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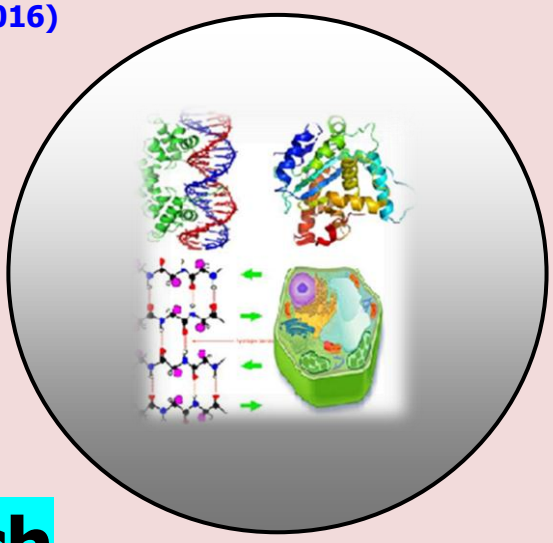

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Occurrence of Health Sustaining Natural Antioxidants in Medicinal Plants and Spices: A Comprehensive Review

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ABSTRACT

The recent escalation in the knowledge of free radicals and ROS in biology is producing a medical revolution that promises a new age of health and disease management. It is ironic that oxygen, an element indispensable for life, under certain situations has deleterious effects on the human body. The demand for natural antioxidant is increasing due to its unquestionable advantages compared with the addition of antioxidants directly to the food. Therefore, the search for antioxidants perceived as natural, namely those that naturally occur in herbs and spices, is a field attracting great interest. There is consistent evidence from human and animal studies that strenuous physical exercise may induce a state wherein the antioxidant defenses of several tissues are overwhelmed by excess reactive oxygen. There has recently been a remarkable increment in scientific articles dealing with oxidative stress. Consequently, knowledge about reactive oxygen and nitrogen species metabolism; definition of markers for oxidative damage; evidence linking chronic diseases and oxidative stress; identification of flavonoids and other dietary polyphenol antioxidants present in plant foods as bioactive molecules; and data supporting the idea that health benefits associated with fruits, vegetables in the diet are probably linked to the polyphenol antioxidants they contain. In addition, more than 8,000 polyphenolic compounds have been identified in various plant species and reported to possess many useful properties including antiallergic, antiinflammatory, antimicrobial, antiviral, antioxidant, oestrogenic, enzyme inhibition, vascular and cytotoxic anti- tumor activity. Dietary antioxidants, such as water-soluble vitamin C and phenolic compounds, as well as lipid-soluble vitamin E and carotenoids, present in vegetables contribute both to the first and second defense lines against oxidative stress. As a result, they protect cells against oxidative damage, and may therefore prevent chronic diseases, such as cancer, cardiovascular disease, and diabetes. Brassica vegetables, which include different genus of cabbage, broccoli, cauliflower, Brussels sprouts, and kale, are consumed all over the world.

While use of synthetic antioxidants (such as butylated hydroxytoluene and butylated hydroxyanisole) to maintain the quality of ready-to-eat food products has become commonplace, consumer concern regarding their safety has motivated the food industry to seek natural alternatives. Phenolic antioxidants can inhibit free radical formation and/or interrupt propagation of autoxidation. Fat-soluble vitamin E (α-tocopherol) and water-soluble vitamin C (L-ascorbic acid) are both effective in the appropriate matrix. Plant extracts, generally used for their flavoring characteristics, often have strong H-donating activity thus making them extremely effective antioxidants. This antioxidant activity is most often due to phenolic acids (gallic, protocatechuic, caffeic and rosmarinic acids), phenolic diterpenes (carnosol, carnosic acid, rosmanol and rosmadial), flavonoids (quercetin, catechin, naringenin, and kaempferol), and volatile oils (eugenol, carvacrol, thymol and menthol). Some plant pigments (anthocyanin and anthocyanidin) can chelate metals and donate H to oxygen radical's thus slowing oxidation via 2 mechanisms. Tea and extracts of grape seeds and skins contain catechins, epicatechins, phenolic acids, proanthocyanidins and resveratrol, all of which contribute to their antioxidative activity. The objective of this article is to provide an impending overview of clinical manifestation resulted due to overload of free radicals and natural antioxidants, their mechanisms of action, nutritional prophylaxis & imminent therapeutic applicability. The significance of this area of research, current state of information, and possibilities of further investigation are precisely delineated.
Keywords: Immunocompetence, Phytochemicals; β-carotene, Free radicals, Oxidative stress, ROS, SOD, Environmental pollution, Nucleic acids, Flavonoids and Carotenoids.

INTRODUCTION

It is well known that many botanicals possess natural antioxidants with high antioxidant activity. And investigations on these were initiated based on their uses in traditional folkloric medicines. Antioxidants are the nutritional equivalents and are loyal protectors and nurturers of our cells, repelling disease, and promoting good health. Antioxidants can come from healthy eating or in the form of supplements, and they include a family of naturally formed components like vitamin A, β-carotene, lycopene, vitamin E, and more. They are believed to protect cells from free radicals (Fig. 1), harmful oxygen molecules thought to damage cells that result in cancer, atherosclerosis, Alzheimer's disease, and rheumatoid arthritis, and they may be the underlying reason why we age. In nature due to instinctive oxidation process - an apple slice turns brown; fish becomes rancid; a cut on skin is raw and inflamed. All of these result from a natural process called oxidation (Asha et al., 2012).

It happens to all cells in nature, including the ones in your body. To help your body protect itself from the rigors of oxidation, Mother Nature provides thousands of different antioxidants in various amounts in fruits, vegetables, whole grains, nuts, and legumes. When your body needs to put up its best defense, especially true in today's environment, antioxidants are crucial to your health. As oxygen interacts with cells of any type - an apple slice or, in your body, the cells lining your lungs or in a cut on your skin -- oxidation occurs. This produces some type of change in those cells. They may pass away, such as with rotting fruit. In the case of cut skin, dead cells are replaced in time by fresh, new cells, resulting in a healed cut. This birth and death of cells in the body goes on continuously, 24 hours a day. It is a process that is necessary to keep the body healthy (Rani et al., 2014).

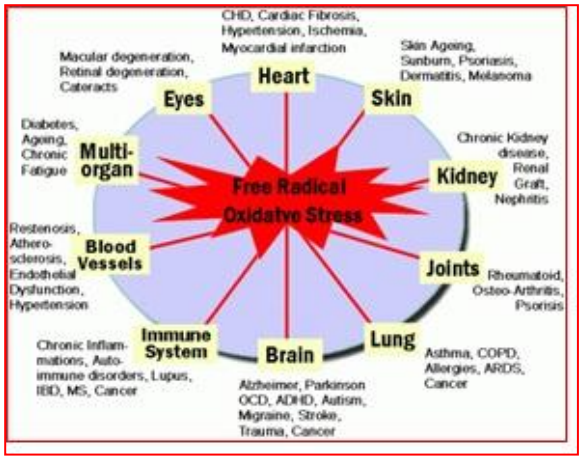

Figure 1. Free Radical Oxidation Stress resulting in Various Diseases.

Oxidation is a very natural process that happens during normal cellular functions. Yet there is a downside. While the body metabolizes oxygen very efficiently, 1% or 2% of cells will get damaged in the process and turn into free radicals. "Free radicals" is a term often used to describe damaged cells that can be problematic. They are "free" because they are missing a critical molecule, which sends them on a rampage to pair with another molecule. "These molecules will rob any molecule to quench that need. When free radicals are on the attack, they don't just kill cells to acquire their missing molecule. "If free radicals simply killed a cell, it wouldn't be so bad… the body could just regenerate another one," he says. "The problem is, free radicals often injure the cell, damaging the DNA, which creates the seed for disease." When a cell's DNA changes, the cell becomes mutated. It grows abnormally and reproduces abnormally -- and quickly. Normal cell functions produce a small percentage of free radicals, much like a car engine that emits fumes. But those free radicals are generally not a big problem. They are kept under control by antioxidants that the body produces naturally. External toxins, especially cigarette smoke and air pollution, are "free radical generators. Cigarette smoke is a huge source of free radicals. In fact, our food and water also harbor free radicals in the form of pesticides and other toxins. Drinking excessive amounts of alcohol also triggers substantial free radical production. Free radicals trigger a damaging chain reaction, and that's the crux of the problem (Maheshwari et al., 2013).

Epidemiological studies and a substantial body of evidence have linked the production of free radicals with the occurrence of cardiovascular diseases, carcinogenesis, rheumatoid arthritis and denegerative processes associated with aging. Antioxidants aid in the prevention by scavenging the excess free radicals, hence preventing the formation of reactive oxygen species in the body. The use of synthetic antioxidants such as butylated hydroxytoluene, butylated hydroxyanisole, tert-butylhydroquinone and propyl gallate has been negatively perceived by consumers due to safety and health effects. Hence, there is an increasing interest in the search of natural antioxidants from plant sources. Most of the potentially harmful effects of oxygen are due to the formation and activity of a number of chemical compounds, known as ROS, which have a tendency to donate oxygen to other substances. Free radicals and antioxidants have become commonly used terms in modern discussions of disease mechanisms.

Free radicals are formed naturally in the body, but their production is increased by factors such as smoking, alcohol, air pollution, infection, stress, excessive sunlight, and toxins like radiation and asbestos. A wide variety of physiological and dietary antioxidants act in concert to evade such a stress. Submaximal long-duration exercise training may augment the physiological antioxidant defenses in several tissues; however, this enhanced protection may not be sufficient to completely protect highly fit individuals from exhaustive exercise-induced oxidative stress. Regular physical activity in association with dietary habits that ensure adequate supply of a combination of appropriate antioxidants may be expected to yield desirable results (Bhati et al., 2013, Balsano and Alisi, 2009). Carotenoids get involved in an entire antioxidant network of physiological systems of the body. A number of nutrients must come together in synergy to afford effective antioxidant protection. Carotenois are sacrificial antioxidants and help save other antioxidants by means of absorbing free radical hits. One mole of carotenoid absorb up to ~ 15 attacks, facilitating redox reaxtion continuing without uninterrupted mode of action. Weakness of one antioxidant moiety results collapse of entire network (Balakrishnan and Anuradha, 1998).

OXIDATIVE STRESS, FREE RADICALS AND ANTIOXIDANTS

We are exposed to electromagnetic radiation from the environment, both natural and from man-made sources. Low-wavelength electromagnetic radiation (e. g., γ- rays) can split water in the body to generate hydroxyl radical, OH*. This fearsomely-reactive radical, once generated, attacks whatever it is next to. Its lifetime *in vivo* is vanishingly small because hydroxyl radical reacts at its site of formation, usually leaving behind a legacy in the form of propagating free-radical chain reactions (Fig. 2).

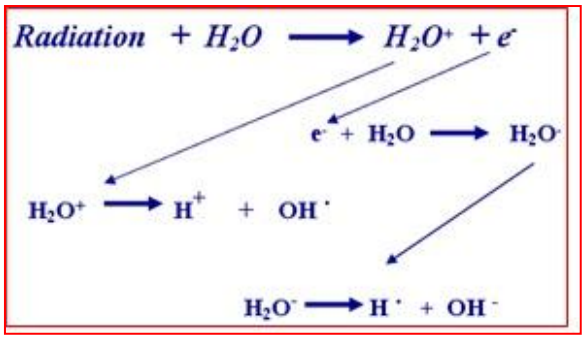

Figure 2. Splitting of Water by Radiation.

The body makes another oxygen radical (ie, the unpaired electron is located on oxygen), superoxide (0;-). Superoxide is made by adding one electron to the oxygen molecule (Fig. 3). It is generally poorly reactive. Some superoxide is made by "accidents of chemistry", in that many molecules in the body react directly with oxygen to make superoxide. Examples include the catecholamines, tetrahydrofolates, and some constituents of mitochondrial and other electron-transport chains. Activated phagocytes (neutrophils, monocytes, macrophages, eosinophils) generate large amounts of superoxide as part of the mechanism by which foreign organisms are subsided. During chronic inflammations, this normal protective mechanism may become damaging. About 1-3% of the oxygen we breathe in is used to make superoxide. Since human beings consume a lot of oxygen.

Another physiological free radical is nitric oxide (NO*), which is made by vascular endothelium as a relaxing factor, and also by phagocytes and in the brain. Nitric oxide has many useful physiological functions, but excess NO can be toxic (Chaudhary et al., 2013).

Neither superoxide nor NO is highly reactive chemically, but under certain circumstances they can generate more toxic products. Free radicals are dangerous because they don't just damage one molecule. One free radical can set off a whole chain reaction. When a free radical oxidizes a fatty acid, it changes that fatty acid into a free radical, which then damages another fatty acid. It's a very rapid chain reaction." These external attacks can overwhelm the body's natural free-radical defense system. In time, and with repeated free radical attacks that the body cannot stop, that damage can lead to a host of chronic diseases, including cancer, heart disease, Alzheimer's disease, and Parkinson's disease. Oxidative damage in skin cells is caused by cumulative sunlight. But if free radicals are in an internal organ - for example, if asbestos is in your lungs -- it stimulates free radical reactions in lung tissue. Cigarette smoke has active free radical generators. That's why stopping smoking is the biggest step anyone can take to preserving their health. In the 21st century, people need to get more antioxidants in their diet to offset all these assaults. These toxins are ubiquitous in the environment (Chauhan and Maheshwari, 2013).

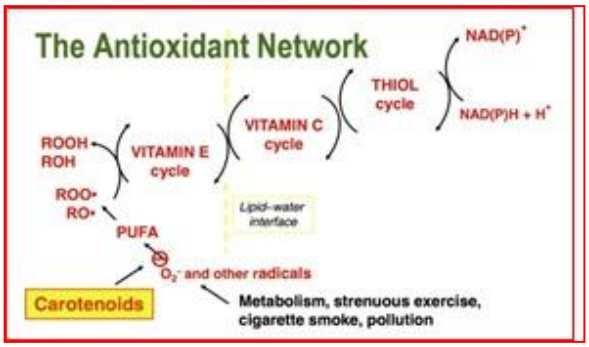

Figure 3. Pathways of ROS generation and clearance.

The oxidative burden on the body is much, much, much higher than it was 200 years ago, in dweller of a city. It's a fact of modern life, so we have to take that into consideration. Someone compensate for the effects of environmental toxins if consume multiple servings of fruits and veggies. Body simply doesn't produce enough antioxidants to do all that. What exactly do they do? Antioxidants work to stop this damaging, disease-causing chain reaction that free radicals have started. Each type of antioxidant works either to prevent the chain reaction or stop it after it's started. For example, the role of vitamin C is to stop the chain reaction before it starts. It captures the free radical and neutralizes it. Vitamin E is a chain-breaking antioxidant. Wherever it finds sit in a membrane, it breaks the chain reaction (Ghasemzadeh and Ghasemzadeh, 2011).

Flavonoids are the biggest class of antioxidants. Some 5,000 flavonoids in various foods have identified in various veggies, cereals, fruits and spices. Polyphenols are a smaller class of antioxidants, which often refer to as "phenols". We have clear science about antioxidants, that our bodies need a NADN (Natural Antioxidant Defense Network), for lack of a better term like a country needs a military system, the human body needs defense workers at all levels -- lieutenants, corporals, generals, staff sergeants - in the form of antioxidants.

The body needs a mix of vitamins and minerals, such as vitamins A, C, E, and beta-carotene, to neutralize this free radical assault. We can't rely on a few blockbuster foods to do the job," says Blumberg. "You can't eat nine servings of broccoli a day and expect it to do it all. We need to eat many different foods. Each type works in different tissues of the body, in different parts of cells. Some are good at quenching some free radicals, some are better at quenching others. When you have appropriate amounts of different antioxidants, you're doing what you can to protect yourself. Multivitamins and vitamin supplements can provide the body with an antioxidant boost. Yet getting too much of some supplements, like vitamin E, can be harmful. Fruits, vegetables, whole grains, legumes, and nuts contain complex mixes of antioxidants, and therein lies the benefit of eating a variety of healthy foods. Researchers continue delving into the mysteries of fruits and vegetables, identifying the complex antioxidants they contain. Quercetin, luteolin, hesperetin, catetchin, even (-)-epigallocetechin are some of the the blockbuster flavonoids in our foods (Gutteridge and Halliwell, 1994, Halliwell et al., 1992, Halliwell, 2005).

Oxidative damage results when the critical balance between free radical generation and antioxidant defenses is unfavorable. Oxidative stress, arising as a result of an imbalance between free radical production and antioxidant defenses, is associated with damage to a wide range of molecular species including lipids, proteins, and nucleic acids. Short-term oxidative stress may occur in tissues injured by trauma, infection, heat injury, hypertoxia, toxins, and excessive exercise. These injured tissues produce increased radical generating enzymes (e.g., xanthine oxidase, lipogenase, cyclooxygenase) activation of phagocytes, release of free iron, copper ions, or a disruption of the electron transport chains of oxidative phosphorylation, producing excess ROS. The initiation, promotion, and progression of cancer, as well as the side-effects of radiation and chemotherapy, have been linked to the imbalance between ROS and the antioxidant defense system. ROS have been implicated in the induction and complications of diabetes mellitus, age-related eye disease, and neurodegenerative diseases such as Parkinson's disease. A role of oxidative stress has been postulated in many conditions, including anthersclerosis, inflammatory condition, certain cancers, and the process of aging. Oxidative stress is now thought to make a significant contribution to all inflammatory diseases (arthritis, vasculitis, glomerulonephritis, lupus erythematous, adult respiratory diseases syndrome), ischemic diseases (heart diseases, stroke, intestinal ischema), hemochromatosis, AIDS (acquired immunodeficiency syndrome), emphysema, organ transplantation, gastric ulcers, hypertension and preeclampsia, neurological disorder (Alzheimer's disease, Parkinson's disease, muscular dystrophy), alcoholism, smoking-related diseases, and many others (Maheshwari et al., 2013, 2014).

Heart diseases continue to be the biggest killer, responsible for about half of all the deaths. The oxidative events may affect cardiovascular diseases therefore; it has potential to provide enormous benefits to the health and lifespan. Poly unsaturated fatty acids occur as a major part of the low density lipoproteins (LDL) in blood and oxidation of these lipid components in LDL play a vital role in atherosclerosis. The 3 most important cell types in the vessel wall are endothelial cells; smooth muscle cell and macrophage can release free radical, which affect lipid peroxidation. With continued high level of oxidized lipids, blood vessel damage to the reaction process continues and can lead to generation of foam cells and plaque the symptoms of atherosclerosis. Oxidized LDL is antherogenic and is thought to be important in the formation of anthersclerosis plaques. Furthermore, oxidized LDL is cytotoxic and can directly damage endothelial cells.

Antioxidants like β-carotene or vitamin E play a vital role in the prevention of various cardiovascular diseases (Maheshwari, 2013). Reactive oxygen and nitrogen species, such as super oxide anion, H_2O_2, hydroxyl radical, and NO and their biological metabolites also play an important role in carcinogenesis. ROS induce DNA damage, as the reaction of free radicals with DNA includes strand break base modification and DNA protein cross-links. Numerous investigators have proposed participation of free radicals in carcinogenesis, mutation, and transformation; it is clear that their presence in biosystem could lead to mutation, transformation, and ultimately cancer. Induction of mutagenesis, the best known of the biological effect of radiation, occurs mainly through damage of DNA by the $HO^{\cdot}$ Radical and other species are produced by the radiolysis, and also by direct radiation effect on DNA, the reaction effects on DNA. The reaction of $HO^{\cdot}$ Radicals is mainly addition to double bond of pyrimidine bases and abstraction of H from the sugar moiety resulting in chain reaction of DNA. These effects cause cell mutagenesis and carcinogenesis lipid peroxides are also responsible for the activation of carcinogens (Maheshwari and Rani, 2013). Antioxidants can decrease oxidative stress induced carcinogenesis by a direct scavenging of ROS and/or by inhibiting cell proliferation secondary to the protein phosphorylation. β-carotene may be protective against cancer through its antioxidant function, because oxidative products can cause genetic damage. Thus, the photo protective properties of B-carotene may protect against UV light induced carcinogenesis. Immunoenhancement of β-carotene may contribute to cancer protection. β-carotene may also have anticarcinogenic effect by altering the liver metabolism effects of carcinogens. Vitamin C may be helpful in preventing cancer. The possible mechanisms by which vitamin C may affect carcinogenesis include antioxidant effects, blocking of formation of nitrosanimes, enhancement of the immune response, and acceleration of detoxification of liver enzymes. Vitamin E, an important antioxidant, plays a role in immunocompetence by increasing humoral antibody protection, resistance to bacterial infections, cell-mediated immunity, the T-lymphocytes tumor necrosis factor production, inhibition of mutagen formation, repair of membranes in DNA, and blocking micro cell line formation. Hence vitamin E may be useful in cancer prevention and inhibit carcinogenesis by the stimulation of the immune system. The administration of a mixture of the above three antioxidant reveled the highest reduction in risk of developing cardiac cancer. The human body is in constant battle to keep from aging. Search suggests that free radical damage to cells leads to the pathological changes associated with aging. An increasing number of diseases or disorders, as well as aging process itself, demonstrate link either directly or indirectly to these reactive and potentially destructive molecules. The major mechanism of aging attributes to DNA or the accumulation of cellular and functional damage. Reduction of free radicals or decreasing their rate of production may delay aging. Some of the nutritional antioxidants will retard the aging process and prevent disease. Based on these studies, it appears that increased oxidative stress commonly occurs during the aging process, and antioxidant status may significantly influence the effects of oxidative damage associated with advancing age. Research suggests that free radicals have a significant influence on aging, that free radical damage can be controlled with adequate antioxidant defense, and that optimal intake of antioxidant nutrient may contribute to enhanced quality of life (Rani et al., 2013). Recent research indicates that antioxidant may even positively influence life span. Proteins can be oxidatively modified in three ways: oxidative modification of specific amino acid, free radical

mediated peptide cleavage, and formation of protein cross-linkage due to reaction with lipid peroxidation products. Protein containing amino acids such as methionine, cystein, arginine, and histidine seem to be the most vulnerable to oxidation. Free radical mediated protein modification increases susceptibility to enzyme proteolysis. Oxidative damage to protein products may affect the activity of enzymes, receptors, and membrane transport. Oxidatively damaged protein products may contain very reactive groups that may contribute to damage to membrane and many cellular functions. Peroxyl radical is usually considered to be free radical species for the oxidation of proteins. ROS can damage proteins and produce carbonyls and other amino acids modification including formation of methionine sulfoxide and protein carbonyls and other amino acids modification including formation of methionine sulfoxide and protein peroxide. Protein oxidation affects the alteration of signal transduction mechanism, enzyme activity, heat stability, and proteolysis susceptibility, which leads to aging (Rani et al., 2014).

Oxidative stress and oxidative modification of biomolecules are involved in a number of physiological and pathophysiological processes such as aging, artheroscleosis, inflammation and carcinogenesis, and drug toxicity. Lipid peroxidation is a free radical process involving a source of secondary free radical, which further can act as second messenger or can directly react with other biomolecule, enhancing biochemical lesions. Lipid peroxidation occurs on polysaturated fatty acid located on the cell membranes and it further proceeds with radical chain reaction. Hydroxyl radical is thought to initiate ROS and remove hydrogen atom, thus producing lipid radical and further converted into diene conjugate. Further, by addition of oxygen it forms peroxyl radical; this highly reactive radical attacks another fatty acid forming lipid hydroperoxide and a new radical. Thus lipid peroxidation is propagated. Due to lipid peroxidation, a number of compounds are formed, for example, alkanes, malanoaldehyde, and isoprotanes. These compounds are used as markers in lipid peroxidation assay and have been verified in many diseases such as neurogenerative diseases, ischemic reperfusion injury, and diabetes. Many experiments clearly provide evidences that DNA and RNA are susceptible to oxidative damage. It has been reported that especially in aging and cancer, DNA is considered as a major target. Oxidative nucleotide as glycol, dTG, and 8-hydroxy-2-deoxyguanosine is found to be increased during oxidative damage to DNA under UV radiation or free radical damage. It has been reported that mitochondrial DNA are more susceptible to oxidative damage that have role in many diseases including cancer. It has been suggested that 8-hydroxy-2-deoxyguanosine can be used as biological marker for oxidative stress. The term antioxidant originally was used to refer specifically to a chemical that prevented the consumption of oxygen. In the late 19th and early 20th century, extensive study was devoted to the uses of antioxidants in important industrial processes, such as the prevention of metal corrosion, the vulcanization of rubber, and the polymerization of fuels in the fouling of internal combustion engines. Early research on the role of antioxidants in biology focused on their use in preventing the oxidation of unsaturated fats, which is the cause of rancidity. Antioxidant activity could be measured simply by placing the fat in a closed container with oxygen and measuring the rate of oxygen consumption. However, it was the identification of vitamins A, C, and E as antioxidants that revolutionized the field and led to the realization of the importance of antioxidants in the biochemistry of living organisms. The possible mechanisms of action of antioxidants were first explored when it was recognized that a substance with antioxidative activity is likely to be one that is itself readily oxidized.

Research into how vitamin E prevents the process of lipid peroxidation led to the identification of antioxidants as reducing agents that prevent oxidative reactions, often by scavenging ROS before they can damage cells. Antioxidants act as radical scavenger, hydrogen donor, electron donor, peroxide decomposer, singlet oxygen quencher, enzyme inhibitor, synergist, and metal-chelating agents. Both enzymatic and nonenzymatic antioxidants exist in the intracellular and extracellular environment to detoxify ROS. Two principle mechanisms of action have been proposed for antioxidants. The first is a chain-breaking mechanism by which the primary antioxidant donates an electron to the free radical present in the systems. The second mechanism involves removal of ROS/reactive nitrogen species initiators (secondary antioxidants) by quenching chain-initiating catalyst. Antioxidants may exert their effect on biological systems by different mechanisms including electron donation, metal ion chelation, co-antioxidants, or by gene expression regulation. The antioxidants acting in the defense systems act at different levels such as preventive, radical scavenging, repair and de novo, and the fourth line of defense, i.e., the adaptation. *The first line of defense* is the preventive antioxidants, which suppress the formation of free radicals. Although the precise mechanism and site of radical formation *in vivo* are not well elucidated yet, the metal-induced decompositions of hydroperoxides and hydrogen peroxide must be one of the important sources. To suppress such reactions, some antioxidants reduce hydroperoxides and hydrogen peroxide beforehand to alcohols and water, respectively, without generation of free radicals and some proteins sequester metal ions (Sharma and Maheshwari, 2013). Glutathione peroxidase, glutathione-s-transferase, phospholipid hydroperoxide glutathione peroxidase (PHGPX), and peroxidase are known to decompose lipid hydroperoxides to corresponding alcohols. PHGPX is unique in that it can reduce hydroperoxides of phospholipids integrated into biomembranes. Glutathione peroxidase and catalase reduce hydrogen peroxide to water. *The second line of defense* is the antioxidants that scavenge the active radicals to suppress chain initiation and/or break the chain propagation reactions. Various endogenous radical-scavenging antioxidants are known: some are hydrophilic and others are lipophilic. Vitamin C, uric acid, bilirubin, albumin, and thiols are hydrophilic, radical-scavenging antioxidants, while vitamin E and ubiquinol are lipophilic radical-scavenging antioxidants. Vitamin E is accepted as the most potent radical-scavenging lipophilic antioxidant. *The third line of defense* is the repair and *de novo* antioxidants. The proteolytic enzymes, proteinases, proteases, and peptidases, present in the cytosol and in the mitochondria of mammalian cells, recognize, degrade, and remove oxidatively modified proteins and prevent the accumulation of oxidized proteins. The DNA repair systems also play an important role in the total defense system against oxidative damage. Various kinds of enzymes such as glycosylases and nucleases, which repair the damaged DNA, are known. There is another important function called adaptation where the signal for the production and reactions of free radicals induces formation and transport of the appropriate antioxidant to the right site. Cells are protected against oxidative stress by an interacting network of antioxidant enzymes. Here, the superoxide released by processes such as oxidative phosphorylation is first converted to hydrogen peroxide and then further reduced to give water. This detoxification pathway is the result of multiple enzymes, with superoxide dismutases catalyzing the first step and then catalases and various peroxidases removing hydrogen peroxide. Superoxide dismutases (SODs) are a class of closely related enzymes that catalyze the breakdown of the superoxide anion into oxygen and hydrogen peroxide.

SOD enzymes are present in almost all aerobic cells and in extracellular fluids. There are three major families of superoxide dismutase, depending on the metal cofactor: Cu/Zn (which binds both copper and zinc), Fe and Mn types (which bind either Fe or Mn), and finally the Ni type which binds nickel. In higher plants, SOD isozymes have been localized in different cell compartments. Mn-SOD is present in mitochondria and peroxisomes. Fe-SOD has been found mainly in chloroplasts but has also been detected in peroxisomes, and Cu, Zn-SOD has been localized in cytosol, chloroplasts, peroxisomes, and apoplast. In humans (as in all other mammals and most chordates), 3 forms of superoxide dismutase are present. SOD1 is located in the cytoplasm, SOD2 in the mitochondria, and SOD3 is extracellular. The first is a dimer (consists of 2 units), while the others are tetramers (4 subunits). SOD1 and SOD3 contain Cu and Zn, while SOD2 has Mn in its reactive center. Catalase is a common enzyme found in nearly all living organisms, which are exposed to oxygen, where it functions to catalyze the decomposition of hydrogen peroxide to water and oxygen. Hydrogen peroxide (H_2O_2) is a harmful by-product of many normal metabolic processes: to prevent damage, it must be quickly converted into other, less dangerous substances. To this end, catalase is frequently used by cells to rapidly catalyze the decomposition of H_2O_2 into less reactive gaseous O_2 and H_2O molecules. All known animals use catalase in every organ, with particularly high concentrations occurring in the liver. The glutathione system includes glutathione, glutathione reductase, glutathione peroxidases, and glutathione S-transferases. This system is found in animals, plants, and microorganisms. Glutathione peroxidase is an enzyme containing four selenium-cofactors that catalyze the breakdown of hydrogen peroxide and organic hydroperoxides. There are at least4 different glutathione peroxidase isozymes in animals. Glutathione peroxidase 1 is the most abundant and is a very efficient scavenger of H_2O_2, while glutathione peroxidase 4 is most active with lipid hydroperoxides. The glutathione S-transferases show high activity with lipid peroxides. These enzymes are at particularly high levels in the liver and also serve in detoxification metabolism (Sharma and Maheshwari, 2013). Ascorbic acid or “vitamin C” is a monosaccharide antioxidant found in both animals and plants. As it cannot be synthesized in humans and must be obtained from the diet, it is a vitamin. Most other animals are able to produce this compound in their bodies and do not require it in their diets. In cells, it is maintained in its reduced form by reaction with glutathione, which can be catalyzed by protein disulfide isomerase and glutaredoxins. Ascorbic acid is a reducing agent and can reduce and thereby neutralize ROS such as hydrogen peroxide. In addition to its direct antioxidant effects, ascorbic acid is also a substrate for the antioxidant enzyme ascorbate peroxidase, a function that is particularly important in stress resistance in plants. Glutathione is a cysteine-containing peptide found in mostforms of aerobic life. It is not required in the diet and is instead synthesized in cells from its constituent amino acids. Glutathione has antioxidant properties since the thiol group in its cysteine moiety is a reducing agent and can be reversibly oxidized and reduced. In cells, glutathione is maintained in the reduced form by the enzyme glutathione reductase and in turn reduces other metabolites and enzyme systems as well as reacting directly with oxidants. Due to its high concentration and central role in maintaining the cell's redox state, glutathione is one of the most important cellular antioxidants. In some organisms, glutathione is replaced by other thiols, such as by mycothiol in the actinomycetes, or by trypanothione in the kinetoplastids (Sharma et al., 2013). Melatonin, also known chemically as N-acetyl-5-methoxytryptamine, is a naturally occurring hormone found in animals and in some other living organisms, including algae.

Melatonin is a powerful antioxidant that can easily cross cell membranes and the blood–brain barrier. Unlike other antioxidants, melatonin does not undergo redox cycling, which is the ability of a molecule to undergo repeated reduction and oxidation. Melatonin, once oxidized, cannot be reduced to its former state because it forms several stable end-products upon reacting with free radicals. Therefore, it has been referred to as a terminal (or suicidal) antioxidant. Vitamin E is the collective name for a set of 8 related tocopherols and tocotrienols, which are fat-soluble vitamins with antioxidant properties. Of these, α-tocopherol has been most studied as it has the highest bioavailability, with the body preferentially absorbing and metabolizing this form. It has been claimed that the α-tocopherol form is the most important lipid-soluble antioxidant, and that it protects membranes from oxidation by reacting with lipid radicals produced in the lipid peroxidation chain reaction. This removes the free radical intermediates and prevents the propagation reaction from continuing. This reaction produces oxidized α-tocopheroxyl radicals that can be recycled back to the active reduced form through reduction by other antioxidants, such as ascorbate, retinol, or ubiquinol. Uric acid accounts for roughly half the antioxidant ability of plasma. In fact, uric acid may have substituted for ascorbate in human evolution. However, like ascorbate, uric acid can also mediate the production of active oxygen species.

If 2 free radicals meet, they can join their unpaired electrons and make a covalent bond (a shared pair of electrons). Thus superoxide and nitric oxide combine:

$O_2{}^{*-} + NO^{\cdot} \longrightarrow ONOO^{-}$ (peroxynitrite)

At physiological pH, peroxynitrite damages proteins directly, and decomposes into toxic products that include nitrogen dioxide gas ($N0_2$ &), hydroxyl radical, and nitronium ion ($N0_2{}^{+}$). Hence at least some of the toxicity of excess nitric oxide may involve its interaction with superoxide. In addition, superoxide can react with iron and Cu- ions, eventually to made hydroxyl radical. Radical plus non-radical Most molecules in the body are not radicals. Hence any reactive free radical generated is likely to react with a non-radical. When a free radical reacts with a non-radical, a free-radical chain reaction results and new radicals are formed. Attack of reactive radicals on membranes or lipoproteins starts lipid peroxidation,l which is particularly implicated in the development of atherosclerosis. If hydroxyl radicals are generated close to DNA, they can attack the purine and pyrimidine bases and cause mutations. For example, guanine is converted into 8-hydroxyguanine and other products. Superoxide dismutases (SOD) convert superoxide to hydrogen peroxide (Fig.4 & 5)

$2O_2{}^{*} + 2H^{+} \longrightarrow H_2O_2$

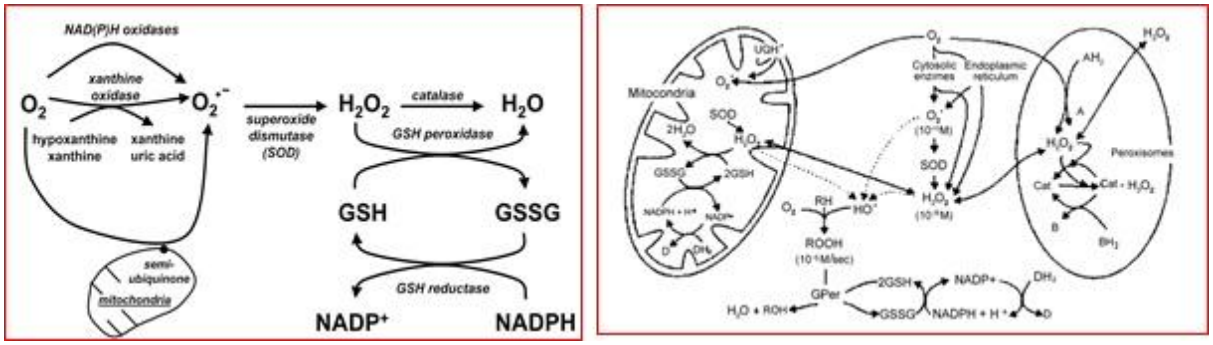

Figure 4 & 5. Superoxide to H_2O_2 by SOD.

Chemicals with multiple double bonds neutralize free radicals by reacting with them.

FREE RADICAL GENERATION AT THE FOREFRONT

A free radical can be defined as any molecular species capable of independent existence that contains an unpaired electron in an atomic orbital. The presence of an unpaired electron results in certain common properties that are shared by most radicals. Many radicals are unstable and highly reactive. They can either donate an electron to or accept an electron from other molecules, therefore behaving as oxidants or reductants. The most important oxygen-containing free radicals in many disease states are hydroxyl radical, superoxide anion radical, H_2O_2 oxygen singlet, hypochlorite, nitric oxide radical, and peroxynitrite radical. These are highly reactive species, capable in the nucleus, and in the membranes of cells of damaging biologically relevant molecules such as DNA, proteins, carbohydrates, and lipids. Free radicals attack important macromolecules leading to cell damage and homeostatic disruption. Targets of free radicals include all kinds of molecules in the body. Among them, lipids, nucleic acids, and proteins are the major targets. Free radicals and other ROS are derived either from normal essential metabolic processes in the human body or from external sources such as exposure to X-rays, ozone, cigarette smoking, air pollutants, and industrial chemicals. Free radical formation occurs continuously in the cells as a consequence of both enzymatic and nonenzymatic reactions. Enzymatic reactions, which serve as source of free radicals, include those involved in the respiratory chain, in phagocytosis, in prostaglandin synthesis, and in the cytochrome P-450 system. Free radicals can also be formed in nonenzymatic reactions of oxygen with organic compounds as well as those initiated by ionizing reactions. Free radical reactions are expected to produce progressive adverse changes that accumulate with age throughout the body. Such “normal” changes with age are relatively common to all. However, superimposed on this common pattern are patterns influenced by genetics and environmental differences that modulate free radical damage. These are manifested as diseases at certain ages determined by genetic and environmental factors. Cancer and atherosclerosis, two major causes of death, are salient “free radical” diseases. Cancer initiation and promotion is associated with chromosomal defects and oncogene activation. It is possible that endogenous free radical reactions, like those initiated by ionizing radiation, may result in tumor formation. The highly significant correlation between consumption of fats and oils and death rates from leukemia and malignant neoplasia of the breast, ovaries, and rectum among persons over 55 years may be a reflection of greater lipid peroxidation. Studies on atherosclerosis reveal the probability that the disease may be due to free radical reactions involving diet-derived lipids in the arterial wall and serum to yield peroxides and other substances. These compounds induce endothelial cell injury and produce changes in the arterial walls. Exercise appears to increase reactive oxygen species, which can result in damage to cells. Exercise results in increased amounts of malondialdehyde in blood and pentane in breath; both serve as indirect indicators of lipid peroxidation. However, not all studies report increases; these equivocal results may be due to the large inter subject variability in response or the nonspecificity of the assays. Some studies have reported that supplementation with vitamins C and E, other antioxidants, or antioxidant mixtures can reduce symptoms or indicators of oxidative stress as a result of exercise. However, these supplements appear to have no beneficial effect on performance. Exercise training seems to reduce the oxidative stress of exercise, such that trained athletes show less evidence of lipid peroxidation for a given bout of exercise and an enhanced defense system in relation to untrained subjects.

Whether the body's natural antioxidant defense system is sufficient to counteract the increase in reactive oxygen species with exercise or whether additional exogenous supplements are needed is not known, although trained athletes who received antioxidant supplements show evidence of reduced oxidative stress. Until research fully substantiates that the long-term use of antioxidants is safe and effective, the prudent recommendation for physically active individuals is to ingest a diet rich in antioxidants. An antioxidant is a molecule stable enough to donate an electron to a rampaging free radical and neutralize it, thus reducing its capacity to damage. These antioxidants delay or inhibit cellular damage mainly through their free radical scavenging property. These low-molecular-weight antioxidants can safely interact with free radicals and terminate the chain reaction before vital molecules are damaged. Some of such antioxidants, including glutathione, ubiquinol, and uric acid, are produced during normal metabolism in the body. Other lighter antioxidants are found in the diet. Although there are several enzymes system within the body that scavenge free radicals, the principle micronutrient (vitamins) antioxidants are vitamin E (α-tocopherol), vitamin C (ascorbic acid), and B-carotene. The body cannot manufacture these micronutrients, so they must be supplied in the diet (Reddy, 2011).

ANTIOXIDANTS OF NATURAL AND SYNTHETIC ORIGIN

Synthetic and natural food antioxidants are used routinely in foods and medicine especially those containing oils and fats to protect the food against oxidation. There are a number of synthetic phenolic antioxidants, butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) being prominent examples. These compounds have been widely uses as antioxidants in food industry, cosmetics, and therapeutic industry. However, some physical properties of BHT and BHA such as their high volatility and instability at elevated temperature, strict legislation on the use of synthetic food additives, carcinogenic nature of some synthetic antioxidants, and consumer preferences have shifted the attention of manufacturers from synthetic to natural antioxidants. In view of increasing risk factors of human to various deadly diseases, there has been a global trend toward the use of natural substance present in medicinal plants and dietary plats as therapeutic antioxidants. It has been reported that there is an inverse relationship between the dietary intake of antioxidant-rich food and medicinal plants and incidence of human diseases. The use of natural antioxidants in food, cosmetic, and therapeutic industry would be promising alternative for synthetic antioxidants in respect of low cost, highly compatible with dietary intake and no harmful effects inside the human body. Many antioxidant compounds, naturally occurring in plant sources have been identified as free radical or active oxygen scavengers. Attempts have been made to study the antioxidant potential of a wide variety of vegetables like potato, spinach, tomatoes, and legumes. There are several reports showing antioxidant potential of fruits. Strong antioxidants activities have been found in berries, cherries, citrus, prunes, and olives. Green and black teas have been extensively studied in the recent past for antioxidant properties since they contain up to 30% of the dry weight as phenolic compounds (Roberfroid and Calderon, 1995). Apart from the dietary sources, Indian medicinal plants also provide antioxidants and these include (with common/ayurvedic names in brackets) *Acacia catechu* (kair), *Aegle marmelos* (Bengal quince, Bel), *Allium cepa* (Onion), *A. sativum* (Garlic, Lahasuna), *Aleo vera* (Indain aloe, Ghritkumari), *Amomum subulatum* (Greater cardamom, Bari elachi),

Andrographis paniculata (Kiryat), *Asparagus recemosus* (Shatavari), *Azadirachta indica* (Neem, Nimba), *Bacopa monniera* (Brahmi), *Butea monosperma* (Palas, Dhak), *Camellia sinensis* (Green tea), *Cinnamomum verum* (Cinnamon), *Cinnamomum tamala* (Tejpat), *Curcma longa* (Turmeric, Haridra), *Emblica officinalis* (Inhian gooseberry, Amlaki), *Glycyrrhiza glapra* (Yashtimudhu), *Hemidesmus indicus* (Indian Sarasparilla, Anantamul), *Indigofera tinctoria, Mangifera indica* (Mango, Amra), *Momordica charantia* (Bitter gourd), *Murraya koenigii* (Curry leaf), *Nigella sativa* (Black cumin), *Ocimum sanctum* (Holy basil, Tusil), *Onosma echioides* (Ratanjyot), *Picrorrhiza kurroa* (Katuka), Piper beetle, *Plumbago zeylancia* (Chitrak), *Sesamum indicum, Sida cordifolia,Spirulina fusiformis* (Alga), Swertia decursata, Syzigium cumini (Jamun), *Terminalia ariuna* (Arjun), *Terminalia bellarica* (Beheda), *Tinospora cordifolia*(Heart leaved moonseed, Guduchi), *Trigonella foenum-graecium* (Fenugreek), *Withania somifera*(Winter cherry, Ashwangandha) and *Zingiber officinalis* (Ginger).

In the last decade, preventive medicine has undergone a great advance, especially in developed countries. Research has demonstrated that nutrition plays a crucial role in the prevention of chronic diseases, as most of them can be related to diet. Functional food enters the concept of considering food not only necessary for living but also as a source of mental and physical well-being, contributing to the prevention and reduction of risk factors for several diseases or enhancing certain physiological functions. A food can be regarded as functional if it is satisfactorily demonstrated to affect beneficially one or more target functions in the body, beyond adequate nutritional effects, in a way which is relevant to either the state of wellbeing and health or reduction of the risk of a disease. The beneficial effects could be either maintenance or promotion of a state of wellbeing or health and/or a reduction of risk of a pathologic process or a disease. Whole foods represent the simplest example of functional food (Sadhu, et al. 2003).

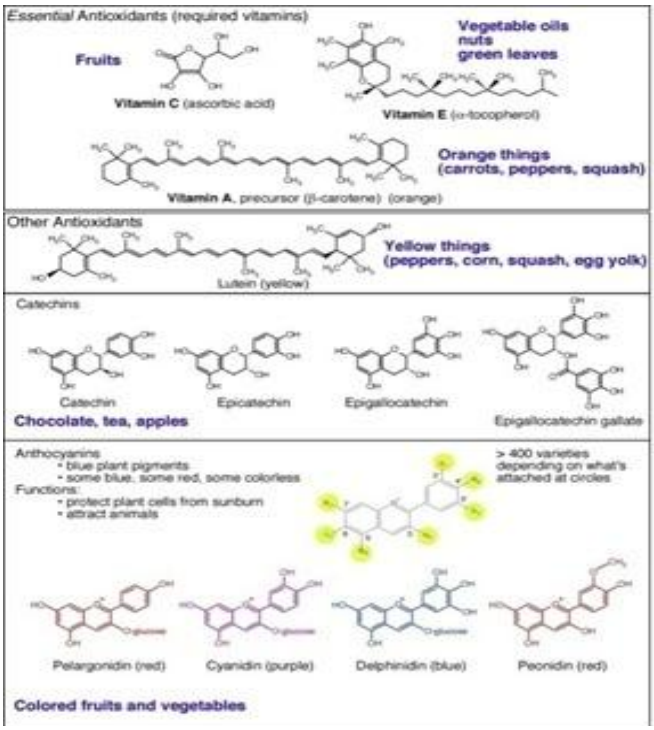

Figure 6. Various Antioxidants occurring in Colored Fruits & Veggies.

THE MOST COMPREHENSIVE STUDY OF THE ANTIOXIDANT CONTENT OF COMMON FOODS

Rank	Fruits & Veggies	Serving Size	Antioxidant Capacity/ Serving
1	Small red beans, dried	1/2 cup	13727
2	Wild blueberries	1 cup	13427
3	Red kidney beans, dried	1/2 cup	13259
4	Pinto beans	1/2 cup	11864
5	Blueberries, cultivated	1 cup	9019
6	Cranberries	1 cup	8983
7	Artichoke hearts, cooked	1 cup	7904
8	Blackberries	1 cup	7701
9	Dried prunes	1/2 cup	7291
10	Raspberries	1 cup	6058
11	Strawberries	1 cup	5938
12	Red delicious apple	One	5900
13	Granny Smith apple	One	5381
14	Pecans	1 ounce	5095
15	Sweet cherries	1 cup	4873
16	Black plum	One	4844
17	Russet potato, cooked	One	4649
18	Black beans	1/2 cup	4181
19	Plum	1	4118
20	Gala apple	1	3903

Broccoli, carrots, and tomatoes are considered functional foods because of their high contents of physiologically active components (sulforaphen, B-carotene, and lycopene, respectively). Green vegetables and spices like mustard and turmeric, used extensively in Indian cuisine, also can fall under this category. “Nutraceutical” is a term coined in 1979 by Stephen DeFelice. It is defined “as a food or parts of food that provide medical or health benefits, including the prevention and treatment of disease.” (Fig 6) Nutraceuticals may range from isolated nutrients, dietary supplements, and diets to genetically engineered “designer” food, herbal products, and processed products such as cereals, soups, and beverages. A nutraceutical is any nontoxic food extract supplement that has scientifically proven health benefits for both the treatment and prevention of disease.[84] The increasing interest in nutraceuticals reflects the fact that consumers hear about epidemiological studies indicating that a specific diet or component of the diet is associated with a lower risk for a certain disease. The major active nutraceutical ingredients in plants are flavonoids. As is typical for phenolic compounds, they can act as potent antioxidants and metal chelators. They also have long been recognized to possess anti-inflammatory, antiallergic, hepatoprotective, antithrombotic, antiviral, and anticarcinogenic activities.

Ingredients that make food functional are dietary fibers, vitamins, minerals, antioxidants, oligosaccharides, essential fatty acids (omega-3), lactic acid bacteria cultures, and lignins. Many of these are present in medicinal plants. Indian systems of medicine believe that complex diseases can be treated with complex combination of botanicals unlike in west, with single drugs. Whole foods are hence used in India as functional foods rather than supplements. Some medicinal plants and dietary constituents having functional attributes are spices such as onion, garlic, mustard, red chilies, turmeric, clove, cinnamon, saffron, curry leaf, fenugreek, and ginger. Some herbs as Bixa orellana and vegetables like amla, wheat grass, soyabean, and Gracinia cambogia have antitumor effects. Other medicinal plants with functional properties include *A. marmelos, A. cepa, Aloe vera, A. paniculata*, *Azadirachta indica*, and *Brassica juncea*.

RESEARCH TRIUMPH

An extensive review of the literature on the role of oxidative stress in influencing assisted reproduction and its outcome is described by Agarwal et al. (2006). Free radicals or reactive oxygen species mediate their action through many of the proinflammatory cytokines and this mechanism has been proposed as a common underlying factor for endometriosis, ovarian cancer, polycystic ovary disease, and various other pathologies affecting the female reproductive process, as highlighted in this review. Oxidative stress, sperm DNA damage, and apoptosis have been implicated in male infertility. Elevated reactive oxygen species levels correlate with the poor fertility outcomes seen in the assisted reproductive technology setting. Oxidative stress has been implicated in male and female infertility, including fetal dysmorphogenesis, abortions, and intrauterine growth restriction. Accurate evaluation of seminal oxidative stress by standardized assays may help in the diagnosis and management of male infertility. There is evidence in the literature on the beneficial effects of oral antioxidant supplementation in male infertility. Current ongoing trials will provide answers on the safety and effectiveness of antioxidants in improving maternal and fetal outcomes. Further studies need to be conducted to determine if antioxidant supplementation will prevent fetal developmental defects in high-risk pregnancy with diabetes. Asthma is a chronic disease characterized by inflammation of the airways (Buse and Lemanske 2001), a complex disorder characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and an underlying inflammation. The interaction of these features determines the clinical manifestations and severity of asthma, and it has been reported as a disease of increasing prevalence. The pathogenesis of asthma is unknown but imbalances between oxidants and antioxidants are believed to play a fundamental role. One key component of the oxidant-antioxidant hypothesis centers on the huge burden of oxidants derived from inflammatory cell infiltration into the lung. The eosinophil, in particular, is implicated as a major source of oxidative injury, including protein nitration (MacPherson et al. 2011). Dysfunctional mitochondria in lung cells are another potential source of oxidants. Mitochondrial injury to airway epithelium occurs in murine models of allergic asthma (Aguilera-Aguirre et al. 2009; Mabalirajan et al. 2008). There is evidence to support its role in human asthma as well, including increased oxidative injury to mitochondrial epithelial cell superoxide dismutase (SOD)(Comhair et al. 2005), enhanced mitochondrial proliferation in bronchial smooth muscle (Trian et al. 2007), and mutations in mitochondrial DNA (Reddy 2011). Overall, this oxidative burden, generated by both inflammatory and lung cells, can overwhelm antioxidant defense to cause oxidant stress during asthma.

This stress can alter or inactivate the function of essential proteins, lipids and nucleic acids culminating in severe cell injury, dysfunction and death. Among many unknown and complicated mechanisms, involvement of airways inflammation with an oxidant/antioxidant imbalance such as reactive oxygen species (ROS) can lead to lung injury as a result of direct oxidative damage to epithelial cells and cells shedding. As inflammation is often associated with an increased generation of reactive oxygen species (ROS), it is rational to surmise that an oxidant stress could be mechanistically important in asthma. ROS have been shown to be associated with the pathogenesis of asthma by inducing bronchial hyperreactivity as well as directly stimulating histamine release from mast cells and mucus secretion from airway epithelial cells (Ryszard 2000). The great external surface area (1–2) m^2 of the human airway epithelium plus its direct contact with the environment, makes the respiratory tract a major target for oxidative injury from inhaled oxidants such as cigarette smoke, ozone, hyperoxia, nitrogen and sulphur oxides and other airborne pollutants. It has been well recognized that biological systems are capable of forming highly reactive moieties, both free radicals and non-radicals named reactive oxygen species (ROS) and reactive nitrogen species (RNS). Free radicals can especially be generated in a wide variety of chemical and biological systems, including the formation of plastics, the ageing of paints, the combustion of fuels and in the human body. In living organisms, the levels of free radicals and other 'reactive species' are controlled by a complex web of antioxidant defences, which minimize (but do not completely prevent) oxidative damage to biomolecules (Roberfroid and Calderon 1995; Gaston et al. 1994; Halliwell (2005). These biologically active species serve in cell signaling as messenger molecules of the autocrine or paracrine system (Saran and Bors 1989; Suzuki et al. 1997) and also in host defense, (biocidal effects against microbial and tumor cells) (Babior 1978) but their excessive production may result in tissue injury and inflammation (Halliwell et al. 1992; Gutteridge and Halliwell 1994). Reportedly, any excessive production of oxidants is kept to a minimum by a well-coordinated and efficient endogenous antioxidant defense mechanism. It has been proposed that a deficit in the precise balance between exposure to oxidants and endogenous antioxidants results in oxidative stress which appears to be involved in the pathogenesis of a growing number of diseases, including lung pathologies such as respiratory distress syndrome, asthma, idiopathic and iatrogenic pulmonary fibrosis, cystic fibrosis, HIV-associated lung disease, lung cancer and other pulmonary diseases and conditions (Clement and Housset 1996; Barnes 1995) . As excessive ROS levels damage lipids, proteins and nucleic acids through oxidation and thus are associated with various diseases, such as atherosclerosis, arthritis, neurodegenerative disorders, and cancers , a regular supplement of antioxidants can assist the endogenous defense systems to counterbalance the harmful effects of excessive ROS (Balsano and Alisi 2009; Kaur and Geetha 2006). Another source of natural antioxidants is naturally occurring from traditional Chinese medicines sources, have been identified as free radical or active oxygen scavengers (Duh 1998; Pan et al.2007). Natural antioxidants can protect the human body from free radicals and retard the progress of many chronic diseases as well as retard lipid oxidative rancidity in foods or medicinal materials (Kang et al. 2008). Among the many mentioned sources of naturally occurring antioxidant, Seahorse (Hippocampus kuda Bleeker) has been well known for its special medicinal composition. According to Zhong-Ji Qian et al., the methanol extracts of seahorse contained high amount of phenolic compounds and those extracts exhibited good antioxidant activity by effectively scavenging

various free radicals such as DPPH radicals, hydroxyl radicals, superoxide anion radicals, alkyl radicals, and reducing the ferric to ferrous ion in different antioxidant systems.

In a search for treatment that might stop the recurrent attacks of breathlessness and wheezing to make it more susceptible to at least, providing relief for asthmatic patients, and if possible to treat the asthmatic disease, a method has emerged that seems to be extremely useful for application of natural sources of antioxidants for treatment of asthma. The method was using finely extracted powders from the seahorse (*Hippocampus kuda*) and *Rhizoma Homalomenae* (with a ratio of 1: 1 w/w) in honey to form into pill of 500mg. All the hand-rolled pills were dried in an oven at 55°C until the moisture content of the pill was consistent.In this paper, successful application of extracted powders from the seahorse (*Hippocampus kuda*) and *Rhizoma Homalomenae* together with honey in the form of medical pill for treatment of asthma is reported. Phenolic antioxidants such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT) and monotertiary butylhydroquinone (TBHQ) are hindered phenols with antimicrobial activity. The antimicrobial activity of phenolic antioxidants appears to depend on the presence of a hydroxyl group on the molecule, the lipid solubility of the compound and the degree of steric hindrance. The use of phenolic antioxidants in food products is regulated by federal agencies. In general, these compounds are permitted in concentrations up to 200 ppm, based on the fat or oil content of the food product. Certain food products have special regulations. The antimicrobial activity of phenolic antioxidants has been studied in meat and its products, poultry and its products, milk and its products, seafood, rice, applesauce and food ingredients. The antimicrobial activity of phenolic antioxidants is modified by at least 10 factors such as microbial species/strain, stressed microorganisms, type and concentration of phenolic antioxidants, concentration of microbial challenge, combination of phenolic antioxidants, combination of phenolic antioxidants with other antimicrobials, combination of phenolic antioxidants with temperature and food additives, food components, carriers of phenolic antioxidants and the mode of addition of phenolic antioxidants. The antimicrobial activity of phenolic antioxidants in foods has been examined against growth and by-products of bacteria (gram positive and negative, spore and nonspore formers, spoilage and pathogenic), molds and yeasts. The concentration of phenolic antioxidants that had antimicrobial activity in food products was in the range of 30–10,000 ppm. The mechanism of inhibition by phenolic antioxidants has been found to affect the function and composition of the cellular membrane, the synthesis of DNA, RNA, protein and lipid, and the function of the mitochondrion. Radical scavenging capacity and antioxidant activity of an E vitamer fraction from rice bran were investigated. The E vitamer fraction was prepared by a liquid-liquid extraction method. The free radical scavenging capacity of the E vitamer fraction was measured by the 1,1-diphenyl-2-picrylhydrazyl radical (DPPH) method at the concentration range of 2.5 to 640 ppm, whereas the antioxidant activities were measured by both the reducing power and ferric thiocyanate (FTC) methods at different concentrations (0, 2.5, 10, 40, and 160 ppm). Radical scavenging capacity of the fraction was effective up to 160 ppm, then remained stable. Also, at a concentration of 160 ppm, it was highly effective in inhibiting linoleic acid peroxidation. Similarly, superoxide scavenging and antioxidant activities of the E vitamer fraction were compared with those of the synthetic phenol compounds. Results showed that with a concentration of the E vitamer fraction at 160 ppm, the antioxidant activity was comparable to both butylated hydroxytoluene (BHT, 160 ppm) and butylated hydroxyanisole (BHA, 160 ppm).

No significant differences (P > 0.05) were found among them. The E vitamer fraction may be a good substitute for the synthetic phenol antioxidants currently used in industry because the former is more natural and comparatively effective in its radical scavenging capacity and antioxidant activity. During 16 h heating at 180 °C, the oxidative stability (OS) of virgin olive oil (VOO) as affected by the same concentrations (200 ppm) of tertiary-butylhydroquinone (TBHQ) and unsaponifiable matters of bene kernel (UKO) and hull (UHO) oils in terms of the inhibitory effect on the formation of conjugated diene hydroperoxides (OS_{CDV}) and off-flavor carbonyl compounds (OS_{CV}) was investigated. TBHQ was not able to considerably increase the OS_{CDV} (7.51) of the VOO (7.2) and showed no synergistic effect with indigenous antioxidative compounds of the VOO (IOV) in this respect. However, it could significantly improve the OS_{CV} (from 2.49 to 4.52), which was mainly due to its synergism with the IOV. The UKO increased considerably the OS_{CDV} (to 11.8), and its OS_{CV} (4.22) was nearly the same as that of TBHQ. The IOV still had marked contributions to the prevention of VOO oxidation but the majority of stabilizing effect was related to the UKO and its synergism with the IOV. The OS_{CDV} in presence of the UHO was less than that of the VOO (5.96), although it significantly increased the OS_{CV} (to 5.2), mainly due to the stabilizing effect of UHO and its synergism with the IOV (Saran and Bors, 1989). *In vitro* reducing power tests of tea polyphenols (Tp), *tert*-butylhydroquinone (TBHQ), and monoglyceride citrate (MGC) revealed that, at certain concentrations, Tp + TBHQ displayed a strong reductive capacity. Moreover, 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical-scavenging activity tests showed that Tp + TBHQ was effective ($p < 0.05$) in quenching DPPH radicals. The effectiveness of Tp + TBHQ towards the radical-scavenging activity was also found to be increased when their concentrations were increased. The oxidation stability of flaxseed oil (FO) was investigated as a function of time at high temperature, in the absence and presence of antioxidants; the peroxide value (PV) and *p*-anisidine value of FO were determined as indicators of oxidation at 60°C during 20 days. The results revealed that $Tp_{200} + TBHQ_{100}$ (subscripts refer to amounts in mg/kg) had noticeable reduction effects on the oxidation (PV and *p*-anisidine) of FO compared with $TBHQ_{200}$ regarding the PV, and when compared with the mixture of $TBHQ_{100} + MGC_{100}$ regarding the *p*-anisidine value. However, according to Rancimat tests, the ternary mixture ($Tp_{200} + TBHQ_{100} + MGC_{100}$) was found to be more effective in controlling FO oxidation. The induction periods for FO containing $Tp_{200} + TBHQ_{100} + MGC_{100}$, $TBHQ_{100} + MGC_{100}$, and $Tp_{200} + TBHQ_{100}$ were 8.305, 6.905, and 6.8020 h, respectively, whereby no significant differences were observed between $TBHQ_{100} + MGC_{100}$ and $Tp_{200} + TBHQ_{100}$ ($p < 0.025$).

Practical applications: Flaxseed oil is an unstable vegetable oil due to its high content of PUFA, which are mainly composed of α-linolenic acid (ALA). One effective way to ensure a high quality of lipids and lipid-containing products, and to prolong their storage time, is to stabilize them by addition of suitable antioxidants. The stabilization of FO will help to increase both its shelf life and to improve its use in different applications. According to recent studies, FO contains many components that are beneficial for human health, especially ALA which can contribute to increasing the DHA and EPA content in the body. FO is believed to provide benefits in the prevention and treatment of heart diseases, arthritis, inflammatory, and autoimmune diseases. The vitamin E family consists of eight isomers known as alpha-, beta-, gamma-, and delta-tocopherols and alpha-, beta-, gamma-, and delta-tocotrienols.

Numerous studies focused on the health benefits of these isomers have been performed since the discovery of vitamin E in 1922. Recent discoveries on the potential therapeutic applications of tocotrienols have revolutionized vitamin E research. Nevertheless, despite the abundance of literature, only 1% of vitamin E research has been conducted on tocotrienols. Many new advances suggest that the use of tocotrienols for health improvement or therapeutic purposes is promising. Although the mechanisms of action of tocotrienols in certain disease conditions have been explored, more detailed investigations into the fundamentals of the health-promoting effects of these molecules must be elucidated before they can be recommended for health improvement or for the treatment or prevention of disease. Furthermore, many of the studies on the effects of tocotrienols have been carried out using cell lines and animal models. The effects in humans must be well established before tocotrienols are used as therapeutic agents in various disease conditions, hence the need for more evidence-based human clinical trials. The antifungal effect of butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), tertiary butylhydroquinone (TBHQ) and propyl gallate (PC) alone or in combination on three toxigenic strains of aspergilli (NRRL 2999, NRRL 4123, NRRL 5835) and three nontoxigenic strains of aspergilli (NRRL 5521, NRRL 5917, NRRL 5918) was examined in a solid medium and in salami. BHT and PG (0.001,0.005,0.01,0.02g per plate) did not inhibit growth, sporulation, and toxigenesis of all six cultures. Aflatoxin production by toxigenic aspergilli (B_1, B_2, G_1 and G_2) in the presence of BHA, TBHQ, and a combination of BHA and TBHQ was reduced significantly ($P < 0.05$). In salami BHA, TBHQ alone or in combination at 100 ppm significantly ($P < 0.05$) decreased the aflatoxin production by aspergilli when compared to control samples. A combination of BHA and TBHQ showed synergistic inhibition in both studies (solid medium and salami studies). Effects of synthetic phenolic antioxidants (BHA, BHT, and TBHQ) on the methylene blue (MB) sensitized photooxidation of linoleic acid as compared with that of α-tocopherol have been studied. Their antioxidative mechanism was studied by both ESR spectroscopy in a 2,2,6,6-tetramethylpiperidone (TMPD)-methylene blue (MB) system and spectroscopic analysis of rubrene oxidation induced by a chemical source of singlet oxygen. Total singlet oxygen quenching rate constants (k_{ox-Q}+k_q) were determined using a steady state kinetic equation. TBHQ showed the strongest protective activity against the MB sensitized photooxidation of linoleic acid, followed by BHA and BHT. TBHQ (1×10^{-3} M) exhibited 86.5% and 71.4% inhibition of peroxide and conjugated diene formations, respectively, in linoleic acid photooxidation after 60-min light illumination. The protective activity of TBHQ against the photosensitized oxidation of linoleic acid was almost comparable to that of α-tocopherol. The data obtained from ESR and rubrene oxidation studies clearly showed the strong singlet oxygen quenching ability of TBHQ. The k_{ox-Q}+k_q of BHA, BHT, and TBHQ were determined to be 3.37×10^7, 4.26×10^6, and 1.67×10^8 M^{-1} s^{-1}, respectively. The k_{ox-Q}+k_q of TBHQ was within the same order of magnitude of that of α-tocopherol, a known efficient singlet oxygen quencher. There was a high negative correlation (r^2–0.991) between log (= k_{ox-Q}+k_q) and reported oxidation potentials for the synthetic antioxidants, indicating their charge-transfer mechanism for singlet oxygen quenching. This is the 1st report on the kinetic study on k_{ox-Q}+k_q of TBHQ in methanol as compared with other commonly used commercial synthetic antioxidants and α-tocopherol.
Current research suggests that wine contains substances that may reduce the mortality rate from coronary diseases.

The oxidation of low-density lipoprotein (LDL) is thought to be a key step in the development of atherosclerosis. Phenolic fractions of a Petite Syrah wine were evaluated for their antioxidant activity in inhibiting LDL oxidation *in vitro*. The more active fractions contained components of the catechin family. The catechin oligomers and the procyanidin dimers (B_2, B_3, B_4, B_6, B_8) and trimers (C_1, C_2) were extracted, isolated and purified from grapes seeds. These compounds were tested for their inhibition of LDL oxidation, along with other monomeric wine phenolics. The procyanidin dimers B_2 and B_8, and trimer C_1, and the monomers catechin, epicatechin and myricetin had the highest antioxidant activity. The procyanidin dimers B_3, B_4 and C_2 and the monomers gallic acid, quercetin, caffeic acid, and rutin, and a group of compounds that included the dimer B_6, ellagic acid, sinapic acid, cyanidin had lower antioxidant activity and α-tocopherol had the least activity. Thus, the numerous phenolic compounds found in wine are potent antioxidants in inhibiting LDL oxidation *in vitro*. Paper aims to review the role of free radical-induced tissue damage and antioxidant defence mechanisms in inflammatory diseases that involve pathogenic processes similar to the periodontal diseases. There is a clearly defined and substantial role for free radicals or reactive oxygen species (ROS) in periodontitis but little research has been performed in this area. This paper reviews the considerable data available relating ROS activity and antioxidant deference to inflammatory diseases and attempts to draw parallels with periodontitis in an effort to stimulate more periodontal research in this important area. The recent discovery of the transcription factor nuclear factor κB (NF-κB) is reviewed and several potential pathways for cytokine-induced periodontal tissue damage, mediated by NF-κB, are discussed. Emphasis is placed on cytokines that have been studied in periodontitis. principally TNF-α IL-I, IL-6. IL-8 and β-interferon. The link between cellular production of such important mediators of inflammation and the antioxidant (AO) thiols. cysteine and reduced glutathione (GSH), is discussed and it is hypothesised that NF-κB antagonists may offer important therapeutic benefits (Yadav et al., 2013).

Antioxidants may be present in foods as endogenous factors or may be added to preserve their lipid components from quality deterioration. Synthetic antioxidants such as butylated hydroxyanisole (BHA (butylated hydroxytoluene (BHT (propyl gallate (PG) and tert-butylhydroquinone (TBHQ) are commonly used in food formulations. However, due to safety concerns, interest in natural antioxidants has intensified. To address the demand by consumers, mixed tocopherols, herbal extracts such as those of rosemary and sage, as well as tea extracts have been commercialized for food and nutraceutical applications. An overview of the topic is provided in this article. In recent years, the concept of cancer chemoprevention has matured greatly. Significant reversal or suppression of premalignancy in several sites by chemopreventive agents appears achievable. This article summarizes experimental data on chemopreventive effects of tea polyphenols in different tumor bioassay systems. Tea (*Camellia sinensis*) is cultivated in about 30 countries, and is the most widely consumed beverage in the world. Three main commercial tea varieties—green, black, and oolong—are usually consumed, but most experimental studies demonstrating the antimutagenic and anticarcinogenic effects of tea have been conducted with water extract of green tea, or a polyphenolic fraction isolated from green tea (GTP). The majority of these studies have been conducted in a mouse skin tumor model system where tea is fed either as water extract through drinking water, or as purified GTP.

GTP has been shown to exhibit antimutagenic activity in vitro, and inhibit carcinogen- as well as UV-induced skin carcinogenesis in vivo. Tea consumption has also been shown to afford protection against chemical carcinogen-induced stomach, lung, esophagus, duodenum, pancreas, liver, breast, and colon carcinogenesis in specific bioassay models. Several epicatechin derivatives (polyphenols) present in green tea have been shown to possess anticarcinogenic activity; the most active is (−)-epigallocatechin-3-gallate, which is also the major constituent of GTP. The mechanisms of tea's broad cancer chemopreventive effects are not completely understood. Several theories have been put forward, including inhibition of UV- and tumor promoter-induced ornithine decarboxylase, cyclo-oxygenase, and lipoxygenase activities, antioxidant and free radical scavenging activity; enhancement of antioxidant (glutathione peroxidase, catalase, and quinone reductase) and phase II (glutathione-*S*-transferase) enzyme activities; inhibition of lipid peroxidation, and anti-inflammatory activity. These properties of tea polyphenols make them effective chemopreventive agents against the initiation, promotion, and progression stages of multistage carcinogenesis. To test the feasibility of dry milling oats (*Avena sativa* L.) to concentrate antioxidant activity and phenolic antioxidants, groats were pearled for 5 to 180 s. These treatments removed <1 to 15% of the weight. The material obtained from short pearling times was mostly bran. Longer pearling times increased the amount of starchy endosperm in the pearlings. Antioxidant activity of 80% ethanol extracts, measured by β-carotene bleaching and by reduction of the free radical, 2,2-diphenyl-1-picrylhydrazyl, was highest in the short-pearling-time fractions and decreased as more endosperm tissue was included. Likewise, there was a decreasing concentration of total phenolics, determined colorimetrically, and of several simple phenolic acids, determined by high performance liquid chromatography, as more material was pearled from the groats. In contrast, concentrations of avenanthramides were not correlated with pearling time, indicating that they were more uniformly distributed in the groats. Natural antioxidants have recently gained increased interest because of the belief that natural food ingredients are better and safer than synthetic ones. The review presents the results on stabilisation of the main edible oils with different types of natural antioxidants. Sources of natural antioxidants are spices, herbs, teas, oils, seeds, cereals, cocoa shell, grains, fruits, vegetables, enzymes, proteins. Researchers concentrate on ascorbic acid, tocopherols and carotenoids as well as on plant extracts containing various individual antioxidants such as flavonoids (quercetin, kaemferol, myricetin), catechins or phenols (carnosol, rosmanol, rosamaridiphenol) and phenolic acids (carnosic acid, rosmarinic acid). Ascorbyl palmitate is regarded as a 'natural' antioxidant because it is hydrolysed in the body to ascorbic and palmitic acids. Among the herbs of the *Lamiaceae* family, rosemary has been more extensively studied and its extracts are the first marketed natural antioxidants. Oregano, which belongs to the same family, has gained the interest of many research groups as a potent antioxidant in lipid systems. The review concerns the following main topics: stabilisation of oil with individual natural antioxidants, interaction of antioxidants with synergists, stabilisation of oil with extracts or dry materials from different plant sources (e.g. herbs and spices), stabilisation at frying temperatures and in emulsions. Six phenolic antioxidative compounds [5-caffeoylquinic acid (chlorogenic acid), 3,5-dicaffeoylquinic acid, quercetin 3-galactoside, quercetin 3-glucoside, quercetin 3-(6-malonylglucoside), and quercetin 3-(6-malonylgalactoside) (tentative)] were identified from the leaves of *Corchorus olitorius* L. (moroheiya) by NMR and FAB-MS.

The contents of these phenolic compounds, ascorbic acid, and α-tocopherol in C. olitorius leaves were determined, and their antioxidative activities were measured using the radical generator-initiated peroxidation of linoleic acid. The results obtained showed that 5-caffeoylquinic acid was a predominant phenolic antioxidant in *C. olitorius* leaves. Strenuous physical activity is known to increase the production of reactive oxygen species (ROS), associated with depletion of antioxidant defence. In the present work we evaluated the level of lipid peroxidation and antioxidant components in blood of sportsmen under resting conditions and compared the data obtained with those in age- and sex-matched sedentary controls. A significant increase was noted in the levels of thiobarbituric acid reactive substances (TBARS) and conjugated dienes while a decrease was observed in ascorbic acid and glutathione levels in sportsmen. α-Tocopherol was unaltered in plasma of sportsmen as compared to controls. The activity of superoxide dismutase was increased (52 per cent) and glutathione peroxidase was decreased (43 per cent) in the erythrocytes of sportsmen compared to controls. Basal glutathione levels were negatively correlated with conjugated dienes and maximal oxygen uptake (VO_{2max}) of the subjects. Dietary supplementation with antioxidant vitamins has been shown to be beneficial in combating oxidative stress without enhancing performance while exogenous glutathione was found to influence the endurance capacity of athletes. Such studies demonstrate the critical role played by glutathione and suggest that intervention trials should include a mixture of antioxidants rather than a single antioxidant

CONCLUSION

Free radicals damage contributes to the etiology of many chronic health problems such as cardiovascular and inflammatory disease, cataract, and cancer. Antioxidants prevent free radical induced tissue damage by preventing the formation of radicals, scavenging them, or by promoting their decomposition. Synthetic antioxidants are recently reported to be dangerous to human health. Thus the search for effective, nontoxic natural compounds with antioxidative activity has been intensified in recent years. In addition to endogenous antioxidant defense systems, consumption of dietary and plant-derived antioxidants appears to be a suitable alternative. Dietary and other components of plants form a major source of antioxidants. The traditional Indian diet, spices, and medicinal plants are rich sources of natural antioxidants; higher intake of foods with functional attributes including high level of antioxidants in antioxidants in functional foods is one strategy that is gaining importance. Newer approaches utilizing collaborative research and modern technology in combination with established traditional health principles will yield dividends in near future in improving health, especially among people who do not have access to the use of costlier western systems of medicine. One of the most important steps you can take to prevent heart disease, cancer, Alzheimer's, and Parkinson's disease is to eat plenty of antioxidant-rich foods. Antioxidants are bounteous in plant foods, particularly those that have bright colours. Because there are many different types of antioxidants that can protect your tissues from different types of damage, it is best to eat a wide range of antioxidant-rich foods. How much you benefit from the antioxidants found in the foods you eat depends on how well you breakdown and absorb these foods. One of the best ways of making sure that you are getting plenty of antioxidants in your diet is to strive to eat lots of fresh vegetables. If you just don't have the time to eat a large green salad every day, consider buying a good juicer and drinking a fresh vegetable juice on a daily basis.

Another more convenient option is to use a high quality super green food product. It is best to limit the amount of sweet fruits that you eat according to your dental health and blood sugar and insulin levels. When washing and preparing vegetables and fruits, be sure to wash non-organic varieties with extra care to help remove pesticide residues. This is especially important for vegetables and fruits that are known to be heavily contaminated with pesticides. The highest ranked foods in four major categories are as follows - Fruits: blueberries, cranberries, and blackberries; Vegetables: beans, and surprisingly, russet potatoes; nuts: pecans, walnuts, and hazelnutsp; Spices: cinnamon, oregano, and ground cloves.

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