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ANTIOXIDANT CHEMISTRY IN HUMAN HEALTH

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ABSTRACT

Physiological processes in a healthy organism are mediated via reactive species i.e. free radicals and their reactive metabolites. These reactive species also forms the basis of prevention mechanism of an organism against invading pathogens. A certain concentration of these reactive species is very essential for sustaining normal metabolism functions of living organisms. Under oxidative stress conditions these reactive species exert harmful effects on important biomolecules. To deal with oxidative stress and its related disorders antioxidant mechanisms are in place as protection against these reactive species. Both endogenous and exogenous or dietary antioxidants are very important. The article presents detailed discussion of the various types of reactive species, present in the living systems as defence against invading pathogens, their origin, positive functions and effects in the health condition oxidative stress. Endogenous as well as exogenous antioxidant prevention mechanism is also discussed.

Keywords: Antioxidants, Free radicals, Oxidative stress, Flavonoids, Enzymes, Carotenoids, Tocopherols etc.

ANTIOXIDANT CHEMISTRY- AN INTRODUCTION

Antioxidants[1-2] are compounds that delay or prevent auto-oxidation of important biomolecules. Antioxidant compounds find applications in both health management and food quality maintenance of packaged food[3] in terms of increasing shelf life of food constituents. The regulatory bodies for food supply categorize *antioxidants* under food additives and define them as "substances used to preserve food by retarding deterioration, rancidity or discoloration due to oxidation". Study of Antioxidants in the food sector is primarily aimed at better food quality maintenance through prevention of oxidation. On the other hand, in a biological system, an antioxidant is defined as "a substance that when present at low concentration, compared to an oxidizable substrate, would significantly prevent oxidation of that substrate. In the health sector, the study of antioxidants is in relation to addressing the oxidative stress[4] related disorders. These free radicals target important biomolecules such as DNA, Lipids and Proteins. In the case of lipids, auto oxidation is the oxidative deterioration of unsaturated fatty acids via an autocatalytic process consisting of a free radical chain mechanism[5]. The chain includes initiation, propagation and termination reactions that could be cyclical once started. Antioxidants provide defence mechanism against the free radicals[1-2]. Antioxidants are classified as primary or chain breaking and secondary or preventive antioxidants. This classification is based on the chemical structure and properties and the location of molecules within the cells. Antioxidant potential is related to activation energy, rate constants, oxidation reduction potentials and the antioxidant solubility. The antioxidant potential is also related to the bond dissociation energies of antioxidant for abstraction of a hydrogen atom. Most effective antioxidant is one that can interrupt the free radical chain reaction. The present article presents an overview of the antioxidant science. The article presents detailed discussion of the various types of reactive species oxidants, present in the living systems as defence against invading pathogens, their origin, positive functions and effects in the health condition; oxidative stress. Endogenous as well as exogenous antioxidant prevention mechanism is also discussed.

OXIDANTS IN LIVING ORGANISMS

Biochemical reactions taking place in cells and organelles of an organism are the driving force for sustainability of life. Majority of these reactions involve free radicals (FR), having one or more

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unpaired electrons these are highly reactive in nature. These free radicals are electron deficient species and hence act as oxidising species in various biochemical reactions. Further reactions of these free radicals produce various reactive species, which may be another free radical or a non radical species and these are called reactive metabolites (RM).

These FR and RM are derived mainly from three elements i.e. oxygen, nitrogen and sulphur. If these FR & RM are derived from oxygen, these are termed as reactive oxygen species (ROS). $O_2^{-\bullet}$, $^{\bullet}OH$, $^{\bullet}OOH$, $NO^{\bullet}$, H_2O_2, HOCl and $^1O_2$ etc. are the examples of reactive oxygen species participating in various biochemical reactions. On the other hand if these reactive species are derived from nitrogen, these are called reactive nitrogen species (RNS) and the examples include $NO^{\bullet}$, $^{\bullet}OONO$, $^{\bullet}NO_2$ and HOONO. The reactive sulphur species; RSS are formed as a result of reactions of ROS with thiols.

it cannot diffuse too far because of the limited lipid solubility. Mitochondria, which is the centre for production of energy through generation of ATP's, is the major site for producing superoxide radical anion. Electron transfer from mitochondrial electron transport chain is responsible for reduction of oxygen (in presence of H^+ ions) to water, however, approximately 1 to 3% of all the electrons leak from the system and lead to formation of $O_2^{-\bullet}$. Upon phagocytises of leukocytes, monocytes and macrophages, containing NADPH oxidase, these cells produce a burst of superoxide anions which exhibit antibacterial activity. Superoxide anion is converted into hydrogen peroxide, a non radical ROS. H_2O_2, in contrast to $O_2^{-\bullet}$, can easily diffuse across the plasma membrane. Hydrogen peroxide is also produced by the action of the enzymes, xanthine oxidase, amino acid oxidise and NADPH oxidase.

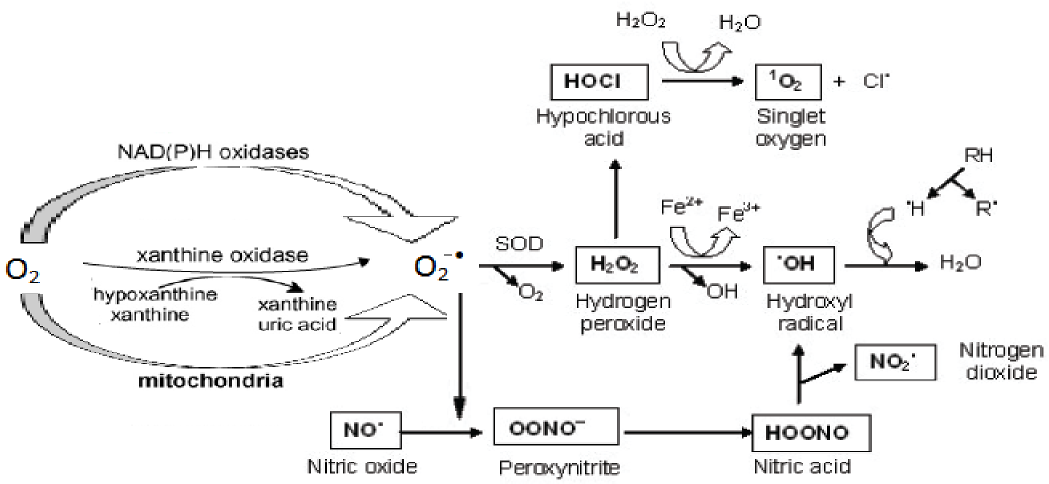

Fig.1: Production of various reactive species ROS, RNS etc.

SOURCES AND POSITIVE FUNCTIONS OF ROS AND RNS

ROS are produced in an organism as a result of cellular metabolic processes[4] occurring in an organism. Reactive oxygen species such as superoxide radical anion ($O_2^{-\bullet}$), hydroxyl radical ($^{\bullet}OH$) and hydrogen peroxide (H_2O_2) have rich physiological significance. Superoxide anion is formed by single electron insertion into the molecular oxygen. There are enzymes namely Nicotine Adenine Dinucleotide Phosphate (NADPH) Oxidase and xanthine oxidase along with mitochondrial electron transport system which catalyse the formation of superoxide radical anion (Fig. 1). Superoxide anion, with only single unpaired electron is a very reactive ROS, however

In the presence of ferric ions (Fe^{3+}), hydrogen peroxide may also lead to the formation of the most potent hydroxyl ($^{\bullet}OH$) free radical through a succession, non enzymatic reactions called Haber–Weiss and Fenton reactions.

$$Fe^{3+} + O_2^{-} \xrightarrow{\bullet} O_2 + Fe^{2+}$$

Haber –Weiss reaction

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3} + OH^{-} + {}^{\bullet}OH$$

Fenton reaction

Although H_2O_2 is not a free radical, yet it is classified as ROS because of its ability to generate $^{\bullet}OH$ as specified above in Haber – weiss and Fenton reactions. Hydroxyl free radical ($^{\bullet}OH$) is the most dangerous of the ROS because it is a very short lined species with a half life of approximately 10^{-9} s and this accounts for its highly reactive nature. Hypochlorous acid is formed as a result of reaction between H_2O_2 and Cl^- ions. Hypochlorous acid, HOCl is highly oxidative in nature and hence also plays an important role in killing invading pathogens.

The simplest form of peroxyl radicals is the hydroxy peroxyl radical ($^{\bullet}OOH$) and has a role in fatty acid peroxidation and this leads to rearrangement of membrane structure. Another non radical reactive species derived from molecular oxygen is singlet oxygen i.e. $^1O_2$, which is formed as a result of shifting of one unpaired electron upon absorption of energy.

Free radicals and their reactive metabolites, thus, provide a natural defence mechanism for prevention from invading pathogens. Besides this, they play an irreplaceable role in several biochemical reactions i.e. *Hydroxylating*, *carboxylating*, *peroxydating* reactions or in reduction of ribonucleotides. These species also have regulatory ability in signal transduction processes during transduction of intercellular information. As an example, $NO^{\bullet}$ is formed form arginin by the action of NO-synthase. At low concentrations, $NO^{\bullet}$ has an independent role in transmission of nerve impulse[6] and during vasodialating processes. Thus under normal physiological conditions a certain level of concentration of free radicals FR and their reactive metabolites RM are essential for normal functioning of an organism.

OXIDATIVE STRESS and ENDOGENOUS ANTIOXIDATIVE MECHANISM

In response to certain stimulus (external factors), such as smoke, high environment pollution level (SPM levels), constant exposure to ionising radiations, drugs and pesticides etc., certain ROS and RNS producing pathways gets triggered leading to excess production of ROS.

In order to deal with excess production of ROS, RNS etc. the human body in equipped with a variety of antioxidants mechanism systems[7]. The prevention of an organism is organised at three levels –

(a) Level 1 of the protection mechanism comprise of antioxidant systems that prevent free radical formation, for example, *Alopurinol* helps in inhibition of xanthine oxydase in order to stop the production of $O_2^{-\bullet}$. Presence of chelating agents which bind to the free metal ions, leading to reduction of their activity in catalytic production of free radicals.

(b) The second line of defence comes into play at the insufficiency of the first line of defence against excessively produced ROS and RNS. To deal with ROS the body has evolved a mechanism leading to production of low molecular weight antioxidants which act as scavengers and trappers of FR by turning them into non radical and non toxic species.

(c) At the failure of second level of protection the repair systems are also in place as the third level of defence mechanism, which recognise impaired molecules and decompose them. For example *proteinases* act on oxidatively modified proteins, *lipases* act on oxidatively damaged lipids and *DNA repair system* repirs the DNA at sites of modified DNA bases.

All the antioxidant compounds which are formed inside the body are called *endogenous antioxidant*s. The endogenous antioxidants can be divided into two main groups as enzymatic and non enzymatic antioxidants.

The primary defence is composed of three important enzymes. These enzymes prevent the formation or neutralize free radicals. *Glutathione peroxidise* by virtue of electron donating ability reduce peroxides and thus eliminates peroxides as potential substrate for the *Fenton* reaction. *Catalase* has the ability to convert H_2O_2 into H_2O and molecular oxygen. One of the biggest advantages of *catalase* is that on an average one molecule of *catalase* approximately converts six billion superoxide radical into H_2O_2 and thus provides substrate molecules for the activity of catalase. Several other enzymes are also involved in providing secondary antioxidant defence mechanism. These include *Glutathione reductase* and *Glucose-6-phosphate dehydrogenase*. *Glutathione reductase* converts oxidised form of *Glutathione* to its reduced form and recycles the *Glutathione*. *Glucose-6-phosphate dehydrogenase* in the glycolysis process regenerates NADPH. These two enzymes, instead of direct neutralization of free radicals provide a supporting mechanism to help regenerate other endogenous antioxidants.

A number of non enzymatic low molecular weight endogenous antioxidants are produced by cells of different organelles and the examples include *Vitamins*, *Enzyme cofactor* (Q_{10}), nitrogen containing compounds such as *Uric acid* and *Peptides* such as *Glutathione*. Vitamin A is produced as a result of breakdown of β-carotene.

It is formed in liver. The ability of Vitamin A to neutralize peroxyl radicals makes it a potential antioxidant as it stops the propagation of lipid peroxidation through the peroxyl radical. Cofactor Q_{10} plays very important role in the respiratory chain and other cellular metabolism. It is present in all living cells. Coenzyme not only prevents the formation of lipid peroxyl radicals but also has the ability to neutralize these radicals after their formation. It also helps in regeneration of *Vitamin E*. *Uric acid* is formed as a result of purine nucleotide metabolism in humans. *Uric acid* helps in prevention of over production of oxo-heme oxidants. These oxidants are formed as a result of reaction of haemoglobin with peroxides. Besides this *Uric acid* is a potent scavenger of $^1O_2$ and $^\bullet OH$. More importantly it also prevents the lysis of erythrocytes by peroxidation. *Glutathione* an endogenous tripeptide protects the cells against free radicals by either hydrogen atom transfer (HAT) or single electron transfer (SET) mechanism to the free radicals.

When the balance between production of FR and RM on the one hand and antioxidative protection of the organism on the other is disturbed, this leads to uncontrolled production of FR and RM. This condition is known as oxidative stress.

HEALTH EFFECTS OF OXIDATIVE STRESS

Proteins, deoxyribonucleic acid DNA, ribonucleic acid RNA, Sugars and lipids are the main targets of the ROS, RNS, RSS, etc. Oxidative modification of proteins occurs mainly by the following three pathways- (i) Oxidative modification of specific amino acid, (ii) Free radical mediated peptide cleavage and (iii) cross linkage of proteins due to reaction with lipid peroxidation products.

The damage induced by FR and RM to DNA may be through either or both the chemical as well was as structural modification of the DNA. This involves the production of base-free sites, deletions, modification of all bases, frame shifts, DNA strand breaks, DNA-protein cross links and chromosomal arrangements. Hydroxyl free radical, $^\bullet OH$, are very dangerous for the damage of DNA as this radical may react with all the components of the DNA molecule; the purine and pyaimidine bases as well as the deoxyribose backbone. At the same time peroxyl radical also intervene in DNA oxidation.

Fatty acids in the lipids of food tissues may be either saturated or unsaturated. These fatty acids may be part of the neutral triglyceride fraction or part of the phospholipid fraction. The electron deficient centres in the side chains of the fatty acids are susceptible for attack by the ROS. Lipid peroxidation occurs via chain reaction mechanism and is initiated when a hydrogen atom ($H^\bullet$) is abstracted from a fatty acid (L:H), thereby, forming a lipid free radical (L). It is easier to remove a hydrogen atom from poly unsaturated fatty acid (PUFA) as compared to mono unsaturated fatty acid (MUFA) and the saturated fatty acid (SFA) because of the enhanced ability of lipid radical to undergo molecular rearrangement in the case of PUFA. This accounts for the initial step in the lipid peroxidaton. The initiation step which involve abstraction of an $H^\bullet$ atom is thermodynamically unfavourable and is usually initiated by the presence of other very reactive species such as other free radicals ($R^\bullet$), singlet oxygen ($^1O_2$), decomposition of hydroperoxides (ROOH) or photosensitizers etc. Molecular rearrangement of the resulting lipid radical can lead to the production of a conjugated diene system. A high energy lipid peroxyl radical forms as a result of molecular oxygen insertion in a lipid radical. The lipid peroxyl radicals can abstract $H^\bullet$ hydrogen atom from another unsaturated fatty acid (L:H) and thus forms hydroperoxide (LOOH) and a new lipid free radical ($L^\bullet$). It means a chain reaction is initiated resulting in the transformation of polyunsaturated fatty acids into lipid hydroperoxides.

$$L{:}H + O{::}O + \longrightarrow I\,L^\bullet + HOO^\bullet \quad (1)$$

$$L^\bullet + O{::}O \longrightarrow LOO^\bullet \quad (2)$$

$$LOO^\bullet + L{:}H \longrightarrow LOOH + L^\bullet \quad (3)$$

$$LO{:}OH \longrightarrow LO^\bullet + HO^\bullet \quad (4)$$

Lipid hydroperoxides (LOOH) are the primary products of the lipids oxidation. Lipid hydroperoxide are very unstable and may decompose to yield hydroxyl ($OH^\bullet$) and alkoxy free radical ($LO^\bullet$). These are tasteless and odourless, however, in presence of metal ions, exposure to light and thermal energy, easily decompose to secondary products such as aldehydes and malondialdehydes (MDA's). These low molecular weight compounds are volatile and produce off odours. Isoprostanes are another type of lipid peroxidation products, which are produced via the peroxidation of arachidonic acid. These chemical species are found to be at elevated levels in plasma and breath condensates of asthmatic people.

It is important to note that depending on the type and level of RM, duration of exposure, antioxidant status of cell, activation of cellular repair system, cells exposed to RM can respond differently by way of increased proliferation, halted cell cycle, senescence and apoptosis or necrosis. More importantly the response of cells to these reactive species is dependent on the type of cells. *Oxidative stress* is therefore a very complex phenomenon and is associated with a number of diseases[8-12] such as *Atherosclerosis*, neurodegenerative diseases such as *Alzheimer's* and *Paskinson's* disease, *Diabetes Mellitus* and various metabolic syndromes in addition to *skin* and *tumor disease*, *psychic impairments* etc.

Thus at certain level of concentrations free radicals (FR) and reactive metabolites (RM) are very important for proper functioning of an organism. However, at increased concentration levels they become harmful to an organism, causing very serious diseases. More importantly physiological processes such as ageing have also been associated with the action of FR and RM and the antioxidants.

EXOGENOUS OR DIETARY ANTIOXIDANTS

At the insufficiency of endogenous antioxidants protection system, dietary antioxidants play very big role in order to maintain low levels of free radicals. These dietary antioxidants are called exogenous antioxidants[13-14]. These exogenous antioxidants, present in fruits[15] and vegetables, are the secondary metabolites resulting from the cellular metabolism in plants. Spice and herbs that are used in food for flavouring purpose and for physiological effects in *Ayurvedic medicines* contain very high concentration of naturally occurring phenolic compounds which exhibit antioxidant properties. These naturally occurring antioxidant compounds, depending on the chemical structure, are classified as *Flavonoids*, *Phenolic acids*, *Carotenoids*, *Tocopherols*, *Antioxidative minerals* and *Organo-Sulphur* compounds.

Ascorbic acid and tocopherols, generically known as *Vitamin C* and *Vitamin E*, respectively, exist in several isoforms. *VitaminC* exists as L-ascorbic acid and L-dehydroascorbic acid. Both these forms are absorbed through gastrointestinal tract and gets interchanged enzymatically *in vivo*. Vitamin C is an effective scavenger of $O_2^{-\bullet}$, $^{\bullet}OH$, $^{\bullet}OOH$, $^1O_2$ and reactive nitrogen oxides. Vitamin E comprises of eight isoforms with four tocopherols and four tocotrienols. Vitamin E is found in plasma, red cell and various tissues and protects the integrity of lipid structures in the cell membranes. In fact Vitamin E is the only major lipid soluble, chain breaking antioxidant found in plasma and acts as trapper of peroxyl radicals. Vitamin C also helps in regeneration of Vitamin E from the tocopheroxyl radical and therefore by reinstating its antioxidant potential shows synergistic antioxidant behaviour with VitaminE.

Flavonoids[16] are the most important class of compounds. A number of experimental studies have established the importance of flavonoids in terms of their antioxidant activity. The antioxidant activity of *flavonoids* is not only due to radical scavenging ability but also due to inhibition of *Xanthineoxidase*, an enzyme responsible for production of superoxide free radicals. *Flavones*, *flavonols*, *dihydroflavonols*, *flavanoles* and *flavanones* are the subclasses within the flavonoid class of compounds. The common characteristic of flavonoids is the presence of 15-*Carbon* flavan structure[17]. The flavan structure comprise of three rings; ring A, ring B and the ring C. The level of saturation of the C ring forms the basis of difference between subclasses of flavonoids. Individual compounds within each of these subclasses are characterized by the substitution pattern and the number and location of phenolic –OH groups on the flavonoid skeleton. This accounts for different radical scavenging ability of various flavonoids.

Phenolic acids are composed of hydrocinnamic and hydroxy benzoic acids and also exist as esters and glycosides. Gallic acid is the most promising compound of hydroxyl benzoic acid group and cinnamic acid is the precursor of the hydrocinnamic acids.

Of the various naturally occurring pigments, *carotenoids* represent an important class and are synthesized by plants and only microorganisms. *Carotenoids* are further classified as carotenes and xanthophylls. Carotenes are hydrocarbons which contain specific end groups like *lycopene* and β-carotene. On the other hand oxygenated carotenoids are known as xanthophylls, e.g. zeaxanthin and lutein. Carotenoids are potent $^1O_2$ quenchers. The quenching of $^1O_2$ forms excited carotenoids, which dissipate the acquired energy through vibrational degradation of the molecules as a result of solvent interaction and once again achieve the ground state of the molecule. Elongated conjugation of double bonds within the structure of carotenoids accounts for their ability to quench $^1O_2$ via this mechanism and makes these compounds as perpetual antioxidant system. However, phenoxyl free radical can completely destroy these pigments. In trace quantities, minerals are also important dietary constituents and have important role in metabolism. *Selenium* (Se) and *Zinc* (Zn) are two important minerals which can also be classified as antioxidant minerals. The antioxidant activity is not due to independent selenium, rather, Se is very important constituent of enzymes which exhibit antioxidant activity. For example metalloenzymes, glutathione peroxidise, thridoxin reductase etc. are enzymes which acquire their activity due to presence of selenium. Zn is also an important element and is quite important in the prevention of formation of free radicals. It is an important constituent of superoxide dismutase (SOD) enzyme that converts $^1O_2$ into H_2O_2. Zinc also acts as inhibitor of NADPH oxidase which catalyzes the production of the superoxide radical from oxygen using NADPH. Interestingly, zinc also competes with Copper for binding to the cell wall and in turn decreases the production of $^{\bullet}OH$.

Curcuminoids[18], found in the rhizomes of the plant *curcuma longa* (turmeric), are another class of compounds that are currently the focus of enormous research interest owing to their tremendous antioxidant potential as chain breaking antioxidants.

CONCLUSIONS

The article presents discussion of the various types of reactive species, present in the living systems as defence against invading pathogens, their origin, positive functions and effects of oxidative stress. Endogenous as well as exogenous antioxidant prevention mechanism has also been discussed.

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