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Review article:

Vitamin C in Human Health: Biochemistry, Physiology, and Pathophysiology

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ABSTRACT

Ascorbic acid (vitamin C) is a water-soluble micronutrient essential for various physiological processes in humans, who must obtain it through diet due to an inability to synthesize it endogenously. Functioning as a potent antioxidant and a cofactor for numerous enzymes, vitamin C plays critical roles in collagen biosynthesis, immune support, wound healing, and the maintenance of skin health. It is actively accumulated in body tissues, especially the skin, where it protects against oxidative stress and promotes dermal integrity. In collagen formation, vitamin C acts as a cofactor for prolyl and lysyl hydroxylases within the endoplasmic reticulum, enabling hydroxylation of proline and lysine residues—key modifications for the structural integrity, folding, and extracellular secretion of collagen fibrils. As an antioxidant, it neutralizes reactive oxygen species and works synergistically with other antioxidants, while at high concentrations, it may exhibit pro-oxidant behavior in the presence of transition metals. In the immune system, vitamin C enhances cellular functions and reduces susceptibility to infections. Deficiency leads to scurvy, marked by impaired collagen synthesis, hemorrhages, poor wound healing, and in severe cases, fatal complications. Ascorbic acid also contributes to neurotransmitter synthesis and cholesterol metabolism. Dietary sources rich in ascorbic acid include citrus fruits, berries, and cruciferous vegetables, with intestinal absorption mediated primarily by sodium-dependent vitamin C transporters (SVCT1 and SVCT2). Given its diverse biological roles, adequate intake of vitamin C is essential for maintaining homeostasis and mitigating oxidative and inflammatory pathologies.

Keywords: Ascorbic acid, antioxidant, skin health, scurvy

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1. INTRODUCTION

Ascorbic acid (vitamin C) is a water-soluble micronutrient required for multiple biological functions. Ascorbic acid (vitamin C), the antiscorbutic vitamin, cannot be synthesized by humans and other primates and must be obtained from the diet. Ascorbic acid is an electron donor and acts as a cofactor for fifteen mammalian enzymes. Vitamin C levels in tissue and plasma are influenced by utilization, renal excretion, absorption, and consumption. To be biologically meaningful or to be clinically relevant, in vitro and in vivo studies of vitamin C actions must consider physiologic concentrations of the vitamin (1,2).

Vitamin C (ascorbic acid) is a simple low-molecular-weight carbohydrate with an ene-diol structure, making it a common and essential water-soluble electron donor in nature. It is synthesized by all species except higher-order primates, guinea pigs, and a few bat, fish, and bird species. The gene encoding for i-gulonolactone oxidase—the enzyme catalyzing the final step in the biosynthesis of

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ascorbic acid—has evolved into a nonfunctional state in all of the latter due to the accumulation of mutations and/or deletions; thus, these species rely on an adequate supply of vitamin C from their diet (3).

2. STRUCTURE OF ASCOBIC ACID

Vitamin C is known as ascorbic acid or l-ascorbic acid according to the IUPAC-IUB Commission (2-oxo-l-theo-hexono-4-lactone-2, 3-enediol). Figure 1 shows the ascorbic acid chemical structures. Ascorbic acid has a near planar five-member ring; the two chiral centers at positions 4 and 5 determine the four stereoisomers. Some vitamin C action is retained by dehydroascorbic acid, the oxidized form of ascorbic acid, which can exist as a dimer or as a hydrated hemiketal. According to electrochemical research, ascorbic acid and dehydroascorbic acid combine to form a reversible redox couple (1,4).

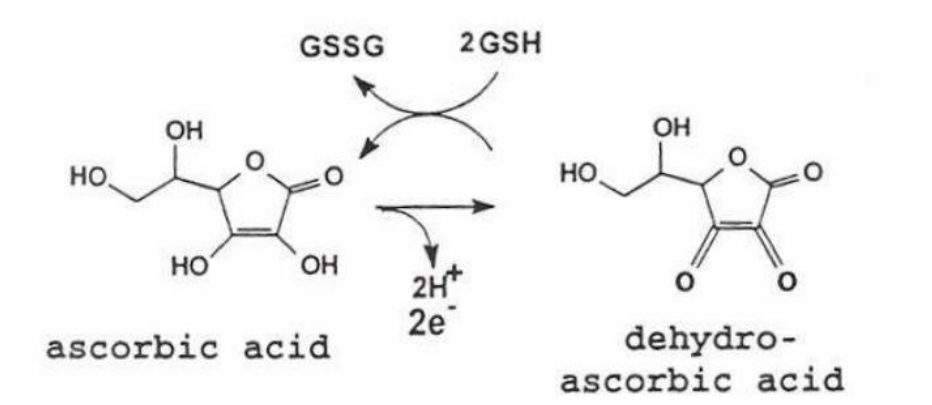

Figure (1): Ascorbic acid and dehydroascorbic acid. Ascorbic acid is the reduced form of vitamin C. The oxidized form, dehydroascorbic acid, can be reduced back to ascorbic acid by glutathione (GSH) (1).

3. FUNCTION OF ASCORBIC ACID

Vitamin C is essential for the development and maintenance of connective tissues. It is essential for wound healing, bone formation, and gum health maintenance. Vitamin C plays an important role in several metabolic functions, including the activation of the B vitamin, folic acid, the conversion of cholesterol to bile acids, and the conversion of the amino acid, tryptophan, to the neurotransmitter, serotonin. It functions as an antioxidant, protecting the body from free radical damage. It is used as a therapeutic agent in many diseases and disorders. Vitamin C helps prevent infections, strengthens the immune system, and reduces the intensity of allergic reactions (5).

- **IN SKIN**

Vitamin C concentrations in normal skin are high, equivalent to those in other bodily tissues, and significantly higher than those in plasma, suggesting active accumulation from the circulation. With concentrations probably in the millimolar range, the majority of vitamin C in the skin seems to be found in intracellular compartments. It is transported into cells from the blood vessels present in the dermal layer.

The skin's high vitamin C content suggests that it serves several vital biological functions that are related to skin health. Based on what we know about vitamin C function, attention has been focused on collagen formation and antioxidant protection;

however, evidence is emerging for other activities (6).

Ascorbic acid reduces reactive oxygen species (ROS). These ROS are generated by a variety of exposome factors, including air pollution from vehicle and factory emissions, UV radiation from the sun, and nanoparticle deposits on the skin, all of which contribute to skin inflammation and aging. Additionally, ROS can damage the electron transport chain and mitochondria, two essential components for energy production. Vitamin C also acts as a cofactor in the biosynthesis of procollagen and elastin, induces collagen synthesis in human skin fibroblasts, and increases dermal thickness. However, vitamin C is only one member in the antioxidant arsenal that includes enzymatic defenses (catalase, glutathione peroxidase, and superoxide dismutase) and other non-enzymatic defenses (vitamin E, glutathione, uric acid, and other putative antioxidants such as carotenoids) (6,7).

- **IN COLLAGEN FORMATION**

Ascorbic acid is required for appropriate collagen development because it contributes to the synthesis of hydroxyproline and hydroxylysine in collagen. Collagen triple helix stability is provided by hydroxyproline; its absence causes structurally unstable collagen that is not secreted from cells at a normal rate. For collagen's intermolecular crosslinks to form, hydroxylysine is essential. Furthermore, hydroxylysine glycosidically bonds particular carbohydrate residues to collagen, a mechanism that may be crucial for controlling the production of crosslinks (8).

In the process of collagen biosynthesis, the amino acids proline and lysine present on the unfolded collagen chains are subjected to hydroxylation by the prolyl 4-hydroxylases, prolyl 3-hydroxylases, and lysyl hydroxylases of 2-OGDD, which are located within the lumen of the endoplasmic reticulum (ER). The reaction requires oxygen, 2-oxoglutarate, Fe2+, and Asc- to return iron to its ferrous form following oxidation while maintaining enzyme activity. Procollagen strands fold form a triple helix when proline hydroxylation is complete. This allows for the glycosylation of hydroxylated lysyl groups on the strand terminals to provide pepsin resistance before secretion to the extracellular matrix. In this way, the hydroxylation of proline constitutes a Vitamin C-regulated “quality checkpoint” in collagen biosynthesis. In the absence of Vitamin C, the activity of the hydroxylases is impaired, leaving procollagen strands unfolded and retained in the ER, effectively preventing assembly and secretion of stable collagen (9).

- **IN WOUND HEALING**

The skin serves as a barrier to protect the body from external germs, and as the body's largest tissue, so any wound must be treated immediately and efficiently. Normal skin contains high levels of vitamin C, which promotes essential and well-known activities such as wound healing, collagen synthesis, and antioxidant protection against UV-induced photodamage. The fundamental purpose of dermal fibroblasts is to produce and secrete extracellular matrix, which is crucial for healing wounds. Ascorbic acid, a cofactor that scavenges free radicals, is necessary for dermal fibroblasts to produce collagen. Ascorbic acid (AA) promotes the expression of wound-healing factors and reduces the expression of pro-inflammatory factors in skin wounds. In addition, AA plays an important role in all three phases of wound healing, including inflammation, proliferation, and regeneration (6,10).

- **AS AN ANTIOXIDANT**

Vitamin C (L-ascorbic acid) is known as an antioxidant for most people. However, its physiological importance is far broader and includes a wide range of actions, from facilitating iron absorption to involvement in hormones and carnitine synthesis to playing crucial roles in epigenetic processes. On the other hand, excessive amounts function more as a pro-oxidant than an antioxidant (11).

Ascorbic acid interacts with small molecule antioxidants such as tocopherol, glutathione, and thioredoxin, but it also promotes the biosynthesis and activation of antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. Additionally, ascorbic acid stimulates the expression of genes encoding antioxidant proteins by increasing the activity of many transcription factors (Nrf2, Ref-1, and AP-1). It also enhances the activity of other exogenous antioxidants, particularly polyphenols. In this connection, both DNA, protein, and lipids are protected against oxidation. Although ascorbic acid has strong antioxidant properties, it can also have pro-oxidant effects in the presence of free transition metals. This could be the cause of the kidney's careful regulation of plasma levels at the level of absorption and excretion. It's interesting to note that, in comparison to other vitamins, vitamin C is present in most cells in millimolar concentrations, which are far higher than its plasma concentrations (11,12).

AA converts to the ascorbate radical by providing an electron to the lipid radical, thus ending the lipid peroxidation chain reaction. The pairs of ascorbate radicals react rapidly to produce an ascorbate molecule and a dehydroascorbate molecule (without antioxidant activity), the latter being transformed back to ascorbate by the addition of two electrons, most probably due to the action of oxidoreductase (13).

The pro-oxidative activity of ascorbic acid shown in Figure 2 is associated with the interaction with transition metal ions (especially iron and copper). When ascorbate concentrations are high, vitamin C catalyzes the reduction of free transition metal ions, resulting in the production of oxygen radicals. Hydrogen peroxide and reduced iron ions combine to generate peroxide ions or reactive hydroxyl radicals. In the presence of oxygen, this process takes place. Furthermore, a 3 mg/day excess of vitamin C can affect iron, copper, and vitamin B12 absorption. While there is extensive evidence of vitamin C pro-oxidative abilities in the presence of transition metals in vitro, there is no convincing and unambiguous evidence of such in vivo activity. This could be the consequence of carefully controlled metal metabolism, where specific proteins sequester metals like Fe or Cu (14,15).

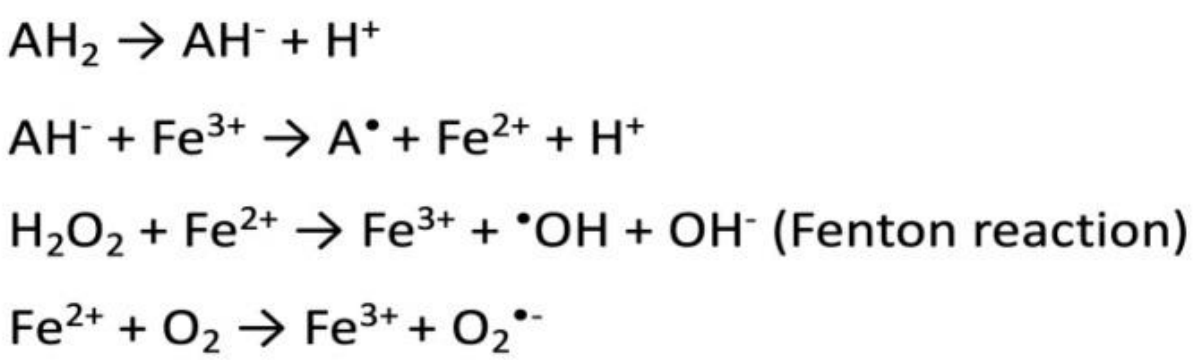

Figure 2: Scheme of hydroxyl radical generation according to Fenton's predictions. AH_2—ascorbic acid; AH^-—ascorbate anion; A•—ascorbyl radical; •OH—hydroxyl radical; O^-_2—superoxide anion (14).

- **IN IMMUNE SYSTEM**

Vitamin C concentrations in plasma and leukocytes rapidly decline during infections and stress. Vitamin C supplementation has been shown to enhance human immune system functions, including chemotaxis, lymphocyte proliferation, natural killer cell and antimicrobial activity, and delayed-type hypersensitivity. Vitamin C helps cells retain their redox integrity, protecting them from reactive oxygen species produced during the respiratory burst and the inflammatory response. This nutrient plays important roles in immune function and the modulation of host resistance to infectious agents, reducing the risk, severity, and duration of infectious diseases (16).

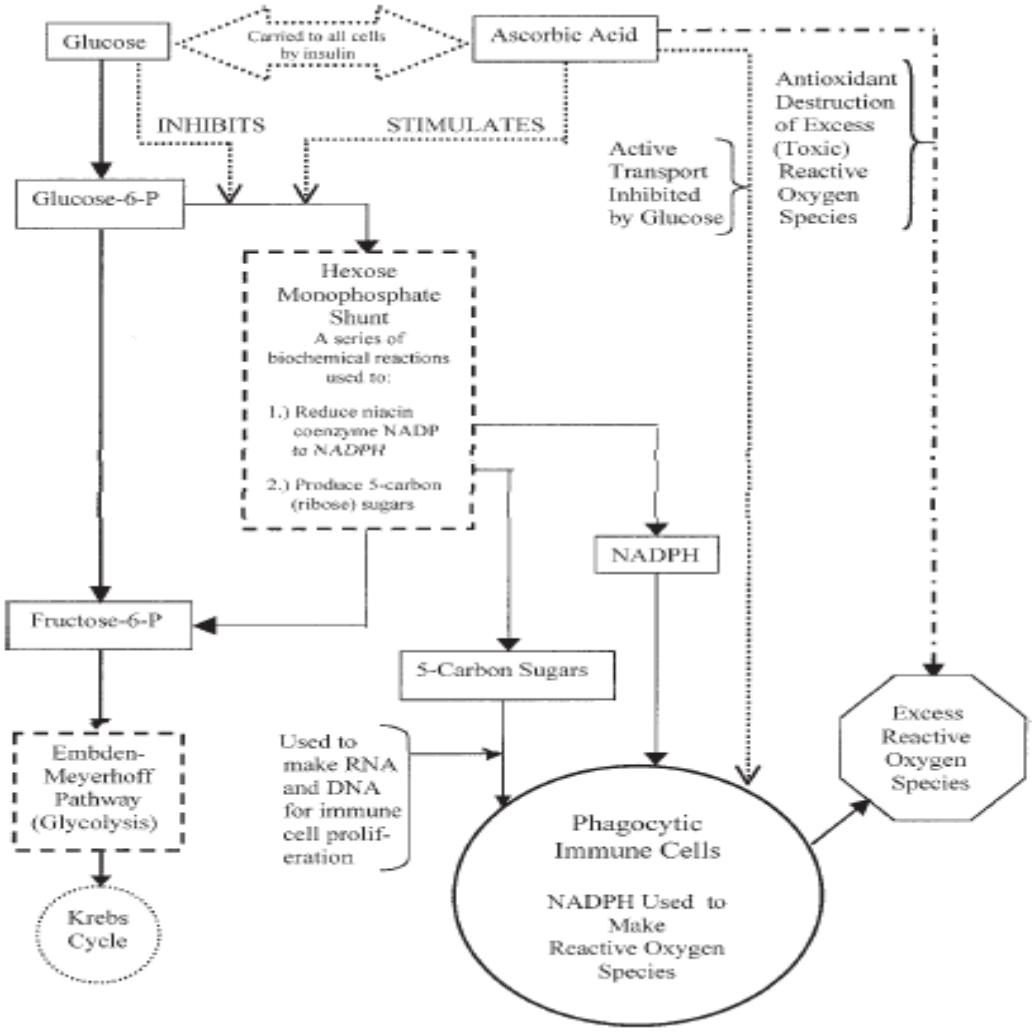

Figure (3): An overview of the interaction between ascorbic acid and the immune system. Starting in the upper left corner of the diagram, insulin delivers both glucose and ascorbic acid to all cells in the body, including phagocytic cells, which seek, attack, and eliminate bacteria, viruses, tumor cells, and other microscopic cellular waste from the blood. This common transport mechanism shows the struggle between glucose and ascorbic acid and explains why, in order to have a beneficial impact, large doses of ascorbic acid are required to overcome glucose inhibition. Glucose not only inhibits ascorbic acid transport to all cells of the body, but it also prevents ascorbic acid from stimulating the hexose monophosphate (HMP) shunt (17).

- **SYNTHESIS OF NOREPINEPHRINE FROM DOPAMINE**

Ascorbic acid enhances catecholamine biosynthesis at two steps. It starts by recycling tetrahydrobiopterin, which tyrosine hydroxylase requires for synthesizing L-3,4-dyhydroxyphenylalanine (L-DOPA), the first and rate-limiting step in the pathway. Additionally, it is the major and most likely physiological electron donor to dopamine β-hydroxylase (DβH), which in secretory granules converts dopamine (DA) to norepinephrine (NE). During this step, AA donates an electron to the hydroxylation reaction and becomes the ascorbate radical, which is then recycled back to AA by electron transfer across the granule membrane from cytoplasmic AA via a cytochrome b561. The transfer is driven by ATP-dependent generation of a favorable proton gradient into the vesicle (18).

4. DEFICIENCY OF ASCORBIC ACID

Scurvy, a vitamin C deficiency, can result from a diet deficient in vitamin C for one to three months or less (19). In contrast to other animals, humans need an exogenous source of ascorbic acid, which is produced through the metabolism of glucose. Because vitamin C is heat-sensitive, cooking methods influence the bioavailability of this nutrient in food. Accordingly, the following are high-risk categories or risk factors for vitamin C deficiency:

- Individuals with poor dietary habits who consume food of poor nutritional value.
- Limited access to or the inability to afford fresh fruits and vegetables.
- Alcoholism.
- Infants exclusively fed cow's milk.
- Individuals with gastrointestinal disorders such as inflammatory bowel disease.
- Smoking was demonstrated as a significant risk factor in the NHANES.
- Low socio-economic status.
- Elderly individuals on a "tea-and-toast" diet.
- Eating disorders and psychiatric illness.
- Long-term use of certain medications, such as corticosteroids or proton pump inhibitors, can alter the absorption and bioavailability of vitamin C in the diet.
- Abdominal surgeries, such as small bowel resection or bariatric surgery, which affect gut absorption.
- Obesity.
- Dialysis (20,21).

Scurvy symptoms can include anemia, myalgia, bone pain, easy bruising, swelling, petechiae, perifollicular hemorrhages, corkscrew hairs, gum disease, poor wound healing, mood changes, and depression. The lower limbs are frequently where perifollicular hemorrhages and simple bruises initially appear. The characteristic skin lesions are often misdiagnosed as hematological disorders or vasculitis. If left untreated, symptoms including generalized edema, severe jaundice, hemolysis, abrupt spontaneous bleeding, neuropathy, fever, and convulsions can be fatal (20).

Strong clinical and experimental evidence indicates that prolonged latent vitamin C insufficiency causes hypercholesterolemia and accumulation of cholesterol in specific organs. When individuals and animals with hypercholesterolemia consume ascorbic acid supplements, their plasma cholesterol levels often drop significantly. Hypovitaminosis C in animals given cholesterol and cholic acid increased the cholesterol content of the gallstones. The composition of biliary bile acids changed significantly. Reductive formation of deoxycholic acid decreased, and oxidative formation of ketonic bile acid increased (22,23).

A significant advance in recent years has been the development of a model of chronic latent scurvy in the guinea pig. Chronic dietary inadequacy of vitamin C may influence the pathogenesis of atherosclerosis as it affects not only plasma cholesterol and triglyceride concentrations but also the integrity of the vascular wall. A series of investigations on guinea pigs with chronic latent

vitamin C deficiency found clear evidence that bile acid production is impaired. Indirect evidence strongly suggests that this results from a decrease in the activity of the microsomal enzyme cholesterol 7 alpha-hydroxylase (22).

5. TREATMENT

Scurvy is treated with vitamin C supplements and the correction of the conditions that caused the insufficiency. A wide range of replacement doses has been used successfully. For children, recommended doses are 100 mg of ascorbic acid given three times daily (orally, intramuscularly, or intravenously) for one week, then once daily for several weeks until the patient is fully recovered. Adults are usually treated with 300 to 1000 mg/day for one month (21).

6. AA SOURCES

Ascorbic acid can be found in citrus fruits and vegetables such as lemon, orange, strawberry, tomato, tamarind, amla, and Brussels sprouts. Animal sources of ascorbic acid are low in content because the vitamin C content is generally low, except animal livers, which are taken sparingly, and some fish eggs, where the levels are often less than 30-40 mg/100 g. Therefore, plant sources are essential as they contain higher levels of ascorbic acid (5,000mg/100g). Vitamin C absorption occurs mostly through passive diffusion in buccal cavities. However, active sodium-dependent

The transport of vitamin C in the gastrointestinal tract is facilitated by sodium-dependent vitamin C transporters (SVCT) (11,24).

TABLE 1: RDA (Recommended Dietary Allowance) for vitamin C in people of different categories and age groups (24).

Age group	Male	Female	Pregnant women	Lactating mothers
Zero to six months	40 mg	50 mg	-	-
Seven months to one year	50 mg	50 mg	-	-
One to three years	15 mg	15 mg	-	-
Four to eight years	25 mg	25 mg	-	-
Nine to thirteen years	45 mg	45 mg	-	-
Fourteen to eighteen years	75 mg	65 mg	80 mg	115 mg
Nineteen years and above	90 mg	75 mg	85 mg	120 mg

Conflict of interest: NIL

Funding: NIL

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