

Review Article**ROLE OF ANTIOXIDANTS AND NUTRITION IN OXIDATIVE STRESS: A REVIEW****MAYURA A KALE^{1*}, SUPARNA M BINDU², PRATIMA KHADKIKAR¹**

¹Government College of Pharmacy, Osmanpura, Aurangabad 431005, Maharashtra, India, ²MGM's Medical College and Hospital, N-6, CIDCO, Aurangabad, Maharashtra, India
Email: kale_mayura@yahoo.com

Received: 18 Feb 2015, Revised and Accepted: 20 Mar 2015

ABSTRACT

Human body is known to experience positive stress that keeps it vigilant and protects it from biological and physical threats. This stress turns negative when a person is confronted with continuous challenges. Also, stress and nutrition have always run in synergism with each other. Nutritional value of a person's diet depends on the overall mixture or balance of food that is eaten over a period of time, as well as on the needs of the individual. The body relies on obtaining its anti-oxidants from food and other supplements. These nutritional requirements of antioxidants are enormously altered in diseased conditions.

In view of the immense medicinal importance of antioxidants, an effort has been made in this article to bring together information about the role of nutrition and antioxidants such as carotenoids, vitamins, some important minerals in combating free radical generation and in general, boosting normal immune mechanisms. The present review is an attempt to generate interest in the scientific fraternity of their immense potential in preventing and treating several common diseases.

Keywords: Antioxidants, Free radicals, Balanced diet, Nutrition, Oxidative stress, Vitamins.

INTRODUCTION

Human body is designed to experience stress and react to it. Stress can be positive, keeping us alert and ready to avoid danger. Stress becomes negative when a person faces continuous challenges without relief or relaxation between challenges. As a result, the person becomes overworked and stress-related tension builds. Also, stress and nutrition have always been linked to each other and someone with a healthy and balanced diet is likely to be far less stressed than someone with a poor diet. Food acts as medicine, to maintain, prevent and treat diseases. The nutrients in food enable the cells in our bodies to perform their necessary functions. When nutrient intake does not regularly meet the nutrient needs dictated by the cell activity, the metabolic processes slow down or even stop. We all know that we need to get a basic balance of nutrients every day. But, some of our processed foods include chemically-altered fats and sugars that may be giving our bodies the wrong signals. Consumption of such unhealthy food has thus increased the occurrences of physiological problems like obesity, anaemia, diabetes, cancers, heart problems and many psychological diseases. The industrial revolution has also made a significant impact on pollution. Many pollutants are being ingested or inhaled by us, also contaminating food and plants. This has dramatically affected the immunity and hence the health status of humans. The immune cells of our body are weakened due to the presence of free radicals generated through the intake of such contaminants [1-3]. Free radicals knock out communication between immune cells affecting proper operation. Also, these have been found to cause over production of nitric oxide in the macrophages thereby damaging them and impairing their normal function as protective invaders [4]. There are various factors such as excessive exercise, excessive stress, air pollution, cigarette smoking, food and water pollution, ultra-violet sunlight, medication and radiation which are responsible for generation of free radicals. Such free radicals can initiate chain reactions, thus damaging the tissues and causing development of many degenerative diseases. In this review article, we focus on the various measures to prevent and/or combat such disastrous effects [5-7].

Role of nutrition

We know that consuming the right quantity and the right types of food makes a balanced diet. The quantity of food intake is decided by our build, sex, activity and metabolic rate. The right types of food are

important because the body needs a wide range of nutrients in varying amounts in order to function healthily. Our diet should contain protein, fats, carbohydrates and fiber in the form of fresh vegetables and fresh fruit, all in the right amounts, providing you with a good supply of essential amino acids, essential fatty acids, vitamins, minerals, and of course fresh drinking water. Avoiding foods which are rich in some or all of the nutrients the body needs and filling up on those which lack nutritive value is hazardous to health. No single food will provide all the essential nutrients that the body needs to be healthy. A diet that includes a variety of different foods is most likely to provide all the essential nutrients. Knowing what foods contain which nutrients, why they are needed and just how much is needed, will help us to build a healthy body and a healthy life. In summary, if we do not get an adequate supply of essential nutrients, it can result in failure to flourish, poor growth and development, poor physical and mental health, various infections, diseases and in worst cases, even death.

Dietitians have isolated seven main categories of nutrients, each of them present in certain types of food; carbohydrates (sugar compounds), proteins, fats, vitamins (nutrients that exist in every organism, but as the quantity is minimal, they must be supplemented) and minerals (such as calcium, magnesium, iodine, phosphorus, sodium, zinc.), fiber and water. Carbohydrates can be found in rice, bread, grain products and also in some sweet fruits (bananas, pears), while the products with the highest level of fats (especially the fatty acids) are vegetables, seeds and marine oils. Fibers which help in digestion are mostly present in vegetables, certain types of fruit and in whole grains. Proteins are highly important constituents of our body (present in skin, hair and muscles and also in meat, fish, eggs, vegetables, dairy and soy products [8]).

Hence, by consuming the right proportions of these nutrients, we can help the damaged cells to rejuvenate and carry out their normal functions.

Nowadays, vitamin supplements are found in almost every store and many of them are available in specific products such as vitamin A can be found in apricots, carrots, butter. Minerals are usually elements of certain kinds of foods, the most common example being the addition of iodine to the diet, through the popular "iodized salt". Also, most health experts assess that our body needs at least two liters of water daily because it is the main component (we are about

70% water) and around 20 % to be taken from food or different beverages including water, juice, and coffee. All these nutrients prevent the normal body mechanism from oxidative stress that is free radical degenerative mechanism [9].

Role of antioxidants

In human body, cells use oxygen for catabolism of proteins and fats which supply them energy. The human body obtains its energy by consuming nutrients and oxygen as fuel. It also makes use of oxygen to help the immune system, destroys foreign substances and fight diseases. A deeper study at cellular level reveals the role of mitochondria in reducing oxygen concentration by the transfer of electrons to create energy in the form of ATP and generation of water molecule. This process happens almost every time but sometimes instead of generating water, a "free radical" is produced. The part of the body that undergoes the most free radical damage wears out first and potentially develops degenerative diseases [10].

This is the darker side of oxygen often referred to as oxidative stress, which seems to be the underlying cause of all degenerative diseases. Free radicals are mainly oxygen molecules or atoms that have at least one unpaired electron in their outermost orbit. In the process of utilization of oxygen during normal metabolism within the cell to create energy, active free oxygen radical is created. These essentially have an electrical charge and want an electron from any molecule or substance in the vicinity to produce reactive oxygen species (ROS) [11]. These have such violent movement that they have been shown chemically to create bursts of light within the body. Antioxidants stop these free radical chain reactions by slowing down other oxidation reactions and removing ROS. If the free radicals are not rapidly neutralized by antioxidants, these may create even more volatile free radicals and cause damage to the cell membrane, vessel wall, proteins, fats, or even the DNA of the cell. Also, ROS are believed to cause and aggravate several human pathologies such as neurodegenerative diseases, cancer, stroke and many other ailments.

There are hundreds of antioxidants of natural and synthetic origin. The interest of such compounds is due to their effective role against the destructive actions of free radicals. Some of the recent and specific contributions of a few important antioxidants have been discussed below.

Carotenoids

Carotenoids are the colorful plant pigments some of which the body can turn into vitamin A, are powerful antioxidants that can help prevent some forms of cancer and heart disease, and act to enhance our immune response to infections. These are precursors of vitamin A and are sometimes called as provitamin A. The most important beta-carotene is bright-orange one because it yields more vitamin A than the other types. Some other carotenoids, such as lycopene are orange-red pigments found in tomatoes and watermelon. These do not convert to vitamin A, but still are of value because they have potent antioxidant properties. There is also abundant evidence that lycopene helps reduce the risk for prostate cancer. Most other carotenoids, such as alpha-and gamma-carotenes, cryptoxanthin, beta-zeacarotene zeaxanthin, lutein, capsanthin, and canthaxanthin have less vitamin A activity than beta-carotene, but possess anticancer activity.

Carotenes are valuable preventive medicines that are used to a larger extent among other antioxidants. Also, research has shown that people who eat a lot of foods rich in beta-carotene--the carotenoid with the greatest vitamin A value, are less likely to develop lung cancer. Even among smokers, lung cancer is less likely to occur in those people who eat a diet that includes lots of vegetables and fruits containing beta-carotene. A well known property of the carotenoids is the fact that they are capable of protecting the surrounding normal tissue from potential damage created by the inflammatory response of the immune system. Supplementation of the carotenoids can increase the number and effectiveness of the T-helper cells and natural killer cells which constitutes an important part of our defense system against cancer cells. This greatly improves tumor surveillance of immune system [12].

Coenzyme Q10 (CoQ10)

It is also known as ubiquinone, ubidecarenone, coenzyme Q and chemically is a 1,4-benzoquinone, where Q refers to the quinone functional group, and 10 refers to the number of isoprenyl chemical subunits in its tail. It is an oil-soluble, vitamin-like substance present in most eukaryotic cells, primarily in the mitochondria. It actively participates in generating energy in the form of ATP and ninety five percent of the human body's energy is produced in this way. Hence, the organs with the higher energy requirements such as the heart, liver and kidney have the very high CoQ10 concentrations.

Ageing process results in the decrease in CoQ10 levels and makes the mitochondria vulnerable to oxidative damage. CoQ10 is critical for the optimal function of the immune system because of its major role in the production of energy in the immune system. Supplementation of CoQ10 has been shown to reverse these problems and significantly enhance the immune system [13].

Vitamin C

Vitamin C also known as ascorbic acid is one of the safest and most effective nutrients. It is an important nutrient or micronutrient necessary for human life. Recent studies have shown that this vitamin is the best antioxidant within the plasma or fluid of the blood primarily because it is water soluble. It protects the LDL cholesterol from becoming oxidized within both the plasma and the subendothelial space [14]. The major benefits of vitamin C include protection against immune system deficiencies, cardiovascular disease, prenatal health problems, eye disease, and even skin wrinkling. It is also necessary for the maintenance of healthy connective tissue, which gives support and structure for other tissues and organs and helps in healing wounds.

Vitamin C is highly concentrated in the fluid within the eye and is a very important antioxidant for the retina. Recent studies have indicated that the supplementation with vitamin C can slow down the progression of age-related macular degeneration [15].

Silicon

Silicon supports collagen found in skin thereby giving a more youthful and supple appearance while helping prevent the development of wrinkles. This mineral is also important because of its ability to strengthen the connective tissue matrix which strengthens bone. Silicon can even reduce swelling of joints that are due to injury which in turn will allow them to heal more quickly. Silicon also aids with digestive function because it maintains the tissues that are found along the body's digestive tract. Using a silica supplement can decrease intestinal and stomach inflammation as well as help eliminate problems such as constipation, diarrhoea and ulcers. Silicon is an essential mineral for helping keep blood vessel walls supple and strong. It may even help clear up plaques as well as prevent heart disease. Hence, it improves cardiovascular health of a person. Silica does wonders at helping develop a lustrous and beautiful head of hair because it repairs the majority of the collagen and connective tissues found in the body and this will in turn improve strength of hair. Patients with osteoporosis in whom the generation of new bone is desirable, need increased amount of silicon [16].

Glutathione

Glutathione is the most potent intracellular antioxidant present in every cell. Among the various antioxidants and detoxifying enzymes existing in mitochondria, mitochondrial glutathione (mGSH) has come out as the main category of protection for the maintenance of the appropriate mitochondrial redox environment to avoid or repair oxidative modifications leading to mitochondrial dysfunction and cell death. mGSH is found in plentiful quantity in mitochondria and is extremely versatile in its ability to oppose hydrogen peroxide, lipid hydroperoxides, or xenobiotics, mainly as a cofactor of enzymes such as glutathione peroxidase or glutathione-S-transferase (GST). Owing to the involvement of mGSH in different pathologic conditions such as hypoxia, ischemia/reperfusion injury, aging, liver diseases, and neurologic disorders, it is becoming evident that it has an important role in the pathophysiology and

biomedical strategies aimed to boost mGSH levels [17]. Supplementation with the precursors of glutathione have shown significant enhancement of the overall immune system. Even patients of HIV infections have experienced this positive effect [18].

Boron

Boron is an interesting nutrient when it comes to bone metabolism. It has been a known fact that arthritis is associated with a dietary deficiency of the mineral boron. Boron is a membrane catalyst which allows various ions to pass through the cell membrane, particularly phosphates to support synthesis of ATP. This will give energy for efficient repair. It is obvious that in osteoarthritis, the cartilage is worn out, if it is because it lacks the necessary energy for cell division which explains the action of boron. Also, studies have shown that people who had been taking boron supplement have harder bones than the others who do not. This also supports the fact that boron does influence calcium metabolism. Recent research has shown that lack of boron is one of the main causes of osteoporosis. The studies took boron in supplementation and concluded that the urinary excretion of calcium is decreased by approximately 40 percent. Boron also increases magnesium concentration and decreases phosphorus levels [19].

Zinc

Zinc is an essential trace element for humans, animals and plants. It is vital for many biological functions. Zinc is found in all parts of the body, but muscles and bones contain most of the body's zinc (90%). Zinc is especially important for the growing fetus whose cells are rapidly dividing. It also helps to avoid congenital abnormalities and pre-term delivery. Among all the vitamins and minerals, zinc shows the strongest effect on the immune system. It plays a unique role in the T-cells. Low zinc levels lead to reduced and weakened T-cells which are not able to recognize and fight off certain infections. An increase of the zinc level has proven effective in fighting pneumonia and diarrhea and other infections. Zinc can also reduce the duration and severity of a common cold. Zinc is also used as an anti-inflammatory agent and can help to soothe the skin tissue, particularly in cases of poison ivy, sunburn, blisters and certain gum diseases. This mineral is important for the normal functioning of vitamin D. Studies have shown lower zinc levels in serum and bones of patients with osteoporosis [20].

Antioxidants in food

Spices, herbs, essential oils and cocoa are rich in antioxidant properties in the plant itself and *in vitro*, but the serving size is too small to supply antioxidants via the diet. Typical spices high in antioxidants that are confirmed *in vitro* are clove, cinnamon, oregano, turmeric, cumin, parsley, basil, curry powder, mustard seed, ginger, pepper, chili powder, paprika, garlic, coriander, onion, cardamom and a few more. Some herbs with high antioxidant potential are sage, thyme, marjoram, tarragon, peppermint, oregano, savory, basil and dill weed. Dried fruits are a good source of antioxidants by weight or serving size because water has been removed making the ratio of antioxidants higher. A few examples of this category are pears, apples, plums, peaches, raisins, figs and dates. Deeply pigmented fruits like cranberries, blueberries, plums, blackberries, raspberries, strawberries, blackcurrants, figs, cherries, guava, oranges, mango, pomegranate and grape juice also have significant antioxidant properties [21, 22]. Also, there are a few cooked vegetables which are rich in antioxidants such as artichokes, cabbage, broccoli, asparagus, avocados, beetroot and spinach. Typical nuts are pecans, walnuts, hazelnuts, pistachio, almonds, cashew nuts, macadamia nuts and peanut butter are also moderate antioxidants [23]. Sorghum bran, cocoa powder, and cinnamon are rich sources of procyanidin antioxidants found in many fruits and some vegetables [24].

Future prospects

Currently, human studies exploring the efficiency of antioxidants in prevention and treatment of various diseases are being studied worldwide. Few antioxidants including edaravone (for ischemic stroke), N-acetylcysteine (for combat acetaminophen toxicity), alpha-lipoic acid (for diabetic neuropathy) and some flavonoids

(polyphenolic compounds present in dietary plants), such as micronized purified flavonoid fraction (diosmin and hesperidin) and oxeirutins (for chronic venous insufficiency) as well as baicalin and catechins (for osteoarthritis) have found clinical acceptance. However, despite much enthusiasm in the 1980s and 1990s, many well known agents such as antioxidant vitamins A and E [25] and also more recently developed compounds such as nitrones have not successfully passed the scrutiny of clinical trials for prevention and treatment of various diseases. This has given rise to a pessimistic view of antioxidant therapy, however, the evidence from human epidemiological studies about the beneficial effects of dietary antioxidants and preclinical *in vitro* and animal data are convincing ones. Target oriented antibiotics are used in degenerative diseases like oxidative stress, cancer, autoimmune diseases, neurodegenerative diseases, diabetes, chronic, fatigue and fibromyalgia. In such stressful conditions, antioxidants are more preferred than synthetic medicaments as the latter cause many adverse effects, resulting in permanent damage of visceral organs [26]. However, in case of antioxidants, these stressful conditions can be solved internally and permanently without deleterious effects. Highly potent antioxidants such as fruits and vegetables are easily available, inexpensive and more reliable than any synthetic marketed medicament. Semi-synthetic antioxidants such as vitamins and mineral salts are also available in the market. These have high potency, do not have side-effects and possess high safety index. Many research studies have confirmed the importance of antioxidants as a result of which some research centers have started to adopt various strategies to protect crucial tissues and organs against oxidative damage induced by free radicals. Many novel approaches related to this have been and are being made and significant findings have come to light in the last few years. Coordinated research involving biomedical scientists, nutritionists and physicians can make the significant difference to human health in the coming decades [27].

CONCLUSION

Antioxidants are emerging as prophylactic and therapeutic agents. Some of these possess pharmacological action and are used for treatment of diseases. Many are being used as nutritional supplements for prophylaxis of certain diseases along with mainstream therapy. However, there are several factors related to dietary antioxidants such as poor solubility, inefficient permeability instability, extensive first pass metabolism and rapid gastrointestinal degradation, which have limited their extensive use. Hence, there is need to develop new drug delivery systems to improve the performance of antioxidants. Also, we know that antioxidants counteract the detrimental effects of free radicals. Hence, a therapeutic strategy may be formulated where antioxidant capacity of the cells may be used for long term effective treatment. However, the exact role of antioxidant supplementation in disease prevention still remains a debatable issue. Furthermore, extensive research is needed before this supplementation can be recommended as an adjuvant therapy. Nowadays, we find an overabundance of antioxidant supplements available over the counter and their usage is unorganized. It is the view of the authors that an availability of antioxidants must be regulated by prescription from certified health professionals. The public may however be advised about the advantages of antioxidants and they should be encouraged to take the food containing fresh fruits, green leafy vegetables, seeds, nuts and vegetable oils which are rich sources of antioxidants.

CONFLICT OF INTERESTS

The authors declare no conflict of interest

ACKNOWLEDGEMENT

The authors are thankful to the Principal, Government College of Pharmacy, Aurangabad, and Dean, MGM's Medical College and Hospital, Aurangabad, Maharashtra, India for providing literature survey facility to carry out this review work.

REFERENCES

1. Davis C. Oxidative stress: The paradox of aerobic life. *Biochem Soc Symp* 1995;61:1-31.

2. Davis K. Oxidative stress, Antioxidant defenses and damage removal, repair and replacement system. *Life* 2000;50:279-89.
3. Moller P, Wallin H, Knudsen I. Oxidative stress associated with exercise, Psychological stress, and lifestyle factors. *Chemo-Biological Interactions* 1996;102:17-36.
4. Koppenol WH. Peroxynitrite, a Cloaked oxidant formed by nitric oxide and superoxide. *Chem Res Toxicol* 1992;5:834-42.
5. Satchek JM. Role of vitamin e and oxidative stress in exercise. *Nutr* 2001;17:809-14.
6. McCord Joe. The evolution of free radical and oxidative stress. *Am J Med* 2000;108:652-9.
7. Elsayed NM. Antioxidant mobilization in response to oxidative stress: a dynamic environmental-nutritional interaction. *Nutr* 2000;17:828-30.
8. Keservani RK, Vyas N, Jain S, Raghuvanshi R, Sharma AK. Nutraceutical and functional food as future food: a review. *Pharm Lett* 2010;2(1):106-16.
9. Götz ME, König G, Riederer P, Youdim MB. Oxidative stress: free radical production in neural degeneration. *Pharmacol Ther* 1994;63(1):37-122.
10. Lien AP, Hua H, Chuong PH. Free radicals, Antioxidants in disease and health. *Int J Biomed Sci* 2008;4(2):89-96.
11. Klaus A, Hirt H. Reactive oxygen species: metabolism, Oxidative stress, and signal transduction. *Annu Rev Plant Biol* 2004;55:373-99.
12. Shklar G, Schwartz J. The effectiveness of mixture of beta-carotene, alpha-Tocopherol, Glutathione and ascorbic acid for cancer prevention. *Nutr Cancer* 1993;20:145-51.
13. Stephen T, Sinatra MD. The Coenzyme Q10 phenomenon. 1st ed. New York: Keats Publishing Inc; 1998.
14. Lenhart S. Vitamins for management of cardiovascular disease. *Pharmacol* 1999;19:1400-14.
15. Evans JR, Lawrenson JG. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration: Cochrane database of systematic reviews. 1st ed. New York: John Wiley and Sons, Ltd; 2012.
16. Garson LR, Kirchner LK. Organosilicon entities as prophylactic and therapeutic agents. *J Pharm Sci* 1971;60(8):1113-27.
17. Marí M1, Morales A, Colell A, García-Ruiz C, Fernández-Checa JC. Mitochondrial Glutathione, a key survival antioxidant. *Antioxid Redox Signaling* 2009;11(11):2685-700.
18. Jariwalla RJ, Lalezari J, Cenko D, Mansour SE, Kumar A, Gangapurkar B. Restoration of blood total glutathione status and lymphocyte function following aliphatic acid supplementation in patients with HIV Infection. *J Altern Complement Med* 2008;14(2):139-46.
19. Price CT, Langford JR, Liporace FA. Essential nutrients for bone health and a review of their availability in the average north american diet. *Open Orthopaedics J* 2012;6:143-9.
20. Disilvestro RA. Zinc in relation to diabetes and oxidative stress. *J Nutr Med* 2000;130:1509-11.
21. Stein J. Purple grape juice improves endothelial function and reduces susceptibility of LDL cholesterol to oxidation in patients with coronary artery diseases. *Circulation* 1999;100:1050-5.
22. Bagchi D. Free radicals and grape seed proanthocyanidin extract: importance in human health and disease prevention. *Toxicol* 2000;148:187-97.
23. Emilio R. Health benefits of nut consumption. *Nutr* 2010;2(7):652-82.
24. Wan Y, Vinson JA, Etherton TD, Proch J, Lazarus SA, Etherton PM. Effects of cocoa powder and dark chocolate on LDL Oxidative susceptibility and Prostaglandin concentrations in Humans. *Am J Clin Nutr* 2001;74:596-602.
25. Esterbauer H. Role of vitamin e in preventing the oxidation of low-density lipoprotein. *Am J Clin Nutr* 1991;53:312S-321S.
26. Shinde A, Ganu J, Naik P. Effect of free radicals and antioxidants on oxidative stress: a review. *J Dental Allied Sci* 2012;1(2):63-6.
27. Devasagayam TP, Tilak JC, Boloor KK, Sane KS, Ghaskadbi SS, Lele RD. Free radicals and antioxidants in human health: Current status and future prospects. *J Assoc Physicians India* 2004;52:794-804.