved in the respiratory chain,

Free radicals	Name	Symbol
Oxygen radicals		
	Oxygen (bi-radical)	$O^{\bullet}_2$
	Superoxide ion	$O^{\bullet}_2$
	Hydroxyl	$OH^{\bullet}$
	Peroxyl	$ROO^{\bullet}$
	Alkoxyl	$RO^{\bullet}$
	Nitric oxide	$NO^{\bullet}$
Non-reactive oxygen radical		
	Hydrogen peroxide	H_2O_2
	Organic peroxide	ROOH
	Hypochlorous acid	HOCL
	Ozone	O_3
	Aldehydes	HCOR
	Singlet oxygen	$^1O_2$
	Peroxynitrite	ONOOH

Table 1. Free radicals and non-reactive radicals of oxygen species.

cytochrome P450 system, phagocytosis and prostaglandin synthesis. Some of these endogenous sources of free radicals generation include reactions in the mitochondria, phagocytes, inflammation, arachidonate pathways, etc. Also, reactions involving iron and other transition metals, peroxisomes, xanthine oxidase, etc. are also endogenous sources of free radicals.

Physiological sources: Certain physiological state or processes like stress, emotion, aging, etc. mental status and disease conditions are also responsible for the formation of free radicals. For example, hyperglycemia is a major source of free radicals in diabetes patients through various metabolic pathways which include increase flux of glucose through the polyol pathway, increase formation of advanced glycation end-products (AGEs) and activation of their receptors, activation of protein kinase C (PKC) isoforms, activation of overactivity of hexosamine pathway and decrease antioxidant defense [9].

2.3. Generation and chemical reactions of free radicals

Free radicals are generated through various physiological processes in living organisms. Once generated, they can react with other biomolecules to attain stability.

Superoxide ($O^{\bullet}_2$) is generally produced when a single electron is added unto oxygen. In living systems, superoxide can be generated through several mechanisms [10]. Several molecules such as flavine nucleotides, adrenaline, thiol compounds, glucose, etc. can be oxidized in the presence of oxygen to generate superoxide and these reactions are greatly accelerated by the presence of transition metals such as iron or copper. During the electron transport chain in the inner mitochondrial membrane, oxygen is reduced to water thereby producing free radical intermediates that subsequently reacts with free electrons to produce superoxide [11]. Certain reactions by enzymes such as cytochrome p450 oxidase in the liver releases free electrons that can react with oxygen to produce superoxide. Other enzymes can neutralize nitric oxide thereby producing superoxide [12]. Also, phagocytic cells during respiratory burst can generate superoxide [13].

Hydrogen peroxide (H_2O_2): Hydrogen peroxide is mostly produced from the spontaneous dismutation reaction of superoxide in biological systems. Also, several enzymatic reactions including those catalyzed by D-amino acid and glycolate oxidases can directly produce H_2O_2 [14]. Generally, H_2O_2 is not a free radical but it is considered as a reactive oxygen species (ROS) because it can be transformed to other free radicals such as hydroxyl radical which mediate most of the toxic effects ascribed to H_2O_2. Myeloperoxidase can decompose H_2O_2 into singlet oxygen and hypochlorous acid, a mechanism which phagocytes utilize to kill bacteria [15]. However, H_2O_2 is a weak oxidizing agent that might directly damage enzymes and proteins which contain reactive thiol groups. One of the most vital properties of H_2O_2 over superoxide is its ability to freely traverse cell membranes [16].

Hydroxyl radical ($OH^{\bullet}$) is one of the most important free radicals as it is extremely reactive with almost all type of biomolecules including amino acids, sugars, lipids and nucleotides. Most ROS are usually converted to hydroxyl radical. Thus, it is usually the final mediator of most free radical induced tissue damage [17]. Hydroxyl radical is generated by various mechanisms but the most important is the in vivo mechanism due to decomposition of superoxide

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and hydrogen peroxide catalyzed by transition metals [18]. Transition metals generally contain one or more unpaired electrons and thus are capable to transfer a single electron. Iron and copper are the most common transition metals capable of generating free radicals and much implicated in human diseases. As shown by Fenton [19], hydrogen peroxide can react with iron II (or copper I) to generate hydroxyl radical:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\bullet} + OH^{-}. \quad (1)$$

At physiological pH, iron is usually oxidized to Fe^{3+} and chelates to biological molecules. Thus, for Fenton reaction to occur, iron must be converted to its reduced form Fe^{2+}. Superoxide radicals can reduce Fe^{3+} to Fe^{2+} ions thereby enabling the Fenton reaction.

$$Fe^{3+} + O_2^{-} \rightarrow Fe^{2+} + O_2. \quad (2)$$

net reaction (Haber-Weiss reaction):

$$O_2^{-} + H_2O_2 \rightarrow OH^{-} + OH^{\bullet} + O_2. \quad (3)$$

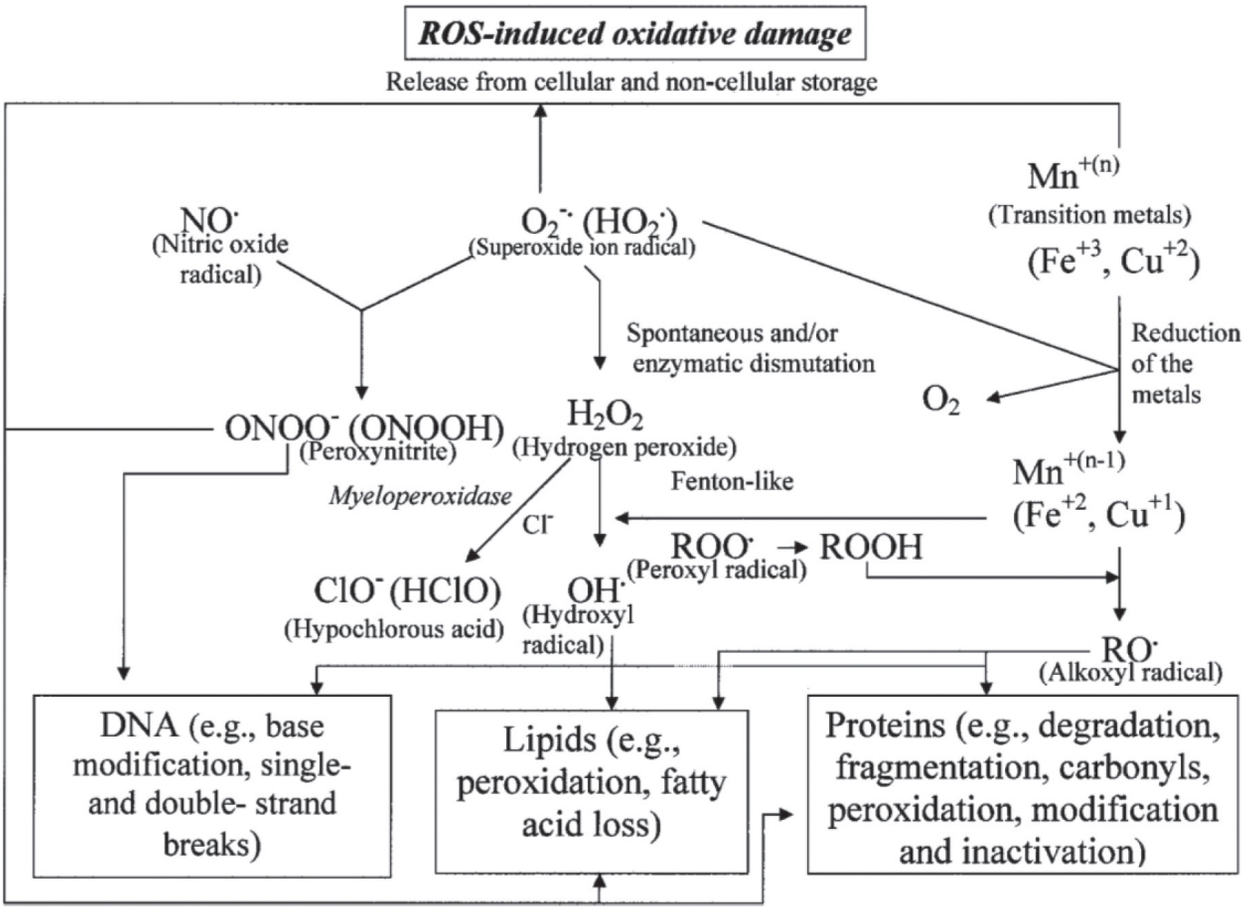

Figure 1. Reactive oxygen species (ROS)-induced oxidative damage. Source: Kohen and Nyska [21].

Nitric oxide ($NO^{\bullet}$) otherwise known as nitrogen monoxide is a radical produced by the oxidation of one of the terminal guanido nitrogen atoms of L-arginine catalyzed by the enzyme nitric oxide synthase (NOS) [6]. L-arginine and L-citrulline are both converted to nitric oxide. Nitric oxide can further react with superoxide to form peroxynitrite.

$$NO^{\bullet} + O^{\bullet}{}_2^{-} \rightarrow ONOO^{-}. \quad (4)$$

Protonated form of peroxynitrite (ONOOH) acts as a powerful oxidizing agent to sulfhydryl (SH) groups thereby causing oxidation of many molecules and proteins leading to cellular damage [20]. It can also cause DNA damage such as breaks, protein oxidation and nitration of aromatic amino acid residues in proteins. Reactive oxygen species and their oxidative stress induced damaged is summarized in **Figure 1**.

3. ROS induced oxidative damage

Continual influx and generation of ROS from endogenous and exogenous sources lead to oxidative damage of cellular components and may impair many cellular functions [22]. The most vulnerable biological targets to oxidative damage include proteins, enzymes, lipidic membranes and DNA [5].

Lipids: All cellular membranes are generally vulnerable to oxidative damage since they are highly rich in unsaturated fatty acid. The lipid damage due to ROS usually known as lipid peroxidation occurs in three stages [23]. The first stage, known as initiation involves the attack of a reactive oxygen metabolite capable of abstracting a hydrogen atom from a methylene group in the lipid due to the presence of a weak double bond. As such, the remaining fatty acid radical retains one electron and stabilizes by rearrangement of the molecular structure to form a conjugated diene. In the propagation stage, the fatty acid radical reacts with oxygen to form $ROO^{\bullet}$. The $ROO^{\bullet}$ is capable of abstracting another hydrogen atom from a neighboring fatty acid molecule, which again leads to the production of fatty acid radicals. These propagation reactions occur repeatedly leading to the peroxidation of several unsaturated lipid in the membrane. The $ROO^{\bullet}$ becomes a lipid hydroperoxide which can further be decomposed to an aldehyde or form cyclic endoperoxide, isoprotans, and hydrocarbons. The last stage which is chain termination occurs following interaction of one $ROO^{\bullet}$ with another radical or antioxidants.

Initiation:

$$RH + R^{\bullet} \rightarrow L^{\bullet} + RH \quad (5)$$

Propagation:

$$R^{\bullet} + O_2 \rightarrow LOO^{\bullet} \quad (6)$$

$$LOO^{\bullet} + LH \rightarrow LOOH + L^{\bullet} \quad (7)$$

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$$LOOH \rightarrow LO^{\bullet} + LOO^{\bullet} + \text{aldehydes} \quad (8)$$

Termination by another radical:

$$LOO^{\bullet} + OH^{\bullet} \rightarrow LOOH + O^{\bullet} \quad (9)$$

Termination by an antioxidant:

$$LOO^{\bullet} + \alpha - \text{tocopherol} - OH \rightarrow LOOH + \alpha - \text{tocopherol} - O^{\bullet} \quad (10)$$

Proteins: Proteins are major targets for attack by ROS predominantly by the $OH^{\bullet}$, $RO^{\bullet}$ and nitrogen-reactive radicals causing damage. Hydrogen peroxide and superoxide radicals have weak effects on proteins except for proteins containing SH groups. Following interaction with ROS, proteins can undergo direct damages such as damaging specific amino acid residues and changing their tertiary structures and indirect damages such as peroxidation, degradation and fragmentation. The consequences of protein damage include loss of enzymatic activity and altered cellular functions. Protein oxidation products are usually keto, aldehydes and carbonyls compounds. Oxidation of tyrosine by $ONOO^{\bullet}$ and other nitrogen reactive radicals leads to the formation of 3-nitrotyrosine which is a detectable marker for protein oxidation. Oxidation of proline and glutamate by $OH^{\bullet}$ radicals usually leads to the formation of hydroxyproline and glutamyl semialdehyde. Following protein oxidation, proteins are susceptible to many changes in their function which include inactivation, chemical fragmentation and increased proteolytic degradation [24].

Nucleic acid: Though DNA is a stable molecule, ROS can interact with it to cause several types of damages which include double- and single- DNA breaks, modification of DNA bases, loss of purines (apurinic sites), DNA-protein cross-linkage, damage to the deoxyribose sugar and damage to the DNA repair system. Hydroxyl radical is the most detrimental ROS that affects nucleic acids [25]. For example, $OH^{\bullet}$ can attack guanine and adenine to yield an oxidation product, 8-hydroxydeoxyguanosine [26] and hydroxyadenine respectively. Also, hydroxyl radicals can attack pyrimidines leading to the formation of thymine peroxide, thymine glycols, 5-(hydroxymethyl) uracyl, and other such products. ROS such as $O^{\bullet}_2$ and H_2O_2 do not have direct interaction with DNA and hence do not lead to damage at their physiological concentrations. Transition metals such as iron that have high-binding affinity to DNA sites can catalyze the production of $OH^{\bullet}$ which in turns attack DNA.

4. Oxidative stress and human diseases

When the concentration of ROS exceeds those of antioxidant neutralizing species, a condition known as oxidative stress occurs. As reviewed from Rahman et al. [27], oxidative stress has been implicated in several diseases including atherosclerosis, cancer, malaria, rheumatoid arthritis, chronic fatigue syndrome, and neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease [28]. Evidence via monitoring biomarkers

such as the presence of ROS and RNS as well as antioxidant defense has indicated oxidative damage may be implicated in the pathogenesis of these diseases [29]. Elevated levels of free radicals such as 4-hydroxy-2,3-nonenal (HNE), acrolein, malondialdehyde (MDA) and F2-isoprostanes have been observed in Alzheimer's disease [30, 31]. Oxidative stress also contributes to tissue injury following hyperoxia and irradiation. Evidence from studies have shown oxidative stress to play an important role in the pathogenesis and development of metabolic syndrome related disorders such as obesity, hypertension, diabetes, dyslipidemia etc. as well as in cardiovascular related diseases such as myocardial infarction, aortic valve stenosis, angina pectoris, atherosclerosis and heart failure [32–35]. Cancer is another disease associated with ROS as ROS have been suggested to stimulate oncogenes such as Jun and Fos whose overexpression is directly associated with lung cancer [36]. In lung cancers, p53 can be mutated by ROS thereby losing its function of apoptosis and functioning as an oncogene [37]. Also, the development of gastric cancer has been thought to be due to increase production of ROS and RNS by *Helicobacter pylori* infection in human stomach [29]. Excess ROS in human kidney leads to urolithiasis [29]. ROS have also been reported to damage cellular components in cartilage leading to osteoarthritis [38] and has been shown to be involved in damaging the islets cells of the pancreas [39]. More so, hyperglycemia triggers ROS production in both tubular and mesangial cells of human kidney, making functional and structural changes in glomeruli causing diabetic nephropathy [40].

5. Defense mechanism against free radicals

In response to the prevailing level of free radicals both from exogenous and endogenous sources, the human body developed a defense mechanism for protection against cellular damages. These may involve direct and indirect mechanisms put in place by the body.

5.1. Indirect defense mechanisms

Firstly, the indirect mechanisms are those mechanisms that do not directly act on the free radicals to eliminate them or convert them to less reactive forms. Rather this indirect system can act in several ways. Certain regulatory mechanisms can control and regulate processes that lead to the endogenous production of ROS [41]. This may be transcriptional control of the enzymes that are involved in the generation of endogenous ROS. Another indirect approach consists of certain molecules and enzymes that are transported to oxidative-damage sites for repair of macromolecules. This may include repair of damage DNA, protein or lipids. For examples damage oxidized adducts of DNA such as 8-hydroxy-2-deoxyguanosine, thiamine glycol, and apurinic can be removed from a nucleotide sequence and replaced by a normal nucleotide base [42]. Also, certain molecules that can donate hydrogen atoms to damaged molecules are also considered as repair compounds. Molecules such as ascorbate or tocopherol can donate hydrogen atom to a fatty acid radical on cell membrane thereby repairing the membrane. Certain natural cellular or surface barriers such as the skin or cell membranes act as indirect defense system against ROS by preventing exogenous ROS from entering the body or preventing certain endogenous ROS from reaching the target macromolecules. Though these indirect defense mechanisms are helpful against ROS, they are usually non-specific and do not act directly on the ROS.

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5.2. Direct defense mechanism

This category of defense system which constitutes the antioxidant system is the most important because they directly act on free radicals either by decomposing, scavenging or converting free radicals to less reactive forms. This defense mechanism constitute two groups; the enzymatic and non-enzymatic antioxidants.

5.2.1. Enzymatic antioxidants

The enzymatic antioxidants include superoxide dismutase (SOD), catalase, glutathione reductase (GRx) and glutathione peroxidase (GPx).

Superoxide dismutase (SOD): SOD is an enzymatic antioxidant that exists in three forms in mammalian tissues and differs on their cofactor, subcellular location and tissue distribution. 1. Copper zinc superoxide dismutase (CuZnSOD) is present in the cytoplasm and organelles of almost all mammalian cells [43]. This enzyme has a molecular mass of about 32,000 kDa with two protein subunits, each containing a catalytically active copper and zinc atom. 2. Manganese superoxide dismutase (MnSOD) has a molecular mass of 40,000 kDa and is found in the mitochondria of almost all cells [44]. It consists of four protein subunits, each containing a single manganese atom. 3. Extracellular superoxide dismutase (ECSOD) is a secretory copper and zinc containing SOD which is different from CuZnSOD [45]. It is synthesized only in fibroblasts and endothelial cells and expressed on the cell surface where it binds to heparan sulfates. Following its release from heparin, it is secreted into extracellular fluids and enters into the circulation. Superoxide dismutase catalyzes the dismutation of superoxide to hydrogen peroxide:

$$O_2^- + O_2^- + 2H^+ \rightarrow H_2O_2 + O_2. \quad (11)$$

The hydrogen peroxide can then be removed by catalase or glutathione peroxidase.

Catalase: Catalase was the first antioxidant enzyme to be characterized. It is located mostly within the peroxisomes of cells which contain most of the enzymes capable of generating hydrogen peroxide. It consists of four protein subunits, each containing a haem group and a molecule of NADPH [46]. Catalase is mostly present in liver and erythrocytes showing the greatest activities but is found in other tissues. It catalyzes the conversion of hydrogen peroxide to water and oxygen in two stages:

Stage 1: $\text{Catalase–Fe(III)} + H_2O_2 \rightarrow \text{compound I}$

Stage 2: $\text{Compound I} + H_2O_2 \rightarrow \text{catalase–Fe(III)} + 2H_2O + O_2$

Glutathione peroxidases (GPx): Glutathione peroxidase is an enzyme which is synthesized mainly in the kidney and found in almost all tissues although it is highly found in the liver [47]. Its subcellular location is usually the cytosol and mitochondria. Selenium serves as its cofactor located at the active site of the enzyme and deficiency of selenium greatly affects the activity of the enzyme [48]. Glutathione peroxidases catalyze the oxidation of reduced glutathione (GSH) decomposing hydrogen peroxide or another species such as a lipid hydroperoxide:

$$ROOH + 2GSH \rightarrow GSSG + H_2O + ROH. \quad (12)$$

The fact that GPx also acts on lipid hydroperoxides suggest it may be involved in repairing cellular damages due lipid peroxidation [49]. The activity of GPx is dependent on the constant availability of reduced glutathione which is regenerated from oxidized glutathione (GSSG).

Glutathione reductase (GRx): GRx is a flavine nucleotide dependent enzyme and has a similar tissue distribution to glutathione peroxidase [49]. The role of GRx is to generate GSH from GSSG using NADPH in order to increase the ratio of reduced to oxidized glutathione:

$$GSSG + NADPH + H^+ \rightarrow 2GSH + NADP^+. \quad (13)$$

The NADPH required by this enzyme to replenish the supply of reduced glutathione is provided by Glucose-6-phosphate dehydrogenase (G-6-PD) in the pentose phosphate pathway.

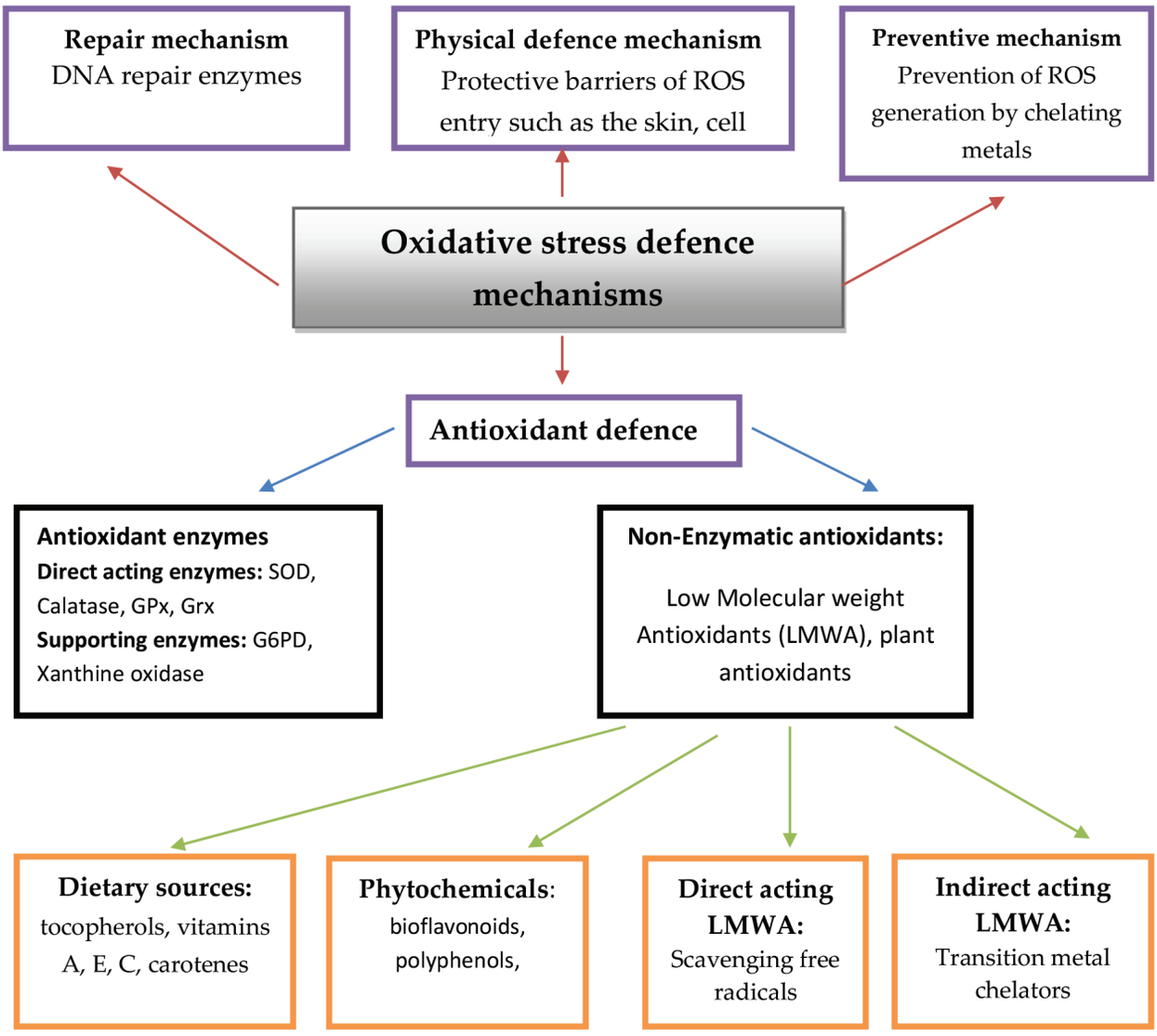

Figure 2. Oxidative stress defence mechanism.

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Competing pathway that utilizes NADPH such as the aldose reductase pathway may lead to a deficiency of reduced glutathione thereby limiting the action of glutathione peroxidase.

5.2.2. Non-enzymatic antioxidants

The non-enzymatic antioxidants are usually low-molecular-weight antioxidant (LMWA) compounds capable of preventing oxidative damage either by directly interacting with ROS or indirectly by chelating metals [50]. Transition metals are directly chelated by some of this LMWA thereby preventing them from participating in metal-mediated Haber-Weiss reaction [51]. Other direct acting LMWA molecules scavenge free radicals by donating electrons to free radicals to make them stable thereby preventing attacks of biological targets. These LMWA molecules also called scavengers may be advantageous over enzymatic antioxidants as they can penetrate cellular membranes and be localized in close proximity to the biological target due to their small size. More so, these non-enzymatic antioxidants can interact together to scavenge free radicals and their scavenging activity may be synergic. Most scavengers originate from endogenous sources, such as biosynthetic processes and waste-product generation by the cell. However, the number of LMWA synthesized by the living cell or generated as waste products such as histidine dipeptides, glutathione, uric acid, lipoic acid and bilirubin is limited [52]. More so, the concentration of scavenger must be sufficiently high to compete with the biological target on the deleterious species [50]. As such, exogenous sources of non-enzymatic antioxidants especially from plant diet and phytochemicals are needed to supplement the endogenous non-enzymatic antioxidants. The oxidative stress defense mechanism in humans is summarized in **Figure 2**.

6. Plants as source of antioxidants

Plants have long been consumed as food which is rich in vitamins and other nutrients that are useful for the body. Also, various plants were used in folk medicine for various therapeutic purposes. Though these uses, the notion of plant as a source of antioxidant became more evident in recent time as oxidative stress was considered a major attribute to most diseases in humans and the antioxidant defense system in human was usually not sufficient to overcome the free radical level in the body. As such, plants have gained considerable interest as a source of antioxidants and so much research has been done to identify plants substances with antioxidant activities.

Like other humans, plants do have enzymatic and non-enzymatic antioxidant defense systems to protect them against free radicals. The enzymatic system includes catalase, SOD, glutathione peroxidase(GPx), and glutathione reductase (GRx) [7], while non-enzymatic systems consist of low molecular weight antioxidants (LMWA) such as ascorbic acid, proline, glutathione, carotenoids, flavonoids, phenolic acids, etc. and the high molecular weight antioxidants (HMWA) which are mostly secondary metabolites such as tannins [53]. The possible reason for the presence of these antioxidants in plants is that plants lack an immune system unlike animals thus, utilize the antioxidant defense system to protect them against microbial pathogens and animal herbivores. Also, these phytochemicals serve as a defense system against environmental stress.

6.1. Non-enzymatic plant antioxidants and their mode of action

Though plants have enzymatic antioxidants, it is usually difficult to isolate these enzymes for therapeutic uses in humans. Also, they are usually denatured during food processing, preparation and not sufficiently present in diets such as fruits and vegetables. On the contrary, non-enzymatic antioxidants are readily present in plants leaves, fruits and food in sufficient amounts and can easily be extracted from plants. For these reasons, this section will focus on the non-enzymatic plant antioxidants.

Glutathione: Glutathione is a low-molecular-weight, tripeptide of glutamic acid-cysteine-glycine containing a thiol. It exist as GSH in its reduced form and 2 GSH molecules can be joined via oxidation at their SH groups of the cysteine residue into a disulfide bridge to form GSSG which is the oxidized form.

GSH generally acts as a cofactor for glutathione peroxidase, thus serving as an indirect antioxidant by donating the necessary electrons for the decomposition of H_2O_2. GSH can directly scavenge ROS such as $ROO^{\bullet}$, $OH^{\bullet}$ and $RO^{\bullet}$ radicals as well as $^{\bullet}O_2$ and $HCLO^{\bullet}$. Upon reacting with ROS, GSH becomes a glutathione radical, which can be reconverted to its reduced form [54]. Glutathione also has other cellular functions such metabolism of ascorbic acid [55]. Also, glutathione prevents the oxidation of SH protein groups and acts as a chelating agent for copper preventing its participation in the Haber-Weiss reaction [54].

Vitamin E (α-tocopherol): Vitamin E is a lipid soluble antioxidant that functions as an efficient 'chain breaker' during lipid peroxidation in cell membranes and various lipid particles including low-density lipoprotein (LDL). Its role is to scavenge lipid peroxyl radicals ($LOO^{\bullet}$) and to terminate the lipid peroxidation chain reactions [56].

$$LOO^{\bullet} + \alpha - \text{tocopherol–OH} \rightarrow LOOH + \alpha - \text{tocopherol–}O^{\bullet}. \quad (14)$$

Also, α-tocopherol can scavenge other ROS, such as $^{\bullet}O_2$ to become tocopherolquinone and subsequently tocopherylquinone. However, it is not an efficient scavenger of $OH^{\bullet}$ and alkoxyl ($^{\bullet}OR$) radicals in vivo [57]. The resultant tocopheroxyl radical in these reactions can be recycled to its active form but this radical is relatively stable in normal circumstances and insufficiently reactive to initiate lipid peroxidation itself, which makes it a good antioxidant [58].

Ascorbic acid (Vitamin C): Ascorbic acid is a water-soluble antioxidant. It also functions as a chain breaker to terminate the lipid peroxidation chain reaction. In this reaction, it donates an electron to the lipid radical ($LOO^{\bullet}$) to become ascorbate radical. Two molecules of ascorbate radicals can react rapidly to produce a molecule of ascorbate and a molecule of dehydroascorbate which do not have any scavenging activity. Dehydroascorbate can be reconverted to ascorbate by the addition of two electrons catalyzed by oxidoreductase. More so, ascorbate can react with GSH to regenerate vitamin E in cell membranes [59].

Vitamin A: Though not fully understood, vitamin A is considered as a vital antioxidant that prevents humans LDL against copper stimulated oxidation [60]. The antioxidant potential of vitamin A was first revealed by Monaghan and Schmitt who showed that vitamin A can protect lipids against rancidity [61].

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Bioflavonoids: This is a group of natural benzo-γ-pyran derivatives which are widely distributed in fruits and vegetables. They are the most abundant polyphenols found to possess strong antioxidant activities in scavenging free radicals. They have generally been reported to protect against hydroxyl radical induced DNA damage [62]. Also, bioflavonoids are capable of chelating metal ions, such as copper or iron thereby preventing the generation of ROS [63]. These bioflavonoids include flavonol, flavones, flavonolols, flavan-3-ols, flavonone, anthocyanidin, isoflavone, etc.

Flavonoids: In plants, most flavonoids are attached to sugars (glycosides), although they are occasionally found as aglycones. Most flavonoids are not completely absorbed and reach the circulatory system except for some flavan-3-ols and proanthocyanidins. **Quercetin** is a flavonol, known to protect DNA from oxidative damage resulting from the attack of $^{\bullet}OH$, H_2O_2, and $O_2^{\bullet}$ on DNA oligonucleotides. However, at high concentrations of cupric ion, quercetin is reported to be a carcinogenic agent by enhancing DNA damage via ROS [64]. Therefore, it is very important to consider the concentration of the chelating metal ions such as copper or iron while evaluating the protective or degenerative effects of quercetin and other bioflavonoids. **Anthocyanidin** is a class of flavonoids with antioxidant potentials. They are effective in the inhibition of lipid oxidation due to their metal ion-chelating activity.

In general, flavonoids are oxidized by radicals, resulting in a more stable, less-reactive radical. In this reaction, flavonoids stabilize the ROS by reacting with them to become a flavonoids radical. This is achieved due to high reactive hydroxyl group of the flavonoids as shown below.

$$\text{Flavonoid(OH)} + R^{\bullet} \rightarrow \text{flavonoid}(O^{\bullet}) + RH \tag{15}$$

where $R^{\bullet}$ is a free radical and $O^{\bullet}$ is an oxygen free radical.

As reviewed from Nijveldt et al. [65], certain flavonoids can directly scavenge superoxides as well as peroxynitrite. Other flavonoids may act as antioxidants by inhibiting the activity of free radical generating enzymes such as xanthine oxidase and nitric-oxide synthase. Quercetin, rutin and silibin have shown to inhibit xanthine oxidase activity while silibin has been reported to inhibit nitric` oxide dose dependently. By scavenging radicals, flavonoids can inhibit LDL oxidation in vitro. This action protects the LDL particles and, theoretically, flavonoids may have preventive action against atherosclerosis.

Carotenoids: Carotenoids are among the common lipid soluble phytonutrients synthesized from phytoene. They include Xanthophyll (zeaxanthine, lutein) and Carotines (lycopene, b-carotene), the latter been the most abundant. Carotenoids are generally known to scavenge peroxyl radicals which are generated during the process of lipid peroxidation of cell membrane. As such, scavenging of peroxyl radicals prevents cellular lipids and membrane damage. Carotenoids are highly lipophilic and are known to play an important role in the protection of cellular membranes and lipoproteins against ROS due to their peroxyl radical scavenging activity [66]. **Lycopene** is the most potent antioxidant naturally present in many fruits and vegetables. The high number of conjugated double bonds in lycopene endows it with singlet oxygen quenching ability. Lycopene demonstrate the strongest singlet oxygen quenching ability as compared to α-tocopherol or β-carotene [67]. **β-carotene** is a naturally occurring orange-colored carotenoid, abundantly found in yellow orange fruits and in dark-green leafy vegetables [68]. Just like lycopene, β-carotene is well-known to quench singlet

Plant	In vitro antioxidant											In vivo antioxidant activity					Protective against Damage in vivo		Ref
	RP	HPS	DS	SS	AS	HS	NS	FS	TAC	TPC	TPC	GSH	CA	SOD	GRx	GPx	PCC	MDA	
Torilis leptophylla	✓	✓	✓	✓	✓	✓	–	–	✓	✓	✓	✓	–	–	–	–	–	✓	[78]
Clausena anisata	–	–	✓	–	–	–	–	✓	–	✓	✓	–	–	–	–	–	–	–	[79]
Peltophorum africanum	–	–	✓	–	–	–	–	✓	–	✓	✓	–	–	–	–	–	–	–	[79]
Zanthoxylum capense	–	–	✓	–	–	–	–	✓	–	✓	✓	–	–	–	–	–	–	–	[79]
Nypa fruticans Wurmb	✓	–	✓	–	✓	–	–	–	–	✓	✓	–	–	–	–	–	–	–	[80]
Artemisia absinthium	–	–	–	–	–	–	–	–	–	–	–	–	✓	✓	✓	✓	✓	✓	[81]
Vitex doniana	–	–	✓	–	–	–	–	–	–	–	–	–	✓	✓	–	–	–	✓	[82]
Mucuna pruriens	–	–	✓	–	–	–	–	–	–	–	–	–	✓	✓	–	–	–	✓	[82]
Schotia latifolia Jacq	✓	–	✓	–	✓	–	✓	–	–	✓	✓	–	–	–	–	–	–	–	[83]
Asphodeline Anatolica	✓	–	✓	–	✓	–	–	✓	✓	–	–	–	–	–	–	–	–	–	[84]
Ziziphus mauritiana Lam.	–	–	✓	–	–	–	✓	–	–	–	–	–	–	–	–	–	–	–	[85]
Helichrysum longifolium DC	✓	✓	✓	✓	✓	–	✓	–	✓	✓	✓	–	–	–	–	–	–	–	[86]
Strychnos henningsii Gilg	✓	✓	✓	✓	✓	–	✓	–	✓	✓	✓	✓	✓	✓	–	–	–	✓	[87]
Citrus sinensis	–	–	✓	–	–	–	–	–	–	✓	✓	–	–	–	–	–	–	–	[88]
Citrus anrantifolia	–	–	✓	–	–	–	–	–	–	✓	✓	–	–	–	–	–	–	–	[88]
Citrus limonum	–	–	✓	–	–	–	–	–	–	✓	✓	–	–	–	–	–	–	–	[88]
Acalypha manniana	–	–	✓	–	–	–	–	–	–	✓	✓	–	–	–	–	–	–	–	[89]
Chrysophyllum albidum	✓	✓	–	–	–	–	–	–	–	✓	✓	–	✓	–	–	–	–	✓	[90]
Murraya Koenigii	✓	✓	–	–	–	–	–	–	–	✓	✓	–	✓	–	–	–	–	✓	[91]

Legend: ✓ indicates present while – indicates not evaluated. RP: reducing power activity, HPS: hydrogen peroxide scavenging activity, NS: nitrogen oxide scavenging activity; FS: FRAP scavenging activity, DS: DPPH radical scavenging activity, SS: superoxide anion scavenging activity, AS: ABTS radical scavenging activity, HS: hydroxyl radical scavenging assay, TAC: total antioxidant capacity, TPC: total phenolic content, TFC: total flavonoid content, GSH: reduced glutathione, CA: catalase activity, SOD: superoxide dismutase activity, GPx: glutathione peroxidase, GRx: glutathione reductase, MDA: malondialdehyde, PCC: protein carbonyl content, Ref: references.

Table 2. Some plants with ***in vitro*** and ***in vivo*** antioxidant activities.

Oxidative stress diseases	Plant	Phytochemical	Mechanism of action	References
Cardiovascular disease	*Euterpe oleracea*	Flavonoids	*In vitro* atheroprotective effects	[92]
	Flos chrysanthemi	Flavonoids	Vasodilating effects and protected vasodilator reactivity	[93]
	Gnetum macrostachyum	Stilbenoids	Antioxidant and anti-inflammation activities	[94]
	Polyphenols	Crocin, carotenoid	protected oxidative stress-induced apoptosis of platelets	[95]
Anti-obesity	*Vaccinium floribundum* *Aristotelia chilensis*	Anthocyanins, proanthocyanidins	Limits adipogenesis and inflammatory pathways in vitro	[96]
	Grape products	Polyphenol	Antioxidant action, blocking proinflammatory cytokines	[97]
Diabetes	*Ascophyllum nodosum*	Phenolics	Antioxidant activity and anti-diabetic effect	[98]
	Chrysobalanus icaco	Polyphenolics	Strong antioxidant action and reduction of glycemia in rats	[99]
	----------	Curcumin	Anti-inflammatory and anti-oxidant activities	[100]
	Polyphenol	Butein	Inhibit formation of nitric oxide in vitro and protecting pancreatic β-cells against cytokine-induced toxicity	[101]
Cancer	Polyphenols	Ellagitannins and epicatechin	Anticarcinogenic properties	[102]
	Green tea, grape seeds	Polyphenols, proanthocyanidins	Protect the skin from the adverse effects of UV radiation preventing risk of skin cancers	[103]
Aging	*Elaeis guineensis leaves*	Methanol extract	High antioxidant activities and potential ability as an anti-aging agent	[104]
	Epigallocatechin gallate	Crude extract	Extended lifespan of healthy rats by reducing the damage of liver and kidney and improving age-associated inflammation and oxidative stress through inhibiting NF-β signaling	[105]
Alzheimer's disease	*Crataegus pinnatifida fruit*	Crude extract	Potential neuroprotective activity for preventing oxidative-related disorders in vitro	[106]

Oxidative stress diseases	Plant	Phytochemical	Mechanism of action	References
	Aegle marmelos	Ethyl acetate extract	Antioxidant activity as well as potential acetylcholinesterase inhibitory property	[107]
		Curcumin	Reduced levels of oxidative stress and attenuated increased acetylcholinesterase in mice	[108]

Table 3. Some plants/phytochemicals with therapeutic effects on oxidative stress-related diseases and possible mechanism of action.

oxygen with higher efficiency as compared to the α-tocopherol. More so, β-carotene can be cleaved by β-carotene-15,150-dioxygenase into the two molecules of vitamin A, another antioxidant.

Hydroxycinnamates: Hydroxycinnamic acids which include ferulic acid, caffeic acid, p-coumaric acid, sinapic acid are another category of dietary antioxidants that are known to protect LDL from oxidation and can prevent coronary heart disease and atherosclerosis [69]. In vitro studies involving human LDL as the oxidizing substrate have shown hydroxycinnamic acids to have higher antioxidant activity than hydroxybenzoic acids [70].

6.2. Plants with antioxidant properties

Several plants are known to possess antioxidant properties due to the presence of certain phytochemicals that have been shown to exhibit antioxidant activities in *in vitro* and *in vivo* studies as well as in humans. Consumption of vegetables and fruits rich in antioxidant phytochemicals has proven to increase the antioxidant capacity of serum/plasma. For example, consumption of strawberries, red wine, vitamin C or spinach in elderly women significantly increased the total antioxidant capacity of serum as well as plasma vitamin C levels [71]. Also, another study showed the plasma antioxidant capacity to significantly increase after consuming 10 servings of fruits and vegetables per day for 15 days [72]. Apart from vitamins present in these fruits and vegetables, other plant phytochemicals could be accountable for the increased total antioxidant capacity in serum as other studies have shown the presence of anthocyanins in human serum [73]. More so, apples are highly rich in phenolics and flavonoids thus polyphenols may also be accountable for total antioxidant activity in serum. As such, phytochemicals in fruits and vegetables could interact together such that their additive and synergistic effects could potentiate their antioxidant activities [74]. The pathogenesis of some chronic diseases such as cardiovascular diseases, type 2 diabetes, cancer etc. is accompanied by chronic inflammation which is mediated by the release of free radicals by inflammatory cells [75, 76]. Several antioxidant phytochemicals including resveratrol, anthocyanins, and curcumin, have been found to have anti-inflammatory action via inhibition of prostaglandin production, enzyme inhibition and nuclear factor-kB activity, as well as increase of cytokine production [77]. This section highlights on some plants which have shown to possess antioxidant activities *in vitro* and *in vivo* as well as antioxidant phytochemicals against certain oxidative stress diseases with their mode of action as summarized in **Tables 2** and **3**.

7. Conclusion

Obvious deleterious effects of free radicals as regards man's heath cannot be over emphasized. Oxidative stress due to overwhelming levels of free radicals has promoted the progression of diseases such as diabetes, cancer, cardiovascular diseases, atherosclerosis etc. and even aging. Plants phytochemicals and some vitamins have shown to possess antioxidant properties capable of scavenging free radicals, preventing cellular damages and related diseases via several mechanisms. As such, plants phytochemicals are now being considered as the most sustainable alternative source of antioxidants to supplement the endogenous oxidative stress defense system in humans. Continuous efforts are needed to characterize plants phytochemicals for their antioxidant potentials and mode of action for various therapeutic uses against oxidative stress-related diseases while regular consumption of fruits and vegetables are encouraged for the prevention of these diseases.

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