# Invited Article

## Antioxidants in Health and Disease: Review of Clinical Trials

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## Abstract

Free radicals play an important role in several biological processes such as cell signaling and redox regulation. However, prolonged exposure to free radicals leads to oxidative damage. Subsequently, it has been implicated in the progression of several diseases like cancer, cardiovascular disease, neurological disease, pulmonary disease, rheumatoid arthritis, nephropathy, ocular disease and pre-eclampsia. The antioxidant defense system within the body may confer protection to oxidative damage by scavenging free radicals. Antioxidants also may be obtained from dietary sources/ supplements. The efficacy of antioxidant intake on initiation and progression of chronic diseases will be reviewed.

Chettinad Health City Medical Journal 2013; 2(4): 113 - 122

## Introduction

Oxygen is an element that is crucial for the sustenance of life on earth. It is paradoxical that this indispensable element can cause harmful effects in humans under certain circumstances. Much of the detrimental consequences of oxygen are attributed to its ability to form free radicals[1]. A free radical is a reactive molecule that contains at least one unpaired electron in its outer orbit, and is capable of independent existence[2]. Accumulation of these molecules in the body results in oxidative stress, a process by which physiologically important molecules such as carbohydrates, proteins and lipids are damaged[3]. However, the body can employ antioxidants to impede the threat of free radical attack[4].Antioxidants are potent scavengers of free radicals[1]. They function by donating an electron to a free radical or by eliminating initiators of free radicals[5]. Antioxidants may be classified as endogenous or exogenous depending on their mode of acquisition by the body[1]. Endogenous antioxidants are naturally produced by the body[1].Superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase are enzymatic systems within the body that function as antioxidants[1]. Lipoid acid, glutathione, L-arginine, coenzyme Q10, melatonin, uric acid and bilirubin are examples of non-enzymatic antioxidants that are produced during metabolism[3,4]. On the other hand, exogenous antioxidants cannot be synthesized biologically, and must be supplied through the diet and/or supplements[1]. Vitamin E ( alpha - tocopherol), vitamin C (ascorbate), beta-carotene (provitamin A carotenoid), trace elements such as selenium, manganese, zinc, flavonoids, lycopene, omega-3 and omega-6 fatty acids are some antioxidants that can be obtained from the diet[1]. Fruits, vegetables, nuts, herbs, spices and beverages are identified as natural sources of such exogenous antioxidants[6]. A delicate balance between prooxidant and antioxidant substances is achieved by the production and scavenging of free radicals[3]. Under optimal physiological conditions, this equilibrium marginally shifts to favor a prooxidant status and maintains mild oxidative stress within the body[3]. Antioxidants perform a dual role; of scavenging free radicals while still allowing a sufficient amount to persist and carry out vital functions[7]. Some of the important biological functions of free radicals are cell signaling and redox regulation[3]. However, an acute shift towards prooxidant status will lead to oxidative damage[7]. Additionally, lack of regulation of free radicals is implicated in the pathogenesis of several disease states such as cancer, cardiovascular disease, neurological disease, pulmonary disease, rheumatoid arthritis, nephropathy, ocular disease and pre-eclampsia[1].The purpose of this paper is to review some of the clinical trials that have explored the influence of antioxidant intake from food and supplements on the prevention of initiation and progression of certain chronic diseases. Additionally, the paper will discuss about the use of antioxidants in health maintenance.

## Cancer

Mortality and morbidity associated with cancer is a major public health problem. It was estimated that 12.7 million people were affected by cancer worldwide in 2008[8]. Furthermore, about 7.6 million deaths were attributed to cancer[8]. Breast cancer and lung cancer are the leading causes of cancer death among females and males, respectively[8]. The development of cancer is a multistage process that involves initiation, progression

and promotion of the tumor[9]. Free radicals can wreck havoc at all stages of cancer development[9]. The influence of free radical induced- deoxyribonucleic acid (DNA) alterations on carcinogenesis may be mediated by epigenetic effects on gene expression, mutations and chromosomal rearrangements[10]. Tobacco smoke, ultraviolet (UV) radiation, consumption of red meat and alcohol, and obesity have been identified as risk factors for various types of cancer owing to their ability to generate oxidative stress[11]. The antioxidant status of cancer patients has been found to be significantly lower than that of normal individuals, as demonstrated by reduced levels of glutathione, glutathione peroxidase, superoxide dismutase, vitamin C and E in cancer patients[12]. Observational studies have reported that the intake of fruits and vegetables confer protection against cancers of the lung, breast, stomach, pharynx, esophagus and pancreas[13]. Given that fruits and vegetables are rich sources of antioxidants, it can be reasoned that antioxidant supplementation reduces the risk of cancer. On the contrary, clinical trials testing the efficacy of antioxidant supplementation for cancer prevention have yielded limited success. The alpha-tocopherol and beta-carotene (ATBC) study sought to determine the effectiveness of alpha-tocopherol and beta-carotene supplementation in reducing the occurrence of lung cancer among male smokers, aged 50-69 years. Results of this trial demonstrated that the incidence of lung cancer was significantly higher among individuals receiving beta-carotene[14]. The Beta-Carotene and Retinol Efficacy Trial (CARET) also found that the relative risk of lung cancer was greater in participants who received beta-carotene and retinol supplementation when compared to placebo[15].

Participants for this trial included men who were substantially exposed to asbestos due to their occupation. The Linxian study was conducted in Linxian, a rural county belonging to north-central China. The population in this region was reported to be disproportionately affected by high rates of esophageal and gastric cancers[16], as well as subclinical deficiencies of retinol, carotenoids, tocopherols and other vitamins. The following combination of supplements were used in the Linxian study: Supplement A consisting of retinol palmitate and zinc; Supplement B including riboflavin and niacin, Supplement C comprising of vitamin C and molybdenum, and Supplement D consisting of beta-carotene, selenium and alpha-tocopherol. The eight intervention groups received AB, AC, AD, BC, BD, CD, ABCD, or placebo.The only significant outcome was that the group which received supplement D had a lower risk for stomach cancer mortality when compared to the other groups[17]. The Women's Antioxidant Cardiovascular Study (WASC) indicated that vitamin C, alpha-d-tocopherol acetate and beta-carotene did not reduce total cancer incidence in women with a history of cardiovascular disease (CVD) or three or more risk factors for CVD[18]. A reduction in non-Hodgkin's lymphoma risk was observed in women receiving beta-carotene[18]. However, lung cancer incidence was higher among women receiving vitamin C[18].

Results from the Selenium and Vitamin E Cancer Prevention Trial (SELECT) established that selenium, vitamin E or selenium and vitamin E combination did not reduce prostate cancer risk in a group of healthy men[19]. Thus, results from human clinical trials that explore the efficacy of antioxidant supplementation on cancer incidence have been inconclusive.

## Cardiovascular disease (CVD)

CVD is the leading cause of death worldwide, and accounted for approximately 17 million deaths in 2008[20]. Diseases of the cardiac muscle tissue and the vascular system, such as atherosclerosis, ischemic heart disease (IHD), stroke, congestive heart failure (CHF), are responsible for CVD. An inappropriate diet, obesity, physical inactivity, alcohol abuse and cigarette smoking are some of the modifiable risk factors of CVD[21]. The effects of risk factors on CVD may be mediated by oxidative stress, which in turn can cause oxidation of low-density lipoprotein (LDL) and disruption of vascular homeostasis. Thus, a diet rich in antioxidants may protect against the risk of CVD. A greater intake of fruits and vegetables has been associated with a lower risk of CVD[22]. The Heart Outcomes Prevention Evaluation (HOPE) was a large scale trial that reported no significant differences in myocardial infarction (MI), stroke and death from cardiovascular causes between vitamin E supplemented and placebo groups[23]. In contrast to the HOPE Trial, other studies that have researched the influence of antioxidant supplementation on CVD risk illustrate the beneficial effects of vitamin E. The Secondary Prevention using Antioxidants of Cardiovascular Disease in Endstage renal disease (SPACE) trial showed a significant decrease in fatal and non-fatal AMI, ischemic stroke, peripheral vascular disease, and unstable angina in CVD patients receiving vitamin E supplement when compared to the placebo group[24]. Similarly, Cambridge Heart Antioxidant Study (CHAOS)study indicated that vitamin E supplementation decreased the incidence of CVD death and non-fatal MI in coronary artery disease (CAD) patients[25]. The Nurses Healthy Study (NHS) determined vitamin A, vitamin C and vitamin E intake obtained from food sources and supplements in a population of middle-aged women. Results from this study reported no association between vitamin A, vitamin C and coronary disease risk[26]. However,intake of vitamin E from food sources was inversely related to risk of death from major coronary events[26]. The use of vitamin E supplements for more than 2 years was associated with a reduction in coronary disease risk[27]. The Physician's Health Study (PHS) showed that beta-carotene did not reduce cardiovascular mortality in the supplemented group versus the placebo group[28]. Results from the CARET trial indicated an increased risk for cardiovascular death in individuals treated with beta-carotene and retinol than the control group[15]. Additionally, the ATBC study did not establish a beneficial effect of beta-carotene on cardiac-related mortality in male smokers with a history of MI[29].Thus, vitamin E supplements have shown a greater therapeutic potential for CVD when compared to other antioxidants.

## Pre-eclampsia

Pre-eclampsia during pregnancy is marked by high

blood pressure and proteinuria[30]. Clinical manifestations of pre-eclampsia include birth of small-for-gestational-age infant, poor growth of the infant and premature birth, neonatal morbidity and mortality, and conditions that affect liver, kidneys, brain or blood clotting system for the woman[31]. The presence of free radicals may lead to injury of endothelial cells that line the inside surfaces of blood vessels, which in turn results in the clinical symptoms of pre-eclampsia[32]. Predisposition for LDL, resistance to oxidative stress, and antioxidant intake are the major determinants of a woman's response to oxidative stress[33]. Since a dietary deficiency of antioxidants is associated with this disorder, antioxidant supplementation may be employed as a potential measure to help prevent and treat this condition. Interventional studies have evaluated the use of vitamin C and E combination[34,36], vitamin C and E in combination with allopurinol[37],vitamin C alone[38], red palm oil[39], lycopene[40] and selenium[41] in pre-eclampsia. Pregnant women at low, moderate or high risk of developing pre-eclampsia were included for participation in these studies. Women with pre-eclampsia were excluded from participation. The primary outcomes examined were pre-eclampsia, severe pre-eclampsia, preterm birth, small-for-gestational age infants, and infant mortality. No significant differences were reported in the risk of any of the primary outcomes between the antioxidant supplemented and control group for the trials. Women allocated to lycopene had a greater reduction in the relative risk of pre-eclampsia. However, results from this study were based on a small group of women. The existing body of literature does not favor the use of antioxidants during pregnancy to reduce pre-eclamptic risk.

## Diabetes mellitus

Diabetes mellitus is a chronic, multiorgan disease that can severely damage the eyes, kidneys, nerves, heart and/ or blood vessels[42]. Globally, it is estimated that the number of adults affected by diabetes was 285 million in the year 2010, and will increase to 439 million by 2030[43]. India and China are expected to be disproportionately burdened by the increase in diabetes prevalence[43]. This condition is characterized by hyperglycemia that arises out of abnormalities in insulin secretion or insulin action[42]. Hyperglycemia can trigger generation of free radicals, thereby creating a state of oxidative stress that is involved in pathogenesis of diabetes and its related complications[43]. Small scale trials have shown the beneficial effects of antioxidants on diabetes-related complications. Supplementation with vitamin E[44] and vitamin E plus C[45] positively influenced endothelial-dependent vasorelaxation in Type I diabetic patients. However, a positive effect was not observed for Type 2 diabetic patients supplemented with vitamin E plus C[45]. In another study, significant improvement in renal function was observed in Type 2 diabetic patients supplemented with vitamin E plus C[46]. The Primary Prevention Project (PPP) trial demonstrated no beneficial effect of vitamin E for diabetic subjects[47]. However, the population for the PPP trial was not restricted to diabetic patients. In contrast, the alpha-lipoic acid in Diabetic Neuropathy (ALADIN)[48], ALADIN II[49], ALADIN III[50], DEKAN (Deutsche kardialeautonomeneuropathie)[51] and SYDNEY[52] trials were limited to a population of diabetic subjects. ALADIN, ALADIN II and ALADIN III studies demonstrated significant improvements in patient symptoms, nerve function, and neuropathy impairment score, respectively, in diabetic patients who were supplemented with alpha-lipoic acid[48,50]. In the DEKAN study, cardiac autonomic neuropathy was found to be improved in the alpha -lipoic acid treated group versus placebo group[51]. The SYDNEY trial showed advancements in sensory symptoms of diabetic polyneuropathy upon alpha-lipoic treatment[52]. In summary, large scale clinical trials that involve alpha-lipoic acid treatment have proved to be more effective than trials involving vitamin E treatment.More basic and clinical research is required to test the efficacy of antioxidants, such as alpha-lipoic acid, in improving the prognosis of diabetes.

## Chronic obstructive pulmonary disease (COPD)

COPD is a common lung disease characterized by airflow limitation attributed to disrupted alveolar attachment, mucus hypersecretion and inflammatory obstruction of the airway[53]. It is a major public health burden worldwide, and is estimated to affect about 14 million people in the United States[53]. Smoking and environmental pollution are two major risk factors for COPD[53]. Oxidative stress from exposure to tobacco and air pollutants may deplete plasma antioxidant capacity, thereby leading to inflammation and mucus secretion[54]. Intake of antioxidants via diet/supplements has been suggested as an ideal way to boost the lung antioxidant system[55]. Moreover, it has been associated with improved lung function, and is suggested as a strategy to enhance COPD outcomes[56]. The Women's Health Study (WHS) established that vitamin E supplementation lead to a decrease in the risk of chronic lung disease in women[57]. Lykkesfeldt et al, have shown that supplementation of vitamin C, vitamin E and beta-carotene enabled repletion of ascorbic acid in smokers[58]. N-acetyl-L-cysteine (NAC) is a nutritional supplement that has been used to strengthen antioxidant defense system in patients with COPD. NAC has been found to decrease oxidative stress in airways of COPD patients[59], and alleviate bronchial hypersecretion[60]. Although the use of antioxidants in COPD shows potential, more research is required to formulate recommendations on antioxidant supplementation for COPD management.

## Antioxidants in health maintenance

A prolonged exposure to free radicals may occur as a consequence of normal physiological processes, such as aging and intense exercise, thereby disrupting the delicate balance that exists within our body[7]. Normal individuals can incorporate antioxidant rich foods into their diet to protect themselves from oxidative damage, and thus maintain their health. Anlasik et al, reported a positive association between fruit and vegetable intake and antioxidant status in a group of healthy elderly subjects[61]. On the other hand, intake of antioxidant supplements is recommended only when a reduced antioxidant status is identified[7]. For example, several

micronutrient deficiencies have been associated with increased morbidity and mortality in children belonging to Africa and Asia[62]. Some of the deficient micronutrients include vitamin A and zinc[62], which also function as antioxidants. In such cases, supplementation may markedly improve clinical manifestations of the deficiency[63,64]. It is vital to apply caution when using supplements for healthy individuals since intake of high amounts of antioxidant supplements may lead to antioxidative stress[65]. Hence, precise determination of individual's free radical and antioxidant levels is required before prescribing antioxidant supplements [7].

## Conclusions

Several observational studies have demonstrated the beneficial effect of antioxidant rich diets on disease outcomes. However, discrepancy exists between observational studies and clinical trials that test the efficacy of antioxidants in disease prevention. The lack of adequate success in clinical trials can be viewed from different perspectives. Firstly, several physiological factors influence nutrient bioavailability. Some of the factors include age, gender, ethnicity, body weight, genetic composition and stage of the disease. These factors affect the extent to which antioxidants are utilized by the body, as well as the ability of an individual to respond to antioxidant supplementation. Knowledge of physiological variables that influence antioxidant bioavailability is essential to determine critical aspects of clinical trials, such as effective supplement dosage and duration of treatment. Moreover, a host of lifestyle behaviors are responsible for determining the health of individuals. Antioxidant intake in combination with physical activity, alcohol and tobacco moderation may yield profound benefits in disease management. Thus, multifactorial interventions may serve as alternative strategies in disease management. Finally, investigations on the effects of nutrients in isolation may provide valuable information regarding its mode of action, but do not elucidate the phenomenon of total diet. The intrinsic nature of diet is characterized by several interactions between bioactive dietary components, some of which still remain unexplained. Hence, antioxidant supplements must be prescribed with caution and the use of antioxidant rich foods as disease prevention agents may hold promise in future clinical trials.

Table1. Summary of selected clinical trials testing efficacy of antioxidants in cancer[66]

| Name of study | Trial | Primary outcome | Study population | Relative Risk(Confidence Interval) | Interpretation of results |
|---|---|---|---|---|---|
| ATBC | α-tocopherol(50mg), or β-carotene (20 mg), or both versus placebo | Lung cancer incidence | 29,133 male smokers 50–69 years of Age, with a history of MI, followed for 5–8 years | Lung: 0.98 (0.81–1.19) α-tocopherol vs placebo 1.16 (0.97–1.38) β-carotene vs placebo 1.15 (0.96–1.38) both vs placebo | A significant increase in incidence of lung cancer for β-carotene supplemented group. No significant decrease in incidence of lung cancer for any of the other supplemented groups |
| CARET | β-carotene (30 mg) plus retinol (25000 IU) vs placebo | Lung cancer incidence | 14,254 smokers+4060 asbestos workers followed for 4 years | Lung: 1.36 (1.07–1.73) β-carotene plus retinol vs placebo | A significant increase in lung cancer incidence in β-carotene plus retinol supplemented group |
| Linxian Study | Intervention groups: AB, AC, AD, BC, BD, CD, ABCD, or placebo. Supplement A: retinol (5000 IU), zinc (22.5 mg). Supplement B: riboflavin (3.2 mg) Supplement C: vitamin C (120 mg), molybdenum (30 μg). Supplement D: β-carotene (15 mg), selenium (50 μg), α-tocopherol (30 mg) | Gastric and esophageal cancer mortality | 29,584 adults ages 40–69 followed for 6 years | Esophagus: 0.97 (0.81–1.17) A vs no A 0.90 (0.75–1.08 B vs no B 1.06 (0.88–1.28) C vs no C 1.00 (0.84–1.21) D vs no D Stomach: 1.05 (0.86–1.27) A vs no A 1.08 (0.89–1.31) B vs no B 1.06 (0.87–1.28) C vs no C 0.81 (0.66–0.98) D vs no D | A significant decrease in stomach cancer mortality for group supplemented with D. |
| WASC | Vitamin C (500 mg), vitamin E (600 IU qOD), β-carotene (50 mg qOD), 3 combinations of 2 agents, And all 3 vs placebo. | CVD incidence | 7627 women at least 40 years of age who did not have cancer. Average follow-up 9.4 years | Lung: 1.84 (1.14–2.97) any vitamin C vs placebo 1.25 (0.79–1.97) any vitamin E vs placebo 1.26 (0.80–1.99) any β-carotene vs placebo | Lung cancer incidence was significantly higher in women receiving vitamin C. No significant decrease in incidence of total cancer/ specific cancer in any other supplemented group. |
| SELECT | selenium (200 μg), vitamin E (400 IU), or both vs placebo | Prostate cancer incidence | 35,533 men age ≥50 years without any suspicion for prostate cancer followed for 7-12 years | Prostate: 1.13 (0.99–1.29) vitamin E vs placebo 1.04 (0.90–1.18) selenium vs placebo 1.05 (0.91–1.20) both vs placebo | No significant decrease in incidence of prostate cancer in any of the supplemented groups |

Table 2. Summary of selected clinical trials testing efficacy of antioxidants in CVD

| Name of study | Trial | Primary outcome | Study population | Relative Risk (Confidence Interval) | Interpretation of results |
|---|---|---|---|---|---|
| HOPE | Vitamin E (400 IU) vs placebo and ramipril (10 mg/day) vs placebo | Myocardial infarction, stroke and death from cardiovascular causes | Patients aged ≥ 55 with a high risk for CVD. 1838 and 1816 subjects were diabetic in the treatment and control arm, respectively | CVD death: 1·05 (0.90-1.22) vitamin E vs placebo MI:1.02 (0.90-1.15) vitamin E vs placebo Stroke: 1.17 (0.95-1.42) vitamin E vs placebo | No apparent beneficial effect of vitamin E |
| SPACE | Vitamin E (800 IU) versus Placebo | Total CVD endpoints | 196 patients with CVD and undergoing chronic hemodialysis | Total CVD endpoints (including sudden death): 0·54 (0·33–0·89)vitamin E vs placebo MI(including sudden death): 0·45 (0·20–0·99) vitamin E vs placebo | Significant reductions in total CVD endpoints and MI in subjects receiving vitamin E |
| CHAOS | Vitamin E supplements (400-800 IU) vs placebo | Incidence of cardiovascular death and non-fatal MI | 2,002 patients with coronary artery disease (CAD) | Cardiovascular death and non-fatal MI: 0.53 (0.34-0.83) vitamin E vs placebo | A significant reduction in cardiovascular death and non-fatal AMI in vitamin E supplemented group |
| NHS | Classification of participants into quintiles based on vitamin A, vitamin C, vitamin E intake from food and supplements | Incidence of cardiovascular death | 34,486 postmenopausal women with no cardiovascular disease followed for 7 years | Coronary Heart Disease (CHD) death: 0.38 (0.18–0.80) vitamin E vs placebo | A significant decrease in vitamin E intake from food and death from CHD |
| PHS | aspirin (325 mg on alternate days),β-carotene (50 mg on alternate days), both active agents vs placebo | Incidence of CVD death, MI and stroke | 22,071 male physicians, aged 40 to 84 years with no history of CVD events | CVD death: 1.09 (0.93–1.27) β-carotene vs placebo MI:0.96 (0.84–1.09) β-carotene vs placebo Stroke:0.96 (0.83–1.11) β-carotene vs placebo | No significant decrease in CVD endpoints in the supplemented group. |
| CARET | β-carotene (30 mg) plus retinol (25000 IU) vs placebo | Lung cancer incidence | 14,254 smokers+4060 asbestos workers followed for 4 years | CVD death: 1.26 (0.99- 1.61) β-carotene plus retinol vs placebo | Increased risk in incidence of cardiovascular death in supplemented group |
| ATBC | α-tocopherol (50mg), or β-carotene (20 mg), or both versus placebo | Lung cancer incidence | 29,133 male smokers, aged 50–69 years with a history of MI, followed for 5–8 years | CHD deaths: 1.75 (1.16-2.64) β-carotene vs placebo 1.33 (0.86-2.05) α – tocopherol vs placebo 1.58 (1.05-2.40) both vs placebo | Significant increase in incidence of fatal deaths from CHD in β-carotene and β-carotene plus α-tocopherol groups. |

Table 3. Summary of selected clinical trials testing efficacy of antioxidants in pre-eclampsia

| Author of study | Trial | Main outcome | Study population | Relative Risk (Confidence Interval) | Interpretation of results |
|---|---|---|---|---|---|
| Beazley D et al. | Vitamin C (1000 mg) and vitamin E (400 IU) vs placebo | Rate of pre-eclampsia | 100 women pregnant at 14 weeks 0 days to 20 weeks 6 days with a history of pre-eclampsia, chronic hypertension, insulin-requiring diabetes mellitus, or multiple gestation | Rate of pre-eclampsia: 0.92 (0.4-2.13) treatment vs placebo | No significant reduction in the incidence of main outcomes in the supplemented group when compared to the placebo group |
| Rumbold AR et al. | Vitamin C (1000 mg) and vitamin E (400 IU) vs placebo | Incidence of pre-eclampsia, death of infant and small-for gestational age infants | 1877 nulliparous women pregnant between 14 and 22 weeks with normal blood pressure at the first measurement in pregnancy, and at trial entry | Pre-eclampsia: 1.20 (0.82–1.75) treatment vs placebo Death of infant: 0.79 (0.61–1.02) treatment vs placebo Small for gestational age infants: 0.87 (0.66- 1.16) treatment vs placebo | No significant reduction in the incidence of main outcomes in the supplemented group when compared to the placebo group |
| Spinnato JA et al | Vitamin C (1,000 mg) and vitamin E (400 IU) | Incidenceof pre-eclampsia | 739 women diagnosed with pre-eclampsia or with a history of pre-eclampsia | Pre-eclampsia: 0.87 (0.61-1.25) treatment vs placebo | No significant reduction in incidence of pre-eclampsia in supplemented group when compared to the placebo. |
| Gülmezoğlu AM et al. | Vitamin E (800 IU), vitamin C (1000 mg), and allopurinol (200 mg) | Prolongation of pregnancy and assessment of lipid peroxides | 56 women with severe pre-eclampsia between 24 and 32 weeks of gestation | Delivery within 14 days: 0.68 (0.45-1.04) treatment vs placebo | No significant differences in prolongation of pregnancy in study group when compared to placebo. Furthermore, there were no differences in lipid peroxide levels |
| Steyn PS et al. | Vitamin C (250 mg) two times a day until 34 weeks' gestation | Incidence of pre-eclampsia, preterm labor | 200 women less than 26 weeks' gestation and with a history of a previous mid-trimester abortion or previous preterm labor | Pre-eclampsia: 1.00 (0.21-4.84) vitamin C vs placebo Preterm birth: 1.43 (1.03-1.99) vitamin C vs placebo | The incidence of preterm birth was higher in women supplemented with vitamin C |
| Merchant AT et al. | Multivitamin containing thiamine (20 mg), riboflavin (20 mg), B-6 (25mg), B-12 (50 microg), C (500 mg), E (30 mg), and folic acid (0.8 mg), β-carotene (30 mg) plus preformed vitamin A (5000 IU)versus placebo | Hypertension during pregnancy | 1078 HIV-positive pregnant Tanzanian women between 12 and 27 week gestation | Hypertension during pregnancy: 0.62 (0.40–0.94) multivitamin vs placebo 1.00 (0.66–1.51) vitamin A vs placebo | Women supplemented with multivitamin were less likely to develop hypertension during pregnancy |
| Mahdy ZA et al. | Tocotrienol-rich fraction (TRF) of palm oil (100 mg) vs placebo | Hypertension during pregnancy | Healthy women pregnant between 12 and 16 weeks gestation | Pregnancy induced hypertension: 0.36 (0.12–1.09) palm oil vs placebo | No benefits of palm oil in reducing the risk of pregnancy induced hypertension |

Table 4. Summary of selected clinical trials testing efficacy of antioxidants in diabetes

| Name of study | Trial | Primary outcome | Study population | Relative Risk (Confidence Interval) | Interpretation of results |
|---|---|---|---|---|---|
| PPP | Aspirin (100 mg) vs placebo and vitamin E (300 mg) vs placebo | CVD deaths | 2062 diabetic patients aged ≥50 years | Cardiovascular death: 1.23 (0.69-2.19) aspirin vs placebo Cardiovascular death: 1.07 (0.61-1.90) vitamin E vs placebo | Vitamin E supplementation did not significantly reduce incidence of CVD death in diabetic subjects |
| ALADIN | α-lipoic acid (1200mg, 600 mg, or 100 mg) vs Placebo for 3 weeks | Symptoms of diabetic peripheral neuropathy | 328 non-insulin-dependent diabetic patients with symptomatic peripheral neuropathy | - | Significant improvement in symptoms in α-lipoic acid supplemented group |
| ALADIN II | α-lipoic acid (1200mg or 600 mg) vs placebo for 24 months | Neuropathic symptoms | 65 diabetic patients | - | Statistically significant improvements in peripheral nerve function parameters |
| ALADIN III | α-lipoic acid (600 mg) vs placebo for 6 months | Neuropathy impairment score | 509 Type II diabetic patients aged 18-65 years | - | Improvements in neuropathy impairment score after 19 days of treatment, which was maintained for up to 7 months |
| DEKAN | α-lipoic acid (800 mg) vs placebo for 4 months | Cardiac autonomic neuropathy, as indicated by heart rate variability | 73 non-insulin-dependent diabetes mellitus patients | - | Improved cardiac autonomic neuropathy in α-lipoic acid treated group |
| SYDNEY | α-lipoic acid (600 mg) vs placebo for 14 treatments | Neuropathic sensory symptoms | 120 diabetic patients with symptomatic diabetic sensorimotor polyneuropathy | - | Improvement in sensory symptoms such as pain, prickling and numbness in α-lipoic acid treated group |

Table 5. Summary of selected clinical trials testing efficacy of antioxidants in COPD

| Name/ author of study | Trial | Primary outcome | Study population | Hazard ratio (Confidence Interval) | Interpretation of results |
|---|---|---|---|---|---|
| WHS | Vitamin E (600 IU every other day) and aspirin (100 mg every other day) vs placebo | Incidence of chronic lung disease | 38,597 women aged ≥ 45 without chronic lung disease followed for 10 years | Chronic lung disease: 0.90 (0.81-0.99) vitamin E vs placebo | Vitamin E supplementation lead to reduction in risk of chronic lung disease |
| Lykkesfeldt et al. | Vitamin cocktail containing vitamin C (272 mg), α-tocopherol acetate (31 mg), and folic acid (400 μg) vs placebo for 3 months | Plasma antioxidant status | 37 smokers and 38 nonsmokers with self-reported low fruit and vegetable intake | - | Ascorbic acid was depleted in smokers, and increased after supplementation. |
| De Benedetto et al. | NAC (600 mg)vs placebo for 2months | $H_2O_2$ content in the exhaled air condensate (EAC) | 55 males and females, aged, 41–75 years, non-smokers/ ex-smokers for at least 5 years, and affected by moderate COPD | - | NAC decreased oxidant stress in airways, as indicated by H2O2 content in EAC |

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### Sexual Selection is Safe Selection

Why are the women more attracted to slimmer and fitter men? If you accept Darwin's ideas, it is due to sexual selection: certain bodily or facial features are indicators of better health and better genes. The findings of a new study published in American Journal of Human Biology (news release, Feb. 18, 2014), apparently supports this. The study, which the authors claim to be the first of its kind, was carried out in University of Wroclaw in Poland, on 90 healthy men and 103 healthy women. Nose and throat swabs were collected from them to find out who among them were colonised by six potentially harmful bacterial species including staphylococci and streptococci. It was found that men with lean body mass and low fat content were less likely to be colonised by bacteria than their fatty cohorts. They were not only carrying less fat but also less germs. The authors feel that the lean, fit men are likely to be more immunocompetent. However, similar association was not observed in women.
(http://as.wiley.com/WileyCDA/PressRelease/pressReleaseId-110307.html)

- Dr. K. Ramesh Rao