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Antioxidant Supplementation and Free Radicals Quelling; the Pros and Cons

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Authors' contributions

This work was carried out in collaboration between all authors. Author BKMM wrote the first draft of the manuscript. Authors SCM and CED managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

An antioxidant is a substance that inhibits oxidation of biomolecules by free radicals. Its primary role is to decrease or inhibit synthesis, scavenge and neutralise the effects of free radicals. A delicate balance is often maintained between antioxidant and free radical. Free radicals being highly active, can react with various important classes of biological molecules such as nucleic acids, lipids and proteins, altering their normal redox state leading to an aberration in their role in cellular metabolism/regulation and tissue structural architecture ultimately leading to cellular injury or death which is known to be deleterious to health. However, free radical is also beneficial to health, if this balance is maintained. Therefore, this review will be throwing light on the relationship between antioxidant and free radicals. Some insight into the benefits of free radical were discussed.

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1. INTRODUCTION

An antioxidant is a substance that inhibits oxidation of biomolecules by free radicals. Its significant role is to decrease or inhibit synthesis, scavenge and neutralise the effects of free radicals [1]. On the other hand, free radicals are unstable molecules that strive for stability. Thus, they bind readily to nearby molecules to maintain stability. Homeostatic mechanism maintains the activity of prooxidants, oxidants and antioxidants in a physiological balance. Therefore, any tilt in this balance leads to oxidative stress.

2. MECHANISM OF OXIDANT GENERATION

Free radicals are uncharged molecules (typically highly reactive and short-lived) that have an unpaired valency electron [2]. They are unstable. Hence, they strive for stability. Usually, bonds do not split in such a manner that leaves a molecule with an odd or unpaired electron. But whenever a weak bond exist it could split as such, leading to the formation of free radicals. Free radicals are highly unstable and reactive with other compounds, in a bid to capture the needed electron to gain stability. Therefore, free radicals attack the nearest stable molecule, abstracting its electron. When the "attacked" molecule loses its electron, it also becomes a free radical itself, setting up a cascade of a chain reaction. Therefore, a state of imbalance between the systemic reactive oxygen species and a biological system's ability to readily detoxify the reactive intermediates or to repair the resulting oxidative damage is called oxidative stress [3].

3. ACTIVITIES OF FREE RADICAL AND ANTIOXIDANT IN OXIDATIVE STRESS

Breach in the delicate balance between antioxidants and free radical can lead to excessive reactive(ROS) which attack bases in nucleic acids, amino acid side chains in proteins and double bonds in unsaturated fatty acids, and cause oxidative stress, which can damage DNA, RNA, proteins and lipids resulting in an increased risk for cardiovascular disease, cancer, autism and other diseases. On the other hand, an excess antioxidant can serve as prooxidant leading to cascade of adverse effects.

4. FREE RADICAL-INDUCED CELLULAR INJURY (DAMAGE)

Free radicals being highly active in large concentration, tend to adversely react with various important classes of biological molecules such as nucleic acids, lipids, and proteins, altering their normal redox state leading to an aberration in their role in cellular metabolism/regulation and tissue structural architecture ultimately leading to cellular injury or death [4]. The following are mechanism of oxidative stress induced-cellular injury.

4.1 DNA Damage

Free radicals can react with the nucleic acid in DNA strand. Guanine is the most susceptible DNA base because of its low oxidation potential and thus leading to multiple oxidized guanine products [5]. This may result to mutation, strand break, cross-linking of DNA strands, and formation of adducts in DNA sequences leading to formation of oncogenes and aberrant genes; if proteins involved in regulation of genetic expression or cellular growth are affected; this may lead to unregulated cellular proliferation and production of oncoproteins whose growth is not amenable to regulation thus leading to various cancers. It may also lead to the production of proteins with suboptimal functions.

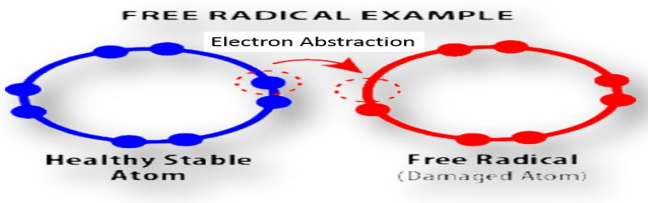

Fig. 1. On the right is a stable molecule with complete electron pairs giving it stability while on the right is an unstable molecule with an unpaired electron trying to steal an electron to achieve stability

4.2 Cytoskeletal Damage

Oxidative stress can lead to alteration of structural proteins which may lead to a dysmorphic structural configuration of proteins and cytoskeletal damage, thus altering the extracellular matrix (ECM), often referred to as "connective tissue [6]. Most of these forms the cytoskeleton of the vasculatures, hence, their alteration may lead to endothelial dysfunction leading to invasion and accumulation of inflammatory cells, smooth muscle cells, lipids, and connective tissues in the intima-media. This atherosclerotic vascular lesion is best termed a fibroinflammatory lipid plaque (atheroma). This forms a nidus for the emergence of microvascular and macrovascular diseases.

4.3 Lipid Peroxidation

Attack of Polyunsaturated fatty acids (PUFA) by free radicals may lead to lipid peroxidation resulting in production of peroxyl prooxidants which instigate cascades of free radical thus, increasing oxidative stress. It produces a variety of oxidised products including reactive electrophiles, such as epoxides and aldehydes, which are capable of further modifying DNA, protein, and other macromolecules. [7]. This may lead to disruption of cellular and lysosomal membrane leading to failure of membrane-associated transporters such as Na-K ATPase pump and calcium pumps, leading to accumulation of fluid and calcium within the cytosol. Therefore, increased cytosolic calcium activates a number of enzymes such as phospholipases and ATPases whose deleterious effect on cells can lead to autolysis.

4.4 Protein Oxidation

Proteins perform several vital roles in the human body such as catalytic, kinetic, signalling and carrier functions. Oxidation of protein most often results from oxidative stress. This may lead to denaturation of protein leading to gross changes in the secondary-tertiary structure of proteins which may stall their functions and cause their precipitation. This has been implicated in diseases such as Alzheimer's, Huntington's and Parkinson's diseases etc.

5. BENEFITS OF FREE RADICALS

Free radicals despite their well-known adverse effect have beneficial effects. It plays an important role in both innate and adaptive immunological reactions thus useful in immunological response against infections. The phagocytes kill ingested pathogens with oxidants [8] and also plays a significant role in cell growth regulation thus helps in removal of oncogenic cells.

It also plays essential roles in signal transduction. Reactive oxygen species induce various biological processes such as gene expression by stimulating signal transduction components such as Ca^{2+} signalling and protein phosphorylation. Though the exact mechanism of action is uncertain. Reactive oxygen species produced by non-phagocytic NADPH oxidase isoforms play a key role in the regulation of intracellular signalling cascades in various non-phagocytic cells such as fibroblasts, endothelial cells, vascular smooth muscle cells, cardiac myocytes, and thyroid tissue. Nitric oxide(NO), a free radical signal-transducing agent, serves as an intercellular messenger for modulating vasodilatation, thrombosis, and neural activity. It relaxes vascular smooth muscles and inhibits platelet aggregation by binding to the haem moiety of cytosolic guanylate cyclase, activating guanylate cyclase activity, thus increasing intracellular levels of cyclic-guanosine 3',5'-monophosphate, which then leads to vasodilation presumably by reduction of the intracellular free Ca^{2+} concentration.

Free radical was proposed to sense oxygen tension and triggers biochemical and physiological adaptation to restore homeostasis; hypoxia paradoxically stimulates reactive oxygen species (ROS) release from the mitochondria which can subsequently regulate the transcriptional and posttranslational response to low-oxygen conditions [9]. Therefore, Free radical generation is involved in mitochondrial aerobic metabolism which generates ATP that are essential in the generation of energy, synthesis of essential molecules and involved in various cellular metabolism.

6. SOURCES OF FREE RADICAL GENERATION

Free radical can be generated in the body endogenously or exogenously.

7. ENDOGENOUS SOURCE

Human physiological metabolism produces free radicals. The various intracellular organelles

such as mitochondria, endoplasmic reticulum and peroxisomes in which high oxygen consumption metabolism occurs tend to generate free radicals.

8. MITOCHONDRIA

In the mitochondria, the superoxide radicals are produced at two major sites in the electron transport chain, namely complex I (NADH dehydrogenase) and complex III (ubiquinone cytochrome c reductase) [10]. The higher the metabolic rate, the greater it's production.

9. PEROXISOMES

Peroxisomes play a major role in the breakdown of very long chain fatty acids via beta-oxidation. Peroxisomes contain oxidative enzymes, such as oxidase, a peroxisomal enzyme containing FAD. Its function is to oxidize D-amino acids to the corresponding imino acids, producing ammonia and hydrogen peroxide. Peroxisomal enzymes such as acyl CoA oxidases, D-amino acid oxidase, L-α-hydroxy oxidase, xanthine oxidase, D-aspartate oxidase have also been shown to produce different ROS [11].

10. ENDOPLASMIC RETICULUM(ER)

The endoplasmic reticulum functions in lipid manufacturing and metabolism, the production of hormones, Protein synthesis and detoxification. The enzymes of endoplasmic reticulum such as cytochrome p-450, b5 enzymes and diamine oxidase generate ROS during their activities [12]. Another important thiol oxidase enzyme, Erop1p catalyses the transfer of electrons from dithiols to molecular oxygen which results in the formation of H_2O_2 [13].

11. EXOGENOUS SOURCES

Exogenous sources of free radical generation are pollution, alcohol, tobacco smoke, heavy metals, transition metals, industrial solvents, pesticides, certain drugs like halothane, paracetamol and radiation.

12. DRUGS

Some drugs can increase the production of free radicals for example chemotherapies, antiretroviral, analgesics, antibiotics, non-steroidal anti-inflammatory and anti-psychotics. Metabolism of a drug may generate a reactive intermediate that can reduce molecular oxygen directly to generate ROS. Antipsychotic chlorpromazine associated with dermal toxicity (sun-burn-like reaction and hyperpigmentation) appears to undergo photodechlorination with resultant excitement of chlorpromazine which converts it to excited state with subsequent energy transfer to molecular oxygen and generation of both excited singlet oxygen and superoxide species [14]. Doxorubicin, an anthracycline antibiotic exhibit dose-dependent cardiotoxicity. Under aerobic conditions, these are unstable and readily reduce molecular oxygen to the ROS superoxide anion and H_2O_2 [15]. Drugs such as antibiotics that depend on quinoid groups or bound metals for activity example nitrofurantoin, antineoplastic agents as bleomycin, anthracyclines (Adriamycin) and methotrexate, possesses pro-oxidant activity [16]. Anti-inflammatory drugs such as diclofenac are extensively metabolized to generate reactive metabolites capable of interacting with protein and nonprotein –SH groups. Also, radicals derived from penicillamine, phenylbutazone, some fenamic acids and the amino salicylate component of sulphasalazine might inactivate protease and deplete ascorbic acid accelerating lipid peroxidation [17,18].

13. RADIOTHERAPY

Radiotherapy injury is majorly caused by free radicals. Electromagnetic radiation (X rays, gamma rays) and particulate radiation (electrons, photons, neutrons, alpha and beta particles) transfer their energy to cellular components such as water forming a primary radical. These primary radicals can undergo secondary reactions with dissolved oxygen or with cellular solutes causing cascade of free radical reactions.

13.1 Tobacco Smoking

It has been shown that tobacco smoke oxidants, severely deplete intracellular antioxidants in the lung cells in vivo by a mechanism that is related to oxidant stress [19]. It has been estimated that each puff produces oxidative chemicals [20]. These include aldehydes, epoxides, peroxides, and other free radicals that may be sufficiently long-lived as to survive to cause damage to the alveoli. In addition, nitric oxide, peroxyl radicals and carbon centred radicals are present in the gas phase. In addition, it also contains other relatively stable radicals in the tar phase. Examples of radicals in the tar phase include the semiquinone moieties derived from various

quinones and hydroquinone. Again, micro-haemorrhages are most probably the cause of iron deposition found in smokers' lung tissue which reacts with hydrogen peroxide to produce hydroxyl radical [21]. It was also found that smokers have elevated amounts of neutrophils in the lower respiratory tract that could contribute to a further elevation of the concentration of free radicals [22].

13.2 Inorganic Particles

Inhalation of inorganic particles also known as mineral dust (e.g. asbestos, quartz, silica) can lead to lung injury that seems at least in part to be mediated by free radical production. Asbestos inhalation has been linked to an increased risk of developing pulmonary fibrosis (asbestosis), mesothelioma and bronchogenic carcinoma. Silica particles as well as asbestos are phagocytosed by pulmonary macrophages. These cells then rupture, releasing proteolytic enzymes and chemotactic mediators causing infiltration by other cells such as neutrophils, thus initiating an inflammatory process [23], the activities of these inflammatory cells produce large quantity of free radicals and other reactive oxygen species [24]. Furthermore, asbestos fibres contain iron, which may have been derived from haemoglobin liberated from micro-haemorrhages. This iron can stimulate the formation of hydroxyl radicals.

13.3 Gases

Ozone is not a free radical but a very powerful oxidising agent. Ozone (O_3) contains two unpaired electrons and degrades under physiological conditions, suggesting that free radicals are formed when ozone reacts with biological substrates. In support of this hypothesis, ozone can generate lipid peroxidation in-vitro, although similar findings in-vivo have not been demonstrated [25].

13.4 Others

Fever, excess glucocorticoid therapy and hyperthyroidism decrease oxygen tolerance in experimental animals. The decrease is attributable to the increased generation of oxygen-derived radicals that accompanies increased metabolism. In addition, a wide variety of environmental agents including photochemical air pollutants as pesticides, solvents, anaesthetics, exhaust fumes and the general class of aromatic hydrocarbons, also cause free radical damage to cells.

14. CLASSIFICATION AND ROLES OF ANTIOXIDANT

Antioxidants may be classified based on the following characteristics: a. Nature of antioxidant substances b. Mechanism of action c. Order or line of defence

15. CLASSIFICATION OF ANTIOXIDANTS

It may be endogenous, exogenous, synthetic or naturally-occurring.

16. BENEFICIAL EFFECTS OF ANTIOXI-DANTS

Antioxidants are involved in the following normal physiological processes: Nutrition, Cell growth and division, Cryoprotection, Nerve conduction, improvement of immune response, Cancer prevention and prevention against infections e.g. measles, reduction of sick cell crises in Sickle Cell, Anaemic patients and prevention of cardiovascular diseases.

17. CONSEQUENCES OF ANTIOXIDANT DEFICIENCIES AND ANTIOXIDANT SUPPLEMENTATION

Antioxidants deficiencies has been implicated in certain disease conditions. One or more antioxidants deficiencies have been implicated in the following pathological processes: Cancer, Glutathione 6 phosphatase deficiency (G6PD deficiency-induced haemolytic anaemia), Iron overload, Wilson's disease, Sickle cell crises, Neurodegenerative disease, Atherosclerosis, CVD, Kwashiorkor, Inflammatory diseases, Non-alcoholic and alcoholic liver diseases, Preeclampsia etc. Despite the role of antioxidant in prevention of diseases, the benefits of exogenous antioxidant supplementation are ambiguous [27,28]. Antioxidant supplements has been found to play a role in prevention, modulation and treatment of diseases. However, there is notable controversy over the dose-response effect, especially when consumed over a long period of time. Most antioxidant supplements have no established dosages. Genetics, environmental conditions and physiological factors greatly affect the outcome of antioxidant therapy.

Table 1. Antioxidants classified into three broad classes namely; nature of antioxidant substances, mechanism of action and order or line of defence

Nature of antioxidant substances	Mechanism of action	Order or Line of defence
Vitamins/Pre-vitamins Vitamin A β-carotene vitamin C vitamin E **Sulfhydryl-containing compounds** Cysteine/N-acetylcysteine Glutathione D-penicillamine **Intracellular and serum proteins** Transferrin Ferritin Lactoferrin Ceruloplasmin Haptoglobin **Antioxidant Enzymes** Superoxide dismutase (SOD) Catalase Glutathione peroxidase (GPx) **Metal chelators** D-Penicillamine Ethylene diamine tetra Acetic acid(EDTA) Diethylenetriamine pentacetic acid(DTPA) **Enzyme cofactors** Selenium	**They decrease the rate of chain initiation** example Catalase Other peroxidases Chelators of metal Ions example EDTA, DTPA, Phytic acid **Chain-breaking antioxidants** They interfere with chain propagation. They decrease the chain lengths of FRR examples: Antioxidant enzymes: SOD, catalase, GPx Antioxidant vitamins: vitamin A, vitamin C, vitamin E, β-carotene Urate α-lipoic acid melatonin Synthetic compound, example: Ethoxyquin 21-aminosteroids 2-methylaminochromans 2-mercaptoethylamine (2- MEA)	**1st line of defence** (metal binding proteins) They serve as 1st line defence against free radicals. They ensure that metals, ferrous and cuprous ions, remain cryptic. Examples: Transferrin, Lactoferrin, Haptoglobin, Ceruloplasmin, ferritin, albumin. **2nd line of defence** (Antioxidant enzymes). They depend on cofactors, some of which act as antioxidant metals e.g. selenium Examples: SOD, Catalase, GPx **3rd (final)line of defence** (exogenous and endogenous antioxidant compounds) They are involved in direct neutralization of free radicals. They function as scavengers of free radicals

Table 2. Classification of antioxidants based on source. [26]

Antioxidant defense system	
Endogenous antioxidants	**Exogenous antioxidants**
Enzymatic antioxidants • Superoxide dismutase (SOD): enzyme detoxifying superoxide radical ($O_2^{\cdot-}$) • Catalase (CAT) and glutathione peroxidase (GPx): enzymes involved in the detoxification of peroxides (CAT against H_2O_2, and GPx against both H_2O_2 and ROOH) • Glutathione reductase: enzyme involved in the regeneration of glutathione • Thioredoxin reductase: enzyme involved in the protection against protein oxidation • Glucose-6-phosphate dehydrogenase: enzyme involved in the regeneration of NADPH **Non-enzymatic antioxidants (principal intracellular reducing agents)** Glutathione (GSH), uric acid, lipoic acid, NADPH, coenzyme Q, albumin, bilirubin	**Prinicipal dietary antioxidants from fruits, vegetables and grains** • **Vitamins**: vitamin C, vitamin E • **Trace elements**: zinc, selenium • **Carotenoids**: β-carotene, lycopene, lutein, zeaxanthin • **Phenolic acids**: chlorogenic acids, gallic acid, cafeic acid, etc., • **Flavonols**: quercetin*, kaempferol*, myricetin* • **Flavanols:** proanthocyanidins and catechins • **Anthocyanidins**: cyanidin* and pelagonidin* • **Isoflavones**: genistein*, daidzein* and glycitein* • **Flavanones**: naringenin*, eriodictyol* and hesperetin* • **Flavones**: luteolin* and apigenin*

*and their glucosides.

18. ADVANTAGE OF NATURAL ANTIOXIDANTS OVER SUPPLEMENTS

Many studies have shown that people who ate fruits and vegetables were less likely to have cancer. And according to a meta-analysis by Jie Luo et .al [29], lung cancer patients who were given a diet rich in natural antioxidants were more likely to live longer [29].

Overall, a varied and balanced diet that includes antioxidant-rich foods and drinks (e.g. fruits, veggies, whole grains, cereals, tea, and coffee) may be considered healthier than taking antioxidant supplements. Free radicals are also beneficial to the body, suppressing their production with supplements is not necessarily beneficial. Therefore, artificial antioxidant supplements may cause more harm than good. Natural foods and drinks are good sources of antioxidants, a healthier option because it has lesser tendency to overwhelm the antioxidant system, less prone to toxicities, do not contain additives. It is easily absorbed and utilised by the body, it has less tendency to interact with other drugs example vitamin E supplements can interact with anticoagulants. Some natural antioxidants from fruits and vegetables has isoforms that cannot be supplemented example vitamin E in food has 8 isoforms while supplements can only provide one of its isoform. It is cheaper and sustainable especially in prevention and management of chronic diseases where there may be need to take it for a long time.

19. ADVERSE HEALTH EFFECT OF ANTIOXIDANT SUPPLEMENTS

19.1 Hinders Endogenous Antioxidants Production

The body has the ability to produce its own natural antioxidants, which is optimized by the inductive effect of ROS.Therefore, excessive antioxidant supplementation may stall this inductive effect. Although, supplements provide antioxidants, they may not be able to make up for the endogenously produced ones especially enzymatic antioxidants which are produced naturally in the body.

19.2 Pro-oxidants at High Concentrations

Antioxidants become “unstable” and “reactive” when they lose or receive electrons in the presence of reactive species [30]. In some conditions antioxidants exhibit pro-oxidant effects and can become harmful. Their redox potential (tendency to acquire electrons and thereby be reduced) could be related to the toxic effects of antioxidants. Brody found that vitamin C supplements can act as a pro-oxidant when taken at high concentrations. Vitamin C reacts not only with free radicals, but also with other molecules in the body [31,32]. One of these reactions is the Fenton Reaction, Ascorbic acid has a number of known interactions with metal ions. These interactions involve redox reactions including the reduction reactions of Fe(III) to Fe(II), through the Fenton reaction [33]. It produces extra free radicals, so the antioxidant supplements become ineffective at stopping the production of free radicals. Ascorbic acid can be transformed into an ascorbyl radical and hydroxycinnamic acid whose phenolic groups are transformed into phenoxy reactive groups [34,35]. Retinal and carotenoid radical are produced by the oxidative cleavage of β-carotene in the presence of oxygen and ferrous ion [36,37].

19.3 Generation of Reactive Oxygen Species by the Fenton Reaction

Reaction 1. $AscH^- + Fe^{3+} \rightarrow Fe^{2+} + Asc^+ + H^+$

Reaction 2. $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^+ + OH$

The pro-oxidant or antioxidant effects of some antioxidants depend on their concentration. For example, at higher concentrations lipoic acid and dihydroxy lipoic acid (DHLA) become pro-oxidants [38].

In a study at dosage of 150mg/kg in a rat model cardiac function reduced, total antioxidant reduced, infarct size increased and evidence of cytotoxicity was observed but on the contrary the rat model that received 30 mg/kg showed evidence of cardio protection [39]. In another work, high dose of vitamin C and vitamin B_3 were shown to have cytotoxic effect on colon cancer cells having BRAF and KRAS mutations by inducing oxidative stress unlike at smaller doses where both exhibited cell proliferative and anti-oxidative activities [40]. However, Ascorbate cytotoxic potential through an epigenetic modulator effect or through tumour killing by oxidative stress may be beneficial in cancer treatment [41].

20. TOXICITIES

High doses of vitamin A, D, E or K (fat-soluble antioxidants) over a long duration can lead to

hypervitaminosis. Water-soluble antioxidants can also give rise to side effects if taken in large doses, e.g. vitamin B6 can cause neurological damage, whereas vitamin C can cause nausea, abdominal cramps, fatigue, headaches, diarrhoea and kidney stones. High doses of vitamin C may result to iron toxicity and may increase the risk of Hyperoxaluria which in turn can lead to Oxalate stones which most likely may cause urolithiasis. Abuse of Vitamin A may lead to Hypervitaminosis A which presents like a pseudotumor. A study on effect of high and low dosage of vitamin C on platelet function showed no effect on platelet indices, functional fibrinogen levels nor platelet function. However, Platelets exposed to 3 mmol/L showed decline in platelet function [42]. In a meta-analysis, high-dose supplements of vitamins A, E, D, C and folic acid was found not to be effective for prevention of disease and it can even be harmful to the health [43].

21. CARCINOGENIC TENDENCY

Alpha- Tocopherol/Beta- Carotene Cancer Prevention Study (ATBC) trial investigation on the use of alpha-tocopherol and/or beta-carotene supplements to reduce the incidence of lung and other cancers in middle-aged male smokers in Finland. Initial results of the trial, reported in 1994, showed an increase in the incidence of lung cancer among the participants who took beta-carotene supplements (20 mg per day); in contrast, alpha-tocopherol supplementation (50 mg per day) had no effect on lung cancer incidence. Later results showed no effect of beta-carotene or alpha-tocopherol supplementation on the incidence of urothelial, pancreatic, colorectal, renal cell, or upper aerodigestive tract cancers [44].

Carotene and Retinol Efficacy Trial (CARET) U.S. trial also examined the effects of daily supplementation with beta-carotene and retinol (vitamin A) on the incidence of lung cancer, other cancers, and death among people who were at high risk of lung cancer because of a history of smoking or exposure to asbestos. Results showed that daily supplementation with both 15 mg beta-carotene and 25,000 International Units (IU) retinol for 12 years was associated with increased lung cancer and increased mortality [45].

Selenium and Vitamin E Cancer Prevention Trial (SELECT) a U.S. trial investigated on whether daily supplementation with selenium (200 µg), vitamin E (400 IU), or both would reduce the incidence of prostate cancer in men ages 50 and older. Results showed that the use of these supplements for a median duration of 5.5 years did not reduce the incidence of prostate or other cancers [46]. After an average of 7 years (5.5 years on supplements and 1.5 years off supplements), there were 17 percent more cases of prostate cancer among men taking vitamin E alone than among men taking placebo [47]. Another study revealed that vitamin C at millimolar concentrations significantly reduced the cell viability as well as invasiveness, and induced apoptosis in human malignant melanoma cells. In contrast, vitamin C at micromolar concentrations promoted cell growth, migration, cell cycle progression, and protected against mitochondrial stress. Though the mechanism has not been fully elucidated. Vitamin C may exert pro- or anti-melanoma effect depending on concentrations [48].

22. REDUCES HEALTH-PROMOTING EFFECTS OF EXERCISE

In the early 2000s, there were controversial reports over the use of high doses of antioxidants to enhance exercise. A German study found that the supplements could actually blunt some of the benefits of exercise. After four weeks, men that trained for five days a week not taking the supplements had an improvement in insulin sensitivity and a boost in their antioxidant system compared to those on vitamin E(400 IU a day) and vitamin C (1,000 milligrams) [49].

In another study 54 participants in their twenties who undertook an endurance training program; half took vitamin C (1,000 milligrams a day) and vitamin E (235 IU), while the other half took a placebo. After 11 weeks, of aerobic exercise the antioxidant group had significant smaller increases in markers for the production of new muscle mitochondria [49].

There is growing evidence of the negative effects of antioxidant supplementation in exercise performance in both animal and human studies. Hence, Mari et al. [50] opined that" antioxidant supplements are, at the least, useless" [50]. A review by Merry and Ristow [50] reached similar conclusions. They stated that there is no convincing evidence to support antioxidant supplementation in regards to training adaptations, and further suggested it may hamper or prevent the signalling of important adaptations such as the production of new

muscle mitochondria, muscle growth in response to training, and improved insulin sensitivity [51]. Another research study by Ristow et al [49] also found that taking antioxidant supplements could decrease the health-promoting effects of exercise [49]. Antioxidant supplements during exercise hinders health benefits of exercise [49]. Morrison et al. [52] found that Vitamin C and E supplementation did not attenuate skeletal muscle oxidative stress or gene expression, however it did hinder other skeletal muscle adaptation in young healthy males (such as superoxide dismutase and mitochondrial transcription factor A) [52]. Santos et .al [53], also confirmed that taking a vitamin E supplement 1 hour prior to exercise reduced inflammation markers which aids cellular adaptation [53]. Bjornsen and colleagues looked at the effects of Vitamin C and E supplementation on lean muscle mass. They found that antioxidant supplementation delayed increases in lean body mass in strength training [54].

23. INTERFERS IN CANCER THERAPY

A study on breast cancer found that 70% of women who took vitamin supplements during their cancer treatments, experienced a reduced effectiveness in their therapies (e.g. radiation therapy, chemotherapy) [55,56]. This was attributed to the ability of the supplement antioxidant to protect cancer cells by removal of the cancer-fighting free radicals often produced by the chemotherapy. A study at Cedars-Sinai Heart Institute showed that cardiac stem cells that were loaded with high doses of antioxidants developed genetic abnormalities that predisposed to cancer development [57]. In a recent study, Doxorubicin-mediated oxidative stress induced apoptosis was found to be attenuated by an antioxidant, N-acetylcysteine, in TP53 wild cells; however, N-acetylcysteine caused a synergistic increase in the apoptosis rate in TP53-altered cells [58].

24. INTERFERENCE IN LABORATORY TESTS

Consuming large amounts of vitamin C can be a source of interference in laboratory analysis such as aspartate transaminase, glucose, uric acid, bilirubin, lactate dehydrogenase, total cholesterol and triglycerides. Most of these reactions involve redox reaction. Consumption of ascorbate leads to analytical error because of its ability to oxidize redox dye in colorimetric assays [59]. Vitamin C is a strong reducing agent found at high levels in various foods, and it may influence the results of urine strip tests even at an ordinary consumption levels [60].

25. INCREASES MORTALITY

A metanalysis, revealed that there was no evidence to prove the benefits of taking antioxidant supplements. Moreover, those who took beta-carotene and possibly vitamins A and E had an increased risk of early death [61].

In a study done by Sayin et al. [62], in mouse models of B-RAF and K-RAS-induced lung cancer, intake of antioxidant supplements N-acetylcysteine (NAC) and vitamin E led to a higher mortality rate and accelerated tumour progression [62]. This may be as a result of the ability of the antioxidant supplement to inhibit ROS leading preservation of DNA damaged and p53 expressed tumour cells. p53 induces cathepsin Q which due to lack of reactive ROS cannot execute DNA damage-Induced necrosis (programmed death) to eliminate the tumour cell [63]. A 300 µg/day dose of selenium taken for 5 years in a country with moderately-low selenium status increased all-cause mortality 10 years later [64]. A metanalysis shows further that selenium does not improve cancer risk. However, more research is needed to assess whether selenium may modify the risk of cancer in individuals with a specific genetic background or nutritional status, and to investigate possible differential effects of various forms of selenium [65].

26. BENEFICIARIES OF ANTIOXIDANT SUPPLEMENTATION

People who may benefit from antioxidant supplements include pregnant and breastfeeding women, chronic alcoholics, drug users, those on long-term restrictive weight loss diets, the elderly, and those with malabsorption (e.g. diarrhoea, pancreatitis, coeliac disease and cystic fibrosis). Vegans, particularly if pregnant may benefit from vitamin B12 supplements.

27. CONCLUSION

Free radicals are produced during cellular metabolism and functional activities and have important roles in cell signalling, apoptosis, gene expression and ion transportation. Therefore, it's suppression via over dosage of antioxidant therapy may be deleterious to health.

28. RECOMMENDATION

Achieving a balance between antioxidant and free radical should be an important consideration in antioxidant therapy for prevention or cure of diseases. Fruits and vegetable intake as a source of antioxidant should rather be encouraged.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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