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AN OVERVIEW: ANTIOXIDANT ACTIVITY WITH MEDICINAL PLANTS

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Radical Scavenging, Antioxidant, Medicinal plants, Phyto compounds, Free radical, Reactive oxygen species.

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ABSTRACT

Antioxidant of medicinal plant origin may exert their effects on biological systems by different mechanisms. Efforts have been made to explore the structure and functional groups that involve removing the oxidants that most often occurs in the biological systems. Some of the mechanisms have been dealt in this review. Many oxidants have been implicated in a number of disease, removal or minimization of oxidants exposure and at the same time increasing the antioxidant ability of the biological system may reduce the damage. Medicinal plants produce significant amounts of antioxidants such as flavonoids, phenolics and polyphenolics compounds to preven the body from oxidative stress that could be caused by reactive oxygen and nitrogen species.

INTRODUCTION:

An antioxidant is a molecule capable of inhibiting 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 redicals. In turn, these radicals can start chain reactions that damage cells. Antioxidants terminate these chain reactions by removing free radical intermediates, and inhibit other oxidation reactions. They do this by being oxidized themselves, so antioxidants are often reducing agents such as thiols, ascorbic acid or polyphenols.

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 peroxidises. Low levels of antioxidants , or inhibition of the antioxidant enzymes, cause oxidantive 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 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 preservatives in food and cosmetics and preventing the degradation of rubber and gasoline.

THE OXIDATIVE CHALLENGE IN BIOLOGY:

The structure of the antioxidant vitamin ascorbic acid (vitamin C). A paradox in metabolism is that while the vast majority of complex life on Earth requires oxygen for its existence, oxygen is a highly reactive molecule that damages living organisms by producing reactive oxygen species. Consequently, organisms contain a complex network if antioxidant metabolites and enzymes that work together to prevent oxidative damage to cellular components such as DNA, proteins and lipids. In general, antioxidant systems either prevent these reactive species from being formed, or remove them before they can damage vital components of the cell. However, since reactive oxygen species do have useful functions in cells, such as redox signaling, but instead to keep them at an optimum level. The oxygen species produced in cells include hydrogen peroxide (H_2O_2),

hypochlorous acid (HOCL), and free radicals such as the hydroxyl radical (OH). And the superoxide anion (O_2). The hydroxyl radical is particularly unstable and will react rapidly and non-specifically with most biological molecules. This species is produced fro hydrogen peroxide in metal-catalyzed redox reactions such as the Fenton reaction. These oxidants can damage cells by starting chemical chain reactions scuh as lipid peroxidation, or by oxidizing DNA or proteins. Damage to DNA can cause mutations and possinly cancer, if not reversed by DNA repair mechanisms, while damage to proteins causes enzyme inhibition, denatration and protein degradation.

The use oxygen as part of the process for generating metabolic energy produces reactive oxygen species. In this process, the superoxide anion is produced as a by-product of several steps in the electron transport chain. Particularly important is the reduction of coenzyme Q in complex III, since a highly reactive free radical is formed as an intermediate (Q.-). This unstable intermediate can lead to electron "leakage" , when electrons jump derectlty to oxygen and form the superoxide anion, onstead of moving through the normal series of well-controlled reactions of the electron transport chain. Peroxide is also produced from the oxidation of teduced flaavoproteins, such as complex I. However, although these enzymes can produce oxidants, the relative importance of the electron transfer chain to other processes that generate peroxide are also produced during photosynthesis, particulary under conditions of high light intensity. This effect is party offset by the involvement of carotenoids in photoinbhibition, which involves these antioxidants reacting with over-reduced forms of the photosynthetic reaction centres to prevent the production of reactive oxygen species.

PHENOLIC COMPOUNDS:

Phenolic compounds possess one of more aromatic rings and one or more hydroxyl groups. They are the products of secondary metabolism in plants, providing essential functions in the reproduction and the growth of the plants; acting as defense mechanisms against pathogens, parasites, and predators, as well as contributing to the color of plants. In addition to their roles on plants, phenolic compounds in diet provide health benefits.

PHENOLIC ACIDS:

The simplest Phenolic compounds commonly found in plants. Generally they can be classified in two broad categories based on their chemical nature. Benziic acid derivatives and cinnamic acid derivatives.

FLAVONOIDS:

Flavonoids are a group of polyphenolic compounds, which are widely distributed throughout the plant kingdom. Many have low toxicity in mammals. Flavonoids exhibit several biological effects such as anti-inflammatory, anti-hepatotoxic and anti-ulcer actions. They also inhibit exzymes such as aldose reductase and xanthine oxidase. They are potent antioxidants and have free radical svavenging abilities. Many have antiviral actions and some of them provide protection against cardiovascular mortality. They have been shown to inhibit the growth of various cancer cell lines in vitro, and reduce tumour development in experimental animals.

Flavonoids occur as aglycones, glycosides and methylated detivatives. The flavonoid aglycone consists of a benzene ring (A) condensed with a six memberring (C), which in the 2-position carries a phenyl ring (B) as a substituent. Six-member ring condensed with the benzene ring is either a flavonols and flavonoens or its dihydroderivativve (flacanols and flavanones). The position of the benzenoid substituent divides the flavonoid class into flavonoids (2-position) and isoflaconoids (3-position). Flavonols differ from flavonones by hydroxyl group the 3-position and C2-C3 double bonds. Flavonoids are often hydroxylated in position methyl ethers and acetylesters of the alcohol group are known to occur in nature. When glycosides are formed, the glycosidic linkage is normally located in positions 3 or 7 and the carbohydrate can be L-rhamnose, D-glucose, gluco-rhamnose, galactose or arabinose.

TERPENOIDS:

The term perpene refers to a hydrocarbon molecule, while terpenoid refers to a terpene that has been modified, for example by the addition of oxygen. Terpenes or isoprenoids, are one of the most diverse classes fo secondary metabolits which play variety fuctional rolesin plants as hormones (gibberellins, abscisic acid), photosynthetic pigments (phytol, polysaccharide assembly (polyprenly phosphates), and structural components of membranes (phytosterols). More than 55,000 different terpenoids have been isolated, and this number has almost dounled each decade, many of which are of plant origin. Terpenoids are essential for plant growth, development, and general metabolism. Terpenods are found in almost all plant species.

In plants, terpenoid biosynthesis occurs by two different pathways to synthesize the main building block Inositol [yrophosphate (IPP), (a) the Mevalonic acid pathway or HMG-CoA reductase pathway that occurs in cytosol and produces IPP for sesquiterpenoids, (b) methylerythritol phosphate/1-deoxy-D-zylulose (MEP/DOX) pathway IPP in the choloroplasr for mono and diterenoids.

Generally based on the number of building blocks, i.e., isoprenoid units, terpenoids are classified into several classes, such as Hemeterpene, monoterpenes (e.g., carvone, geraniol, d-limonene, and perillyl alcohol), diterpenes (e.g., retinol land trans-retinoic acid), and Ursolic Acid (UA),and tetraterpenes (e,g., α-carotene, β-carotene lutein, and lycopene). Different terpenoids molecules have antioxidant, antiviral, antibacterial, antimalarial, antiinflammaatory, inhibition of cholesterol synthesis, antiallergenic, antihyperglycemic, immumomodulatory and anticancer activities.

ALKALOIDS:

Alkaloids are a diverse group of low molecular weight, nitrogencontaining compounds mostly derived from amino acids. Alkaloids are thought to play a defensive role in the plant against herbivores and pathogens. Plant-derived alkaloids currently in clinical use include analgesics, anti-neoplastic agent, gout suppressant, muscle relaxants, antiviral, cytotoxic, antinociceptive, anitcholinergic, anti-inflammatory and DNA-binding activities and some of them have also beeb used in the treatment of Alzheimer's disease, myasthenia gravis and myopathy

Alkaloids can be classidied into frmilies, on the basis of structural similarities and the amino acids that are used for their biosynthesis. Some alkaloids are also produced using building blocls derived from other secondary metabolic pathways, such as terpenoids, polyketides and peptides. Some of the important classes of alkaloid are shown below: Terpenoid Indole Alkaloids (TIAs) comprise a family of greater than 3000 compounds that includes the antineoplastic agent's vinblastine and camptothecin, the antimalarial drug quinine, and the rat poison strychnine. Some TIAs have been proposed to play a role in the defense of plants against pests and pathogens. TIAs consist of an indole moiety provided by tryptamine and a terpenoid component derived from the iridoid glucoside secologanin.

The benzylisoquinoline alkaloids are a very large and diverse class of alkaloids with > 2500 defined structure. This family contains such varied physiolofically active members as emetine (an antiamiebic), colchicines (a microtubule disrupter and gout suppressant), berberine (an antimicrobial against eye and intestinal infections), morphine (a narcotic analgesic), codeine (a narcotic analgesic and antitussive), and sanguinarine (an antimicrobial used in oral hygiene.

Tropane alkaloids (TPAs) occur mainly in the Solanaceae. There prinicipal characterstics pytollic ring derived from the ornithine and arginine aminoacids by a chemical reaction caaylsed by ornithine decaboxylase and Arginine decarboxylase respectively. This class of alkaloid includes the anticholinergic drugs atropine, hyoscyamine, and scopolamine, and the narcotic tropical anesthetic cocaine. Although nicotine is not a member of the tropane class, the N-methyl-

Δ^1- pyrrolinium cation involved in TPA biosynthesis is alos an intermediate in the nicotine pathway.

Purine alkaloids such as caffeine, theobromine, and theacrine are widely distributed in the plant kingdom. Caffeine, a nonselective adenosine A_1 and A_{2A} receptor antagonist, is the most widely used psychoactive substance in the world. Evidence demonstrates that caffeine and selective adenosine A_{2A} antagonists interact with the neuronal systems involved in drug reinforcement, locomotors sensitization, and therapeutic effect in Parkinson's disease (PD).

ENZYME SYSTEMS:

As with the chemical antioxidants, cells are protected against oxidant stress by an interacting network of antioxidant enzymes. Here, the superoxide released by processes such as oxidative hposphorylation 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 catalying the first step and than catalases and various peroxidises removing hydrogen to antioxidant defences can be hard to separate from one another, but the generation of transgenic mice lacking just one antioxidant enzyme can be informative.

SUPEROXIDE DISMUTASE, CATALASE AND PEROXIREDOXINS:

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 extraellular fluids. Superoxide dismutase enzymes contain metal ion cofactors that, depending on the isozyme, can be copper, zinc, mahganese iron. In humans, the copper/zinc SOD is present in the cytosol, while manganese SOD is present in the mitochondrion. There also exists a third foem of SOD in extracellular fulids, which contains copper and zinc in tis actie sites. The mitochondrial isozyme seems to be the most biuologically important of these three, since mice lacking this enzyme die soon after birth. In contrase, the mice lacking copper/zinc SOD (Sod 1) are viable but have numeeous pathologies and a reduced lifespan (see article on superoxide), while mice without the extracellular SOD have minimal defects (sensitive to hyperoxia). In plants, SOD isozymes are present in the cytosol and mitochondria, with an iron SOD found in chloroplasts that is absent from vertebrates and yeast.

Catalases are enzymes that catalyse the conversion of hydrogen peroxide to water and oxygen, using either an iron or manganese cofactor. This protein is localized to peroxisomes in most eukaryotic cells. Catalase is an unusual enzyme since, although hydrogen peroxide is its only substrate, it follows a ping-pong mechanism. Hers, its cofactor is oxidised by one molecule of

hydrogen peroxide and then regenerated by transferring the bound oxygen to a second molecule of substrate. Despite its apparent importance in hydrogen peroxide removal, humans with genetic deficiency of catalase-"acatalasemia"- or mice genetically engineered to lack catalase completely, suffer few ill effects. Decameric structure of AhpC, a bacterial 2-cysteine peroxiredoxin from *Salmobella typhimurium.*

Peroxiredoxins are peoxidases that catalyze the reduction of hydrogen peroxide, organic hydroperoxides, as well as peroxynitrite. They are divided into three classes: typical 2-cysteine peroxiredoxins; typical 2-cysteine peroxiredoxins; and 1-cysteine peroxiredozins. These enzymes share the same basic caralytic mechanism, in which a redox-active cysteine (the peroxidatic cysteine) in the active site is oxidized to a sulfenic acid by the peroxide substrate. Over-oxidant of this cysteine residue in peroxiredoxins inactivates these enzymes, but this can be reversed by the action of sulfiredoxin. Peroxiredoxin 1 0r 2 have shortened lifespan and suffer from haemolytic anaemia, while plants use peroxiredoxins to remove hydrogen peroxide generated in chloroplasts.

THIROREDOXIN AND GLUTATHIONE SYSTEMS:

The thioredoxin system contains the 12-kDa protein thioredoxin and its companion thioredoxin reductase. Proteins related to thiroredoxin are present in all swquenced organisms with plants, such as *Arabidopsis thaliana*, having a particularly great diversity of isoforms. The active site of thioredoxin consists of two neihouring cysteines, as part of a highly conserved CXXC motif, that can cycle between an active dithiol acrs as an efficient reducing agent, scacenging reactive oxygen species and maintaining other proteins in their reduced state. After being oxidized, the active thioredoxin is regenerated by the action of thioredoxin reductase, using NADPH as an electron donor.

The glutathione system includes glutathione, glutathione reductase, glutathione peroxidises and glutathione *S*-transferases. This system is found in animals, plants and microorganisms. Glutathione peroxidise is an enzyme containing four selenium-cofacrots that catalyzes the breakdown of hydrogen peroxide and organic hydroperoxides. There are ar lease four different glutathione peroxidise isozymes in animals. Glutathione peroxidise 1 is the most abundant and is a very efficient scavenger of hydrogen peroxide, while glutathione peroxidise 4 is most active with lipid hydroperoxides. Surprisingly, glutathione peroxidise 1 is dispensable, as mice lacking this enzyme have normal lifespans, but they are hypersensitive to induced oxidative stress. In addition, the gultatiione *S*- transferases show high activity with lipid peroxides. These enzymes are at particularly high levels in the liger and also serve in detoxification metabolism.

OXIDATIVE STRESS IN DISEASE:

Further information : Pathology. Free-radical theory of aging

Oxidative stress is thought to contribute to the development of a wide range of diseases including Alzheimer's disease, Parkinson's disease, the pathologies caused by diabetes, rheumatoid arthritis, and neurodefeneration in motor neuron diseases. In many of these cases, it is unclear if oxidants trigger the disease, or if they are produced as a secondary consequence of the disease and from general tissue damage; one case in which this link is particularly well-understood is the role of oxidative stress in cardiovascular disease. Here, low density lipoprotein (LDL) oxidation appears to trigger the process of atherogenesis, which results in atherosclerosis, and finally cardiovascular desease.

A low calorie diet extends median and maximum lifespan in many animals. This effect may involve a reduction in oxidative stress. While there is some evidence to support the role of ixidative stress in aging inmodel organisms such as *Drosophila melanogaster and Caenorhadbitis elegans*, the evidence in mammals is less clear. Indeed, a 2009 review of experiements in mice concluded that almost all manipulations of antioxidant systems had no effect on aging. Diets high in fruit and vegerables, which are high in antioxidants, promote health and reduce the effects of aging, however antioxidant vitamin supplementation has no detectable effect on the aging process, so the effects of fruit and vegetables may be the fact that consuming antioxidant molecules such as polyphenols and vitamin E will produce changes in other parts of metabolism so it may be these other effects that are the real reason these compounds are important in human nutrition.

HEALTH EFFECTS:

DISEASE TREATMENT:

The brain s uniquely vulnerable to oxidative injury, due to its high metabolic rate and elecated 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, while the experimental drug NXY-059 and ebselen 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.

DISEASE PREVENTION:

People who eat fruits and vegetables have a lower risk of heart disease and some neurological diseases, and there is evidence that soem types of vegetables, and fruits in general, protect against soem cancers. Since fruits and vegetables happen to be good sources of antioxidants, this suggested that antioxidants might prevent some types of diseases. This idea has been tested in clinical trials and dose not seem to be true, as antioxidant supplements have no clear effect on the risk of chronic diseases such as cancer and heart disease. This suggests that these health benefits come from other substances in fruits and vegetables (possibly flavonoids), or come form a complex mix of substances.

It is thought that oxidation of low density lipoptein 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, kn doses ranging from 50 to 600 mg per day. None of these trials found a statistically singnificant 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 singnificant decrease in oxidative stress. Overall, despite the clear role of oxidative stress in cardiovascular disease, controlled studies using antioxidant vitamins have oserved no reduction in either the risk of developing heart desease, or the rate of progression of existing disease.

While several trials have investigated supplements with high doses of antioxidatns, the "*Supplementation 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 beta carotene, 100 µg of selenium, and 20mg 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 ogerall survival, cancer, or heart disease. 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 the polyphenol, resveratrol (from grape seeds or knotweed roots), combinations of antioxidants, like the "ACES" products that contain beta carotene (provitamin A), vitamin C, Vitamin E and Selenium, or herbs that contain antioixidants-such as green tea and juaogulan. 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, and if they are actually beneficial, which antioxidant(S) are needed and in what amounts. Indeed, some authors argue that the hypothesis that antioxidants could prevent chronic diseases has now been disproved and that the idea was misruided form the beginning. Rather, dietary polyphenols may have non-antioxidant roles in minute concentrations that affect cell-to-cell signaling, receptor sensitivity inflammatory enzyme activity or gene regulation. For overall life expectancy, it has even beeb suggested that moderate levels of oxidative stress may increase lifespan in the woem *Caenorhabditis elegans,*by inducing a protective response to increased levels of reactive oxygen species. The suggestion that increased life expectancy comes from increased oxidantive stress conflicts with results seen in the yeast *Saccharomyces cerevisiae*, and the situation in mammals is even less clear. Nevertheless, antioxidant supplements do not appear to increase life expecrancy in humans

PHYSICAL EXERCISE:

During exercise, oxygen consumption can increase by a factor of more than 10. This leads to a large increase in the production of oxidants and results in damage that contributes to muscular fatigue during and after exercise. The inflammatory response that occurs after strenuous exercise is also associated with oxidative stress, especially in the 24 hours after an exercise session. The immume system response to the damage done by exercise peaks 2 to 7 days after exercise, which is the period during which most of the adaptation that leads to greater fitness occurs. During this process, free radicals are produced by neutrophils to remove damaged tissue. As a result, exvessive antioxidant levels may inhibit recovery and adaptation mechanisms. Antioxidant levels may inhibit recovery and adaptation mechanisms. Antioxidant supplements may also prevent any of the health gains that normally come from exercise, such as increased insulin sensitivity. The evidence for benefits from antioxidant supplementation in vigorous exercise is mixed. There is strong evidence that one of the adaptations resulting from exercise is a strengthening of the body's antioxidant defences, particularly the glutathione system, to regulate the increased oxidative stress. This effect may be to some extent protective against diseases which are associated with oxidantive stress, which would provide a partial explanation for the lower incidence of major diseases and better health of those who undertake regular exercise.

However, no benefits for physical performace to athletes are seen with vitamin E supplementation. Indeed, despite its key role in preventin lipid membrane peroxidation, 6 weeks of vitamin E supplementation had no effect on muscle damage in ultramarathon rn=unners.

Although there is some evidence that vitamin C supplementation icreased the maoun tof intense exercise that can be doen and vitamin C supplemenratio before strenuous exercise may reduce the amount of muscle damage. Jowever, other dtudies found no such effects, and some research suggests that supplementation with amounts as high as 1000 mg inhibits revovery.

USES IN TECHNOLOGY:

FOOD PRESERVATIVES:

Antioxidants are used as food additives to help guard against food deterioration. Exposure to oxygen and sunlight are the two main factors in the oxidation of food, so food is preserved by keeping in the dark and sealing it in containers or even coatin it in wax, as with cucumbers. However, as oxygen is also important for plant respiration, storing plant materials in anaerobic conditions produces unpleasant flavours and unappealing colors. Consequently, packaging of freash fruits and vegerables contains an $\sim 8\%$ oxygen atmosphere. Antioxidants are an especially important class of preservatives as, unlike bacterial or fungal spoilage, oxidation reactions still occur relatively rapidly in frozen or refrigerated food. These presefatives include natural antioxidants such as ascorbic acid (AA, E300) and tocopherols (E306), as well as synthetic antioxidant such as propyl gallate (PG, E310), tertiary butylhydroquinone (TBHQ), butylated hydroxyanisole (BHA< E320) and hutylaed hydroxytoluene (BHT, E321).

The most common molecules attacked by oxidation are unsaturated fats; oxidation causes them to turn rancid. Since oxidized lipids are ofen discoloured and usually have unpleasant tastes such as metallic or sulfuous flavours, it is important ot avoid oxidation in fat-rich-foods. Thus, these foods are rarely preserved by drying; instead, they are preserved by smoking, salting of fermenting. Even less fatty foods such as fruits are sprayed with sulphurous antioxidants prior to air drying, oxidation is often catalyzed by metal, which is why fats such as butter should never be wrapped in aluminium foil or kept in metal containers/ some fatty foods such as olive oil are partially protected from oxidation by their natural content of antioxidants, but remain sensitive to photooxidation. Antioxidant preservatives are also added to fat-based consmetics such as lipstick and moisturizers to prevent rancidity.

INDUSTRIAL USES:

Antioxidants are frequently added to industrial products. A common use is as stabilizers infuels and lubricants to prevent oxidation, and in gasoline to prevent the polumerization that leads to the formation of engine-fouling residues. In 2007, the worldwide market for industrial antioxidant has

a total volume of aroud 0.88 million tons. This created a revenue of circa 3.7 billion US- dollars (2.4 billion Euros).

They are widely used to prevent the oxidative degradation of plumers such as rubbers, plastics and adhesives that causes a loss of strength and flexibility in these materials. Polymers containing dounle bonds in their main chains, such as such as natural rubber and polybutadiene, are especially susceptile to oxidation and ozonolysis. They can be protected by antiozonants. Soild polymer products start to crack on exposed surfaces as the material degrads and the chains break. The mode of cracking caries between oxgen and ozone attack, the foemer causing a "crazy paving" effect, while ozone attack produces deeper cracks aligned at right angles to the tensile strain in teh product. Oxidation and UV degradation are also frequently linked, mainly because UV radiation creates free radicals by bond breakage. The free radicals then react with oxygen to produce peroxy radicals which cause yet further damage, often in a chain reaction. Other polymers susceptible to oxidation include polypropylene and plynethylene. The former is more sensitive owing to the presence of secondary carnon atoms present in every repeat unit. Attack occurs at this point because the free radical formed is more stable than one formed on a primary carbon atom. Oxidation of polyethylene tends to occur ar weak links in the chain, such as branch points in low density polyethylene.

FREE RADICAL SCAVENGING:

Searching and identifying natural and safe antioxidants, especially of plant origin, have neen notably increased in recent years. Assays based on the use of O_{2^-} and OH, DPPH, $ABTS^+$, and N, *N-dimethyl-p-phenylenediamine* dihydrochloride cation radical ($DMPD^{+\cdot}$). are amoung the most popular spectrophotometric methoids for determination of the antioxidant capacity of foods, beverages and vegetable extracts. DPPH and $ABTS^{+\cdot}$ Scavenging methods have been the most commonly used to evaluate the antioxidant activity of compounds due to their simple, rapid sensitive and reproducible procedures. Thus, the radical scavenging assays in the cell-free systems for antioxidant studies are often considered by researchers before further studies in cellular lines and/or animal models.

SCAVENGING SUPEROXIDE AND OTHER ROS:

Superoxide ($O_2^{-\cdot}$), a predominant cellular free radical, is involved in a large number of deleterious changes often associated with an increase in preoxidantive processes and linked to a low antioxidant concentration. Although $O_2^{-\cdot}$ Itself is not so reactive to niomolecules, it helps in generation of more powerful. OH and $ONOO^-$. In phagocytes, $O_2^{-\cdot}$ Is produced in large quantities

by the enzyme NADPH oxidase for killing pathogens. $O_2^{-\cdot}$ Is also a by product of mitochondrial respiration, as well as seceral other enzymes such as NADH oxidase, XO, monooxygenases and cyclooxygenases.

Direct scavenging of $O_2^{-\cdot}$ Has been a model for determining the antioxidant activities. In the chemical systems, $O_2^{-\cdot}$ Can be generated enzymatically or non-enzymatically form quinine derivatives, such as 6-anilino-5, 8-quinolinequinone (LY83583), 1,4-benzoquinone, 1,4-naphthaquinone, 2-methyl-1, 4-naphtjaquinone, riboflavin, etc. In the presence of enzymes such as NADPH-cytochrome P450 reductase and mitochondrial NADH-ubiquinone oxidoreductase or thiol compounds such as glutathione and L-cysteine, LY83583 undergoes a one-electron reduction due to low redox potential (-0.3 V *versus* SCE), followed by formation of LY83583 semiquinone antion radical. Under an aerobic condition, this species interacts with molecular oxygen to from $O_2^{-\cdot}$ And original quinines. $O_2^{-\cdot}$ Is also generated in riboflavin/methionine/illuminate and assayed by the reduction of Nitro blue tetrazolium (NBT) to form blue formazan. Briefly, the reaction mixture is illuminated at 25^0C for 40 min. And $O_2^{-\cdot}$ Generated from the photochemically reduced tiboflavin can reduce NBT to form blue formazan which has absorbance at 560nm. This system can be used to determine the radical scavenging activity of antioxidants. Antioxidants can be added to the reaction mixture to scavenge $O_2^{-\cdot}$, thereby inhibiting the NBT reduction. Decreased absorbance of the reaction mixture indicates increased $O_2^{-\cdot}$ Scavenging activit. The percentage of $O_2^{-\cdot}$ Scacenged is calculated by the absorption change. NBT salt and other tetrazolium salts are chromogenic probes useful for $O_2^{-\cdot}$ Determination. These probes are also widely used for detecting redox potential fo cells for viability, proliferation and cytotoxicity assays. In the cell culture system, $O_2^{-\cdot}$ Can be increased by treating cells with a mitochondrial respiratory complex III inhibitor, antimycin A.

Assessment of low-level $O_2^{-\cdot}$ In non-phagocytic cells in crucial for assessing redox- dependent signalling pathways and the role of enzymes such as the NADPH oxidase complex. Many probes and methods, such as enzymatic (cytochrome c, aconitase), spectrophotometric (NBT), chemiluminescent(lucigenin [Luc], coelenterazine, etc), fluorescent [dihydroethidium (DHE) and MitoSOX], as well as electron paramagnetic resonance (EPR) spin trapping, have been used to detect the production of $O_{2=\cdot}$ (see review [40]). Among these probes, Luc luminescence is a more specific measure of $O_2^{-\cdot}$ It involves several steps such as single-electron reduction of Luc^{2+} to $Luc^{+\cdot}$,coupling of $Luc^{+\cdot}$ With $O_2^{-\cdot}$ Yielding a dioxetane, decomposition of the dioxetane into two molecules of the *N-methyl* acridone, one of which is in the electronically excited state, and finally

emission of a photon form the excited state acridone as it teturns to the groud state (Fig. 4). Because $Luc^{+\cdot}$ Is readily autoxidized to Luc^{2+} and reduces O_2 to $O_2^{-\cdot}$ Luc^{2+} cannot precisely determine the cellular levels of $O_2^{-\cdot}$ Nevertheless, Luc luminescence is still widely used in contro conditions due to the convenience and sensitivity of luminescence methods.

DHE is a useful fluorogenic probe for the detection of ROS including $O_2^{-\cdot}$. dhe has been used increasingly as a probe for $O_2^{-\cdot}$ In biological systems because DHE is a hydrophobic, uncharged compound that is able to cross extra-and intracellular membrans. It undergoes significant oxidation in resting leukocytes, possibly thorugh the uncoupling of mitochondrial oxidative phosphorylation. Cytosolic DHE displays blue fluorescence. Whereas after oxidation of by oxidants such as $O_2^{-\cdot}$ And H_2O_2, it becomes 2-hyderoxyenthidium (2-EOH) and ethidium, which intercalates cellular DNA, staining the nucleus with a bright red fluourescence. Its oxidantion by different oxidizing systems has been used increasingly for fluorescent analysis of ROS output in cells and tissues. Determination of total DHE fluorescence in cells has been performed extensively in the literature for assessment of ROS and, more specifically, of $O_2^{-\cdot}$. its main drawback is that the total fluorescence of DHE is a sum of the composite spectra of all different products and thus likely reflects preferentially a measure of total cell redox staste rather than production of a specific intermediate. Both 2-EOH and ethidium are fluorescent products that are difficult to discriminate them by conventional fluorescence microscopy or fluorometry. Thus, high-performance liquid chromatography (HPLC) analysis of DHE-derived fluorescent compounds (2-EOH and ethidium) has beeb developed in order to achieve separation and individual analysis of such products. This techniqye provides a significant increase in the accuracy of ROS output determinations and is a meaningful advance towards the precise quantification of this species in cells and tissues. Recent studies of HPLC separation and analysis of those two main products indicated that 2-EOH is generated specifically by $O_2^{-\cdot}$ Oxidation of DHE< whereas ethidium is associated mainly with pathways involving H_2O_2 and metal-based oxidizing systems, including heme proteins and preoxidases. More information about the DHE fluorescent probe is available in a recent review by Laurindo *et al*. mitoSOX ^{TM} Red mitaochondrial superoxide indicator, a modified DHE, is a novel fluorogenic dye for highly selective edetection of superoxide in teh mitochondria of live cells. It is readily oxidized by superoxide inside the motobjondrion but not by other ROS-or RNS-generation systems, and oxidation of the probe is prevented by SOD. The oxidation product becomes highly fluorescent upon binding to nucleic acids.

Several other fluorescent reagents such as fluorescein and rhodamine are also used to detect ROS including $O_2^{-\cdot}$ Although they are not specific to $O_2^{-\cdot}$ Non-fluorescent 2',7',-dicholorodihydrofluorescein diacetate (H_2DCFDA) is a cell-permeable indicator for ROS, and it may be extremely useful for assessing cellular oxidative stress. After the acetate groups of H_2DCFDA are removed by intracellular esterases, the non-fluorescent H_2DCFDA is oxidized to the highly fluorescen 2',7',-dichlorofluorescein (DCF), which can be monitored by a fluorometer using excitation sources and filters appropriate for the fluorescein. Fluorescein ahs an absorption maximum ar 494 nm and emission maximum of 521 nm. H_2DCF has beeb shown to be oxidized of DCF in human neutrophils by H_2O_2 and nitric oxide and $FeSo_4$; in the cell-free system by $ONOO^-$ and horseradish peroxidise (HRP) alone; HRP in combination with H_2O_2; $FeSO_4$ alone; and a mixture of $FeSO_4$ and H_2O_2. The oxidation by Fe^{2+} in the presence of H_2O_2 was reduced by the. OH radical scavenger formation and the iron chelator deferoxamine. 2',7',-dichlorodihydrofluorescein (DCFH) was insensitive to nitricoxide and H_2O_2 in the cell-free system. Thus Myhre *et al*. Suggest that the DCF assay is only suitable for measurements of $ONOO^-$and H_2O_2 in combination with cellular peroxidases, peroxidases alone and OH, while it is not suitable for measurement of nitricoxide, HOCL or $O_2^{-\cdot}$ In biological systems. However, in neutrophils, H_2DCFDA has proven useful for flow cytometric analysis of nitric oxide, forming a product when it reacts with H_2O_2 . other studies reported that oxidation of H_2DCFDA was not directly sensitive to signlet oxygen, but siglet oxygen can indirectly contribute to the formation of DCF through its reaction with cellular substrates that yield peroxyl products and peroxyl radicals. Importantly, DCF itself can also act as a photosensitizer for H_2DCFDA oxidation, both priming and accelerating the formation of DCF; thus care must be taken when using DCFH to measure oxidative stress in cells as a result of both visible and UV light exposure.

For the measurement of $O_2^{-\cdot}$ Scavenging activity by H_2DCFDA in a cell-free system, briefly, H_2DCFDA mixed with esterase at pH 7.4 is incubated at 37^0C for 20 min. And placed on ice in the dark until immediately prior to the study. H_2DCFDA is deacetylated to non-fluorescent DCFH by esterase an dsubsequently oxidized to non-fluorescent DCFH by esterase and subsequently oxidized to highly fluorescent DCF by $O_2^{-\cdot}$. The extent of conversion of DCFH into DCF is stoichiometrically related to the amount of $O_2^{-\cdot}$. The fluorescence intensity of oxidized DCFH is measured by using the fluorescence reader at excitation and emission wavelengths of 485 and 530 nm, respectively, for 1 hr with or without the addition of 2-methy-1,4-naphthaquinone (50mM) as an $O_2^{-\cdot}$ Source.

Dihydrorhodamine 123 (DHR 123) is another commonly used fluorescent mitochondrial dye. DHR123 itself is non-fluorescent, but is readily enters most of the cells and is oxidized by oxidative spexies or by cellular redox systems to the fluorescent rhodamone 123 that accumulates in mitochondrial membranes. DHR123 is useful for detecting ROS including $O_2^{-\cdot}$(in the presence of peroxidise or cytochrome c)and $ONOO^-$.

SCAVENGING HYDROXYL RADICAL AND OTHER ROS:

Hydroxyl radical. (OH) is extremely reactive, more toxic than other radical species and can attack biologic molecules such as DNA, proteins and lipids. OH is widely believed to be generated form the Fe^{2+}(or Cu^+)/H_2O_2 fenton reaction system, by simply incubating $FeSO_4$ and H_2O_2 in aqueous solution. Thus, OH scavenging activity of antioxidants can be accomplished through direct scavenging or preventing of. OH formation through the chelation of free metal ions of converting H_2O_2 to other harmless compounds. The scavenging ability of antioxidants can be determined by Gutteridge method, which is monitored in the Fe^{3+}-EDTA-$H_2O_2^-$ deoxyribose system. The extent of deoxyribose degradation by the . OH formed can be measurd directly in the aqueous phase by thiobarbituric acid reactive species (TBARS) assay at 532 nm. This method is based on the fact that the degradation of deoxyribose by. OH forms a reactive species malondialdihyde, which forms an adduct with thibarbituric acid (TBA). The adduct, MDA-TBA, has an absorption at 532 nm that can be assayed spectrophotometrically. By this assay, the ability of several antioxidants to scavenge. OH has been studied and compared with that of DMTU, uric acid, trolox and mannitol.

Another method uses a spin-trapping agent 5,5-dimethyl-1-pyrroline-N-oxide (DMPO) to trap the generated. OH radical. DMPO reacts with .OH to form a DMPO-OH radical, which can be monitored by EPR spectrum. Comparison of the EPR intensities of DMPO-OH radical in the absence and presence of antioxidants can measure the radical scavenging ability of the antioxidants. For example, Kang *et al*. Studies the.OH scavenging activity of ginsenosides.

STABLE RADICAL SCAVENGING:

The interaction between free radicals (such as $O_2^{-\cdot}$and .OH) and antioxidants can show direct evidence for antioxidants to scavenge free redicals. It has been widely used ot evaluate the radical scavenging ability of antioxidants. For models, radical scavenging research tends to use more stable redicals as probes. Radicals such as DPPH, galvinoxyl, $ABTS^+$ and $DMPD^+$ aare stable and coloured. DPPH and gavinoxyl radicals are commercially available, and $ABTS^+$ and $DMPD^{+\cdot}$ Radicals can be generated freshly before the assay by oxidizing the neutral molecules with

potassium persulphate and $FeCl_3$, respectively. These redicals have strong absorption in the visible region, while their absorption decreases proportionally upon receiving an electron or hydrogen from the antioxidants. Thus, the radical scavenging capacity of the antioxidants can be obtained based on the absorption change. The detailed method description for this free radical scavenging test is available from a previous report, where teh antioxidant and radical scavenging properties of curcumin are studied.

DPPH has been widely used to evaluate the free radical scavenging effectiveness of various antioxidant substances. In the DPPH assay, the antioxidants are able to donate a hydrogen to reduce the stable radical DPPH to the yellow-coloured non-radical diphenyl-picrylhydrazine (DPPH-H). DPPH is usually used as a reagent to evaluate free radical scaavengin gactivity of antioxidants based on the absorption change of DPPH at 517 nm measurd spectrophotometrically. Similar to DPPH, galvinoxyl is a stable phenoxy radical that exhibitis characteristic UV absorption ar 429 nm in ethanol solution. $ABTS^{+\cdot}$ Radicals are more reactive than DPPH radicals, and the reactions with $ABTS^{+\cdot}$ Radicals involve a single-electron transfer process. Bleaching of a pre-formed solution of the blue-green radical cation $ABTS^{+\cdot}$, which has an absorption at 734 nm, has been extensively used to evaluate the antioxidant capacity of complex mixtures and individual compounds. The reaction of the performed radicals with free radical scavengers can be easily monitored by following the decrease of the sample absorbance at 734 nm. The principle of the $DMPD^{+\cdot}$ Assay is very similar to that of $ABTS^{+\cdot}$. The UV-visible spectrum of $DMPD^{+\cdot}$ Shows a maximum absorbance at 505 nm.

These free radical scavenging reactions need the antioxidant to donate an electron or an active hydrogen atom such as one in reactive hydroxyl group. Generally, antioxidants that are molecules bearing active hydroxyl froups, such as vitamins E and C, polyphenol and flavonol compounds, are potent redical scavengers interestingly, Liu and colleagues found that ecdysteroids, which do not have active hydroxyl groups, are also active antioxidants and free-radical scavengers. The most acative hydrogen of the ecdysteroid may be H-9, which is an allylic hydrogen and furthermore, conjugation with the 6-carbonyl group further weaknes the C-H-9 bond. It is well known that allhylic hydrogens are very active and easily abstracted by fee radicals.

In the current review, we focused maibly on the scavenging of reactive species centred on oxygen, nitrogen and chlorine. These assays were commonly used to search and identify natural and safe antioxidants. Other species such as RSS have been considered as a separate class of oxidative stressors, which may provide new antioxidant drug targers. RSS are formed in vivo

under conditions of oxidative stress. RSS are likely to include disulphide-S-oxides, sulfenic acids and thiyl radicals, and are predicted to modulate the redox status of biological thiols and disulphides.

PLANTS AS ANTIOXIDANTS:

An antioxidant is any substance that, when present at low concentrations significantly delays or prevents oxidation of cell content like proteins, lipids, carbohydrates and DNA. Antioxidants can be classified into three main types: first line defence antioxidants, second line defence antioxidants and third line defence antioxidants.

SOD, CAT, GTx, glutathione reductase and some minerals like Se, Mn, Cu, Zn come under first line defence antioxidants. SOD mainly acts by quenching of superoxide (O_2-), catalase by catalyzing the decomposition of hydrogen peroxide (H_2O_2) to water and oxygen. Glutathione peroxidase is a selenium containing enzyme which catalyses the reduction of H_2O_2 and lipid hydroperoxide, generated during lipid peroxidation, to water using reduced glutathione as substrate. Selenium and vitamin E both appear to be necessary for efficient scavenging of peroxides from cytosol and cell membrane, respectively. Cu exerts its antioxidant activity through the cytosolic syperoxide dismutase. Zinc is an element for normal growth, reproduction and other different functions of the body. It is a component of several enzymes like cytoslic superoxide dismutase, alcohol dehydrogenase, alkaline phosphatise, carbonic anhydrase, etc.

Glutathione (GSH), vitamin C, uric acid, albumin, bilirubin, vitamin E (mainly α-tocopherol), carotenoids, flavonoid, etc., comes under second line defence antioxidants. β-catotene is an excellent scavenger of singlet oxygen. Vitamin C interacts directly with radicals like O_2^-, HO (hydroxyl). GSH is a good scavenger of many free radicals like O_2^-, HO and various lipid hydroperoxides and may help to detoxify many inhaled oxidizing air pollutants like ozone, NO_2 and free radicals in cigarette smoke in the respiratory tract. Vitamin E scavenges peroxyl radical intermediates in lipid peroxidaion and is responsible for protecting PUFA (poly unsaturated fatty acid) present in cell membrane and low density lipoprotein (LDL), against lipid peroxidation. Flavonoids are phenolix compounds, present in several plants, which inhibit lipid peroxidation and lipoxyhenases.

The most important chainbreaking antioxidant is α-tocopherol, present in human membranes. Vitamin C and α-tocopherol both help to minimize the consequences of lipid peroxidation in membranes. A major antioxidant defence of human body is to prevent O_2^- and H_2O_2 from reacting to form dangerous species such as hydroxyl ions, by binding transition metal ions, by binding

transition metal ions in forms that will not stimulate free radical reactions. Thus, safe sequestration of iron and copper ions into forms that will not catalyse free radical reactions is an important antioxidant strategy in the human body.

Third line antioxidants are a complex group of enzymes for repair of damaged DNA, damaged protein, oxidized lipids and peroxides and also to stop chain propagation of peroxyl lipid radical. These enzymes repair the damage to biomolecules and recinstitute the damaged cell membrane, e.g. lipase, proteases, DNA repair enzymes, transferase, methionine sulphoxide reductase, etc.

In ayureda formulation of some *rasayanas* with defined antioxidant properties has been done. Rasayanas are a group of non-toxic polyherbal drug preparation, which are immunostimulatroy and thereby prevent the causation of disease and promote health and longevity.

It is reported that when the balance between ROS producton and antioxidant defences is lost, 'oxidative stress' results which through a series of events deregulates the cellular functions and leads to various pathological conditions, viz. AIDS, ageing, arthritis, asthma, atherosclerosis, autoimmune diseases, broncho-pulmonary dysplasia, carcinogenesis, cardiovascular dysfunction, cataract, diabetes, gastro-duodenal pathogenesis, genetic disorders, inflammatory diseases, ischemia reperfusion injury, liver disorders, muscular dystrophy, neurodegenerative diseases, parkinsons dementia, Alzheimer's disease, amyotropic lateral sclerosis, pulmonary fibrosis, radiation damage, retinopathy, theumatism,skin disease porphyria and senile dementia stroke.

THE ANTIOXIDANT ACTIVITY OF SOME IMPORTANT MEDICINAL PLANTS:

Curcuma domestica, cuscuta reflexa, Daucus carota, Emblica officinalis, Foeniculum, Glycyrrhiza indica, momordica charantia, ocimum sanctum, psoralea corylifolia, santalum album, solanum chirayita, withania somnifera, allium sativum, asparagus racemosus, baccharis coridifolia, bryonia alba, cichorium intybus, cinnamomum zeylanicum, crithmum maritimum, cynara scolymus, Emilia sonchifolia, eucalyptus camaldulensis, eucommia ulmoides, garcinia kola, ginkgo biloba, lavandula angustifolia, lyceum barbarum, Melissa officinalis, murraya koenigii, myrica gale, panax ginseng, picrorrhiza kurroa, piper nigrum, plantago asiatica, prunus domestica, rhazya stricta, epsmarinus officinalis, salvia officinalis, salvia triloba, solanum melongena, solanum tuberosum, syzygium caryophyllatum, thymus zygis, tinospora cordifolia, uncaria tomentosa, zingiber officinale, eucommia ulmoides, olive, hemidesmus indicus, caesalpinia sappan, ocimum spp, rosmarinus officinalis, rubus, ribes and aromia spp, plumbago zeylanica, pilostigma reticulatum, berberis vulgaris, triticum aestivum, acacia mabgium and A. Auriculiformis, rhizophora mangle, diospyros malabarica, ligustrum vulgare, L. delvayanum,

decalepis hamiltonill, sechium edule, hyphaene thebaica, draba memorosa, acacia Arabica, asparagus racemosus, psidium guajava, asparagus racemousus, psidium guajava, vernonia amygdalina, commelina bengalensis, desmodium gangeticum, malus domestica, tilia argentea, crataegi folium, polygonum bistorta, pandanus odoratissimus, hyoscyamus squarrosu, blechnum orientale, pseudarthria viscid, boerhaavia erecta, helichrysum longifolium, calendula officinalis, majorana hortensis, cymbopogon citrates, thymus vulgaris, canthium coromandelicum, carica papaya, dolichandrone atroviens, adina cordifolia, azadirachta indica.

ANTIOXIDANT ACTIVITY OF TERPENOIDS: CAROTINOIDS:

Carotenoids are natural pigments synthesized by plants and microorganisms, but not by animals. Carotenoids are classified as follows: carotenoid hydrocarbons are known as carotenes and contain specific end groups. Lycopnenes have two acyclic end groups. β-Carotene has two cyclohexene type end groups. Oxyjenated carotenoids are known as xanthophylls. Examples of these compounds are a zeaxanthin and lutein (hydroxyl), spirilloxanthin (methoxy). Echinenone(oxo) and anteraxanthin (epoxy).

Carotenoids exert many important functions, among which are the outstanding antioxidant effects in lipid phases by free radical scavenging of singlet oxygen quenching. With regard to antioxidants activity in biological systems, carotenoids appear to be involved protection against both singlet and triple ozygen(as radical chain-breaking antioxidants). The best documented antioxidant action of carotentoids is their ability to quench dinglet oxygen (which is known to be fapable of damaging glipids, DNA and of being mutagenic). This results in an excited acrotenoid, which has the ability to dissipate newly acquired energy through a series of totational and vibrational interactions with the solvent, thus regenerating the original unexcited carotenoid, which can be reused for further cycles of singlet oxygen quenching: $^1O_2 + Q^3\ O_2 + {}^3Q$ where $^1O_2$ represents singlet oxygen, Q denotes quencher molecules, $^3O_2$ and ^3Q denotes triple oxygen and quencher respectively. The quenching activity of a carotenoid mainly depends on the number of conjugated double bonds of the molecule and is influenced to a lesser extent by carotenoid end groups (cyclic or acyclic) or the nature of substituents in carotenoids containgin cyclic end groups. Lycopene (eleven conjugated and two non conjugated double bonds) is among the most efficient singlet ixygen quenchers of the natural carotenoids. The prevention of lipid peroxidation by carotenoids has been suggested to be mainly via singlet oxygen quenching.

β- Carotene is also scavenger of peroxyl radicals, especially at low oxygen tension. This activity may be also exhibited by others carotenoids. The interactions of carotenoids with peroxyl radicals may precede via an shown to be highly resonance stabilized and are predicted to be relativelt unreaction. They may further undergo decay to renerate non radical products and may terminate readical reactions by binding to the arracking free radicals. Carotenoids act as antioxidants by reaction more rapidly with peroxyl radicals than do unsaturated acyl chains. In this process, carotenoids are destroyed.

ANTIOXIDANT ACTIVITIES OF ALKALOIDS: BERBERINE:

The antioxidant activity of berberine has been widely demonstrated. First, it was reported that berberine can scavenge reactive oxygen species (ROS) and reactive nitrogen species (RNS) in similar fashion with flavonoids. For instance, among tha RNS, peroxynitrites (ONOO-) generated through the reaction between nitric oxide ($NO^{\cdot}$) and superoxide anion radical. Secondly, berberine can inhibit lipid peroxidation and show protective effects against low-density lipoprotein (LDL) oxidation. Thirdly, it has inhibitory effects on lipoxygenase and xanthine oxidase, two important ROS-derived sources. Berberine also significantly increased superoxide dismutase activity and decreased superoxide anion and malonidaldehyde (MDA) formation In addition, it was found that berberine can also bind catalyzing metal ions (transition metals like iron and cupper ions), which can reduce the concentration of metal ions in lipid peroxidation.

PREVENTION OF LIPID PEROXIDATION:

Lipid peroxidation refers to the oxidative deterioration of lipids containing any number of carbon-carbon double bonds, such as unsaturated fatty acids, phospholipids, glycolipids, cholesterol esters and cholesterol itself. ROS attack the unsaturated fatty acids which contain multiple double bonds and the methylene CH_2- groups with especially reactive hydrogen atoms, and initiate the radical peroxidaiton chain reactions. Radical scavengers can directly react and quench peroxide radicals to terminate the chain reaction. Lipid peroxidation and DNA damage are associated with a variety of chronic health problems, such as cancer, ageing and atherosclerosis.

Antioxidant compounds may scavenge ROS and peroxide radicals, thereby preventing or treating certain pathogenic conditions. Lipid peroxidation has beeb extensively used as a research model for identifying natural antioxidants as well as the studies of their mechanisms of action. Studies on antioxidants such as vitamins, polyphenols (green tea), flavones and ginsenosides against free radical-induced lipid peroxidatin have beeb undertaken in several systems scuh as lipid, human red cells, huma LDl and rat liver microsomes in homogeneous solution or mecelles.

The antioxidant activity of thiese polyphenols depends significantly on the structure of the molecules, the initiation conditions and the structure of the molecules, the initiation conditions and the microenvitonment of the molecules, the initiation conditions and the microenvironment of the reaction medium. *In vitro* lipid peroxidation such as linoleic acid can be either initiated thermally by using a water soluble azo initiator 2, 2'-azobis 92-amidinopropane) hydrochloride (AAPH) , or initiated by metal ions Fe^{2+} or Cu^{+} with H_2O_2 (Fenton recomposes action). AAPH decomposes at physiological temperature (37^0C) in aqueous solutions to generate alkyl radical (R). , which in the presence of oxygen is converted to the corrrespondin gperoxyl radicals (ROO). Because AAPH is water soluble, the rate of free-radical generation form AAPH can be easily controlled and measured. It has been extensively used as a free-radical initiator for biological and related studies and the haemolysis induced by AAPH provides a good approach for studying membrane damage induced by free radicals. Fe^{2+}or Cu^{+} react with H_2O_2 and generate highly reactive OH. These radicals ('.OH, R. And ROO.) abstract an active methylene hydrogen from linolein acid to form lipid radical and lipid peroxide in the presence of O_2 an dstart the chain reaction. Briefly, linolenic acid substrate (or its analogues) can be incubated with initiator (either AAPH [114] or Fe^{2+}/H_2O_2 in the absence or presence of antioxidants in homogenous solution or SDS micelle. Peroxidaion on the reaction conditions. Hydroperoxide substitution at the C-9 or C-13 positions produces either trans, trans or cis, trans conjugated dienes. These are the major products in the absence of antiouxidants and show characteristic ultraviolet absorption at 235 nm that can be used to monitor the formation of the total hydroperoxides during the peroxidation after separation of the reaction mixture by HPLC in some studies a colour indicator benzoyl leucomethylene blue can be use to reduce the linoleic acid hydroperoxide to linoleic acid hydroxide, while itself is oxidazed to methylene blue which shows a absorption at 666 nm. In the presence of antioxidants, the antioxidant first inhibits the formation of linoleic acid hydroperoxides by scavenging peroxide and .OH radicals and also inhibits the formation of the colour indicator methylene blue by reduction of the linoleic acid hydroperoxide to the linoleic acid hydroxide. By comparing the formation kinetics of hydroperoxide in the presence and absence of antioxidants, the inhibitory in the presence and absence of antioxidants, the inhibitory ability of antioxidants can be evaluated and expressed as the total antioxidant activity. This test has beeb used to identify the key antioxidant in bread crust. By using synthesized methyl esters of the linoleic acid hydroperoxide as the substrate, the reductive activity of antioxidants can be measured. The difference between the total antioxidant activity and the reductive is the radical scavenging activity.

Other models of lipid peroxidation include the lipid peroxidation of LDL, human red cell and pospholipid microsomes. These models are very similar to those of linoleic acid peroxidation. Instead of pure linoleic acid, human red cells, LDL or microsomes are used as the lipid substrate. Erythrocyte membranes are rich in polyunsaturated fatty acids, which are very susceptible to oxidative stress mediated by free radicals. In the human red cell system, briefly, AAPH-PBS solution has beeb to a suspension of erythrocytes in PBS to which an antioxidant is added in advance to a certain concentration, and the suspension is incinated at 37^{o}C. samples are taken from the above incubation mixture and centrifuged, and the supernatant is analysed for haemoglobin (haemolysis) at 540 nm. Peroxidation of polyunsaturated lopids in red cell membranes causes a quick damage and the membrane losses its intrgrity, leading to the release of haemoglobin (haemolysis) and intracellular K^{+} oins. When antioxidants such as curcumin are present the system, peroxyl redicals can be converted to non-reactive species, and thereby the radical-induced lipid peroxidation and haemolysis can be inhibited.

LDL has a highly-hydrophobic core consisting of polyunsaturated fatty acid linoleate and about 1500 esterified cholesterol molecules. The peroxidation of LDL can be initiated either thermally by a water-soluble azo initiator, AAPH, or photochemically by a triplet sensitizer benzophenone. The peroxidation of LDL can be measured by the formation of conjated dienes (absorbance at 235 nm) as above or the rate of oxygen intake. A new method is to quantify the decomposition product of hyroperoxide of LDL oxidation, hexanal, by headspace GC analysis. Hexanal production correlates well with the odiation of polyunsaturated fatty acid in LDL and reflects the degree of LDL odiation *in vitro*. The addition of antioxidants can inhibit the formation of lipid dienes or the rate of oxygen intake. The method from apple peels and green tea leaves, vitamins, and resveratrol and its analogues. Peroxyl radical-initiaed LDL oxidation in these studies is similar to the LDL oxidation under physiological conditions in human being compared with the Cu^{2+}- induced LDL oxidation model.

Similar to erythrocyte membranes, microsomes (especially smooth endoplasmic reticulum) are particularly susceptible to oxidative stress because of their high polyunsaturated fatty-acid content. Iron (Fe^{2+} combined with a reducing reagent) is usually used for generating. OH radicals to induce microsome peroxidation, which can be measured by the TBA method. Antioxidants may inhibit the formation of TBA reactive species. Thus, the antioxidation activity of the antioxidant can be determined.

Lipid peroxidation processes involve radical formations including initiator radicals (R., .OH), and ROO. Radicals. The antioxidant may directly react with initiator radicals or lipid peroxides, and it may also inhibit the formation of active radicals. These mechanisms of action of any antioxidant are critical and warrant for further investigations with radical scavenging with radical scavenging assays and ion chelating tests.

PREVENTION OF DNA DAMAGE:

The .OH and $ONOO^-$ radicals generated from nitric oxide and $O_2^{-\cdot}$ Can react directly with plasmid DNA macromolecules *in vitro* to cleave (or'nick') one DNA strand, causing oxidative DNA damage. Cell death and mutation caused by this DNA damage are implicated in neurodegenerative and cardiovascular diseases, cancer and aging. Treating these conditions with antioxidants is of growing interest. At the same time, the DNA or plasmid damage has beeb used as models for the study and idenfification of antioxidants. A typical research model of DNA damage caused by Cu^+ induced. OH has been developed. Briefly, metal-free plasmid DNA is combined with Cu^{2+} ., ascorbic acid and H_2O_2 at pH 7. Cu^{2+} is reduced to Cu^+ insity with ascorbic acid. The .OH radical generated by Cu^+/H_2O_2 cleaves one DNA strand, causing the normally supercoiled plasmid DNA to unwind. The degree of DNA kamage is assessed using electrophoresis to separate the damaged and undamaged forms. Adding antioixdiants such as selenium can inhibit. .OH- induced DNA damage. Thus, the antioxidant potential of certain compounds canbe quantified and directly compared. DNA damage also produces carbonyls (aldehydes and ketones), which react with TBA to form TBARS which can be measured directly in the aqueous phase by TBARS assay at 532 nm

PREVENTION OF PROTEIN MODIFICATION:

Besides lipid peroxidation and DNA damage, ROS also cause protein modification by nitration or chloration of amino acids. Peroxynitrite, 0=N-O-O^-, formed *in vivo* by the reactionof $O_2^{-\cdot}$ With free radical nitric oxide by a diffusion –controlled reaction, is an powerful oxidant and nitrating agent. `$ONOO^-$ is a much more powerful oxidant $O_2^{-\cdot}$ And can damage a wide variety of molecules including DNA and proteins in cells. $ONOO^-$ and its protonated form peroxynitrous through one- or two-electron oxidation processes. $ONOO^-$ reacts uncleophilically with CO_2 *in vivo* to form introsoperozycarbonate, which is the predominant pathway for $ONOO^-$. $ONOOCO_2^-$ homolyses to form carbonate radical (CO_3^-) and nitrogen dioxide radical (NO_2). .NO_2 is also a RNS which in turn can nitrate tyrosine to nitrotyrosine. These radicals are believed to cause $ONOO^-$ related cellular damage . $ONOO^-$ itself is also a strong oxidant and can react directly with electron-rich

groups, such as sulfhydryls, iron-sulphur centres, zinc-thiolates and the active site sulfhydryl in tyrosine phosphatise. Another pathway utilizes heme protein myeloperoxidase (MOP)-generated HOCI, which reacts with NO_2^- to form nitryl chloride (NO_2Cl), which may spontaneously decompose to NO_2 and Cl. These products may be responsible for the chlorinating and nitrating behaviour of Cl-NO_2. HOCl reacts with a wide varietly of biomolecules including DNA, RNA fatty acid groups cholesterol and proteins. The presence of nitroturosine or chlorotyrosine has been as biomarker of damage by RNS *in vivo*.

These modifications often result in the alteration of protein fuction of structure and, usually, the inhibition of enzyme activites. Proteins containing nitrotyrosine residues have been detected in different pathologic conditions, including diabetes, hypertension and atherosclerosis, all associated with enhanced oxidative stress, including increased production of $ONNO^-$.in order to attenuate the protein modification caused by $ONOO^-$ and HOCl, antioxidants and antioxidant enzyme are used. Antioxidants or enzyme like CAT which can eliminate H_2O_2 should also inhibit the formation of HOCl; likewise, SOD or antioxidant such as curcumin and polyphenols may scavenge $O_2^{-\cdot}$, and inhibit the formation of $ONOO^{-\cdot}$ however, the formation of $ONOO^-$ from nitric oxide and $O_2^{-\cdot}$ Is three times faster than the scavenging of $ONOO^-$ directly by using natural safe ingredients from the medicinal herbs may be a rational alternative for preventive and therapeutic interventions in diseases. Indeed, reactions of $ONOO^-$ with phenoic compounds are widely reported in the literature. Scavenging of $ONOO^-$ by antioxidants nased on assays involving tyrosine nitration is suggested as a useful research tool which may provide additional valuable information on the antioxidant profile of the biomolecules. Generation of $ONOO^-$ in vivo has been implicated in a wide range of human diseases. Agents that are able to protect against $ONOO^-$ dependent damage may be therapeutically useful.

CONCLUSIONS:

Oxidative stress caused by ROS results in an increased risk for many diseases such as inflammatory disease, cardiovascular disease, cancer, diabetes, Alzheimer's disease, cataracts, autism and aging. Antioxidants may directly react with the reactive radicals ro destroy them by accepting or donating electron(S) to eliminate the unpaired condition of the radical, or they may indirectly decrease the formation of free radicals by inhibiting the activites or expressions of free radical generating enzymes or by enhancing the activites and expression of other antioxidant enzymes. Many research models have been established inchemical and/or biological systems for studying the mechanisms of action of antioxidants and for idenrifying new antioxidants, especially

form natural substances. We have reviewed tha antioxidant mechanisms and experimental approaches such as direct radical scavenging, ion chelating and enzyme activities in cell-free chemical systems. The preventive and inhibitory effects of antioxidants on lipid peroxidation. DNA damage and protein modification caused by ROS are also discussed. The chemical approaches are simple and facilitate the study of the total antioxidant activity of antioxidants and the precise mechanisms of action of antioxidants. However, cell-free systems do not take bioavailability and metabolic factors into consideration, and thereby the data generated from these systems require the confirmation form cell-based systems or *in vivo* studies. Recently , clinical data has shown a correlation between various types of oxidative stress measurements and clinical findings in actual individuals with diseases. For example, a significant correntlation was found between the degree of mercury intoxication and oxidative stress biomarkers present in autism patients. Also, the correlation has been observed between tissue culture models os oxidative stress and the actual pathologies observed in clinical diseases.

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