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Review Article

NATURAL ANTIOXIDANTS OUR BODYGUARD: A REVIEW

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Abstract

An antioxidant is a molecule that inhibits the oxidation of other molecules. Oxidation forms free radicals that damage the cells. Natural antioxidants are found in most fresh food, capable of removing oxidative stress by removing free radical intermediates, and inhibit other oxidation. When a cut apple turns brown, that is through oxidation. Lemon juice, a natural antioxidant, will slow the process. Natural antioxidants perform the same function in the body. So, natural antioxidants terminate these chain reactions & oxidative damage. Natural antioxidants are found to show effects in preventing many diseases like CVS, cancer, eye problems, lung diseases, skin protection, immunity, ageing and many others. Antioxidants are widely used as preservative in food and cosmetics. Also to prevent degradation of rubber and gasoline. Plants and animals have complex system of multiple types' antioxidants such as glutathione, vitamin C, vitamin E, vitamin A, as well as enzymes like catalase, superoxide dismutase, and various peroxidases. Insufficient level of antioxidants, or inhibition of antioxidant enzyme, increases oxidative stress and it starts to damage or kill cells. Oxidative stress damage cell structure and cell function by over reactive oxygen containing molecule. So, it seems that a healthy diet is one which contains a good source of natural antioxidants.

Keywords: Oxidative stress, ROS, Free radicals, Scavenge, Chain reaction.

INTRODUCTION

Oxidation: Oxidation is a chemical reaction that can produce free radicals, which start chain reactions that damage cells. It is generally accepted that oxidation is a typical free radical chain process consisting of initiation, propagation and termination steps.

1. **Initiation**: thermal or photochemical hemolytic cleavage of a lipid Substrate (RH, i.e., an unsaturated fatty acid).

2. **Propagation**: two different reactions can be visualized:

2.1 Addition of molecular oxygen to lipid radicals (R•) and formation of peroxyl radicals (ROO•).

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2.2. Abstraction of a hydrogen atom from RH by ROO• to generate a lipid Hydro peroxide (ROOH) and another radical R•.

3. **Termination**: Radical – Radical coupling reaction that interrupt the free radical chain propagation process.[1]

Oxidants

1ROS and RNS: - Oxygen (O2) is essential to the life of aerobic organisms. However, its metabolites represent a potential threat to all living organisms. Indeed, O2 is metabolized in animal tissue by successive reductions in superoxide anion (O2), hydrogen peroxide (H2O2), and hydroxyl radical (.OH). These different metabolites are called reactive oxygen species (ROS). ROS are either free radicals (with an unpaired electron in their outer orbital sphere) (O2. .OH) or nonradical(H2O2, singlet oxygen (1O2) Nitric

oxide (NO.), some functions of which overlapwith ROS, is synthesized from L-arginine and oxygen by enzymes called NO synthases and is part of the reactive nitrogen species (RNS) [2]

2. OxidativeStress: - Oxidative stress is defined by an imbalance between ROS and antioxidants, ROS being in excess. Moreover, excessive production of ROS or RNS induces mitochondrial damage, leading to a sharp decrease in ATP and cell death by necrosis [2]

Antioxidants

Antioxidants inhibit the production of ROS by direct scavenging, decrease the amount of oxidants in and around our cells, prevent ROS from reaching theirbiological targets, limit the propagation of oxidants such as the one that occurs during lipid peroxidation, and thus oxidative stress [2] Types of antioxidants are

1. Endogenous Antioxidants: - Endogenous antioxidants are essentially enzymes that catalytically remove oxidants. Major endogenous antioxidants are superoxide dismutase, superoxide reductase, catalase, and glutathione peroxidase. These enzymes play a key role in decreasing the content of oxidants and preventing oxidative damage. Other endogenous antioxidant molecules, such as hemeoxygenase, minimize the availability of oxidants. This enzyme is strongly induced by oxidative stress and removes an oxidant (heme) while generating a putative antioxidant (bilirubin that is sensible to 1O2) and a prooxidant (iron). In addition, high ferritin levels result in an increased iron scavenging capacity that may confer increased resistance to oxidative stress [2]

2. Exogenous Antioxidants: - Exogenous antioxidants include antioxidants that cannot be synthesized by our body such as vitamins, trace elements, and phytoantioxidants. Vitamin E (tocopherol) is the most powerful liposoluble antioxidant. It inhibits the peroxidation of membrane lipids. It reacts with free radicals to form the radical tocopheryl, a stable substance that stops the chain reaction of the membrane lipids. It works in conjunction with other antioxidants such as vitamin C and selenium. Vitamin C is a water-soluble vitamin and has a strong antioxidant activity that protects cells against damage by free radicals [2]

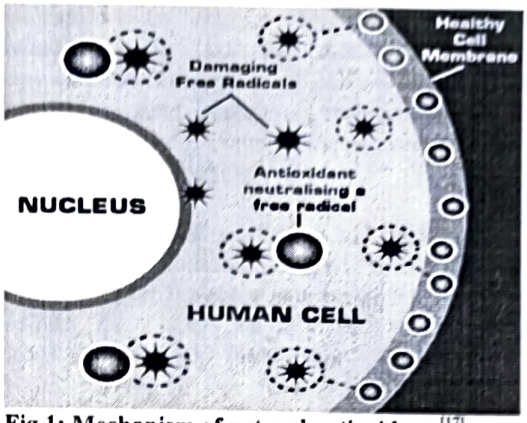

Fig 1: Mechanism of natural antioxidant [17]

Antioxidants help in:

- . Destroying the free radicals that damage cells.
- Promoting the growth of healthy cells.
- Protecting cells against premature, abnormal ageing.
- Help fight age-related macular degeneration.
- Provide excellent support for the body's immune system [3]

CLASSIFICATION [3]

- **Enzymatic antioxidants**: -

1. Primary antioxidants e.g.-SOD, Catalase, Glutathioneperoxidase.
2. Secondary enzymes e.g. - Glutathione reductase,Glucose 6-phosphatedehydrogenase.

- **Non-Enzymatic antioxidants**:-

1. Minerals e.g.-Zinc, Selenium
2. Vitamins e.g.-Vitamin A, Vitamin C, Vitamin E,Vitamin F
3. Carotenoids e.g.-_-carotene, Lycopene, Lutein,Zeaxanthin
4. Low molecular weight Antioxidants e.g.-glutathione,uric acid
5. Organosulfur compounds e.g-Allium, Allylsulfide,indoles
6. Antioxidant cofactors e.g.- Coenzyme O10
7. Polyphenols – _ Flavonoids-
   - Xanthones- e.g.- Mangostin
   - Flavonoids- e.g.- Quercein, Kaempferol
   - Flavanols- e.g.- Catechin, EGCG
   - Flavanones- e.g.- Hesperitin
   - Flavones- e.g.- Chrysin
   - Isoflavanoids- e.g.- Genistein
   - Anthocyanidins- e.g.-Cyanidin, Pelagonidin Phenolic Acid-

- Hydroxycinnamic acids- e.g.- Ferulic, p-coumaric
- Hydroxybenzoic acid –e.g.- Gallic acid, Ellagic acid Gingerol, Curcumin

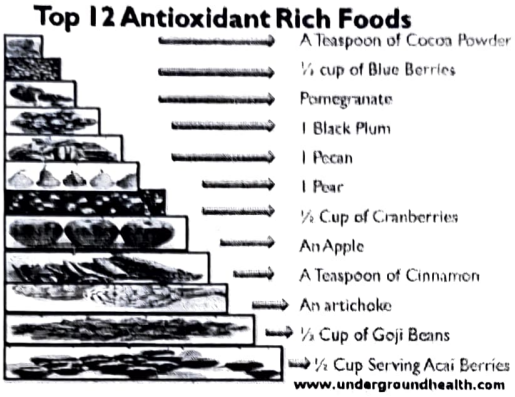

Fig 2: Natural Antioxidant Sources:-[18]

Quantification of Antioxidant Capacity

1. ET- based assay
2. HAT – based assay
3. Electrochemical based assay

APPLICATIONS OF NATURAL ANTIOXIDANTS:-

1. In skin diseases : -

1 Green Tea :- Green tea contains four major flavonoids: epicatechin,epicatechingallate, epigallocatechin, and epigallocatechin-3 gallate. These molecules have the ability to scavenge ROS: O2, OH, H202 [2].

2 Rosemary:- Rosemary contains various antioxidants, in particular phenolic diterpenes, carnosol and carnosic acid . These lipophilic molecules attack lipid free radicals, thereby enabling the reduction of lipid peroxidation and inhibiting oxidative damages to skin surface lipids . Pretreatment of human fibroblasts with carnosic acid resulted in the suppression of metalloproteinase-1 messenger RNA elevation caused by UVA irradiation. Carnosic acid also has photoprotective potential

3 Grape Seeds:- Grape seeds are major sources of resveratrol and quercetin. The stilben resveratrol inhibits lipid peroxidation induced by UVB and significantly decreases UVB-induced skin thickness and edema in hairless mice . The iron chelator flavonoid quercetin maintains and protects the activities of glutathione peroxidase, catalase, and superoxide dismutase after exposure to UV

4 Tomato:- Tomato is rich in lycopene, a widely studied powerful antioxidant and anticarcinogenic carotenoid with strong reducing ability and the most effective carotenoid in the capture of 1O2. Lycopene scavenges lipid radicals, reduces lipid peroxidation, and prevents erythema caused by UV radiation on the skin [2]

2. InAgeing:-

Mitochondrial ROS production and oxidative damage to mitochondrial DNA results in ageing. Further increased lipid peroxidation in cellular membranes due to oxidative stress leads to fatty acid unsaturation. The most recent review on free radicals and ageing' emphasizes that caloric restriction (CR) is the only known experimental manipulation that decreases rate of mammalian ageing, Calorie-restricted mitochondria, similar to those of long-lived animal species, avoid generation of ROS efficiently at complex I with pyruvate and malate. The mitochondrial oxygen consumption remains unchanged, but the free radical leak from electron transport chain is decreased in CR.[4] Vitamin E like antioxidants thus are helpful in preventing ageing. Dietary fruits and vegetables containing ascorbate, carotenoids and tocopherol show significant effect in ageing.

3. In Cardiovascular diseases ;-

Oxidative damage to cholesterol component of the low-density lipoprotein (LDL) leads to oxidised LDL by a series of consecutive events. This induces endothelial dysfunction, which promotes inflammation during atherosclerosis and vascular thrombosis (Heart attack, Shock). Oxidative stress involved in other clinically recognised conditions such as smoking, advanced glycation end-products (AGEs) in diabetes mellitus, shear stress etc. intensify endothelial dysfunction.[4]

Resrveratrol a polyphenolic antioxidant found in skin of grapes and in found in red wine is useful in treatment of acute I-R injury. It also has cardioprotective effect due to enhancement of NO production.[14] Vitamin E, Vitamin C, carotenoids, curcumin, caffeine from tea coffee, glycerrhizinetc shows activity in preventing CVS.

4. In Neurodegenerative diseases:-

Neurodegenerative diseases comprise a condition in which nerve cells from brain and spinal cord are lost leading to either functional loss (ataxia) or sensory dysfunction (dementia). Mitochondrial (Mt) dysfunctions and excitotoxicity and finally apoptosis have

been reported as pathological cause for aging and neurodegenerative diseases such as Parkinson's disease (PD), Alzheimer's disease (AD), Multiple Sclerosis (MS) and amyolotrophic lateral sclerosis (ALS).[10]

Nervous tissue including brain is highly susceptible for free radical damage due to high content of lipids especially polyunsaturated fatty acids. Increased levels of oxidative stress alterations in levels of antioxidant enzymes such as catalase and CuZn- and Mn-SOD in neurons is observed in Alzheimer's disease (AD) . Increased protein oxidation, protein nitration and LP occur in neurofibrillary tangles and neuritic plaques. Lipid peroxidation may promote neuronal death in AD by multiple mechanisms that include impairment of the function of membrane ion-motive ATPases (Na+/K+-ATPase and Ca2+-ATPase), glucose transporters and glutamate transporters. Lipid peroxidation leads to production of the aldehyde 4-HNE that appears to play a central role in the neurotoxic actions.[4]

Phenolic phytochemicals, such as curcumin from turmeric, resveratrol from grape and wine, and EGCG from green tea, not only exhibit potent anti-oxidative and anti-inflammatory properties, acting to scavenge radicals and regulate inflammatory responses ,but also cross BBB to act on target o AD.These compounds activate endogenous pathway to enhance defense and protect against a beta protein and deposition of plaques .[11]

5. In Cancer :-

Phenolic compounds, including their subcategory, flavonoids, are present in all plants and have been studied extensively in cereals, legumes, nuts, olive oil, vegetables, fruits, tea, and red wine. Many phenolic compounds have antioxidant properties, and some studies have demonstrated favorable effects on thrombosis and tumorogenesis and promotion. . Various phytoestrogens are present in soy, but also in flaxseed oil, whole grains, fruits, and vegetables. They have antioxidant properties, and some studies demonstrated favorable effects on animal and cell culture models of cancer. Hydroxytyrosol, phenolics in olives and olive oil, is a potent antioxidant. Resveratrol, found in nuts and red wine, has antioxidant, antithrombotic, and anti-inflammatory properties, and inhibits carcinogenesis. Lycopene, a potent antioxidant carotenoid in tomatoes and other fruits, is thought to protect against prostate and other cancers, and inhibits tumor cell growth in animals. Organosulfur compounds in garlic and onions, isothiocyanates in cruciferous vegetables, and monoterpenes in citrus fruits, cherries, and herbs have anticarcinogenic actions in experimental models, as well as cardioprotective effects.

DNA is a major target of free radical damage. The damages induced are strand breaks (single or double strand), base damage yielding products as 8hydroxyguanosine, thymine glycol or abasic sites, damage to deoxyribose sugar as well as DNA protein cross links. These damages can result in mutations that are heritable change in the DNA that can yield cancer in somatic cells or foetal malformations in the germ cells. Cancer develops through an accumulation of genetic changes. Initiating agents can be tobacco smoking and chewing, UV rays of sunlight, radiation, viruses, chemical pollutants, etc. Promoting agents include hormones (androgens for prostate cancer, estrogens for breast cancer and ovarian cancer). These can initiate carcinogenesis.[4]

The curcumin seem to act strongly *via* inhibition of arachidonate metabolism and through reducing cell proliferation and inducing apoptosis. Dietary administration of curcumin during the promotion/progression stage of colon carcinogenesis significantly inhibits tumor development . Similar levels of inhibition of colon tumorigenesis were achieved when 0.2% curcumin was administered either during initiation and post initiation periods or promotion/progression stage.[5]

6. In Immunity :-

The proliferation ofT and B cells, natural killer cells, and lymphokine-activated killer cells that is required to mount an effective defense against pathogens and tumor cells

appears to be inhibited markedly with age and upon exposure to oxidants It is counteracted by dietary antioxidants. The age-associated decrease in cell-mediated immunity may be due to a decreased level of certain small molecule antioxidants and antioxidant enzyme activities.[6]

The importance of oxidative stress in the regulation/dysregulation of immune system, the use of antioxidants in such diseases has been reasonably proposed. Joint inflammation in rheumatoid arthritis (RA) is characterized

by invasion of T cells in the synovial space and proliferation of activated macrophages and fibroblasts in the synovial intima Therefore, in the rheumatic joint there is an increased activity of fibroblasts and leucocytes which produce ROS . Antioxidants have been successfully used as adjuvant therapy in RA In fact, autoimmune lymphoproliferative syndrome (ALPS), MS, type 1 diabetes and multiple autoimmune syndrome, have been linked to decreased Fas functionality and, as discussed previously, antioxidants may up-regulate Fas and FasL in vitro. Increasing evidence provides support that oxidative stress and apoptosis are closely related physiological phenomena and are implicated in diseases including autoimmune diseases. Therefore molecules that target both apoptosis-related signal transduction and oxidative stress, like antioxidants, are likely to result in the improvement of these pathologies. [12]

7. In Cataract :-

A cataract is a cloudy or opaque area in the lens of the eye.[9] Cataracts are characterized by electrolyte disturbances resulting in osmotic imbalances. Derangements in the function of the membrane resulting in ion imbalance may be due to increased membrane permeability or to a depression of the [Na.sup.+]/[K.sup.+] pump because of interference with the enzyme [Na.sup.+]/[K.sup.+] ATPase. Cataracts are also characterized by aggregates of insoluble proteins.[8] Oxidative insult appears to be involved as a precipitating factor in all cataracts. Lens proteins typically remain in their reduced form. However, in cataractous lenses, the proteins are found in an insoluble, oxidized form. Oxidation cause higher levels of hydrogen peroxide incataractous lenses Normally the lens contains significant levels of reduced glutathione (GSH), which keeps the proteins in their reduced form. However, there are significantly lower levels of GSH in cataractous lenses.[8]

Primary defence that protect the lens from oxidative damage include antioxidant vitamins like vitamin C, vitamin E, carotenoids and antioxidant enzyme system like superoxide dimustase, catalase, glutathione redox cycle. These molecules prevent damaged proteins.[7]

Various antioxidants may be helpful in prevention or reducing the risk of cataract formation. Some may even help improve vision in certain cases. However, not enough research is available to determine which one of these supplements, in what dosage, or in what combinations are most helpful. [9]

In a study of male health professionals in the United States, 36,644 participants, ages 45-75 years, were followed for eight years with periodic dietary questionnaires. Men in the highest quintile for lutein and zeaxanthin intake had a 19-percent decreased risk of cataract extraction when smoking, age, and other risk factors were controlled for.[8]Luteinis potentially helpful in slowing the process of cataract formation. Lutein is a carotenoid found in green and leafy vegetables such as kale and spinach, and it is also available as a supplement. [9]

VitaminE: (1) vitamin E decreases oxidative stress in cataractous lenses; (2) part of vitamin E's protective effect is due to enhancement of GSH levels; and (3) vitamin E seems to be more protective for cortical than nuclear cataracts, at least in this short-term study.[8]

Vitamin C: - Animal experimentation has show some connection of ascorbic acid and its role in cataract formation. Cataracts induced in chick embryos by the application of hydrocortisone were prevented by the introduction of vitamin C to the developing embryo. In addition, vitamin C slowed the decline in GSH levels, which occurred with the cortisone treatment.[8]

Riboflavin :- Riboflavin is a precursor to flavin adenine dinucleotide (FAD), which is a coenzyme for glutathione reductase. In vitro evaluations of surgically removed cataracts have confirmed inactivity of glutathione reductase enzyme activity in a significant number of cataracts. [8]

Melathion :- The pineal hormone, melatonin, is a potent antioxidant and show effect on prevention of cataracts. Injections of melatonin have been found to inhibit both chemical- and UVB-induced cataracts by directly quenching lipid peroxides and indirectly by enhancing the production of the endogenous antioxidant GSH.[8]

8. InCOPD:-

COPD is a group of serious lung diseases that includes emphysema and chronic bronchitis. COPD is typically considered a disease due to cigarette smoking; however it can also occur in non-smokers but expected, this lung condition is more common in smokers, males, older adults, and persons living in urban areas. Oxidative stress and chronic inflammation are responsible for pathogenesis of chronic

obstructive pulmonary disease (COPD). Oxidative stress has important consequences including oxidative inactivation of antiproteases and surfactants, mucus hypersecretion, membrane lipid peroxidation, alveolar epithelial injury, remodeling of extracellular matrix, and apoptosis. Therefore, targeting oxidative stress with antioxidants or boosting the endogenous levels of antioxidants is likely to be beneficial in the treatment of COPD. Antioxidant and/or anti-inflammatory agents such as thiol molecules (glutathione and mucolytic drugs, such as N-acetyl-L-cysteine and N-acystelyn), dietary polyphenol (curcumin -diferuloylmethane, a principal component of turmeric), resveratrol (a flavanoid found in red wine), green tea (theophylline and epigallocatechin-3- gallate), ergothioneine (xanthine and peroxynitrite inhibitor), quercetin, erdosteine and carbocysteine lysine salt, have been reported to control NF-kappaB activation, regulation of glutathione biosynthesis genes, chromatin remodeling and hence inflammatory gene expression. Since a variety of oxidants, free radicals and aldehydes are implicated in the pathogenesis of COPD it is possible that therapeutic administration of multiple antioxidants will be effective in the treatment of COPD.[13]

It is benefit to have regularly drinking fresh vegetable juices that include carrot, celery, beet, parsley, cucumber, and others.

Vitamins C, D, and natural E complex could be of benefit

Omega- 3 fatty acids can be anti-inflammatory agents. Japanese researchers at Kagoshima University Hospital found that supplements of omega-3 fatty acids appeared to improve patients' breathing difficulties -- possibly by countering the airway inflammation seen in those with COPD. Omega-3 polyunsaturated fatty acids are found largely in oily fish, and to a lesser extent in flaxseed, walnuts, soybeans and canola oil. Half of the 64 patients drank a liquid supplement rich in omega-3 fats each day; the other half drank a supplement containing omega-6 fats, another type of polyunsaturated fat found in many foods, including vegetable oils and meat. After two years, patients in the omega-3 supplement group showed an overall improvement on tests that measured their breathing during a short bout of exercise. [13]

Acetylcysteine, Glutamine ,BCAA supplements could be helpful for protein synthesis.

Creatine may help with muscle strength and endurance.

Ginseng improves pulmonary functions and exercise capacity in patients with COPD. Ginseng is a root that has been used to treat patients with various illnesses .The purpose of this study was to evaluate the effects of Ginseng extract (G115) on Pulmonary Function Tests (PFTs), Maximum Voluntary Ventilation (MVV), Maximum Inspiratory Pressure (MIP) and Maximal Oxygen Consumption (VO2max) in patients with moderately-severe Chronic Obstructive Pulmonary Disease. Results: Ginseng 100 mg bid for three months, but not placebo, improved PFTs, MVV, MIP and VO2 max in patients with moderately-severe COPD with no side effects[13]

9. In Reducing exercise damage:-

Plant antioxidants such as lycopene, vitamin C, carotenoids, and stereoisomers of carotenoids should be integrated in the prevention of exercise asthma Studies on the use of vitamin C effect on airways requires measurement of alterations in airway tone and airway obstruction, such as occurs after exercise-induced bronchospasm, or in

NO2-induced airway hyper responsiveness. In asthmatic patients, pretreatment with ascorbic acid has been and resistance to degenerative conditions . LYC-OMATO TM is a new enriched lycopene product of tomato containing other bioactive ingredients such as tocopherols, carotenoids, phytoene. The effect of LYC-O-MATO on hyperreactive airways was examined shown to prevent the significant alterations in pulmonary functions induced by exercise. A natural isomer mixture of b-carotene from the alga Dunaliellabardawil was recently shown to prevent EIA. Studies show the prevention of EIA by lycopene supplementation.It indicated that lycopene and other carotenoids play an important role in human health at rest and following the physical provocation of exercise.show significant results in COPD.[16]

10. In boosting fertility:-

Free radicals have ability to directly damage sperm DNA by attacking purine and pyrimidine bases and deoxyribose backbone. Normally sperm DNA is packed by protamine which prevent attack of free radical. But in infertile men the protamine effect is deficient and sperm DNA is readily attacked by ROS. It also initiate apoptosis in sperm. During normal

conception, oxidative damage to sperm membrane will block fertilization. smoking, dietary deficiencies, excessive alcohol consumption, extreme exercise, urinogenital infections, systemic infections, autoimmunity, chronic diseases like diabetes increases oxidative stress and hence infertility.

Oral antioxidant Astaxanthine, carnitine or combination of cysteine, beta carotene, vitamin E and essential fatty acid shows reduction in seminal ROS level. 1gram of vitamin C, and vitamin E reported significant sperm DNA damage. But still use of antioxidant improves pregnancy chances is less clear.[15]

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