International Multidisciplinary Research Journal 2012, 2(1):18-34
ISSN: 2231-6302
Available Online: http://irjs.info/

INTERNATIONAL MULTIDISCIPLINARY RESEARCH JOURNAL

Antioxidants: elixir of life

Sadaf Kalam*, Rupal Singh, Abin Mani, Jaswant Patel ,Firoz Naem Khan and Adarsh Pandey#

Centre for Scientific Research and Development (C.S.R.D.), People's Group, Bhopal-462037, MP, India.
Department of Botany,SS (P.G.) College,Shahjahanpur-242001,UP,India

Abstract
There has been a current upsurge in the medical implications of free radicals and related species during the past several decades. These chemical species are integral components produced during normal biochemical and physiological processes but leads to oxidative stress when produce in excess and causes potential damage to cells. A wide range of non-enzymatic and enzymatic antioxidant defenses exists to counteract the damaging effects of free radicals. There exist epidemiological evidences correlating higher intake of antioxidant rich foodstuffs with greater free radical neutralizing potential to lower incidence of several human morbidities or mortalities. Gene therapy to produce more antioxidants in the body, novel biomolecules and the use of functional foods enriched with antioxidants are milestones to newer approaches to reduce free radical damage. This paper reviews the biology of reactive species, their pathways through which they relate to the pathology of various diseases and discusses the putative roles that antioxidants, from different sources, play in controlling oxidative stress and reduce the incidence of concerned diseases.

Keywords: Antioxidants, Free radicals, Oxidative stress, Diseases.

INTRODUCTION

Greek physician Hippocrates back in 400 B.C., said, "Let food be your medicine and medicine be your food." Today, good nutrition is more important than anything else. At least four of the 10 leading causes of death in the world like heart disease, cancer, stroke and diabetes are directly related to the way we eat. Recent research has shown a significant relationship between free radicals and these diseases. It is paradoxical that oxygen, which is an element indispensable for life, can have severely deleterious effects on the human body under certain situations. Most potential harmful effects of oxygen can be credited to the formation and activity of a number of chemical compounds, known as reactive oxygen species (ROS), which have a tendency to donate oxygen to other substances. Many such reactive species are free radicals and have a surplus of one or more free-floating electrons rather than having matched pairs and are, therefore, unstable, highly reactive and responsible for deleterious cellular damage. To stabilize and deactivate these species, organisms have developed a complex antioxidants protection system capable of critically maintaining normal cellular and physiological functions.

Free radicals

Free Radicals are highly reactive molecular species with an unpaired electron, which causes them to capture electrons from other substances in order to neutralize themselves. Free radicals derivatives of oxygen like superoxide free radical anion ($O_2\cdot^-$), hydroxyl free radical (OH·), nitric oxide radical (NO·), lipid peroxyl (LO·), lipid alkoxyl (LOO·) and lipid peroxide (LOOH) as well as non-radical derivatives such as hydrogen peroxide and singlet oxygen are collectively known as reactive oxygen species (ROS). The hydroxyl radical (•OH), which is the neutral form of hydroxide ion, has a high reactivity, making it very dangerous radical with a very short *in vivo* half-life of approximately 10^{-9} seconds [1]. These potentially damaging molecules are capable of attacking healthy cells of the body causing them to lose their structure and function [2].

Although the initial attack causes the free radical to become neutralized, another free radical is formed in the process, causing a chain reaction to occur and consequently leads to oxidative stress. Such unstable molecules react easily with essential molecules of our body including DNA, fats and proteins [3]. They are formed as a part of our natural metabolism but also by certain environmental factors-including smoking, pesticides, pollution and radiation. Cell damage caused by free radicals appears to be a major contributor to aging and to degenerative diseases such as cancer, cardiovascular disease, cataracts, immune system decline and brain dysfunction [4, 5]. Overall, free radicals have been implicated in the pathogenesis of at least 50 diseases [6].

Reactive oxygen species (ROS) and reactive nitrogen species (RNS)

ROS and RNS formed *in vivo* such as superoxide anion, hydroxyl radical and hydrogen peroxide are highly reactive and potentially damaging transient chemical species. These are continuously produced during the body's metabolic reactions in small amount, as they are essential for energy supply, detoxification, chemical signaling and immune function. ROS are regulated by endogenous enzymes superoxide dismutase, glutathione peroxidase and catalase but due to overproduction of reactive species, induced by exposure to external oxidant substances or a failure in the defense mechanism, damage to cell structure, DNA, lipids and

Received: Oct 5, 2011; Revised: Dec 20, 2011; Accepted: Dec 25, 2011

*Corresponding Author

Sadaf Kalam
Centre for Scientific Research and Development (C.S.R.D.), People's Group, Bhopal-462037, MP, India.

Tel: +91-9502403852
Email: sadaf2577@gmail.com

proteins [7] occur which increased risk of more than 30 different disease processes [8]. The most notorious among them being neurodegenerative conditions like Alzheimer's disease [9, 10], mild cognitive impairment [11] and Parkinson's disease [12]. Other diseases include highly disabling vascular pathologies like cardiovascular disease and cardiac failure [13], alcohol induced liver disease [14] and ulcerative colitis [15] and cancer caused by a complex of different causes, of which RNS/ROS is a component. Because ROS/RNS production is a naturally occurring process, a variety of enzymatic and non-enzymatic mechanisms have evolved to protect cells against these species [16]. The RNS, for example nitric oxide (NO•) radical, is an abundant reactive radical which acts as an important oxidative biological signaling molecule in a large variety of physiological processes, including neurotransmission, blood pressure regulation, defense mechanisms, smooth muscle relaxation and immune regulation [17]. Examples of such species are listed in Table 1 [18].

Table 1. Examples of Reactive Oxygen Species (ROS)

The Radicals	**The Non radicals**
Superoxide ($O_2^{\bullet -}$)	Hydrogen peroxide (H_2O_2)
Hydroxyl (OH•)	Hypochlorous acid (HOCl)
Peroxyl, alkoxyl ($RO_2^\bullet$, RO•)	Ozone (O_3)
Oxides of nitrogen(NO•, $NO_2^\bullet$)	Singlet oxygen ($^1O_2$)

Pathways leading to generation of free radicals

Free radicals/ROS/RNS are produced mainly from two important sources [19-21] in the biological system i.e. cellular metabolism like mitochondrial electron transport chain, endoplasmic reticulum oxidation, NADPH oxidase, xanthine oxidase, prostaglandin synthesis, reduced riboflavin, nitric oxide synthetase, reperfusion injury, cytochrome P_{450}, activated neutrophils and phagocytic cells and environmental sources like drugs, pesticides, transition metals, tobacco smoke, alcohol, radiations and high temperature. The other metabolic sources of free radicals include ionising radiation which causes lysis of water, reaction of transition metals with O_2 or H_2O_2, and respiratory burst of macrophages [22].

Prooxidants and oxidative stress

Prooxidants are chemicals that induce oxidative stress either through ROS or inhibiting antioxidant systems. Normally, there is equilibrium between a free radical/ROS formation and endogenous antioxidant defense mechanisms, but if this balance is disturbed, it can produce oxidative stress [23, 24]. Oxidative stress is the shift towards the pro-oxidants in pro-oxidant: antioxidant balance that can occur due to increase in oxidative metabolism. It is characterized by a disturbance in the balance between ROS production on one hand and ROS removal and repair of damaged complex molecules (such as proteins or DNA) on the other [25]. Increased oxidative stress at the cellular level may occur due to exposure to alcohol, medications, trauma, cold, infections, poor diet, toxins, radiation and strenuous exercise. Under certain conditions, such as acute or chronic alcohol exposure, ROS production is enhanced or the level or activity of antioxidants is reduced. Oxidative stress is associated with numerous deleterious consequences for the cell such as lipid per oxidation or even cell death.

Damage due to free radicals

Oxidative damage to DNA, proteins and other macromolecules has been implicated in the pathogenesis of a wide variety of diseases. Conditions associated with oxidative damage are heart diseases, cancer, pulmonary disorders, cataracts, diabetes, neurological disorders and aging [26]. Mitochondrial dysfunction may occur due to ROS produced as a consequence of increased oxidative stress and insufficient antioxidant defenses [27, 28]. ROS are potentially damaging transient chemical species which exert oxidative stress towards human cells rendering each cell to face about 10,000 oxidative hits per second [29, 30]. Scientists have exhaustively reviewed the effects of free radicals and antioxidants in normal physiological functions and human diseases [31]. Their have been reports that the most hazardous hydroxyl radical reacts with all components of the DNA molecule, damaging both the purine and pyrimidine bases and also the deoxyribose backbone [32]. Not only DNA is being attacked by ROS but they also attack other cellular components involving polyunsaturated fatty acid residues of phospholipids, side chains of all amino acids residues of proteins, in particular cysteine and methionine residues [33, 34].

Antioxidants

Antioxidants are a broad group of compounds which constitute the first line of defense against free radical damage thus are essential for maintaining optimum health and well-being. They are protective agents, capable of stabilizing or deactivating free radicals before they attack cells. Being beneficial compounds, they control free radical formation naturally and help organisms to deal with oxidative stress caused by free radicals [35]. Exposure to free radicals increases the need for intake of antioxidants. The free radical exposures is increased due to pollution, cigarette smoke, drugs, illness, stress and even exercise. Diets supplemented with antioxidants are now-a-days recognized as an imperative way of protecting cells from adverse effects of free radicals. Identification of pharmacologically potential antioxidant compounds has increased tremendously as they exhibit no side effects for use in preventive medicine and food industry. Antioxidant compounds are present in vegetables, fruits and many natural beverages like tea. Balanced diets are naturally rich in antioxidants. Antioxidants display an array of benefits like they support kidney function, maintain good dental health, improve reproductive function, improve nervous system functioning, have anti-aging effect, protect liver, support immune system and improve defense power of the body. They also reduce obesity, offer protection against digestive disorders, maintain healthy vision and improve quality of sleep. Figure 1 depicts the relative functions of antioxidants.

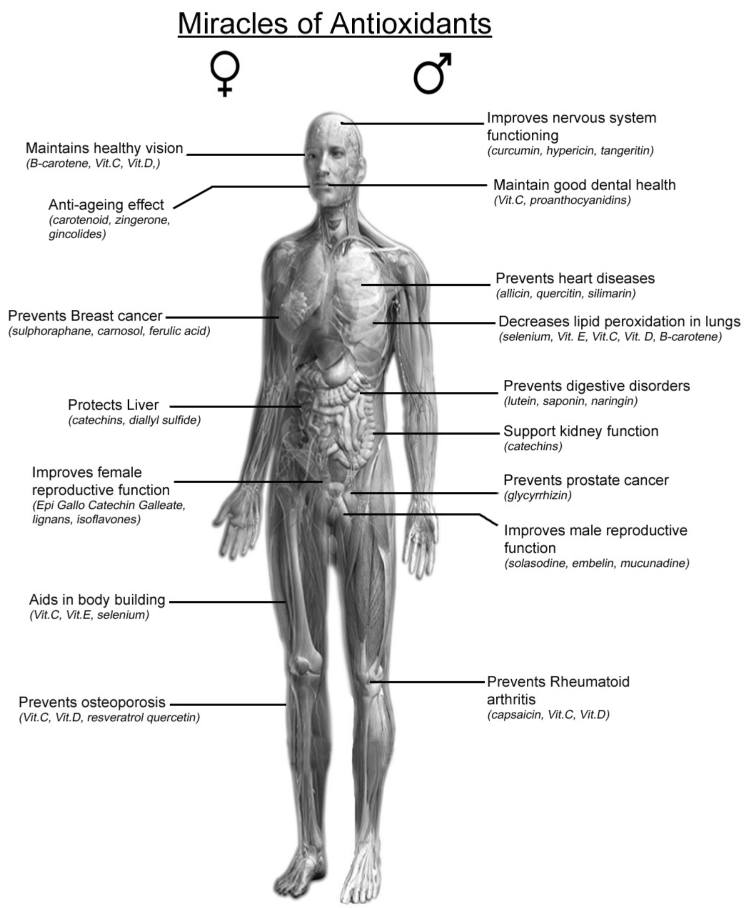

Fig 1. Functions of antioxidants

Antioxidants are a family of compounds considered best to fight against a number of age-related problems such as Alzheimer's disease [36]. Antioxidants can be obtained from a host of fruits, beverages, mushrooms etc. each doing some specific task in shielding the body from the harmful effects of the free radicals. Figure 2 demonstrates mechanism of action of antioxidants.

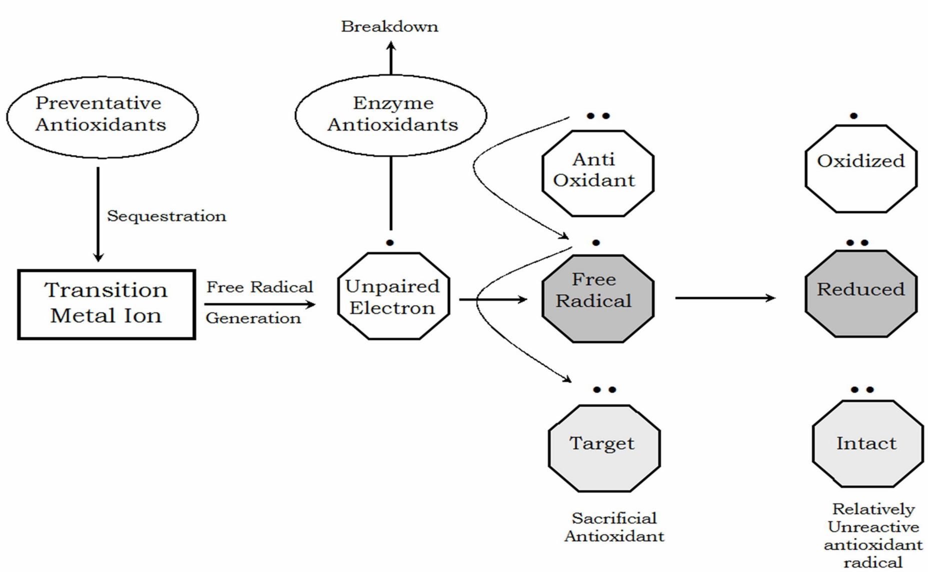

Fig 2. Mechanism of action of antioxidants

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Considered to be wonder element, antioxidants are essential to good health and well-being as the concept of health promotion has become a legitimate part of health care. The ability to utilize oxygen has provided humans with the benefit of metabolizing fats, proteins and carbohydrates for energy [37]. Several studies have been directed towards the evaluation of antioxidant properties of several naturally occurring botanicals and herbs, potentially useful as nutraceutical ingredients [38].

Antioxidant in plant cells

Antioxidant in plant cells mainly include glutathione, ascorbate, tocopherol, proline, betaine and others which are also information rich redox buffers and important redox signaling components that interact with cellular compartments. As an unfortunate consequence of aerobic life for higher plants, ROS are formed by partial reduction of molecular oxygen. The enzymatic and non-enzymatic antioxidants in higher plant cells can protect their cells from oxidative damage by scavenging ROS. Thus, special attention is given to ROS and ROS-antioxidant interaction as a metabolic interface for different type of signals derived from metabolisms and from the changing environment [39]. Besides exacerbating cellular damage, ROS act as ubiquitous signal molecules in higher plants as well as a central component in stress responses [40].

Shielding effect by antioxidants

Humans have evolved a highly complicated antioxidant defense system to combat the damaging effects of free radicals. These includes both endogenous and exogenous components which function interactively and synergistically to neutralize free radicals [41]. These components are (i) Antioxidant enzymes (Superoxide Dismutase, Glutathione peroxidase and Catalase), (ii) Metal binding proteins (Ferritin, Lactoferrin, Albumin and Ceruloplasmin), (iii) Nutrient-derived antioxidants (Ascorbic acid, Tocopherols, Tocotrienols, Carotenoids, Glutathione and Lipoic acid), and (iv) Phytonutrients (Flavonoids, Phenolic acid, Stilbenes, Tannins and Carotenoids). The activity or amount of antioxidant is generally calculated as ORAC values i.e. Oxygen Radical Absorbance Capacity which is a measure of the ability of foods to subdue harmful oxygen free radicals that can damage human body. The ORAC values for two cups of black tea are equivalent to that of one glass red wine or seven glasses orange juice or consuming twenty glasses apple juice. Additionally, dark chocolates snack within a balanced diet can improve DNA resistance to oxidative stress in healthy subjects [42].

Antioxidants and diseases

Antioxidants are intimately involved in the prevention of cellular damage- the common pathway for cancer, aging, and a variety of diseases. Damage to DNA and other cellular organelles by free radicals occupies highest position in the onset and development of diseases. Some diseases have been mentioned below indicating free radicals as their precipitating factor.

Cardiovascular disease

Atherosclerosis and its complications most notably Coronary Heart Disease (CHD) continues to be the major cause of premature death in the development world. Polyunsaturated fatty acid residues in lipoproteins have a chemical structure that makes them a particularly vulnerable target for free radical oxidation [43]. ROS-induced oxidative stress in cardiac and vascular myocytes has been linked with cardiovascular tissue injury [44]. Regardless of the direct evidence for a link between oxidative stress and cardiovascular disease, ROS-induced oxidative stress plays a role in various cardiovascular diseases such as atherosclerosis, ischemic heart disease, hypertension, cardiomyopathies, cardiac hypertrophy and congestive heart failure [45]. The major sources of oxidative stress in cardiovascular system include: (i) the enzymes xanthine oxidoreductase (XOR), (ii) NAD(P)H oxidase (multisubunit membrane complexes), (iii) NOS, (iv) the mitochondrial cytochromes and (v) hemoglobin [46, 47]. NOSs and hemoglobin are also principal sources of RNS, including NO• and SNOs (NO-modified cysteine thiols in amino acids, peptides, and proteins), which convey NO• bioactivity. Oxidative stress is associated with increased formation of ROS that modifies phospholipids and proteins leading to peroxidation and oxidation of thiol groups [48]. Studies have shown an inverse relationship between vitamin C intake and cardiovascular disease mortality in humans [49]. In hypercholesterolemic persons, supplementation with combination of vitamin E and slow-release vitamin C slows down atherosclerotic progression [50].

Human cancer

Under conditions of oxidative stress, abnormal expression of cellular genes can be induced by a wide variety of carcinogens [51]. The by-products of normal metabolism, which increase inflammation and exposure to exogenous sources like nitrogen oxide pollutants, smoking, certain drugs (e.g., acetaminophen, bleomycin) and radiation can induce cancer-causing mutations, lipids and proteins oxidation and alteration in signal-transduction pathways that enhance cancer risk [52]. Antioxidants also show promise in cancer therapy by their palliative action, reducing painful side effects associated with treatment [53]. The major goal of antioxidants in maintaining health is to protect normal cells from events that trigger or enhance cancer and to prevent long-term damage that may occur during cancer therapy and give rise to secondary malignancies in later years [54]. Many cancer patients who are undergoing therapy take antioxidant supplements in an effort to alleviate treatment toxicity and improve long term outcome. The results of epidemiological studies have suggested that consumption of diet rich in carotenoids was associated with reduction in breast cancer risk [55], and a reduced prostate cancer risk was seen with intake of foodstuff that are rich in lycopene [56]. Similarly, intake of allium vegetables (garlic, onions) containing high levels of antioxidant organosulfur compounds is linked with reduced gastrointestinal cancer risk [57] while polyphenols rich green tea has been considerably shown to reduce the risk of breast cancer and ovarian cancer in Asian women [58, 59]. Dietary antioxidants other than vitamin E, vitamin C and the carotenoids may also be of significance in the prevention of degenerative diseases and the maintenance of good health. The role of the antioxidant minerals in the etiogenesis of cancer has been investigated and selenium is emerging as a major prophylactic factor against cancer [60].

Diabetes

Increased oxidative stress plays a major role in the development and advancement of diabetes and its complications [61, 62]. Generally, diabetes is accompanied by increased production of free radicals [63, 64] or impaired antioxidant defenses [65, 66]. Increased oxidative stress has been proposed to be one of the major causes of the hyperglycemia-induced trigger of diabetic complications. Diabetic Hyperglycemia in an organism stimulates ROS formation from a variety of sources. These sources include glucose autooxidation, polyol pathway and non-enzymatic glycation of proteins [67].

There have been found changes in oxidative stress biomarkers including including superoxide dismutase, catalase, glutathione reductase, glutathione peroxidase, glutathione levels, vitamins, lipid peroxidation, nitrite concentration and nonenzymatic glycosylated proteins in diabetic individuals suffering from complications [68]. However, oxidative stress is relatively low in Non-insulin dependent Diabetes mellitus (NIDDM) when compared to insulin dependent Diabetes mellitus (IDDM) suggesting metabolic differences between the two types of diabetes [69]. Various studies show that the antioxidants can help in reducing oxidative stress and alleviate these diabetic complications [70]. Along with antioxidants, advanced glycation end products inhibitors, either introduced endogenously or exogenously, may counteract with the deleterious effects of the ROS/RNS and thus, helpful in prevention or treatment paradigms of this devastating disease [71].

Ischemia-reperfusion (IR) injury

IR injury activated when liver or other organs are briefly subjected to reduce blood supply followed by reperfusion, ultimately leading to cell damage and tissue failure. It has been revealed that ROS are generated during ischemia and reperfusion and may represent pivotal mediators of the resultant pathological complications [72]. Although, there is low oxygen tension during ischemia, moderate ROS generation is substantiated to occur most probably from a mitochondria source [73, 74]. Scientists presented the experimental and clinical evidence about the role of antioxidants in modulating hepatic ischemia-reperfusion injury [75]. The protective effects of antioxidants against brain I/R-induced injury may be mediated by down-regulation of nuclear factor-kappa B (NF-κB) activity in rats [76]. A surplus of antioxidant agents against hepatic IR injury [77] and myocardial IR injury [78] has been tested *in vitro* and *in vivo* and the results emphasized the importance of antioxidative mechanism in cardiac and hepatic protection. Moreover, Ascorbate - a major antioxidant in brain seems to be helpful in scrutinizing chronic cerebral hypoperfusion [79] and resveratrol could protect intestinal tissue against IR injury with its potent antioxidant properties [80].

Alcoholic liver disorder (ALD)

Alcohol promotes the generation of ROS [81] and/or interferes with the body's normal defense mechanisms against free radicals. The ensuing alcohol-induced oxidative stress results in compromised antioxidant defense system, particularly in the patients of ALD [82]. Alcohol breakdown in the liver results in the formation of molecules whose further metabolism in the cell leads to ROS generation. Alcohol also stimulates the activity of enzymes called cytochrome P_{450}s, and alters the level of certain metals in the body, thereby facilitating ROS production. This ROS production and resulting oxidative stress in liver cells play a major role in the development of ALD [83]. Nevertheless, numerous studies have found that administering antioxidants agents can prevent cells from the toxic effects of alcohol. For example, in the intragastric infusion model, the antioxidant vitamin E; the chemical Ebselen, which mimics the actions of glutathione peroxidase; the copper–zinc or manganese SODs; or a GSH precursor, all can significantly prevent or ameliorate alcohol's lethal effects in ALD patients [84-88].

Neurodegenerative disorders (NDD)

NDD are a diverse group of diseases of the nervous system, including the brain, spinal cord and peripheral nerves with different etiologies. Many are hereditary, some are secondary to toxic or metabolic processes, and others result from infections [89]. The brain is vulnerable to oxidative damage because of its high oxygen utilization, high content of oxidizable polyunsaturated fatty acids and the presence of redox-active metal ions [90]. The increased incidence of NDD such as Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), cerebellar disorders, Parkinson's disease (PD), Huntington's disease (HD) and stroke in aged populations may be related to the accumulation of oxidative damage in neurons either primarily or secondarily [91]. Neuroprotective antioxidants can act as protective agent in NDD and are considered a promising approach to slowing the progression and limiting the extent of neuronal cell loss in these disorders [92, 93].

Alzheimer's disease (AD)

The brains of patients with AD exhibit a significant extent of oxidative damage associated with a marked accumulation of amyloid-β peptide (Aβ), the main constituent of senile plaques in brain, as well as deposition of neurofibrillary tangles and neurophil threads [94]. The cognitive function in such patients is inversely associated with systemic oxidative stress and vitamin E can be considered as an effective treatment of this disease [95].

Parkinson's disease (PD)

PD involves a selective loss of neurons in an area of the midbrain called the *substantia nigra* [96]. There is evidence that there are relatively high levels of basal oxidative stress in the *substantia nigra* pars *compacta* (SNc) in the normal brain, but this has been found to be increases in PD patients [97]. A majority of studies indicate the effect of oxidative stress that contributes to the cascade of events leading to dopamine cell degeneration in PD [98]. Supplementation with antioxidants may prevent or reduce the rate of progression of this disease such as L-dihydroxyphenylalanine (L-dopa), the agents used in the treatment of PD, combined with high levels of multiple antioxidants may improve the efficacy of L-dopa therapy [99].

Rheumatoid arthritis (RA)

Rheumatoid arthritis is a systemic autoimmune disease that causes chronic inflammation of the joints and tissue around the joints with infiltration of macrophages and activated T cells [100]. Cellular proliferation of the synoviocytes and neo-angiogenesis leads to formation of pannus which destroys the articular cartilage and the bone [101]. Some studies provide evidences for the involvement of free radicals in the pathogenesis of rheumatoid arthritis [102-103]. The pathogenesis of this disease is linked predominantly with the formation of free radicals at the site of inflammation. Antioxidant supplementation or intake of natural dietary antioxidants possibly plays a protective and an adjuvant role in the treatment of RA [104].

Oxidative Damage to Nucleic Acid

Nucleic acids damage by oxygen free radicals results in producing many different types of lesions. These lesions can be grouped into strand breaks and base modification products [105]. Superoxide produced from the xanthine/ xanthine oxidase system has been shown to cause DNA strand breaks [106]. Hydroxyl free radicals react readily with nucleic acids, yielding many different kinds of products including strand breaks, which are probably the most frequent single lesion. These strand breaks are a result of the attack of the hydroxyl free radicals on the sugar portion, probably carbons 3' and 4', of the macromolecule. Strand breaks have important implications in terms of the development of pathological states because they must be repaired for the cell to function properly. Decrease in total antioxidant capacity of the aged rat plasma and myocardium shows that this decrease may be involved in the mechanisms of free radical- induced damage to DNA during aging [107]. Such oxidative damage to nucleic acids can be decline by supplementation with pure antioxidants or with foods rich in antioxidants [108].

Aging

The process of aging may be characterized as a progressive decline in the physiological functions of an organism with time and results in a decreased resistance to multiple forms of stress as well as an increased susceptibility to various diseases [109]. The free radical theory of aging was first introduced in 1956 by Denham Harman who proposed the concept of free radicals playing a role in the aging process [110]. This theory asserts that many of the changes, such as damage to DNA, protein cross-linking and other changes, that occur in the body with age has been attributed to free radicals. Over time, these damages accumulate and cause aging process. Intense research has been triggered into the field of role of free radicals in biological systems. Superoxide generated adventitiously by the mitochondrial respiratory chain can give rise to much more reactive radicals, resulting in random oxidation of all classes of macromolecules. However, it has become apparent that many downstream consequences of free radical damage can also be caused by processes not involving oxidation. Damage associated with lipid peroxidation and cellular damage by active oxygen species contributes to the pathological changes attributed to aging. Scientists reported a decrease in the rate of free radical mediated lipid peroxidation on supplementation with vitamin E [111].

Longevity genes

The genetics of aging has made substantial strides in the past decade. This progress has been confined primarily to model organisms, such as filamentous fungi, yeast, nematodes, fruit flies, and mice, in which some thirty-five genes that determine life span have been cloned. These genes encode a wide array of cellular functions, indicating that there must be multiple mechanisms of aging. Nevertheless, some generalizations are already beginning to emerge. There are at least four broad physiological processes that play a role in aging: metabolic control, resistance to stress, gene dysregulation, and genetic stability [112].

Researchers proposed that $p66^{shc}$ is part of a signal transduction pathway that regulates stress apoptotic responses and life span in mammals [113]. The SHC1 gene (named after its Src and Collagen homologous regions) is an important candidate gene for longevity in humans as it was found that mice in which p66SHC specific region of the SHC gene is deleted live 30% longer without apparent disease and these mice have lower levels of oxidative stress and apoptosis, both of which have been linked to old age survival in man [114]. Apoptosis and reactive oxygen species have been suggested to play a role in human longevity [115, 116]. Resveratrol, the first gene known to activate complement longevity, prolongs lifespan and retards the expression of age-dependent traits in a short-lived vertebrate [117]. Scientists have reported that the longevity of both invertebrates and vertebrates can be altered through genetic manipulation and pharmacological intervention. Most of these interventions involve alterations of one or more of the following: insulin/IGF-I signaling pathway, caloric intake, stress resistance and nuclear structure [118].

Phytochemicals

Since decades, plants have been recognized to contain many natural substances. Phytochemicals are natural chemical compounds found in plant-derived foods. These natural compounds are widely distributed and some times present in surprisingly higher concentration in plants exhibiting potent antioxidant activity. A wide range of phytochemicals, including flavonoids, carotenoids, polyphenols and organosulfur compounds are antioxidants and dietary intake of such antioxidants plays an important role in the protection of the human beings against free radicals and several other diseases like cardiovascular diseases and cancer [119]. Table 2 lists phytochemicals present in different vegetables and fruits [120].

Table 2. Phytochemicals present in different vegetables and fruits.

Food	Phytochemicals
Allium vegetables (Garlic, onions, chives, leeks)	Allyl sulfides
Cruciferous vegetables (broccoli, cauliflower, cabbage, Brussels sprouts, kale, turnips, kohlrabi)	Indoles/ glusinolates, Sulfaforaphane, Isothiocyanates/ thiocyanates/ thiols
Solanaceous vegetables (tomatoes, peppers, capsicum)	Lycopene, Solasodine, Capsaicin
Umbelliferous vegetables (carrots, celery, parsley, parsnips)	Carotenoids, Phthalides, Polyacetylenes
Composite plants (artichoke)	Silimarin
Citrus fruits (oranges, lemons, grapefruit)	Monoterpenes (limonene), Carotenoids, Tangeritin, Naringin
Other fruits (grapes, berries, cherries, apples, watermelon, pomegranate)	Ellagic acid, Phenols, Flavonoids,

Beans, grains, seeds (soybeans, oats, barley, brown rice, whole wheat, flax seed)	Flavanoids (isoflavones), Phytic acid Saponins
Herbs, spices (ginger, mint, rosemary, thyme, oregano, sage, basil, fennel, garlic, turmeric)	Gingerols, Zingerone, Flavonoids, Monoterpenes (limonene), Ferulic acid, Allicin, Curcumin
Licorice root, Green tea	Glycyrrhizin, Epigallocatechin gallate (EGCG)
Other plants, *Hypericum* sp., Rosemary, *Myrsine* sp., *Macuna* sp., Spinach, Maize	Hypericin, Carnosol, Embelin, Macunadine,Lutein, zeaxanthin

Many clinical and epidemiological studies show a connection between the antioxidant activity of the substances present in the diet and the prevention from such diseases as cardiovascular diseases or carcinogenesis [121, 122].

In traditional medicine and healing, many herbs and medicinal plants are one of the richest reservoirs of antioxidants. In many countries, screening studies were carried out for the comparison of antioxidant activities of medicinal plants typical for the respective country [123, 124]. Plants are known to produce secondary metabolites which possess antioxidant potential which represent a potential source of novel and lucrative compounds with antioxidant activity. Traditional herbal medicines thus constitute an important integral part of the Indian healthcare system. These include tomatoes, yams, carrot, leafy green vegetables, blue-berries, black-berries, cherries, *Ginko biloba*, garlic and green tea [125]. The antioxidant effects in plants are mainly due to the presence of phenolic compounds such as flavonoids, phenolic acids, tannins and phenolic diterpenes [126]. Several epidemiological studies suggest that plants rich in antioxidant play a protective role in health and against disease and their consumption lowered risk of cancer, heart disease, hypertension and stroke [127, 128]. Major groups of phytochemicals contributing to the total antioxidant capacity of plant include polyphenols and vitamins (C & E).

Phenolic compounds

Phenolic compounds of plants are hydroxylated derivatives of benzoic acid and cinnamic acids and have been reported to possess antioxidant effects [129]. Several reports indicate that the antioxidant potential of medicinal plants may be related to the concentration of their phenolic compounds which include phenolic acids, flavonoids, anthocyanins and tannins [130].

Flavonoids

Many studies suggest that dietary factors based on cereals, pulses, spices, dark green leafy vegetables (kale and spinach), citrus fruits, crude palm oil, soybean oil, cod liver oil, sprouts, peppers, whole grain, honey, walnuts and black tea can significantly increase the hepatic antioxidant enzymes and their supplementation reduces the risk of coronary heart disease effectively and safely particularly phenolic compounds like flavonoids. They improve endothelial function and inhibit platelet aggregation in humans [131]. Flavonoids regarded as "super antioxidants" scavenge free radicals associated with oxygen and iron; or by inhibiting oxidative enzymes. Over 4000 flavanoids have been found and fall in four different groups: flavones, flavanones, catechins, and anthocyanins. Certain fruits, flowers, roots, stems, tea, wine, grains and vegetables harbor high quantities of flavonoids. Being rich in flavonoids – apples protect against lung cancer and Blueberries improves memory in animals [132]. Isoflavones of soybeans seems to starve cancer cells and inhibit tumor growth. It also lower blood cholesterol and protect cardiac arteries.

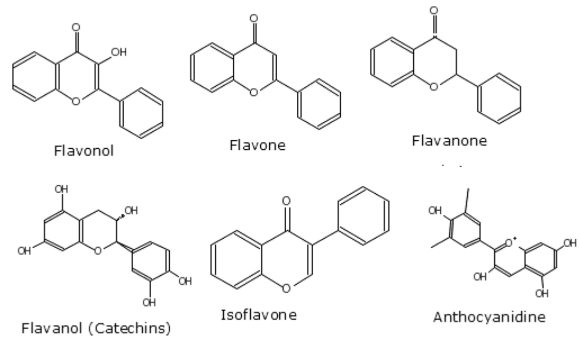

Fig 3.Flavonoids

Bioflavanoids

Oligomeric Proanthocyanidins (Bioflavanoids) have the ability to attach to cells and their proteins for up to 72 hours protecting them from oxidation and free radical damage and replenish antioxidant effect of eye fluid, which help protect the eye against UV rays [133]. Grape seed, red wine, grape skin, peanut skin, and some white wines and fruits are rich in bioflavonoids.

Polyphenols and resveratrol

Polyphenols are another important group of phytochemicals which includes resveratrol (3,4',5-trihydroxystilbene) and protects against cancer by inhibiting cell growth and against heart disease by limiting clot formation. The richest natural sources of resveratrol are dark grape extracts and giant knotweed (*Polygonnum cuspidatum*, a perennial shrub). Resveratrol and its related polyphenols also protect the cell's DNA, block cancer-causing chemicals and radiation and fight free radicals and inflammation. In one study, resveratrol along with quercetin and curcumin (from turmeric), emerged as the most powerful anticancer agents from 22 compounds that were subjected to a battery of tests, including their ability to suppress ornithine decarboxylase, scavenge free radicals and counteract carcinogens [134].

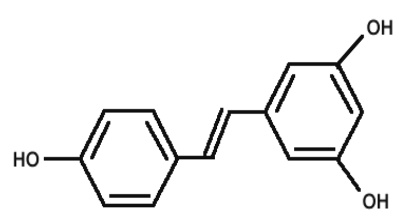

Fig 4. Resveratrol

Carotenoids

Carotenoids are a group of red, orange and yellow pigments found in plant foods, particularly fruits and vegetables. Carotenoids like β-carotene act as a precursor of vitamin A. Both *in vitro* and *in* *vivo* studies show that β-carotene is an effective antioxidant [135]. It is one of the most powerful singlet oxygen quenchers as it can dissipate the energy of singlet oxygen, thus preventing this active molecule from generating free radicals. Its other antioxidant properties include the scavenging of free radicals. Unlike other nutrient antioxidants, β-carotene acts efficiently even at low oxygen pressure [136]. Besides β-carotene, other important dietary carotenoids include α-carotene, lycopene, lutein, zeaxanthin and β-cryptoxanthin. Some studies have confirmed that lycopene has a powerful role as an antioxidant [137]. Tomatoes, with their abundant lycopene, defend against cancer by protecting DNA from oxidative damage [138]. Broccoli sprouts contain an abundance of the cancer-fighting phytochemical sulforaphane. Citrus fruits contains considerable amount of limonene which possess inhibitory activity against human gastric cancer [139]. Table 3 represents antioxidants and their respective color/ pigments in different veggies and fruits.

Table 3. Major antioxidants and their respective color/ pigments from different sources

Antioxidant	Color/Type	Sources
Beta-Carotene	Orange Colors	Sweet potatoes, carrots, squash, apricots, pumpkin, and mangoes
Lutein	Green Colors.	leafy vegetables/greens, spinach
Lycopene	Red Colors	Tomatoes, watermelon, guava, papaya, apricots, pink grapefruit.
Vitamin E	Fat Soluble	almonds, oils (corn and soybean), mangoes, nuts, and broccoli
Vitamin A	Fat Soluble	liver, sweet potatoes, carrots, milk, egg yolks and mozzarella cheese
Vitamin C	Water Soluble	Many fruits and vegetables, cereals, beef, poultry and fish.
Selenium (Mineral)	-	Seafood, poultry and meat products

Naturally occurring antioxidants in leafy vegetables and seeds, such as ascorbic acid, vitamin E and phenolic compounds, posses the ability to reduce the oxidative damage associated with many diseases, including cancer, cardiovascular disease, cataracts, atherosclerosis, diabetes, arthritis, immune deficiency diseases and aging [140, 141] and so they are important in the prevention of human diseases. Antioxidant compound may efficiently function as free radical scavengers, completers of pro-oxidant metals, reducing agents and quenchers of singlet oxygen formation. Antioxidants such as tocopherols and phenolic compounds are often added in oils and fatty acids to retard their auto-oxidation [142].

Medicinal herbs as antioxidants

Indian medicinal herbs were extensively investigated as vital sources of antioxidants. *Aerva lanata* exhibits 1,1-diphenyl-2-picrylhydrazyl (DPPH) scavenging properties [143] and are rich in flavonoids such as Kaempferol 3-rhamnoside and Kaempferol 3-rhamnogalactoside [144]. Its inhibitory effect on microsomal cytochrome P_{450} enzyme or on lipid peroxidation is due to the presence of alkaloids [145]. Similarly, the ability of *Amaranthus paniculatus* extract to act as a free radical scavenger or hydrogen donor was revealed by DPPH radical scavenging activity assay [146]. *Coccinia indica* leaf extract also possess an antioxidant activity which may be attributed its protective action on lipid peroxidation and to the enhancing effect on cellular antioxidant defense contributing to the protective action against oxidative damage [147]. Presence of polyphenolic compounds with antioxidant activity such as quercetin 3-glucuronide isoquercetin and rutin has been reported in seeds of *Coriandrum sativum* while confirmation through DPPH assay [148] and the presence of berberina and phenolic compounds was analyzed in *Coscinium fenestratum* [149]. *Evolvulas alsinoides* ethanolic extract and water infusion have antioxidant effects as depicted by the inhibition of lipid peroxidation and ABTS assay [150]. *Fagona cretica* is known to exhibit strong free radical scavenging properties against reactive oxygen [151]. *Gymnema montanum* also shows antioxidant activity due to the presence of ascorbic acid and α- tocopherol [152]. *Hygrophila auriculata* is an indigenous plant with free radical scavenging and lipid peroxidation activities and inhibits carbon tetrachloride induced oxidative stress and proliferative response [153].

Various species of *Phyllanthus* are known to exhibit potent antioxidant activity. *P. amarus* is rich in polyphenols, tannins, quercetin, catechin and epigallocatechin as potential antioxidants [154]. The n-hexane extract of *P. maderaspatensis* exhibits *in vitro* radical scavenging activity and inhibition of lipid peroxidation [155]. Furthermore, methanolic and aqueous extract of *P. niruri* showed inhibition of membrane lipid peroxidation, scavenging of DPPH radical and inhibition of ROS *in vitro* [156] as well as it inhibit carbon tetrachloride induced formation of lipids peroxide in the liver of rats *in vivo* [157]. Hence, herbal medicines exhibit healing power and are one of the important cultural and traditional recipes for health care and sustainability. The antioxidant activities of these herbal plants and their extracts have a promising role in radical scavenging and in protecting cells from cellular damage.

Garlic

Garlic is rich in antioxidant phytochemicals that comprise organosulfur compounds as well as flavonoids such as allixin, which are capable of scavenging free radicals [158]. The antioxidant compounds present in aged, old garlic extract called “Kyolic” are known to contain radio-protective properties. This aged garlic extract is an odorless preparation made from organic garlic by a process of extraction and aging [159]. It is rich in antioxidant and more effective as an immunomodulating agent compared to fresh garlic [160]. Its major antioxidant compound is S-allyl cysteine, which is well effective in shielding cells from oxidant damage by radiation and anticancer drugs [161]. Garlic antioxidants have been also linked with blood cholesterol lowering properties, cardio-protective aspects, as well as anti-aging properties [162].

Curcumin

Various experimental studies confirm that Curcumin, a yellow pigment in *Curcuma longa*, acts as a potent antioxidant and radical scavenger [163]. Curcumin is also known to possess cancer-preventive antioxidant where it induces apoptosis in colon cancer cells and multiple myeloma cells [164] as well as ovarian cells [165]. It acts as a free radical scavenger, inhibiting lipid peroxidation [166] and oxidative DNA damage and thought to play a vital role against an array of chronic pathological complications such as cancer, atherosclerosis and neurodegenerative diseases [167].

Silibinin

Silibinin is a powerful antioxidant being the product of Milk thistle (*Silibum marianum*) [168]. It is known to induce apoptosis in prostate cancer cells suggesting a potential role in the control of disease [169].

Herbal Tea

There is growing interest in drinking tea all over the world, which could be connected with antioxidative activity, fighting the harmful influence of environmentally generated free radicals. The analysis of DPPH• free radicals scavenging ability by green and black tea aqueous extracts was conducted and found that the green tea aqueous extract showed higher radicals scavenging efficiency than black tea extract [170]. Black tea contains lower levels of catechins and higher levels of tannins [171]. The best abilities of DPPH• free radicals scavenging was affirmed for (±)-catechin, quercitin and rutin, considerably higher than BHT and α- tocopherol.

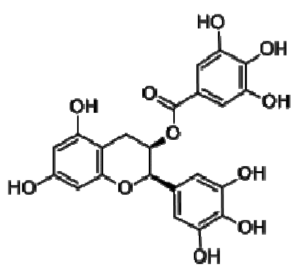

Fig 5. Epigallocatechin Gallate (EGCG)

The major components of black tea include theaflavins (orange pigments) and thearubigins (red pigments). Green tea is rich in polyphenols and flavonoids and contains a characteristic Catechin-Epigallocatechin Gallate (EGCG) which is a superior antioxidant known to inhibit cancer and also is an anti-obese (calorie burning) compound. The antioxidant present in tea reduces cholesterol and risk of heart diseases and boosts immune system [172].

Pomegranate: The "Rising Superfruit"

Antioxidants found in fruits and vegetables are known to provide our bodies with many health benefits. Pomegranate (*Punica granatum*) is one such fruit that contains high levels of antioxidants including polyphenols, such as tannins and anthocyanins. The most abundant polyphenols and a major antioxidant compound present in pomegranate juice are hydrolyzable tannins called Punicalagins that have free radical scavenging properties in laboratory experiments [173]. Most therapeutically beneficial pomegranate constituents are ellagic acid, ellagitannins (including punicalagins), punicic acid, flavonoids, anthocyanidins, anthocyanins, and estrogenic flavonols and flavones [174]. Pomegranate extracts have been shown to scavenge free radicals and decrease macrophage oxidative stress and lipid peroxidation in animals [175] and increase plasma antioxidant capacity in elderly humans [176].

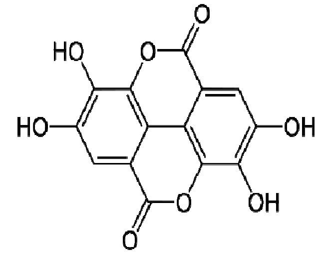

Fig 6.Ellagic Acid

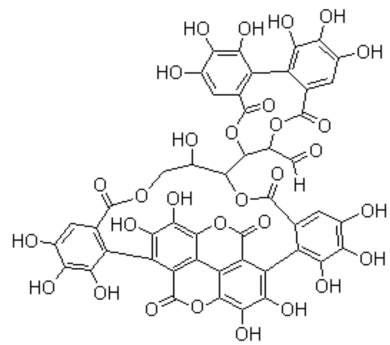

Fig 7.Punicalagin

Mushrooms as a source of antioxidants

Mushrooms have been highly valued across the globe as both food and medicine since times immemorial. They are a group of fleshy macroscopic fungi which until recently as other fungi, were introduced in the plant kingdom because of cell wall and spores [177]. Edible mushrooms are found to contain a noticeable amount of total phenols and can therefore play a major role in exhibiting antioxidant potential. They can be used as easily accessible source of natural antioxidants and as a possible food supplement or as a therapeutic in pharmaceutical industry.

A naturally occurring metabolite is Ergothioneine (ERT) or 2-mercaptohistidine trimethylbetaine found in dietary mushrooms which is a unique powerful antioxidant and naturally occurring amino acid. *Grifola frondosa*, *Pleurotus ostreatus* and *Lentinula edodes* harbor highest amount of ERT. Since it scavenges strong oxidants such as hydroxy radicals, hypochlorite and peroxynitrite *in vitro*, and chelates redox-active bivalent cations such as Cu^{2+}, ERT has been considered to function primarily as an antioxidant within cells. *Ganoderma lucidum*, a medicinally potent mushroom is known to profoundly increase the catalase gene expression and enzyme activities in mouse liver [178]. Functionally catalases are related to peroxidases, both promote H_2O_2 oxidation by mechanisms involving ferryl intermediates [179]. Aqueous extracts from wild *Cordyceps sinensis* could scavenge hydroxyl radicals [180]. Similarly, *Cordyceps militaris* resisted the damage from superoxide anion mainly with superoxide dismutase and resisted the damage from hydrogen peroxide with both catalase and antioxidant compounds [181]. Several commercial mushrooms are reported to be effective against an array of diseases by virtue of their antioxidant potential. The antioxidant activity of *Pleurotus pulmonarius* (Fr.) was found to be due to the presence of phenols [182] and that of *Russula delica* could be credited to the presence of phenols and flavonoids [183].

Endogenous defense mechanisms

Body relies on several endogenous defense mechanisms to help protect against free radical-induced damage. Antioxidant enzymes are scavenger of reactive oxygen intermediates and are involved in many cellular defense systems [184]. Enzymes like glutathione peroxidase, catalase and superoxide dismutase (SOD) metabolize oxidative toxic intermediates and necessitate micronutrient cofactors such as selenium, iron, copper, zinc, and manganese for optimum catalytic activity. During normal physiological process, reactive species are continuously formed but can be removed by antioxidant defense mechanism [185]. Table 4 depicts different endogenous antioxidants along with their functions [186].

Table 4. Antioxidant enzymes and human diseases

Disease	Specification	Main key enzyme/s
Allergy	Intolerance to aspirin	GPX
	Intolerance to other drugs	SOD
	Intolerance to some foods	GPX
	Reaction in skin tests	SOD
Cancer	Bowel	CAT, GPX, SOD
	Breast	GPX
	Colorectal	COX-2
	Kidney	CAT, GPX, SOD
	Leukemia	CAT, GPX, SOD
	Liver	CAT, GPX, SOD
	Skin	GPX
Cardiological and vessels injuries	Ischemia	SOD
	Atherosclerosis	SOD
Infectious disease	Arthritis	COX-2
	Helicobacter pylori	SOD
	Hepatitis	GPX
	HIV	GPX
	Influenza virus	CAT, GPX, SOD
Genetic disorder	Chronic granulomatous disease	CAT
	Down's syndrome	SOD
Neurodegenerative disease	Allergic encephalomyelitis	NOS
	Alzheimer's disease	SOD
	Amyotrophic lateral sclerosis	SOD
	Huntington's disease	SOD
	Parkinson's disease	GPX
	Prion disease	SOD
Metabolic malfunction	Diabetes	CAT, SOD
Ophthalmologic problem	Cataract	CAT, SOD

GPX: Glutathione peroxidase; SOD: Superoxide dismutase; CAT: Catalase; COX-2: Cyclooxygenase-2; NOS: Nitric oxide synthase.

The role of catalase in deterring tumor promotion and enhancing cell survival during periods of oxidative stress supports the antioxidant function of this enzyme [187]. Free radicals such as superoxide radical ($O_2^{\cdot}$), Hydroxyl radical ($OH^{\cdot}$) and other reactive oxygen species (ROS) are associated with cellular necrosis and a variety of pathological conditions such as cancer, degenerative disease in neurons, hepatopathies, atherosclerosis and even aging [188]. The defense systems against free radical in human are a proof of the main role of antioxidant enzymes in blood cells detoxification, showing the coordinated enzymatic mechanism, and the interrelationships between all these enzymatic activities [189].

Synthetic antioxidants

Supplementation with antioxidant could represent an important therapeutic potential to minimize the damage caused by free radicals [190]. Scientists are attempting to develop novel synthetic antioxidants to retard the effects of free radical induced damage in different foodstuffs and human body cells [191]. Many such synthetic compounds have been evaluated for their efficacy as radical scavengers or for their other inhibitory effects. Among them, only four synthetic antioxidants are extensively used in food preservation; namely, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), propyl gallate (PG) and tert-butylhydroquinone (TBHQ) [192, 193]. These synthetic antioxidants are broadly used in food industry but now-a-days use of such compounds in foods has been decreased due to their possible action as promoters of carcinogenesis [194].

CONCLUSION

Free radicals and related species have been implicated in the etiology of myriad of major diseases. Recent research is directed towards formulation of strategies to protect cardinal tissues and organs against oxidative damage induced by free radicals and related chemical entities. The antioxidant defense systems are importance in maintaining normal cellular physiology and fighting against diseases. There are endogenous protective antioxidant mechanisms and dietary antioxidants that are intimately involved in the prevention of cellular damage caused by free radicals. The traditional Indian diet, spices and medicinal plants are rich sources of natural antioxidants. Attention is focused on ROS/RNS- linked pathogenesis of cancer, cardiovascular disease, atherosclerosis, hypertension, ischemia/repurfusion injury, diabetes, neurodegenerative diseases, rheumatoid arthritis and aging. An array of natural products are endowed with antioxidant potential, thus it is a time, after periods of booming research on oxidants and antioxidants to critically reflect on this related subject. Diet rich in antioxidants such as fresh and unprocessed foods, raw fruit and vegetables and other antioxidant supplements are now being renowned as an important means of reducing the toxic effects imposed by free radicals. Therefore, the endogenous antioxidant enzymes and cofactors as well as the extensive assortment of natural antioxidants are concurrently presenting an enormous possibility in improving free radical protection and in the treatment of human diseases.

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