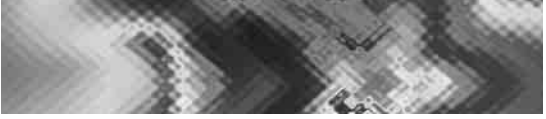

Principles of using anti-oxidants to maintain health and prevent disease

VLADIMIR BADMAEV
MUHAMMED MAJEED

Sabinsa Corporation
121 Ethel Road West, Unit #6
Piscataway, NJ 08854, USA
Tel +1-732-777-1111
Fax +1-732-777-1443
www.sabinsa.com
vebadmaev@attglobal.net

If the scientific and medical community has learned one lesson over time it is that patience and persistence are required to better understand the complex relationships between health and disease. Only such in-depth understanding can result in safe and effective prevention and management of a disease. The availability of oxygen to the body is crucial for its proper metabolism, functioning and well-being. This activity, however, does not occur without certain costs. These costs of oxygen utilization are known as oxidant by-products, free radicals, or reactive oxygen species abbreviated as ROS. The delicate balance between life supporting oxidation, the oxidant by-products and means to prevent the damage by free radicals to the body will be discussed in this article.

THE TRADE-OFF EFFECT

Even the proverbial defense of the body against foreign invasion, like microbial infection, carries a high cost to pay and involves a trade-off. In fact, the defense mechanisms naturally produce oxidants which are able to kill the invading bacteria on one hand, yet cause collateral injury to the body cells. For example, some white blood cells (neutrophils and monocytes) have an enzyme called myeloperoxidase, which is released from storage in those cells when the body is challenged by microbial invasion. This enzyme, together with hydrogen peroxide, has powerful oxidizing potential producing various ROS, e.g. hypochlorous acid, which is a body made antibiotic to control the impending infection. Nitric oxide, another example of ROS, is produced in tissues in response to various stimuli, but also in response to microbial infection. Like myeloperoxidase, nitric oxide plays a major role in the ability of white cells to defend the body against infection.

Perpetual physiological trade-offs are necessary to maintain balance in the body. These are typically handled by the major detox systems of the body, exemplified by a group of enzymes called monooxygenases (isoenzymes of cytochrome P450) and the glutathione system. Monooxygenases, found generously in the gastrointestinal tract, the liver and the lungs, oxidize numerous foreign substances, like drugs and environmental pollutants. This "breakdown" is an essential step that begins the process of eliminating toxins from the body, yet inevitably leads to the formation of ROS. The backup mechanism used to counter monooxygenases generated ROS is the glutathione system. The glutathione molecule consists of three amino acids, and is designed to absorb the ROS before they do damage to tissues, an outcome known as oxidative stress. This all important interaction of glutathione with ROS is made possible by a selenium requiring enzyme called glutathione peroxidase. Unfortunately in the process of absorbing ROS, glutathione itself becomes oxidized and becomes toxic to the tissues. Therefore, glutathione itself is in need of salvaging by the enzyme called reductase. If this mechanism fails, oxidized glutathione is removed from the cell into the interstitial fluid and the blood stream. Thus high levels of oxidized glutathione in the blood are a reflection of oxidative stress in the body. In general, the glutathione status in the body is regarded as a biomarker of well-being and a good predictor of general health.

published by B5 srl
Via Cesare da Sesto, 10
20123 Milano - Italy
Tel. 0039 02 83241119
Fax 0039 02 8376457
www.b5srl.com

THE MEDIATING ROLE

In view of the above discussed trade-off mechanisms that involve inevitable ROS formation, the mediating role of certain biochemical mechanisms has been found necessary to preserve the integrity of cells and tissues. Glutathione, and its enzymes in the glutathione system, emerge as a proficient mediator between the useful and detrimental functions of oxidation. The particular relationships between ROS representatives, like nitric oxide, and the body's own anti-oxidant, glutathione system, may exemplify the importance of this mediating mechanism.

Nitric oxide is known to play several important physiological roles in the body. For example, characteristics of the so called endothelium relaxing factor, which may prevent cardiovascular disease, are identical to that of nitric oxide. This small compound plays a role in the central control of respiratory process, systemic blood pressure and neurotransmission in neuronal connections primarily by increasing the levels of "second messenger" molecule or cyclic AMP. As previously mentioned, nitric oxide is also involved in the immune response as a natural antibiotic. On the other hand, this compound can produce collateral reactions due to its ROS nature, leading to DNA damage and cell death. In experimental conditions it has been shown that the glutathione system, by maintaining adequate levels of reduced glutathione in the cell, is an effective defense mechanism in protecting cells from damage by nitric oxide. Thus the glutathione system indeed mediates and defines what the final role of an important ROS representative, nitric oxide, will be in the body.

ALL IS IN THE BALANCE BETWEEN PRO-OXIDANTS AND ANTI-OXIDANTS

The importance of both the pro-oxidant and anti-oxidant processes in maintaining health calls for balance of these two functions in the body. How well our body withstands aging process can be, to a large degree, determined by how well one can maintain the balance between essential pro-oxidant and **anti-oxidant reactions.**

It seems that the best way to maintain balance between the pro-oxidant and anti-oxidant processes is to support the natural built-in mechanisms to counteract free radicals. These mechanisms are collectively known as the body's anti-oxidant defense system and include, besides the discussed glutathione system, also some important enzymes disabling ROS, i.e. superoxide dismutase (SOD) and catalase. Preventive steps to maintain the readiness of this defense system should not be based on the "pill approach" alone. In fact, it would serve us well to also look to the wisdom of long-standing medical traditions, like that of Ayurveda and related Tibetan medicine. According to this approach none of the techniques devised by man against any disease could be as helpful as the body's own means of fighting disease. These natural means should be supported, during critical moments, by specific treatments. But, in the first place, the individual should be maintained in good shape by: i) proper nutrition; ii) good life-habits, iii) proper adjustment to the seasons of the year, and iv) awareness of our physical and psychological predispositions.

THE OPTIMAL ANTI-OXIDANT

To support the anti-oxidant system of the body, we may resort to supplemental vitamins, minerals and natural compounds such as phenolics or flavonoids, which have the ability to counteract free radical damage. Measured anti-oxidant supplementation is particularly recommended when the anti-oxidant defense is gradually overwhelmed despite proper nutritional and behavioral modifications. This negative occurrence may be due to the aging process, disease, the wear and tear of daily pressures, or from forcible physical exercise, as in the case of professional athletes.

The way to measure an appropriate or "optimal" anti-oxidant is not only by its ability to counteract free radicals but primarily by its safety and versatility (first do no harm). Effective and safe anti-oxidants scavenge free radicals at the cost of becoming weak and short-lived free radicals themselves. Ideally, these "second hand" free radicals should be unreactive products, and should not pose a health hazard. Some synthetic anti-oxidants like BHT or BHA commonly used in the food industry, although powerful scavengers, result in the formation of long-lasting "second hand" free radicals. The other important aspect of an effective and safe anti-oxidant's use is to remember that "more" is not necessarily "better". This means that the anti-oxidant should be used in a quantity that preserves the balance in the body, without shifting that balance into inhibiting the physiological or natural oxidative processes.

A useful addition to the vocabulary on effective and safe anti-oxidants is the term "bioprotectant". Anti-oxidants with "bioprotectant" effects have been defined in laboratory analyses to show that they can: **prevent** free radicals formation in the first place, and **intervene** to neutralize free radicals which have already been formed. This definition of "bioprotectant" activity is based on original research by the authors in cooperation with Rutgers University in New Jersey. The three main phenolic anti-oxidants, or curcuminoids, that were isolated from turmeric root (*Curcuma longa* fam. Zingiberaceae) in specific proportions, i.e. curcumin, demethoxy curcumin and bisdemethoxy curcumin have **bioprotectant properties**. It should be noted that relatively few anti-oxidants nutrients have bioprotectant activities, and most natural and synthetic anti-oxidants can only intervene or quench free radicals. Interestingly, curcuminoids besides being versatile anti-oxidants exert an anti-inflammatory mechanism which is more precise and safe than that of aspirin. For example, a recent study on curcuminoids done at the prestigious Sloan-Kettering Cancer Research Center in New York showed that the anti-inflammatory mechanism of curcuminoids operates by suppressing the enzyme cylooxygenase type 2 (Cox-2) whose excessive activity is responsible for manufacturing the inflammatory compounds (e.g. prostaglandin thromboxane) in the body (the daily recommended anti-oxidant dose of curcuminoids is 50-150 mg; the anti-inflammatory dose is 500 mg tid).

Curcuminoids inhibit several processes that contribute to the survival, proliferation, invasion and metastasis of tumor cells. These processes with which curcuminoids interfere include signaling mechanisms (critical for tumor growth), regulation of apoptosis (cell death), and tumor angiogenesis (new blood vessel formation which feeds tumors). Current research is designed to determine which of these fundamental processes in cancer development account for the clinical effects of curcumin and its derivatives.

Curcuminoids have significant immunomodulating and anti-inflammatory effects by inhibiting the activation of the nuclear factor kappa-B (NF-kB) family of transcription factors,

which are known to be activated in a wide variety of solid tumors and leukemias as well in virtually any form of inflammation in the body. The NF-kB is nicknamed "master switch" of inflammatory reactions. The activation of NF-kB may shield tumor cells from apoptosis, or programmed cell death, promote tumor growth factors and those factors that facilitate invasion and metastasis of tumors. Curcuminoids block the NF-kB mediated gene expression responsible for the chain of events leading to tumor development, progression and expansion as well as broad range of inflammatory reactions in the body.

In the last three years alone there have been several pioneering IND (Investigational New Drug) studies granted by the FDA and other NIH funded studies for the investigation of curcumin and its derivatives in treatment of patients with cancer. Some of the leading cancer research centers in the US, including Houston based MD Anderson Cancer Center, are involved in pre-clinical and clinical research of the anti-cancer mechanism and application of curcuminoids in conditions including multiple myeloma and colon cancer; breast, prostate, head and neck and respiratory tract cancers are being considered next in line for systematic evaluation with curcuminoids therapy.

A particular group of anti-oxidant ingredients that should be mentioned are those which can play a preventive and positive nutritional role in a disease. Nowhere is the need for an appropriate anti-oxidant supplementation more obvious than in the devastating disease of diabetes. The course of diabetes, particularly the adult onset type (NIDDM or Type II diabetes), if diagnosed in its early stages can be dramatically improved with life style and dietary modification, including the use of anti-oxidants. Oxidative stress is one of the major mechanisms in diabetics that leads to accelerated cataract formation and eye retina damage with resulting blindness, as well as nervous and cardiovascular system damage (accelerated atherosclerosis being a major cause of mortality among diabetics).

Some important anti-oxidants in managing diabetes include alpha lipoic acid (used successfully in Europe for several decades to alleviate diabetes caused neuropathy and retinopathy), standardized extract of *Momordica charantia* (fam. Cucurbitaceae), and *Gymnema sylvestre* (fam. Asclepiadecae), minerals like L(+)selenomethionine, zinc monomethionine, magnesium citrate, organic forms of vanadium, and a body-made anti-oxidant Coenzyme Q10. These nutrients, besides being anti-oxidants, can be considered useful in the nutritional support of diabetes.

Selenium, especially in organic form like selenomethionine, is one of the most versatile anti-oxidant minerals. Selenium is an essential trace element in nutrition for the prevention of disease in humans. Epidemiological studies indicate an association between low nutritional selenium status and increased risks of cardiomyopathy, cardiovascular disease and carcinogenesis in various sites of the body. The role of selenium supplementation in the prevention of a virus infection (e.g. prevention of HIV related pathology) has been considered.

Selenoproteins (proteins with selenium in their structure) discovered in mammalian cells may account for the essentiality of selenium in the body anti-oxidant defense (selenium is indispensable in function of glutathione system), the thyroid hormone function, the immune system function, particularly the cellular immunity, formation of sperm and functioning of the prostate gland. The nutritionally recommended dose of elemental selenium is estimated at 50 to 200 μg/day. Recent studies suggest that selenium and vitamin E (alone or in combination) may reduce the risk of developing prostate cancer by 60% and 30%, respectively. This finding led to a large clinical trial nicknamed SELECT which has been conducted on 35,000 North American men by the NIH/NCI to confirm those initial findings.The NCI/NIH utilizes L-seleno-methionine obtain from Sabinsa corporation, SeleniumSelect®. Based on current knowledge of selenium in prevention of cancer the US FDA allows qualified selenium health claims such "Selenium may reduce risk of certain cancers" or "Selenium may produce anticarcinogenic effects in the body".

Another less known and increasingly discussed anti-oxidant is Coenzyme Q10. The nutritional supplementation of Coenzyme Q10, a ubiquitous body made molecule, is of clinical significance since its deficiency has been found in course of aging, physical exhaustion, in patients with diabetes, and with ischemic heart disease. Supplementation with Coenzyme Q10 (daily recommended dose 50 to 120 mg) has been shown to be beneficial in nutritional support of congestive heart failure, dyslipidemia, complications of diabetes, Parkinson's syndrome, and as a potential therapy in some forms of male infertility.

Last but not least, the optimal nutritional support with anti-oxidants should take into consideration the bioavailability, and especially the gastrointestinal absorption, of a supplemented anti-oxidant. To paraphrase the old adage: you are what you eat **as well as** what you absorb. Bioperine® is a patented natural product designed for enhancement of broad range of nutrient bioavailability. Bioperine® consists of 95% pure natural alkaloid piperine, a pungent principle derived from fruits of black pepper. The increased nutrient absorption in the presence of Bioperine® has been achieved with 5 mg of the compound co-administered with the supplemented nutrient. Bioperine® has been evaluated with fat soluble beta-carotene, water soluble vitamin B6, vitamin C, Coenzyme Q10 and mineral selenium in the form of L-selenomethionine in human volunteers. The mechanism(s) by which piperine increases the absorption of diversified nutrients is likely a non-specific and operate directly in the gastrointestinal tract. These mechanisms may involve increased gastrointestinal blood supply, increased micelle formation, and epithelial cell wall modification due to the lipophilic nature of the compound. The most interesting mode of action of piperine may be due to its postulated thermogenic properties and the increase in bioenergetic processes (creating increased demand for the supplied nutrient) in the gastrointestinal epithelium described in literature as its **thermonutrient** activity.

In summary, the perspective of anti-oxidants and their nutritional use in medical practice should be considered in the context of how they can be used to balance the processes that lead to formation of free radicals – the oxidative processes. Only with this perspective can we make a wise choice helping our body, instead of adding a new health burden.

The peer-review references in support of various statements in this article are available upon request.