The Therapeutic and Prophylactic Potentials of Vitamin C

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Abstract

Vitamin C (VC) is considered a powerful antioxidant and enzyme cofactor that is essential in many biochemical pathways, such as redox reactions and collagen production. Scurvy, a historic disease that caused a large number of deaths among sailors in the 15th and 18th centuries, resulted from a clinical shortage of this essential component. The human body is unable to synthesize this material, so it requires exogenous VC to protect tissue integrity. Nowadays, VC gets a lot of interest due to its importance for various biological activities. An increasing number of articles study the relationship between this vitamin and the incidence of serious diseases, along with the progression and recovery of these diseases. In this review, we explore the effect of deficiency as well as the intake of VC on cancer prognosis, musculoskeletal injuries, skin care, immunity, infections, Parkinson's, Alzheimer's, and psychiatric diseases. We concluded that VC intake could increase survival time in cancer patients, improve immunity, relieve allergic symptoms, preserve tissue integrity, protect skin from UV harmful effects, fight skin aging, and improve symptoms in neurodegenerative and psychiatric diseases.

Keywords: vitamin C; cancer, immunity, skin care, Alzheimer's, injuries, allergy, Parkinson's.

1. Introduction

Since the description of the scurvy disease and the subsequent discovery and isolation of VC in the early 20th century, VC has received huge attention in the medical field (1). Its antioxidant activity is behind its unique biological actions (2). Unlike humans, most animals can synthesize this crucial material due to the presence of the gluconolactone-oxidase enzyme (3).

Deficiency of VC in humans can lead to many serious diseases (4). Therefore, a balanced diet that is rich in fresh vegetables and fruits such as lemon, orange, red and green pepper, tomatoes, broccoli, and many leafy vegetables can maintain healthy levels of VC in the body (5).

In the plasma, it is present in two forms: the charged form, ascorbate, that enters the cell by sodium-dependent active transport, and the uncharged form, dehydroascorbate, that is taken up into the cell via a glucose-transporter (6). A plasma level of Ascorbic Acid less than (11µM) considered a state of deficiency (7)

Besides scurvy, a shortage of this nutrient can increase the risk of infections, affect immunity (8), impair wound healing (9), predispose to depression (10,11); furthermore, schizophrenia attacks (12), and epilepsy attacks can be provoked in sensitive patients (13).

In this review, It could be concluded that the intake of this important nutrient through diet or as a pharmaceutical supplement can reverse many of these harmful effects. It can accelerate wound healing (9), modulate immunity (14), stabilize mood (15), enhance cognitive function (16), and decrease the attack rate in schizophrenic (12) and epileptic patients (13). Also, many studies have revealed its beneficial role in cancer (17).

2. Chemistry and Characteristics of VC

VC, known chemically as L-ascorbic acid (L-a), is a dibasic acid attached to a five-membered lactone ring and an enediol group, as shown in Figure 1 (18).

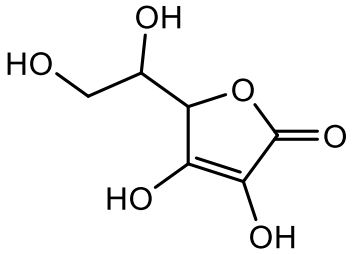
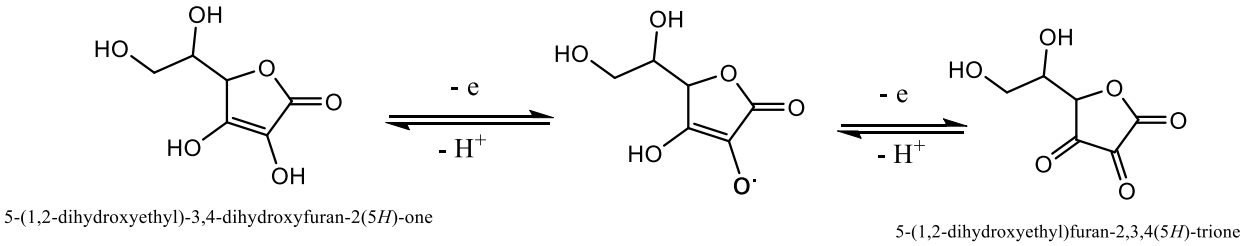


Figure 1: The chemical structure of L-a

The oxidation of L-a results in the formation of dehydroascorbic acid, and a state of equilibrium is present between these two compounds. This reaction is displayed in Equation 1 (18,19).



5-(1,2-dihydroxyethyl)-3,4-dihydroxyfuran-2(5*H*)-one

5-(1,2-dihydroxyethyl)furan-2,3,4(5*H*)-trione

Equation 1: The conversion of L-a to dehydroascorbic acid

The structure of L-a has two asymmetrical carbons; as a result, there are three other stereoisomers of this compound besides L-a itself, which include D-ascorbic acid, D-isoascorbic acid, and L-isoascorbic acid. These three isomers have either very low biological activity or none at all (18). L-a is a powerful antioxidant that has the ability to lose one or two electrons and react with free radicals, so it is considered a potent free radical scavenger in the body (20).

Unlike most animals, humans are not able to synthesize L-a because of the lack of an essential enzyme, namely L-gulono-γ-lactoneoxidase enzyme, which is important in the last step of L-a synthesis from glucose. Based on that, the only source of L-a in humans is from the diet, especially fresh fruits and vegetables, and, if it is not sufficient, pharmaceutical supplements could be used (19). In animals, L-a is synthesized from D-glucose through the glucuronic-acid metabolic pathway. The physicochemical properties of L-a are listed in Table 1 (Information, n.d.,2023)

Table 1: The physicochemical properties of L-a

Molecular Formula	$C_6H_8O_6$
Synonyms	L-ascorbic acid Ascorbic acid Vitamin C Antiscorbutic vitamin
Molecular Weight	176.12 g/mole
Melting Point	190-192 ^oC
Density	1.65 g/cm^3
Description	White to pale yellow powder with a faint acidic odor
Solubility	Water-soluble (300 g/L), insoluble in chloroform, benzene, and ether

3. The Role of VC in a Variety of Diseases

3.1 VC as an Anticancer Agent

Cancer is a group of serious diseases that can invade and destroy many organs in the body. There are many types of cancer, categorized according to the site, tissue, or organ that is affected. Gene alteration or mutation can transform a normal cell into a malignant cell, and at this point, the cancer originated (22,23). All living organisms have many defense mechanisms against harmful agents. Some immune mechanisms, like apoptosis, can detect and destroy harmful invaders or abnormal cells, but sometimes these malignant cells escape from these mechanisms and continue to multiply and expand away from the immune system, leading to clinical illness (24).

The role of VC in the treatment of cancer is still controversial. Since the 1970s, the Cameron team has investigated the effect of VC administration on 100 terminal malignant patients. The results were compared to 1,000 patients who don't take VC. The study shows that there is an improvement in the quality of life and survival time in the VC group (25). Another research in the late 1970s, accomplished by Creagan, shows the failure of high-dose oral VC (10 g/day) in last-stage malignancy (26) . The previous two studies have used oral VC, which shows low bioavailability due to many factors and barriers that affect absorption from the intestine (27).

It is suggested that VC could act as a cytotoxic agent to cancer cells through the formation of hydrogen peroxide, so it may inhibit tumor growth. It damages the cancer cells by boosting the intracellular L-ascorbate engagement through the sodium-dependent VC transporter (SVCT-2) that acts as a prodrug to H_2O_2 (28).

Recent studies have shown promising results when using high-dose intravenous VC (10 g/infusion). It could modulate inflammation, improve quality of life, and may prolong survival time when used with standard therapy as adjuvant treatment (17,29–31). In 2014, a pilot study on stage III-IV ovarian cancer patients investigated the outcomes of adjuvant VC therapy in this type of cancer. One group of them receives only standard therapy, and the second group receives standard therapy plus high intravenous dose VC (75–100 g/infusion, 2 x weekly for 1 year). The results reveal that VC decreases chemotherapy-associated toxicity and prolongs the median time of disease progression/relapse for about 8.7 months compared to the group that does not receive VC therapy (32). Another study on breast cancer patients discovered that the disease and chemotherapy could raise lipid peroxidation and lower antioxidant levels, including VC. As a result, these patients might benefit from consuming VC (33).

3.2 VC as an Immunity Modulating Agent

It is well known that VC plays a crucial role in the host defense system, and supplementing with VC can improve immunity (14). Several studies have shown that VC deficiency can inhibit cellular and humoral immunity (14,34). VC is essential in proliferation and differentiation of immune cells; its presence in these cells, which is 10 to 100 times greater than its quantity in plasma, demonstrates its function in immunity (35).

3.3 VC as an Infection Controlling Agent

Antibacterial activity: It is known that VC has been active against *Mycobacterium tuberculosis* since the 1930s, the causative agent of tuberculosis in humans (8). VC also showed antibacterial activity towards various G+ve and G-ve bacteria *in vitro;* the inhibition of growth was concentration-dependent (36). *Pseudomonas aeruginosa* could be efficiently inhibited from growing *in vitro* by using 0.3 mg/mL VC, while *Staphylococcus aureus* could also be prevented from growing by applying VC at 0.1 mg/mL (37). Unexpectedly, methicillin-resistant *S. aureus* (MRSA) biofilm production may be successfully inhibited by VC (38).

Synergism with other medications: A combination of VC and deferoxamine (an iron chelator) enhances the antimicrobial effect of the drug against G+ve cocci, including *S. aureus* and *S. epidermidis*, as well as G-ve bacilli such as *E. coli*, *K. pneumonia*, and *P. mirabilis* (39). In *Helicobacter pylori* eradication, the dose of clarithromycin could be reduced when using VC as adjuvant therapy (40).

Antiviral activity: VC can be used as adjuvant therapy in COVID-19 patients, according to a related study, the intake of intravenous VC could decrease the duration of hospitalization and improve symptoms for such patients, but it shows no significant effect on mortality or the need for mechanical ventilation in these patients (41).
VC could reduce the duration and severity of the common cold (1); additionally, VC has antiviral activity against influenza and herpes virus, poliovirus, human-lymphotropic virus type 1, human immunodeficiency virus (HIV), parvovirus, and rabies virus (42).

Antifungal activity: A recent study showed that VC could inhibit the growth of *Candida albicans*, whereas in another study, VC exhibited low fungistatic activity against *C. albicans* (37).

3.4 VC as an Allergy Preventing Agent

According to a new study, people with allergic flare-ups had low plasma ascorbate levels, and oxidative stress may be the cause of the inflammation reactions in allergies that affect the skin and the respiratory system (43). In this study, high-dose intravenous VC was used in seventy-one patients with respiratory or skin-related allergies, and there was a significant reduction in allergy-related symptoms (43).

3.5 VC as a Collagen Synthesis Enhancer and Tissue Healing Agent

The relationship between VC and collagen synthesis was discovered after the description of scurvy in the 16th century. It is characterized by bleeding from the nose and gum with the detachment of the gum tissue from the teeth, which is caused by a defect in collagen synthesis. At that time, it was reported that the use of orange or lime led to an improvement in symptoms (4).
In the 20th century, the active factor, VC, in these fruits was discovered, isolated, and used as an important nutrient that prevents scurvy (4). VC is an important factor in collagen synthesis, especially collagen IV, which forms the matrix of the blood vessel wall and is present between the epidermis and dermis. It is also important in the crosslinking of procollagen by hydroxylation (44). It serves as a cofactor for the enzymes prolyl-hydroxylase and lysyl-hydroxylase, which catalyze the hydroxylation of proline and lysine residues in procollagen and encourage the appropriate folding of the stable collagen triple helix (45). VC is also a potent antioxidant that prevents harmful reactive oxidant agents from causing cell death during the inflammation process. A deficiency of VC leads to hemorrhages, along with a weakness of the bone structure (46).
In musculoskeletal injuries, VC has received growing attention for its potential role in the treatment and recovery acceleration. Many studies have been conducted to evaluate the effect of VC on the healing process of tendons and bones. A new study shows that intraperitoneal VC (150 mg) can accelerate the production of collagen I and increase the diameter of fibers in tendon rupture (47). Also, VC could reduce tendon adhesion after tear if injected locally (48).
In bone fractures, VC could increase bone mineralization and collagen production (49). VC antioxidant action can decrease the destructive effect of free radicals if used intraperitoneally (50) and encourage faster recovery compared to control if used intramuscularly (51).
Additionally, recent studies revealed that intraperitoneal VC improves wound healing and quality of life after injury. VC could cause changes in inflammation and proliferation phases after injury, but there was no significant effect on pain management (9).

3.6 VC as a Skin Protecting Agent

It is known that UV exposure can lead to oxidative stress (OS) and skin aging due to the free radicals that cause elastin changes, photoaging, pigmentation, and carcinogenesis (11). Antioxidants are so important to protect the cells against free radicals originated by UV exposure. Sunscreen can prevent only up to 50% of UV, so combining these products with topical VC can prevent skin damage. Recent studies found that using topical VC (10%) can decrease UV erythema and sunburn by 50–60% (52). VC can act as a photoprotecting agent on its own, but when combined with vitamin E, the greatest partner for it, the effect of VC multiplies by four. Hydrophilic VC aids in the renewal and stabilizes the lipophilic vitamin-E antioxidant. As a result, these two vitamins work together to protect the cell's hydrophilic and lipophilic compartments, respectively. Together, they minimize long-term UV damage by drastically lowering cell apoptosis, thymine dimer formation, and carcinogenesis (52).
VC has a role in preventing pigmentation by inhibiting tyrosinase enzyme, which is important in melanin production (53). Using a topical 25% VC formulation for four months has been shown to lessen the skin's melasma-related pigmentation (54).

3.7 VC as a Psychiatric Disorders Therapeutic Agent

Depression is a common mental condition indicated by various fundamental symptoms, including low mood, psychomotor slowdown, anxiety, and somatic ailments (10). Many factors, like biological, psychological, social, and lifestyle, could play a crucial role in the disease's etiology. Besides that, defects in serotonin, norepinephrine, dopamine, and the GABA system were observed in these patients (55,56). In several animal studies, VC showed an antidepressant effect through many mechanisms, including activation of the serotonin receptor, GABA system modulation (15), nitric oxide (NO) level reduction within the hippocampus (57), and potassium channel blockage (58). In addition, the antioxidant effect of VC could decrease OS in the brain (57). Many human studies revealed that VC plasma levels in depressed patients are lower than control (59,60) and that the use of 1 g/day of VC, combined with vitamin A and E, for 45 days has led to improvement in the symptoms of depression (2). Even more, many studies have discovered that depressed people have considerably less VC consumption than healthy individuals (61). In Korea, a new study on adolescent females aged 12–18 years found that depression symptoms are negatively associated with green vegetable intake and VC consumption (62). The use of VC as adjuvant therapy with antidepressant drugs appeared to be very effective; a pilot study revealed that the use of fluoxetine (10–20 mg/day) and VC (1g/day) therapy for six months resulted in a substantial reduction in depression symptoms as compared to the fluoxetine plus placebo group (63). Another trial showed that 0.5 g VC dose every 12 hours raised its levels in plasma and leukocytes. It was also linked to a 34% decrease in mood disturbance in nondepressed hospitalized patients (64). Similar results were found in another study when using the same dose for hospitalized malnourished patients, where VC was associated with about 70% improvement in mood (16). Furthermore, the use of a 0.25 g VC dose every 12 hours for two months, alone or combined with omega-3 fatty acids, considerably decreases the Beck Depression Inventory in depressed male workers (Khajehnasiri et al., 2016).
Schizophrenia is a severe neuropsychiatric illness that affects how a person thinks, feels, and behaves. Its etiology is yet unclear; OS, abnormal immune responses, carbon metabolism, and dopamine system disturbances could be involved (66). A recent study demonstrated that a VC shortage could exacerbate schizophrenia symptoms and that high dosages of this vitamin could correct fundamental metabolic problems and reduce the likelihood of getting the illness (67). Traditional antipsychotic drugs are known to increase OS in the brain; therefore, the use of antioxidants could reverse these harmful effects. As an adjuvant therapy, a new study revealed that the use of VC (1 g/day) along with vitamin-E for 4 months has reduced the side effects of antipsychotic drugs (68). Also, prolonged haloperidol treatment in conjunction with the administration of a mix of omega-3 fatty acids, VC, and vitamin-E significantly improved treatment outcomes. These findings provided evidence in favor of the theory that the supplements used had a good impact on both positive-negative symptoms of

schizophrenia, as well as the severity of side effects brought on by antipsychotic drugs (69).

3.8 VC as Neurodegenerative Diseases Therapeutic Agent

VC has a crucial role in the functions of the central nervous system (CNS), including myelin synthesis, nerve differentiation, catecholamine production, and signal transduction. In addition to its antioxidant protective effect, its significance is demonstrated by the fact that it is concentrated in the CNS more than any other organ (12).

At the same time, neurodegenerative diseases are characterized by increased free radical production, so it is proposed that the VC antioxidant effect could make a positive difference in these diseases (12). VC was found to have an influence on decreasing the intensity of seizures as well as the effects on hippocampal damage brought on by seizures (13); another study showed lower seizure frequency by 70% in epileptic patients after using a combination of VC and vitamin-E therapy (70).

Severe VC deficiency in mice was found to suppress voluntary-motor activity, physical weakness, and increase glucose levels in the CNS; these outcomes were reversed to normal by using a VC supplement (250 mg/kg) (7).

In Parkinson's disease, a chronic neurodegenerative disorder that causes progressive damage to the substantia nigra, which is responsible for motor activity, the exact cause of the illness is still unknown; only 10% of cases are shown to be genetic. A complex of environmental and genetic factors may be involved in triggering the disease (71). Dopamine neurons are known to have a critical role in the control of motor activity and emotions; their degeneration is associated with Parkinson's as well as schizophrenia and psychiatric diseases. An *in vitro* study showed that VC enhances the differentiation of dopamine neurons in the midbrain cells from neural stem cells (72). Another *in vitro* study using human dopaminergic neurons showed that VC could protect them against the glutamate excitotoxicity that occurs in Parkinson's. The study's findings demonstrated VC's capacity to prevent cell death brought on by prolonged glutamate exposure (73). Human studies revealed that Parkinson's disease patients have lower plasma VC levels (74), as well as lower lymphocyte's VC levels. This demonstrates the critical role of VC in the CNS system and is suggested to be used as a biomarker for the disease (75). In the above study, a reported case of a sixty six year old male who had Parkinson's, bipolar disorder and pleural effusion was discovered to have low serum levels of zinc and VC. The movement disorder was restored to normal after one day of intravenous infusion of VC and zinc (74). In elderly Parkinson's patients, VC has been proven to improve L-dopa, one of the main medications used in Parkinson's therapy, absorption, especially in patients with low L-dopa bioavailability (76). Also, an *in vitro* study showed that VC strongly induces the synthesis of L-dopa from pregrown mycelia of *Aspergillus oryzae* fungi (77).

In Alzheimer's disease, a progressive dementia that affects memory and cognitive function, the role of VC was studied in mice that carry the Alzheimer's gene and have induced VC deficiency. The study showed that there is enhanced OS, a high mortality rate, and enhanced seizure onset (78). Another study found that, particularly in the early stages of disease development, even mild intracellular VC deprivation played a significant role in accelerating amyloid aggregation and brain OS in mice (79). A recent study showed a decrease in oxidative damage and behavioral deterioration in Alzheimer's gene mice when treated with a 1% VC solution for 6 months (80). The integrity of the blood-brain barrier (BBB) has a crucial role in cognitive function and dementia onset; VC may prevent cognitive decline and neurodegenerative alterations by preserving the BBB integrity (81). In humans, the studies are still controversial; some studies showed no significant effect of VC supplementation on the progression of this disease (82), and a 16-week's use of VC along with vitamin-E and alpha-lipoic acid did not affect amyloid aggregation but decreased OS markers (83). On the other hand, a 16-week co-supplementation of vitamin-E and VC along with high-dose beta-carotene significantly improved cognitive performance in the elderly (84); additionally, it was discovered that co-supplementation of VC and vitamin-E for longer than 3 years was linked to a lower prevalence and incidence of Alzheimer's disease (85).

Toxicity

VC is a water-soluble vitamin that almost completely absorbed from the gastrointestinal system and eliminated by the kidney. It considered safe nutrient but the daily intake of 700mg or higher could cause acidification of urine and increase the risk of renal stones especially in male (86).

Conclusion

VC is considered an essential nutrient for the human body; it is crucial for the health of the CNS, the integrity of tissue, immunity, and psychiatric health. Its deficiency can lead to many unwanted outcomes, such as increasing the risk of psychiatric diseases, impairing injury healing, allergy flare-ups and impairing immunity function. The intake of VC could have a beneficial effect on the prognosis of cancer as well as on decreasing the harmful effects of cytotoxic therapy. Its administration could also improve motor and cognitive function in neurodegenerative diseases, improve immunity, reduce allergy-related symptoms, stabilize mood, and decrease attacks in psychiatric diseases, in addition to its advantages in cosmetic applications and skin care approaches.

Recommendations

We recommend that more researches must be conducted to explore the additional beneficial effects and biological activities of this crucial nutrient in various health conditions, along with the suggested dose that must be prescribed for each of these conditions.

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