Role of Antioxidants in Anti-aging

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***Abstract*: Intracellular and extracellular oxidative stress initiated by reactive oxygen species (ROS) play a major role in skin aging, which is characterized by wrinkles and atypical pigmentation. Although the free radical theory is widely accepted among scientist, certain conflicts regarding the aging process are confronted by clinicians. The free radical theory of aging hypothesizes that damage at the cellular and tissue levels is caused due to oxygen-derived free radicals which are responsible for the age-related changes. In a normal situation, a balanced-equilibrium exists among oxidants, antioxidants and biomolecules. Excess generation of free radicals leads to oxidation and further contributing to cellular functional impairment, and these radicals may overwhelm natural cellular antioxidant defences. The identification of free radical reactions as promoters of the aging process implies that interventions aimed at limiting or inhibiting them should be able to reduce the rate of formation of aging changes with a consequent reduction of the aging rate and disease pathogenesis. The free radicals present bring about a change in the ageing process as they inhibit the formation of free radicals which brings about a consequent change in the aging rate. This paper reviews data regarding the effects of antioxidants on the anti-aging process and longevity. The role of low molecular weight antioxidants and their role in aging and the effects on cardiovascular diseases and cancer was also discussed.**

***Keywords*: Antioxidant, Free radical, Anti-aging**

INTRODUCTION:

Aging is inevitable, universal, and a biological phenomenon that has various adverse effects on all the multicellular organisms (with few apparent exceptions) and a few unicellular organisms like yeast, protozoa and bacteria [1]. The free radical theory of ageing hypothesizes that oxygen derived free radicals are majorly responsible for the age related damage at cellular level. The identification of the free radical reactions bring about the ageing process and the aim to limit or inhibit these free radicals will reduce the rate of formation of aging changes with a consequent reduction of the ageing rate. Multiple mechanisms underlie the human aging process [2]. Oxygen radicals are required for various physiological and metabolic processes, a stable well balanced level between the radical produce and their antioxidant-linked inactivation is necessary to preserve health. Thus, senescence is the result of an imbalance between free radical production and antioxidant defences, with concomitant oxidative stress and age-dependent functional decline [3].

From a thermodynamic point of view, all aerobic organisms are subject to the action of oxygen. The redox potential of the $O_2/2H_2O$ redox system (approximately + 0.8 V at pH 7) is more positive than those of most other biologically relevant redox systems. Therefore, the oxidation by O_2 of organic compounds will have a negative free enthalpy and should proceed spontaneously. The organic compounds are thermodynamically unstable in an oxygen-containing atmosphere [4]. Molecular oxygen, in its triplet basal state, is rather unreactive due to the spin restriction. However, formation of oxygen free radicals and other reactive oxygen species (ROS) opens the gate for potentially deleterious oxidative reactions of oxygen. Free radicals present help to boost up the aging processes, interventions in limiting these free radicals should bring about the reduced rate of formation of aging changes with a subdued decrease of the aging rate and the disease pathogenesis [5]. Given the large amount of data that is available on the topic anti-oxidation supplementation, this overview is not be exhaustive. However if the antioxidant supplementation is increasing and is well adopted in different countries, supporting data is still scarce. Based on the data produced from various articles, support for antioxidant supplementation has reduced the aging process [6] [7].

FREE RADICAL THEORY OF AGING:

Many theories have been put up and proposed to explain about the aging process, but all the theories proposed has not been accepted. The first theory of aging was proposed by Harman in 1956 [8]. He suggested that free radicals cause a deleterious damage to the tissue cells which bring about the natural aging process. Many hypothesis quoting that damage of DNA and proteins has caused the aging process. The role of free radicals in the process of aging is produced from the field of nutrition which provides the most convincing evidence. Hamilton et al looked upon the similarities of the impaired endothelial functions in aging in humans and also

found a major overproduce of superoxide [9]. This finding is supported by a 2007 study which found that endothelial oxidative stress acquires with aging in healthy individuals and is related to a reduce in endothelium-dependant dilation. Dietary restrictions act to reduce the amount of free radicals formed. The identification of free radicals which act as promotors for the aging process shows that interventions and preventions against the production of free radicals should be implied to bring about a subsequent change in the aging process [10]. Since a variety of substances control and operate synergistically in anti-oxidant defence mechanism, its wide ranged processes may require more advanced approaches to determine if antioxidant therapy may benefit the aging process [11].

ANTIOXIDANTS:

Antioxidants play an important role in overall health. They are natural compounds that are found in most of the food and help in the neutralization of free radicals in our bodies. Free radicals are substances that occur naturally in our bodies but the free radicals attack the fat that is present in our body, protein and the DNA in our cells, which can lead to a wide range of diseases and also help in accelerating the aging process. They basically delay the oxidation process of a substrate while present in minimal amounts. The nutritional antioxidants are free scavengers which act through different mechanisms and in different compartments [12]. They take up iron to decrease the reactive oxygen species produced in the body. They also decrease the peroxide content and neutralize the free radicals. The best antioxidant sources are fruits and vegetables, as well as products derived from plants. Some good choices include blueberries, raspberries, apples, broccoli, cabbage, spinach, eggplant, and legumes like red kidney beans or black beans. They are also found in green tea, black tea, red wine and dark chocolate. Usually, the presence of colour indicates there is a specific antioxidant in that food [13].

Vitamin – C acts as a first defence against free radicals in whole blood and plasma and is a water soluble antioxidant which inhibits the lipid peroxidation and helps in the increase of vitamin E in the membranes. Isoprostanes deliver an optimum estimate of oxidative damage to the cellular lipids (Morrow 2005). Bagi et al has shown from the data produced that vitamin C treatment has decreased high levels of isoprostanes in animal models [14]. Vitamin E protects against oxidative damage as it is a lipid soluble vitamin which can be seen in the cell membranes. It can also become a pro-oxidant in isolated lipoprotein suspensions. Deficiency of vitamin E in animals increases the formation of isoprostanes drastically [15]. In humans with the supplementation of vitamin E, the inhibition of isoprostane formation was found. Vitamin C, Vitamin E, and carotenoids have shown to drastically react against the lipid peroxidation. Melatonin which is synthesized from serotonin participates in the reduction of oxidative damage in the lipid membranes [16]. Nakamura and colleagues suggested that vitamin C plays an important role in preventing pro oxidant effect of vitamin E in the LDL concentration [17].

LOW MOLECULAR WEIGHT ANTIOXIDANTS AND THEIR POTENTIAL ROLE IN AGEING PROCESS:

Both in vivo and in vitro data has shown that there is a relative decrease in the level of antioxidants in age related degenerative diseases [18]. It was shown in both humans and animal skin that the water soluble antioxidants decrease with ageing. Increase in the lipid and protein levels were observed in the skin of aging humans and animals. Ubiquinol level tends to decrease in both humans and animals with aging and also was observed that the plasma levels of ascorbate and urate decrease with aging. It has also been shown that a decrease in the total water soluble antioxidant activity there tends to be a deposition of oxidized adducts [19]. This was observed both in the deeper layers of skin and on the surface. It has been found that skin releases LMWA from its surface. This secretion phenomenon was found to be age dependent. In other studies where elderly subjects where administered with low molecular weight antioxidant (ascorbate) led to a significant reduce of few lipid oxidation products as discussed by the thiobarbituric method [20]. In several studies, subjects aged above 60 years showed a positive outcome on the immune system and was observed with the supplementation of antioxidants (ascorbate, beta carotene and tocopherol) along with vitamins A, B, D [21].

ANTIOXIDANT ADMINISTRATION IN AGEING AND CLINICAL CONDITIONS:

Before the administration of antioxidants in humans throughout the lifespan, another approach to study antiaging effect of antioxidants consists in short term experiments. The experiment included comparison of the functional tests with the status of experimental animals before and after supplementation. Administration of N-tert-butyl-α-phenylnitrone to aged Mongolian gerbils for 2 weeks [22]. This administration had reduced the amount of protein carbonyls in brain that led to a decrease in the number of errors in the radial arm maze patrolling behaviour. Similar studies were conducted on mice for 15 days. Most of the studies proposed by Harman had shown a beneficial effect of dietary supplements, with the average increase of life span being 15-20% [23]. It is clear that the antioxidant supplementation does not lead to maximum life span extension but dietary antioxidant administration helps to reach the end of their life span in animals [24].

ATHEROSCLEROSIS AND CARDIOVASCULAR DISEASES:

In western countries, the major cause of death is due to atherosclerotic diseases in elderly population. Polyphenols and lycopene have been proposed to show delay in the aging process. Resveratrol which is a phytoalexin found in several plants particularly in red grapes has shown to be able to up-regulate the nuclear Liver X receptor α and its target genes in macrophages and thereby reduce the expression of lipoprotein lipase and scavenger receptor [25]. A recent study conducted in cultured human coronary artery endothelial cells has shown a beneficial effect of polyphenols on the expression of the plasminogen activator inhibitor-1 gene [26]. In 1999, an American Heart Association Science Advisory recommended that the general population consume a balanced diet with emphasis on antioxidant-rich fruits, vegetables, and whole grains (Krauss et al 2000) [27]. In a more recent American Heart Association Science Advisory (Kris Etherton et al 2004), the beneficial effects of antioxidant vitamins (such as vitamin E, vitamin C, and β-carotene) on cardiovascular risk has been revised and discussed [28]. Consistently with previous recommendations from

the American Heart Association (Mosca et al 2004) [29] and the American College of Cardiology (Gibbons et al 2003) [30], there is no scientific data yet to justify the use of antioxidant vitamin supplements for cardiovascular risk reduction as it requires further research. Considerable amounts of vitamin E helps in the prevention of cardiovascular disease and cancer from the considered studies [31]. More clinical trials with selected populations are required to determine the effects of vitamin E on cardiovascular disease.

CANCER:

The exact role of antioxidants of carcinogenesis and cancer is still under clinical trials and investigations. Few types of antioxidants have been associated to reduce the risk of cancer. Many clinical trials were conducted to determine the effect of antioxidants on caner. Linxian General Population Nutrition Intervention Trial: This trial was the first large-scale trial to find the effects of antioxidant supplements on cancer risk [32]. Healthy Chinese men and women at increased risk of developing esophageal cancer and gastric cancer were taken up in this trial and were assigned to take a combination of 15 milligrams (mg) beta-carotene, 30 mg alpha-tocopherol, and 50 micrograms (µg) selenium daily for 5 years or to take no antioxidant supplements [33]. The initial results showed that people who took antioxidant supplements resulted in a lower risk of death from gastric cancer but not from oesophageal cancer [34]. However, their risks of developing gastric cancer and/or esophageal cancer were not affected by antioxidant supplementation. Carotene and Retinol Efficacy Trial (CARET), This U.S. trial 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[35]. The trial began in 1983 and ended in late 1995, 2 years earlier than originally planned. Results reported in 1996 showed that daily supplementation with both 15 mg beta-carotene and 25,000 International Units (IU) retinol was associated with increased lung cancer and increased death from all causes (all-cause mortality) [36]. A 2004 report showed that although the elevated risks of lung cancer and all-cause mortality were no longer statistically important as adverse effects lasted for up to 6 years after supplementation had ended [37]. In 2009, additional reports showed that retinol and beta-carotene supplementation had no effect on the incidence of prostate cancer. Authors also discussed that the antioxidants will have beneficial effects on cancer incidence only on healthy individuals who are not exposed to cancer risk [38]. Plakogiannis (Pham and Plakogiannis 2005) found no sufficient evidence that vitamin E is able to reduce the risk of cancer and hence its supplementation for cure of cancer is not recommended [39].

LOGEVITY:

Nutritional supplementation of antioxidants have shown to play a potential role in indicating the aging process and increasing longevity [40]. It is still unclear whether the health benefits from diets at high consumption of fruit and vegetables can be replaced by antioxidant supplementations. Vitamin C, Vitamin E, and carotenoids have shown to drastically react against the lipid peroxidation and function in the aging process as they serve as dietary antioxidants [41]. The antioxidants include superoxide dismutase, carotenoids, alpha-tocopherol, and uric acid [42]. Melatonin participates in the reduction of oxidative damage in the lipid membranes as it is synthesized from serotonin. Melatonin additionally stimulates a number of anti-oxidative enzymes. Unfortunately, current data do not still allow to conclude that melatonin may have a role in extending normal longevity [43]. Moreover, as for many other antioxidants, melatonin can act as a pro oxidants [44].

CONCLUSION:

The beneficial effects of antioxidants have shown to play a major role in the aging process. Although with many clinical trials, mostly in animals the provision of antioxidants maybe provisional and useful, many clinical trials have not been conducted hence accurate results regarding the longevity process is still under due. Current evidence does not allow to recommend antioxidant supplementation as a useful mean to prevent age-related pathophysiological modifications and clinical conditions. However there is no clear evidence that antioxidant may serve this purpose, whereas it seems more likely with the consumption of dietary antioxidants, in combination with a balanced diet and exercise it shows a change in the aging process.

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