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REVIEW PAPER

## Potential clinical uses of commonly available antioxidants

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### ABSTRACT

Antioxidants are used in many clinical conditions including aging and age related conditions. Exact clinical applications are not clear. Hence, this review article aims to identify the clinical conditions which might be benefitted by the administration of antioxidants. Different original articles and review articles published on the utility of antioxidants were selected for review. From the available studies, clinical conditions for the use of antioxidants were identified. Commonly available antioxidants like Vitamin A, Vitamin E and Vitamin C showed efficacy in degenerative diseases, malabsorption states and diabetes mellitus. More findings are awaited with respect to avocado and Vitamin E in cancer and allergic conditions respectively. Lifestyle modifications, eating fresh fruits and vegetables, regular exercises, weight management are advocated in general while specific antioxidants are recommended based on the findings of the clinical studies. Fresh supply of fruits and vegetables are necessary to preserve the naturally available antioxidants in them while steaming method of cooking would aid in preserving them further.

**Keywords:** - Antioxidants, Aging, Free radicals, and Vitamins.

### INTRODUCTION

It is well-known that antioxidants are very useful in many clinical conditions. They are more popular as anti-aging agents. However, exact clinical indications for which they are useful are not clear. Doses of different antioxidants for different clinical indications are also not very clear. It is likely that they would be of very good use in clinical conditions which involve oxidation-induced damage. This review article aims to identify potential clinical uses of commonly available antioxidants like vitamin C, vitamin E etc.

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Antioxidants are free radical scavengers. They can be vitamins, phytochemicals or active ingredients in some food substances or plant sources. This article mainly focuses on commonly available antioxidants like vitamin A, vitamin E and vitamin C. Food sources of antioxidants are useful to know for dietary supplementation of antioxidants (Table I).

**Table 1: Food Sources of Antioxidants**

Name of the antioxidant	Source
Carotenoids	Carrots
Vitamin C	Oranges
Vitamin E	Nuts, seeds, vegetable oil and liver oil
Selenium	Garlic, grains, fish
Flavonoids	Pomegranate, tea
Lycopene	Water melon, tomato

## POTENTIAL CLINICAL USES OF ANTIOXIDANTS

Free radical generation and oxidation damage are seen in many clinical conditions. These include atherosclerosis, cancers, degenerative disorders, inflammatory diseases and of course, aging. They are also involved in the etiology of arthritis [1]. Free radicals are also generated in tobacco chewing, smoking, excessive exposure to sun and exposure to heavy metals [2].

## EFFICACY OF ANTIOXIDANTS

Many antioxidants are likely to be useful in many neurological disorders. Role of oxidative stress in the progression of neurological disorders has been reviewed by Isabella et al [3]. As free radical damage is involved in degenerative neurological diseases, antioxidants would be able to play a major role in arresting the damage and progression of such disease processes.

Betacarotene, vitamin C and vitamin E are claimed to be protective against cancers and atherosclerosis. But, clear evidence for this protection is not available. Some studies also indicate that antioxidants would be harmful in these conditions. However, effect of Vitamin C in reducing the severity of common cold is well-known. Such controversial results in different studies could be due to different dosages adopted in different studies for different clinical situations [4].

Due to such diverse results, clinical caregivers are in a dilemma. At least for the present, lifestyle modifications, eating fruits and vegetables, regular exercise, weight management and avoiding smoking are recommended instead of taking antioxidants [5]. Supplementation of antioxidants may be adopted for those who may have deficient levels of vitamins and minerals as in sailors and patients with gastrointestinal diseases [4].

Free radicals scavenging through antioxidants would help in tackling premature aging, abnormal aging and age-related macular degeneration [2].

## COMMON PREPARATIONS OF ANTIOXIDANTS

Commonly available antioxidant preparations contain vitamins, beta carotene, selenium, zinc, copper, manganese and carnitine [5]. Other commercially available preparations include cholecalciferol,

combinations of vitamins with calcium, lipoic acid, ginkgo biloba, Coenzyme Q, glucosamine, folic acid, silymarin, chromium, cyproheptadine, cod liver oil, L-arginine, N-acetyl cysteine, isoflavones, levomeloic acid, glutamic acid, green tea, ginseng, grape seed extract, ginger, garlic extract, herbal products, probiotics, choline, trace minerals, trace elements, inositol, etc. It is to be noted that not all of these are antioxidants. They are clubbed with vitamins and may appear as antioxidants. Their antioxidant actions have not been studied extensively. One has to rely on studies done for every compound separately and then decide about their clinical utility [5].

## **REVIEW OF AVAILABLE EVIDENCES ABOUT THE UTILITY OF ANTIOXIDANTS**

Pre-treatment with combined curcumin and  $\alpha$ -tocopherol showed protection against cisplatin-induced hepatotoxicity including the biochemical, histological and molecular aspects [6].

Catechu seed extract was found to be a more promising agent for protecting liver from APAP induced hepatotoxicity [7].

Aqueous extract of cardamom CARD down-regulated MDA, inflammatory mediators (IL-1 $\beta$ , IL-6, TNF- $\alpha$  and NF- $\kappa$ b) and apoptotic markers (caspase 3 and 9 and Bax) and amplified the activities of SOD, catalase, GSH-Px and GSH-R in hepatic tissue samples [8].

Role of citrus peel derived antioxidants in cancer therapy has been reviewed by Alaqeel et al. [9]. Many constituents in citrus peel would show benefits in cancer therapy by acting on different stages of cancer development.

Role of hyperglycemia –induced free radical generation has been reviewed by Gonzalez et al. [10]. Benefits of maintaining balance between pro-oxidant status and antioxidant status is very important in free radical damage seen in hyperglycemia.

Studies on resveratrol nano formulations in cancer therapy have been reviewed by Muhammad Sarfraz et al [11]. Prospects of developing nano formulations of resveratrol, which shows benefits against many diseases are discussed.

Pomegranate supplementation in Alzheimer's disease is effective through mechanisms including antioxidant action [12]. Co Q has been found to be effective in suppressive periodontal inflammation [13]. Phyllanthus niruri, a traditional herbal medicine was found to elevate antioxidant levels in liver disease [14].

Role of natural antioxidant sources in food industry and preventing health problems due to use of synthetic antioxidants were discussed in another article by Sofia C et al [15]. Polyphenols from avocado were found to inhibit cancer cells [16]. Flavonoid glycosides were found to have antibacterial activity

[17]. Mixture of flavonoid glycosides and berberine was found to have antibacterial activity [18]. In another study, it was found that Vitamin E decreases the IgE levels in atopic individuals [19].

In this same review article, it is seen that Vitamin E is beneficial in epidermolysis bullosa. It is also seen that Vitamin E did not protect against skin cancer in clinical studies though benefits were seen in mice. In another study, it was noted that Vitamin C and carotenoids showed synergistic effect in producing a limited benefit in cognitive performance [20]. In another study, short term supplementation of Vitamin E showed positive effects on oxidative stress in infertile PCOD patients under evaluation of ovulation induction [21]. In the article by Sima Goodarzi, studies showing effectiveness of antioxidants and studies not showing effectiveness of antioxidants are discussed [22] as depicted in Table-2.

**Table 2: Studies Showing Effectiveness/No Effectiveness of Antioxidants**

<b>Antioxidant studied</b>	<b>Disease condition studied</b>	<b>Result</b>
Vitamin A, vitamin E, Vitamin C	Cirrhosis liver Hepatic encephalopathy	Beneficial
Selenium	Ammonium chloride induced lung damage in mice	Beneficial
Vitamin C and vitamin E	Diclofenac induced nephropathy in rats	Beneficial
Vitamin C	Organophosphorus poisoning in rats	Beneficial
Vitamin C	Role in reducing the development of DM	Beneficial
Vitamin C	Reduces mortality in cardiovascular diseases	Beneficial
Vitamin E	Mucositis induced by 5FU injection in mice	Beneficial
Vitamin E	Cyclophosphamide immunosuppressed broilers	Beneficial
Beta-carotene and retinal	Lung cancer incidence in smokers	Not beneficial
Vitamin C, vitamin E and beta-carotene	Cardiovascular disease	Not beneficial
Vitamin E, selenium	Cancer occurrence	Not beneficial

Omega 3 fatty acid supplementation was found to be beneficial for heart diseases [23]. Gamma tocopherol and delta tocopherol were found to show growth inhibitory activity in cancer cell lines [24]. Due to controversial outcomes in different studies, antioxidants' role is undecided in cancer therapy [23].

Some studies on antioxidants and discussions of the results are found in the publication by the US Dept of Health and Human Services, National Institute of health [25]. They are given below;

In some studies, vitamin E and beta-carotene did not protect against the conditions of lung cancer, prostate cancer besides stroke [25]. Similarly, in PHYSICIANS' HEALTH STUDY II, vitamin C and vitamin E did not show any benefit with respect to cardiovascular diseases, cancer, cataract and stroke.

But, in other studies, vitamin C and Vitamin E and beta carotene showed benefit in macular degeneration but not in cataract [25].

### **REASONS FOR LACK OF BENEFITS IN SOME STUDIES**

Studies showing lack of benefits could be due to variations in dosages adopted. . Doses used might be high when compared with the doses available in natural sources. Other reasons could be the short duration of administration of antioxidants. It is also possible that participants in the study might not have had deficiencies of antioxidants. In some clinical conditions, antioxidants could be of prophylactic value and in some other conditions, they could be of therapeutic value. Suitable clinical studies are warranted to investigate these different possibilities.

In the mini review done by Wenqian Li et al, omega 3 fatty acid, vitamin D, vitamin E, magnesium, zinc, CoQ10 and acetyl levocarnitine were found to be beneficial in different studies on antioxidant imbalance in polycystic ovarian syndrome. However, more clinical trials are needed before any recommendation of antioxidants can be made [26]. Sebastian J. Padayatty et al reviewed the role of Vitamin C as an antioxidant in disease prevention. Vitamin C was noted to yield some protective effect in hypertension and gastrointestinal cancer. However, more clinical studies are again needed before any recommendation can be made [27].

### **OTHER AREAS OF UTILITY OF ANTIOXIDANTS**

Antioxidants play important role useful role in food industry. Besides being used as preservatives, they are also used to develop healthy food products [28]. They are also useful in pharmaceutical industry in various manufacturing processes.

Some readers may be inclined to use natural sources of antioxidants instead of synthetic antioxidant preparations. Antioxidant measurements like ORACLE scores are used in labs to compare different sources of antioxidants. It was found that walnut, amla, coffee, moringa have high level of antioxidants [29].

### **COMBINATION OF ANTIOXIDANTS AND OTHER INFLUENCING FACTORS**

Some studies where antioxidants were combined showed beneficial effects. For ex: glutathione, vitamic C, vitamin E and selenium, when combined showed better effects. It is also to be noted that synthetic sources of antioxidants and natural sources of antioxidants yield some products which are slightly different in chemical structures and efficacies. Of course, mode of extraction and mode of cooking also influence the availability and functions of antioxidants. Naturally available antioxidants could be better than synthetic antioxidants but still they could be toxic when consumption is in excess. Similar dose concerns are also possible with synthetic antioxidants [30].

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## CURRENT STATUS OF USING ANTIOXIDANTS IN CLINICAL PRACTICE

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From the above, it is clear that antioxidants can be useful in many clinical situations though they are harmful in some clinical situations. Controlled clinical studies would shed more light on their clinical utility. In animal models and some clinical studies, antioxidants have shown efficacy in hepatotoxicity, liver diseases, cancer chemotherapy, hyperglycemia-induced free radical damage, Alzheimer's disease, periodontal diseases, antibacterial activity, atopic conditions and macular degeneration. Out of the above, one can prioritize areas for further research. One can focus on utility of antioxidants in hyperglycaemic conditions, allergic conditions, macular degeneration and bacterial infections. More studies on role of citrus peel extract, resveratrol, avocado and vitamin E in cancer can be done. More studies on role of pomegranate, vitamin C and carotenoids in Alzheimer's disease can also be done. Vitamin E can be studied extensively in conditions involving allergy. Specific vitamins or other specific molecules can be used for patients wherever clear trial results are available. For other situations, use of antioxidants has to be put on hold till more results are available. Products like walnut, amla, coffee and moringa can be considered for anti aging purposes as they have high antioxidant scores. One can also adopt other measures like lifestyle modifications, eating fresh fruits and vegetables, regular exercise, weight management and avoiding smoking instead of taking antioxidants till more evidences for use of antioxidants in specific clinical conditions are available. At this juncture, we have to remind ourselves about ideal cooking methods for maximum nutrition. Steaming seems to be better than any other method of cooking like boiling, pressure cooking, microwaving, frying etc [31]. Ideal time to consume fruits and vegetables would be as soon as they are ripe. In everyday life, we can see them locked in transit, in grocery store and in our refrigerators for about two weeks [32]. Thus, consuming fresh fruits and fresh vegetables would augment our antioxidant status and prevent against free radical damage related clinical conditions.

One has to closely keep track of recently reported trial findings. One study has highlighted the protective effect of Vitamin D in reducing the risk of relapse or death in the subgroup of patients with digestive tract cancer who were p53 immunoreactive [33]. Another study has identified Vitamin E as useful for chronic insomnia in postmenopausal women where it also reduced the use of sedative drugs [34]. Vitamin E, when given with atorvastatin showed benefits in terms of insulin sensitivity and improving PPAR- $\gamma$  mRNA expression [35]. Vitamin E also showed preventive effect on bone loss in postmenopausal osteopenic women [36]. In a review article by Rachit Kumar et al, vitamin C benefits in diabetes, neuropathies and endothelial dysfunction are noted [37]. In the same article, beneficial effects of vitamin C in cancer and in improving sperm quality are also noted. In another review article by Nikhil Mehta et al, benefits of using vitamin C in covid – 19 are highlighted. Vitamin C contributes to the beneficial effect through different mechanisms in addition to antioxidant action [38]. Thus, one

can identify commonly available antioxidants of high antioxidant capacity viz vitamin E, vitamin C and vitamin D and keep watching their clinical trial findings before using them in clinical conditions of one's interest.

## LIMITATIONS OF THIS REVIEW

Many clinical studies involve combination of different antioxidants for studying their efficacies instead of any single agent. Clinical outcomes studied are about different clinical situations rather than a specified disease entity. Such clinical outcomes are highly specific in nature and generalizing the outcome of the studies to distinct disease entities becomes difficult.

## SUMMARY

From the review of different studies, it is interesting to note that Vitamin E and statin might be of value in enhancing insulin sensitivity, if future clinical studies bring out favourable findings. Similarly, role of Vitamin D in cancer prevention has to be closely watched for. At present, antioxidants may be useful in neurodegenerative disorders, malabsorption states, diabetes and age-related situations. Walnut, amla, coffee and moringa seem to contain good antioxidant activity and hence, found useful for antioxidant purposes. Roles of Avocado in cancer and vitamin E in allergy states are very interesting to watch for in future.

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