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Role of antioxidants and oxidative stress in cardiovascular diseases

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ABSTRACT

Coronary artery disease (CAD) is a leading cause of death in the western world. Cardiovascular disease (CVD) is a leading cause of mortality and is responsible for one-third of all global death India, for example, approximately 53% of CVD deaths are in people younger than 70 years of age: in china the corresponding figure is 35%. The majority of the estimated 32 million heart attacks and strokes that occur every year are caused by one or more cardiovascular risk factors – hypertension, diabetes and etc. Our review article mainly focused on role of antioxidants and oxidative stress in cardiovascular diseases. We developed a search strategy to find publications about CVD and its Oxidative stress management. So, we searched Science Direct, Medline and PubMed bibliographic databases using the key phrases causes of CVD, antioxidants, oxidative stress, management of CVD and drugs under clinical trials. Our review article results, list out of clinical research studies done in Oxidative stress and antioxidant status in cardiovascular patients during 1999-2009. It has been concluded that, 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 best recommended action is to increase the intake of natural dietary antioxidant vitamins are good for health.

Key Words: Diabetes, Hypertension, Mortality, Stroke

INTRODUCTION

The world is poised for the tidal wave of CVDs. It is responsible for 10% of DALYs (disability adjusted life years) lost in low and middle-income countries and 18% in high income countries [1]. The etiology and pathophysiology of CVDs are complex, but the major risk factors include unhealthy lifestyles and behaviors coupled with a multifactorial complex interaction between environment and genetic factors[2]. Growing evidence suggests that highly reactive oxygen

derived free radicals (ROS) of endogenous or environmental origin play a cognitive role in the genesis and progression of various CVDs [3, 4]. Normally these free radicals are effectively kept in check by the various levels of antioxidant defenses. Imbalance of this reaction either due to excess free radical formation or insufficient removal by antioxidants leads to oxidative stress (OS) [5]. Established risk factors such as tobacco use specially smoking, drinking, diet, pollution, exercises and metabolic abnormalities lead to the increased OS due to excess free radical activity [6] and that, these ROS can stimulate oxidation of low density lipoprotein (LDL), cholesterol, cholesterol derived species, protein modifications which can lead to foam cell formation and atherosclerotic plaques [7]. It is therefore, logical to presume that antioxidants should help to prevent the CVDs. There is supportive evidence that vitamin C and E exert protective effect against CVDs by reducing OS, though some doubts have very recently been raised [8, 9, 10]. Despite ROS and antioxidants being of central attention in CVDs, especially atherosclerosis, hypertension, myocardial infarction and stroke all over the world [11].

Epidemiology

Epidemiologists in India and international agencies such as the World Health Organization (WHO) have been sounding an alarm on the rapidly rising burden of cardiovascular disease (CVD) for the past 15 years. The reported prevalence of coronary heart disease (CHD) in adult surveys has risen four-fold in 40 years areas the prevalence has doubled over the past 30 years [12]. In 2005, 53% of the deaths were on account of chronic diseases and 29% were due to cardiovascular diseases alone [13, 14]. It is estimated that by 2020, CVD will be the largest cause of disability and death in India. The country already has more than 40.9 million people with diabetes and more than 118 million people with hypertension, which is expected to increase to 69.9 and 213 million respectively, by 2025 unless urgent preventive steps are taken [15 – 17]. WHO estimates that India lost 9 billion dollars in national income from premature deaths due to heart disease, stroke and diabetes in 2005, and is likely to lose 237 billion dollars by 2015 [18].

Of further concern is the fact that Indians are succumbing to diabetes, high blood pressure and heart attacks 5–10 years earlier than their Western counterparts, in their most productive years [19, 20]. Unfortunately, scientific data also show that socio-economically disadvantaged sections of the population are now the dominant victims of CVD and its risk factors [21].

Antioxidants

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 [22, 23].

Types of antioxidant defenses

1. Primary or chain breaking antioxidants (scavenger antioxidants): These antioxidants can neutralize free radicals by donating one of their own electrons, 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 catalase 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 their presence results in altered cell metabolism and viability e.g. damaged DNA repaired by enzyme methionine sulphaoxide reductase [24].

Classifications of Antioxidants:

Antioxidants are classified into two broad divisions, depending on whether they are soluble in water (hydrophilic) or in lipids (hydrophobic). In general, water-soluble antioxidants react with oxidants in the cell cytosol and the blood plasma, while lipid-soluble antioxidants protect cell membranes from lipid peroxidation. These compounds may be synthesized in the body or obtained from the diet [25]. The different antioxidants are present at a wide range of concentrations in body fluids and tissues, with some such as glutathione or ubiquinone mostly present within cells, while others such as uric acid are more evenly distributed. Some antioxidants are only found in a few organisms and these compounds can be important in pathogens and can be virulence factors [26].

The relative importance and interactions between these different antioxidants is a very complex question, with the various metabolites and enzyme systems having synergistic and interdependent effects on one another [27, 28]. The action of one antioxidant may therefore depend on the proper function of other members of the antioxidant system. The amount of protection provided by any one antioxidant will also depend on its concentration, its reactivity towards the particular reactive oxygen species being considered, and the status of the antioxidants with which it interacts [25].

Some compounds contribute to antioxidant defense by chelating transition metals and preventing them from catalyzing the production of free radicals in the cell. Particularly important is the ability to sequester iron, which is the function of iron-binding proteins such as transferrin and ferritin [29]. Selenium and zinc are commonly referred to as *antioxidant nutrients*, but these chemical elements have no antioxidant action themselves and are instead required for the activity of some antioxidant enzymes, as is discussed in Table 1.

Table 1: Properties of some Antioxidant Enzymes.

Antioxidant metabolite	**Solubility**	**Concentration in human serum (µM)**	**Concentration in liver tissue (µmol/kg)**
Ascorbic acid (vitamin C)	Water	50 – 60	260 (human)
Glutathione	Water	4	6,400 (human)
Lipoic acid	Water	0.1 – 0.7	4 – 5 (rat)
Uric acid	Water	200 – 400	1,600 (human)
Carotenes	Lipid	B-carotene: 0.5 – 1 Retinol (vitamin A): 1-3	5 (human, total carotenoids)

α-Tocopherol (vitamin E)	Lipid	10-40	50 (human)
Ubiquinol (CoA)	Lipid	5	200 (human)

Ascorbic acid

Ascorbic acid or "vitamin C" is a monosaccharide antioxidant found in both animals and plants. As one of the enzymes needed to make ascorbic acid has been lost by mutation during human evolution, it must be obtained from the diet and is a vitamin [30]. Most other animals are able to produce this compound in their bodies and do not require it in their diets [31]. In cells, it is maintained in its reduced form by reaction with glutathione, which can be catalysed by protein disulfide isomerase and glutaredoxins [32, 33]. Ascorbic acid is a reducing agent and can reduce, and thereby neutralize, reactive oxygen species such as hydrogen peroxide [34]. In addition to its direct antioxidant effects, ascorbic acid is also a substrate for the antioxidant enzyme ascorbate peroxidase, a function that is particularly important in stress resistance in plants [35]. Ascorbic acid is present at high levels in all parts of plants and can reach concentrations of 20 millimolar in chloroplasts [36].

Glutathione

Glutathione is a cysteine-containing peptide found in most forms of aerobic life [37]. It is not required in the diet and is instead synthesized in cells from its constituent amino acids [38]. Glutathione has antioxidant properties since the thiol group in its cysteine moiety is a reducing agent and can be reversibly oxidized and reduced. In cells, glutathione is maintained in the reduced form by the enzyme glutathione reductase and in turn reduces other metabolites and enzyme systems, such as ascorbate in the glutathione-ascorbate cycle, glutathione peroxidases and glutaredoxins, as well as reacting directly with oxidants. Due to its high concentration and its central role in maintaining the cell's redox state, glutathione is one of the most important cellular antioxidants. In some organisms glutathione is replaced by other thiols, such as by mycothiol in the actinomycetes, or by trypanothione in the Kinetoplastids [39 - 44].

Melatonin

Melatonin is a powerful antioxidant that can easily cross cell membranes and the blood-brain barrier [45]. Unlike other antioxidants, melatonin does not undergo redox cycling, which is the ability of a molecule to undergo repeated reduction and oxidation. Redox cycling may allow other antioxidants (such as vitamin C) to act as pro-oxidants and promote free radical formation. Melatonin, once oxidized, cannot be reduced to its former state because it forms several stable end-products upon reacting with free radicals. Therefore, it has been referred to as a terminal (or suicidal) antioxidant [46].

Tocopherols and tocotrienols (vitamin E)

Vitamin E is the collective name for a set of eight related tocopherols and tocotrienols, which are fat-soluble vitamins with antioxidant properties [47, 48]. Of these, α-tocopherol has been most studied as it has the highest bioavailability, with the body preferentially absorbing and metabolising this form [49]. It has been claimed that the α-tocopherol form is the most important lipid-soluble antioxidant, and that it protects membranes from oxidation by reacting with lipid radicals produced in the lipid peroxidation chain reaction [50, 51]. This removes the free radical intermediates and prevents the propagation reaction from continuing. This reaction produces

oxidised α-tocopheroxyl radicals that can be recycled back to the active reduced form through reduction by other antioxidants, such as ascorbate, retinol or ubiquinol [52]. This is in line with findings showing that α-tocopherol, but not water-soluble antioxidants, efficiently protects glutathione peroxidase 4(GPX4)-deficient cells from cell death [53]. GPx4 is the only known enzyme that efficiently reduces lipid-hydroperoxides within biological membranes.

Antioxidants-Present Status in Cardiovascular diseases (CVD)

In humans, antioxidant vitamins by potentiating endothelial nitric oxide levels as well as by inhibiting vascular inflammation, lipid peroxidation, platelet aggregation and oxidation of LDL can also contribute to prevent endothelial dysfunction. Additionally, antioxidants may favorably influence plaque stability. Studies provide direct evidences that antioxidant vitamins can reverse endothelial dysfunction induced by methionine as well as can restore endothelial function in hyperlipidemic children and young smokers. Allopurinol, (xanthine oxidase inhibitor) a potential antioxidant has been shown to reverse endothelial dysfunction in heavy smokers, type-2 diabetics with mild hypertension and in patients of chronic heart failure. 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. Similarly, catalase by enzymatic inactivation of ROS, super-oxide dismutase by regulating the availability of nitric oxide and selenium by increasing glutathione peroxidase activity, might be protective against cardiovascular events in such patients [54].

Natural antioxidants

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 [54, 55].

Oxidative Stress

Oxidative stress is defined in general as excess formation and /in sufficient removal of highly reactive molecules such as reactive oxygen species (ROS), and reactive nitrogen species (RNS). ROS include free radicals such as superoxide ($\bullet O_2$-), hydroxyl (•OH), peroxyl ($\bullet RO_2$), hydroperoxyl ($\bullet HRO_2$-) as well as non radical species such as hydrogen peroxide (H_2O_2) and hydrochlorous acid (HOCl). RNS include free radicals like nitric oxide (•NO) and nitrogen dioxide ($\bullet NO_2$), as well as non radicals such as peroxynitrite (ONOO-), nitrousoxide (HNO_2) and alkyl peroxynitrates (RONOO). Of these reactive molecules, $\bullet O_2$-, •NO and ONOO- are the most widely studied species and play important roles in the cardiovascular complications. In humans, oxidative stress is involved in many diseases, such as atherosclerosis, Parkinson's disease, heart failure, myocardial infarction, Alzheimer's disease, fragile X syndrome and chronic fatigue syndrome, but short-term oxidative stress may also be important in prevention of aging by induction of a process named mitohormesis. Reactive oxygen species can be beneficial, as they are used by the immune system as a way to attack and kill pathogens. Reactive oxygen species are also used in cell signaling [56].

Oxidative stress parameters:

- Superoxide dismutase
- Lipid peroxidation: TBARS, MDA
- Catalase

Superoxide dismutase (SODs)

Superoxide dismutases (SODs) are a class of closely related enzymes that catalyze the breakdown of the superoxide anion into oxygen and hydrogen peroxide. SOD enzymes are present in almost all aerobic cells and in extracellular fluids [57]. Superoxide dismutase enzymes contain metal ion cofactors that, depending on the isozyme, can be copper, zinc, manganese or iron. In humans, the copper/zinc SOD is present in the cytosol, while manganese SOD is present in the mitochondrion. There also exists a third form of SOD in extracellular fluids, which contains copper and zinc in its active sites. The mitochondrial isozyme seems to be the most biologically important of these three, since mice lacking this enzyme die soon after birth [58].

Catalase:

Catalases are enzymes that catalyse the conversion of hydrogen peroxide to water and oxygen, using either an iron or manganese cofactor. This protein is localized to peroxisomes in most eukaryotic cells. Catalase is an unusual enzyme since, although hydrogen peroxide is its only substrate, it follows a ping-pong mechanism. Here, its cofactor is oxidized by one molecule of hydrogen peroxide and then regenerated by transferring the bound oxygen to a second molecule of substrate. Despite its apparent importance in hydrogen peroxide removal, humans with genetic deficiency of catalase "acatalasemia" or mice genetically engineered to lack catalase completely, suffer few ill effects [59, 60].

Peroxiredoxins:

Peroxiredoxins are peroxidases that catalyze the reduction of hydrogen peroxide, organic hydroperoxides, as well as peroxynitrite. They are divided into three classes: typical 2-cysteine peroxiredoxins; atypical 2-cysteine peroxiredoxins; and 1-cysteine peroxiredoxins. These enzymes share the same basic catalytic mechanism, in which a redox-active cysteine (the peroxidatic cysteine) in the active site is oxidized to a sulfenic acid by the peroxide substrate. Over-oxidation of this cysteine residue in peroxiredoxins inactivates these enzymes, but this can be reversed by the action of sulfiredoxin. Peroxiredoxins seem to be important in antioxidant metabolism, as mice lacking peroxiredoxin 1 or 2 have shortened lifespan and suffer from hemolytic anaemia, while plants use peroxiredoxins to remove hydrogen peroxide generated in chloroplasts [61]. The most common prescribed medication in oxidative stress for cardiovascular disease shown in Table 2.

Table 2: Common medications associated with oxidative stress in cardiovascular disease

Pathophysiology	Clinical findings	Treatment
Congestive heart failure	*Left Heart Failure Symptoms* • Progressive breathlessness, that is more marked on exertion. • Paroxysmal nocturnal dyspnea attacks. • Weakness, fatigue, palpitation and pain in	Digoxin Inotropic drugs Diuretics: • Furosemide • Spiranolactone

	the chest. Acute left heart failure is characterized by basal crepitations, tachycardia, cold extremities, facial pallor, hypertension and a galloping rhythm. *Right Heart Failure Symptoms* • Generalized fatigue and weakness including cough, breathlessness, anorexia, abdominal distension, pain and dragging sensation in the right hypochondrium. • Headache, restlessness, insomnia, weight gain, swelling of legs and feet, oliguria and nocturia. • Physical signs include cyanosis, warm extremities, engorged neck veins, elevated jugular venous pressure, enlarged liver and edema over legs and feet. • The size of the heart is generally within normal limits. Pulmonary diastolic murmur is seen due to pulmonary hypertension. Signs of pleural effusion maybe present.	Vasodilators; • Isosorbide dinitrate hydralazine • prazocin ACE inhibitors: • Captopril • Enalapril
Coronary artery disease	• Pain in the retrosternal region, radiating to precordium inner side of left arm, shoulder and back. • The pain maybe severely crushing or choking in nature and is often brought about by exertion or after a heavy meal and by walking in cold weather. It is accompanied by sweating, uneasiness and fear. Acute myocardial infarction. • Chronic ischemic cardiomyopathy. • Coronary heart disease present complications like acute left heart failure, cardiac arrhythmias and congestive failure	Nitroglycerine for angina β-blockers: • Metaprolol • labatalol Ca^{+2} channel blockers Verapamil
Acute myocardial infarction	• Chest pain • Restless, profusely sweating • State of panic.. • Cardiac arrhythmias, ventricular tachycardia, fibrillation or supra-ventricular tachycardia. • Weak peripheral pulse, with cold and sweating extremities and visible pallor, accompanied by hypotension.	First line: morphine aspirin Fibrinolytic agent: Streptokinase
Hypertension	• Headache, • Palpitations, • Tinnitus,	• Diuretics • Beta blockers, • Ca^{+2}channel

	• Giddiness	blockers, • Alpha blockers, • ACE inhibitors
Cardiac arrhythmias	• Irregular heart beats • Ventricular tachycardias and • Ventricular fibrillation. • Extra systoles or ectopic beats, • Supraventricular ectopic beats, • Ventricular premature beats	Beta blockers like Propranolol, acebutalol and atenolol. Other drugs are procainamide, diazepam, lignocaine etc.
Cardiomegaly	• Hypertrophic cardiomyopathy include • Fatigue, • Heaviness in chest, • Shortness of breath, • Palpitations, • Sweating, • High blood pressure etc..	The treatment of cardiomegaly involves treating the root cause of the condition.
Miscellaneous cardiovascular diseases • Fluid around the heart (Pericardial effusion • Atherosclerosis • Infective endocarditis • Valvular heart disease • Congenital heart disease	• Angina on exertion, • Intermittent claudication	HMG-CoA reductase inhibitors: • Atorvastatin • Pravastatin • simvastatin

Evidence from clinical studies of oxidative stress

Hypertension

Lipid peroxidation by-products have been shown to be elevated, whereas levels/activity of anti-oxidant systems has been reported to be decreased in hypertensive subjects. Among the latter, Redon et al observed decreases in the activities of SOD and CAT, as well as an increase in the ratio of oxidized to reduced glutathione [62]. Moreover, many of the adverse effects of hypertension on endothelial function may be reversed by intra-arterial infusion of anti-oxidants, such as vitamin C. Several studies have shown an increase in O_2- levels in hypertension. Other studies implicate NAD(P)H oxidase as a source of excess O_2-. A number of studies have described polymorphisms in the p22*phox* gene, which show an association with atherosclerotic disease or endothelial function. Preliminary results from our group suggest that a single nucleotide polymorphism in the p22*phox* gene may affect arterial compliance. However, treatment with the AT1 (angiotensin II type 1) receptor blocker Candesartan failed to improve endothelial function in one study of hypertensive patients [63], and NAD(P)H oxidase may not be the primary source of excess O_2- in all hypertensive subjects.

Diabetes

Many biochemical pathways strictly associated with hyperglycaemia (glucose auto-oxidation, polyol pathway, prostanoid synthesis and protein glycation) can increase the production of free radicals. Furthermore, exposure of endothelial cells to high glucose leads to augmented production ofO_2^- [64] In further support of the pathological role of oxidative stress, many of the adverse effects of high glucose on endothelial function, such as reduced endothelial-dependent relaxation and delayed cell replication, are reversed by anti-oxidants *in vivo*. A rational extension of this proposed role of oxidative stress is the suggestion that the different susceptibility of diabetic patients to microvascular and macrovascular complications may be a function of the endogenous anti-oxidant status [65].

Hyperlipidaemia

Hypercholesterolemia increases endothelial O_2 atherogenesis. Hypercholesterolemia has been independently associated with increased NADH dependent superoxide production [66]. Endothelial cells, smooth muscle cells, neutrophils and monocytes all have the potential to oxidatively modify LDL, leading to the generation of lipid peroxidation products and ROS. Lipid peroxidation products may contribute to tissue damage through direct cytotoxic actions on endothelial cells or via reactions in which 'modified' LDL is generated and is selectively bound by 'scavenger' receptors. Nourooz-Zadeh et al. demonstrated that oxidative stress is increased in patients with familial hypercholesterolaemia [67, 68].

CHF (chronic heart failure)

In patients with CHF, TBARS and 8-iso-prostaglandin F2*α*, major biochemical consequences of ROS generation, have been found to be elevated in plasma and pericardial fluid respectively [69]. Studies *in vivo* of endothelium-dependent and independent coronary vasodilation in patients with dilated cardiomyopathy have demonstrated a selective impairment of acetylcholine-induced increase in coronary blood flow, compared with that obtained after infusion of adenosine. These original observations suggest that endothelial dysfunction may be evident in CHF patients, possibly due to enhanced ROS activity. Studies by McMurray et al confirmed that ROS activity was increased in plasma of patients with heart failure secondary to coronary artery disease, compared with controls [70]. Plasma malondialdehyde, a marker of lipid peroxidation, is elevated in CHF and is related to exercise intolerance. In other studies, increased concentrations of malondialdehyde and decreased concentrations of glutathione, vitamins C and E were correlated with both NYHA (New York Heart Association) functional class and plasma concentrations of the cytokine, tumour necrosis factor *α*−production and vascular oxidative stress, which may in turn contribute to impaired endothelial damage and Lower levels of ECSOD have also been reported in subjects with coronary artery disease. CHF is a state characterized by a number of processes that may promote ROS generation *in vivo*. These pro-oxidant pathways include cytokine activation, mitochondrial dysfunction, recurrent hypoxia– reperfusion, possibly genetic susceptibilities and activation of the renin–angiotensin system. There are a number of potential cellular sources implicated in enhanced ROS generation in CHF. It has recently been demonstrated that CHF patients may have increased leucocyte O_2− production, which is, in turn, related to severity of disease, as measured by NYHA functional class. Other sources of enhanced ROS generation in human CHF are both the myocardium and peripheral blood vessels. Increased activity of myocardial NADPH oxidase has been reported in heart failure [71].

Hyperhomocysteinaemia

Clinical studies have shown that patients with hyperhomocysteinaemia exhibit endothelial dysfunction and elevated oxidative stress both *in vitro* and *in vivo* [72], however, the mechanisms by which homocysteine affects endothelial function are unclear. It is important to consider that most studies have used concentrations of homocysteine that exceed that observed *in vivo*. The experimental increase of plasma homocysteine concentration by methionine loading rapidly impairs endothelial function and ROS in healthy humans. Increased oxidant stress appears to play a key role in the deleterious endothelial effects of homocysteine, because the administration of an anti-oxidant completely prevents this processes [73].

Cigarette smoking

Serum activities of the anti-oxidant enzymes GPx, glutathione reductase and ECSOD are reported to be lower in smokers than in non-smokers [74]. Serum ascorbic acid and folic acid concentrations also are lower in smokers than in non-smokers, whereas serum malondialdehyde and TBARS are higher [75]. Activities of SOD and CAT in erythrocytes are significantly lower in heavy smokers, light smokers and passive smokers than in non-smokers. It has been observed that passive smokers are affected by the environmental smoke to the same extent as active smokers. Cigarette smoking cessation increases plasma levels of several anti-oxidant micronutrients and improves resistance towards oxidative challenge. A plethora of evidence suggests that administration of anti-oxidants, such as vitamins C and E, suppresses increased smoking-related lipid peroxidation markers in cigarette smokers [76]. The Table no 3 shows the list of research studies.

Table 3: List of clinical research studies done in Oxidative stress and antioxidant status in Cardiovascular patients during 1999-2009.

S.No	Title	Author	Year	Results/ Discussion
1	Oxidative Stress and Cardiac Biomarkers in Patients with Acute Myocardial Infarction	Palanisamy Pasupathi	2009	There is growing evidence that increased free radical production and impaired antioxidant protection is relevant to plaque activation.
2	Oxidative stress and antioxidant status before and after supplementation of A-Z anti-oxidant tablets in coronary artery disease	Abdul Kayyum Shaikh	2009	The study showed that the levels of lipid peroxide were significantly increased (P<0.001) in patients with CAD as compared to control.
3	Oxidative Stress Bio Markers and Antioxidant Status in Cigarette Smokers Compared to Nonsmokers	Palanisamy Pasupathi,	2009	The study shows that there were no significant differences in weight and body mass index between smokers and non-smokers.
4	Oxidative stress in cardiovascular disease	Vijaya Lakshmi SV	2009	The changes in the lifestyle pattern, increasing number of subjects is at risk of vascular disease and there is preponderance of evidence for the association of increased oxidative stress with various vascular diseases.

5	Oxidative stress and antioxidant status in normolipidemic AMI patients	Arun Kumar	2008	The study showed a significant increase in malondialdehyde and conjugated dienes in patients with AMI was observed as compared to controls.
6	Oxidative Stress in Young Subjects With Acute Myocardial Infarction: Evaluation at the Initial Stage and After 12 Months	Rosalia LoPresti,	2008	The study was carried out making a double subdivision regarding either the total number of risk factors or the extent of coronary disease.
7	Smoking induced oxidative stress in serum and neutrophil of the university students.	Santanu Kar Mahapatra	2008	The cigarette smoking was not associated with a reduction in height, although body weights tended to be lower in the smokers than in the non-smokers.
8	Endothelial Dysfunction in Cardiovascular Diseases The Role of Oxidant Stress.	Hua Cai	2008	Many enzymatic systems that are capable of producing ROS, xanthine oxidase, NADH/NADPH oxidase, and uncoupled endothelial nitric oxide synthase have been extensively studied in vascular cells.
9	Oxidative stress and total anti oxidant status in myocardial infarction.	Surekha R H,	2007	The study revealed the importance of determining the total antioxidant status in MI, in addition to the markers of oxidative stress and lipid profiles to enable the formulation of specific antioxidant therapies for an early intervention and better management of the disease.
10	Antioxidant status in patients with acute myocardial infarction.	Neela Patil,	2007	The study indicates an imbalance between oxidant and antioxidant molecules in AMI patients, and magnitude of imbalance is greater in diabetic AMI patients, possibly because of greater inflammation in diabetic patients
11	Oxidative stress and antioxidant status in cardiovascular diseases in population of western Nepal.	Risal S,	2006	OS (oxidative stress) does not appear to be an etiological factor for the cardiovascular diseases; rather slightly raised OS in patients seems to be a consequence.
12	Exercise, oxidative stress and risk of cardiovascular disease in the elderly. Protective role of antioxidant functional foods.	Ana I. Galan	2006	The study demonstrated that besides increasing cardio-respiratory fitness in men and women the long term exercise program administered to elderly people significantly improved some predictors of CVD risk; when the antioxidant food was administered daily and concurrently no ergogenic effects were detected, but additional beneficial effects were observed in oxidative stress status, mean BP and the LDL-C plasma levels, which were

				significantly lower than those observed in the non-supplemented subjects.
13	Assays for oxidative stress and antioxidant status: applications to research into the biological effectiveness of polyphenols.	Andrew R Collins	2005	Supplementation with antioxidants in vivo is the best approach, at least in principle, and experiments should be performed with human subjects if possible.
14	Oxidative stress and the use of antioxidants in diabetes: Linking basic science to clinical practice.	Jeanette Schultz Johansen†	2005	The recent American Heart Association science advisory on the subject of antioxidant vitamins and cardiovascular disease asserted that there is insufficient evidence to justify the use of antioxidant vitamins for cardiovascular disease risk reduction
15	Poly phenols: antioxidants and beyond.	Augustin Scalbert	2005	The antioxidant properties of polyphenols have been widely studied, but it has become clear that the mechanisms of action of polyphenols go beyond the modulation of oxidative stress.
16	Strategies to reduce oxidative stress in cardiovascular disease.	Carlene A.	2004	The study summarizes the extensive array of experimental animal and human data describing pharmacological and molecular approaches to reducing oxidative stress.
17	Assessment of oxidative stress and antioxidant status in age related cataract in a rural population.	A.K. Pradhan	2004	The study stated that enzymatic antioxidant status was studied by estimating serum SOD (superoxide dismutase) and erythrocyte catalase activity.
18	Is Oxidative Stress the Pathogenic Mechanism Underlying Insulin Resistance, Diabetes, and Cardiovascular Disease? The Common Soil Hypothesis Revisited.	Antonio Ceriello	2004	The study suggested that free radical over generation may be considered the key in the generation of insulin resistance, diabetes, and cardiovascular disease.
19	Free radicals and redox signalling in cardiovascular disease.	A M Shah,	2004	Despite the clear evidence for the biological importance of ROS, large antioxidant trials have shown no benefit in reducing cardiovascular events or mortality. However, antioxidant strategies have no place in cardiovascular disease prevention or treatment.
20	Antioxidant Activities and Oxidative Stress Byproducts in Human Hypertension.	Josep Redón,	2003	The study reveals that oxidative stress is increased in hypertensive subjects even in cells other than those present in the vascular wall. This increased oxidative

				stress, not related to BP values, is accompanied by a reduction in the most important antioxidant mechanisms and by the accumulation of ROS byproducts, not only from lipid peroxidation but also from oxidized genomic and mitochondrial DNA
21	Antioxidant Nutrients and Chronic Disease: Use of Biomarkers of Exposure and Oxidative Stress Status in Epidemiologic Research.	Susan T. Mayne	2003	The dietary antioxidants or other nutrients that can alter the levels of these biomarkers are themselves causally related to the development or prevention of chronic Diseases
22	Decreased Serum Total Antioxidant Status and Erythrocyte-Reduced Glutathione Levels Are Associated with Increased Serum Malondialdehyde in Atherosclerotic Patients.	Lulufer tamer	2002	The study suggests that antioxidant agents may have preventive roles in the formation of atherosclerosis.
23	Factors Associated with Oxidative Stress in Human Populations.	Gladys Block1,	2002	The study was the strong and significant association of Iso-P with body mass index. Iso-P may be a sensitive marker of lipid peroxidation derived from oxidation of adipose tissue. The strong relation of both Biomarkers to sex seem extremely important and justify further research.
24	Antioxidant Effects of Vitamins C and E Are Associated With Altered Activation of Vascular NADPH Oxidase and Superoxide Dismutase in Stroke-Prone SHR.	Xin Chen,	2001	The study shows that (1) blood pressure–lowering effects of vitamins C and E are associated with improved endothelium-dependent vasodilation and amelioration of vascular structural changes, (2) vitamin supplementation decreases vascular oxidative stress and improves total antioxidant status, and (3) antioxidant properties of vitamins C and E are associated with decreased activation of NADPH oxidase and increased activity of superoxide dismutase.
25	Role of oxidative stress in cardiovascular diseases.	Dhalla	2000	The existing evidence support the view that oxidative stress may play a crucial role in cardiac and vascular abnormalities in different types of cardiovascular diseases and that the antioxidant therapy may prove beneficial in combating these problems.
26	Status of myocardial antioxidants in ischemia–	Naranjan S	2000	The hypothesis involving the role of ROS in myocardial ischemia–reperfusion injury

	reperfusion injury.			has been supported by a wide range of investigations. Myocardial ischemia–reperfusion has been shown to result in contractile dysfunction, arrhythmias, loss of adrenergic pathways, changes in gene expression, apoptosis as well as necrotic cell death
27	Serum malondialdehyde and prevalent cardiovascular disease in hemodialysis.	Mona Boaz	1999	The study indicated the presence of oxidative stress in HD patients, and is consistent with the theory of oxidative stress as a factor in accelerated CVD in this population.
28	Free radicals in cardiovascular diseases.	Jasmina Mimic-Oka	1999	The study stated that implementation of antioxidant therapies requires a better understanding of the involvement of free radicals and molecular mechanisms by which they exert cytotoxicity in disease states.

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 are good for cardiovascular disease.

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