Chapter 3
Physiological Significance of Oxidative Stress and Anti-oxidative System

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3.1 Introduction

Two valence electrons have parallel spins in each of their two anti-bonding orbitals in molecular oxygen. This spin restriction allows it to accept a pair of electrons from a donor. A redox reaction is a fundamental metabolic activity in living organisms [1]. The movement of a single electron may result in the formation of free radicals and other issues [2]. Free radicals generally show a high level of reactivity. These radicals are extremely unstable and reactive with other chemicals. Guyton de Morveau coined the term "radical" in 1786, and later, Gay-Lussac, Berzelius, and Liebig used it to refer to unaltered atomic groups in numerous substances [3].

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Free radicals not only take part in pathogenic processes but are also essential for many physiological activities of living organisms, such as healthy aging [4]. Lipid peroxidation was reported to have both negative and positive consequences [5]. Free radicals can cause numerous diseases in humans by damaging lipids, proteins, and DNA. ROS and RNS are responsible for cellular damage by substituting macromolecules [6]. There are numerous antioxidants, both natural and artificial. Endogenous antioxidants are characterized as enzymatic or non-enzymatic [7].

3.2 Roots of Oxidative Stress

An imbalance in the production of reactive oxygen species results in the oxidative stress and capacity of an organism's antioxidative defense mechanisms to lessen the harm due to oxidants. As a byproduct of normal aerobic metabolism, ROS may provide a fundamental health concern when the amount increases in response to stress [8]. The mitochondrion is a primary organelle which is taking part in the production of ROS. ATP is produced by numerous processes including the electron transport chain. Only one or two electron of oxygen are reduced instead of four electrons during this process, which is responsible for the formation of O_2 or H_2O_2, which then changes into other ROS [9]. Free radicals may be created by both internal and external processes. Infection, inflammation, ischemia, immune cell activation, cancer, mental stress, and aging contribute to endogenous free radical formation [10].

Numerous studies show that excessive macronutrient intakes might increase oxidative stress. An excessive amount of high caloric intake will increase the number of substrates entering mitochondrial respiration. As a consequence, the number of contributed electrons to the electron transport chain will be surged [11]. When superoxide concentrations cross a certain point, extra electrons may gather at complex III and donate more electrons to molecular oxygen [12].

ROS generation is fundamentally dependent on enzymatic and non-enzymatic processes. Superoxide radical is produced by xanthine oxidase, peroxidases, and NADPH oxidase [10]. The sole class of enzymes with the specific purpose of producing ROS is the NADPH oxidases, which differentiates it from other enzymes producing ROS as the byproduct of their activity [13]. Free radicals may also be created by non-enzymatic processes like oxygen's interactions with organic materials or the radiation that is exposed to cells. Non-enzymatic free radicals production may also take place during mitochondrial respiration [14].

3.2.1 Endogenous Sources of ROS Production

Different cellular organelles with high oxygen consumption rates, including the endoplasmic reticulum, mitochondria, and peroxisomes are examples of endogenous generators of ROS.

3.2.1.1 Production of Oxidative Stress in Mitochondria

Mitochondria generate the majority of the intracellular ROS. Oxidizing radicals are generated at complex-I and complex-III in oxidative phosphorylation [15]. Alongside cytochrome c oxidase, monoamine oxidase, glycerol phosphate dehydrogenase, a-ketoglutarate dehydrogenase, and p66shc also take part in ROS generation within mitochondria [16].

3.2.1.2 Generation of Oxidative Stress in Peroxisomes

The respiratory pathway in peroxisomes involves the transport of electrons from different metabolites to O_2, which ultimately causes the generation of hydrogen peroxides [17]. β-oxidation of fatty acids produces hydrogen peroxide in peroxisomes. $OH^{\bullet}$, H_2O_2, and $O^{2\bullet-}$ are also produced in peroxisome [18].

3.2.1.3 Generation of Oxidative Stress in the Endoplasmic Reticulum

Diamine oxidase, cytochrome b5, and cytochrome P-450 play role in ROS production [19]. Erop1p is a thiol oxidase that leads to the production of H_2O_2 [20]. Auto oxidation of the prostaglandin synthesis, immune cell activation, adrenaline, cytochrome P-450, phagocytic cells, flavin mononucleotide (FMNH2), flavin adenine dinucleotide (FADH2), inflammation, anxiety, mental stress [21], infection, excessive exercise, aging, ischemia, and cancer are other endogenous sources of ROS [19].

3.2.2 Production of Oxidative Stress by Exogenous Sources

Various synthetic products are causing oxidative stress directly or via producing by-products. Some of the major exogenous sources for the generation of oxidative stress are given below (Fig. 3.1).

I. **Smoke-generated oxidative stress**

Smoke from cigarettes comprises a variety of extremely unstable free radicals that increase the generation of ROS and RNS and cause oxidative stress [22]. Lung

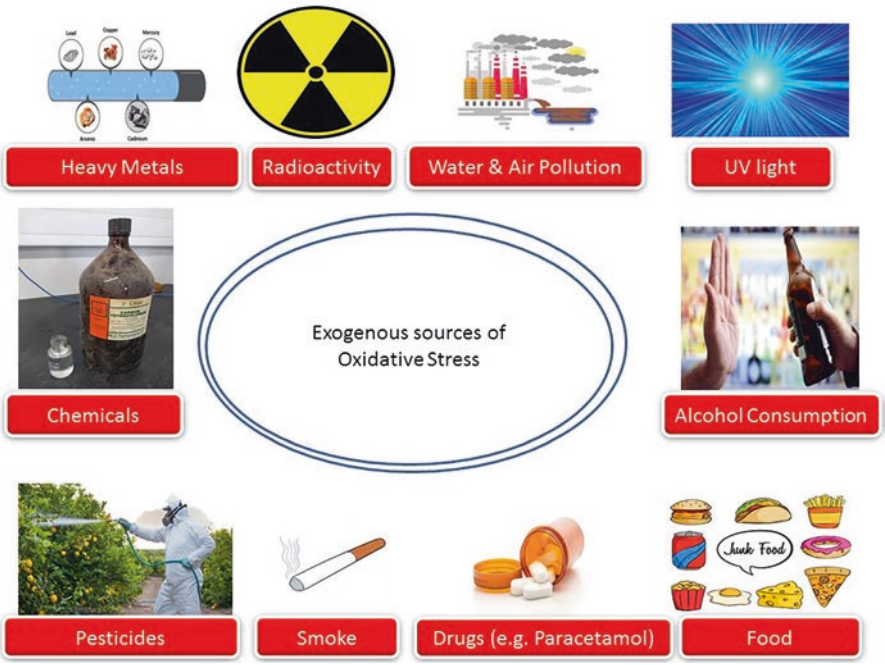

Fig. 3.1 Exogenous sources of oxidative stress

inflammatory cells (macrophages, epithelium, and neutrophils) are affected by cigarette smoke, due to the activation of NADPH oxidase 2, which produces superoxide radicals [23].

II. **Ultra-violet generated oxidative stress**

There are two ways that UV light might harm cellular components. The first method involves the cell and its constituent parts directly absorbing incoming light. This results in the production of an excited state of the molecules following chemical reactions. The second mechanism is photosensitization. Incoming radiation is absorbed by photosensitizers such as bilirubin. As a result, the sensitizers are excited to triple states [24].

III. **Other exogenous sources of oxidative stress**

Other factors like air and water pollution are involved in the production of oxidative stress in the body. Radiations and radioactivity also take part in the production of oxidative stress. Drugs like halothane, bleomycin, paracetamol, doxorubicin, and metronidazole have a record of generation of oxidants. Industrial solvents, pesticides, chemicals like carbon tetrachloride, transition metals, heavy metals, alcohol consumption, and cooking (smoked meat, fat, and junk foods) are also recorded as the sources of oxidative stress [25].

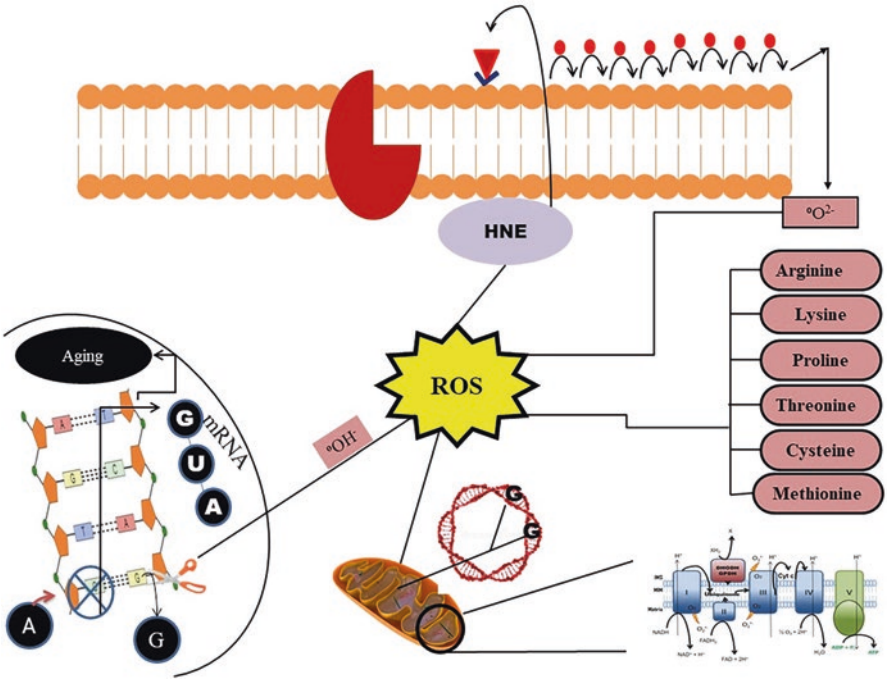

Fig. 3.2 Involvement of ROS in the pathophysiology of cell (**a**) ROS produces lipid peroxides in the cell membrane, inducing lipid peroxidation chain reaction or the generation of aldehydes such as 4-Hydroxy-2-nominal (HNE), that are detrimental to cellular activities via Ca^{2+} signaling and thus cause diseases such as inflammation [26], (**b**) Proteins are primary targets of ROS with reversible or irreversible modifications to the amino acid residues like Cys, Met, Arg and Tyr [26], (**c**) ROS are produced by electron transport chain in mitochondria to a large extent. ROS are generated via single electron leakage in the following situations: (i) during normal ETC function, at complex-I and complex-III; (ii) during conditions of high NADH/ NAD^+ ratio and low electron transport chain activity, (iii) during conditions of a high pool of reduced ubiquinone and transmembrane H^+ gradient, at complex I and (iv) during hypoxic conditions, at complex III [27], (**d**) The oxidative modifications of guanine base is one of the most common forms of DNA damage. Nuclear DNA is far less susceptible to ROS than mitochondrial DNA, which contributes to age-related mitochondrial malfunction. The fact that guanine is quickly oxidized could have important physiological consequences [26].

3.3 Molecular Targets of Free Radicals

Increased generation of RNS and ROS and decreased antioxidant defense result in nitrosative and oxidative stress. Major components of cells (mitochondria, plasma membrane, and DNA molecule) are damaged as shown in Fig. 3.2, leading to multiple disorders [14].

3.4 Role of Oxidative Stress in Health Illness

Oxidative stress is related to the emergence of many acute and chronic ailments in addition to speeding up aging and generating acute illnesses. The impact of oxidative stress on hypertension, Alzheimer's disease, and some malignancies will be covered in this chapter.

3.4.1 Oxidative Stress and Hypertension

The intricate and prevalent cardiovascular risk factor is hypertension [28], which is responsible for morbidity and mortality worldwide [29]. Hypertension is linked with inflammatory processes but is not confirmed whether inflammation is the consequence or cause of hypertension [30]. Tissue damage and remodeling in hypertension ensure its central role in hypertension and its side effects [31].

3.4.1.1 Sources of ROS

Research on ROS sources in hypertension is extensive. These are NADPH oxidase, uncoupled eNOS, xanthine oxidases, and mitochondria [32].

3.4.1.2 Oxidative Stress as a Mediator of Hypertension

In the year of 1991, Nakazono and his colleagues described that the blood pressure of spontaneously hypertensive rats (SHR) was reduced by intravenous injection of a fusion protein composed of human Cu/ Zn SOD and COOH terminal basic peptides with enhanced attraction for heparan sulfate. This result indicated that oxidative stress could be a mediator of hypertension in SHR. Additionally, they discovered that the xanthine oxidase inhibitor oxypurinol decreased the blood pressure in male SHR, correlating hypertension in male SHR to oxidative stress [33].

After 5 years of Nakazono's findings, Rajagopalan and his colleagues reported that administering large doses of angiotensin to rats raised their blood pressure and increased vascular superoxide, which was mediated by NADPH oxidase [34]. Superoxide levels were unaffected by norepinephrine, which raised blood pressure to comparable levels. Vascular dysfunction and constriction were eliminated when researchers administered a liposome-encapsulated superoxide dismutase [35]. These researchers later demonstrated that superoxide probably degraded vascular NO to raise blood pressure [36].

Superoxide binds to the NO generated by endothelial NO synthase (eNOS), forming peroxynitrite. This decreases NO bioavailability which results in vasoconstriction. Furthermore, in the presence of ROS, the eNOS cofactor,

tetrahydrobiopterin (BH4) is converted to dihydrobiopterin leading eNOS to synthesize superoxide [37]. The instability was only partially reversed by the addition of BH4. These researchers hypothesized that peroxynitrite can inactivate eNOS by oxidizing BH4, as well as by damaging the enzyme's heme/heme core [38]. Antioxidants such as vitamins E and C; tempol, apocynin, allopurinol, N-acetylcysteine, and BH4 reduced depression according to a study performed in male animals [39].

3.4.2 Oxidative Stress and Alzheimer's Disease

Clinical symptoms of Alzheimer's disease include a gradual decline in memory and cognitive abilities and severe dementia. Over the next few decades, people with Alzheimer's disease are expected to rise upto 15 million from the present number of over 4 million [40, 41]. When hyperphosphorylated tau protein aggregates bind to Fe3+, neurofibrillary tangles are produced [42]. The amyloid-peptide may form a chelation complex with transition metal ions, which then catalyzes the production of H_2O_2 and the poisonous OH radical [43]. In AD patients, there is significant lipid peroxidation, which could lead to neuronal loss by a variety of pathways, gathered with impaired activity of glucose transporters, ion pumps, and glutamate transporters. Patients with AD have been found to have additional oxidative protein damage indicators like 3-nitrotyrosine and protein carbonyls [44].

3.4.3 Oxidative Stress and Cancer

Cancer ranks among the main causes of mortality in people. Free radicals alter DNA chemically in many ways, make them potentially mutagenic, and contribute to the development of cancer [45, 46]. Cancer cells exhibit increased levels of oxidative stress due to the activation of the oncogenes and loss of tumor suppressors [47]. ROS changes the gene expression and growth signals, which leads to cancer cell proliferation [48].

3.4.3.1 Colorectal Cancer (CRC)

CRC is one of the important types of cancer with 608,000 fatalities per year [49]. ROS from internal and external sources are continually exposed to the gastrointestinal system, especially the colon, and rectum [50]. Epithelial cells are sites where colon cancer begins to develop. These cells have high metabolic rate and divide quickly [51]. This exposure eventually leads to a disrupted intestinal metabolic equilibrium that results in cancer [52].

3.4.3.2 Breast Cancer

ROS damages the breast epithelium which results in hyperplasia of epithelium, breast cancer, and fibroblast proliferation [53]. Thymidine phosphorylase produces oxygen radicals in the carcinoma cell when proteins are quickly glycated. It can be overexpressed in a majority of breast cancer which might cause oxidative stress [54].

3.4.3.3 Prostate Cancer

Cellular growth of prostate cancer is caused by ROS production [55]. Prostate cancer first appears when the protein NADPH oxidase 1 (Nox1) is overexpressed. ROS and Nox1 levels are noticeably greater in prostate cancer [56].

3.4.3.4 Lung Cancer

Among the main global causes of cancer mortality in males, lung cancer has been increasing at a steady rate in recent decades. Approximately 30% of all cancer deaths are caused by lung cancer. Lung inflammation and cancer are two conditions that oxidative stress contributes to significantly [57]. The significant environmental risk factor for lung cancer is cigarette smoking. The particulate matter from cigarette smoke is a complicated combination of several stable ROS and carcinogens with very long half-lives [49].

3.5 Antioxidants and Classification of Antioxidants

Antioxidants may be synthetic or natural. The natural antioxidant system has two categories, enzymatic antioxidants, and non-enzymatic antioxidants as shown in Fig. 3.3 [58]. Free radicals may be stabilized or inactivated by antioxidant enzymes before they damage cellular components. Synthetic antioxidants are chemically prepared substances [58]. Natural antioxidants are further divided into two categories. They may be endogenous and exogenous antioxidants [59]. Exogenous are those antioxidants that we take through food and supplements that are high in antioxidants [60].

Examples of exogenous antioxidants include vitamins, minerals, carotenoids, beta carotene, lycopene, lutein, zeaxanthin, organic sulfur compounds, allium, allyl sulfide, indoles, uric acid, glutathione and polyphenols which are phenolic acids and flavonoids. Flavonoids may be anthocyanidins cyanidin, pelargonidin, isoflavonoids, genistein, flavonols, catechin, EGCG, flavonols quercetin kaempferol, and flavanones. Endogenous antioxidants are the primary defense system including glutathione peroxidase, superoxide dismutase, catalase, and the secondary defense system which includes glucose-6 phosphate dehydrogenase and glutathione reductase.

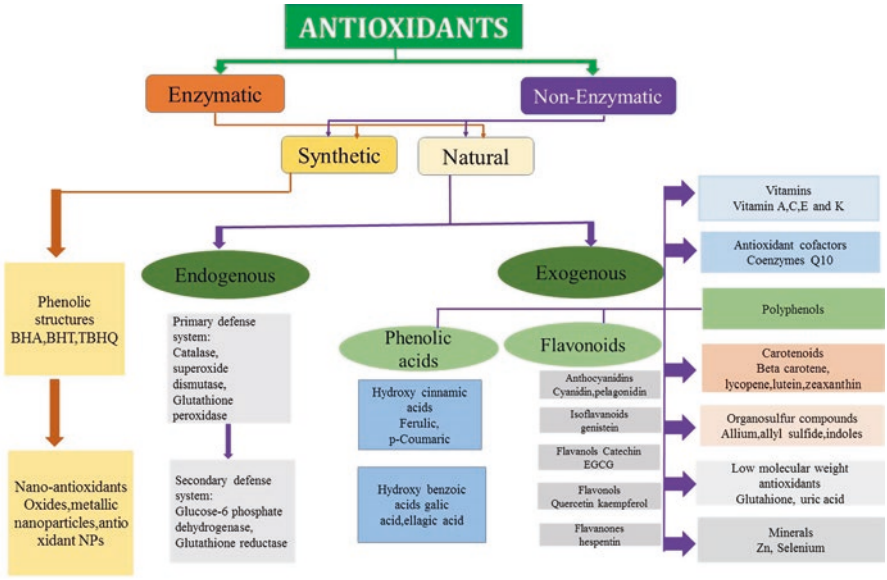

Fig. 3.3 Classification of antioxidants based on enzymatic and non-enzymatic categories

Synthetic antioxidants are also categorized as enzymatic and non-enzymatic antioxidants. They are phenolic structures, nano-antioxidants, oxides, and metallic nanoparticles [61].

3.6 Sources of Antioxidants

Antioxidants are found in natural foods and can also be synthesized. Antioxidants are mostly found in plants [62]. Phenolic structures are endogenous. A brief description of sources of antioxidants is elaborated in Fig. 3.4. We get phenolic structures from apples, grapes, pomace, pomegranate, berries, oranges, tomatoes, olive oil, coffee, and tea. Exogenous may be polyphenols, minerals, carotenoids, vitamins, and organosulfur compounds [63].

Polyphenols are found in spices, berries, nuts, herbs, cocoa powder, flaxseeds, olives, vegetables, coffee, and tea. Polyphenols may trigger apoptosis, inhibit tumor development and increase cell survival since they are prooxidants and antioxidants. However, polyphenols' biological impacts could go well beyond just reducing oxidative stress [64]. Minerals are found in meat, dairy foods, cereals, fish, nuts milk, fruits, and vegetables [65]. Other sources of antioxidants are vitamins which are found in potatoes, citrus fruits, red and green peppers, strawberries, green leafy vegetables, blueberries, blackberries, carrots, and kale [66]. Carotenoids are also the type of antioxidants that are found in spinach, yams, cantaloupe, kale, watermelon, tomatoes, bell peppers, and carrots [67]. Organosulfur compounds are found in

Fig. 3.4 Natural sources of antioxidants enriched with phenolic compounds, polyphenols, minerals, vitamins, carotenoids, and organosulphur compounds

cabbage, broccoli, cauliflower, brussels sprouts, garlic, onion, meat, eggs, and fish [68]. Additionally, there are excellent sources of certain particular antioxidants, such as the allium sulfur compounds found in garlic, onions, and leeks [69]. Anthocyanins are found in berries, grapes, and eggplant [70]. Beta carotene is found in apricots, pumpkins, carrots, mangoes, parsley, and spinach [71]. Flavonoids are found in different fruits, onions, tea, green tea, and apples [72].

3.7 Mechanism of Action of Antioxidants

Reactive intermediates are produced both endogenously and exogenously. Concerning the mechanism of antioxidants, there are five basic ways by which antioxidants work namely (1) radical-scavenging mechanisms (2) H• species donation, (3) oxidant enzyme inhibition, (4) metal chelation, and lastly (5) repair of damaged cell components [73]. Several physical, chemical, and enzymatic factors promote oxidative reactions that result in the loss of an electron from the outermost shell of a given substance [74, 75]. This series of damage is prevented when there are enough antioxidants present in the body through the five mechanisms which are illustrated in Fig. 3.5. The first one employs the free radical scavenging mechanism thus interrupting the chain reactions by inhibiting further oxidation Fig. 3.5 Part 1. The second way of the antioxidant system involves the donation of H^0 species to unstable molecules thus producing a more stable radical which does not contribute to further propagation and is stable comparatively to Fig. 3.5 part 2 [76–87]. The

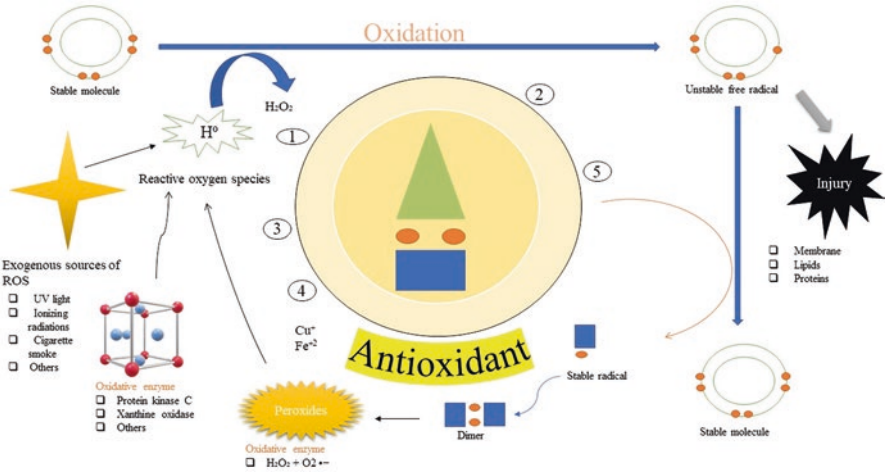

Fig. 3.5 Mechanism of action of antioxidants

third path of the antioxidant system involves the inhibition or deactivation of oxidative enzymes Fig. 3.5 part 03 [88–90]. The fourth mechanism refers to the chelation of different metals such as Fe^2 which results in the production of highly aggressive $HO^{\bullet}$ radical which, in turn, prevents metal-induced free radical formation Fig. 3.5 part 4 [91–95]. The last mechanism, the fifth one, employs the repairing of damaged components of the cell such as proteins, membrane, lipids, and deoxyribonucleic acid (DNA) [83, 96–99]. Depending upon the structure and nature of the antioxidant agents, the said mechanisms may act alone or in association with one another [74, 100, 101].

3.8 Role of Antioxidants in the Treatment of Different Diseases

Antioxidants play a major role in the treatment of different ailments by scavenging free radicals and eliminating them from the body through different processes. Some of them are enlisted below;

3.8.1 Antioxidants and Hypertension

Hypertension is an important cardiovascular issue that contributes to almost half of the prevalent coronary heart diseases and associated disorders like chronic kidney diseases (CKD) [102–107]. In addition, hypertension ranks third among the list of six major factors which cause global diseases [108].

Antioxidant treatment appears to be an effective method for reestablishing a healthy equilibrium between oxidants and antioxidants in hypertensive patients. Antioxidants have promising potential to relieve hypertension in animal models. In spontaneously hypertensive rats (SHR), NO viability was enhanced and blood pressure was lowered after oral administration of lazaroid, the ROS scavenger medicine [109]. Similar results were seen when N-acetylcysteine (NAC), another antioxidant, was used to treat high blood pressure. NAC reduced blood pressure by preventing ROS production and increasing NOS activity [110]. A similar pattern was observed in SHR given the xanthine oxidase inhibitor allopurinol [111]. The bioavailability of nitric oxide was greatly increased, and the treatment blunted the progressive and time-dependent rise in systolic blood pressure [112].

3.8.1.1 Anti-hypertensive Drugs with Antioxidant Properties

Several molecules with anti-hypertensive and antioxidant properties have been discovered so far. Among these celiprolol, nebivolol, propranolol, and carvedilol got major focus [113]. Tissue lipid peroxidation and oxidative stress are both decreased by propranolol [113, 114]. Patients with heart failure can benefit from carvedilol's free radical scavenging properties which decrease lipid peroxidation [113, 115]. However, not all beta-blockers have these antioxidant properties; for example, atenolol has been demonstrated to possess no affect on ROS generation in lining cells [116].

3.8.2 Antioxidants and Aging

Aging is a universal, inevitable, biological phenomenon affecting almost all living organisms from multicellular to unicellular life [117–119]. When we talk about the process behind the oxidative stress associated with aging, we can't find clear data despite the presence of many different hypotheses, most probably elevated levels of RONS, a process that inhibits the proliferation that results due to damage during replication [120].

Several antioxidants are available which have anti-aging properties such as retinoids [121–123], vitamin C [124–129], tea extracts [130–132], grapes seed extracts [133], peptides, and hydroxy acids have anti-aging character. The interesting thing is that almost all of these are antioxidants [134–144].

3.8.3 Antioxidants and Cancer

Antioxidants have the ability to avoid harmful and sometimes carcinogenic effects. Mice that have been exposed to carcinogens or have lost tumor suppressor genes got benefit from many isoforms of glutathione S-transferases (GSTs) which work

together to keep the liver, skin, and colon cancer-free [145–147]. Glutathione Peroxidases (GPXs) can also protect against carcinogen and ROS-induced malignancies initiation in a variety of animals. In colon cancer mouse models, GPX3 inhibits tumor initiation [32]. Similarly, animals with reduced SOD2 expression, either alone or in combination with GPX1 loss, exhibited higher DNA damage and tumor incidence [148, 149].

Catechins, especially epigallocatechin-3-gallate (EGCG), are abundant in green tea (*Camellia sinensis*). Animal studies on carcinogenesis have revealed that EGCG and green tea can reduce tumor growth. Polyphenols found in tea are potent radical scavengers due to the presence of dihydroxy and trihydroxy groups. NRF2-antioxidant response element-dependent upregulation of glutamate cysteine ligase, glutamyl transferase, and heme oxygenase-1 gene expression in EGCG-treated mice [150]. Berberine has been shown to suppress the growth of a wide variety of cancers by binding to oligonucleotides, stabilizing DNA triplexes or G-quadruplexes, and blocking the enzymes telomerase and topoisomerase. Berberine can scavenge reactive oxygen species (ROS), inhibit lipid peroxidation, and decrease metal ion concentrations associated with lipid peroxidation [151].

3.9 Conclusion and Future Perspectives

Oxidative stress arises when the balance between the rate at which oxygen-reactive species are produced and accumulated in cells and tissues and the rate at which the body can eliminate them is disturbed. Mainly ROS is generated as a byproduct of normal cellular reactions. ROS production that is necessarily produced at a limited level is easily diminished, but certain chemicals, drugs, and other sources become responsible for high ROS production. Oxidative stress has a vital role in different diseases including cancer. Antioxidants are substances that counteract oxidative stress. Although a lot of research work regarding the mechanism of product and action of ROS was discovered, more investigations should be done to find out a link between disease and ROS level, food and antioxidant production, and the role of ROS in normal cellular activities. There should be educational seminars and public awareness campaigns that emphasize the importance of antioxidants and encourage antioxidants-enriched diets.

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