

## Antioxidants - A Boon of A Bane- An Update

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**Antioxidants are substances or agents that scavenge reactive oxygen metabolites, block their generation or enhance endogenous antioxidant capabilities. Toxic oxygen metabolites have emerged as a major pathology of tissue injury in a wide variety of diseases. This is because many constituents of the cell are potentially subjected to free radical attack. Antioxidants may be considered as the scavengers of these free radicals. We live in an age in which millions of people worldwide take antioxidants to supplement their diet under the belief that these will help to maintain good health and ward off illness. Although some studies have suggested antioxidant supplements have health benefits, other large clinical trials did not detect any benefit for the formulations tested, and excess supplementation may occasionally be harmful. This article will be discussing in detail whether antioxidants are a boon or bane to us.**

**Key words:** Antioxidants, Free radicals, Reactive oxygen species, Carcinogenesis

Antioxidants are molecules capable of slowing or preventing the oxidation of other molecules which produces free radicals that damage the cells<sup>1</sup>. The term antioxidant refers specifically to a chemical that prevents the consumption of oxygen<sup>2</sup>. A dietary antioxidant is a substance in the food that significantly decreases the adverse effects of reactive oxygen species, reactive nitrogen species, or both on normal physiologic function in humans<sup>3</sup>. Antioxidants are intimately involved in the prevention of cellular damage - the common pathway for cancer, aging, and a variety of diseases. Antioxidants act as "free radical scavengers" and hence prevent and repair damage done by free radicals. Antioxidants can terminate these reactions by removing radical

intermediates and can inhibit other oxidation reactions by being oxidized themselves.<sup>1</sup>

Health problems such as coronary heart disease, macular degeneration, diabetes, cancer and oral mucosal potentially malignant disorders are all contributed by oxidative damage. The presence of antioxidants as ingredients in dietary supplements, and, possibly, the topical application of antioxidants such as vitamins A, C, and E; superoxide dismutase; flavonoids; beta carotene; glutathione; selenium; and zinc, plays a part in slowing down free-radical damage.<sup>4</sup>

Cellular oxidants, called reactive oxygen species (ROS), are constantly produced in animal and human cells. Excessive ROS can induce oxidative damage in cell constituents and promote a number of degenerative diseases and aging. Cellular antioxidants protect against the damaging effects of ROS.<sup>5</sup> However, in moderate concentrations, ROS are necessary for a number of protective reactions like antimicrobial

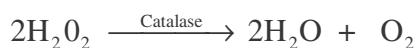
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phagocytosis, detoxification reactions and apoptosis which eliminates cancerous and other life-threatening cells. Excessive antioxidants could dangerously interfere with these protective functions. Thus, there is an ongoing debate whether to use antioxidants or not, as few studies have favored its use while others have shown no effects when used in the treatment of certain diseases. Antioxidants are double-edge sword and should be prescribed cautiously after proper evaluation in the treatment of oral mucosal lesions.<sup>5</sup>

#### Mechanism of action

Cellular oxidants, derivatives of oxygen, which are often called reactive oxygen species (ROS), are constantly produced in our cells<sup>5</sup>. Among cellular ROS, the most aggressive entities are superoxides and hydroxyl radicals<sup>6</sup>. Superoxides, through the reaction catalyzed by superoxide dismutase (SOD), are transformed into the much less reactive hydrogen peroxide moiety (H<sub>2</sub>O<sub>2</sub>). However, when hydrogen peroxide interacts with ions of transition metals such as iron or copper, the most reactive ROS, hydroxyl radicals (OH<sup>•</sup>) are

formed by Fenton reaction<sup>5</sup>. Production of ROS is essential for a number of biochemical reactions involved in the synthesis of prostaglandins, hydroxylation of proline and lysine, oxidation of xanthine and other oxidative processes.<sup>6</sup> An array of powerful cellular antioxidants protects cells from excessive oxidation. Among the endogenous antioxidants that scavenge ROS are glutathione, ubiquinol, bilirubin, uric acid, albumin and others. Potent antioxidant enzymes such as Glutathione peroxidase and catalase protect our cells from oxidative damage by inactivating ROS. Catalase and are enzymes whose role is to safely decompose peroxides. The former is mainly located in peroxisomes and acts upon hydrogen peroxide; the latter is found in the cytosol of mast cells and is active towards both hydrogen peroxide and, if first cleared from membrane phospholipids by a phospholipase, fatty acid hydroperoxides<sup>7</sup>.



**Table 1.** Antioxidants are conveniently classified as:<sup>5</sup>

ROS Scavenging agents	ROS Protective enzymes	Sequestration of transition metal ions
Glutathione	Superoxide dismutase	Transferrin
Uric acid	Catalase	Ferritin
Ascorbic acid	Glutathione peroxidase	Metallothioneins
Albumin	Glutathione reductase	Ceruloplasmin

#### Benefits of antioxidants

Various antioxidants are beneficial to our body mechanism. Some of the most important of them are discussed here.

No single antioxidant can replace the combination of natural phytochemical present in whole foods<sup>3</sup>. Phytochemicals were not giving desired results when they were used as isolated supplements and their bioactivity was reduced. Instead when 400-600gm of whole fruits consumed daily provides over 25000 phytochemicals and also international studies show that there is 50% reduction in the risk of cancer<sup>5</sup>. Rui Hai Liu *et al* performed trials in 2004, which concluded that the major part of total antioxidant activity is from the combination of phytochemicals<sup>3</sup>. Thus, the potent

antioxidant and anticancer activities and the benefits of a diet rich in fruits and vegetables is attributed to the complex mixture of phytochemicals present in whole foods<sup>3</sup>.

Lycopene may have anticarcinogenic and antiatherogenic activities. Lycopene functions as a very potent antioxidant, and this is clearly an important mechanism of action of lycopene. Lycopene exhibits the highest physical quenching rate constant with singlet oxygen.<sup>8</sup> Lycopene has been found to be at least 3-fold more effective than  $\beta$ -carotene in preventing cell death. It can trap singlet oxygen and reduce mutagenesis. In physiological concentrations, it can inhibit human cancer cell growth by interfering with growth factor receptor signaling and cell cycle progression,

specifically in prostate cancer cells, without evidence of toxic effects or cell apoptosis.<sup>9</sup> Lycopene has also been found to inhibit cholesterol synthesis, to inhibit HMG-CoA reductase activity and to upregulate LDL receptor activity in macrophages.<sup>8</sup>

#### **Zeaxanthin is a yellow-colored plant pigments**

It has strong antioxidant properties and is one of two yellow carotenoids found in the retina. It is abundant in spinach, collard greens, kale and corn. It acts to filter and shield harmful blue light from the eye and protects against age-related cataracts and macular degeneration, the leading cause of blindness in people over 65. Macular degeneration is a disease that destroys the central portion of the retina, the light-gathering cells at the back of the eye. As the disease progresses, the center of the field of vision begin to blur, making it difficult to read, drive, and recognize faces. Zeaxanthin and Lutein can restore macular pigment density, which declines with age.<sup>10</sup>

Quercetin is a very potent bioflavonoid found in red wine, green tea, tomatoes, onions, and green beans. A natural anti-oxidant, which protects cells in the body from damage by “free radicals”. Heart disease and high cholesterol is partially caused by free radical damage to blood vessels. May protect against heart attacks and strokes; recommended as a treatment for allergies, hay fever, and asthma because it helps prevent immune cells from releasing histamine, the chemical that initiates the itching, sneezing, and swelling of an allergic reaction; helps prevent itchy eyes, runny noses, and scratchy throats; in animal studies has shown to protect against a variety of cancers; may help stop cancer at its earliest stage by preventing the damaging changes in the cells that initiate cancer.<sup>10</sup>

Hesperidin/Rutin is an antioxidant essential for the proper absorption and use of Vitamin C; promotes vascular health; protects and preserves the structure of capillaries, which will help prevent bruising, varicose veins and haemorrhoids; helps prevent blood clotting and platelet clumping by making the blood less sticky; lowers cholesterol levels; treats and prevents cataracts, glaucoma, and other vision problems; when taken with Vitamin C may reduce the symptoms of oral herpes.<sup>10</sup>

Catechins (Green tea extract) are an

extremely powerful anti-oxidant that helps protect against cancer by blocking the formation of cancer causing compounds, and suppressing the activation of carcinogens; lowers cholesterol levels and reduces the clotting tendency of the blood; stimulates the immune system; fights tooth decay; helps regulate blood sugar and insulin levels; combats mental fatigue; delays the onset of atherosclerosis; has shown to help asthma sufferers; may help prevent an enlarged prostate.<sup>10</sup>

Curcuminoids of turmeric is a powerful anti-oxidant which has shown to be particularly helpful in reducing the “free-radical” damage inflicted on smokers by the carcinogenic chemicals in cigarettes; inhibits the activity of certain proteins that may trigger the growth of breast tumours; prevents LDL cholesterol from becoming oxidized and damaging arteries; lowers cholesterol; prevents plaque formation and inhibits the formation of blood clots by inhibiting platelet aggregation; contains a powerful anti-inflammatory chemical called curcumin that is effective for arthritis symptoms; aids circulation and improves blood vessel health; stimulates the flow of bile and the breakdown of dietary fats; used to treat liver related disorders, such as jaundice; protects against gallbladder disease; contains substances that help prevent the liver from being damaged by toxic chemicals; may help prevent and dissolve gallstones; lessens PMS symptoms by regulating and balancing hormones.<sup>11</sup>

Selenium is an essential trace mineral trace element that is involved in the defense against the toxicity of ROS, the regulation of the redox state of cells and catalyst for the production of active thyroid hormone. Selenium is needed for the proper functioning of the immune system, and appears to be a key nutrient in counteracting the development of virulence and inhibiting HIV progression to AIDS. It is required for sperm motility and may reduce the risk of miscarriage. An elevated selenium intake may be associated with reduced cancer risk.<sup>12</sup>

Zinc's function as an antioxidant was first proposed in 1990. The mechanism of action is the protection of proteins and enzymes against free radical attack, or oxidation. The Zn molecule in Zn-containing enzymes was found to act as an antioxidant and protect specific regions of the enzyme from free radical attack, thus preserving its stability and activity. If zinc is deficient then

the oxidative stress is associated with the development and progression of several different neuropathologies, including Alzheimer's disease, ALS, and Parkinson's disease.<sup>13</sup>

#### **Hazards of antioxidants**

The idea of taking supplements to compensate for a poor diet is attractive and, indeed, vitamin supplements are commonplace. 25% of adults worldwide take a daily supplement that contains vitamins. This possibly presents a risk to the person who takes the antioxidant supplements. Among a large group of pregnant women, it was discovered that 1.4% of them averaged more than 10,000 IU of vitamin A per day from supplements, and it was estimated that 1 of every 57 babies born to this group of women would have a birth defect attributable to their vitamin A intake. The possibility of developing squamous cell carcinoma is a concern when using antioxidants to treat patients with pre-malignant oral lesions and should be expected to occur in some patients.<sup>14</sup> There is possibility that antioxidant supplements promote carcinogenesis instead of retarding it. There is in vitro evidence that ascorbic acid acts as pro-oxidant by increasing oxidative damage. Interestingly, this was also noted in a study that found that artificially induced carcinogenesis in the buccal pouch of hamsters was enhanced by ascorbic acid.<sup>15</sup>

The side effects of 13-cis-retinoic acid are well known and, when used in therapeutic doses, cause symptoms such as cheilitis, dry skin, hypertriglyceridemia, xerostomia, teratogenic effects, and symptomatic hyperostosis to the extent that some patients elect to discontinue its use. There is no apparent risk from a high intake of  $\alpha$ -carotene, ascorbic acid,  $\alpha$ -tocopherol because of the decrease in absorption as the intake increases.<sup>16</sup>

An excess of antioxidants, which interferes with apoptosis, also can be cancer-promoting in people who are constantly exposed to the effect of environmental carcinogenic factors (tobacco smoke, industrial pollutants), which result in a high accumulation of pre-cancerous and cancerous cells. In cancer patients, an excess of antioxidants can interfere with the therapeutic activity of anticancer drugs, which kill cancer cells by ROS-dependent apoptosis.<sup>5</sup>

#### **CONCLUSION**

The discussion in this review shows that the biological effects of antioxidants in humans are controversial. Depending on the oxidative status of cells, antioxidants can be protective against cancer or cancer promoting. Since ROS induce oxidative carcinogenic damage in DNA, antioxidants can prevent cancer in healthy people harboring increased levels of ROS. However, since ROS in moderate concentrations act as indispensable mediators of cancer-protective apoptosis and phagocytosis, in people with a low ROS level, an excess of antioxidants can block these cancer-preventive mechanisms and interfere with apoptosis to further promote cancer.

Unfortunately, antioxidants are not the "magic bullets" for the treatment of pre-malignant oral mucosal lesions or the prevention of second primary malignancies. Therefore the ROS levels, the expected activity of antioxidants, have yet to be measured in people before intake of antioxidant supplements is recommended. However, there is a role if antioxidants are used judiciously in selected cases that can be monitored carefully. An important principle is that the treatment should not be more harmful than the damage that a disease can cause.

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