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Review Article

Mechanisms of Antioxidant Actions and their Role in many Human Diseases: *A Review*

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ABSTRACT: Antioxidants are substances that are available in various natural food products, which play a vital role in reducing body cell damage caused by free radical formation. An imbalance between antioxidants and free radicals contributes to an oxidative stress in the human body. The electron acceptability of O2 produced Reactive Oxygen Species (ROS). The imbalance equilibrium between the production of reactive oxygen species (ROS) and the purification supports a rise in the ROS levels, which is the key cause of disrupted cellular activity. A recent review of excessively mild antioxidants, processes of movement, and their role in many human illnesses.

INTRODUCTION

Oxidative stress is an imbalance situation in which the production of reactive oxygen species (ROS) exceeds the mobile antioxidant capacity. If a certain amount of oxidative damage is close to being below normal circumstances, except that is observed, an increase in the rate of damage due to aging and disease processes, provided that antioxidant and restoration mechanisms have decreased effectiveness [1, 2].

In the cycle of oxidative phosphorylation and the construction of ATP like the instantaneous and final energy supply [3, 4], free radicals may be additionally produced like various reactive species [5, 6]. Throughout oxidation, hydrogen atoms or just electrons are transmitted from one molecule to another, the latter being used as an antioxidant. Antioxidants will also avoid the progress of interactions of free radicals, which would in any other case result in the death of the cell or impairment of it. Nevertheless, the procedure of oxidation performs the required protection of the body from pollution or impairment of tissue; how much is needed; and in which tissues are an exceptionally tuned slice of physiology [7]. Reactive species can also perform roles such as mobile minor messengers or signaling molecules such as nitric oxide [6, 8, and 9].

The cellular signaling network is frequently disrupted by immoderate ROS; besides, the shielding outcomes that greatest alimentary phytochemicals yield are expected to be

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the result of a variety of vital mechanisms [10]. Many experiments have dedicated themselves to the understanding and formulation of mechanistic pathways via which these certainly derivative components can fluctuate the cell's future. These antioxidant features of phytochemicals have been implicated as means of stress-relieving [11, 12].

The defense of endogenous antioxidants as opposed to the oxygen species reactive is supported via herbal antioxidants that maintenance them and maintain the most excellent stability via the ROS counteracting [13].

Sources of free radicals

Free radicals and other ROS are derived either from the human body's enogenous metabolic processes or from external sources. While exposure to radiation, ozone, smoke, cigarettes, air pollution, and industrial chemicals are external sources, Figure 1 [14].

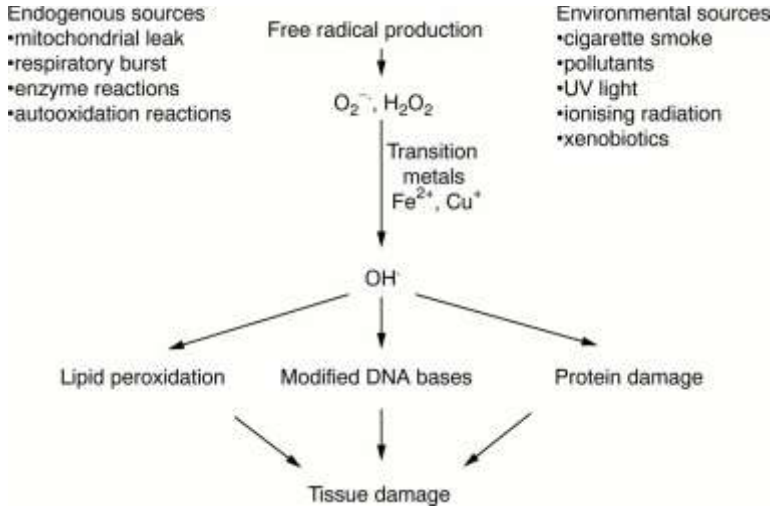

Figure 1. Main sources of free radicals [14].

Antioxidant classification

Antioxidants can be classified as enzymatic and non-enzymatic antioxidants (metabolic and nutrient) antioxidants. The major enzymatic antioxidants at once elaborated on the ROS counterbalancing are glutathione reductase (GRx), catalase (CAT), and superoxide dismutase (SOD) [16, 17, and 18]. SOD, the leading link of protection compared to these radicals, catalyzes the dismutation of the superoxide anion radical to (H_2O_2) via reduction means. The oxidant shaped (H_2O_2) is converted to O_2 and H_2O via (GPx) or (CAT). The enzyme GPx selenoprotein destroys H_2O_2 via utilization to oxidize reduced glutathione (GSH) to oxidized glutathione (GSSG). An enzyme flavoprotein, Glutathione reductase, revives GSH from GSSG, using NADPH as a low foundation of power. In addition to hydrogen peroxide, GPx decreases non-lipid or lipid hydroperoxides when oxidizing glutathione (GSH) [16].

Non-enzymatic antioxidants are additionally categorized as nutrient antioxidants and metabolic antioxidants. Metabolic antioxidants, which belong to the endogenous antioxidants, are made by the assistance of metabolism in the body, such as bilirubin, coenzyme Q-10, glutathione, L-arginine, lipoid acid, melatonin, metal chelating protein, transferrin, uric acid, and so on [19]. Nutrient antioxidants, which belong to exogenous antioxidants, are composites that cannot be made in the body and should be provided by supplements or nutrition for instance carotenoids, diet C, diet E, flavonoids, trace metals (manganese, selenium, zinc), omega- 3, omega-6 and fatty acid. Nutrient antioxidants are connected by the purification of reactive oxygen species (ROS) [20] and play a critical character in supporting endogenous antioxidants for the oxidative tension equation [21]. The scarcity of nutrient antioxidants is one of the motives for several persistent and cancer and degenerative pathologies.

Antioxidant enzymes and their action mechanisms

The antioxidant is a chemical that can avoid or slowly oxidize macromolecules. The role of antioxidants is to stop or decrease these chain reactions by eliminating free radicals or constraining specific oxidation reactions by oxidizing themselves. Antioxidants are too frequently lessening producers, like thiols or polyphenols [20].

The antioxidant enzymes in entirely physical cells comprehend three primary orders of enzymes of antioxidants such as glutathione peroxidases, catalases, and superoxide dismutase (SOD), the entirety of which show indispensable turns in holding cells in their homeostasis. These enzymes' stimulations reveal a special response to contaminant oxidative tension [20]. The role of SOD is to subsist radicals of superoxide and convert them to H_2O_2 [22, 23]. The site of GPx is accomplished with the support of the discount of different natural hydroperoxides, hydrogen peroxide, and lipid hydroperoxides [24]. Glutathione-S-transferases (GST) is a predominant category of enzymes of detoxifying [25]. A multifunctional protein family that is concerned with the detoxification of cytotoxic, genotoxic compounds and tissue protection as opposed to oxidative hazards [26,27]. In addition to other turns in the metabolism of self-evolution, the enzymes are implicated into the xenobiotic's purification, like carcinogens, medicines, and ecological contaminants in creatures, and with confrontation herbicides and insecticide in plants and pests [28].

Some studies have exposed the GPx, [30] and GST is incapacitated with the hydroperoxides support, which utilizes their poisonousness without delay, via oxidation of SH protein corporations or hydroxyl radical development. It is considered from the review that a large quantity of GST isoenzymes additionally exemplifies the GPx effort and catalyzes the markdown of natural hydroperoxides to their equivalent alcohols [31, 32]. Superoxide dismutase motivates the interruption of the superoxide anion to hydrogen peroxide and oxygen. It eliminates O_2 by motivating the dismutation response. If there is a decrease in the levels of the enzyme, the reaction will be sluggish [33]. Catalase is the antioxidant enzyme which catalyzes the two-stage conversion of hydrogen peroxide to water and oxygen as in stage 1 and 2

$$\text{Catalase-Fe (III)} + H_2O_2 \rightarrow \text{Compound I} \qquad \text{Stage 1}$$

$$\text{Compound I} + H_2O_2 \rightarrow \text{Catalase-Fe (III)} + 2H_2O_2 + O_2 \qquad \text{Stage 2}$$

The above-mentioned response rate is extremely high (~107 M / s), which means that the saturation of the enzyme *in vivo* is practically impossible. Catalase is largely present in peroxisomal cells which also produce the most hydrogen peroxide-generating enzymes. Catalase consists of four chains of the polypeptide; every chain holds more than 500 acids of amino acids and encompasses 4 porphyrin heme and a molecule of NADPH. The turnover of catalase is the simplest of all the various enzymes of antioxidants. The disintegration of H_2O_2 through the catalytic undertaking of catalase shadows the pattern of the first-order reaction and its success is set at the H_2O_2 concentration [32, 35].

The glutathione mechanism consists of glutathione reductase, glutathione peroxidase, and glutathione S-transferases. Glutathione S-transferases are the group of enzymatic antioxidants that motivate lipid peroxide break. Glutathione peroxidase in the body results in an unnecessary use of hydrogen peroxide and human hydroperoxides [36].

Glutathione reductase motivates the decline of oxidized glutathione (GS SG) to condensed glutathione (GS H).

Non -enzymatic antioxidants and the mechanisms action

Non-protein thiol and Protein-enchained thiol represent a shielding agent and cell-decreasing contra most inorganic contaminants through the SH-group [37]. Consequently, the headline of the protection contra stress oxidation is the thiol. The thiol degrees can be extended through the appliance of adaptation to a mild oxidative tension by amplifying its production. Glutathione is the mobile antioxidant that achieves an essential part in the redox of the cells [37].

Ascorbic acid is an antioxidant that can only be obtained from the human diet as it cannot be synthesized by the body. Vitamin E has been shown to preserve mobile membranes from oxidation by intermediates free radical and reacting by lipid radicals [39]. Beta carotene has a solid antioxidant area through disposing of singlet oxygen to defend contra attacks of a free radical. It has been found in cabbage, cheese, grains, liver, tomatoes, and milk [40, 41].

Flavonoids play an important position in the safety of oxidative stress [42] with cancer in particular. Flavonoids are commonly present in tea, grains, berries, and cocoa [43]. They are found in high amounts in drinks and nutrients [44] of which the antioxidation has been studied in particular [45]. Natural antioxidants improve ROS' endogenous antioxidants and preserve the highest level of stability with the aid of neutralizing reactive species [46]. Antioxidant phenol-based products are linked to several different processes, such as hydrogen donation, single oxygen quenching, steel ion chelation, and radically hydroxylated and superoxide substrates [47].

The natural antioxidants have a range of biochemical activities, as free radical scavenging, and inhibition of ROS production. The literature suggested that the ingestion of curcumin, garlic, peppermint, pomegranate, rosemary, sea buckthorn seedcake, and sesame had proven protecting impacts in comparison to renal illnesses and nephrotoxic retailers, leading to renal dysfunction in humans and laboratory creatures [13, 47, 48 and 49].

Antioxidants function

The Administration of Food and Drug (FDA) describes antioxidants exclusively as nutritional additions to be used as well as daily food intake in an attempt to combat these illnesses [50]. Antioxidants are recognized to play a key role in the defense of the effects on the use of plant ingredients [51-54]. Regular consumption of greens and fruits has been described as a reduction in the risk of chronic disease [55]. Studies show that an antioxidant rich diet has an actual beneficial effect, fitness affects in the long run [56]. Recently, antioxidants have gained significant interest in radical and oxidative stress, most cancer prophylaxis and treatment, and robustness [57]. Skim milk can also be used as a dietary supplement as an antioxidant activity to minimize the risk of tobacco smoking or tobacco chewing [58]. Both antioxidants are involved as a system of the antioxidant, squad, accountable for avoiding the harmful properties of free radicals and the toxic merchandise of the metabolism. Though, the antioxidant works to exploit free radical development as a coordinated tool, leaving deficiencies in one problem affecting the effectiveness of others [59, 60].

Roles of antioxidants in the prevention of diseases cancer

Antioxidants preserve DNA by failing the impairment of oxidative DNA produced by the free radical and by managing the multiplied strange division of the cell, the central attribute of carcinogenesis. Using *in vitro* and systems of animal modeling, it has been experimentally observed that plant consequent phytochemicals, such as sulforaphanes, isothiocyanates and, allyl sulfides inhibit several pathogens [45] has stated that the aggregate of selenium, E-nutrition, pointedly decreases the risk of progression in many types of tumors, particularly in stomach cancer [61, 62].

Atherosclerosis

Atherosclerosis is a cardiovascular state that begins because of the oxidized fatty acids deposition in the arteries in a plaque formation. Around two-thirds of the serum LDL cholesterol pool is an insufficient density lipoprotein-cholesterol which is assumed to reveal a critical role in improving atherosclerosis [47]. Some plant-derived polyphenols and flavonoids, which occur in some vegetables and fruits, have been revealed to be effective antioxidants that are active in stopping LDL. Oxidation is persuaded via free radicals. The suggested allowance for flavonoids is one gram in a regular diet, which is appropriate for the system of antioxidant protection. Ironically, it has been determined that the antioxidant recreation of certain flavonoids synergistically upsurges when complemented via acid of a-ascorbic to avoid the

oxidation of LDL. Furthermore, aspirin has been shown to prevent atherosclerosis in animal studies [63].

Alzheimer's disease

Alzheimer's disease is featured at an advanced loss of reminiscence as a significant clinical appearance. Research on free radicals recommends that the stress of oxidative triggers neurodegenerative diseases in tandem with AD. Besides, the metal ion plays a critical turn in the development of A D. Nutraceutical. Antioxidants like lycopene, turmeric, curcumin, etc. reportedly have the beneficial effects of a variety of neural disintegration varieties, oxidative tension, and dysfunction of mitochondria [64].

Decreased levels of the antioxidant enzyme, such as superoxide dismutase, is associated with the prevalence of Alzheimer's disease in humans [65]. Reference has been made to the fact that the supplementation of nutritional vitamins E and C to the affected person can substantially increase the values of nutritional vitamins in plasma and minimize the lipoprotein oxidation, although Vitamin E alone does not have any major effects at present. Strong nutraceutical intake is postponing the treatment of dementias such as Alzheimer 's disease [66].

Parkinson's disease

Parkinson's disease outcomes from neuronal cell damage in some parts of the brain and is denoted weakness of muscles, trembling, and trouble walking [3]. In the study [68], it was argued that vitamin E in a diet can also protect contra Parkinson's disease. Also, Glutathione has exposed some encouraging results in initial studies to deal with Parkinson's disease, but side effects, the most beneficial technique of administration, and splendid long-term dosing are not yet clear.

Heart diseases

There are a variety of causes to heart diseases, such as high cholesterol, obesity, diabetes, smoking cigarettes that deliver a forum for the progress of illness of coronary heart. Oxidation of dipped density induces accumulation of fatty acids in the arteries leading to the progress of atherosclerosis, which eventually induces coronary heart disease, heart disease is obtained with age because oxidized fatty acid is more 'sticky' and more likely to bind to the artery walls. An excessive intake of ascorbic acid is thought to restore endothelial dysfunction and to protect circulating lipoprotein from free radicals [69].

Diabetes

Diabetes mellitus (DM) is characterized by hyperglycemia [70]. In addition, oxidative tension because of deficiency of antioxidant defenses can also cause [71, 72]. It is assumed that if ROS is complicated in diabetes genesis, antioxidants may also be an advantageous strategy for diabetes prevention, [73] published that vitamin E supplementation decreases the sensitivity of DL to *in vitro* oxidation and the accessibility of oxidized LDL in kind two diabetics [74]. It is assumed that the unevenness between technology and the subsisting of free radicals is the fundamental reason for diabetes. Insulin should improve the absorption of vitamin C from the cell however in hyperglycemic stipulations this system is disrupted ensuing in a circumstance acknowledged as 'tissue scurvy'. The accession of Vitamin C dominates the glucose of blood, advances endothelium-dependent vasodilation and increases the resistance of lipoprotein in the direction of oxidation in the affected person by both sort one or sort two diabetes mellitus [75].

Skin aging

In the collagen molecule, vitamin C as a cofactor is both needed in order to add hydroxy groupings to the amino acid proline and lysine via prolylhydroxylate and lysyl hydroxylate. Hydroxylation enables the three-fold structure of the collagen molecule to become important for the production and maintenance of scar, blood vessels, and cartilage. Moreover, the mRNA level of Collagen I and III, their treatment enzymes, and the tissue-inhibitor of matrix metalloproteinase 1 in the human derma will tend to increase topically to applied vitamin C [76-78].

Ocular disease

A major factor in the production of cataracts and the age-related retina disease maculopathy is thought to be the oxidative processes. It is suspected that oxidation is a major cause of damage to the lens proteins, caused primarily by UV exposure. The oxidated protein reduces in amount and induces lens cloudiness. The antioxidants and antioxidant enzymes inactivate the deterioration and removal of hazardous free radicals and proteases from the lens; however, oxidative damage happens more quickly. Therefore, the oxidized protein will build up and the damage is permanent over time. Whether antioxidant lowers risks of cataract formation and development are important to evaluate. People that are more likely to be at lower risk for cataracts if those have higher plasma levels of different antioxidant nutrients [79].

Antioxidant biomarkers

Assessable hazard features, biomarkers intermediates have described the progress of evidence-based therapies for cardiovascular conditions such as blood tension and lipoproteins and diabetes such as physical obesity, and recent mainstream glycemic popularity. Nevertheless, there has been a biomarker proliferation that purports to point to food consumption, its metabolic penalties, and genetic predisposition to sickness and untimely mortality [80,81]. When it arises to antioxidants and its healthiness insinuations, the detected fluctuations in intermediates may also have extra side effects. Such biomarkers that symbolize harm and are analogs to what can also occur in tissues possibly will also have value. Examples may be the combination of HbA1c and AGEs for individuals with diabetes, lipid peroxides in lipoprotein conditions, and broken DNA [80,81] even though the data are contradictory.

Antioxidant toxicity

The greatest noticeable detriment to antioxidants is the elimination of the health defending tasks of oxidants consisting of antimicrobial phagocytosis and the purification of complicated and apoptotic functions of cytochrome P-450 for unwanted cells [81-87].

Some antioxidant nutrients, such as Vitamin C, should anticipate oxidant functions that can also be harmful, such as Fenton's reaction as it absorbs metal ions like iron [88-92]. Several medical studies have stated that antioxidants, such as beta-carotene, which is a precursor of Vitamin A, can escalate the danger of most cancers when managed as a remote supplement [89-93]. In the APPP (Australian Polyp Prevention Project) with involvements of a trivial fats diet, beta –carotene., whilst the mixture of low fats and bran of wheat avoided the repetition of massive polyps of adenomatous, beta-carotene expanded the danger of whichever polyp repetition in females [94-97].

CONCLUSIONS

The current study contributes the useful awareness of depicting the oxidative stress and free radicals causing diseases. The antioxidants have a high ability to be used as most traditional treatments of diseases are used. Hence, a diet with good supplementation of vegetables, fruits, and, nuts) that have adequate essential antioxidants such as vitamins A, E, C, etc. may be sufficient to strengthen our body's immune system to prevent many diseases.

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Conflict of interest

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Ethical clearance

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