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Review

Antioxidants: Its medicinal and pharmacological applications

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Antioxidants are essential and important for plants and animals' sustenance. They are substances that protect cells from the damage caused by unstable molecules known as free radicals. The sources and origin of antioxidants which include fruits and vegetables, meats, poultry and fish were treated in this study. The types of antioxidants such as ascorbic acid, glutathione, melatonin, tocopherols and tocotrienols were reported. The classification and characteristics of antioxidant; its measurements and level in food and free radicals were also documented. The Chemistry of antioxidants which include chain reactions, molecular structures, food antioxidants and reaction mechanisms, bio-chemical activity and effects of antioxidants were also reviewed. Further, the medicinal applications, pharmacological effects, therapeutic properties and future choice of antioxidants were reported in this review.

Key words: Antioxidants, ascorbic acid, tocopherols, therapeutic properties, medicinal applications, food antioxidants.

INTRODUCTION

Antioxidants are substances that may protect cells from the damage caused by unstable molecules known as free radicals. Antioxidants interact with and stabilize free radicals and may prevent some of the damage free radicals might otherwise cause. Free radical damage may lead to cancer. Examples of antioxidants include beta-carotene, lycopene, vitamins C, E, A and other substances (Sies, 1997).

An antioxidant is a molecule capable of slowing or preventing the oxidation of other molecules. Oxidation is a chemical reaction that transfers electrons from a substance to an oxidizing agent. Oxidation reactions can produce free radicals, which start chain reactions that damage cells. Antioxidants terminate these chain reactions by removing free radical intermediates and inhibit other oxidation reactions by being oxidized themselves. As a result, antioxidants are often reducing agents such as thiols, ascorbic acid or polyphenols (Sies, 1997).

Although oxidation reactions are crucial for life, they can also be damaging; hence, plants and animals maintain complex systems of multiple types of antioxidants, such as glutathione, vitamin C and vitamin E as well as enzymes such as catalase, superoxide dismutase and various peroxidases. Low levels of antioxidants, or inhibition of the antioxidant enzymes, causes oxidative stress and may damage or kill cells. As oxidative stress might be an important part of many human diseases, the use of antioxidants in pharmacology is intensively studied, particularly as treatments for stroke and neurodegenerative diseases. However, it is unknown whether oxidative stress is the cause or the consequence of disease. Antioxidants are also widely used as ingredients in dietary supplements in the hope of maintaining health and preventing diseases such as cancer and coronary heart disease. Although initial studies suggested that antioxidant supplements might promote health, later large clinical trials did not detect any benefit and suggested instead that excess supplementation may be harmful. In addition to these uses of natural antioxidants in medicine, these compounds have many industrial uses, such as

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preservatives in food and cosmetics and preventing the degradation of rubber and gasoline. For many years chemists have known that free radicals cause oxidation which can be controlled or prevented by a range of antioxidants substances (Bjelakovic et al., 2007). It is vital that lubrication oils should remain stable and liquid should not dry up like paints. For this reason, such oil usually has small quantities of antioxidants such as phenol or amine derivatives, added to them. Although plastics are often formed by free radical action, they can also be broken down by the same process, so they too, require protection by antioxidants like phenols or naphthol. Low density polythene is also of protected by carbon black which absorbs the ultraviolet light which causes radical production (Sies, 1997).

Sources and origin of antioxidants

Antioxidants are abundant in fruits and vegetables, as well as in other foods including nuts, grains and some meats, poultry and fish. The list below describes food sources of common antioxidants. Beta-carotene is found in many foods that are orange in color, including sweet potatoes, carrots, cantaloupe, squash, apricots, pumpkin and mangoes. Some green, leafy vegetables, including collard greens, spinach and kale, are also rich in beta-carotene (Borek, 1991). Lutein, best known for its association with healthy eyes, is abundant in green, leafy vegetables such as collard greens, spinach, and kale. Lycopene is a potent antioxidant found in tomatoes, watermelon, guava, papaya, apricots, pink grapefruit, blood oranges and other foods. Estimates suggest 85% of American dietary intake of lycopene comes from tomatoes and tomato products (Xianquan et al., 2005; Rodriguez-Amaya, 2003).

Selenium is a mineral, not an antioxidant nutrient. However, it is a component of antioxidant enzymes. Plant foods like rice and wheat are the major dietary sources of selenium in most countries. The amount of selenium in soil, which varies by region, determines the amount of selenium in the foods grown in that soil. Animals that eat grains or plants grown in selenium-rich soil have higher levels of selenium in their muscle. In the United States, meats and bread are common sources of dietary selenium. Brazil nuts also contain large quantities of selenium.

Vitamin A is found in three main forms: retinol (Vitamin A1), 3,4-didehydroretinol (Vitamin A2), and 3-hydroxy-retinol (Vitamin A3). Foods rich in vitamin A include liver, sweet potatoes, carrots, milk, egg yolks and mozzarella cheese (Baublis et al., 2000). Vitamin C is also called ascorbic acid and can be found in high abundance in many fruits and vegetables and is also found in cereals, beef, poultry, and fish (Antioxidants and Cancer Prevention, 2007).

Vitamin E, also known as alpha-tocopherol, is found in almonds, in many oils including wheat germ, safflower, corn and soybean oils, and is also found in mangoes, nuts, broccoli, and other foods (Herrera and Barbas, 2001).

Classification of antioxidants

Antioxidants are grouped into two namely;

(1) Primary or natural antioxidants.
(2) Secondary or synthetic antioxidants.

Primary or natural antioxidants

They are the chain breaking antioxidants which react with lipid radicals and convert them into more stable products. Antioxidants of this group are mainly phenolic in structures and include the following (Hurrell, 2003):

(1) Antioxidants minerals - These are co factor of antioxidants enzymes. Their absence will definitely affect metabolism of many macromolecules such as carbohydrates. Examples include selenium, copper, iron, zinc and manganese.
(2) Anti oxidants vitamins – It is needed for most body metabolic functions. They include-vitamin C (Figure 1), vitamin E, vitamin B.
(3) Phytochemicals - These are phenolic compounds that are neither vitamins nor minerals. These include:

Flavonoids: These are phenolic compounds that give vegetables fruits, grains, seeds leaves, flowers and bark their colours. Catechins are the most active antioxidants in green and black tea and sesamol. Carotenoids are fat soluble colour in fruits and vegetables. Beta carotene, which is rich in carrot and converted to vitamin A when the body lacks enough of the vitamin. Lycopene, high in tomatoes and zeaxantin is high in spinach and other dark greens. Herbs and spices-source include Diterpene, rosmariquinone, thyme, nutmeg, clove, black pepper, ginger, garlic and curcumin and derivatives.

Secondary or synthetic antioxidants

These are phenolic compounds that perform the function of capturing free radicals and stopping the chain reactions, the compound include (Hurrell, 2003):

i. Butylated hydroxyl anisole (BHA).
ii. Butylated hydroxyrotoluene (BHT).
iii. Propyl gallate (PG) and metal chelating agent (EDTA).
iv. Tertiary butyl hydroquinone (TBHQ).
v. Nordihydro guaretic acid (NDGA).

Types of antioxidants

Ascorbic acid

Ascorbic acid or "vitamin C" (Figure 1) is a monosaccharide antioxidant found in both animals and plants. As one of the enzymes needed to make ascorbic acid has been lost by mutation during human evolution, it must be obtained from the diet and 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, reactive oxygen species such as hydrogen peroxide (Antioxidants and Cancer Prevention, 2007; Ortega, 2006).

Glutathione

The free radical mechanism of lipid peroxidation: Glutathione is a cysteine-containing peptide found in most forms 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, such as ascorbate in the glutathione-ascorbate cycle, glutathione peroxidases and glutaredoxins, as well as reacting directly with oxidants (Meister and Anderson, 1983). Due to its high concentration and its 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 mycothiol in the Actinomycetes, or by trypanothione in the Kinetoplastids (Fahey, 2001; Fairlamb and Cerami, 1992).

Melatonin

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. Redox cycling may allow other antioxidants (such as vitamin C) to act as pro-oxidants and promote free radical formation. 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 (Reiter et al., 1997; Tan et al., 2000).

Tocopherols and tocotrienols (vitamin E)

Vitamin E is the collective name for a set of eight related tocopherols and tocotrienols, which are fat-soluble vitamins with antioxidant properties. Of these, α-tocopherol (Figure 1) has been most studied as it has the highest bioavailability, with the body preferentially absorbing and metabolizing this form (Herrera and Barbas, 2001). 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. This is in line with findings showing that α-tocopherol, but not water-soluble antioxidants, efficiently protects glutathione peroxidase (GPX4)-deficient cells from cell death. GPX4 is the only known enzyme that efficiently reduces lipid-hydro peroxides within biological membranes (Herrera and Barbas, 2001; Packer et al., 2001).

Characteristics of antioxidants

The major antioxidants currently used in foods are monohydroxy or polyhydroxy phenol compounds with various ring substitutions. These compounds have low activation energy to donate hydrogen. Hence, the resulting antioxidants radical does not initiate another free radical due to the stabilization of the delocalized radical electron. Propagation and initiation of free radicals chain reaction can be delayed or minimized by the donation of hydrogen from the antioxidants and metal chelating agent. The resulting antioxidant free-radical is not subject to rapid oxidation due to its stability. Antioxidants free-radicals can also react with lipid free-radicals to form a stable complex compound thereby preventing some of their damages.

MEASUREMENTS AND LEVEL IN FOODS

Measurement of antioxidants is not a straightforward process, as this is a diverse group of compounds with different reactivities to different reactive oxygen species. In food science, the oxygen radical absorbance capacity (ORAC) has become the current industry standard for assessing antioxidant strength of whole foods, juices and food additives. Other measurement tests include the Folin-Ciocalteu reagent and the Trolox equivalent antioxidant capacity assay. Antioxidants are found in varying amounts in foods such as vegetables, fruits, grain cereals, eggs, meat, legumes and nuts. Other antioxidant

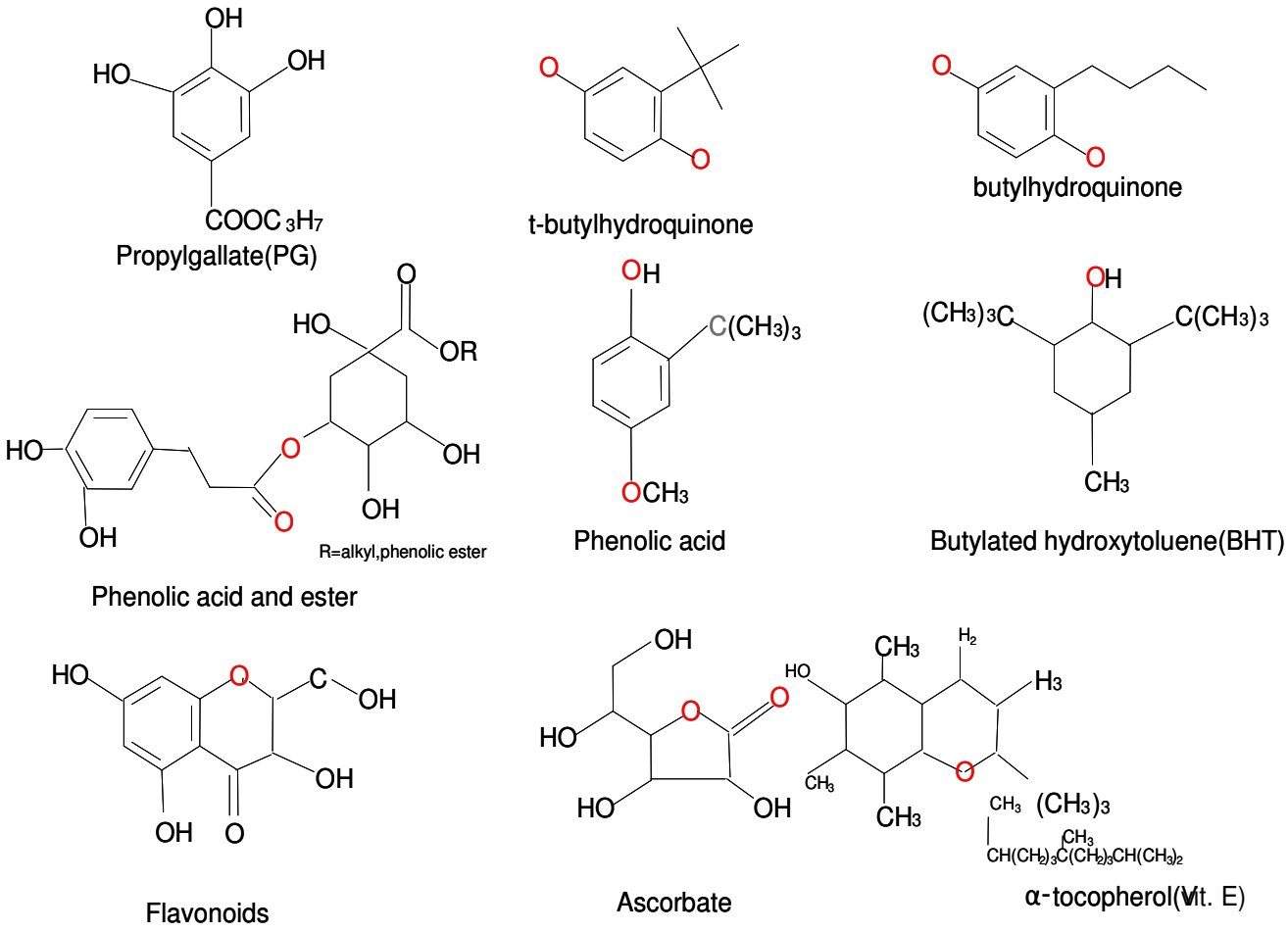

Figure 1. Structures of some antioxidants

compounds are more stable, such as the polyphenolic antioxidants in foods such as whole-wheat cereals and tea (Baublis et al., 2000; Rietveld and Wiseman, 2003). The effects of cooking and food processing are complex, as these processes can also increase the bioavailability of antioxidants, such as some carotenoids in vegetables. In general, processed foods contain fewer antioxidants than fresh and uncooked foods, since the preparation processes may expose the food to oxygen.

Other antioxidants are not vitamins and are instead made in the body. For example, ubiquinol (coenzyme Q) is poorly absorbed from the gut and is made in humans through the mevalonate pathway. Another example is glutathione, which is made from amino acids. As any glutathione in the gut is broken down to free cysteine, glycine and glutamic acid before being absorbed, even large oral doses have little effect on the concentration of glutathione in the body. Although large amounts of sulfur-containing amino acids such as acetylcysteine can increase glutathione, no evidence exists that eating high levels of these glutathione precursors is beneficial for healthy adults. Supplying more of these precursors may be useful as part of the treatment of some diseases, such as acute respiratory distress syndrome, protein-energy malnutrition, or preventing the liver damage produced by paracetamol (Sowell et al., 1994). Other compounds in the diet can alter the levels of antioxidants by acting as pro-oxidants. Here, consuming the compound causes oxidative stress, which the body responds to by inducing higher levels of antioxidant defenses such as antioxidant enzymes. Some of these compounds, such as isothiocyanates and curcumin, may be chemopreventive agents that either block the transformation of abnormal cells into cancerous cells.

FORMATION OF FREE RADICALS

Normally, bonds would not split in a way that leaves a molecule with odd, unpaired electrons. However, when weak bond split, free radicals are formed. Free-radicals are very unstable and react quickly with other compound trying to gain stability.

Generally, free radicals attack the nearest stable

molecules abstracting its electron to attain stability. When the attacked molecule loses its electron, it becomes a free-radical itself, these formations of free-radicals continue on and on and finally result in the disruption of the substance especially in fatty foods. Environmental factors such as pollution, radiation, cigarette smoking and herbicides can also spawn free-radicals in the body but, if antioxidants are not available to check the free-radical production it becomes excessive and cause damage to body and any substance in which oxidation occurs. Of particular interest is the free radical damage in the body system, fatty foods and other substance like polymer and antioxidants mechanism of action in inhibiting these damages (Borek, 1991).

FREE RADICALS DAMAGE AND DISEASES

Free radicals contribute to many different diseases. Chemically, a substance is oxidized when electrons are removed and reduced when electrons are added. All chemical reactions involve the transfer of electrons. The body generates energy by gradually oxidizing its food in a controlled manner and storing it in the form of chemical potential energy called ATP (Adenosinetriphosphate). Free radicals are generated largely during the production of ATP in the mitochondria. During this process, radicals coming out from the mitochondria from reactive oxygen species such as superioxide anion (O_2^-) and hydroxyl radicals ($HO^{\cdot}$) and other reactive oxygen species such as singlet oxygen (O_2^1), destroy the body system especially the site where the free radicals is been generated. The ultraviolet light that penetrate the skin and the air pollutant that is high in smog which we inhale generates free radicals too.

Food, like lipid in the presence of (Fe^{3+}, Fe^{2+}) lead to the production of hydrogen peroxide from which further hydroxyl radicals are generated in a reaction that appear to depend on the presence of iron ions.

The acceleration of hydroperoxide decomposition to form peroxyl radicals and alkoxyl radical.

$Fe^{3+} + ROOH \rightarrow Fe^{2+} + ROO^{\cdot} + H^+$
$Fe^{2+} + ROOH \rightarrow Fe^{3+} + RO^{\cdot} + OH^-$

Formations of alkyl free radicals by direct reaction with fats and oils.

$Fe^{3+} + RH \rightarrow Fe^{2+} + R^{\cdot} + H^+$

Activation of molecular oxygen for singlet oxygen formation

$Fe^{2+} + O_2 \rightarrow Fe^{3+} + O^{2-}$

Mechanisms of metals in accelerating lipid oxidation

Though, these same radicals are potentially dangerous products of cellular metabolism, in that they can directly influence cell growth and development of cell survival and increase the pathogenesis of atherosclerosis that is, oxidation of low density protein. If taken, the food can cause cancer, aging and several other conditions including inflammatory diseases. By producing oxidative damage in DNA (deoxyribonucleic acid) free-radicals can cause brain disease associated with Alzheimer's disease. However, it has been suggested that the extent of damage caused by free-radicals can be modified through three dietary intervention strategies (Ingold, 1968).

THE CHEMISTRY OF ANTIOXIDANTS

It involves the mechanism of action of antioxidant. Two principle mechanisms of action have been proposed for antioxidants. The first is a chain-breaking mechanism by which the primary antioxidants donate electrons to the free radicals present in the system, example lipid radicals. The second mechanism involves removal of ROS (reactive oxygen species) and RNS (reactive nitrogen species) initiator by quenching chain initiator catalyst.

Chain reactions of free radicals

Initiation stage

(1) $RH \rightarrow R^{\cdot} + H^{\cdot}$
(2) $R^{\cdot} \rightarrow R^{\cdot} + O_2 \rightarrow ROO^{\cdot}$
(3) $2ROOH \rightarrow ROO^{\cdot} + RO^{\cdot} + H_2O$

Propagation stage

(1) $R^{\cdot} + O_2 \rightarrow ROO^{\cdot}$
(2) $ROO^{\cdot} + RH \rightarrow ROOH + R^{\cdot}$
(3) $RO^{\cdot} + RH \rightarrow ROH + R^{\cdot}$

Termination stage

(1) $R^{\cdot} + R^{\cdot} \rightarrow R - R$
(2) $R^{\cdot} + ROO^{\cdot} \rightarrow ROOR$
(3) $ROO^{\cdot} + ROO^{\cdot} \rightarrow ROOR + O_2$
(4) Antioxidants + O_2 → oxidized antioxidants (Borek, 1991).

Further, in free radical chain reactions, when fats are in contact with oxygen, it forms unsaturated fatty acids which give rise to free radicals in equation (i). Also hydroperoxide which exist in trace quantities prior to oxidation reaction, break down to yield radicals in equation (iv) which abstract an hydrogen atom from another molecule and become a hydroperoxide producing further radicals. The antioxidants added to it, will neutralize the free radicals by donating one of their

own electrons ending the reactions in equation (vii) and (ix). These occur generally in the body.

FOOD ANTIOXIDANTS AND REACTION MECHANISMS

Food antioxidants include substances that keep edible fats and oils from becoming rancid and prevent fruit and vegetables from turning brown. Examples include butylated hydroxyanisole (BHA) and butylated hydrogenoxytoluene (BHT) (Figure 1), ascorbic acid (Vit.C), α-tocophenol (Vit. E) (Figure 1). Hence, vitamins containing aromatic ring which reacts and destroys the most reactive forms of oxygen radicals, protecting the most unsaturated fatty acids from oxidation and preventing oxidative damage to the membrane (Amitom, 2001).

It is very stable even when it loses its H^+ from OH^- group to the free radicals in PUFA and hence become oxidized. The antioxidant activity of flavonoid has been received by many scientists. They concluded that food possesses the potential to scavenge and quench various reactive oxygen species (ROS). This antioxidant reacts with lipid (fats and oil) and prevents lipid peroxidation that usually occurs in fatty foods at the initial stage by free radical scavengers. The chain breaking antioxidant action of flavonoid (FL-OH) can be represented as shown below:

$$LOO^{\cdot} + FL - OH \rightarrow LOOH + FL - O^{\cdot}$$

Flavonoid → phenonyl radical

Termination of lipid radical ($L^{\cdot}$), lipid peroxy radical ($LOO^{\cdot}$) and alkoxyl radicals ($RO^{\cdot}$) formed by re-initiation of lipid peroxidation induced by metal ions by flavonoids is shown below:

$$LOO^{\cdot}/L^{\cdot}/LO^{\cdot} + FL - OH \rightarrow LOOH/LH/LOH = FL - O^{\cdot}$$

Flavonoid protects the memberane phospholipids PUFA by donating the hydrogen atom (H^+) to quench lipid peroxyl radicals generated as s result of hydroxyl radical attack on the unsaturated carbon chain of PUFA (poly unsaturated fatty acids).

ANTIOXIDANTS SYSTEM IN OUR BODY

The body has developed several endogenous antioxidant systems to deal with the production of ROI. These systems can be divided into enzymatic and non-enzymatic groups.

The enzymatic antioxidants include superoxide dismutase (SOD), which catalyses the conversion of $O_2^{\cdot}O$ to H_2O_2 and H_2O; Catalyse, which then conver H_2O and O_2; and glutathione peroxidase, which reduces H_2O_2 to H_2O.

The non-enzymatic antioxidants include the lipid-soluble vitamins, vitamin E and vitamin A or provitamin A (beta-carotene) and the water- soluble vitamin C. Vitamin E has been described as the major chain-breaking antioxidant in humans. It is located within the membranes, where it interrupts lipid peroxidation and may play a role in modulating intracellular signaling pathways that rely on ROI. Vitamin E can also directly quench. The present study assessed the antioxidant properties of α-tocopherol, α-tocotrienol, which contained 45% tocopherols and 55% tocotrienols. When Vitamin E-deficient rats were fed either α-tocopherol- or α-tocotrienol-enrich diets, α-tocotrienol accumulated in the hearts and liver more slowly than α-tocopherol. The rate of lipid peroxidation induced *in vitro* in heart homogenate from rats supplemented with α-tocotrienol was approximately two-thirds as high as that of α-tocopherol. Thus palm oil vitamin E may be more efficient than α–tocopherol alone in protecting the heart against injury from ischaemia and reperfusion.

In addition, supplementation with α–tocopherol or α-tocotrienol protects skeletal muscles against exercise-induced increases in protein oxidation thus palm oil vitamin E protects against biological systems against both lipid and protein oxidation. The pathogenesis of many diseases can involve free radical-medicated lipid peroxidation in biological membranes. Vitamin E is the major chain- breaking antioxidant in membrane; although it is present in extremely low concentration, it is very efficient in inhibiting the development of conditions such as heart disease, cancer, cataracts, neuropathies and myopathies and other related diseases.

The consumption of berries has been implicated with diverse health benefits such as prevention of stroke, of age-related degenerative diseases and cancer. Some berry constituents have cancer suppressive effects in these were attributed to certain berry phytochemicals with high antioxidative potentials that could contribute to, or enhance by induction, the endogenous antioxidant properties of living cells or organisms (Amitom, 2001).

EFFECTS OF ANTIOXIDANTS

A healthy cell has a mortal enemy which is called a "free radical." Free radicals constantly seek out healthy cells and attack their vulnerable outer membranes eventually causing cellular degeneration and death. Free radicals scientists today, carry out the actual destructive work in disease, in infection, in stress and in aging. Additionally, free radicals can negatively affect athletic performance by slowing or halting muscle growth and by lowering aerobic capacity. Further, free radicals are known to cause defects in normal RNA as well as in life perpetuating DNA, the genetic material of the cells (Warner et al., 2004).

Normal molecules in the body have two (a paired group) electrons in their outer shell. A molecule with a single electron (unpaired) in its outer shell is called a free radical. Free radicals occur naturally when oxygen in the bloodstream combine with any of a diverse group of chemicals including those commonly found in polluted air, in primary and/or second hand cigarette smoke, in known and damage is accelerated by the normal radiation found in sunlight and by increasing exercise, especially running and other aerobic activities. This is easy to understand in that aerobic exercise can increase oxygen consumption ten to twenty times normal values. With more oxygen available in the bloodstream; free radical production soars. The direct muscle destroying activities of the free radicals continue many hours after exercise stops.

The destructive effects of free radicals can be prevented with the addition of anti-oxidants in the diet or by anti-oxidant supplements. A good anti-oxidant complex supplement actually has advantages over diet sources in that the complex has many different specific types of anti-oxidants which seek out and destroy free radicals at many various cellular sites. A single anti-oxidant, for example Vitamin E, only protects the outer fatty layers of the cell. It will not stabilize DNA which, for example, is one the main effects of the anti-oxidant Vitamin C. The process by which different anti-oxidants disperse through the bloodstream to protect the cells at different sites is referred to in science as "anti-oxidant synergy." When a specific anti-oxidant meets a free radical in the bloodstream at its appropriate activity site, it naturally combines with it and coverts the free radical to harmless water and oxygen. As a result, as anti-oxidant increases due to the supplementation of higher amounts of a greater variety of anti-oxidants, cellular damage lessens and performance and health improves. In fact, aside from the numerous scientifically compelling studies addressing the varied health benefits of anti-oxidant supplementation, there have been studies completed, demonstrating a dramatic decrease in injuries in athletic training with the simple addition of a good anti-oxidant complex supplement.

The brain is uniquely vulnerable to oxidative injury, due to its high metabolic rate and elevated levels of polyunsaturated lipids, the target of lipid peroxidation. Consequently, antioxidants are commonly used as medications to treat various forms of brain injury. Here, superoxide dismutase mimetics, sodium thiopental and propofol are used to treat reperfusion injury and traumatic brain injury, are being applied in the treatment of stroke. These compounds appear to prevent oxidative stress in neurons and prevent apoptosis and neurological damage. Antioxidants are also being investigated as possible treatments for neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis and as a way to prevent noise-induced hearing loss (Warner et al., 2004).

Antioxidants can cancel out the cell-damaging effects of free radicals. Furthermore, people who eat fruits and vegetables, which happen to be good sources of antioxidants, have a lower risk of heart disease and some neurological diseases and there is evidence that some types of vegetables and fruits in general, protect against a number of cancers. These observations suggested the idea that antioxidants might help prevent these conditions. However, this hypothesis has now been tested in many clinical trials and does not seem to be true, since antioxidant supplements have no clear effect on the risk of chronic diseases such as cancer and heart disease. This suggests that other substances in fruit and vegetables (possibly flavonoids), or a complex mix of substances, may contribute to the better cardiovascular health of those who consume more fruit and vegetables.

It is thought that oxidation of low density lipoprotein in the blood contributes to heart disease and initial observational studies found that people taking Vitamin E supplements had a lower risk of developing heart disease. Consequently, at least seven large clinical trials were conducted to test the effects of antioxidant supplement with Vitamin E, in doses ranging from 50 to 600 mg per day. However, none of these trials found a statistically significant effect of Vitamin E on overall number of deaths or on deaths due to heart disease. Further studies have also been negative. It is not clear if the doses used in these trials or in most dietary supplements are capable of producing any significant decrease in oxidative stress. Despite the clear role of oxidative stress in cardiovascular disease, controlled studies using antioxidant vitamins have observed no reduction in either the risk of developing heart disease, or the rate of progression of existing disease.

While several trials have investigated supplements with high doses of antioxidants, the "Supplémentation en Vitamines et Mineraux Antioxydants" (SU.VI.MAX) study tested the effect of supplementation with doses comparable to those in a healthy diet. Over 12,500 French men and women took either low-dose antioxidants (120 mg of ascorbic acid, 30 mg of vitamin E, 6 mg of β-carotene, 100 µg of selenium and 20 mg of zinc) or placebo pills for an average of 7.5 years. The investigators found there was no statistically significant effect of the antioxidants on overall survival, cancer, or heart disease. However, in a post-hoc analysis they found a 31% reduction in the risk of cancer in men, but not women. Many nutraceutical and health food companies sell formulations of antioxidants as dietary supplements and these are widely used in industrialized countries. These supplements may include specific antioxidant chemicals, like resveratrol (from grape seeds or knotweed roots), combinations of antioxidants, like the "ACES" products that contain β-carotene (provitamin A), vitamin C, vitamin E and selenium, or herbs that contain antioxidants - such as green tea and jiaogulan. Although some levels of antioxidant vitamins and minerals in the diet are required for good health, there is considerable doubt as to whether these antioxidant supplements are beneficial or harmful (Warner et al., 2004).

The medicinal efficacy of antioxidants

Antioxidants do not always protect us from cancer; US researcher has shown (Wilson and Gelb, 2002). Some tumour cells can actually use antioxidants to protect themselves from natural cellular defense mechanisms, enabling them to survive and proliferate. The study provides insight into altered metabolism of tumour-forming cells and could help improve current treatments. Joan brugge and her group from Harvard Medical School in Boston, US were investigating changes in breast cancer cells that allow them to survive without being attached to the normal extracellular matrix (Schäfer and Karger, 2009).

They found that treating cells with vitamin E like antioxidants blocked the usual programmed cell death cycles, allowing the cells to survive free from their usual scaffolding by switching their metabolism to use fatty acids rather than glucose as fuel.

Normal cells need to be attached to a matrix to function properly and even survive. They went further that as a potential tumour cells start to proliferate rapidly and they quickly run of space to stay attached to the matrix, so have to find ways to dodge the normal mechanisms by which detached cells programme to die. One of the most common mechanism of cell death is apoptosis (a kind of programmed cell suicide), but the team found that when they blocked the apoptosis pathways, the detached cells still died, which hinted at a major change in the metabolism of cells. They found that there was several reduction in ATP [adenosine triphosphate] in cells within 24 h of attachment. Cell use ATP as an energy source, so it seemed that part of the reason detached cells is metabolism of glucose and the teams found that detached cell lose the ability to transport glucose through their cell membranes. ‘We found that expressing a cancer-causing gene called ErbB2, which is altered in many human tumor, allows the cells to transport glucose even when they are not attached’(Rietveld and Wiseman, 2003).

Glucose is not just used for energy generation; it is also the source of natural cellular antioxidants. When they looked at detached cells, they found raised levels of highly oxidising reactive oxygen species, which they reasoned could be a second line of defence against tumour generation in detached cells. 'We were curious what would happen if we neutralised the reactive oxygen species [without using ErbB2 to restore glucose transport], and that is when we got this really surprising result.'

The researchers checked to see if the antioxidants were also promoting glucose uptake (Blot et al., 1993), but they were not, so the team reasoned that the cells must be getting energy from another source. 'Other labs have shown that matrix-attached cells can use fatty acid oxidation as a source of energy when they are deprived of glucose. That suggested that perhaps the detached cells were not able to exploit that pathway because the reactive oxygen species were inhibiting it. 'We found that fatty acid oxidation was severely reduced in detached cells, but that it increased on treatment with antioxidants.' This meant that treating cells with antioxidants, rather than preventing the formation of tumours, allowed the cells to bypass another natural defence mechanism.

The really interesting thing that this work shows is that the physiology and metabolism of the cells change profoundly after detachment,' comments Doug Conklin from the University at Albany Cancer Research Center in Albany, US.' The fact that the chemistry of these cells is different could possibly regulate whether or not they go on to become metastatic [form tumors at other locations around the body].

Conklin was also interested in the team's findings about using fatty acid oxidation as a source of energy: 'Fully-fledged tumor cells are not eating fats; they spend a lot of energy synthesizing fatty acids, so using them as an energy source would be a futile cycle. This could give some insight into how the cells' metabolism changes in the early stages of tumor formation. Study shows that vitamin C anticancer effects may be compromise by fat.

MEDICINAL APPLICATIONS OF ANTIOXIDANTS

Anti-cancer agent in medicinal chemistry

Lanthanides as anti-cancer agents

The application of inorganic chemistry to medicine is a rapidly developing field, Novel therapeutics and diagnostic metal complexes are now having an impact on medical practice. Advances in bio-coordination chemistry are crucial for improving the design of compounds to reduce toxic side effects and understand their mechanisms of action. A lot of metal –based drugs are widely used in the treatment of cancer (Xianquan et al., 2005). The clinical success of cisplatin and other platinum complexes is limited by significant side effects acquired or intrinsic resistance. Therefore, much attention has focused on designing new coordination compound with improved pharmacological properties and a broader range of antitumor activity (Blot et al., 1993). Strategies for developing new anticancer agents include the incorporation of carrier groups that can target tumor cells with high specificity. Also of interest is to develop complexes that bind to DNA in a fundamentally different manner than cisplatin, in an attempt to overcome the resistance pathway that has evolved to eliminate the drug. This review focuses on recent advancement in developing lanthanide coordination complexes.

Lycopene as a potential anti cancer agent

Dietary chemoprevention has emerged as a cost-effective approach to control most prevalent chronic diseases including cancer. In particular, tomato and

products are recognized to confer a wide range of health benefits. Epidemiology studies have provided evidence that high consumption of tomatoes effectively lowers the risk of reactive oxygen species (ROS)-mediated diseases such as cardiovascular diseases and cancer by improving the antioxidant carotenoid reported to be more stable and potent singlet oxygen quenching agent compared to other carotenoids. In addition to its antioxidants properties, lycopene shows an array of biological effects including cardio protective, anti-inflammatory, anti-mutagenic and anti-carcinogenic activities. The cancer activities of lycopene have been demonstrated both *in vitro* and *in vivo* tumor models (Blot et al., 1993).

Selenium derivatives as cancer preventive agents

The role of selenium in the prevention of cancer has been recently established by laboratory experiments, clinical trials and epidemiological data. Consequently, selenium supplementation has moved from the realm of correcting nutritional deficiencies to one of pharmacological intervention, especially in the clinical domain of cancer chemoprevention and in the control of heart failure.

Lipoic acid, **the antioxidant's antioxidant**

Lipoic acid protects against diseases of aging, this offer powerful antioxidant protection against three common afflictions (two of them potentially disastrous) association with the aging stroke, heart attack and cataracts. It does it by suppressing the action of free radicals in the cells of the brain, heart and eyes. Lipid acid has an unusual relationship with four other important antioxidants: glutathione, coenzymeQ10, vitamin C and vitamin E. Memory loss is not considered to be not considered to be a disease at least not until it is a component of a full-fledged dementia, such as Alzheimer's disease-but it is certainly another hallmark of aging.

Unlike lipoic acid other antioxidants are either primarily water-soluble or fat-soluble, but not both. This means that they have different (often overlapping) domain are free radical scavengers. What is good is that lipoic acid not only acts as a primary antioxidant in brain cells but serves to boost glutathione levels through the antioxidant network interactions.

Diabetes, a terrible yet largely preventable disease, is practically epidemic in the western world, especially the United States, because of our tendency to obesity due to poor diet and lack of exercise. Since lipoic acid is the most versatile and powerful antioxidant in the entire antioxidants defense network.

Gene therapy promises to be one of the most exciting and fruitful avenues of medical practice in the twenty-first century and it offer powerful antioxidant protection against common afflictions.

Significance of antioxidants in red cells

Erythrocytes containing abnormal haemoglobin with high affinity for red cell. Since HbS is known to have high affinity for red cell membrane and sickle cells are particularly susceptible to membrane lipid peroxidation, the behaviour of erythrocyte antioxidant system has been evaluated in 20 subjects, heterozygous for sickle cell anaemia. These subjects have shown normal levels of reduced glutathione, increased superoxide dismutase and glutathione peroxidase activities and low catalase activity. These data suggest that such an unbalanced antioxidant system cannot prevent damage by the enhanced production of oxygen free radicals by membrane-bound HbS molecules (Hail et al., 2008; Gutter, 1991).

Antioxidants therapy in acute central nervous system injury

Free radicals are highly reactive molecules generated predominantly during cellular respiration and normal metabolism imbalance between cellular production of free radicals and ability of cells to defend against them is referred to as oxidative stress (OS) (Gutter, 1991). OS has been implicated as a potential contributor to acute central nervous system (CNS) injury by ischemic or hemorrhagic stroke or trauma. The production of reactive oxygen species (ROS) may increase, sometimes drastically leading to tissues damage via several different cellular molecular pathways. Radicals can cause damage to cardinal cellular components such as lipids, proteins and nucleic acid e.g DNA leading to subsequent cell death by modes of necrosis or apoptosis. The damage can become more widespread due to weakened cellular antioxidant defense systems. Moreover, acute brain injury increases the level of excitoxic amino acids (such as glutamate), which also produce ROS, thereby promoting parenchymatous destruction. Therefore, treatment with antioxidants may theoretically act as tissue damage and improve both the survival and neurological outcome, several such agents of widely varying chemical structures have been investigated as therapeutic agents for acute CNS injury, although, a few of the antioxidants showed some efficacy in animal models or in small clinical studies. Better understanding of the pathological mechanisms of acute CNS injury would characterize the exact primary targets for drug intervention improved antioxidant design should take into consideration the relevant and specific harmful free radical (Cheremisinoff, 1989).

A vast amount of circumstantial evidence implicates oxygen-derived free radicals (especially superoxide and hydroxyl radicals) and high-energy oxidants such as peroxynitrite as mediators of inflammation, shock and ischemia/reperfusion injury.

THERAPEUTIC PROPERTIES OF ANTIOXIDANTS

Antioxidants are very important in the treatment of fried Reich ataxia, a rare progressive condition that causes damage to the nervous system. It is inherited in an autosomal recessive pattern, meaning that, an affected gene must be inherited from each parent for the disease to develop in their child it is most common recessively inherited worldwide. The progression of the disease cannot be easily assessed by clinical examination test. Evaluation of diseases is done by standard neurological scales.

Abnormal high levels, oxidative damage to the cells occurs leading to several pathological conditions, rheumatoid arthritis, hemorrhagic shock, cardiovascular system disorder, cystic fibrosis, metabolic disorder, gastrointestinal, ulcerogenesis and acquired immunodeficiency. Pharmacological applications of leutinide are as agent in radio immunotherapy and photodynamic.

CONCLUSION

Many substances consumed by man either through foods, drinks and inhalation, even effect of exogenous material (ultraviolet radiation) on the skin may be destructive to the health and thus, shortening the life span of man. Free radicals when generated in the body system of man causes damage to which eventually leads to death at shorter time (Borek, 1991). Continuous usage of the same vegetable oil which is not even properly stored and re-using the already fried oil (rancid) lead to generation of free radicals through lipid peroxidation. The reasons sometimes could be for economic reason but then it is highly damaging to the health. Smoking and chronic alcoholism is socio-cultural problem in the world today because uncontrolled cigarette smoke intake reduces the level of many important antioxidants in the serum, which is detrimental to the health (Cheremisinoff, 1989).

Report has shown that proper intake of antioxidant will help quench all these inevitably free radicals in the body thus, improving the health by lowering the risk of various diseases such as cancer. Antioxidants are also important in body lotions creams, so as to protect the skin from sun exposure and decrease skin roughness, wrinkles depth, ultraviolet induced skin cancer and skin swelling from sunlight. To cap it up, there is need for proper orientation on the necessity of proper intake of balance diet which will definitely supply the much needed antioxidants. The RDA has been previewed therefore, people will have lower health risks and tend to live longer and have fewer disabilities.

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