Antioxidants Against Free Radicals

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Free radicals are atoms with one or more unpaired electrons, which creates an imbalance in the how the atoms function. They are formed when oxygen interacts with certain molecules. Once formed these highly reactive radicals can start a chain reaction which results in damage to important cellular components such as DNA, or the cell membrane. Cells may function poorly or die if this occurs. To prevent free radical damage the body has a defense system of antioxidants.

Antioxidants protect against cellular damage caused by free radicals, which would otherwise be the common pathway for cancer, aging, and a variety of diseases. Following is a discussion about some of the most common and valuable antioxidants that we can use in supplemental form to protect ourselves.

VITAMIN A

Beta-carotene is perhaps best known for the fact that the body can convert it into vitamin A. This takes place in the intestinal wall (although some diabetics have problems making this conversion). Since beta carotene is only converted to vitamin A as the body needs it, it is virtually impossible for beta carotene to cause vitamin A toxicity.

Antioxidant effects

In addition to functioning as a vitamin A precursor, beta-carotene has also been shown to provide other significant health benefits. Beta-carotene has antioxidant activities and prevents lipid peroxidation.[1] Serum beta-carotene levels are inversely related to C-reactive protein levels and the white blood count. These markers are markers of inflammation and are associated with suboptimal cardiovascular function.[2] The antioxidant effects of beta-carotene may reduce free radical-induced DNA damage.[3] [4]

Reduced risk of mutated lung cell growth

In addition, as intake of beta-carotene from food increases, the risk of mutated lung cell growth is reduced[5]. It is possible that similar benefits may be realized from supplementation of natural beta-carotene. Beta-carotene has also been shown to be effective in reducing the risk of pre-mutated cells the mouth. In one study[6], people with such cells received 180 mg of beta-carotene twice weekly. After 6 months, the results were a reduced frequency of the mutated cells, and inhibition of new lung cell mutations. In a similar study[7], 60 mg twice daily of beta-carotene was also found to be effective for the same purpose.

Does beta-carotene increase the risk of lung cancer in smokers?

No, it does not. This misconception was based upon one flawed study in which smokers using beta-carotene were thought to be at a greater risk of lung cancer (*N Engl J Med* 1994; 330:1029–35). However, a more thorough follow-up analysis which looked at the diets and other dietary supplements taken, revealed that the smokers' actual danger was due to low total antioxidant levels, not to the fact that they took beta-carotene (*Am J Epidemiol* 2004; 160(1):68-76). This makes sense given the fact that antioxidants function interdependently, and so should be taken together.

VITAMIN C

Vitamin C is probably best known for its effects as an antioxidant and its role in maintaining proper immune function.[8] Many of the beneficial effects of vitamin C are attributed primarily to antioxidant and free radical scavenging effects. Vitamin C readily undergoes reversible oxidation and reduction in the body.[9] Vitamin C decreases oxidants in gastric juice, lipid peroxidation, and oxidative DNA and protein damage.[10] Vitamin C might reduce oxidative stress caused by the large number of oxidants in cigarette smoke.[11]

VITAMIN E

The term vitamin E describes a family of eight antioxidants: four tocopherols and four tocotrienols. Alpha-tocopherol is the only form of vitamin E that is actively maintained in the human body; therefore, it is the form of vitamin E found in the largest quantities in blood and tissues.[12] It is also the only form that meets the latest Recommended Dietary Allowance (RDA) for vitamin E. Nevertheless the other tocopherols and tocotrienols have significant contributions to make toward human health. These other tocopherols include the beta, gamma, and delta tocopherols; and are considered isomers. In this context, the term isomer refers to compounds with the same structural formula but different spatial arrangements of atoms.[13] In addition, there is a family of natural compounds related to vitamin E called tocotrienols, which also have distinct health benefits. These tocotrienols are also found in alpha, beta, delta and gamma isomers.

Alpha-tocopherol

The main function of alpha-tocopherol in humans appears to be that of an antioxidant. Free radicals are formed primarily in the body during normal metabolism and also upon exposure to environmental factors, such as cigarette smoke or pollutants. Fats, which are an integral part of all cell membranes, are vulnerable to destruction through oxidation by free radicals. The fat-soluble vitamin, alpha-tocopherol, is uniquely suited to intercept free radicals and thus prevent a chain reaction of lipid destruction. Aside from maintaining the integrity of cell membranes throughout the body, alpha-tocopherol also protects the fats in low density lipoproteins (LDLs) from oxidation. Lipoproteins are particles composed of lipids and proteins that transport fats through the bloodstream. LDLs specifically transport cholesterol from the liver to the tissues of the body. Oxidized LDLs have been implicated in the development of cardiovascular diseases. When a molecule of alpha-tocopherol neutralizes a free radical, it is altered in such a way that its antioxidant capacity is lost. However, other antioxidants, such as vitamin C, are capable of regenerating the antioxidant capacity of alpha-tocopherol.[14] [15]

Several other functions of alpha-tocopherol have been identified that are not likely related to its antioxidant capacity. For instance, alpha-tocopherol appears to also affect the expression and activities of molecules and enzymes in immune and inflammatory cells. Additionally, alpha-tocopherol has been shown to inhibit platelet aggregation and to enhance vasodilation.[16] [17]

The practical application of these cardiovascular benefits were demonstrated in two studies that showed that men and women supplementing with at least 100 IU of alpha-tocopherol daily had a 37–41% drop in the risk of suboptimal heart function.[18] [19] Perhaps most significant is the now famous Cambridge Heart Antioxidant Study, where there was a 77% drop in suboptimal heart function in subjects who were given 400–800 IU alpha-tocopherol daily.[20]

Other research has shown that alpha-tocopherol may slow the progression of suboptimal memory functioning[21], and may lower the risk of developing it.[22] In addition, research indicates that alpha-tocopherol has been successfully used for a variety of other health-related situations, including acne, seasonal pollen reactions, mutated cell growth, constipation, respiratory issues, bowel sensitivity, breast health, visual functioning, menopause, joint health, and premenstrual symptoms.[23]

Gamma-tocopherol

Interestingly, the most common form of vitamin E in plants and in the American diet is gamma-tocopherol.[24] Although the exact role of gamma-tocopherol in human health is unclear, metabolic research suggests that it is needed for use by the body.[25] Some in-vitro (test tube) and animal research indicates that gamma-tocopherol may play an antioxidant role in protecting the body from free radical damage.[26] [27] In fact, some research has indicated that gamma-tocopherol specifically protects against peroxynitrate, a powerful and harmful mutagenic radical.[28] Peroxynitrate is involved in creating inflammation that may further contribute to and/or be a causative factor in various disease states. This study showed that gamma-tocopherol demonstrated an ability to trap this harmful mutagen. Furthermore, gamma-tocopherol has also been shown to possess anti-inflammatory activity by blocking cyclooxygenase[29], an inflammatory chemical produced in the body. Consequently, it makes sense that some research has shown that increased blood levels of gamma-tocopherol were associated with a significantly reduced risk of developing prostate cell mutations and poor cardiovascular function.[30] [31] Some of this same research also showed similar protective effects were only seen with alpha-tocopherol and selenium when gamma-tocopherol levels were also high. Other research has shown that gamma-tocopherol assists in the excretion of sodium from the body.[32]

Delta-tocopherol

Although delta-tocopherol appears to have the least vitamin E activity, it seems to provide other advantages. In-vitro research showed that delta-tocopherol was highly effective at inhibiting the growth of mutated liver cells. In comparison, gamma-tocopherol showed weak effect of inhibition and alpha-tocopherol did not show any inhibition effect at all.[33] In similar research on human breast cells with these three tocopherols, only delta-tocopherol was effective at inhibiting mutated cell growth.[34] In other research, delta-tocopherol was

shown to have the highest antioxidant activity against free radical damage in human blood, followed by gamma-tocopherol and alpha-tocopherol, respectively.[35]

Alpha-, beta- and delta-tocopherol together
Research has shown a combination of alpha-, beta- and delta tocopherol together is more effective than alpha-tocopherol alone. For example, in one study, a mixture of these tocopherols was shown to have a stronger effect at inhibiting free radical damage to human blood cells than alpha-tocopherol alone.[36] The authors of this study also noted that this tocopherol mixture has been found to counteract the development of poor arterial function, whereas intake of large amounts of pure alpha-tocopherol has shown only a slight or no effect in clinical studies. In another study, the combination of tocopherols was shown to have a synergistic effect in inhibiting platelet aggregation above and beyond the effect of the individual tocopherols.[37]

Tocotrienols
Although tocotrienols have little actual vitamin E activity, they do have significant antioxidant effects. As a matter of fact, they have better distribution in the fatty layers of the cell membranes, which makes them superior antioxidants.[38] [39] Tocotrienols have been shown to elicit powerful antioxidant and anti-mutagenic properties, as well as supporting healthy cholesterol levels within a normal range.

In addition to their antioxidant function, tocotrienols help maintain a healthy cardiovascular system[40], including protection against oxidative damage to LDL cholesterol.[41] In one study, many patients were able to promote healthy arterial function due to tocotrienol supplementation.[42] Tocotrienols have also been shown to help support healthy cholesterol levels within a normal range.[43] [44] [45]

Although a good deal of the research on tocotrienols has centered on gamma-tocotrienol, the other tocotrienols have also been shown to have valuable activity. For example, in-vitro studies indicate that the various tocotrienols may have antimutagenic benefits, particularly against breast and skin cells.[46] [47] [48] [49] [50] In one study, alpha-, gamma-, and delta-tocotrienols were all shown to be effective at inhibiting the growth of mutated mouse breast cells.[51] Another study demonstrated that alpha-, gamma-, and delta-tocotrienols helped reduce the growth of the mutated cells.[52] Similar results were achieved in a study where gamma- and delta-tocotrienol inhibited the growth of mutated human breast cell.[53]

Combining tocopherols and tocotrienols
We know from the previous data presented that combining tocopherols has value over the isolated use of just alpha-tocopherol. But what happens when the tocopherols *and* the tocotrienols are combined?

In one study, a combination of tocopherols and tocotrienols where shown to significantly promote healthy cholesterol levels within a normal range in mice fed high-fat/high-cholesterol diets, compared to mice given only the combination of tocopherols with the same diet.[54] Clearly, the full spectrum of vitamin E isomers has greater value for promoting cardiovascular health.

In addition, research has shown that alpha-tocopherol, alpha-tocotrienol and gamma-tocopherol significantly decreased the suboptimal blood flow to the brain, while gamma-tocotrienol, delta-tocopherol and delta-tocotrienol showed no effect.[55] Only a combination of the isomers provides the necessary specific tocopherols and tocotrienols to provide this benefit.

PANTOTHENIC ACID
Pantothenic acid is a component of coenzyme A (CoA), an essential coenzyme in a variety of reactions that sustain life. CoA is required for chemical reactions that generate energy from food (fat, carbohydrates, and proteins). The synthesis of essential fats, cholesterol, and steroid hormones requires CoA, as does the synthesis of the neurotransmitter, acetylcholine, and the hormone, melatonin. Heme, a component of hemoglobin, requires a CoA-containing compound for its synthesis. Metabolism of a number of drugs and toxins by the liver requires CoA.[56]

In addition, pantothenic acid is intimately involved in adrenal function, and the production of adrenal hormones associated with stress.[57] Experimentally-induced pantothenic acid deficiency has been associated with somnolence, fatigue, headache, paresthesia of the hands and feet followed by hyperreflexia and muscle weakness in the legs, cardiovascular instability, gastrointestinal (GI) complaints, changes in disposition, and increased susceptibility to infections.[58]

SELENIUM
Selenium functions as a constituent of the antioxidant enzyme glutathione peroxidase, which detoxifies products of oxidized fats, and is found in the red blood cells. Selenium plays a fundamental role in regulating thyroid and other functions of the human body including reproduction, autoimmunity, glucose metabolism and bone metabolism.[59]

Selenium and immunity
Selenium deficiency has been associated with impaired function of the immune system.[60] Moreover, selenium supplementation in individuals who are not overtly selenium deficient appears to stimulate the immune response. In two small studies, healthy individuals[61] [62] and individuals with suboptimal immune response[63] supplemented with selenium for eight weeks showed an enhanced immune cell

response to foreign antigens compared with those taking a placebo. A considerable amount of basic research also indicates that selenium plays a role in regulating the expression of cell-signaling molecules called cytokines, which orchestrate the immune response.[64]

Selenium and mutated cell growth
Geographic studies have consistently observed higher levels of mutated cell growth rates in populations living in areas with low soil selenium and relatively low dietary selenium intakes. Results of epidemiological studies of mutated cell growth incidence in groups with less variable selenium intakes also show a trend for individuals with lower selenium levels (blood and nails) to have a higher incidence of several different types of mutated cell growth.[65]

Some studies have reported that low dietary selenium intakes are associated with increased risk of mutated prostate cell growth. A case-control study within a prospective study of over 50,000 male health professionals in the U.S. found a significant inverse relationship between selenium levels and the risk mutated prostate cell growth.[66]

L-GLUTATHIONE
Reduced glutathione (GSH) is a tripeptide consisting of of L-glutamine, L-cysteine, and glycine.[67] It is naturally present in fruits, vegetables, and meats, and also synthesized in the body—primarily in the liver.[68] [69] GSH is involved in DNA synthesis and repair, protein and prostaglandin synthesis, amino acid transport, metabolism of toxins and carcinogens, immune system function, prevention of oxidative cell damage, and enzyme activation. It is a powerful antioxidant providing protection against oxidative damage from free radicals.[70] [71]

Glutathione deficiency
Glutathione deficiency is associated with aging, age-related macular degeneration (AMD), diabetes, lung and gastrointestinal disease, pre-eclampsia, Parkinson's disease and other neurodegenerative disorders, and poor prognosis in AIDS.[72] [73] [74] [75] [76] [77] [78] [79] [80] [81] [82] [83] [84] [85] [86] Oxidative stressors that can deplete GSH include ultraviolet and other radiation, viral infections, environmental toxins, household chemicals, heavy metals, surgery, inflammation, burns, septic shock, and dietary deficiencies of GSH precursors and enzyme cofactors.[87] [88] [89] [90] [91] [92]

Replenishment of GSH is an important goal to prevent depletion and deficiency. In addition, there are some specific situations where GSH supplementation may be indicated. These situations are outlined below.

Detoxification
Water soluble toxins can pass through our bodies unchanged and be eliminated in the stool, sweat or urine. Fat soluble toxins, however, cannot be excreted without undergoing metabolic transformation (detoxification) in the liver so that they can become water soluble. Liver cells have sophisticated mechanisms to break down toxic substances. These include both endogenous (produced by the body) and exogenous (obtained from the environment; i.e., xenobiotics) substances. Every drug, chemical, pesticide and hormone, is broken down or metabolized via detoxification pathways in the liver.[93] [94] [95] Phase 2 of the detoxification process involves the coupling (attaching) or conjugation of a water soluble substance which is endogenously produced or sourced by the body, to the toxin. This makes the toxic molecule more water soluble and therefore less toxic. If the molecule is large, it is then excreted via the bile. Otherwise, it is excreted in the urine.[96] [97] GSH is one of the primary conjugating agents in phase 2, and a number of toxic molecules pass through the glutathione conjugation pathway. A deficiency of this GSH can reduce the clearance of toxins from the body.

Proliferation of mutated cells
Preliminary evidence suggests GSH intake from fruits and vegetables might be associated with a reduced risk of mutated pharyngeal cell growth.[98] In a clinical study, patients with a proliferation of mutated colon cells were given 800 mg of GSH twice per day for at least three months. After an average of 21 weeks, 36 percent of the patients "recovered with normal diet [and] increased weight."[99]

Seasonal infective agents
GSH may inhibit the activity of enzymes that help the certain seasonal infective agents colonize cells lining the mouth and throat. In animal research there was lower tissue levels of the infective agents in mice fed glutathione-enriched drinking water compared to untreated mice.[100]

Chemotherapy toxicity
Administering glutathione by intravenous injection seems to help prevent chemotherapy toxicity, improve quality of life, and provide a neuroprotective effect.[101] [102] [103] [104] [105] [106] [107] [108] [109] [110] [111]

Male fertility
In a study of male fertility, glutathione was supplied in a dose of 600 mg, and administered intramuscularly for two months. In comparison to a placebo, the treatment group showed a statistically significant effect on sperm motility, specifically in the percentage of sperm demonstrating forward motility.[112]

N-ACETYL CYSTEINE

N-acetyl cysteine (NAC) is the precursor to glutathione.[113] It stimulates glutathione synthesis and promotes liver detoxification; as well as acting as a powerful scavenger of free radicals.[114 115] Reactive oxygen species (ROS) such as hydrogen peroxide and hydroxyl-free radicals reduce intracellular and extracellular concentrations of glutathione. N-acetyl cysteine is a very efficient way to replenish glutathione and reduce damage caused by ROS.[116 117]

Effective against toxicity
Historically the most prevalent and well-accepted use of NAC has been as an antidote for acetaminophen (Tylenol®, paracetamol) poisoning.[118] The resultant liver toxicity is due to an acetaminophen metabolite that depletes the liver cells of glutathione and causes liver cell damage and possibly even death. NAC has also been effective for heavy metal poisoning by gold, silver, copper, mercury, lead, and arsenic, as well as in cases of poisoning by carbon tetrachloride, acrylonitriles, halothane, paraquat, acetaldehyde, coumarin, and interferon.[119] Since detoxification of mercury depletes glutathione, the use of NAC doubly makes sense.

Beneficial for mitochondrial dysfunction
A major cause of mitochondrial dysfunction is due to changes that take place in the respiratory chain where oxidative phosphorylation occurs. Researchers studied the effects of NAC on key elements of the respiratory chain in older rats.[120] After 20 weeks of treatment they found that the activities of respiratory chain were significantly higher in the treated rats compared to the controls. NAC also helped to maintain levels of the important mitochondrial antioxidant, glutathione, as well as prevented cell death in *in-vitro* studies.[121] In other in-vitro studies, NAC protected cells from programmed cell death (apoptosis) by promoting oxidative phosphorylation, mitochondrial membrane integrity, and mitochondrial homeostasis.[122]

COENZYME Q_{10}

Although structurally related to vitamin K, coenzyme Q10 (CoQ10) is not a vitamin, but rather a coenzyme that helps to utilize oxygen as part of its important role in cellular energy metabolism. Research has also shown that CoQ10 functions in a number of other beneficial ways including free radical scavenging.[123] Following is a brief review of that research.

Free radicals
As previously described, free radicals are atoms with unpaired electrons. In the process of trying to balance itself by gaining or losing an electron, the free radical causes oxidative damage on a cellular level. CoQ10 has the unique property of being able to accept or donate an electron without itself becoming a free radical. By doing this CoQ10 can help neutralize free radicals and the oxidative damage they cause. This is significant since numerous disease states are thought to be due to excessive oxidative stress of free radicals, including hydroxyl radical, peroxynitrite, superoxide anion and hydrogen peroxide. In addition, CoQ10 may inhibit certain enzymes involved in the formation of these free radicals.

Cardiovascular support
CoQ10 has been reviewed in the scientific literature and found to be used in oral form to support cardiovascular fuction.[124]

Healthy heart function
In one study, patients with suboptimal heart function experienced a significant reduction in pain, and abnormal heartbeat when supplemented with 120 mg of CoQ10 daily.[125] In another one study, patients with suboptimal heart function were found to experience a faster loss of CoQ10 during exercise.[126] To compensate, 150 mg of CoQ10 given to patients with suboptimal heart function which not only increased their blood levels of CoQ10, but also increased their ability to exercise longer.[127]

A meta-analysis of eight controlled clinical trials of CoQ10 supplementation in people with suboptimal heart function revealed a significant improvement in several important cardiac parameters.[128] Other research on CHF patients using CoQ10 has shown similar benefits, including the improvement of quality of life, as well as survival.[129 130]

High blood pressure
Research indicates that CoQ10 affects blood vessels in a way that should cause support healthy blood pressure.[131] In fact, this has been substantiated in a number of studies where CoQ10 significantly promoted healthy blood pressure within a normal range.[132 133 134 135] All of these studies used at least 50 mg of CoQ10 taken twice daily. You should expect about 10 weeks of supplementation to pass before looking for results.

Mutated breast cell growth
Biochemical, biomedical and clinical research on CoQ10 and its relationship to reducing the growth of mutated breast cells has evolved internationally over 35 years. In published research, patients were able to reduce the spread of mutated breast cell growth by supplementing with 390 mg of CoQ10 daily.[136] These was also seen when CoQ10 was used at a lower doses of 90 mg daily in combination with other antioxidants including vitamin C, Vitamin E, beta-carotene, selenium, and essential fatty.[137] Without the benefit of other antioxidants, however the 390 mg dose of CoQ10.[138]

Blood glucose levels
Research has shown that some individuals with higher blood glucose levels may have a deficiency of CoQ10, which may be further exacerbated by the use

of certain commonly used drugs. Such a deficiency of CoQ10 in the pancreas could impair aspects of energy metabolism and the biosynthesis of insulin.[139]

Periodontal disease

Did you know that in Japan over half the dentists recommend supplements of CoQ10 to promote healthy gums? There are very good reasons for this. First of all, research has shown that patients with suboptimal gum health have a CoQ10 deficiency of in their gums.[140] Secondly, treatment with CoQ10 in these significant improvement in the condition of the gums.[141] The reason that CoQ10 works may have to do with an ability to inhibit bacterial growth due to improved oxygen metabolism at the cellular level (bacteria often do not survive in the presence of oxygen).

ALPHA LIPOIC ACID

AIpha Lipoic Acid (ALA), also known as thioctic acid, has gained considerable attention as an antioxidant. ALA combats particularly nasty free radicals such as superoxide radicals, hydroxyl radicals, hypochlorous acid, peroxyl radicals, and singlet oxygen, thereby reducing oxidative stress. ALA is a small molecule, soluble in both water and fat. This allows it to work both inside the cell and at the membrane level, making ALA a particularly valuable antioxidant.

Oxidative stress and ALA

In general, antioxidants provide a preventive measure against the hazards of oxidative stress with their ability to neutralize, balance and sponge up free radicals by coupling with unpaired electrons. ALA is unique since it not only acts as antioxidant against free radicals, but it also helps in the regeneration process of expended antioxidants, returning them to their reduced, antioxidant-potent form. In other words, it helps to recycle other antioxidants. Consequently, ALA is a key ingredient in providing the maximum interaction among antioxidants, enhancing their cell protection abilities. It has the unique ability to enhance the power of vitamins E and C and Glutathione. This results in an antioxidant network which provides more complete cell protection from destructive free radicals.[142] In animal research, ALA reversed a number of age-related changes in the brains of rats, including increased activity of antioxidant enzymes and decreased production of free radicals.[143]

The metabolic antioxidant

In addition to its antioxidant functions, ALA also has a metabolic role to play in the body: It facilitates the production of energy by aiding in the metabolism of glucose, and in the mitochondrial Krebs cycle which produces adenosine triphosphate (ATP, the energy currency of the body).[144] This energy production is vital for athletes and active individuals to function at maximum efficiency, or peak levels. Since ALA has both antioxidant and metabolic functions, it is considered to be a metabolic antioxidant.

Other uses for ALA

In his book, *The Wrinkle Cure*, Dr. Nicholas Perricone[145] recommends ALA as part of a strategy for maintaining healthy skin and reducing the potential for wrinkles. ALA also has value as part of a complete program for facilitating the liver's detoxification process.[146] In research, 150 mg of ALA per day for one month was shown to improve visual function in people with inner ocular pressure.[147] Finally, in a preliminary trial[148] three patients with suboptimal liver function and dilated veins in the esophagus received a combination of 300 mg ALA twice daily, 300 mg silimarin from milk thistle three times daily, and 200 mg selenium twice daily). After five to eight months, all three patients had significant improvements in their liver function and overall health (note: they also used other supportive supplements which included vitamin C and B vitamins).

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