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ROLE OF ANTIOXIDANTS IN PREVENTION OF CANCER : A REVIEW

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ABSTRACT

The realization that reactive oxygen species and oxidative stress play an important role in the etiology and progression of major human degenerative diseases has triggered enormous and worldwide interest in endogenous and exogenous antioxidants. Antioxidants are capable of stabilizing, or deactivating, free radicals before they attack cells. Antioxidants are absolutely critical for maintaining optimal cellular and systemic health and well-being. A biological antioxidant may be defined as "a substance present in low concentrations compared to an oxidizable substrate (eg., proteins, lipids, carbohydrates and nucleic acids) that significantly delays or inhibits oxidation of a substrate. Antioxidants may be considered as the scavengers of free radicals". To protect the cells and organ systems of the body against reactive oxygen species, humans have evolved a highly sophisticated and complex antioxidant protection system.It involves a variety of components, both endogenous and exogenous in origin, that function interactively and synergistically to neutralize free radicals.

Keywords:-Antioxidants, Free Radicals, Oxidizable Substrate

INTRODUCTION

Even with improved living standard of modern life, many diseases still develop and the factors are likely to be as follows: imbalanced diet, overly consuming high levels of calories, absorbing few fibers, and the lack of vitamins and mineral substances. As a result, the patients of all kinds of chronic diseases are increasing by record numbers.

Free radicals are atoms or molecules that contain one or more unpaired electrons. Many radicals are highly reactive and can function as reducing or oxidizing agents by donating electrons to or removing electrons from other molecules. Small amounts of free radicals are constantly being generated in all living organisms. Although free radicals are potentially harmful to cellular components, a substantial body of evidence supports a role for these highly reactive chemical molecules in fundamental cellular reactions and cell–cycle regulation.

Nature has endowed each cell with adequate protective antioxidant mechanisms against any harmful effects of free radicals for eg., superoxide dismutase (SOD), glutathione peroxidase, glutathione reductase, thioredoxin, thiols and disulfide bonding are buffering systems in every cell. Antioxidants are substances or agents that scavenge reactive oxygen metabolites, block their generation or enhance endogenous antioxidants capabilities [1]. Moureu&Dufraise (1921) introduced the term "antioxygen" to describe these compounds that act catalytically by retarding oxidation [2].

Free Radicals

Oxygen is a highly reactive atom that is capable of becoming part of potentially damaging molecules commonly called "free radicals." A free radical can be defined as chemical species possessing unpaired electron [3].Free radicals are capable of

attacking the healthy cells of the body, causing them tolose their structure and function. Reactive oxygen species (ROS) is a term which encompasses all highly reactive, oxygen-containing molecules, including free radicals. Types of ROSinclude the hydroxyl radical (OH^-), the superoxide anion radical ($SO2^-$), hydrogen peroxide (H2O2), singlet oxygen (O^-), nitric oxide radical (NO^-), hypochlorite radical ($HOCl^-$), and various lipid peroxides. All are capable of reacting with membrane lipids, nucleic acids, proteins and enzymes, and other small molecules, resulting in cellular damage [4].

VARIOUS ROS & CORRESPONDING NEUTRALIZING ANTIOXIDANTS

Free radicals	**Corresponding neutralizing antioxidants**
Hydroxyl radical	Vitamin C, Glutathione, Flavonoids, Lipoic Acid
Superoxide radical	Vitamin C, Glutathione, Flavonoids, SOD
Hydrogen peroxidase	vitamin C, Glutathione, Beta Carotene, Vitamin E, CoQ10, Flavonoids, Lipoic Acid
Lipid peroxides	B- carotene, Vitamin E, ubiquinone, flavonoids, Glutathione peroxidas

ROS are generated by a number of pathways. Most of the oxidants produced by cells occur as [5]

1. A consequence of normal aerobic metabolism: approximately 90% of the oxygen utilized by the cell is consumed by the mitochondrial electron transport system.
2. Oxidative burst from phagocytes (white blood cells) as part of the mechanism by which bacteria and viruses are killed, and by which foreign proteins (antigens) are denatured.
3. Xenobiotic metabolism, i.e., detoxification of toxic substances.

Consequently, things like vigorous exercise, which accelerates cellular metabolism; chronic inflammation, infections, and other illnesses; exposure to allergens and the presence of "leaky gut" syndrome; and exposure to drugs or toxins such as cigarette smoke, pollution, pesticides, and insecticides may all contribute to an increase in the body's oxidant load[5].

Oxidative stress and disease

The body is normally in a steady state condition with free radicals being continuously generated andquenched. However, the accumulated long-term damage done by free radicals is implicated innumerous degenerative diseases. Evidence from many has heavily implicated oxidative stress in aspectrum of diseases and of states of body dysfunction, Oxidative stress has been shown variouslyas depressed levels of antioxidant substances (e.g., vitamin E, urate), low levels of enzymes whichform part of the antioxidant defence system, and increased levels of oxidation products (e.g.,malondialdehyde, DNA damage).

A well-known example of an oxidation product apparently leading to disease is oxidized cholesterolin low-density lipoprotein (LDL). This is more atherogenic than native LDL, thereby implicatingoxidative stress in atherosclerosis and coronary heart disease (U-ID)[6]. The following is a partial list of the conditions considered to be associated with oxidative stress: in atherosclerosis and coronary heart disease (CHD).

The following is a partial list of the conditions considered to be associated with oxidative stress; animpaired immune system and increased risk of infectious disease [7]; cancer [8]; diabetes (bothnoninsulin-dependent and insulin-dependent diabetes) [9,10]; autoimmune conditions includingrheumatoid [11] and ankylosing spondylitis [9]; various respiratory diseases [12]; eye disease,including cataracts [13] and retinal damage leading to age-related macular degeneration [14]; Alzheimer's disease[15]; and schizophrenia [16].

How important are antioxidants?

The possible benefit of vitamin C and p-carotene has been studied in other conditions apart fromcancer and CHD. Epidemiological evidence suggests that vitamin C protects against cataracts [13] asthma [12] and a decline in pulmonary function [17]. As emphasized earlier such associationsmust be viewed cautiously. However, in the case of vitamin C and asthma, there is also somesupporting evidence from intervention studies [12]. Supplemental doses of p-carotene and ofvitamin C each help prevent oxidative damage of DNA [18, 19], while O-carotene also improvesimmune function [20].

Studying the relationship between antioxidant status and disease has proven to be a highlyprofitable line of research. It has expanded our knowledge concerning the etiology of numerousdiseases and the means by which they might be prevented. But it is essential to take a balancedperspective and avoid the danger of over-enthusiasm for the potential of antioxidants.

The importance of the association between oxidative stress and disease should not be exaggerated.Halliwell et al [21] pointed out that disease processes can give rise to oxidative stress (in addition tothe reverse). Halliwell [22] also noted that: "In most human diseases oxidative stress is a secondaryphenomenon, not the primary cause of the disease." Likewise, Dusinska *et al.* [9] caution that therole of oxidative DNA damage in carcinogenesis has not been proven and that there are manyinconsistencies in therelationship. Red wine has significant antioxidant activity [23] but evidencefrom case-control and prospective studies indicate that it has a no greater protective associationwith CHD than any other type of alcoholic beverage [24].

Taking the evidence as a whole it is difficult to escape the lack of convincing evidence that placesoxidative stress at the center of any disease process or gives antioxidants a major role in theprevention of disease. While many studies have shown associations between intake of antioxidantsand disease risk, very few studies have provided evidence that antioxidants actually prevent anydisease. Conversely, there is strong evidence that fruits and vegetables prevent cancer, CHD andpossibly other diseases. We cannot at this time say how much of this, if any, is due to antioxidantsand how much to nutrients and phytochemicals.

Role of vitamins as antioxidants

Antioxidants namely Vitamin A, E, C, and lycopene as they are the mostcommonly used antioxidants in treatment of oral leukoplakia to assess the outcomemeasures such as clinical resolution, adverse effects, recurrence and malignanttransformation.

Vitamin A

Retinoids are promising chemopreventiveagents. They exert a beneficial effect onepithelial differentiation and can inhibitmalignant transformation and suppress tumorpromotion; hence more clinical trials are triedwith vitamin A and its analogues than otherantioxidants like lycopene, alpha-tocoferol andascorbic acid [25]. Fat soluble vitamin A mainly obtained from animal foods like meat, milk, egg yolk etc., and main function of vitamin A in retinal form is to maintain vision [26] and main tanance of epithelial integrity and is needed for proper haematological, immune and reproductive functions of the body.

Theeffects of retinoids are mediated by retinoid acid receptors (RARs) and retinoid X receptors (RXRs). Three subtypes, designated as α, β and both RARsand RXRs, have been described. Recently, retinoids have been implicated in the induction of cell death in many tumor-derived culture cell systems in bothretinoid receptor-dependent and independent manners. The continued development of new synthetic drugs to up-regulate RA receptors and receptorindependent drugs would be valuable. It appears that exploiting the apoptotic potential of Oral Squamous Cell Carcinoma would lead to contemporarytherapies that might be less toxic to normal cells due to their physiologically controlled survival pathways. It is suggested that these newer therapies wouldalso be effective in treatment of epithelial dysplasia. Ideally, the root of cancer control lies in instituting chemoprevention.

In addition to thechemotherapeutic and chemopreventive agents, a number of dietary components and micronutrients are emerging with considerable potential for theinduction of apoptosis. These agents include green tea constituents (EGCG and others), and a number of other phytochemicals, such as carotenoids(lycopene) and retinoids [27].

Vitamin E

Vitamin E exhibits antioxidant properties by acting as a lipid soluble free radical scavenger in cell membrane. Thus, vitamin E may be involving in both initiation and promotion stages. Among the other potentially anti-carcinogenic effect of vitamin e are its ability to inhibit the formation of the carcinogenic chemical nitrosamine from nitrites in some foods, and its ability to promote immune system function [28]. Tocoferol (AT) is the commonest and most active form of vitamin E. It is found in plant oil, margarine, and green leaves. Tocoferol is an effectiveantioxidant at high levels of oxygen, protecting cellular membranes from lipidic peroxidation. Main actions of AT includes;

- Free radical scavenging
- Maintenance of membrane integrity,
- Immune function
- Inhibition of cancer cell growth/differentiation
- Cytotoxicity
- Inhibits mutagenicity and nitrosamine formation
- Inhibition of DNA and RNA, protein synthesis in cancer cells

Recent studies by BalwantRai et al (2008) [29] have proved that antioxidants such as Vitamin C and Vitamin E may be utilized in oral Lichenplanus patients to counteract free radical mediated cell disturbances.

Vitamin C

Vitamin C (ascorbic acid) also act as antioxidant, and through its ability to scavenge free radicals, it may be protective effects on biopolymers such as DNA. Like vitamin E, vitamin c may be protective for both initiation and promotion of carcinogenesis. Also, like vitamin E, it is thought to prevent formation of nitrosamine (by converting nitrite to nitrous oxide) and to influence immune system function. Vitamin C has also been reported to affect liver enzymes responsible for detoxification and transformation of carcinogens [28]. L-ascorbic acid (L-AA), the so-called vitamin C, is found in citrus fruits such as kiwi, strawberries, papaya, and mango. It has been suggested that a dailyintake of at least 140mg/day is required for smokers because they usually present a reduction of the L-AA concentration in serum leukocytes. L-AA hasanti-oxidizing properties and reacts with superoxide produced as a result of the cells' normal metabolic processes; this inactivation of superoxide inhibitsthe formation of nitrosamines during protein digestion and helps avoid damage to DNA and cellular proteins [30]. LAA apart from being antioxidant also hasfollowing actions:

- Enhances chemotaxis, phagocytosis, collagen synthesis
- Inhibits nitrosamine formation
- Enhances detoxification via cytochrome P 450

- Blocks formation of fecal mutagens
- Reduces oncogene expression

Other antioxidants

Lycopene

The prominent carotenoid in serum is the antioxidant red pigment called lycopene. This is a fat-soluble red pigment found in some fruit and vegetables.The primary sources of lycopene include tomatoes, apricots, papaya and other yellow fruits. In particular, lycopene and other carotenoids rich foods alsoare inversely related to upper digestive tract neoplasms including oral cancer [27]. Lycopene has been hypothesized to prevent carcinogenesis andatherogenesis by protecting critical cellular biomolecules, including lipids, lipoproteins, proteins, and DNA. Lycopene has the uncommon feature of gettingbound to chemical species that react to oxygen, thus being the most efficient biological antioxidizing agent [31].

Green Tea

One of the richest sources for polyphenols is from the tea leaves of Camellia sinensis. The tea leaves contain approximately 40% polyphenols by dryweight. The majority of the tea consumed in the world is black tea (78%) while green tea consumption comprises 20%10. In vitro studies showed thatgreen tea causes reversible G1 arrest of the cell cycle by inhibition of Rb phosphorylation in oral leukoplakia [32]. EGCG alone or green tea polyphenolswere able to induce apoptosis in oral squamous carcinoma cells, while normal human epidermal keratinocytes survived [33]. EGCG or a mixture of greentea polyphenols (GTPP) induced TNF-a gene expression and TNF-α release from cells [34]. The evidence from these studies attests to the feasibility thatEGCG is a potential candidate for prevention of human oral cancer.

Carotene

β -carotene is a vitamin A precursor commonly found in dark green, orange or yellowish vegetables, such as spinach, carrots, sweet potato, mango,papaya, and oranges. Main actions of beta-carotene include;

- Anti-oxidant and free radical scavenging
- Immunomodulation, stimulation of increase in the numbers of T-helper and NK cells as well as cells with IL-2 receptors
- Inhibition of mutagenesis
- Inhibition of cancer cell growth

β -carotene is especially used for scavenging free radicals in areas of low oxygen concentration. A result from a recent study has demonstrated that onethird of patients (15 out of 46) that used 360 mg β carotene per week during 12 months presented a complete resolution of oral leukoplakia [35].

Natural sources of antioxidants

Fruits, Vegetables and Cancer

The purported close association between a state of oxidative stress and disease implies thatantioxidants will be protective against these same diseases. Particularly important in this regard isthe strong inverse relationship seen between intake of fruit and vegetables and the risk of cancer[36] with an overall risk reduction of between 30 and 50% [37]. If these impressive benefits are aresult of the intake of antioxidants, then the obvious protective substances may be vitamin C and thecarotenoids.

Epidemiological data link vitamin C intake with reduced risk of several cancers, especially oral cavity, esophagus, stomach and, to a lesser extent, colon and lung [38,39]. Likewise, theepidemiological evidence clearly shows a strong inverse association between the intake of β-caroteneand the risk of several cancers, especially lung and stomach [40]. Some attention has beenpaid to other carotenoids. Epidemiological studies have reported that a-carotene has an inverseassociation with cancer of a similar

strength to that seen for p-carotene [41]. Lycopene, a carotenoidpresent in tomatoes, has attracted much attention recently; it shows a strong inverse relationshipwith several types of cancer, especially prostate, lung and stomach [42]. A weaker association hasbeen described for lutein [41]. Each of these substances is an antioxidant. It must be stressed,however, that "association does not prove causation." In reality, vitamin C and carotenoids may beacting merely as surrogate measures of fruit and vegetables and it is other components of thesefoods that prevent cancer. The crucial evidence - the gold standard - is a controlled clinical trial. Butthe results of three such trials provided no evidence of cancer prevention by supplements of β-carotene [43-47].

There is some evidence of protection against cancer by supplemental p-carotene based on early endpoints.One study reported significant reversal of leukoplakia, a precancerous oral lesion [48]. Similarly, another study observed partial regression of precancerous changes of the stomach [49]. Atrial on Filipino betel nut chewers reported a reduction in numbers of buccal mucosa cells withmicronuclei [50]. This indicates the prevention of precancerous changes of the oral cavity.

Let us now address the question as to why trials using p-carotene failed to prevent cancerPossibilities that have been suggested include: the wrong carotenoid was given. or it was given atthe wrong dose, or for an insufficient duration, or at the wrong stage of carcinogenesis However,another very real possibility is that antioxidants are not the common denominator between fruit,vegetables and the prevention of cancer. Other factors that may offer a partial explanation are.

1. There is a strong inverse relationship between the intake of dietary fiber and colon cancer [51].There is also evidence suggestive of an inverse relationship between fiber and breast cancer [52].However, as vegetables (and, to a lesser extent, fruit) are a major source of fiber, part of thisassociation may represent confounding by associated substances.

2. Cruciferous vegetables - broccoli, cabbage, cauliflower, brussels sprouts, and others – containphytochemicals which induce the synthesis of detoxifying enzymes and may thereby beanticarcinogenic [53]. This helps explain the epidemiological evidence indicating a protectiverelationship between these vegetables and colon cancer [54].

CONCLUSION

An increasing public awareness ofantioxidants may prompt a patient's request to betreated without surgery if a premalignant lesion isdiscovered. Reactive oxygen species likemalondialdehyde (MDA), nitroxide (NO), lipidperoxidation, and decreased activities ofantioxidants including glutathione (GSH),ascorbic acid (AA), glutathione peroxidise (GPx), glutathione reductase (GR), superoxidedismutase (SOD), and catalase associated with tobacco users and potentially malignantdisorders, produce both phenotypic andgenotypic alterations which may progress tocancer. Antioxidantsnutrients can play a significant role in theprevention of oral cancer.

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