

Review Article

VITAMIN C AND ITS ROLE IN BODY

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ABSTRACT

Ascorbic acid or Vitamin C is very important in our body because of its antioxidant property. But the main problem; that vitamin C uses is to maintain the stability as well as its drug distribution system. Vitamin C also plays a protective role in diabetes, cancer, heavy metal toxicity or poisoning, etc. Vitamin C is found in many sources present in nature, including tomatoes, broccoli, etc. Many factors in the body, as well as outside the body, affect the content of vitamin C in the body or sources like the season, climate, and pollution affect the content in fruits and vegetables besides sex, age, pregnancy, lactation, etc. affect the vitamin C content in the body. It is extensively used in the common cold, wound healing process, cancer, heavy metal poisoning or toxicity, and even in men's fertility. In this article, we focused on the general aspects: its bioavailability, sources, its toxicity and deficiency, and factors affecting vitamin C level as well as its use in humans. In the last, we conclude, the excess or lack of Vitamin C, both conditions have affected the human body in a significant range. It plays a protective role against many disorders and is required for kids, men, women, and even old-aged patients.

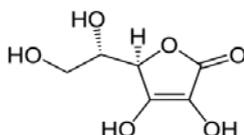
Keywords: Vitamin C, Ascorbic acid, Applications, Toxicity, Cancer, Tissue healing, Fertility, Common cold

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INTRODUCTION

Ascorbic acid or Vitamin C is made up of 6 carbons as glucose and hydrophilic [1]. Vitamin C can exist in reduced forms that is ascorbic acid or ascorbate, whereas it can also exist in an oxidized form that is dehydroascorbic acid (DHA), made up by reduction of ascorbic acid [2]. It has some necessary anatomical and catabolism action in human beings, but human beings don't have the L-gulonolactone oxidase enzyme so that's why it is not formed in human beings. Vitamin C is just acquired through edibles or external sources. Scurvy is a disease condition occurring due to the lack of vitamin C and considered via the fragility in tissue, capillary, and poor wound healing as well. But the cases of scurvy are rare in the present time. Ascorbic acid is a prominent element within the food, as well as pharmaceutical fields [3]. Structure of Ascorbic acid in fig. 1.

Vitamin C is known to play its antioxidant properties in a significant range and is also known to play countless functions for maintaining optimal health to protect the human from various diseases [4, 5]. The deficiency of vitamin C, called hypovitaminosis C, is connected with symptoms like low mood [6]. More serious deficiencies are often related to a variety of clinical aspects [7] and prolonged deficiency even results in scurvy syndrome, a case in which an individual is determined usually for heart problems in public nowadays [8]; if this condition isn't treated within the time then it may lead to death. The high ingestion concentration of Vitamin C in the body in different conditions is a topic of discussion and suggestion values are not common [9].



Vitamin c is a precious component of our body that protects us from diseases. In this article, we mainly describe the general aspects, factors that affect the vitamin C level in the body, and applications with future perspectives. Through this article, we conclude that even minute deficiency of vitamin C is associated with a serious condition, whether it is in the form of disease or it may directly affect the population and it is important for all kids, men, women, and old aged patients to keep fit, healthy, improve immunity and heart functions,

and skin functions. It is used in cancer, diabetes mellitus, hypertension, sickle cell anemia, etc. as a supplement.

Search criteria

This review was made after reviewing approx 300 articles from 1940 to 2020, which were found on electronic database systems like PubMed, Science Direct, and Google Scholar by using keywords like vitamin C, vitamin C and their Applications, Pharmacology, and Toxicity of vitamin C, Ascorbic Acid, vitamin C and deficiency, Cancer, etc. After analyzing all articles, few articles were found to be effective for the study about vitamin C. Then, a comparative study is presented in this review to make it more informative and relevant.

Sources of vitamin C

Vegetables and fruits like citrus fruits, strawberry, tomato, broccoli, Indian gooseberry, turnip, sprouted grains, red peppers, green peppers, and many green veggies are rich in vitamin C content. Vitamin C is found in animal sources at a very low concentration about; 30-40 mg/100g whereas, plant sources may have vitamin C concentration up to 5000 mg/100g. So plants are becoming important sources of vitamin C. It can be absorbed either by passive diffusion in the buccal cavity or by Sodium dependent active Vitamin C transporters in GIT (Gastro-Intestinal Tract) [10, 11].

Bioavailability of vitamin C

The absorption and renal excretion of vitamin C decide the extent of bioavailability in the body. The main source of ascorbic acid is diet or supplements. The consumption of vitamin C from any dietary source is absorbed either from the small intestine through epithelial cells by SVCT1 (Sodium dependent active Vitamin C transporters-1) or circulates into the capillaries and further in the bloodstream [11, 12]. This circulating amount of ascorbic acid vitamin C is then undergoing a general filtration mechanism in Bowman's capsule form kidney and the ascorbic acid is reabsorbed in PCT (Proximal Convoluted Tubule) [12]. Variance between the filtered and reabsorbed volume of ascorbic acid establishes renal excretion [13]. If the vitamin C is available in a low concentration, it undergoes absorption in the small intestine and undergo excretion [14], whereas if the vitamin C is available in a high concentration, it is regulated via SVCT1 [15] and this decides the absorbed amount from intestine and excretion from the kidney [16]. So this is

concluded that the level and the bioavailability is regulated by absorption through intestine and excretion through kidney as well.

There are many other reasons that play a major role in reducing bioavailability including alcohol intake, stress, usage of antibiotics, smoking, fever, viral illness, painkiller, heavy metal toxicity, exposure to carbon monoxide or petroleum products, even more. Perhaps, increased consumption of vitamin C is seen in these situations that results in the deficiency of vitamin C. The appliance through which the low vitamin C serum level occurs in the body is not well cleared yet [17]. Higher ingestion of Vitamin C may cause diarrhoea and GIT disturbance. The other side effects are easily treated by reducing the dosing of ascorbic acid [19].

Factors affecting vitamin c status

Season and climate

The most important sources of vitamin C are fruits and vegetables and are easily available with different concentrations of vitamin C depending upon the climate as well as season. According to studies from England and China, there is a concentration difference up to 10 $\mu\text{mol/l}$ of vitamin C in fruits and vegetables depending on the season, as the highest amount of vitamin C is found in winter as in autumn [20, 21]. According to a China study, the amount of vitamin C found is much higher in winter as compared to spring [22]. This clearly shows the kind and concentration of vitamin C-rich vegetables and fruits that are consumed in winter. This type of condition is observed in different parts of India like in the northern part of India, in which less deficiency is seen in the seasons of winter; but in south India, the high deficiency rate is observed in winter seasons as compared to the northern part [23]. This is likely to show about the altered climatic as well as agricultural conditions throughout the different parts of India. According to the scientist Bates *et al.* [24], a report shows that change in season with higher consumptions and blood status as compared to the low difference in individuals that have low consumptions and status, this is because of a decreased body area and consumption of the vitamins. Fluctuations in climatic conditions are also responsible for the impact of vitamin C concentration on the populations [25]. This may result in increased dependence on local crops that may drop their vitamin content previous to intake [26].

Pollution

According to WHO information over 80% of the population that lived in urban regions are exposed to such air quality levels beyond the WHO limits, with LMICs experiencing the most elevated openings. About 7M unexpected deaths are caused by air pollution across the world every year and this primarily due to the expanded deaths from strokes, coronary disbalances, cellular breakdown in the lungs, and severe respiratory diseases [27]. Air pollution in the environment is likely caused by smoking from burning biomass, and smoking tobacco worldwide. Smoking tobacco is the main one of the causes that decrease the vitamin C status in both non-smoking adults and kids [28, 29, 30]. According to scientists Tribble *et al.* [29] reports tackled down that amount of the nutrient C in inactive smokers was lower than the non-exposed non-smokers. Deficiency of vitamin C that is Hypo-vitaminosis C was seen in 12% of inactive smokers but it was not seen in the case of a non-exposed non-smoker.

Sex

Female tents need a higher amount of vitamin C than males [31]. The UK males have a lack of vitamin C than females, as indicated by McCall *et al.* [32]. This difference of vitamin C content between male and female is because of the high fat-free mass in male [33]. There is also the difference in diet intake between men and women, in which female intake is higher than men [31]. It can be noticed that in pregnancy and lactation conditions, ladies have low amounts of vitamin C because of the hemodilution and proper development of foetus. The doctors from different nations have recommendations for the high dietary intake for male and for pregnant and lactating females, differing according to their body weight [9].

Age

Few studies have been carried out in individuals matured >60 y that have a lower vitamin C amount than the young age group people in

the same country. Many studies have shown that old aged people have a deficiency of vitamin C to a great extent, mainly in males and the aged males have the concentration of vitamin C concentration as compared to older women [34, 23, 32, 35]. Scientist Schleicher *et al.* traced a graph in which the curve is U-shaped for vitamin C amount from age group 6 to 60 y [36]. It is because of the lower weight of kids and old patients, and those who have low intake of vitamin C, are likely to have a deficiency of vitamin C.

Pregnancy and lactation

Generally, pregnant women have low levels of vitamin C compared to non-pregnant women [37]. It is often possible because of the hemodilution, and active transmission of nutriment, and vitamins through mother to vertebrate [38]. Deficiency of vitamin C in pregnant women may raise the risks of many complications. In that case, supplementation therapy with vitamin C for pregnant women may decrease some complications during pregnancy [39]. Some studies of highly economic countries that include ladies with regular vitamin C levels have not shown any beneficial effect from supplementation [40]. But, in some studies of low-income countries, that include ladies with vitamin C deficiency show potential edges together with a decrease rate of complications in pregnancy [41]. It's significant that the recently discovered epigenetic restrictive undertaking of vitamin C may have vital roles to play in the development of fetal [42]. A study related to animal models has been shown that parental vitamin C will regulate desoxyribonucleic acid (DNA) methylation and germline development [43]. The lactating women probably have a lower vitamin C level because the vitamin C is being transferred to the growing baby via breast milk. Several authorities are making improved recommendations in order to increase the needs of pregnant and lactating ladies, with higher than their customary diet endorsements of +10-20 mg/day for pregnant ladies and +20-60 mg/day for fresh ladies [9].

Smoking

Smoking is the main source of oxidative stress and oxidants in the body [44]. Several studies have shown a higher lack of vitamin C in smokers than non-smoker persons. McCall *et al.* [13] said that smokers are more likely to have a deficiency than non-smokers over 7 times and Wrieden *et al.* [16] showed the level of deficiency in male and female smokers over 2 to 3 times. Due to the low diet intake of vitamin C and higher intake of fat make smokers at the higher risk of vitamin C deficiency. Generally, smokers need more vitamin C as related to non-smokers due to the vitamin C deficiency [45, 46]. A study by Kallner *et al.* [47] which shows an increase in vitamin C turnover in smokers by more than 35-40% compared with non-smokers. Several international regulatory bodies have taken into account the increased needs of smokers by offering additional recommendations ranging from 20 to 80 mg/day for adults [9]. However, this additional intake may not be enough to compensate for the increased demand of smokers. Moreover, in some countries, there is still an upward tendency in smoking rates, which may affect the vitamin C level and increase the need for vitamin C [27].

Disease state

Various disease states can affect the vitamin C level in the body like inflammation and increased oxidative stress. Various diseases are associated with a lack of vitamin C; such as cardiovascular disease, congestive heart failure, metabolic disorders, and chronic inflammatory conditions etc. [5, 48]. Some acute infectious disease states can result in inflammation and ultimately result in decreased plasma as well as vitamin C concentrations, whereas chronic infections like Human infection virus (HIV), *Helicobacter pylori* and tuberculosis, are common in many lower-middle-income region [49, 50]. An increased demand vitamin C is needed in infectious diseases and as the severity of the infection increases, the demand of vitamin C also increases so as to achieve the normal level [51]. Decrease vitamin C level is also seen in the global coronavirus pandemic (SARSCoV2) [52]. People who have a negligible level of vitamin C have an increased possibility of vitamin C deficiency and as those are deficient then higher intake of vitamin is needed to raise the deficient state [52, 53].

Table 1: A summary of above discussed factors affecting vitamin C status is given below

Factors	Their affect
Season and climate	May increase or decrease the Vitamin C content in vegetables and fruits [20, 21]
Pollution	Due to air pollution, it may affect the Vitamin C content [28, 29]
Sex	Female tents need a higher amount of vitamin C than males [31].
Age	matured>60 y have a lower vitamin C amount than the young age group people [34, 35]
Pregnancy and lactation	pregnant women and lactating women have low levels of vitamin C [37]
Smoking	Smokers are likely to have Vitamin C deficiency [13]
Disease state	Disease states like inflammation and increased oxidative stress cause the low Vitamin C levels [5, 48].

Vitamin C in human beings

Vitamin C plays a vital role in human beings for growth as well as for proper health. Either excess of vitamin C or deficiency of vitamin C may lead to disturbance in human health. Some of the important benefits have been discussed below, shown in fig. 2 below:

Vitamin C in common cold

Being helpful for the treatment of scurvy, it is also helpful in the management of common colds. This concept was described by Paul and suggested that 1 to 3 gram of dose is effectively used for treatment [54]. Vitamin C plays an important role in the common cold. It's a controversial phase and studies are continuing in this phase [55]. Many studies show that the change in dose amount doesn't show any effect in prophylactic response, but it mainly affects the symptoms of cold in the manner of decreasing the severity and duration as well. According to many studies, the 1 gram/day of vitamin C dose isn't effective in the management of the common cold during the winter seasons [56]. Immunodeficiency is the common thing in common colds. Many discussions are continuing about vitamin C in boosting immunity in rhinitis cases. The ascorbic acid plays an important role in immunity and stimulates the proliferation of T-cells in respect to infection. T-cells are effective in the treatment of infected organs via either increasing the production of cytokines or via promoting the B-cells to produce immunoglobulins or antibodies to monitor the infective reaction. The ascorbic acid does this work by blocking the pathway that results in apoptosis of T-cells, thus maintaining them. This is the proposed mechanism behind the enhancement of the immune system in the case of rhinitis when vitamin C is administered [57, 58].

Vitamin c in tissue healing

It is a process that needs collagen to be synthesized and accumulated and further their crosslinks with fibers to provide sufficient strength to damaged organs. In the terms of collagen synthesis, ascorbic acid is beneficial for the wound healing process as indicated by several studies. As per the new study, the wound healing process was achieved by giving maximum tensile strength to scar tissue of guinea pigs after the administration of vitamin C [59]. Ascorbic acid or vitamin C is required in a huge amount for post-operative patients as they have fast utilization in the body to synthesize collagen for the wound healing process at the site of injury. Hence, the recommended dose for post-operative patients is 500 mg-1 gram in order to provide a sufficient supply of ascorbic acid for the wound healing process [60]. Jagetia *et al.* suggested that the ascorbic acid in pre-treatment during the injury and trauma conditions was helpful for promoting the wound healing process and proposed a strategy regarding the vitamin C for accelerating the wound healing process in these cases [61].

Vitamin c infertility

Vitamin C is used in male infertility in the case of non-specific seminal infections [62]. But, the exact action of ascorbic acid remains unclear yet in the case of male fertility. A scientist named Chinoy said that vitamin C is an important component for promoting integrity in the structural and functional basis as well as in the reproductive system. In guinea pigs, it showed some degenerative changes in testes, as well as vas deferens [63].

Antioxidant is the main property of ascorbic acid and this property plays a major role up to 65% in men infertility [64]. There is a concentration difference of ascorbic acid between plasma

concentrations and the seminal plasma up to 10 times more and this concentration difference was also found in the seminal plasma of fertile and the seminal plasma of infertile men [65, 66]. Deficiency of ascorbic acid may cause increased oxidative damage in organs caused by ROS (Reactive Oxygen Species). The 25% to 45% concentration of ROS was found in the semen of infertile men [67]. As per the studies, the supplements of vitamins C are beneficial in many terms that lead to affecting the fertility of men like it reduces the ROS concentration, increases sperm quality [68], decreases sperm DNA oxidation as well as decreases sperm membrane lipid peroxidation [69]. The supplements of vitamin C as antioxidants are helpful in enhancing sperm quality in a dose-dependent manner [68]. Supplementation of Vitamin C also has an effective role in women infertile in the terms of increasing the levels of progesterone in the case of luteal phase defect [70].

Vitamin C in cancer

Vitamin C has preventive properties in the case of carcinoma or cancer and this concept was first described in 1949 by Cameron *et al.* He described that vitamin C at a high dose is helpful in improving the life of patients with fatal cancer [71]. But, the primary documented study was done by Pauling and Cameron in 1970 in which they administered vitamin C to cancer patients. They administered 10 grams of vitamin C daily to patients of cancer in a group of 100 people and compared their results with the group of 1000 people who are suffering from cancer and are treated with only standard therapy. The compared results has been ascertained that 10.3 % patients who were taking vitamin C exist or survived but all the patients who were taking standard therapy died [72]. Higher ingestion of Vitamin C is related with a low number of risks for non-hormonal [73] as well as hormonal cancers like breast, rectum, esophagus, stomach, pancreas and oral cavity cancers [74, 75].

There are several mechanisms which follow the involvement of vitamin C in the therapy are as follows: stimulates the collagen formation, prevent viruses that involved in cancer, enhances wound healing process in cancer patients, prevents free radical formation and their damage to tissues, enhancement of vitamin C deficiency, prevent spread of cancer by suppressing enzymes, improves the immune system, reducing toxicity of drugs used in chemotherapy [73]. The role of vitamin C in cancer management has been described by many studies in two ways: that, at the higher concentration of vitamin C, cancer cells do not develop or lead to shrinkage of cancer cells [76, 77]. The administration of vitamin C via intravenous route may increase the effectiveness up to 70-fold as compared to oral route administration [78]. Most of the studies may conclude that vitamin C gives the beneficial result at a higher dose in the development of tumours as well as their mechanism of action also contributes to the anti-cancer effect [79].

Vitamin c in heavy metal toxicity

Heavy metals may result in dangerous toxicity in human beings. These metals toxicity either via redox cycling, for example like chromium, iron, vanadium and copper etc. or via making of Reactive Oxygen Species [ROS] in shape of superoxide ion, example like lead, mercury, nickel etc. and after that disturbed calcium level, damage in DNA, and lipid peroxidation occur as a part of homeostasis [80].

The vitamin C is helpful in the lead poisoning cases and it was also proved by various studies. The lead toxicity is extensively harmful for the brain, kidneys, testes, and liver [81]. Arsenic poisoning shows its toxic effect via oxidative stress and lipid peroxidation as well. If

excess amounts of the arsenic is present in water, then it leads to molecular ailments [82]. As per a study, the arsenic may cause lipid peroxidation in excess amount in rats during the lactation and maturation phase and this has retreated with the supplements of vitamin C, E and Zn [83]. Cadmium also comes under the toxic metal category and is mainly found in industrial area. Vitamin C provides protection in cadmium poisoning in rats when its brain and lungs are affected [84]. Vitamin C is also recognised to relapse the haematological changes in cadmium poisoning and mercury poisoning [85]. Hence we can say that Vitamin C or Ascorbic acid have protective properties in heavy metal toxicity.

Vitamin c in diabetes

Diabetes creates a serious condition in the future as it can affect 360 million people [86]. Many Symptoms like deteriorated, over the long term damage and abortion of many organs are happening in diabetic patients. Kidney, blood vessels, nerves, eyes and heart are mainly affected due to the high level of glucose in the human body [87]. Oxidative stress [69] is mainly induced by ROS [19] in Hyperglycaemia. The increased production of ROS is seen in both types of diabetes that lead to oxidative stress with onset of diabetes, this statement is proved by several experiments and studies as well [88]. Vitamin C is helpful in reducing the many developing risks of diabetes. The plasma level of Vitamin C, and ingestion of veggies, fruits connected with risks of Diabetes Mellitus of type 2, this statement is recognized by the study of Norfolk Prospective [89]. In the diabetic cases, vitamin C and E are reduced trauma in tissue as well as in blood. MOA (Mode of action) behind this is monitoring the antioxidant action and modifying lipid content [69]. Many microvascular and macrovascular complications have been connected with diabetes. Hyperglycaemia is liable for Reactive Oxygen Species [ROS], which occur in diabetic cases that result in endothelial impairment [90]. Hence, vitamin C is capable of blocking the impaired hyperglycaemic dysfunction in diabetic cases [91]. Neuropathy is also one of the complications among diabetic patients. There are many reasons that show the significant lowering vitamin C level in patients of diabetes and polyneuropathy [92]. In the dieabetic patient, the importance of ascorbic acid and other antioxidants is described by many authors [93].

Vitamin c toxicity

People, who suffer from G6PD deficiency (glucose-6-phosphate dehydrogenase) which is treated by ascorbate supplements in higher amounts, are at most probably chances of hemolysis. According to a report, a 32 y old patient from Nigeria got a supplement of 40 grams of ascorbic acid thrice in a week for about 1 mo, while taking vitamin C every day. When this dose of ascorbic acid increased to 80 grams, acute hemolysis occurred to that patient [94].

There are a few other examples of vitamin C toxicity [95, 96, 97]. The widespread use of ascorbic acid in supplements and food additives make the surety to use ascorbic acid. The recommended average dose of vitamin C in American people is not less than three times in a day at 180 mg/day. This recommended dose is based on the pharmacokinetic studies of vitamin C. More than 80% of the dose is absorbed in the body after the administration of 180 mg/day dose. The absorptive capacity of the dose in the intestine seems to be achieved by oral intake of 3 g/day of ascorbic acid (this capacity is indicated by pharmacokinetic studies). The excessive ascorbate absorption is eliminated by the kidney but avoids increasing Vitamin C level in the tissue.

An average excretion of oxalate is 20-30 mg/day. That is half of oxalate comes from vitamin C metabolism. If a person is taking 5 grams of ascorbic acid daily, it is observed that it faces an average increase of 14.8 mg in urinary excretion of oxalate [98]. Thus, we can say that higher intake of ascorbic acid poses a possibility of calcium oxalate stone formation in mostly healthy patients eliminating those people who are likely to have kidney stones [99, 100]. Many researchers assumed that people with kidney stones have unusual metabolism of ascorbic acid and/or unusual absorption of oxalate ions. It is recommended that people having renal failure or kidney stone shouldn't take vitamin C at high dose [99-102].

People who are getting hemodialysis and/or ambulatory peritoneal dialysis are likely to have low vitamin C status as compared to healthy patients. For enhancing the vitamin C level, ascorbic acid supplements can be helpful. A normal dose of ascorbic acid supplement (50 mg/day) may be helpful in restoration of normal vitamin C levels without causing kidney stones that is without increasing plasma oxalate concentration. But a 500 milligram per day dose of ascorbic acid supplementation up to 3 w may result in increased levels of plasma oxalate [103]. vitamin C toxicity is also associated with other effects like hyperuricemia, systemic regulation, vitamin B12 deficiency but it seems rare [95-97].

CONCLUSION

Ascorbic acid or vitamin C has been extensively studied by many scientists as well as its use has also been increased in recent times. It is a resourceful molecule that is used in many fields of pharma and science. Since, many studies show the effective role in men's infertility, cancer treatment, and diabetes and even in neurodegenerative disorders. Ascorbic acid is extremely used to convey the many medicinal agents in the body for promoting the healthy body. But its stability is a main factor that resists its use. The optimum intake of supplements is advantageous to health since its excess can cause hypervitaminosis C and its deficiency may result in scurvy. It is very beneficial for heart, skin health, as well as immunity in the covid-19 era. It is used mainly for antioxidant properties that reduce the reactive oxygen species in the body that are generated by many disease states like infertility, heavy metal toxicity, diabetes, etc. Its toxicity may be connected with kidney stones, vitamin B12 deficiency, and systemic regulations. In the last, we concluded, vitamin C has a vital part in keeping human health but it needs more study that shows its beneficial as well toxic effects and come up with new results as the present era of immunity is continuously changing.

CONSENT FOR PUBLICATION

Not applicable.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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