

The Antioxidant Paradox

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INTRODUCTION

Natural plant-based manures and composts were the main fertilizers to enhance agricultural farm food production and keep the health of farm soil intact till the early 1930s. However, these practices changed post-World War, and farmers became more reliant on chemical fertilizers, other agrochemicals, and farm machineries.^[1] Certainly, these modernizations in farm practices led “green revolution” post-1960s and increased the yield of food crops many folds.^[2] However, it drastically and negatively affected nutrient qualities and quantities in cultivated food crops.^[3] Later on, the introduction of food-processing techniques postindustrialization further impinged on the nutrient qualities and quantities of food materials. Although these developments facilitated human life and lifestyle in many ways, drastic depletion of micronutrients, phytochemicals, vitamins, and minerals during processing of food materials compromised health conditions of individuals.^[4]

Consumption of highly processed food materials devoid of a number of important phytochemicals, micronutrient vitamins, minerals, and other essential co-factors provided highly fertile soil sprouting many disorders collectively called metabolic disorders or diseases of modernization such as obesity, diabetes mellitus, cardiovascular diseases, hypertension, cancer, and inflammatory disorders. The genesis of these disorders is thought to be due to the imbalance in the natural biochemical and physiological homeostatic processes operating in the body.^[5] To traverse such imbalances, exogenous manipulators and interventions as medicaments were designed and developed. However, inappropriate understanding of the complexity of human physiological and operating biochemical processes further complicated and exacerbated the troubles of industrialized human society.

Imbalance in antioxidant defense in the body is understood as an important phenomenon leading to the genesis of diseases of multifactorial nature the modern human society is encountering today.^[5] Therefore, the concepts of the development of antioxidants as a therapeutic base to combat such diseases were evolved,^[6] and a number of antioxidant-based

therapeutics were developed. The realization that in the course of food processing number of important micronutrients and phytochemicals bearing antioxidant properties are lost, therefore, emphasis was laid on the development of natural antioxidant supplements.

THE ANTIOXIDANT PARADOX

Recent disclosures on antioxidant therapeutics have found that antioxidants can work as a double-edged sword if inappropriately used. The robust analytical methods applied by Bjelakovic *et al.* in 53 randomized clinical trials with low-risk bias revealed the fact that intake of β -carotene and Vitamin E as antioxidant supplements beyond the recommended daily allowances rather increased the all-cause mortality in humans.^[7] The dose of Vitamin A also shed doubts on its beneficial effect, and a significant association with increased mortality in meta-regression analysis was noticed in this scrutiny.^[7]

Recent studies have demonstrated that detoxification of reactive oxygen species and increase in intracellular antioxidants may turn pro-tumorigenic.^[8,9] Similarly, intake of natural antioxidant supplements has been warranted for their adverse health effects even in healthy humans for, they may increase the rate of malignancies.^[10] Supplementation of β -carotene in smokers and carotenoid treatment in tuberculosis patients have been observed to aggravate the rate of lung cancer.^[11-13] Increased risk of skin malignancies has been reported in women taking antioxidant supplements.^[14] Increased consumption of tea and coffee has become *à la mode* in the modern society. These flavonoid-rich beverages have been suspected to promote the risk of central nervous system tumors and childhood leukemia.^[15-17] It has been opined recently that excessive antioxidant therapy can act as a potential immunosuppressant and increase the likelihood of developing malignancies by compromising the natural immune protection system and direct cell and DNA damage.^[18]

Antioxidants are supposed to maintain the health of cells. This presumption encouraged people worldwide to consume a host of phytochemical supplements bearing antioxidant properties including Vitamin E, β -carotene, N-acetylcysteine, lycopene, selenium, and green tea catechin-enriched products. In a recent study, it was observed that N-acetylcysteine increased lymph node metastases sparing the number and size of primary tumors in mice.^[19] N-acetylcysteine and Vitamin E analog (Trolox) substantially accelerated the migration and invasion of human malignant melanoma cells without affecting their proliferation. These antioxidant compounds were shown to activate RHOA protein

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which helps cells to spread all over the body.^[19]

In a double-blind, randomized, placebo-controlled trial, supplementation of high doses of dietary antioxidants (containing lycopene, selenium, and green tea catechins) in men with multifocal high-grade prostatic intraepithelial neoplasia and/or atypical small acinar proliferation was found to be associated with a higher incidence of prostate cancer.^[20]

DECIPHERING THE RIDDLE

The puzzle of antioxidants promoting cancer has been explained vividly. It has been suggested that in the case of excess antioxidant consumption, the cancer cells smartly steal and store exogenous antioxidants and thereby improve their protective armamentarium.^[21] Antioxidant supplementation to lung cancer cells has been found to decommission tumor suppressor gene p53 and thereby promote metastases.^[22] Although there are literatures reporting the cancer-preventive role of antioxidants,^[23-25] the antioxidant activity may be a simple epiphenomenon of that molecule or the formulation and still undiscovered property in a particular molecule whom we call antioxidant, may have cancer-promoting activity.^[21] It is important to remember that the human body has its own antioxidant defense system comprising of glutathione, catalase, peroxidases, etc. In the event of excessive exogenous supply of antioxidants, this endogenous defense mechanism may be compromised by adaptive negative feedback response.^[21]

The fundamentals of antioxidant therapy revolve around oxidative stress. Yet, there is no consensus to measure the desirable and/or undesirable level of oxidative stress. It is well known that physical activity increases the level of oxidative stress. This stimulus in fact upregulates the endogenous antioxidant defense mechanism. This phenomenon is called hormesis.^[21] This feedback mechanism is developed by eukaryotes in an adaptive manner to respond to our activities. Therefore, pampering the natural adaptive mechanisms by exogenous supplementation of antioxidants may negatively affect and influence the inbuilt endogenous defense mechanism. Such activities may later affect our natural defense mechanism, compromising the immune response.^[18]

Antioxidants are advocated to counter oxidative stress, which is a life-threatening process involved even partially in the development of a number of disease conditions. However, they may turn pro-oxidant depending on the environment they are exposed to.^[5,26] Plants of Brassicaceae/Cruciferae family have been used by humankind since ancient times as salads.^[27] The isothiocyanates/sulforaphane compounds present in the leaves of these plants display multiple therapeutic activities.^[27] Although these compounds also display antioxidant properties, they are shown to promote low level of oxidative stress and thereby help increase the levels of endogenous antioxidant defenses.^[28] Therefore, the pro-oxidant activities displayed by these natural compounds in fact support the hormetic feedback mechanism in the body. The pro-oxidant activity of isothiocyanates helps in the upregulation of antioxidant response elements (ARS), which stimulates increase in cellular antioxidant defenses.^[29] These disclosures warrant adequate understanding of the pathophysiology of the disease process and mechanism of antioxidant action and use thereof.

Oxidative stress has been identified as one of the important risk factors promoting complications in diabetic patients. Hence, the usefulness of antioxidant therapy in mitigating the development of diabetic complications is highly advocated and promoted. However, the usefulness of biomarkers of oxidative stress in predicting the risks of diabetic complication development is still unclear. Adverse cardiovascular events are one of the important risks in diabetic patients. In a recent clinical analysis, however, the six broad-spectrum plasma biomarkers (advanced oxidation protein products, oxidative hemolysis

inhibition assay, ischemia-modified albumin, fluorescent-advanced glycation end products, carbonyls, and total reductive capacity of plasma) of oxidative processes were not significantly associated with major adverse cardiovascular event occurrence and were not able to improve major adverse cardiovascular event risk discrimination and classification beyond classical risk factors in type 2 diabetes mellitus patients.^[30] High levels of polyphenols in food materials are responsible for potent antioxidant activities. However, imprudent use of high level of polyphenols can augment postprandial hyperglycemia and hyperlipidemia^[31-33] and may adversely affect their management. Polyphenols are also known to modulate the activities of metabolic enzyme;^[34] therefore, consideration of such molecules or the concentrates based merely on their antioxidant activity should be made with caution.

CONCLUSION

The general belief that natural and green products are harmless is not always the truth. And so happens with the faith toward the health benefits of antioxidants. In fact, a balanced human diet contains substantial amount of natural antioxidants and micronutrients that the body absorbs in desired and required amount accordingly. Hence, the approach should be educating people to take unprocessed healthy whole grains/vegetables/fruit-based diet. The urge of injudicious supplementation of additional amount of such complements may turn harmful as is being reported for additional antioxidant supplementations. Upanishads say that “*food is eldest of all creatures. Therefore, it is called the medicament of all.*” These lines were well endorsed by the father of modern medicine Hippocrates who said “*Let food be thy medicine and medicine be thy food.*” Regarding additional fortification and supplementation of micronutrients and/or antioxidants as is becoming a trend today, Hippocrates warned: “*Everything in excess is opposed by nature.*”

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