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Review Article

Antioxidants for the Prevention and Treatment of Non-communicable Diseases

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Abstract

Abiotic environmental stress causes plants and animals to produce excessive superoxide radicals that are extremely toxic and reactive, thereby causing injury to tissue resulting in the occurrence of several disorders. Antioxidants can counteract free radicals by preventing non-communicable diseases. There are natural and synthetic antioxidants. Natural antioxidants in fruits, vegetables, and spices can be consumed, while synthetic antioxidants are produced in laboratories via chemical processes. This review focused on the sources, pharmacological properties, applications, and prospects of natural and synthetic antioxidants, as well as exogenous and endogenous antioxidants. A literature search was done using different search engines like Google Books, Science.gov, Microsoft Academic, Worldwide Science, ResearchGate, Bielefeld Academic Search Engine (BASE), Medline, and PubMed Central. Different keywords, such as antioxidants, free radicals, oxidative stress, superoxide radicals, and oxygen radicals, were used. The relevant literature was collected and used in this review. Antioxidants inhibit oxidation and help to prevent non-communicable diseases, such as aging and inflammatory processes, tumors, kidney and liver diseases, coronary heart disease, cataracts, renal toxicity, and neurological diseases. It was found that antioxidants in the diet have the capacity to prevent oxidative anxiety-related disorders.

Introduction

Antioxidants are agents that slow or prevent oxidative injury to a target molecule in living organisms. They are secondary metabolites in the human body as well as in fruits and vegetables.[1] To avoid oxidation of the vulnerable substrate, plants create a remarkable array of antioxidants, such as alkaloids, phenolics, and vitamins C and E.[2] Because the human body cannot produce sufficient antioxidants to protect people from the continual threat of reactive oxygen species (ROS), plant-based dietary antioxidants are thought to play a crucial role in sustaining human health.[3] A single antioxidant molecule may bind with one ROS at a time and neutralize it by discarding its electrons, thus putting an end to the carbon-stealing reaction.[4] Antioxidants also act as scavengers by preventing cell and tissue damage. Preventative processes, repair mechanisms, and physical and antioxidant defenses all help cells defend against excess free radicals.[5]

Antioxidants can be broadly classified into natural and synthetic. This classification depends on their sources that is either produced by living organisms or synthesized in a laboratory. However, they are further subdivided into smaller groups based on their bioactivity (enzymatic and non-enzymatic antioxidants), solubility (water-soluble and fat-soluble antioxidants), and size (small molecule and large molecule antioxidants) (Fig. 1). There are other possible classifications of antioxidants, such as endogenous and exogenous antioxidants; primary and secondary antioxidants.[6] Enzymatic antioxidants break down and remove free radicals by converting harmful oxidative products into hydrogen peroxide that is further metabolized by catalase into water in a stepwise reaction in the presence of cofactors.[7] Non-enzymatic antioxidants inhibit reactions involving free radicals.[5,8] Water-soluble antioxidants, such as vitamin C can be found in cellular fluids like cytosol and cyto-

Keywords: Antioxidants; Free radicals; Oxidative stress; Medicinal; Pharmacological.
Abbreviations: BHA, butylated hydroxyanisole; BHT, butylated hydroxytoluene; MAPKs, mitogen-activated protein kinases; NF-αβ, nuclear factor kappa B; ROS, reactive oxygen species.

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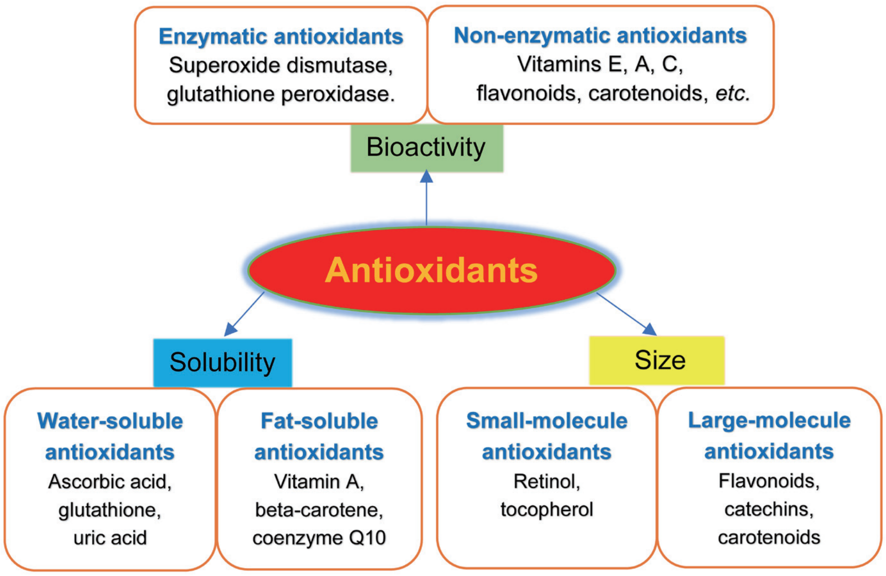

Fig. 1. Different classes of antioxidants.

plasmic matrix, whereas vitamin E, lipoic acid, and carotenoids are lipid-soluble antioxidants and are mostly found in a cellular membrane.[9] In radical scavenging processes, small molecule antioxidants scavenge ROS and transport them away. On the other hand, large molecule antioxidants clean the ROS and stop them from damaging other important proteins.[10] Endogenous antioxidants are the antioxidants made by the human body, while exogenous antioxidants are obtained through a person's diet by supplementation. However, the endogenous and exogenous antioxidants can work synergistically to maintain or establish a redox balance. Furthermore, primary antioxidants interact with the oxidants (free radicals) to transform them into more stable, non-reactive products. They are therefore known as the chain-breaking antioxidants because they can directly interact with the radicals to transform them into non-radicals, consequently preventing them from further peroxidation.[11] Secondary antioxidants are referred to as preventive antioxidants or hydroperoxide decomposers and can convert hydroperoxides into non-reactive products. They maintain the required antioxidant level in the body by reducing the level of peroxides and making nicotinamide adenine dinucleotide phosphate (NADPH) and glutathione available for the primary antioxidant enzymes.[12]

In addition, antioxidants are believed to act through two different mechanisms. The first mechanism is the chain-breaking reaction wherein the primary antioxidant gives an electron to the existing free radical. The second step includes neutralizing the chain initiating catalyst, which removes the ROS initiators (secondary antioxidants).[13] Antioxidants also influence biochemical pathways through a series of processes; namely, donating electrons, metal ion chelation, co-antioxidants, and genomic modulation.

Consuming antioxidants regularly will aid in eliminating the naturally occurring free radicals in the body, thus enhancing wellness by reducing the chance of non-communicable diseases like cancer, diabetes, cataracts, renal toxicity, coronary heart diseases, as well as liver and kidney diseases. Antioxidants can also protect the skin against sunlight exposure dryness, wrinkles, UV-induced skin cancer, and sun-induced skin edema, hence the need to campaign on the medical importance or advantages of antioxidants. Many of these antioxidants have gained attention in clinical studies and can be used in the management of non-communicable diseases. Therefore, this review aimed to explore and offer an insight into the medicinal uses of antioxidants in non-communicable diseases, thus improving the management of these diseases.

Free radicals and oxidative stress

Oxidative stress is a result of an increase in the generation of free radicals or a decrease in the number of antioxidants.[14] Oxidative stress causes the imbalance of free radicals and antioxidants. Free radicals are unstable and highly reactive when reacting with other species. In addition, metabolic pathways produce free radicals, that can destroy carbohydrates, lipids, proteins, and nucleic acid.[15] Likewise, free radicals have dual actions depending on their concentration. While a high concentration of free radicals could damage the living process, a low concentrations could prevent infections.[9] Furthermore, the accumulation of free radicals damages the biological components of proteins, lipids, and DNA, as it breaks down single and double strands of DNA, degrades nitrogenous bases, and transforms and cross-links DNA with proteins.[16] These impaired DNA modifications can accelerate aging and cause neurodegenerative, carcinogenesis, autoimmune, cardiovascular, and other diseases.[11] Hence, oxidative stress is critical for the pathogenesis of some diseases (Fig. 2). As such, free radicals can oxidize the protein's backbone and its side chains, which would react with their functional groups to generate the carbonyl function. By disrupting the cellular membrane, free radicals can also break down peptide bonds, oxidize amino acids, as well as cause lipid peroxidation. Thus, the accumulation of free radicals in the body could trigger an array of non-infectious diseases. As a result, antioxidants help to keep them at the lowest concentration in the body.

Antioxidants and mechanisms of action

Antioxidant defenses vary per species, but are universal.[17] As a result, the oxidation reaction is necessary for life since it aids in the maintenance of the human body's composite structure, but it

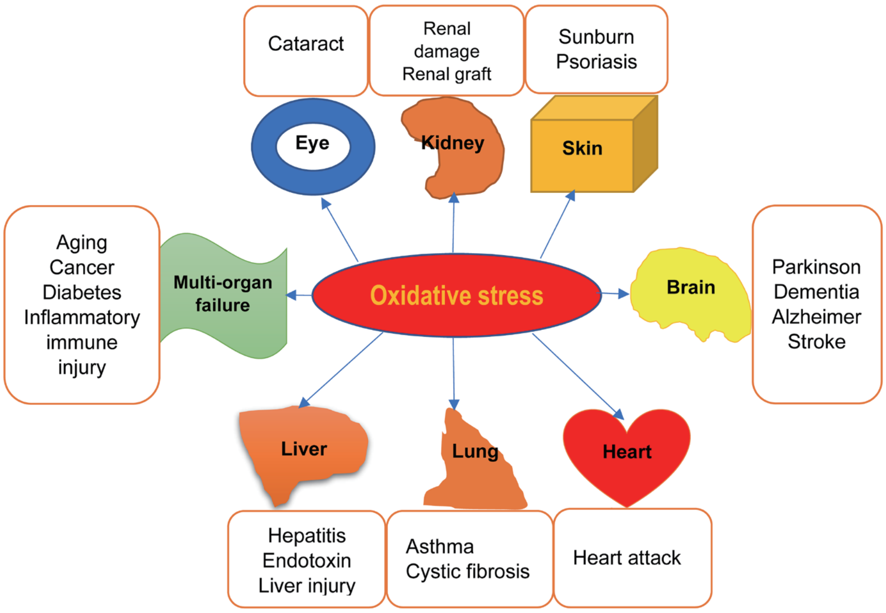

Fig. 2. Diseases caused as a result of oxidative stress.

could also be harmful when allowed to proceed unchecked.[18] Oxidation is a chemical process that generates high ROS, which leads to a series of chain reactions to destroy cells. Thus, a variety of non-living factors would increase the amount of ROS in the body, consequently causing tissue damage and diseases.

Antioxidants can neutralize ROS to protect against or treat oxidative stress-related diseases.[10] They neutralize free radicals and are essential for maintaining optimal cellular functions. Moreover, they are crucial for the protection of the biological system by preventing the formation of new radicals, trapping free radicals to prevent chain reactions, and repairing the damage caused by free radicals.[19]

Antioxidants in the defense systems operate on a variety of levels, including prevention, antiradical, repair, as well as adaptation.[10,11] Furthermore, antioxidants can scavenge reactive radicals to prevent a chain initiation and/or disrupt the chain propagation processes. The repair antioxidants in mammalian cells' cytosol and mitochondria identify, break down, and eliminate oxidatively damaged proteins, thus preventing oxidative protein buildup.[17] The signal for free radical generation and reactions causes the creation and distribution of the relevant adaptive antioxidants to the appropriate places.

Natural and synthetic antioxidants

Natural antioxidants are a group of antioxidants that are either synthesized in the human body or are obtained from other natural sources that are consumed. Natural antioxidants are widely found in food materials and medicinal plants and exert numerous biological effects ranging from anti-aging, anticancer, and anti-inflammation to anti-atherosclerosis.[18] In addition, natural antioxidants coming from vegetables and fruits are of the utmost importance; however, antioxidants from other foods and agricultural products should not be ignored.[19] Natural antioxidants from plants are primarily classified into three categories; namely, polyphenols, carotenoids, and vitamins. They are important components of some plant parts. Phenolic compounds are diverse in structure ranging from simple molecules, such as ferulic acid, vanillin, etc. to more complex polyphenols, such as flavonoids and tannins.[20] Some phenolics in addition to their antioxidant activities also possess antimicrobial activities, thus exerting an effect on the food texture and flavors.[21] An array of vitamins has also been shown to possess antioxidant activity, in which the most important of these are vitamins E and C. Vitamin E is a lipid that comprises tocopherols and tocotrienols, which occur in four isomeric forms (α, β, γ, and δ), but only the α-tocopherol is of nutritional importance.[22] The α-tocopherols can be found in legumes and cereals.[23] Vitamin C is water-soluble and is present in fruits and vegetables. Vegetables and fruits are good sources of carotenoids as well, but the carotenoids that are known to possess antioxidant activities are β-carotene, α-carotene, lycopene, and lutein (Fig. 3).[24] In addition to their antioxidant activity, carotenoids are used as coloring agents in food.[25] Nonetheless, a major concern in exploring the antioxidants from food and medicinal plants is the effective extraction from various sources.

On the other hand, synthetic antioxidants (Fig. 3) are chemically produced compounds that do not occur in nature, but can be added to food as preservatives to inhibit lipid oxidation.[26] Because of the instability of the natural antioxidants, synthetic antioxidants have been used in stabilizing fats and oil and have been used as antioxidants in human food for many decades.[27] Synthetic antioxidants are commonly used in food production, and they include butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), propyl gallate (PG), and *tert*-butyl hydroquinone (TBHQ). In addition, 2-naphthol (2NL), 4-phenyl phenol (OPP), and 2,4-dichlorophenoxyacetic acid (2,4-DA) are the ones mostly used in fruits and vegetables.[22] However, though synthetic antioxidants are still being used for the preservation of food, researchers have raised safety issues concerning their continued use. Such health issues that have been linked to protracted intake of synthetic antioxidants include triggering certain disease conditions.[28,29] Kornienko *et al*.[30] reported that an intake of a high dose of synthetic antioxidants in food could induce DNA damage and cause premature senescence. Specifically, BHT and BHA have been found to cause a damaging effect on the liver and are carcinogenic as well.[31] Considering some of the nondesirable health effects of synthetic antioxidants,

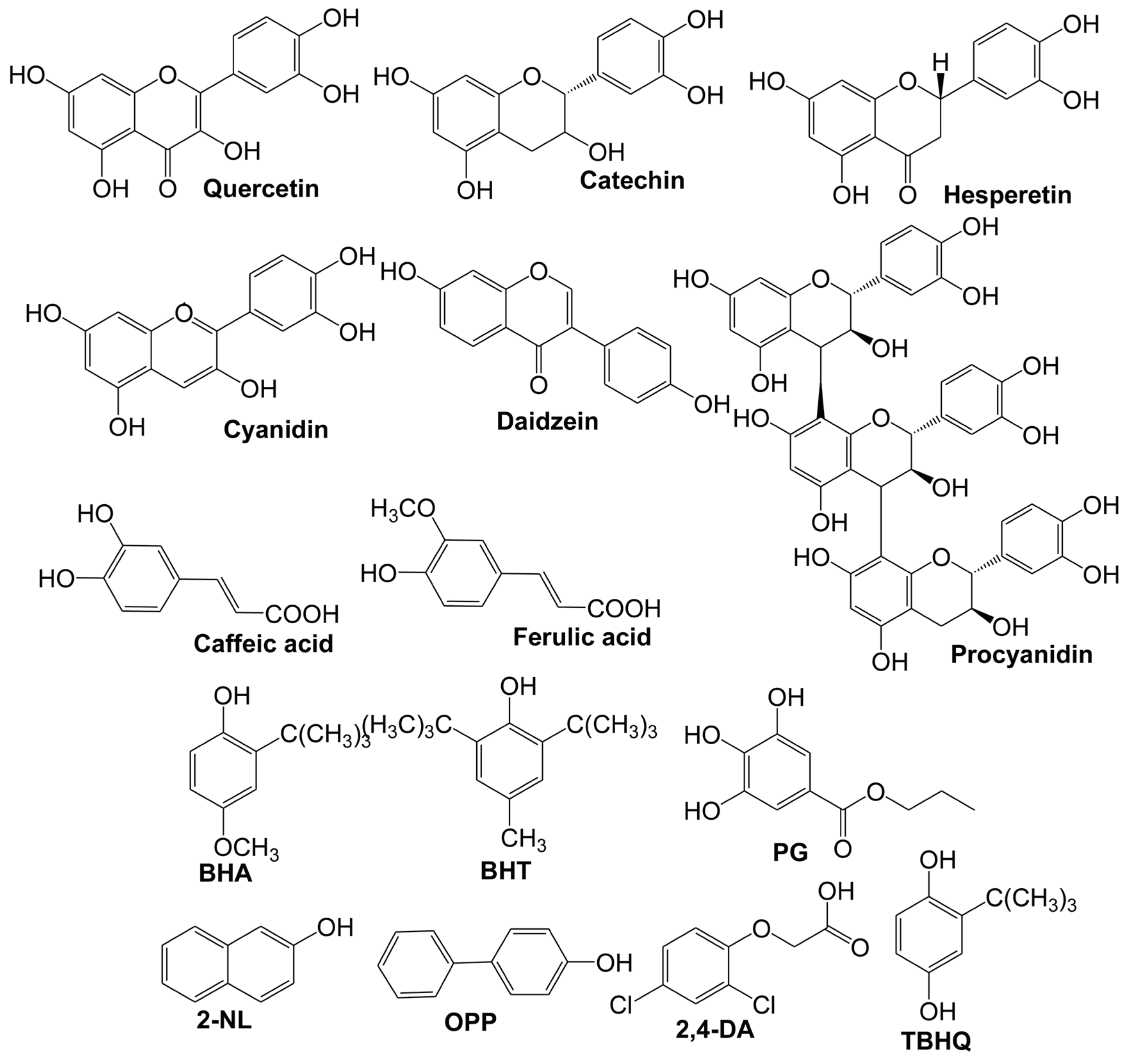

Fig. 3. Chemical structure of some phenolic and synthetic antioxidants in fruits. 2-NL, 2-naphthol; BHA, butylated hydroxyanisole; BHT, butylated hydroxytoluene; OPP, 4-phenylphenol ; PG, propyl gallate; TBHQ, tert-butyl hydroquinone.

replacing synthetic antioxidants with larger natural antioxidants is important to meet dietary needs.

However, synthetic antioxidants are cost-efficient, have a wide availability, and provide stability advantages over natural antioxidants,[22] but have been associated with some deleterious side effects in human cells giving rise to controlled usage/consumption.[20] As a consequence, this has fueled the search for safe natural antioxidants with characteristics of higher performance and sustainability, as consumers have a stronger preference for natural antioxidants, which can be broadly grouped into plants, animals, and microorganisms.[22]

Antioxidants' origin and sources

Plant sources of antioxidants

Plants are the major source of many antioxidants in nature. According to previous research,[32] the reasons for the synthesis and accumulation of these antioxidants in plants are 1. the normal physiologic functions, and protection against pathogenic microbes and animal herbivores, and 2. capacity to build them in response to environmental stress conditions. Some of these antioxidants accumulate as colored pigments in the leaves, fruits, nuts, and roots of many plants. These colored pigments, such as beta-carotene, lutein, lycopene, and zeaxanthin, are all carotenoids either in their primary or secondary forms and abound in leafy vegetables and fruits. For instance, beta-carotene accumulates in carrots, leafy vegetables, spinach, and tomatoes.[33] Lutein accumulates in green leafy vegetables, and zeaxanthin accumulates in spinach, while lycopene is abundant in tomatoes, watermelon, guava, pink grapefruit, and blood oranges.[25] Likewise, studies have shown that some green tea leaves and herbs[31] are better antioxidants than vegetables and fruits.[20] Some herbs, such as *Cissus quadrangularis* L, *Erythrina abyssinica* Lam. Ex. DC., and *Adenium multiflorum Klotzsch* used in the management of animal wounds in Zimbabwe have antioxidant activities.[34] However, among the herbs tested, *C. quadrangularis* leaf extract exhibited superior antioxidant activity. Another type of antioxidant that accumulates in plants is vitamins like A, C, and E. Vitamin A is known to be abundant in sweet potatoes, vitamin C (ascorbic acid) in fruits and vegetables as well as in cereals, while vitamin E (α-tocopherol) accumulates in some plant oils, such as wheat germ oil, soybean oil, and corn oil. Essential oils from oregano and clove were found to have potential antioxidants probably due to the high phenolic contents.[35] As a result, the accumulation of these antioxidants in plants could be dependent on some intrinsic and extrinsic factors. For instance, cultural practices, genotypes, and environmental conditions influenced the accumulation of lycopene in tomato fruits.[36] Some authors[30–37] also observed that the reported high activities of antioxidants from plants were based on *in vitro* studies without corresponding *in vivo* studies. The implication was that the potency of antioxidants from plants as widely acclaimed may not be 100% correct. According to the authors, during the *in vivo* studies, the antioxidant activity was influenced by bioavailability, gut absorption, metabolism, and other factors.[32]

Animal sources of antioxidants

Animals or animal products are not significant sources of antioxidants in nature due to their low concentrations in comparison with plant-based antioxidants.[38] According to a previous report,[39] the concentrations and types of antioxidants accumulated in animals/animal products depend on the constituents of the animal feed.[40] Some animal products, such as fish lipid, egg, and milk contain selenium and fat-soluble vitamins. Some antioxidants in milk, especially casein, occur as protein fractions whose antioxidant activities increase after digestion into peptides.[38] Uric acid can also be formed by the ruminal breakdown of microbial nucleotides and be an important milk antioxidant. The antioxidants from an animal are mainly from protein-rich compounds of animal products, which are digested by proteases either from the animal or by some microflora of the animal/animal products into peptides.[40] Nevertheless, few antioxidative peptides from the hydrolysis of animal protein were reported elsewhere.[40] According to some reports in the literature, the antioxidants from animal and insect sources have not been commercialized because their antioxidant activities and safety profiles still need to be validated.[41,42]

Microbial sources of antioxidants

The microbial community probably contains the largest reservoir of antioxidants in nature. This may be due to the diversity of the bacterial, fungal, and microalgae species. The microbial diversity and their metabolic activities define the diverse biosynthetic pathways that produce the varied bioactive compounds. As such, the term "fermentation" has been used to describe the process of producing various compounds by microorganisms. Thus, the fermentation processes can lead to either an intracellular or extracellular production of bioactive compounds which can be recovered either as an intact whole cell or cell-free extract using organic solvents. In addition, in the bacterial community, both the gram-positive and gram-negative bacteria have the potential to produce antioxidant compounds.[43] However, the *Streptomyces spp* and lactic acid bacteria are probably more prominent in antioxidant production. An extract of a *Streptomyces variabilis* (EU841661) isolate had scavenging activities against free radicals and hydrogen peroxide at a concentration of 5.0 mg/mL and 0.05 mg/mL, respectively.[44] Another previous study indicated that *L. plantarum* AR501 had the scavenging activity against the α-diphenyl-β-picrylhydrazyl (DPPH) free radical and hydrogen radical *in vitro*. Moreover, oral administration of *L. plantarum* AR501 produced functional foods to alleviate oxidative damages in a mouse model of oxidative injury.[43] Superoxide dismutases (SODs) are produced in high concentrations by aerobic microorganisms, such as *Corynebacterium glutamicum.*[43] Probiotic bacteria (*Streptococcus thermophiles*) and many lactic acid bacteria (*Lactobacillus* spp) are excellent sources of many types of antioxidants either as intact whole cell or cell-free extracts.[45] Some species of *Streptomyces* also produce antioxidants like carotenoids. It was reported that *Streptomyces chrestomyceticus* produced lycopene, a type of carotenoid, which could be used as a coloring agent in the food industry.[43] Furthermore, *Xanthophyllomyces dendrorhous* could produce high amounts of antioxidants like carotenoids. The concentration and activities of antioxidants produced by microorganisms are dependent on some physicochemical parameters of the fermentation processes,[46] as well as the type of organic solvent used for antioxidant extraction.[47]

There are myriads of fungal species that produce antioxidants, including filamentous fungi, such as *Aspergillus* spp and *Penicillium* spp. *Aspergillus saitoi* and *Penicillium roquefortii* IFO 5956 contain a bioactive compound (2,3-dihydroxybenzoic acid) with high antioxidant properties.[43] *Aspergillus* spp and *Penicillium* spp can also produce antioxidants, such as citrinin, protocatechuic acid, curvilic acid, atroventin, and gallic acid.[43] Antioxidant activity produced by fungal species sometimes depends on the food substrate/fermentation medium. For instance, a methanolic extract of some fermented soybean foods presented antioxidant compounds of a high activity.[48] It is further believed that fungal fermentation produce more antioxidants than those produced by bacterial fermentation.[43]

The microalgal antioxidants are similar to plant antioxidants probably because of the similar characteristics shared by both in terms of the physiology and environmental impact. For instance, both plants and microalgae obtain their food through the process of photosynthesis and receive the same or similar environmental stimulation that triggers oxidative stress. Microalgal species are very diverse and apparently are the richest source of antioxidants in nature. Microalgae accumulate different types of antioxidants, such as polysaccharides, carotenoids, sterols, vitamins (A, C, D, K, and E), flavonoids, amino acids, polyunsaturated fatty acids, minerals, sulfated polysaccharides, sulfolipids, peptides, coenzyme Q, phycocyanin, and scytonemin (a source of blue-green algae).[7] Although all the antioxidants produced by microalgae are not commercialized, some of them that are widely produced with a high market value, include lutein, astaxanthin, and *β*-carotene.[49] Under environmentally stressed conditions, every micro-algae species is a potential source of antioxidants although the concentrations and types of antioxidants would depend on the type of stress to which the organism is subjected. Stressed conditions are known to induce enzymatic and non-enzymatic antioxidants in different microalgae species in response to the ROS.[50] The different types of abiotic stress for the induction of antioxidants in microalgae species have been reviewed.[49] The authors acknowledged that different stressors induced the accumulation of different enzymatic/non-enzymatic antioxidants in diverse species of green microalgae. A recent report[51] revealed that *Desmodesmus subspicatus* LC172266 accumulated carotenoids under nutrient-rich conditions, which would suggest that some microalgae species may spontaneously produce some types of antioxidants. However, the authors were of the view that the accumulated antioxidant may be a primary carotenoid called lutein.

Comparatively, microbial antioxidant productions have more prospects in terms of commercialization than plants or animal resources. This assertion is not just based on the many antioxidants produced by microbes, but on the potential of optimizing productivity through genetic, metabolic, and environmental engineering.[52–55]

Medicinal uses of antioxidants

Medicinal plants are possible sources of antioxidants and anti-inflammatory compounds that could be used in the management of different diseases. Preclinical and clinical studies of some antioxidants are summarized in Table 1.[15,56–72] An imbalance of natural antioxidants causes free radical generation from numerous environmental and biological sources, which would result in a wide range of inflammatory illnesses.[73] Additionally, oxidative stress and its accompanying components have now become a major public health concern.[74] As such, therapeutic plant extracts and their isolated active ingredients have a wide range of therapeutic effects against a wide range of acute and chronic disorders. Anti-inflammatory studies have shown that extracts and their organic products exercise their bioactivity by inhibiting two main signaling pathways, mitogen-activated protein kinases (MAPKs), and nuclear factor kappa B (NF-κB), that are responsible for producing a variety of proinflammatory mediators.[74,75] Alkaloids, polyphenols, terpenoids, and flavonoids are well-studied phytonutrients for anti-inflammatory activity.[14,76] Plants that contain these phytoconstituents are used as anti-inflammatory agents.

In oxidative damage and the progression of carcinogenesis, two distinct processes are thought to be involved. The first mechanism is through gene expression regulation. Growth signals and proliferation can be stimulated by epigenetic changes in gene expression.[77] Radicals cause genetic changes, such as mutations and chromosomal conformational changes, which might contribute to the onset of carcinogenesis in the second mechanism.[78]

Antioxidants can also act as anticancer agents[74,78,79] because they can scavenge free radicals that can cause DNA conformational changes, DNA/protein cross-links, and DNA damage,[16] leading to cell mutation, transformation, and cancer.[80] As a consequence, antioxidants can inhibit the growth of oxidative cancer cells by neutralizing free radicals.[81]

A β-carotene, as an antioxidant, can protect against cancer development.[2,82] Its photoprotective activities may guard against UV light-induced cell damage and cancer development, and its immunoenhancement may help to protect against cancer progression.[6] Likewise, vitamin C may aid in the prevention of cancer because it has potent antioxidant activity to inhibit the development of nitrosamines, enhance the immunological response, and produce the detoxification of liver enzymes.[82,83] Additionally, vitamin E improves immunocompetence by boosting humoral immune responses, bacterial infection resistance, cellular-immunity, tumor necrosis factor generation by inflammatory cells, and inhibiting mutagenesis, DNA repair, and microcell formation.[84,85] As a result, vitamin E may be beneficial in preventing cancer and inhibiting carcinogenesis through regulating immune function.

Diabetes is a metabolic disorder marked by relative or absolute insulin secretion deficits leading to chronic hyperglycemia and carbohydrate, lipid, and protein metabolism abnormalities.[16] The metabolic disorders cause a variety of complications. Additionally, diabetes mellitus has been linked to increased formation of free radicals and a reduction in antioxidant activities, which also results in the imbalance between the generation of ROS and antioxidants, thus leading to oxidative damage to cell proteins, lipids, and nucleic acids.[11,86] Glucose autoxidation is the most important factor in the generation of free radicals among the different variables that cause increased oxidative stress. Other factors also elevate the levels of pro-oxidants, imbalance in cellular oxidation, and a reduction in antioxidant defense. Low concentrations of ascorbate, glutathione, and superoxide dismutase are the most prevalent antioxidant deficits during the pathogenic process of diabetes. Therefore, plants, especially those with high quantities and potent antioxidant chemicals, can treat oxidative stress-related diseases like diabetes mellitus. Many studies have also examined the impact of their antioxidant components on diabetes complications to achieve promising results by demonstrating the benefits of plants with high antioxidant levels in the treatment of diabetes.[1,3,11]

In addition, antioxidant consumption from fruits and vegetables aids in the management of cardiovascular illnesses. Because oxidative processes can alter cardiovascular disorders, they have the potential to deliver tremendous health and lifespan benefits. Polyunsaturated fatty acids make up a large portion of low-density lipoproteins (LDL) in the blood, and their oxidation plays an important function in atherosclerosis.[87] With a high quantity of oxidized lipids in the blood, blood vessel damage occurs, which can result in the formation of foam cells and plaque leading to atherosclerosis. Atherogenic oxidized LDL is thus thought to be essential in the production of atherosclerosis plaque. Moreover, oxidized LDL is cytotoxic and can directly harm endothelial cells.[88] Likewise, antioxidants like β-carotene and vitamin E are important in preventing cardiovascular disorders.[82]

Due to the ever-increasing resistance to synthetic antibiotics, we must shift our focus to natural antioxidant-based antibacterial products, which have a range of scientific diversity and provide an effective therapeutic benefit while preventing microbes from replication and developing resistance. Phenolics are also important antibacterial antioxidants because they inhibit the growth of bacteria and their pathogenic activity.[87] Antioxidants act as antibacterial reagents by inhibiting nucleic acid production, the permeability of the outer membrane, and cytoplasm leakage. Antioxidants' antibacterial effect may be owing to their ability to chelate iron, which is essential for the existence of all bacteria.[88] Polyphenols break the cell wall, enhance cytoplasm membrane permeability, as well as release lipopolysaccharides.

However, antioxidant efficacy against microbial infections is becoming more generally accepted.[89] They also function in tandem with modern antimicrobial drugs to combat drug-resistant microbes. Hence, antioxidant structure determines its antimicrobial effect. Synthetic antibiotics have a speedy therapeutic impact when used to treat microbial infections, but they also represent a substantial risk of gastrointestinal and renal toxicity, and microbial resistance.[88] Nonetheless, natural antioxidants in their purest form have outstanding antibacterial activity against common microbes without evidence to develop resistance to these substances by reinforcing the desire to research natural products to replace synthetic antibiotics.[90] Yet, even though antioxidants function slowly to inhibit microbial growth, their effect is consistent, and a thorough assessment in determining the antimicrobial profile of isolated antioxidants could aid in the use of phytochemicals against microbial infections with minimal toxicity as well as the risk of bacterial resistance.[91]

Liver diseases have also been linked to oxidative stress. Oxidized proteins and a reduction in antioxidant levels contribute to the development of liver diseases.[1,92] However, antioxidants, both natural and synthetic, have been utilized to treat liver disease. When antioxidants were given orally or intraperitoneally, animal studies showed a significant beneficial effect on liver disease.[5] As a result, a large-scale model would be required to determine their safety and effective dose, optimum treatment absorption, duration, and bioavailability.

Resveratrol guards the liver against cholestasis, alcohol, and toxic damage by boosting the lipid profile and reducing liver fibro-

Table 1. Classification, preclinical, and clinical studies of some antioxidants

Antioxidant	Class	Mechanism/Pharmacokinetics	Medicinal Uses	Models	Reference
Morin	Natural	Morin suppresses the activation of NFekB on kidney models during the existence of free radicals.	Anti-aging	Kidney of rats	57
Ascorbic acid Polyphenols Tocopherols	Natural	They improved the endogenous ROS- elimination system in mammalian tissue and helped in the possible management of skin infections and aging.	Prevent skin aging	Not specified	58
Cyanobacterial phycobiliproteins (PBPs)	Natural	They slow aging and related diseases.	Strong anti-aging agent	Rat	56
Lycopene		Decreases nitric oxide, ROS, and lipid peroxyl radical. Lycopene has multiple conjugated double bonds that stimulates its anti-oxidant property. It also slows activation of the mTOR/AMPK cascade pathway linked with aging.	Anti-aging	Not specified	59
Methylene Blue (MB)	Synthetic	Effective in stimulating skin fibroblast multiplication and delaying cellular senescence.	Anti-aging	Human	60
Resveratrol	Natural (phenolic)	Inhibits pro-inflammatory cytokines like IL-1 and TNF-a that are periodontitis mediators. It stops liver steatosis through the intonation of insulin conflict and lipid profile on different models.	Anti-inflammatory Anti-cancer Hepatoprotective	Humans Rats and Humans Wistar rats	61 15 62
Quercetin 7-rhamnoside (Q7R)	Natural	Q7R produced hepatoprotection against CCl_4 induced hepatotoxicity and cytoprotective, antioxidant effects on H_2O_2 treated human liver cells.	Hepatoprotective	Humans	63
Trans-4-hydroxystilbene (THS), Resveratrol, RES, Piceatannol, PIC	Natural	Foraged DPPH and OH radicals and stop the accumulation of ROS in neurons.	Neuroprotective	Rats	64
Quercetin + Curcumin	Natural	They control hyperglycemia by promoting the stimulation and release of insulin.	Anti-diabetic	Rats	65
Setanid		Act by an antitoxic and antiangiogenic mechanism.	Anti-inflammatory HIV infected patients	humans	66 67
Quercetin	Natural	Normalized paracetamol-induced liver and kidney damage by inhibiting oxidative injury	Anti-inflammatory, hepatoprotective	Humans	68
Curcumin	Natural	Reduce malondialdehyde (MDA) concentration and oxidative stress levels significantly. Maintenance of body function and mitochondrial redox balance	Hepatoprotective Nephroprotective Anti-inflammatory Synergistic effects	humans Humans Humans	69 69 70 70,71
Epigallocatechin-3-gallate (EGCG)	Natural (Catechin)	React with superoxide anions and -OH, and is also able to chelate metal ions	Anti-inflammatory	Not specified	72

CCl, carbon tetrachloride; DPPH, α-diphenyl-β-picrylhydrazyl; ROS, reactive oxygen species.

sis and cirrhosis.[93] In diverse models, this would prevent hepatic steatosis by inducing insulin conflict and altering the lipid profile. In Wistar rats, preclinical research demonstrated that resveratrol had a therapeutic impact on liver disease.[1] Yet, greater clinical trials would be needed to give scientific evidence for the management of liver disorders. When there is an imbalance between oxidants and antioxidants in the liver, oxidative stress occurs, thereby impairing liver function.[93] Nevertheless, silymarin was discovered to have the greatest hepatoprotective impact[94] though additional clinical trials would be important to ascertain the significance of the antioxidants on liver function.

In addition, curcumin's nephroprotective effect was connected to the bodily function and mitochondrial redox equilibrium.[95] In patients and laboratory animals, antioxidant prophylaxis reduced renal adverse effects.[96] Green tea extracts (phenolic chemicals) were also found to enhance kidney function and reduce the levels of blood urea nitrogen and serum creatinine.[97] Furthermore, antioxidants derived from plants can be combined with nephrotoxic drugs like cisplatin, contrast media, and others. Natural antioxidants defend bioactive molecules by protecting free radicals from cisplatin-enhanced mitochondrial oxidation, but do not affect the drug's action.[78] In patients with low antioxidant levels, administration of vitamin C protects the kidneys by lowering the ROS, and their oxidative damage.[6] Additionally, endogenous vitamin C acts as an enzyme cofactor to have a renal protective impact.[98]

Phenolic diet consumption provides protection against cardiovascular and neurological illnesses, such as Parkinson's, early onset dementia, and motor neuron disease.[15] Antioxidant neuroprotective activities were investigated by suppressing the ROS in *in-vitro* and *in-vivo* studies.[99] Resveratrol increased the enzyme activity like catalase, SOD, heme oxygenase, and glutathione peroxidase while inhibiting xanthine oxidase.[100] In addition, antioxidant supplementation could help people ameliorate stress-related mental and severe anxiety.[1]

Antioxidant micronutrients like retinol and ascorbic acid may also help prevent eye disorders.[101] Natural antioxidants including flavonoids, vitamins, phenolic acids, and carotenoids could help prevent eye defects.[102] It has also been found that nanotechnology-based formulations of antioxidant biomolecules could improve bioavailability, solubility, and stability, as well as activity.[103] Treatment of eye defects, such as cataracts could be conducted by using nanoparticle-based antioxidant biomolecules that would be effective, biodegradable, and non-toxic.[104] Moreover, natural antioxidants have been used as therapeutic reagents to slow the progression of cataracts.[1] Vitamins C and E and curcumin, having antioxidant and anti-cataract properties, can be included in the diet to help protect against free radicals.

In addition, free radicals that could cause degenerative changes linked with aging,[11,105] DNA, or the buildup of physiological and structural damage are the primary cause of aging.[11] Reducing free radicals or slowing their formation with antioxidants would help delay the process of aging. Hence, increased oxidative stress would be prevalent in aged people, and antioxidants could have a major effect on oxidative damage.[56] The antioxidant defense could minimize free radical damage, and adequate consumption of antioxidant nutrients could improve the quality of life and help people live longer.[11]

Future prospects

Various antioxidants can understand, prevent, and treat acute and chronic diseases like neurodegenerative diseases, eye defects, cancer, aging, diabetes, liver disease, and cardiovascular diseases. Despite discoveries in treatments and diagnosis of these diseases as well as the modifications of the old approaches, these diseases are still quite prevalent with high socio-economic impacts. Therefore, there is a need to continually discover this important therapeutic group of compounds to ignite the zeal for further research and development. The diversity and ubiquity of natural antioxidants in plants and animals are factors that elicit the continual discovery of their roles in these diseases. Therefore, the antioxidant effects of medicinal plants are required to allow their use in medical applications due to their efficacy and safety. Since a plethora of natural antioxidants has been discovered from plants and animals, there are still many more to be identified considering the biodiversity of this source. Moreover, there are underutilized sources of antioxidants among the available ones. Therefore, more research on the potential of antioxidants may lead to a better understanding of how they work to prevent the oxidative process. Furthermore, antioxidant supplements can be recommended for patients who are suspected of having excessive levels of ROS. However, more research would be needed to confirm their efficacy. Because numerous habits and environmental factors enhance the formation of ROS and damage the body, it would sometimes be necessary to change certain lifestyle behavior.

Conclusions

Antioxidants can scavenge free radicals, hence prevent acute and chronic diseases like neurodegenerative diseases, eye defects, cancer, aging, diabetes, liver disease, and cardiovascular disease. Though oxidative stress affects biological systems in several ways, there are enough antioxidant defenses to slow the advancement of the damage. This review provided sufficient information on the classification (natural and synthetic), mechanisms (sequestration of free radicals and ROS), and sources (plants, animals, and microorganisms) of antioxidants, as well as their roles in preventing non-communicable diseases. There are still many unidentified, neglected, or underutilized sources of antioxidants, especially vegetables and fruits, which could be explored as a game-changing strategy in the prevention and treatment of non-communicable diseases. Diet is a key part of the antioxidant defense system since it provides important antioxidants like vitamin C, vitamin E, and carotenoids. As a result, foods high in these nutrients should be included in a regular diet.

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Conflict of interest

The authors state no conflict of interest.

Author contributions

Study concept and design (TOA, CON), acquisition of data (TOA), drafting of the manuscript (TOA, CON), critical revision of the manuscript for important intellectual content (TOA, BOE, CNE, CON), administrative, technical, or material support (BOE, CNE), and study supervision (CON). All authors have made a significant contribution to this study and have approved the final manuscript.

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