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Antioxidants: Balancing the Good, the Bad and the Ugly

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Abstract

Antioxidants refer to the molecules that react with oxy radicals not only to delay their function, but also to neutralize them and subsequently reduce oxidative stress and protect us from diseases state. Despite our own endogenous response, several factors contribute to diminish our self-defense mechanism resulting in loss of control in preventing ourselves from free radical damage. Antioxidant supplementation is becoming a high-priority to protect our health and from progression of several life-threatening diseases.

Keywords: Antioxidants; Free radicals; Healthy Food; Phytonutrients/phytochemicals; Supplement

Abbreviations: ROS: Reactive Oxygen Species; RNS: Reactive Nitrogen Species; DNA: Deoxyribonucleic Acid; MsrA: Methionine Sulfoxide Reductase A; HO: Heme Oxygenase; 4-HNE: 4-Hydroxynonenal; TCA: Tricarboxylic acid; Nrf2: Nuclear Factor Erythroid 2-Related Factor; COX-2: Cyclooxygenase-2; SOD: Superoxide Dismutase; DPPH: 1,1-Diphenyl-2-picryl hydrazyl.

Introduction

Free radicals and antioxidants

Nevertheless, oxygen is profoundly essential for the survival; however, reduction of molecular oxygen sequentially produces oxy radicals such as hydroxyl radicals, hydrogen peroxide, superoxide anion radicals often called as free radicals, reactive oxygen species (ROS) and reactive nitrogen species (RNS) like nitric oxide radical. Though some amount of these free radicals essentially involves keeping us healthy, however, excess of unsuppressed ROS and RNS could be deleterious to our health. Even though our body has its own self-defense mechanism to neutralize oxy radicals through the gainful employment of endogenous anti-oxidants, however, oxidative stress, environmental effect, food-habits as well as aging process, reduce human's auto-immune empowerment. Once these free radicals overpower human's innate anti-oxidant capacity ('state of oxidative stress'), they attack healthy cells and other organs and ultimately damage healthy cellular DNA causing the progression of several life-threatening diseases like cancer [1,2], diabetes mellitus [3,4], rheumatoid arthritis [5], ulcers [6], stroke [7], cardiovascular diseases [8]. Uncontrolled free radicals are responsible for other health disorders such as Parkinson's disease [9], eye diseases [10] inclusive of cataracts [11], noise induced hearing loss [12,13], aging related disorder [14] and disorient humans being from leading healthy life-style.

Antioxidants [15] refer to the molecules that react with oxy and other radicals not only to delay their function, but also to neutralize them and subsequently protect us from oxidative stress [16] and keep us away from other diseases. The major classes of antioxidants are i) enzymatic antioxidants, ii) non-enzymatic antioxidants and iii) metal binding proteins [17] that play the decisive role for controlling our body over oxy-radical and damage from other radicals.

Many methods are now well recognized and are in use for the measurement of antioxidants capacity. Very recently, three consecutive reports [18-20] elaborated in detail with mechanistic approach on the measurement of antioxidants capacity or its activity.

Enzymatic antioxidants are mainly endogenous as they exist in our body and are very powerful antioxidants. Despite number of enzymes in our body belonging to this group, three super active enzymes are superoxide dismutase, catalase and glutathione. They catalyze the decomposition of superoxide, hydrogen peroxide and organic peroxides and detoxify oxy radicals and convert them finally into oxygen, water and alcohols. Metal binding proteins [17] such as albumin, transferrin, ferritin, lactoferrin are present in our body and protect us from severe damage by trapping free radicals.

Non-enzymatic antioxidants are mostly exogenous as our body hardly produce them and need to be outsourced. They are i) nutritional antioxidants such as vitamin C, vitamin E, carotenoids, ii) mineral constituents like selenium and iii) natural antioxidants: derived from natural sources often known as phytonutrients/phytochemicals.

Antioxidants and Human Health Benefits

Antioxidants in food [21,22]

Dietary foods are substantial source of antioxidants. Antioxidants, present in food are both nutritional like vitamin C, vitamin E, carotenoids and non-nutrients such as polyphenols and others elements. Vitamin C is a water soluble antioxidant and is highly active to neutralize oxy radicals in aqueous phase whereas vitamin E is a fat soluble antioxidant and secure our cell membrane from lipid peroxidation. The major sources of vitamin C in foods are grapefruits, oranges, lemon, tomato, sweet red peppers, cauliflower, sweet potato, black berry whereas sources of vitamin E are white beans, vegetable oils, sunflower seeds, almonds and peanuts. Carotenoids [23] defend us by quenching singlet oxygen oxy radicals and other ROS generated in our body. Best sources of carotenoids are carrots, cantaloupes, palm, apricots, mangoes, tomato and gac fruit (*Momordica*

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cochinchinensis). Vegetables that deliver high content of polyphenol as antioxidants are spinach, cabbage, broccoli, beetroot, lettuce and asparagus. Most of the fruits like papaya, bananas, oranges, apple, and all varieties of melons, jackfruits, mango, grapes, guava, cherries and all varieties of berries including dried fruits such as raisins, figs and dates have notable contribution to supply polyphenol antioxidants in our body. Spices that have prominent role in our daily food-needs with adequate quantity of polyphenols as antioxidants are turmeric, garlic, clove, cinnamon, cumin, mustard seed, ginger, coriander, pepper, chilli powder, cardamom. Nuts such as cashew, walnuts, and pistachio also contribute modest polyphenol antioxidants.

Phytochemicals as antioxidants

Healthy food habits always keep the diseases at bay. However, it is quite common that it could not be accomplished routinely. Simultaneously, oxidative stress in course of time results in the deficiency of vital nutrients, minerals and antioxidants and as a whole our body instigates free radicals and ROS generation. It thus necessitates presence of adequate antioxidants to rescue our body from free radical damage. Keeping healthy and protecting our health from further deterioration, dietary antioxidant supplementations [24] are becoming a high priority. Phytochemicals/phytonutrients are found to be safe since ancient time possessing minimum side effects.

While it is impractical to list out all the redox complications relating various diseases in this short review, the authors are content to point out that at least in the cancerous situations several enzymes implicated in oxidative stress have abnormal expression. MsrA associated with reduction of S-stereoisomer of sulfoxide in methionine residues in enzymes is under expressed in human breast cancer [25] whereas over expression Heme Oxygenase (HO) potentiates cancerous growth in pancreatic cancer [26]. Similarly anti-oxidants can induce expression of detoxification phase-II enzymes in both neurons and astrocytes in neurodegerative diseases. Importance of oxidative hypothesis in atherosclerosis has been well-known. Over oxidation in lipids leading to reactive carbonyls such as 4-hydroxynonenal (4-HNE), acrolein, malondialdehyde etc that ultimately react with DNA bases causing adverse effects; oxidation of essential proteins especially in their cysteine residues, DNA oxidation, down-regulation of Phase-II anti-oxidant enzymes, all-together contribute to disease generation and progression. Intervention in any of these processes by plant-derived anti-oxidants known for their safety and efficacy would be a welcome factor in mitigating these conditions. Some representative and promising candidates with high potential as antioxidant supplements are addressed as under.

***Curcumin* [27-29]:** The major constituents of natural turmeric, namely curcuminoids, are known for their use as anti-inflammatory agent over centuries. Recent study reveals that intake of *curcumin* upto 12 g/day is safe with minimal toxicity [28]. Strong antioxidant effect of *curcumin*, a major property of curcuminoids, is responsible for not only their role as excellent anti-cancer agent but also for the prevention of other human diseases. The importance of the phenolic groups present in curcuminoids for the anti-oxidant activity is readily gleaned from the greatly diminished anti-oxidant activity of its mono- and di-glucuronide metabolites derived from *curcumin* [29].

Tetrahydrocurcumin [30,31]: This metabolite of *curcumin* has been found to be an effective antioxidant, surpassing *curcumin* in that respect and has been termed as a cascade anti-oxidant in the same way Carnosic acid-Rosmanol cascade has been referred [31]. Its antioxidant nature is found to be highly beneficial for slowing down the aging process and finds extensive use as one of the active cosmetic ingredients.

Tea polyphenols [(–)-Epigallocatechin gallate (EGCG), (–)-Epigallocatechin (EGC), (–)-Epicatechin gallate (ECG) and (–)-Epicatechin (EC)] [30,32-36]: These are important tea antioxidants with outstanding capability to quench the free radicals and subsequently to reduce the oxidative stress [32] and prevent cancer and cardiovascular diseases [33]. A recent paper on the use of green tea polyphenols brings out the impact of their anti-fatigue properties emphasized the importance of their anti-oxidant activity [34]. Its antioxidant effect is found to be beneficial for maintaining healthy eye [35,36].

Resveratrol [37-41]: Sources are red grapes, blue berries, red wine, dark chocolate and peanut skin. High content of resveratrol is found in Itadori tea. Itadori tea is mainly consumed in Japan and China and in use as natural medication [38]. It's wonderful antioxidant activity benefiting us from several diseases including cancer risk is summarized in recent reviews [39,40]. Recently synthetic resveratrol (>99%) (150 mg/day) was found safe in human health and has been approved by European Commission to use it as food supplement in form of tablet or capsule [41].

Garcinol [42,43]: Isolated from *Garcinia indica*. Garcinol is natural polyphenol with substantial antioxidant activity with potential of cancer prevention and several health benefits recently reviewed [43].

Pterostilbene [44-46]: This vital anti-oxidant is present in *Pterocarpus marsupium* extracts and is an excellent activator of Nrf2 transcription a responsible factor for several anti-oxidant enzymes. Pterostilbene is a better inhibitor of colon carcinogenesis. Its potent anti-diabetic activity is again ascribed to its anti-oxidant activity [45]. Its ability to inhibit an oxidative enzyme such as COX-2 was shown in a clinical trial [46].

Triterpenoids: Oleanolic acid [47,48], Ursolic acid [47] and Betulinic acid [49]: Oleanolic and Ursolic acids are effective inducers of metallothionein, a small cysteine-rich protein that acts like the anti-oxidant enzyme glutathione.

Flavonoids: Sources are in wide variety of vascular plants and also in fruits, vegetables, tea, and cocoa. Flavonoids enhance the antioxidants capacity of endogenous antioxidants [50].

Alkaloids [51-54]: Naturally occurring alkaloids possess antioxidant activity [51] with promising impact on health disorder [52]. They are found efficacious to use as anticancer agents [53,54].

Amla [55]: Amla is one of the most outstanding herbal products known since time immemorial. Its ability to attenuate oxidative stress has been well documented even though the consistent presence of the well-known anti-oxidant vitamin C as major constituent in the herbal extracts has been disputed [56]. β-Glucogallin (1-O-galloyl-β-D-glucose) is found one of its active antioxidant constituents with impressive photoprotection proficiency [57].

***Boswellia serrata* extract:** *Boswellia serrata* gum resin is known as Indian frankincense [58] and in use as medicine for the treatment of several diseases since ancient times. Major constituents in *Boswellia serrata* include β-boswellic acid, keto β-boswellic acid and acetyl keto-β-boswellic acid. *Boswellia serrata* extract inhibits IL-1β expression and it is believed that uncontrolled expression of IL-1β results in the depletion of SOD leading to reduced collagen synthesis. Boswellic acids, especially acetyl-11-keto boswellic acid, are also inhibitors of 5-lipoxygenase, an oxidative enzyme implicated in leukotriene formation [59].

Salacinol: It is a novel, structurally unique anti-diabetic molecule isolated from *Salacia reticulata* documented in traditional medicine. Recent antioxidant analysis study reveals that *Salacia reticulata* possesses superior antioxidant activity [60,61] compared to other species of this family [60]. It is concluded that better DPPH radical scavenging activity of *Salacia reticulata* is due to the presence of higher content of salacinol, kotalanol and magneferin in *Salacia reticulata* [60].

Forskolin: This diterpene natural molecule isolated from *Coleus forskohlii* reduces oxidative stresses via its antioxidant ability [62], possesses anti-diabetic activity [63] and presently in use as an anti-obesity preparations [64].

Conclusion

Antioxidants are mostly consumed through our diets; however the quantity may not be sufficient enough for our daily needs. This behooves to boost ourselves with supplementary anti-oxidants. Numerous studies have been performed demonstrating the potential benefit of antioxidants supplementation [24,59,65-67] despite concerns expressed on the use of excess antioxidants supplements [68].

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