

Role of antioxidants in disease and cancer prevention: A literature review

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The debate about the role of antioxidant therapy in disease or cancer prevention has long-loomed. Oxidative damage induced by free radicals has been implicated in most inflammatory and degenerative diseases. Antioxidants may have a role in carcinogenesis, while antioxidant-containing fruits, vegetables may protect against some of these diseases while the role of supplements containing antioxidants in the prevention of chronic diseases remains unproven. This review provides basic information about antioxidants and summarizes different studies

reported in literature about the role antioxidants in disease or cancer prevention. Data were collected from review articles, cross-sectional studies, randomized control trials, open-label studies, critical reviews, Cochrane data base system reviews, meta-analysis, population based trials, different phase-I and phase-II trials reported in literature between 1993 to 2014. (Rawal Med J 201;40:319-324).

Key words: Free radicals, anti-oxidants, cell damage, carcinogenesis.

INTRODUCTION

Since last few decades there is an upsurge in the domains of preventive medicine and especially the role of antioxidants and free radicals in disease prevention. Free radicals are formed when an atom or a molecule either gains or loses an electron. They are formed naturally in the body as a result of metabolic activity and play an important role in many normal cellular processes.¹ They are highly reactive chemicals capable of causing potential harm to cells especially at high concentrations. They damage all major components of cells, including mitochondria, proteins, DNA and cell membranes. The cell damage especially to DNA may play a role in the development of cancer and other disease conditions.² Ionizing radiations and other environmental toxins such as cigarette smoke, high oxygen concentration and some metals may contain high amounts of free radicals or stimulate the body's cells to produce abnormally high concentrations of free radicals in the body. Reactive oxygen species (ROS) are the most common type of free radicals that contain the element oxygen, produced in living tissue.^{1,2}

Free radicals are neutralized by antioxidants (free radical scavengers) in the body, which prevent them from causing damage. Antioxidants are extremely

vital for maintaining most favorable systemic and cellular well being and health. A biological antioxidant is considered scavenger of free radicals, which are present in low concentrations, compared to an oxidizable substrate (e.g. lipid, proteins, carbohydrates and nucleic acids) and considerably delays or inhibits oxidation of a substrate.³ Humans have developed an extremely sophisticated and composite antioxidant protection system to defend the cells and organ systems against reactive oxygen species. It engages a variety of mechanism, both exogenous and endogenous, which function synergistically, and interactively to neutralize the free radicals.⁴ Some of the antioxidants are produced endogenously in the body. The body mostly relies on exogenous (external) sources of antioxidants, which are obtained primarily from the diet and are called dietary antioxidants. Vegetables, fruits and grains are rich sources of antioxidants. Some dietary supplements available commercially also contain antioxidants.^{1,2}

Low levels of antioxidants in the body leads to oxidative stress, which may damage or kill cells. This cellular oxidative stress appears to be important in pathogenesis and outcome of many diseases.⁵ The antioxidants have been widely used as dietary supplements and have been investigated

for the prevention of diseases such as cancer, coronary heart disease and potentially malignant lesions and conditions.^{3,6}

CLASSIFICATION OF ANTIOXIDANTS

Dietary antioxidants include vitamin A, vitamin C, vitamin E (alpha-tocopherol), lycopene, beta-carotene.² Selenium (the mineral element) is also considered a dietary antioxidant, but its antioxidant effects are most likely due to the antioxidant activity of proteins having selenium as an essential component.⁵ They are classified in different ways.

First classification is in two groups i.e., Enzymatic antioxidants and Non-enzymatic antioxidants. Enzymatic antioxidants include catalase, glutathione peroxidase, glutathione transferase, glutathione reductase, superoxide dismutase, malondialdehyde. The non-enzymatic antioxidants comprise of vitamin A, vitamin E, nutrient-alpha tocopherol, beta carotene, glutathione, ascorbate, selenium- and non-nutrient- ceruloplasmin, transferrin, uric acid, peptides camosine.⁷

The second classification groups them in Natural antioxidants, which comprise of enzymes (e.g., superoxide, hydroxyl and glutathione peroxidase) and low molecular weight (LMW) antioxidants. LMW antioxidants are further subdivided into lipid-soluble (carotenoids, tocopherol, bilirubin and some polyphenyls) and water-soluble (uric acid, ascorbic acid, polyphenyls) antioxidants. Synthetic antioxidants include butylated hydroxyl toluene butylated hydroxyl anisole, and tertiary butylated hydroxyl quinone.⁸

ROLE IN PREVENTION OF CELL DAMAGE

Antioxidants are intimately involved in the prevention of cell damage, which is responsible for different diseases and carcinogenesis. This is still controversial whether antioxidants can protect us from diseases like lichen planus, leukoplakia, oral cancer, carcinoma in situ, cancers of the upper aero digestive tract i.e. esophagus, pharynx, larynx and increase life expectancy.^{9,10}

Free radicals have been implicated in most degenerative and inflammatory process and induced oxidative damage in the cell.⁸ Antioxidants are responsible for carcinogenesis whereas the fruits

and vegetables containing antioxidants may protect the body against some of these diseases. The role of supplement antioxidants in the prevention of chronic diseases still remains unproven. It is proposed that they are useful in chemoprevention and in the management of a variety of precancerous lesions and other free radical related diseases.⁹ Whereas in a randomized trial, The Physicians' Health Study II showed no support for the use of antioxidants in cancer prevention.¹¹

ROLE OF ANTIOXIDANTS IN PREVENTION OF CANCER

Animal and laboratory studies have shown that increased levels of exogenous antioxidants prevented damage caused by free radicals, which leads to cancer development.¹² In humans, many observational, case-control and cohort studies were conducted to investigate whether dietary or supplementary antioxidants are helpful in lowering the risk or mortality from cancer or not. Overall, these studies showed mixed results and need to be viewed with caution because observational studies have limitation in adequately controlling biases that might influence study outcomes.⁶

Much debate has arisen whether the use of antioxidant supplements modify the effectiveness of cancer chemotherapy or not. Literature shows limited data in both sample size and quality concluding that certain antioxidants may reduce adverse effects and toxicities.¹³ Antioxidants have dichotomous behavior in carcinogenesis i.e., they suppress the carcinogenesis by preventing oxidative damage to DNA and at the same time promote the carcinogenesis by enhancing the survival of metabolically impaired cells.¹⁰

In vitro experiments to study the effects of after atmospheric pressure non-thermal (APNT) plasma and ROS against the antioxidant defense mechanism, cellular metabolic activity and apoptosis induction in cancer cells concluded failure of antioxidant defense machinery along with compromised redox status, might cause malignant cell sensitization. This suggests a promising approach especially in solid tumor therapy by delivering a lethal dose of APNT plasma to tumor cells while sparing normal healthy tissues.¹²

Ganesan et al reported drastically reduced levels of antioxidants during carcinogenesis and emphasized on further research to explicate the significance of antioxidant supplements in early stages of oral cancer.¹⁴

HARMFUL EFFECTS OF ANTIOXIDANTS

Studies show that the antioxidant intake in high-doses may be harmful in some cases. Some research has linked the high consumption of beta-carotene with increased risk of carcinoma lung among smokers.¹⁵ Similarly, an increased risk of carcinoma prostate and stroke (hemorrhagic) is observed with use of vitamin E supplements in high doses.¹⁶ Antioxidant supplements may also interact with certain drugs and dietary supplements e.g. vit. E may increase bleeding risk among people on anticoagulant therapy. There are conflicting reports about the effects of antioxidant during cancer treatment.^{15,16} The National Cancer Institute (NCI) recommends that those patients who are under cancer treatment should consult their physicians before taking these supplements.^{15,17}

REVIEW OF PIVOTAL STUDIES

The randomized controlled trials are considered to provide more reliable and strongest evidence regarding any harm or benefit of an intervention related to health. Different randomized controlled trials have been conducted worldwide under supervision of NCI studying role of dietary antioxidant and supplements for cancer prevention.

Linxian General Population Nutrition Intervention Trial: In this trial, Chinese healthy men and women who are at high risk of developing esophageal and gastric cancer were randomly assigned to take alpha-tocopherol, beta-carotene and selenium regularly for 5 years or to take no antioxidant supplements. The initial results showed that the antioxidant supplements had a lower death risk in gastric but not from esophageal cancer but the risks of developing esophageal or gastric cancer were unaffected.¹⁸ After ten years of antioxidant supplementation study concluded that there was no reduced mortality from gastric cancer in persons who used antioxidant supplements.¹⁹

Carotene and Retinol Efficacy Trial (CARET):

In this trial, effects of beta-carotene and retinol (vitamin A) on lung and other cancer incidence and mortality among high risk people of lung cancer were studied. The trial began in 1983 and ended in late 1995, 2 years earlier than originally planned. Results were statistically insignificant regarding incidence and mortality.²⁰ Additional results showed that Retinol and beta-carotene had no effect on prostatic cancer incidence.²¹

Heart Outcomes Prevention Evaluation The Ongoing Outcomes (HOPETOO) Study:

In this international trial, effects of alpha-tocopherol incidence, mortality from cancer and cardiovascular diseases in diabetic and cardiovascular disease people were studied. The results showed no effect of daily supplementation with alpha-tocopherol for 7 years on any of the outcomes.²²

Alpha-Tocopherol/Beta-Carotene Cancer Prevention Study (ATBC):

In this, the use of supplements containing alpha-tocopherol and/or beta-carotene for 5 to 8 years were studied as to whether they are helpful in reducing the incidence of lung and other cancers in middle-aged male smokers. Preliminary results showed high incidence of lung cancer among those who used beta-carotene as compared to alpha-tocopherol. But overall results showed no effect of alpha-tocopherol or beta-carotene on the incidence of urothelial, renal, colorectal, pancreatic, oropharyngeal, laryngeal or esophageal malignancies.²³⁻²⁵

Women's Health Study (WHS): The effects of beta-carotene, Vit. E and aspirin were studied on cancer and cardiovascular disease incidence in American women above 45 years of age. The results showed no harm or benefit among the participants.²⁶

Selenium and Vitamin E Cancer Prevention Trial (SELECT):

In this trial, the daily supplementation with Vit. E or selenium, or both were studied on carcinoma of prostate incidence among men of age 50 and above. Results showed that intake of these supplements for a median duration of 5.5 years has no effect in reducing the incidence of prostate or other cancers.¹⁶ Updated findings from the study conclude that there was no difference in prostate cancer risk among men who used selenium alone or vitamin E plus selenium as

compared with men who used placebo.²⁷

Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) Study: The effects of daily supplementation of Vit. C, Vit E, beta-carotene, and minerals (selenium and zinc) together were studied for a median of 7.5 years on the incidence of cardiovascular diseases and cancer among French men and women. Results showed no effect on the incidence of cancer or cardiovascular disease or on all-cause mortality.^{28,29}

Physicians' Health Study I (PHS I): In this trial, long-term effects of beta-carotene incidence, mortality of cancer among male physicians in United States showed that the supplementation had no effect on any outcomes in nonsmokers or smokers.³⁰

Physicians' Health Study II (PHS II): This trial showed that the use vitamin E on alternate days, vitamin C daily, or a combination of both for a median of 7.6 years showed no reduction in incidence of prostate cancer, melanoma, leukemia, lymphoma and lung, pancreas, colon, rectum or bladder cancer.¹¹

United States Preventive Services Task Force (USPSTF) systematic review conducted for the about the use of minerals and vitamins for cancer and chronic disease prevention shows no benefit in preventing cancer and these diseases.³¹

Cortés-Jofré and his colleagues found no evidence for recommending Vit. A, C, E, selenium supplements alone or in different combinations in carcinoma lung prevention or mortality in healthy people. In contrary, there is some evidence that beta-carotene use could be associated with slight increase in incidence and mortality of lung cancer among smokers or persons exposed to asbestos.³²

In cardiovascular diseases the Ye et al in meta-analysis of randomized controlled trials concludes that the antioxidant supplementation has no effect on the incidence and mortality of major cardiovascular events, myocardial infarction, stroke, total death, and cardiac death.³³

In skin cancer, Ezzedine et al reported that the risk cancers associated with intake of antioxidant decreases after stopping the supplementation which supports a causative role of antioxidants in skin cancers.³⁴

Gao et al also reported that the treatment with antioxidants after skin was damage by UVR, might cause further detrimental effects on apoptosis and cell cycle control process.¹⁰

Unlike the studies mentioned above, the AREDS (Age-Related Eye Disease) Study conducted at National Eye Institute in collaboration with NIH and NCCIH reported beneficial effect of combination of antioxidant (vitamin C, vitamin E, and beta-carotene) supplements along with zinc. This study showed almost 25% reduced the risk of age-related macular degeneration among those who had the intermediate or advanced stage of this disease.³⁵ Subsequently, follow up study (AREDS2) reported that by adding lutein and zeaxanthin improved the effectiveness of supplement as compared to those who are not using beta-carotene and consuming lutein and zeaxanthin in small amounts.^{35,36}

Different observational studies on the typical eating habits, lifestyles, and health histories of people have shown that those who consume more fruits and vegetables are less prone to many diseases, like cardiac diseases, hypertension, cancer, cataract and stroke. These studies can only give an idea about possible link between dietary or lifestyle factors and disease risk, but they fail to show that one factor may influence the other factor directly or indirectly. For example, a person who use more antioxidant-rich foods may also be more likely to do exercise and less likely to smoke. It may be that these factors, rather than antioxidants, account for their lower disease risk.³

CONCLUSION

Several randomized controlled trials conducted in last two decades shows mixed results. Some concluded that the people who took antioxidant supplements during cancer therapy or other disease process have worse outcomes and in some scenarios they are helpful up to a certain extent. Most of these trials have not clearly proved that the high doses of antioxidant supplements are helpful in disease prevention. Further randomized controlled trials on large scale are needed to provide clear scientific evidence about the potential benefits or harms of taking antioxidant supplements during cancer treatment.

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