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OVERVIEW OF FOODS WITH ANTIOXIDANT EFFECTS-CLINICAL RELEVANCE

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ABSTRACT: *Aging and some age-related diseases or disorders such as coronary heart disease and even cancer may be associated with accumulated or excess free radicals, which are generated during active metabolic processes in the human body. Some natural food substances do contain some compounds with antioxidant properties which scavenge these excess free radicals. Some of these naturally occurring antioxidants in our foods include not only vitamins C, E, and beta carotene but some trace elements such as copper and selenium that occur in form of antioxidant metalloenzymes. Other forms of antioxidants found in the plant-derived foods include flavonoids and polyphenols. When diets, which are rich in increased amounts and a wide variety of antioxidant nutrients, are taken, these offer the individual health benefit or improvement. It is ill-advised for an individual to take a range of antioxidant supplements, because the usefulness or benefits of these supplements may yet need further research or investigative studies to establish or determine their efficacy. Thus, it advisable to take a balanced diet of natural foods with mixed plant-based foods because these are healthier than depending on antioxidant supplements.*

KEYWORDS*:* Plant-Based Foods; Phytochemicals; Antioxidant Supplements.

INTRODUCTION

Naturally the foods we eat consist of molecules, which are broken down and used for growth, for maintenance and repair and as a source of energy[1]. The substances in our food which provide us structural materials or energy are called nutrients. Nutrients may be classified as macronutrients and micronutrients[2]. Macronutrients are: water, carbohydrates, proteins and lipids. Nutrients which are essential or required by our body in trace amounts and these include vitamins and minerals are called micronutrients. Micronutrients are not used up for energy or destroyed by our body.[3,4]

In addition to containing vitamins and minerals, balanced diets or foods also contain substances called antioxidants. These are substances or compounds which play crucial role in the prevention of many diseases or disorders as well as cancer. Antioxidants are also said to slow the aging process[5]. They protect cells in our body from damage that are caused by highly reactive molecules. These highly reactive molecules are called free radicals [4]. Failure of antioxidants to adequately antagonize the toxicity of free radicals causes oxidative stress [6,7] which ultimately leads to acute and chronic immune; and non-immune injuries to tissues[8] .

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Free Radicals

Free radical species are unstable and highly reactive or destructive chemicals (i.e. unstable atoms or molecules). Free radicals have an incomplete electron shell that makes them more chemically reactive than molecules with complete electron shells[9]. They become stable by acquiring electrons from nucleic acids, lipids, proteins, carbohydrates or any nearby molecule causing a cascade of chain reactions resulting in cellular damage, cellular degeneration, premature aging, disease and cancer. Free radicals are produced by many cells in our body physiologically during normal metabolic processes[10] (Table 1). For example; superoxide radical and nitric oxide radicals are produced by phagocytic cells such as neutrophils and macrophages and these free radicals make it easier for them to kill bacteria. The nitric oxide radical has physiological actions, which include relaxation of vascular smooth muscle and thus, vasodilation leading to more blood flow to area of inflammation (1-11). Some of the free radicals may be present for considerable lengths of time because of their atypical structure while a majority of them have very short free existence before taking an extra electron or giving one off. Free radicals perform other valuable physiological tasks in our body[11]. Even though our body through the renal, hepatic, lung and skin physiological functions can eliminate the free radicals but these actions are not enough, thus, resulting in the accumulation of free radicals thereby leading to aging, disease states and even cancer. Excessive free radicals may also be produced in our body (Table 1). Free radicals are also exogenously produced when our body is triggered by such factors which include, cigarette smoke, drugs or some medications, poisons, excessive alcohol intake, excessive fat intake, too much exercise, lack of oxygen or reduced oxygen supply, Pesticides ,Ionizing radiation or other environmental pollutants ,Ultraviolet light (due to too much exposure to sunlight) or illness increases its free radical production thereby releasing more of unstable molecules or atoms, which it needs (2-10) (Table 1).

They are two major types of free radical species; reactive oxygen species (ROS) if they contain oxygen with an unpaired electron and reactive nitrogen species (NOS) if they have nitrogen with an unpaired electron. An example of reactive nitrogen species includes nitric oxide radical ($NO^{\cdot}$)[3,12]

Reactive Oxygen Species

The three major types of reactive oxygen species are; superoxide ($O_2^{\cdot}$), hydrogen peroxide, hydroxyl ($HO^{\cdot}$). The superoxide radical is formed when electrons leak from the electron transport chain. The dismutation of superoxide results in the formation of hydrogen peroxide (H_2O_2). Hydrogen peroxide is not a free radical but it is a potentially toxic oxidant and so must be eliminated from the body (Table 1). The hydroxyl ion is highly reactive and can modify purines and pyrimidines and cause strands to break resulting in DNA damage. Our body may repair the damaged DNA by DNA replication but defective repair leads to altered DNA which can lead to cancer formation. Some oxidase enzymes can directly generate the hydrogen peroxide radical. Reactive oxygen species have been implicated in more than hundred diseases.[3,8,13]

In a healthy body reactive oxygen species (ROS) and antioxidants remain in balance. The chemical reaction that occurs when free radical reacts with another substance in the body is known as oxidation, thus as free radical attacks cells or tissues it causes a disease condition known as oxidative stress. Oxidative stress (OS) occurs when the balance is disrupted towards an overbalance of reactive oxygen species (ROS) or free radicals.[12]

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OXIDATIVE STRESS AND ANTIOXIDANTS

Oxidative Stress

Overproduction of free radicals (when the ROS and the RNS are in excess) will lead to damage proteins, lipids and DNA (genetic materials) and so exert an oxidative stress on our body. Oxidative stress leads to cell death, contributes to premature aging, degenerative disorders, promotes malignant growth (cancers) and some inflammatory diseases including rheumatoid arthritis, lupus erythematosus and glomerulonephritis. Oxidative stress has also been implicated in atherosclerosis, ischemic heart disease, stroke, hypertension, and a range of neurological disorders, including multiple sclerosis, Alzheimer's disease, Parkinson's disease and others [3,12,13,14]. The wide diversity of disorders or diseases associated with oxidative stress is due to the widespread production of superoxide radicals in the mitochondria of all cells that have aerobic respiration. Oxidative stress can be combated by natural body antioxidants (endogenous antioxidants) and by dietary (exogenous) or nutrient antioxidants [14-17].

The Antioxidant System

Our body can protect itself against oxidative stress via various means, which include both enzymatic and non-enzymatic methods. Antioxidants are scavenging molecules that convert reactive oxygen species (ROS) to water (H_2O) to prevent overproduction of reactive oxygen species. There are two types of antioxidants in the human body: enzymatic antioxidants and non-enzymatic antioxidants [4,18].

Enzymatic antioxidants – are also known as natural or endogenous antioxidants as stated above. They neutralize excessive ROS and RNS and so prevent them from damaging the cellular structure. Enzymatic antioxidants, which help to prevent the excessive accumulation or upsurge of free radicals are composed of superoxide dismutase (SOD), catalase, glutathione peroxidase and glutathione reductase, which also causes reduction of hydrogen peroxide to water. As stated above hydrogen peroxide is not a free radical but it is a potentially toxic oxidant and so must be eliminated from the body. The hydrogen peroxide is eliminated by the action of catalase to give water and oxygen from two molecules of hydrogen peroxide. Hydrogen peroxide can also be eliminated by the action of the enzyme glutathione peroxidase in which hydrogen peroxide reacts with NADPH + H^+ to form NADP and water [4,6,14,15](Table 2).

Non-enzymatic antioxidants – are also known as synthetic antioxidants or dietary or natural-occurring antioxidant vitamins. The body's complex antioxidant system is influenced by dietary intake of antioxidant vitamins and minerals such as ascorbic acid or vitamin C, tocopherols and tocotrienols or vitamin E, selenium, zinc, taurine, hypotaurine, glutathione, beta carotene and carotene (provitamin A). Vitamin C or ascorbic acid is a chain breaking antioxidant that stops the propagation of the peroxidative process and also helps to recycle oxidized vitamin E and glutathione.

One of the most important non-enzymatic ways in which our body protects itself from oxidative stress is the action of glutathione. Glutathione in a reduced form can react with some free radicals and thus, reduce their damaging effect on our body. Because of this reaction glutathione is one of the major cellular antioxidant. Other non-enzymatic antioxidants in the body include cysteine, transferrin and caeruloplasmin.

Vitamin C or ascorbic acid (a powerful antioxidant is water soluble, it is not lipid soluble) aid vitamin E or α-tocopherol and tocotrienol in the lipid form (vitamin E is lipid soluble) function

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as important antioxidants by taking unpaired electrons from the body's excess free radicals, even though in the above reactions vitamins C and E themselves become free radicals by gaining an unpaired electron. Due to their chemical structure they become weaker free radicals than the ones they have earlier reacted with or oxidized. Many other substances present in our foods (primarily fruits and vegetables) have been shown to or contain antioxidant properties (Table 3). Many laboratories are carrying out research to discover potential food components in plant stems, leaves, and roots extracts for the potential health benefits of their antioxidant contents[4,12].

Some trace elements found in our foods exert their in vivo antioxidant effects as metallo-enzymes. These include: copper [which may be part of the superoxide dismutase, (SOP)] and selenium (metal component of glutathione peroxidase). Phytochemicals are compounds which are found in vegetables together with fruits and legumes (i.e. they are rich in plant-based foods). Though these phytochemicals are found in very small or minute amounts they act as very potent or effective antioxidants (see Table 3). They advance or promote health and help in the prevention of coronary heart disease (keep cholesterol from depositing on the walls of the arteries and thus, lower the progress of arteriosclerosis) and cancer [15,17].

CLINICAL RELEVANCE/APPLICATION OF ANTIOXIDANTS

Aging and Age-related diseases and Antioxidants

Free radicals which are produced endogenously due to the body's metabolic processes or endogenously due to environmental contaminants including tobacco smoke leads to the oxidation in living cells when these are accumulated in the our body. Thus, the accumulated free radicals cause oxidative stress and the damage to the cellular structure that leads to premature aging and age-related diseases. Because of the above there is much interest in the antioxidant components of our diet and also our nutrient supplements. Most our plant-derived foods are said to be protective against age-related diseases such as coronary heart disease and cancer, instead of aging itself. It has been shown by epidemiological studies that subjects taking diets containing moderate to high proportions of fruit and vegetables have lower mortality rate and reduced risk of developing coronary heart disease, cancers, cataracts and macular degeneration, cognitive impairment and Alzheimer's disease [4,12,14,15]. The cause of these finding above may be due to combinations of nutrient and also to the non-nutritive components in these foods. The survival advantage may be predicted in cohort studies if the food constituents of the diet are varied mainly or essentially from plant supplies.

Food and Enough Antioxidant Nutrients

Any subject who takes excessive dietary fat, excessive smoking and/or alcohol consumption, which causes excessive oxidation, may increase the required antioxidant nutrients higher than that commonly available in our food. Because there are a lot of different antioxidants in our food is an advantage getting these substances of varied chemical structures in the human foods (Table 3). Reactive oxygen species and reactive nitrogen species may be eliminated in a lipid soluble medium to a water soluble medium via the availability of ubiquinone or coenzyme Q_{10}, vitamin E and vitamin C without passing through lipid peroxide formation. There may be need for combining additional reducing systems such as: Glutathione, Glutathione disulphide, Dihydrolipoate/lipoate, NADPH/NADP+ and NADH/NAD+ if oxidation has occurred, the

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micronutrients need to regenerated by any of the above reactions in the normal physiological setting.

Some of the antioxidants are effective when ingested with a group of antioxidants. A mixture of antioxidants can improve gastrointestinal absorption. A good example of this includes lycopene absorption when it is taken as a mixture with beta carotene[17-20].

Subjects who take good and balanced diet daily, which include bread and cereals, vegetable and fruit, meat or meat substitutes and dairy products do not need vitamin and mineral supplements. The natural foods as given above mixed with plant-based foods provide a balanced diet and a good source of vitamins and minerals whether they are taken fresh or processed (1). Some of our native or traditional diet does provide enough antioxidant nutrients. But we need to find out or investigate through serious research studies if we get enough quantities of these nutrients needed for optimal health. We need to know if we take enough fruits as the source of antioxidants daily.

Benefits and Safety of Antioxidant Nutrients Supplements

Most individual believe that the foods they eat may not be providing all the nutrients that their bodies require. Some even believe that if enough of the essential nutrient is good then more of it is better. If high quantities of antioxidant nutrients are taken the excess may act as pro-oxidants and therefore cause oxidative stress[17-21]. Pro-oxidant activity may cause useful or damaging consequences in the body physiological system [21].

Present results of researches or studies on the beneficial effects of micronutrients supplements have not shown if these supplements improve health or lessen the risk of disease where the natural foods cannot [22,23]. Some antioxidants supplements may improve a healthy diet but there are some inconsistent data in relation to their adverse outcomes. A good example is the favourable effects of vitamin E is seen in relation to Alzheimer's disease and prostate cancer while the use of increased doses of vitamin E lead to high risk of mortality from some cancers, and possibly fatal myocardial infarction and haemorrhagic stroke[27,28]. There is high incidence rate of tumours when beta carotene supplements are taken, this may be due to the isomer used or because they have been used in isolation. When antioxidant supplements are used it is impossible to evaluate or estimate how much of the suppression of the oxidation is compatible with good health, since free radicals are physiologically needed for the defence mechanisms in our body.

Clinical Practice and Nutrients with Antioxidants

Increased intakes of natural antioxidant nutrients from foods seem to give some health advantages than supplements. When an individual takes a diet with increased amounts of fruits and vegetables, which means a decreased level of fat intake and it is an increased intake of fibre that offer protection against most diseases. Intake of vitamins and mineral supplement cannot be equated to unhealthy lifestyle practices or poor food habits[22-28]. Patients as well as normal healthy subjects are often advised by most physicians to take a wide diversity of cereals, fruit and vegetables in sufficient quantities rather than relying on few antioxidant supplements.

Antioxidants have several functions and may act via other mechanisms rather than as antioxidants. Few do have some healing and beneficial effects which are yet to be proved scientifically because action of antioxidant estimated in vitro may not be appropriate in vivo. Disease prevention via administration of dietary supplements is a valuable purpose and in order

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to evaluate the pharmacologic and toxicologic outcomes dose response studies are necessary. It is improper to promote antioxidants as therapeutic agents if their effectiveness is not established or confirmed and their toxic effects are not definite. It is quite reasonable to imagine assertions that a wide range of plant-based foods have preventive and healing properties. Some of the plant-based foods can protect individuals against excess oxidant action and at the same time maintaining the required degree of such action for protection against infection.

CONCLUSION

Nutritional supplements are foods or nutrients specifically used for improvement or to complement the nutritive value of foods. It is known now that some condiments like herbs and spices are also resources of antioxidants. Plant-based foods are very rich in all the necessary nutrients for healthy life except vitamin B_{12}. The advantages of antioxidants depend on their range and interactions. We may optimize health by encouraging the intake of a wide range of healthy foods, but we cannot, thus far, be sure of the dangers and advantages of receiving antioxidant supplements.

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APENDIX

TABLE1: Production of Reactive Oxygen

Reactive oxygen species endogenous causes	**Reactive oxygen species exogenous causes**
a. Mitochondria of aerobic cells b. Peroxisomes c. NADPH oxidase d. Other enzymes	a. Ionizing radiation b. Ultraviolet rays c. Drugs or medications d. Poisons e. Inflammatory cytokines f. Pesticide residues in fresh and process foods g. Environmental pollutants, CO, SO_2, tobacco smoke, atmospheric fumes and gases h. Heavy metal residues (lead, mercury, etc.) in air, water and foods i. Additives in most processed foods

TABLE 2: Endogenous Antioxidants

Antioxidants	Physiological Action
Enzymes	
Catalase	Catalyzes the formation of water and oxygen from hydrogen peroxide molecules
Superoxide dismutase	Catalyzes or converts superoxide radicals to hydrogen peroxide (H_2O_2), which is then removed by catalase or other antioxidants
Glutathione peroxidase	Catalyzes a reaction of H_2O_2 and NADPH + H^+ to NADP and H_2O
Non-enzyme: Glutathione (Tripeptide)	This reacts with specific or some free radicals and render them harmless

TABLE 3: Different Food Sources of Antioxidants

Components	Antioxidant	Food Sources
Vitamins	Ascorbic acid or Vitamin C	Fruits and vegetables: citrus fruits, guava, sweet and red pepper, black currant, acerola, Strawberry, etc.
	α-Tocopherols and Tocotrienols under Vitamin E	Grain germ especially wheat, sunflower seed, oil-bearing nuts, various oils including olive, sunflower, peanut, red palm oil (very

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		rich natural source of vitamin E), Butter, fish – flatfish, caviar, etc.
	Beta (β) Carotene, other carotenoids or provitamin A	Pigmented leafy vegetables and fruits, red palm oil, tomatoes, carrot
Essential trace Elements	Copper [It is an essential part of the superoxide dismutase (SOD)]	Sources include molasses, oil-bearing nuts, wheat germ, brewer's yeast, oysters
	Selenium is very effective against free radicals generated in the body as an oxidant (It is an essential part of the glutathione peroxidase)	Sources include cocoa, nuts, wheat germ, brewer's yeast, molasses are major sources, it is abundant in legumes and oil-bearing nuts Animal sources include fish, shellfish and meat.
Macronutrient-derived	Peptides e.g. Glutathione	Whey protein, etc.
Phytochemicals* (food components of vegetables with fruits and legumes). The phytochemicals have potent antioxidants scavenging free radicals. They also have antiviral, anti-allergic, anti-inflammatory and anti-cancer properties. Few do have hormonal activity.	Isoflavones e.g. Genistein and Daidzein	Soymilk or beverages. Tofu is a soy product
	Flavonoids: Have potent antioxidant and free radical-scavenging characteristics. e.g. Quercetin	Apples, tea, onions, red wine, pepper, coloured berries, etc.
	Polyphenols	Grapes, mangoes, tomatoes, red palm oil, herbs – thyme, etc.
	Catechins	Green tea, onions, apples, etc.
Zoochemicals – Food components of animal origin	Ubiquinone (Coenzyme Q_{10})	Endogenous source as our body can synthesize it. Exogenous sources include meat, fish, etc.
	Glutathione	Meat, etc.

* These are powerful antioxidants that help in the prevention of coronary heart disease and cancer

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