DRUG REVIEW

Antioxidants and Cardiovascular Health

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Introduction

Free radicals (FR) derivatives of oxygen like superoxide free radical anion ($O_2^{\cdot -}$), hydroxyl free radical($OH^{\cdot}$), lipid proxyl ($LO^{\cdot}$), lipid alkoxyl ($LOO^{\cdot}$) and lipid peroxide (LOOH) as well as non-radical derivatives such as hydrogen peroxide and singlet oxygen are collectively known as reactive oxygen species (ROS). FR and ROS production in the animal cell is inevitable. Normally, there is an equilibrium between a free radical/ reactive oxygen species formation and endogenous antioxidant defense mechanisms, but if this balance is disturbed, it can produce oxidative stress (1-3). This state of oxidative stress can result in injury to all the important cellular components like proteins, DNA and membrane lipids which can cause cell death. In recent years increasing experimental and clinical data has provided compelling evidences for the involvement of FR/ROS in large number of pathophysiological states including cardiovascular diseases (1,2). Studies evaluating benefits from antioxidant therapy in cardiovascular diseases have shown mixed results. Many studies suggest their supplementation to be protective (4-6). However, there are conflicting reports also which question the rationale for antioxidant supplementation (7-9) or in some cases detrimental to the cardiovascular health (10,11).

Antioxidants compounds are exogenous or endogenous in nature which either prevent the generation of toxic oxidants, intercept any that are generated and inactivate them and thereby block the chain propagation reaction produced by these oxidants (12,13).

Types of antioxidant defenses (14)

1. Primary or chain breaking antioxidants (scavenger antioxidants): These antioxidants can neutralize free radicals by donating one of their own electron, ending the electron “stealing” reaction.
2. Secondary or preventive antioxidants: They act through numerous possible mechanisms like a) sequestration of transition metal ions which are not allowed to participate in metal catalyzed reactions. b) removal of peroxides by catalases and glutathione peroxidase, that can react with transition metal ions to produce ROS. c) removal of ROS etc.
3. Tertiary antioxidant defenses: These are the repair processes, which remove damaged biomolecules before they can accumulate and before their presence results in altered cell metabolism and viability e.g. damaged DNA repaired by enzyme methionine sulphaoxide reductase.

Table 1, 2 & 3 shows sub-classification of known antioxidants and their mechanism of defense against ROS in biological system.

Table 1. Antioxidants in biological system

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	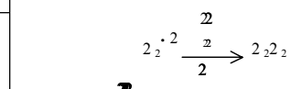	
	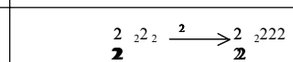	
	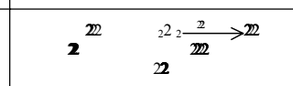	
		
	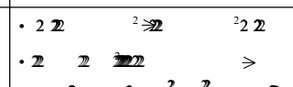	
	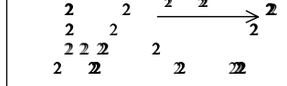	
	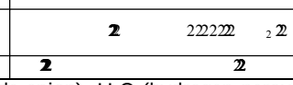	
	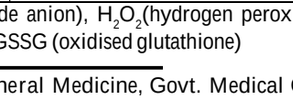	
	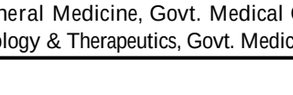	

$O_2^{\cdot -}$(superoxide anion), H_2O_2(hydrogen peroxide), GSH (reduced glutathione), GSSG (oxidised glutathione)

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Table 2. Antioxidants in biological system

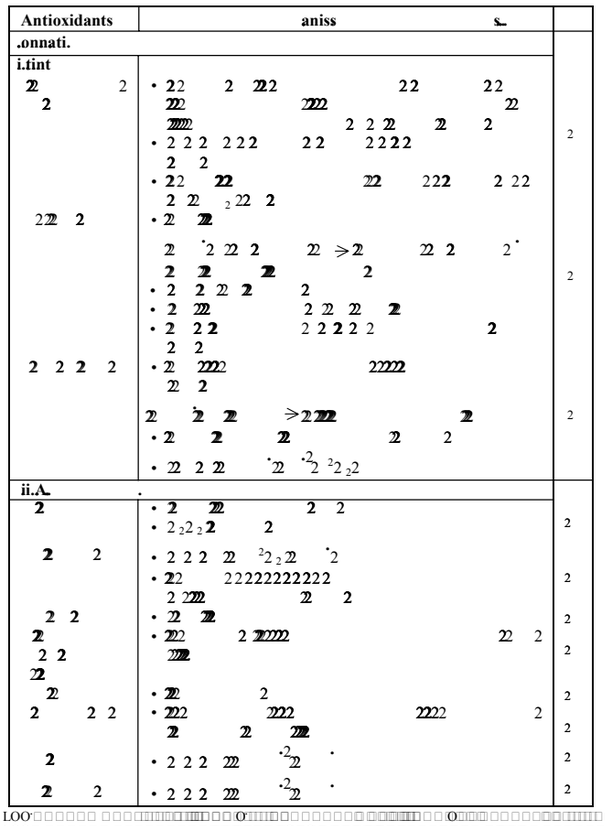

Table 3. Antioxidants in biological system

Drugs having antioxidant properties (12)
Probucol,
Xanthine oxidase inhibitor (allopurinol, folic acid)
NADPH inhibitors (adenosine, calcium channel blockers)
Inhibitors of iron redox cycling (deferoxmine, apotransferin, ceruloplasmin)
Some Non-steroidal anti-inflammatory agents (15)
Oral anti-diabetic agents (16) like (metformin, gliclazide & troglitazone)
Statins (17) (atorvastatin, simvastatin, pravastatin & rosuvastatin)

Antioxidants-Present Status in Cardiovascular diseases (CVD)

Endothelial dysfunction has relevance to the pathogenesis, progression and prognosis of a wide spectrum of cardiovascular diseases (18). The assumption that oxidation of LDL, loss of nitric oxide and the vascular inflammatory response modulated by oxidative stress mediates endothelial dysfunction would implicate a potential for antioxidant therapies to ameliorate endothelial dysfunction. This assumption is supported by one of the study done in LDL receptor deficient mice, which showed vitamin-E supplementation can revert these changes (19). In humans, antioxidant vitamins by potentiating endothelial nitric oxide levels (20) as well as by inhibiting vascular inflammation (21), lipid peroxidation (21), platelet aggregation (21) and oxidation of LDL (21-24) can also contribute to prevent endothelial dysfunction. Additionally, antioxidants may favourably influence plaque stability (25). Studies provide direct evidences that antioxidant vitamins can reverse endothelial dysfunction induced by methionine (26) as well as can restore endothelial function in hyperlipidemic children (27) and young smokers (28). Allopurinol, (xanthine oxidase inhibitor) a potential antioxidant has been shown to reverse endothelial dysfunction in heavy smokers (29), type-2 diabetics with mild hypertension (30) and in patients of chronic heart failure (31). The Secondary Prevention with Antioxidants of Cardiovascular disease in End-stage renal disease study (SPACE) (4), Transplant Associated Arteriosclerosis Study (TAS) (5) showed positive results by indicating significant decrease in primary end points in the form of various cardiovascular events and deaths. In one of the study, Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) (6), combination of natural antioxidant with ascorbic acid resulted in significant increase in plasma levels of antioxidants and ascorbic acid. Significant decrease in the rate of progression of carotid intimal medial thickness was also observed in the treatment group. Moreover, no deleterious effects were observed with this therapy, thereby clearly indicating that antioxidants slow down atherosclerotic progression. In coronary artery disease patients, it is suggested that increasing glutathione-1 peroxidase activity might lower the risk of cardiovascular events (32). Similarly, catalase by enzymatic inactivation of ROS (33), super-oxide dismutase by regulating the availability of nitric oxide (34) and selenium by increasing glutathione peroxidase activity (35), might be protective against cardiovascular events in such patients.

However, the results of prospective antioxidant clinical trials (7-9) have been disappointing with regard to primary end point of cardiovascular events, as these trials found no overall protective relation between them. Thus, they have raised considerable doubt about antioxidant related cardiovascular protection in myocardial-infarction, stroke or other CVS events. Not

only this vitamin antioxidants may not only be ineffective but can also produce deleterious effects to vascular health (10,11). Beta-carotene supplementation has been suggested to produce significant increase in stroke incidence (10) and overall cardiovascular deaths (11).

Concerns

The biggest doubt, which antioxidants raises is that of suicidal oxidative stress, induced by certain antioxidants, which can act as pro-oxidants in high concentrations and can cause the cell to undergo severe oxidative stress ultimately resulting in suicidal cell death (36). In addition number of questions like appropriate timing of administration, dosage and duration of antioxidant therapy still need to be determined.

Natural anti-oxidants

Many studies suggest that dietary factors based on cereals, pulses, spices, dark green leafy vegetables such as kale and spinach, citrus fruits, crude palm oil, soybean oil, cod liver oil, sprouts, peppers, whole grain, honey, walnuts and black tea can significantly increase the hepatic antioxidant enzymes and their supplementation reduces the risk of coronary heart disease effectively and safely particularly phenolic compounds like flavonoids present in fruits and vegetables. They improve endothelial function and inhibit platelet aggregation in humans. Therefore, helpful in maintaining vascular homeostasis, endothelial function and helpful in conditions like acute coronary syndrome, including myocardial infarction and unstable angina (37-39). Moreover, due to some of the concerns associated with the use of pharmacological/ synthetic antioxidants and the fact that dietary antioxidants supplementation is as effective and safe, it is recommended that all good sources of natural antioxidants should be increased in the diet for prevention and treatment of various cardiovascular conditions.

Conclusion

Presently, there are convincing evidences suggesting increase intake of antioxidants to be protective in cardiovascular diseases. However, irrational and non-judicial use of antioxidants can also increase the risk of potential toxicity. In spite of these concerns they have gained very important status. The best recommended action is to increase the intake of natural dietary antioxidant vitamins for good cardiovascular health.

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