REVIEW ARTICLE

Therapeutic Potential of Vitamin C: An Overview of Various Biological Activities

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ABSTRACT

Vitamins are vital nutrients that are required for different body functions properly, and they are provided to the body externally through diet. Vitamin C, also known as ascorbic acid, is an essential nutrient that is required for the proper running of different body functions. It is a water-soluble vitamin and lost during the processing of food. The main sources of vitamin C are citrus fruits (kakadu plum, acerola cherries, guavas, kiwi, lemon, lychees, kale, oranges, peaches, tomatoes, black currant, thyme, parsley, rose hips, kale and strawberries), green leafy vegetables (chilli peppers, tomato, sweet yellow peppers, parsley, brussel sprouts, potatoes, mustard spinach and broccoli), fortified cereal and some animals. Vitamin C deficiency leads to scurvy, which mainly affects older, malnourished adults. Vitamin C acts as a strong antioxidant, and this property enriches various biological activities. It is believed that high dose of vitamin C may help in reducing the risk of various diseases like cancer, diabetes, cardiovascular disorders, blood pressure, respiratory syndromes, common cold, reproduction, cognitive diseases, skin problems, age-related muscular degeneration, cataract and may enhance immunity. This mini-review article has been planned to discuss sources, deficiency symptoms, daily requirements, therapeutic potential, and various biological activities of vitamin C. Various therapeutic and pharmacological activities of vitamin C will be discussed in detail with suitable examples.

Keywords: Ascorbic acid, Antioxidant, Biological activities, Citrus, Medicinal uses, Sources, Vitamin C.

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INTRODUCTION

Vitamins are vital nutrients that are required for different body functions properly and are not prepared by the body. They are provided to the body externally through diet. Vitamins can be classified into two groups, one which is water-soluble and another is fat-soluble.[1] Vitamin C, also known as ascorbic acid, comes under the category of water-soluble vitamins. A severe form of vitamin C deficiency is known as scurvy, which mainly affects older, malnourished adults. Ascorbic acid is an organic acid and gets protonated to ascorbate either by the lose of hydrogen or maybe di-anion. The body does not synthesize vitamin C, and it is supplied to the body by dietary sources. It commonly occurs in plants (fruits and vegetables) and animal liver and kidney. The deficiency of this vitamin causes scurvy, a widespread connective tissue weakness, and capillary fragility. Vitamin C contains six atoms of carbon, six oxygen atoms, and eight hydrogen atoms allocated on the lactone ring (molecular formula: $C_6H_8O_6$ and molecular mass: 176.12 g/mol). Vitamin C exhibits two pairs of stereoisomers as L- and D-ascorbic acid and L- and D-isoascorbic acid but vitaminic activity is exhibited by D-ascorbic acid and D-isoascorbic acid only.[2-3]

SOURCES OF VITAMIN C

Vitamin C is obtained from citrus fruits, green leafy vegetable (including kakadu plum, acerola cherries, rose hips, chili peppers, guavas, sweet yellow peppers, black currants, thyme, watermelon, parsley, mango, grapefruit, mustard spinach, kale, kiwi fruit, broccoli, brussels sprouts, pineapple, lemons, lychees, American Persimmons, papayas, strawberries, oranges, tomatoes, turnip greens, winter squash, potatoes, Indian gooseberry, snow peas, raspberries, blueberries, cranberries, cauliflower, and cantaloupes), fortified cereal and their juices are also richest sources of vitamin C. Some of the richest sources of vitamin C are listed in Table 1. Some of the animals (such as calf, lamb, goat milk, cow milk, and human milk) also serve as a source of vitamin C; they prepare vitamin C by own, and chiefly vitamin C is present in the liver.[2,4]

DEFICIENCY SYMPTOMS

Vitamin C plays a role in many oxidative and other metabolic reactions. At cell and tissue level ascorbic acid is essential for the synthesis of collagen and intercellular material. If dietary intake is inadequate, vitamin C deficiency may develop. Too

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Table 1: Richest sources of vitamin C (Source: https://ndb.nal.usda.gov/ndb/).

Sr. No.	*Plant*	*Biological name*	*Weight (g)*	*Measure*	*Vitamin C content (mg per measure)*
1	Kakadu plum	Terminalia ferdinandiana	100.0	1.0 cup	5300.0
2	Acerola cherries	*Malpighia emarginata*	98.0	1.0 cup	1644.0
3	Rose hips	*Rosa canila*	127.0	1.0 cup	541.0
4	Guavas	*Psidium guajava*	165.0	1.0 cup	376.7
5	Sweet yellow peppers	*Capsicum annuum*	186.0	1.0 large pepper	343.3
6	Peaches	*Prunus persica*	250.0	1.0 cup	235.5
7	Pokeberry shoots	*Phytolacca Americana*	160.0	1.0 cup	217.6
8	Black currants	*Ribes nigrum*	112.0	1.0 cup	202.7
9	Mustard spinach	*Brassica rapa var. perviridis*	150.0	1.0 cup	195.0
10	Kiwi fruit	*Actinidia deliciosa*	180.0	1.0 cup	166.9
11	Drumstick pods	Moringa oleifera	100.0	1.0 cup	141.0
12	Litchis	*Litchi chinensis*	190.0	1.0 cup	135.8
13	Oranges	*Citrus sinensis*	170.0	1.0 cup	120.7
14	Tahitian taro	*Xanthosoma brasiliense*	125.0	1.0 cup	120.0
15	Green peppers	*Capsicum annuum*	149.0	1.0 cup	119.8
16	Mammee-apple	*Mammea Americana*	846.0	1.0 fruit	118.5
17	Pumelo	*Citrus maxima*	190.0	1.0 cup	115.9
18	Lemons	*Citrus limon*	212.0	1.0 cup	112.4
19	Broccoli	*Romanesco broccoli*	114.0	1.0 stalk	106.2
20	Strawberries	*Fragaria ananassa*	255.0	1.0 cup	105.6
21	Nance	Byrsonima crassifolia	112.0	1.0 cup	103.6

little vitamin C can lead to signs and symptoms of deficiency, including anemia, bleeding gums, decreased immunity, capillary fragility, dry and splitting hair, gingivitis, nosebleeds, possible weight gain rough, dry, scaly skin, swollen and painful joints, cartilage and bone lesions, decreased healing of wounds and weakened tooth enamel. A severe form of vitamin C deficiency is known as scurvy, which affects older, malnourished adults.[5]

RECOMMENDED DIETARY ALLOWANCE (RDA)

For adults, a daily requirement of 30 to 60 mg of ascorbic acid has been recommended. However, there may be variations in individual requirements depending on various factors such as age, gender, pregnancy, and illness.[5-6]

BIOLOGICAL ACTIVITIES OF VITAMIN C

Vitamin C is a vital vitamin for the numerous physical and chemical functions of the body. Vitamin C shows various biological and pharmacological activities, including antioxidant, anticancer, antidiabetic, anti-obesity, antihypertensive, anti-hypercholesterolemic activity, photo-protection, used in neurological diseases, enhance immunity, synthesize amino acid and in repairing of teeth and bones. It can also increase the absorption of iron and enhance wound healing (Figure 1).

Antioxidant activity

Vitamin C acts as an excellent antioxidant. This property of vitamin C results in beneficial effects in a number of diseases, including hypertension, hypercholesterolemia, diabetes,

Table 2: Recommended daily intake of vitamin C at different periods of life.

Sr. No.	*Life stage*	*Recommended daily intake*[*]
1	Infants (0–6 months)	40 mg
2	Infants (7–12 months)	50 mg
3	Children (1–3 years)	15 mg
4	Children (4-8 years)	25 mg
5	Children (9–13 years)	45 mg
6	Teens-boys (14–18 years)	75 mg
7	Teens-girls (14–18 Years)	65 mg
8	Adults (male)	90 mg
9	Adults (female)	75 mg
10	Pregnant teens	80 mg
11	Pregnant women	85 mg
12	Breastfeeding teens	115 mg
13	Breastfeeding women	120 mg

[*]Add 35 mg for smokers (Source: https://ods.od.nih.gov/factsheets/VitaminC-Consumer/).

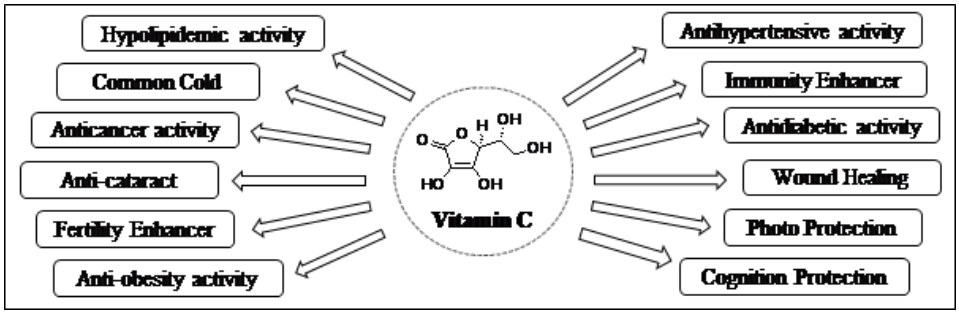

Figure 1: Biological/pharmacological/therapeutic activities/benefits of vitamin C on human health.

cancer, cold and age-related muscular degeneration (AMD), and contract.[7]

Mechanism of antioxidant action

The antioxidant mechanism of vitamin C involves neutralization of free radicals by donating a single electron and terminating the chain reaction of electron knocking out a reaction. On the other hand, vitamin C does not form a free radical by releasing a single electron due to their stable or behave as forager assist in preventing the cell and tissue from harm that could lead to cellular harm and disease.[7]

Anticancer activity

First-time anticancer activity of vitamin C was reported in 1930s and become the topic of discussion from that time to till now. Selective cell toxicity caused by high doses of vitamin C *in vitro* and mouse model, but the mechanism remained mysterious. The research is still continuing on the remediation of cancer by a high dose of vitamin C. It was reported that a high dose of vitamin C has a positive effect on a life of cancer patients with incurable cancer.[7-14] It was reported that cultured human colorectal cancer cells with KRAS or BRAF mutations were selectively killed when exposed to high levels of vitamin C. This effect is due to increased uptake of the oxidized form of vitamin C, dehydroascorbate (DHA), via the GLUT1 glucose transporter. Increased DHA uptake causes oxidative stress as intracellular DHA is reduced to vitamin C, depleting glutathione. Thus, reactive oxygen species accumulate and inactivate glyceraldehyde 3-phosphate dehydrogenase (GAPDH). Inhibition of GAPDH in highly glycolytic KRAS or BRAF mutant cells leads to an energetic crisis. One report recommended that the pharmacological dose shows the potential in the remediation of tumour[7-8]. Lee *et al*., made an effort to show that *in vitro* anticancer activity of high dose vitamin C mix with the traditional treatment of breast cancer. High doses of vitamin C dormant the production of MDA-MB-231, MCF-7, and SK-BR3 cells but not normal breast cells (MCF10A). Administration of a high dose of vitamin C with anticancer drugs resulted in inhibition of the production of breast cancer cells than anticancer drugs alone. Because of antioxidant properties, vitamin C save cells from toxic compounds. The general reason behind the cancer is the continuing attack of DNA by reactive oxygen species. Antioxidant properties of ascorbic acid play an important role in inhibiting the destruction of DNA, eminent in a cell at the cite of chronic inflammation, and various pre-neoplastic lesions[15-21].

Cardiovascular diseases

It was reported that the person who takes high plant products in his diet could reduce the risk of cardiovascular diseases. Because of the antioxidant property of vitamin C, a high dose of ascorbic acid-rich fruits and vegetables could be beneficial in preventing cardiovascular disorders in patients with hypertension, hypercholesterolemia and diabetes as well as healthy adults. Vitamin C improves both endothelial function and insulin sensitivity in patients with cardiovascular disease. However, the mechanism is not fully recognized because, in plant products, various other phytochemical compounds are also present, which may have powerful antioxidant action.[22-26] Various prospective studies on the relation of vitamin C and cardiovascular disorders were reported. For example, the National Health and Nutrition Examination Surveys (II and III) and the Eastern Finland Study supported a protective role for vitamin C in risk reduction for several endpoints that represent cardiovascular diseases and coronary artery disease, in separate models.[27-29] With regard to peripheral arterial disease, data from the Rotterdam study revealed that vitamin C had a significant protective effect, but only among women.[30] The ARIC study assessed dietary antioxidants and carotid IMT in men and women aged 55-64 years. When comparing the highest versus the lowest quintile, they found that vitamin C was significantly and inversely related to carotid IMT thickness. This occurred only in women and only in the older group after adjusting for all covariates.[31] Overall, there was some encouraging but not overwhelming support for vitamin C as a protector against cardiovascular disorders.[32]

Blood pressure

High blood pressure (BP) is a strong determination of cerebrovascular and coronary disease. Since the 1960s, numerous attempts have been made for the diagnosis and cure of hypertension. Hypertension can increase the risk of cardiovascular disease. It is believed that by controlling over hypertension, the risk of cardiovascular disease can be reduced. Generally, hypertension can be cured by pharmacological and non-pharmacological factors. Pharmacological factors have a great influence on hypertension than non-pharmacological factors because non-pharmacological factors are weak, but some non-pharmacological factors like obesity intake of

sodium and fat in the diet, drinking of alcohol have a strong influence on the blood pressure.[33-36] In one study, it is found that there is a converse association with plasma ascorbic acid and hypertension. Men having serum ascorbic acid of 0.5 mg/dL had an average systolic pressure of 122 mmHg correlate with an average of 113 mmHg for men having serum ascorbic acid of 0.9 mg/dL, comparative of -7%.

Similarly, men had comparable variance in diastolic of 78 mmHg vs. 73 mmHg, -6% comparative alterations. The frequency of high blood pressure was 7.5% in low serum ascorbic acid cluster against 1.0% among those having high concentration.[37] A finding showed a considerable swing for both systolic and diastolic pressure over-concentration of plasma ascorbic acid with -5% variance in systolic pressure and -4% variance in diastolic pressure between the maximum and minimum concentrations of plasma ascorbic acid.[38-39] Further similar considerable reverse trend was found between ascorbic acid and systolic as well as diastolic BP in Chinese-American males and females of aged range between 60 to 96 years who were not taking anti-hypertensive drugs the variance between average systolic and diastolic BP level in maximum and minimum concentrations were -21 mmHg (-14%) and 8 mmHg (-9%) respectively. With decreased vitamin C plasma concentration resulted in a decreased level of 6-keto-protaglandin-F, the metabolic prostacyclin. Therefore, an antioxidant in the diet increased the formation of the prostacyclin via forage free radicals and peroxide; these are responsible for the prevention of prostacyclin formation over a certain limit. That is why vitamin C and hypertension are associated with each other. A sufficient dose of Vitamin C in diet could show a lowering of blood pressure, but when dietary fat is decreased.[40-41]

Diabetes

An individual suffering from diabetes has a poor level of plasma vitamin C, and distorted turnover of vitamin C have been observed.[42-45] It is believed that oxidative stress is a significant factor which increases diabetic risk. The enhancement in oxidative stress and hyperglycaemia can increase *in vivo* ascorbate destruction. Dietary intake of vitamin C showed recovery of glycemic control and vascular health and reduced glycosylated hemoglobin and erythrocyte sorbitol. Further, it was observed that vitamin C dietary intake could alter insulin activity in an individual suffering from diabetes.[46-47] The women who were taking a high dose of vitamin C had a lesser chance of gestational diabetes than those who were taking a low dose of vitamin C. Still, there is no such negative relationship between total intake of vitamin C and chances of gestational diabetes.[48-53]

Myeloma and obesity

It is believed that about 20% of all cancer are credited to obesity. Obesity is the condition of extreme adiposity, which is generally identified by body mass index (BMI) $\geq$30 kg ((weight in kg)/(height in m)^2) and it is an improvable chance factor for some malignancies such as last stage cancer disease, cancer succession and chemo-resistance. Obesity starts as a consequence of the general condition of energy disparity, and the relation between obesity and cancer depends on genetic prediction, anthropometric constraints (such as BMI and value of body fat mainly visceral fat), and way of life and high or low caloric diet.[54] Because of antioxidant properties and also act as a precursor for different metabolic coenzymes, vitamin C could prevent the occurrence of myeloma. Ascorbic acid has a defensive mechanism during the repair of immune haematosis. Ascorbate acts as an antioxidant as well as pro-oxidant in the presence of metal ion during the oxidative process. It is antioxidant property that shields the cells and tissues from the oxidative stress because of its translation to the oxidized form dehydroascorbic acid which is reduced to vitamin C within the cell, thus resulting in decreased intracellular concentration of reactive oxygen species.

Furthermore, it increases oxidative metabolism by inhibiting the consumption of pyruvate for glycolysis. This characteristic can inhibit the proliferation of tumor cells but not normal cells. At pharmacological concentration, ascorbate applies cytotoxic effect tumor cell via the initiation of hydrogen peroxide reliant cytotoxicity. Vitamin C interferes with the consumption of iron, by liberation of inducing factors from mitochondria, increasing the occurrence of p21, cellular calcium, and p53. Ascorbate reduced mitochondrial membrane ability and stimulated caspase three, resulting in apoptosis in melanoma A-375 cells. Vitamin C also reduced hypoxia-inducible factor-1 concentration via the prevention of cyclooxygenase-2 expression. Vitamin C can accelerate the outcome of various antineoplastic mediators.[55-59]

Common cold

In the 1970s, Pauling carried out four blind studies to investigate the effect of vitamin C on the common cold. It was observed that vitamin C has a negative effect on the common cold. It was suggested that 1000 mg ascorbic acid may decrease the chance of cold by 45% and integrated morbidity approximate 63%. Database chochrane review indicated that the utilization of prophylactic ascorbic acid can decrease the time period of the common cold in children and adults. It could be due to the antihistamine activity of vitamin C.[60-62]

Age-related macular degeneration (AMD) and cataract

The people aged older than 50 years suffer from low eyesight, there are two significant reasons for this: AMD and cataract. Oxidative stress could attribute for both causes. Therefore, the researcher gets curious to investigate the function of ascorbic acid and antioxidants to remediate these syndromes. Numerous investigations are done to account for the role of ascorbic acid in these syndromes. In one study, it was reported that the antioxidant might reduce cellular retina damage via reacting with free-radical, which are created through the progression of absorption of light. It was reported that individuals who take high dose of vitamin C in diet may have decreased chances of AMD and cataract. Outcomes of two studies suggest that vitamin C at a dose higher than 300 mg may help in decreasing the chances of cataract development by 75%.[63-67]

Vitamin C in age-related cognitive decline and Alzheimer's disease

The role of vitamin C in brain progression is not yet known, but it is believed that an appropriate concentration of vitamin C may result in the protection and progression of the brain throughout life.[68] Various studies have shown the relationship between vitamin C supplement and cognitive power in nourishing persons aged ≥ 60. Since the 1970s sample at aged ≥ 65 in British, ascorbic acid supplement was only a nutritional aspect that predicts cognitive ability. A further parallel study was done on people aged between 60 and 94, and similar result were observed.[69-70] An investigation by a French group observed a direct relationship between supplement of fruits and vegetables, mainly those which contain vitamin C in high amounts and verbal memory. The individuals who were suffering from cognitive disorders have a low level of ascorbic acid and other antioxidants than the healthy ones. Investigation of a cohort of Japanese-American men from the Honolulu-Asia aging study showed a considerable shielding outcome of vitamin C on cognitive roles like attention, memory, and language estimation and mainly in state of vascular dementia. Therefore, it is suggested that high intake of vitamin C may help in cognitive ability.[71-73]

Vitamin C in skin disorders

Photoprotection

Antioxidant activity of vitamin C helps in the shielding of skin from the Ultraviolet (UV)-rays. With the exposure to UV light, vitamin C increased the transport protein. Supplementary of keratinocytes on the administration of ascorbic acid decreased the harm by the UV light.[74-75]

Wound healing

Healing of wound is illustrated with formation of connective tissue; the main part of this tissue is collagen. Ascorbic acid plays a vital role in the formation of connective tissue. Mainly vitamin C is needed for the hydroxylation of proline and lysine residues throughout collagen biosynthesis.[76-79] Dietary intake of the vitamin C is essential to heal wounds as ascorbic acid can be oxidized throughout collagen formation.[80-81] The new tissue reformed by the assist of collagen skeleton. This role is performed by ascorbic acid which is the co-factor for collagen synthesis.[82-83]

Immunity

Vitamin C supports immune system of the body and plays two functions: neutralize reactive oxygen species formed by phagocytes throughout their oxidative destruction of foreign microbes and stimulate different parts of immune system.[47] In worrying conditions adrenal gland respond by liberating hormone that activates "fight or flight" reaction. It has been reported that 200 mg of ascorbic acid can decrease the degree of stress hormone. Stress restrains the immune system. A high dose of vitamin C accelerated the degree of antibody, which fights against viruses and microbes in stressed rats as well as unstressed rats, along with large antibody growth in the unstressed rats.[7,36] *In vitro* investigation demonstrated that ascorbate successfully neutralizes reactive oxidant formed by phagocytes to demolish invading bacteria. Generally, the level of vitamin C is high in the plasma have been shown to reduce the capability of a destructive consequence of hypochlorous acid and superoxide (strong oxidants) produced through stimulated neutrophils and monocytes devoid of damaging of bacterial activity.[44-45]

In respiratory symptoms

In the early times, scientists were inquisitive to investigate the function of ascorbic acid in the remediation and inhibition of respiratory symptoms.[84] But the study didn't satisfactorily explain the positive role of a high dose of vitamin C on asthma. Further new studies suggested that dietary supplementation of vitamin C can help in shielding against the harmful effects of contaminated air and decreases the risk of respiratory symptoms like bronchitis, wheezing, and respiratory tract infection. Critical respiratory symptoms and reduced pulmonary function have been related to cigarette smoking.[85-87] While smoking will enhance the need for vitamin C, but mechanism for the negative association of smoking and vitamin C was not established. The decrease in level of vitamin C could be due to its function in deactivating various oxidants in the cigarette smoke.[88-90]

Role in reproduction

Some proof indicates that vitamin C may be facilitating the reproduction function. It is believed that supplementary intake of ascorbic acid increases the fertility in some persons. As ascorbate accumulates in the ovary as well as testis and medication of a few men with additional vitamin C led to better sperm quality and reproductive results. It is believed that the mechanism involved in the reproductive function is antioxidant activity and co-factor for collagen and hormone synthesis. Thus, ascorbic acid could aid in the fertility and reproduction quality for both males and females.[91-92]

CONCLUSIONS

Vitamin C present in almost every fruit and vegetable but chiefly present in citrus fruits and green leafy vegetables; acts as a potent antioxidant, and this property enrich various biological and pharmacological activities beneficial for human health. Higher plasma concentration of vitamin C may be the ideal nutrition marker for overall health. It is used as therapeutic agent in many diseases and disorders. It was reported that the administration of a high dose of vitamin C might help in reducing the risk of various diseases like cancer, diabetes mellitus, cardiovascular disorders, hypertension, respiratory syndromes, common cold, reproduction, cognitive diseases, skin problems, AMD, cataract and could also enhance immunity. Ascorbic acid has shown promise as a powerful memory-improving agent, particularly effective in aged animals. Hence, ascorbic acid might prove to be a useful memory-restorative agent in the treatment of dementia seen in elderly individuals. Vitamin C protects the immune system,

reduces the severity of allergic reactions, and helps fight off infections.

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