Free Radicals: Implications in Etiology of Chronic Diseases and Their Amelioration through Nutraceuticals

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ABSTRACT
Background: Free radicals are highly reactive molecular species with an unpaired electron in the outer valence orbitals which causes them to capture electrons from other substances in order to neutralize themselves. As a by-product of oxidative biochemical reactions in the cells, these chemical moieties get commonly produced. During the past several years, there has been a mounting concern in the medical implications of free radicals. They can adversely alter many crucial biological molecules leading to loss of form and function. The association between free radicals, antioxidants and functioning of various organs and organ systems is highly complex. Free radicals induce oxidative/nitrosative stress leading to cellular redox imbalance inducing pathogenesis of several diseases. Free radical damage effectively contributes to the etiology of several chronic health problems such as cardiovascular disease, diabetes, cancer, neurodegenerative disorders and other chronic conditions. Antioxidants are a broad group of nutritional elements which constitute the first line of defense against free radical damage. Nutraceuticals and phytochemicals thus represent an important natural source of antioxidative therapies apart from endogenous mechanisms. Objective: The present study highlights generation of free radicals, role of oxidative stress in pathogenesis of chronic diseases and the protective action of antioxidants. The putative role of nutraceuticals/phytonutrients as antioxidative therapeutic agents is also discussed. Conclusion: Research indicates that functional food is the chief source of mental and physical well-being, thus contributing to prevention and reduction of risk factors for several diseases. Thus, the search has been strengthened for exploring effective, nontoxic natural phytochemicals with antioxidative activity in addition to endogenous antioxidant defense systems to combat the dreadful effects of free radicals and their counterparts.

Key words: Free radicals, ROS, RNS, oxidative stress, antioxidants, human pathologies, antioxidative therapies
Pharmacologia 6 (1): 11-20, 2015

INTRODUCTION
Nutrition plays an essential and fundamental role in maintaining overall health of an individual. Poor nutrition tends to have a considerable impact in implication of chronic diseases. Greek physician Hippocrates back in 400 B.C., said, “Let food be thy medicine and medicine be thy food”. At least four of the 10 leading causes of death in today’s world like heart disease, cancer, stroke and diabetes can be related to dietary habits. During past several years, medical research indicates a significant relationship between free radicals and antioxidants followed by the implications of these unstable entities in several chronic ailments (Aruoma, 1994; Rao et al., 2006; Lobo et al., 2010). It is paradoxical that oxygen which is an element indispensable for life, can have severely deleterious effects on the human body under certain situations. Nutraceutical word is the amalgamation of “nutrition” and “pharmaceutical” and was coined in 1989 by Stephen DeFelice. Nutraceuticals have been considered to be alternative medicines for the past few years (Kaur et al., 2012).

FREE RADICALS
Free radicals are highly reactive molecular species with an unpaired characterization of natural antioxidant
having less or no electrons in the outer orbital. Free radicals that are normal metabolites in aerobic biological systems have varied reactivities, ranging from the high reactivity of hydroxyl radical \( (t_{1/2} = 1 \text{ msec}) \) to the low reactivity of melamins \( (t_{1/2} = \text{ days}) \), with the intermediate reactivity of nitric oxide \( (t_{1/2} = 1-10 \text{ sec}) \) and ubisemiquinone \( (t_{1/2} = 10 \text{ msec}) \). Estimates indicate that the average person has around 10000-20000 free radicals attacking each body cell each day (Valdez et al., 2000; Valko et al., 2001). Targets of free radicals include all kinds of biologically relevant molecules in the body including lipids, nucleic acids and proteins, leading to cell damage and homeostatic disruption.

**Reactive oxygen species (ROS) and reactive nitrogen species (RNS):** Oxygen molecules are pioneers for radical reactions. When \( \text{O}_2 \) gains 1 electron, it turns into a superoxide anion radical, \( \text{O}_2^- \). The addition of a second electron (together with 2 protons) turns the latter into hydrogen peroxide, \( \text{H}_2\text{O}_2 \). Peroxide is not a radical but it easily gains a third electron giving rise to a hydroxyl radical, \( \text{OH}^+ \) and hydroxyl ion, \( \text{HO}^- \). Hydroxyl radical-\( \text{OH}^+ \), a very active chemical particle, easily initiates uncontrolled chain reactions. Free radical chain reactions gravely damage important biomolecules in vitro, causing oxidative damage to DNA, proteins and other macromolecules. In biochemical literature, ROS are traditionally considered as highly dangerous particles (Fridovich, 1998). The hydroxyl radical (\( \text{OH}^+ \)) 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^-7 sec. The term Reactive Oxygen Species (ROS), often used in the biomedical free radical literature has been a collective term that includes not only oxygen-centered radicals such as \( \text{O}_2^- \) and \( \text{OH}^+ \) but also some nonradical derivatives of oxygen, such as hydrogen peroxide \( \text{(H}_2\text{O}_2) \), singlet oxygen \( \text{O}_2^* \) and hypochlorous acid \( \text{(HOCl)} \). A similar term, Reactive Nitrogen Species (RNS), is also becoming widely used. Some of these species are much less ‘reactive’ than others, e.g., \( \text{NO}^- \) and \( \text{NO}^\cdot \) react directly with less number of molecules in the human body, in comparison to \( \text{OH}^+ \). When generated in vivo, \( \text{OH}^+ \) will react at its site of formation (Halliwell, 2006). Thus, ROS and RNS formed in vivo are considered to be 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 (Gutowski and Kowalczyk, 2013).

The 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 proteins occur which increases the risk for more than 30 different disease processes viz., muscle atrophy, atherosclerosis, multiple sclerosis, autoimmune disease, emphysema and cataract to name a few (Percival, 1998).

Free radicals, oxidative stress and antioxidants share an intricate relationship in maintaining health, aging and age-related diseases (Fig. 1). Prooxidants are chemicals which act by triggering oxidative stress by increasing free radicals leading to cell damage or through ROS production or inhibiting antioxidant systems. Oxidative stress is the shift towards the pro-oxidants in pro-oxidant: Antioxidant balance that can occur due to increase in oxidative metabolism. Thus, oxidative stress, defined as “the imbalance between oxidants and antioxidants in favor of the oxidants potentially leading to damage” has been suggested to be the cause of aging and various disease in humans and is believed to be a critical concept in maintaining a healthy biological system (Kalam et al., 2012). Oxidative stress induced by free radical is counter-balanced by the body’s endogenous antioxidant systems (Wong et al., 2000). “Antioxidants and free radicals exhibit ‘yin-yang relationship’ as propounded in more than 2000 years old traditional Chinese medicine system.” An imbalance between the generation of free radicals and antioxidants,
including some co-factors may lead to implications for aging, diabetes, cardiovascular disease, cancer, neurodegenerative disorders and other chronic conditions.

**Pathways and sources leading to generation of free radicals:** Free radicals/ROS/RNS are produced mainly from different sources 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 P450, activated neutrophils and phagocytic cells and environmental sources like drugs, pesticides, transition metals, tobacco smoke, alcohol, high temperature, redox cycling of xenobiotics, exposure to physicochemical agents like ionizing radiations such as X-rays and γ-rays besides visible light or UV in the presence of oxygen and an endogenous compound or a drug that act as photosensitizer (Sen et al., 2010). The generation of ROS and the accumulation of mitochondrial DNA (mt DNA) damage, are the common underlying pathophysiological mechanism in many diseases caused by mitochondrial dysfunction (Pieczeniak and Neustadt, 2007).

**ROS-stimulated oxidative damage in biomolecules:** ROS, depending upon their nature, can react with major biomolecules such as lipid, protein and DNA, producing different types of secondary radicals like lipid radicals, sugar and base derived radicals, amino acid radicals and thyl radicals. These radicals in the presence of oxygen are converted to peroxyl radicals. Peroxyl radicals tend to initiate chain reactions in biological systems. The highest concentration of unsaturated fatty acids is present in lipid components of cellular membranes thus making them vulnerable to the oxidation by ROS. The ROS react with membrane lipids causing lipid peroxidation, resulting in the formation of lipid hydroperoxide (LOOH) which can further decompose to an aldehyde such as malonaldehyde, 4-hydroxy nonenal (4-HNE) or form cyclic endoperoxide, isoprostans and hydrocarbons. The consequences of lipid peroxidation are cross linking of membrane proteins, change in membrane fluidity and the formation of lipid-protein, lipid-DNA adduct which may be detrimental to the functioning of the cell. ROS possess the potential to interact with proteins directly and indirectly both, resulting into peroxidation, changes in their tertiary structure, proteolytic degradation, protein-protein cross linkages and fragmentation. Free radicals such as -O**2H** can fragment and crosslink proteins. The side chains of all amino acid residues of proteins, in particular tryptophan, cysteine and methionine residues are susceptible to oxidation by ROS. Carbonyls such as aldehydes and ketones are normal protein oxidation products (Bent and Hayon, 1975). During the oxidation of aromatic residues, the formation of phenoxyl radicals from tyrosine and their conversion into dityrosine and further products can occur, especially if there are no reductants to repair the tyrosyl radicals (e.g., thiols, vitamin E) and if there are vicinal tyrosyl radicals. Histidine in reactions with free radicals can form some imidazole decay products or in some cases, aspartic acid and can also form some histidine derivatives (Dean et al., 1997).

DNA is a stable, well-protected molecule but ROS can interact with it and cause several types of damage including modification of DNA bases, single and double strand DNA breaks loss of purines, damage to the deoxyribose sugar, DNA-protein cross-linkage and damage to the DNA repair system (Beckman and Ames, 1997). The O**2H** radical reacts with DNA producing a variety of adducts. It can attack purine and pyrimidine bases to form O**2H** radical adducts which are both oxidizing and reducing in nature. This induces base modifications and sometimes release of bases. Some of the important base modifications include 8-hydroxydeoxyguanosine (8-OHdG), 8 (or 4,5-) hydroxyadenine, thymine peroxide, thymine glycols and 5-(hydroxymethyl) uracil. Free radicals can also attack the sugar moiety which can produce sugar peroxyl radicals and subsequently inducing strand breakage. The consequence of DNA damage is the modification of genetic material resulting into cell death, mutagenesis, carcinogenesis and aging (Kunwar and Priyadarsini, 2011). All ROS are not capable of damaging DNA but OH**•** radicals are the major source of endogenous DNA damage in aerobic organisms (Marnett, 2000). Oxygen-free-radical damage nucleic acids resulting in production of many different types of lesions which can be grouped into strand breaks and base modification products (Cooke et al., 2003). Superoxide produced from the xanthine/xanthine oxidase system has been shown to cause DNA strand breaks. 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.

**ANTIOXIDANTS**

'Antioxidants' are substances that neutralize free radicals or their actions (Sies, 1996). Being protective agents, they are 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. Exposure to free radicals necessitates intake of antioxidant supplemented diets to shield cells from the adverse effects of free radicals. A free radical is referred to as “Electron thief” and antioxidant as “electron donor” (Fig. 2). The antioxidant offers the free radical the extra electron, so the free radical does not have to steal one.

The body relies on several endogenous defense mechanisms to help protect against free radical-induced damage (Kumar et al., 2008; Rahman, 2007; Adachi et al., 1994). There is currently considerable interest in dietary antioxidants as bioactive components of food. 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 and 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.

**Nonspecific antioxidant molecules:** Due to the generation of highly reactive oxidants, such as hydroxyl radical •OH, mammalian cell is constantly undergoing wear and tear causing grave damage to cell which has to be restricted. Thus, a second line of defense against free radical attack is constituted by nonenzymatic antioxidant molecules, such as vitamin E, vitamin C, ubiquinone or Coenzyme Q and carotenoids. Reduced glutathione might act as a cellular antioxidant while α-tocopherol might function as chain-breaking antioxidants because they effectively interrupt free radical propagation reactions (Paravicini and Touyz, 2008).

**Free radicals induced human pathologies:** Free radicals induce oxidative stress which has been implicated in the etiology of myriad of chronic diseases including atherosclerosis, cancer, neurodegenerative diseases, such as Alzheimer’s and Parkinson’s disease, diabetes mellitus, inflammatory diseases, as well as psychological diseases and aging processes (Durackova, 2010).

**Role of oxidative stress in cardio-vascular diseases:** Cardiovascular disease is the major cause of mortality around the world. It may be broadly classified into coronary heart disease, cerebrovascular disease and peripheral vascular disease, in which the blood supplies to the heart, the brain and the peripheral vasculature, respectively, are compromised (Ross, 1999). Common to each of these classifications is the formation of an atherosclerotic plaque or lesion (atheroma) which can occlude small blood vessels and disrupt blood flow (Ross, 1993). This leads to acute manifestations such as

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**Fig. 2: Relationship between radicals and antioxidants**

<table>
<thead>
<tr>
<th>Radical</th>
<th>Antioxidant</th>
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<tbody>
<tr>
<td>Superoxide ( \text{O}_2^- )</td>
<td>SOD, Lipoic acid</td>
</tr>
<tr>
<td>Hydrogen peroxide ( \text{H}_2\text{O}_2 )</td>
<td>Catalase, Glutathione peroxidase</td>
</tr>
<tr>
<td>Hydroxyl radical ( \text{OH}^- )</td>
<td>Vit C, Lipoic acid</td>
</tr>
<tr>
<td>Peroxyl Radical (PUFA + ( \text{O}_2 ))</td>
<td>Vit E, Beta carotene, lycopene</td>
</tr>
<tr>
<td>Singlet oxygen ( \text{O}_2^1 )</td>
<td>Lycopene, carotenes, lutein, lipoic acid, Glutathione, Vit E</td>
</tr>
<tr>
<td>Hypochlorous radical ( \text{OCI}^- )</td>
<td>Lipoic acid</td>
</tr>
<tr>
<td>Peroxynitrite Radical ( \text{ONOO}^- )</td>
<td>Lipoic acid</td>
</tr>
<tr>
<td>Ozone ( \text{O}_3 )</td>
<td>Vit C</td>
</tr>
</tbody>
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myocardial infarction and stroke in which tissue oxygen and nutrient supply are severely compromised (Rader and Daugherty, 2008). Atherosclerosis is a complex disorder involving numerous cell types which contribute to the initiation and formation of atherosclerotic lesions. Production of oxygen free radicals is the key to the progression of this potentially fatal inflammatory disorder at a number of cellular sites, along with reduced cell antioxidant capacity (Pearson and Faux, 2009). The ROS participate in normal cell signaling as mediators regulating vascular function (Harrison et al., 2003). The loss of myocytes through apoptosis or programmed cell death, has been reported in the infarct regions of myocardium from myocardial infarction patients as well as from patients with end-stage heart failure (Narula et al., 1996). Any acute or chronic cardiac stress conditions, resulting in a relative deficit in the myocardial ‘antioxidant reserve’, are associated with an increase in myocardial ‘oxidative stress’ (Singal et al., 1998). Direct involvement of oxidative stress in apoptosis has been demonstrated in a variety of cell types (Hockenbery et al., 1992). Antioxidant vitamins, such as vitamin C, carotenoids and vitamin E, have been shown to decrease lipid peroxidation and reduce atherogenesis and the risk of coronary heart disease. Vitamin E being a ‘chain breaking’ antioxidant acts to protect polyunsaturated fatty acids from oxidation by interrupting the chain reaction of lipid peroxidation in the membrane (Packer, 1991).

The ROS generated by mitochondria play an important role in signaling pathways which contribute to cardiovascular disease. In few cases the primary stimulus for the activation of these pathways has been identified. The vasoactive agents such as angiotensin II (Kimura et al., 2005), Epidermal Growth Factor (EGF) (Krieg et al., 2004), transforming growth factor-β (TGF-β) (Herrera et al., 2001) and Tumor Necrosis Factor-α (TNF-α) (Chen et al., 2004) are capable of modulating mitochondrial ROS production. The mitochondrial contribution to growth factor signaling response appears to involve the transactivation of growth factor receptors and is associated with the protection against oxidative stress (Chen et al., 2004; Daugherty et al., 1994).

Role of oxidative stress in diabetes: Diabetes Mellitus (DM) is a group of metabolic diseases characterized by abnormal insulin secretion, derangement in carbohydrate and lipid metabolism and is diagnosed by the presence of hyperglycemia. This clinical metabolic syndrome is also characterized by hypertriglyceridemia, reduced HDL (good cholesterol) and abnormal postprandial lipemia finally leading to atherosclerosis. Type 1 diabetes or Insulin-Dependent Diabetes Mellitus (IDDM) is a complex, multifactorial disease involving severe destruction of the insulin-producing pancreatic β-cells. Oxidative stress may play an important role in diabetes, not just because of its role in the development of complications but because persistent hyperglycemia, secondary to insulin resistance, may induce oxidative stress and contribute to β-cell destruction in type 2 diabetes (Mohora et al., 2007). In diabetes, oxidative stress seems caused by both increased production of ROS, sharp reductions in antioxidant defenses and altered cellular redox status (West, 2000; Goldstein et al., 2005). Although the source of this oxidative stress remains unclear, it has been suggested that the chronic hyperglycaemia in diabetes enhances the production of ROS from glucose autoxidation, protein glycation and glycoxidation which leads to tissue damage (Brownlee, 2000). The increase in the level of ROS in diabetes could be due to their increased production and/or decreased destruction by nonenzymic and enzymic catalase (CAT), reduced glutathione (GSH) and superoxide dismutase (SOD) antioxidants (Lipinski, 2001; Slatter et al., 1999; Jakus, 2000).

Role of oxidative stress in carcinogenesis: Cancer is a synonym for malignant neoplasm. It is a genetic disease, a process leading a cell from a healthy to a precancerous state and finally to an early stage of cancer. Cancer development takes place in three major stages: Initiation, promotion and progression. Carcinogenesis involves a cascade of events involving mutation and the subsequent selective clonal expansion of the mutated cell. Cancers evolve by a reiterative process of clonal expansion, genetic diversification and clonal selection within the adaptive landscapes of tissue ecosystems (Greaves and Maley, 2012; Cadet et al., 2010). There exists an intricate inflammatory network. Chronic inflammation is induced by biological, chemical and physical factors and is in turn associated with an increased risk of several human cancers (Bartsch and Nair, 2006). The link between inflammation and cancer has been suggested by epidemiological and experimental data (Grivennikov et al., 2010) and confirmed by anti-inflammatory therapies that show efficacy in cancer prevention and treatment (Gonda et al., 2009). Carcinogens induce carcinogenesis by myriad modes of action, including production of ROS. Initiation of carcinogenesis starts just after an inflammatory stimulus which is either mediated by ROS and may be direct (oxidation, nitration, halogenation of nuclear DNA, RNA and lipids) or may be mediated by the signaling

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pathways activated by ROS. The $\text{H}_2\text{O}_2$, another example of ROS, are short-lived but the most damaging radicals within the body and may be formed either by dismutation from superoxide anion or spontaneously in peroxisomes from molecular oxygen (Ray and Hussain, 2002; Bellezza et al., 2010; Hanahan and Weinberg, 2000; Barkett and Gilmore, 1999).

Role of oxidative stress in neurodegenerative diseases (NDD): Brain is one of the most metabolically active organs of the body along with the spinal cord comprising Central Nervous System (CNS) which, even at rest, utilizes an estimated 20% of the total oxygen uptake. 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 (Marksbery, 1997). The NDD includes Alzheimer’s Disease (AD), Amyotrophic Lateral Sclerosis (ALS), cerebellar disorders, Parkinson’s Disease (PD), Huntington’s Disease (HD) and stroke in aged populations. These may be related to the oxidative damage in neurons either primarily or secondarily (Rao and Balachandran, 2002). Oxidative stress plays a ubiquitous role in NDD. However, high levels of oxidative stress can cause necrosis, ATP depletion and prevention of controlled apoptotic death (Beal, 2005). Though CNS has a high requirement for oxygen but unexpectedly, is relatively deficient in the enzymes that metabolize a number of oxygen-based reactants to innocuous species (Nunomura et al., 2006). Being the power house of the cell, mitochondria are directly associated and susceptible to oxidative stress. There has been increasing evidence suggesting that mutations acquired during aging by mtDNA (mitochondrial DNA) contribute to physiological decline occurring with age and age-related neurodegeneration (Lin and Beal, 2006; Shukla et al., 2011). Therefore, oxidative stress is an important factor in neurodegenerative diseases, as the damage of the neurons could be due to either an increase in oxidative process or a decrease in anti-oxidant defenses or both.

Antioxidative therapies: Nutraceutical antioxidants provide strong scientific support to be developed as novel therapies for ameliorating myriad of diseases. Several of these natural antioxidants not only actively scavenge free radicals but they also function as modulators of pro-survival or pro-apoptotic signaling pathways. Henceforth, these natural compounds may elicit a greater potential as effective therapeutic agents than traditional medicines with only one mechanism of action. The advancement of this research may lead to the development of nutritional products (nutraceuticals) and semisynthetic analogs that preserve substantial antioxidant capacity but produce minimal side effects (Vidya and Devasagayam, 2007).

According to a “French Paradox” there exists an interesting co-relation between the healthful and nutritive properties of red wine and cardiovascular health. The French paradox is an incentive for more research in countries with low Coronary Heart Disease (CHD) incidence and probably more protective CHD risk factors (Ferrieres, 2004). After virtually 20 years of research study, there is now escalating evidence that small doses of wine intake would prove to be beneficial for the cardiovascular health, acting through a variety of mechanisms that target all the crucial steps of atherosclerosis, from the early formation of the atherosclerotic plaque to its life-threatening complications viz., ulceration, thrombosis, vessel occlusion and infarction (Lippi et al., 2010). These beneficial effects can be attributed to the synergic properties of several biochemical components of wine (alcohol, resveratrol and especially polyphenolic compounds), particularly the red varieties.

A wide variety of antioxidant compounds derived from natural products (nutraceuticals) have demonstrated neuroprotective activity in either in vitro or in vivo models of neuronal cell death or neurodegeneration, respectively (Kelsey et al., 2010). Antioxidants can thus act as a protective agent in neurodegenerative diseases and can be considered as a promising approach to slowing the progression and limiting the extent of neuronal cell loss in these disorders (Moosmann and Behl, 2002; Kannappan et al., 2011). Some nutraceuticals are well known, like epigallocatechin 3-gallate (EGCG) from green tea and resveratrol from grapes which displays neuroprotective effects (Dungan et al., 2001). Antioxidant nutrients may complement the therapies to reduce oxidative stress during diabetes. Dietary supplementation with antioxidant rich food can help diminish oxidative stress associated with NIDDM. However, chronic diabetic complications can be prevented and cured with certain nutritional antioxidants. Primary among these are vitamin E (α-tocopherol) and lipoic acid (thiotic acid). Vitamin E is a fat-soluble vitamin that effectively scavenges the peroxyl radical in cell membranes, thereby inhibiting lipid peroxidation. Prospective epidemiological studies demonstrate that high serum vitamin E levels are associated with decreased risk of NIDDM (Tapas et al., 2008). In addition to this many other antioxidant nutrients have been reported to be beneficial for subjects with NIDDM. Flavonoids are a class of secondary plant phenolics with significant antioxidant and chelating properties, ubiquitously found.
in commonly consumed fruits, vegetables and beverages such as red wine and tea. They have been demonstrated to protect against oxidative stress in type 1 and 2 diabetes (Salonen et al., 1995). Specifically, the flavonoids inhibit lipid oxidation and delay the depletion of lipid-soluble antioxidants. Serum levels of carotenoids, another group of antioxidant compounds often present in edible plants, were inversely related to fasting serum insulin levels (Lean et al., 1999). The protective effects of flavonoids in biological systems are ascribed to their capacity to transfer electrons free radicals, chelate metal catalysts, activate antioxidant enzymes, reduce alpha-tocopherol radicals and inhibit oxidases (Ford et al., 1999).

Dietary and endogenous antioxidants react with oxidizing free radicals and prevent cellular damage by eliminating them. Involvement of chemotherapeutic agents in cancer treatment may lead to the generation of free radicals causing cellular damage and necrosis of malignant cells. So, a concern arises as to whether exogenous antioxidant compounds taken concurrently during chemotherapy could reduce the beneficial effect of chemotherapy on malignant cells. Oxidative damage to nucleic acids can be declined by supplementation with pure antioxidants or with foods rich in antioxidants (Hirano et al., 2001) which would check the development of malignancies due to mutations. The study of antioxidant use in cancer treatment is a rapidly evolving area. Antioxidants have been extensively studied for their ability to prevent cancer in humans (Singal et al., 1998). Thus, there is a current need for exploring new therapies which would increase the efficacy of cancer treatment. Appropriate use of antioxidants along with chemotherapy may be an effective measure for curing cancer thereby facilitating cancer therapy to the pinnacle of success. Widely characterized anti-tumor flavonoids include epigallocatechin gallate (from green tea), genistein (from soy and red clover) curcumin (from turmeric), silibinin (from milk thistle) and quercetin (from many yellow vegetables) (Bushman, 1998; Miodini et al., 1999). Nutraceuticals are compounds showing great potential in nutritional industry due to their capacity to combat severe and chronic diseases and preventing the emergence of other diseases. Thus these substances tend to modify body’s physiological processes (Jain and Ramawat, 2013). Synopsis of free radical formation, oxidative stress and pathogenesis of chronic diseases is represented in Fig. 3.
CONCLUSION

Free radicals/ROS/RNS are produced mainly from diverse sources in the biological system causing a cascade of oxidation events leading to disruption of cellular membranes and attacking other major cell organelles. An antioxidant usually works by retarding this process of oxidation caused by these unstable entities. Most of the chronic diseases arise due to improper nutrition or are indirectly related to diet so, a central role is being played by nutrients in the prevention of such ailments.

ACKNOWLEDGMENTS

Sadaf Kalam would like to express her deepest appreciation towards her mentor Prof. Appa Rao Podile, Department of Plant Sciences, University of Hyderabad, for his incessant support and encouragement during the writing of this manuscript. The authors would like to thank Prof. Abul Kalam Department of Linguistics, MANUU, Hyderabad for his critical evaluation and suggestions during the drafting of this manuscript. The authors would also like to acknowledge Mr. S.N. Vijaywargia, Chancellor, Peoples’ University, Bhopal, (M.P) for his encouragement and moral support.

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