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A Review of the Applications of Vitamin C to Treat Human Diseases

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Abstract

Vitamin C, a ubiquitous water-soluble vitamin, has been demonstrated to have several biological activities, including the promotion of collagen production, enhancement of immunity, facilitation of iron absorption, and improvement of fat metabolism. Thus, it has a multitude of applications in the medical field, such as whitening, antioxidation, and the prevention of a wide range of diseases. Conversely, its lack of stability and low permeability limit its applicability. This review presents a summary of the physicochemical properties, delivery strategies, and biological activities of vitamin C. Additionally, this review provides an overview of its preventive and therapeutic effects on diseases such as cataracts, tumors, and cardiovascular conditions. Finally, this review explores the prospective applications of vitamin C as a pharmaceutical agent. A variety of vitamin C derivatives and delivery systems have been developed to overcome the instability and low permeability of vitamin C. However, several challenges persist, including the uncertain efficacy of derivatives and the complexities associated with the implementation of delivery systems. It is anticipated that future advancements will facilitate the development of delivery forms and the utilization of vitamin C in novel applications.

Keywords
- vitamin C
- ascorbic acid
- free radicals
- antioxidant
- biological activities

Introduction

Vitamin C (VC), also known as *L*-ascorbic acid (AA), one of the water-soluble vitamins, is an essential substance for maintaining the normal physiological state of the human body. VC plays a critical role in physiological functions such as promoting collagen production, enhancing immunity, and improving fat metabolism. Therefore, VC has a wide range of applications in the medical field.

In nature, VC can be synthesized by most animals and plants, but the gene for *L*-gluconolactone oxidase, which synthesizes VC, is mutated in humans, resulting in the inability to synthesize VC.[1] The primary source of VC for humans is through the daily diet. Approximately 90% of the daily intake of VC in the general population is derived from fruits and vegetables. The VC content of common fruits and vegetables is listed in ►**Table 1**.[2] A plasma concentration of VC below 10 μmol/L is associated with the development of scurvy, which presents with symptoms such as impaired wound healing, gingivitis, and ecchymosis.[3–5] The deficiency of VC is mainly caused by inadequate dietary intake, although other factors, including smoking, pregnancy, age, genetic susceptibility, and some metabolic diseases such as hypertension and diabetes, also contribute to its prevalence.[3,6] The

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Table 1 Food sources of vitamin C

Fruit	
Source (portion size)	**Vitamin C content (mg)**
Strawberries (1 cup, sliced)	95
Papaya (1 cup, cubes)	85
Kiwi (1 medium)	75
Orange (1 medium)	70
Cantaloupe (1/4 medium)	60
Honeydew melon (1/8 medium)	40
Fresh grapefruit (1/2 fruit)	40
Vegetables	
Source (portion size)	**Vitamin C content (mg)**
Raw pepper, red or green (1/2 cup)	65
Broccoli, cooked (1/2 cup)	60
Kale, cooked (1 cup)	55
Fresh snow peas, cooked (1/2 cup)	40
Mustard greens, cooked (1 cup)	35
Baked sweet potato (1 medium)	30
Cauliflower, raw or cooked (1/2 cup)	25

Source: Reproduced with permission from Levine et al,[2] copyright 1999 American Medical Association.

recommended dietary allowance for women and men is 75 and 90 mg/d, respectively.[7] For most adults, 200 mg/d is the optimal intake.[6,8]

Due to its strong water solubility and electronegativity, VC cannot penetrate the lipid bilayer easily. Therefore, the absorption of VC does not depend on simple diffusion, but rather on facilitated diffusion mediated by glucose transporters (GLUT) and active transport mediated by sodium-dependent VC transporter (SVCT).[9] In the intestine, VC can be oxidized to dehydroascorbic acid (DHA), which is then immediately reduced to AA after it is transported into the cell via GLUT.[10,11] This process is known as the AA cycle.[12] Two distinct forms of SVCT are present in the human body: SVCT1 and SVCT2. These transporters facilitate the uptake of AA into cells.[9] SVCT1 is subject to feedback inhibition by AA concentration,[13,14] whereas SVCT2 is responsive to changes in intracellular AA levels, which may be crucial for maintaining intracellular AA homeostasis.[14,15]

When the daily intake of VC exceeds 400 mg, the plasma concentration of VC is fully saturated, resulting in a steady-state plasma concentration of ~80 μmol/L.[16] Excessive VC is usually excreted in the urine. VC is well tolerated by the human body; however, short-term supplementation of VC has been associated with gastrointestinal adverse reactions, including abdominal distension, flatulence, diarrhea, and abdominal pain. At the same time, VC participates in the metabolic process, whereby it produces oxalic acid. Consequently, the risk of developing kidney stones is elevated when individuals consume a substantial amount of VC

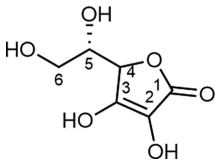

Fig. 1 The structure of vitamin C.

over an extended period. In addition, the ingestion of large quantities of VC may also result in relative deficiencies of other vitamins in the body.[3,17]

This article will provide an overview of the physicochemical properties, biological activities, and delivery mode of VC. In conjunction with developments in clinical and research practice, this article will examine the preventive and therapeutic effects of VC in the management of skin conditions, cataracts, tumors, cardiovascular diseases (CVDs), and other diseases.

Overview

The Structure and Properties of Vitamin C

VC is an acidic polyhydroxyl compound comprising carbon, hydrogen, and oxygen with a molecular formula of $C_6H_8O_6$ and an IUPAC name of 2,3,4,5,6-pentahydroxy-2-hexenoide-4-lactone, with a molecular weight of 176.1 g/mol. The structural formula is shown in ►**Fig. 1**.

The structure of VC contains enediol groups, of which C_3–OH exhibits strong acidity. This is influenced by the conjugation effect ($pK_a = 4.17$). In contrast, C_2–OH is weakly acidic due to intramolecular hydrogen bonding ($pK_a = 11.75$). Accordingly, VC exists in the form of anion under physiological conditions.[14] The structure of VC contains conjugated structures, which result in ultraviolet absorption. The maximum absorption wavelength is ~245 nm, which provides a method for the detection of VC content. The double bond between C_2 and C_3 yields two electrons, which are subsequently lost by VC to generate AA free radicals (semi-hydroascorbic acid). The majority of these free radicals have a lifetime of less than a millisecond and exhibit reduced activity.[18] When VC loses its second electron, it forms a substance that is more stable than the ascorbate radical: DHA. Both AA free radicals and DHA can be reduced to AA. Once the five-membered loop of DHA is hydrolyzed and broken to produce 2,3-diketo-1-gulonic acid (this process is irreversible), the reduction of DHA to AA is no longer possible. The detailed oxidation process of VC is shown in ►**Fig. 2**.

Some biological processes within the human body may result in the production of highly reactive and potentially harmful free radicals, and these free radicals can be removed by VC. In this process, VC itself is converted to less active ascorbate radicals. These results indicate that AA is an effective antioxidant and free radical scavenger.[19]

Commercially Available Formulations and Delivery Systems for VC

Most VC-related dosage forms are oral preparations, external dosage forms, and injections. A large number of VC products

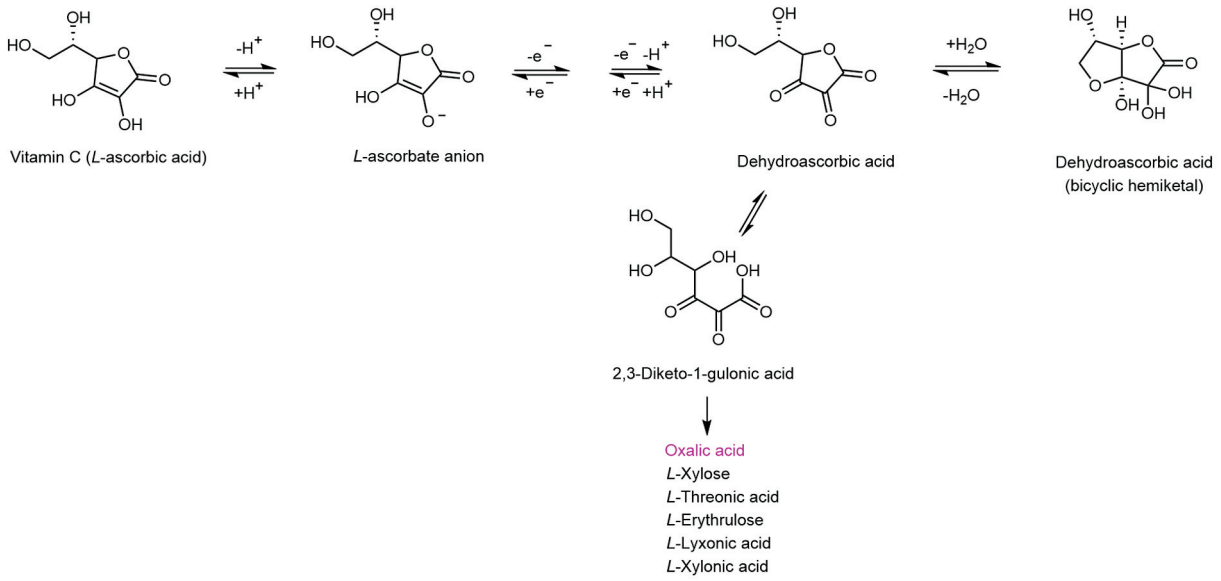

Fig. 2 Oxidation of ascorbic acid.

are approved by the National Medical Products Administration (NMPA) annually. The VC-related preparations approved by NMPA from 2021 to 2023 are shown in ►**Table 2**. To reduce VC degradation, achieve targeted drug delivery, and improve therapeutic efficacy, researchers have developed different drug delivery systems to deliver VC, such as polymeric nanoparticles, liposomes, microemulsions, and micelles (►**Fig. 3**).

Nanoparticles made of natural polymers have low toxicity, high biocompatibility, and sufficient degradability.[1] Chitosan is a kind of hydrophilic polysaccharide. Chitosan-based drug delivery systems have the following advantages: increased solubility, controlled drug release, enhanced drug targeting, and improved absorption.[20] Alishahi et al[21] adopted the ionotropic gelation method and used tripolyphosphate as a cross-linking agent to prepare VC-chitosan nanoparticles, which realized the encapsulation of VC within the nanoparticle. The obtained nanoparticles improved the stability of VC in the gastrointestinal tract and showed consistent VC release for up to 48 hours.

Liposomes are phospholipid bilayer vesicles composed of amphiphilic molecules, which can load hydrophobic and hydrophilic molecules and have the advantages of low toxicity and high biocompatibility.[22,23] Orally administered VC is easily degraded in the gastrointestinal tract, and liposomes can provide a hydrophilic–hydrophobic interface to avoid VC degradation.[24,25] Liposomes can also reduce gastrointestinal interference and prolong the release of VC.[26] Jiao et al[27] used chitosan-coated liposomes to deliver VC and folic acid, which improved the antioxidant efficacy of the preparation. Therefore, the use of liposome delivery technology can improve the bioavailability of VC to a certain extent and avoid the risks associated with intravenous administration.[26,28,29]

Microemulsion is a transparent, thermodynamically stable colloidal system formed spontaneously from oil, water, and emulsifier, with an average particle size of 10 to 100 nm. The microemulsion has low surface tension, high interfacial tension, and solubilization properties.[30] In addition to the above nano-preparations, currently, researchers use VC to develop new drug delivery systems to achieve targeted drug delivery. Sawant et al[31] used polyethylene glycol phosphatidylethanolamine to prepare palmitoyl ascorbate micelles, which improved the solubility of palmitoyl ascorbate and increased the accumulation of palmitoyl ascorbate at the tumor site through the high permeability and enhanced permeability and retention effect (EPR effect) of solid tumors, showing good antitumor activity. Xiao et al[32] used AA derivatives as liposome ligands and used VC to bind to the receptor-ligand of GLUT1 and SVCT2 to deliver drugs targeted to the brain, indicating that AA has the potential to enhance brain targeting of drugs in the central nervous system. Luo et al[33] used ascorbate-coupled polylactic acid-hydroxyethyl copolymer to promote oral drug absorption through SVCT1. Inoue et al[34] used AA derivative ascorbic acid 2-phospho-6-palmitate trisodium to form micelles and used as drug carriers to improve drug skin permeability.

In general, these drug delivery systems address the limitations of VC, namely its poor stability and strong hydrophilicity, through enhanced encapsulation and targeted drug delivery thereby improving the absorption of VC *in vivo*. However, the current industrial technologies impose constraints on the large-scale clinical application of these delivery systems.

Biological Activity

VC Promotes Collagen Formation

VC plays a pivotal role in the posttranslational modification of procollagen, a crucial coenzyme factor in collagen biosynthesis.[35] VC facilitates the synthesis of collagen, a fundamental protein in the extracellular matrix, by regulating the structure and secretion of procollagen.[36] Procollagen is synthesized in the endoplasmic reticulum and consists of

Table 2 Approved vitamin C commercial formulations from 2021 to 2023

Dosage form	Drug name	Active agent	Specification	Number of manufacturers of the same type	The most recent approval date	Indications
Tablets	Vitamin C tablets	Vitamin C	25 mg; 50 mg; 100 mg;	584	2023-03-27	Scurvy; chronic iron poisoning; idiopathic methemoglobinemia; liver cirrhosis; acute hepatitis
Tablets	Vitamin C Yinqiao tablets	Vitamin C; acetaminophen; chlorpheniramine maleate	Each tablet contains 49.5 mg of vitamin C, 105 mg of acetaminophen, and 1.05 mg of chlorpheniramine maleate	292	2022-07-22	Influenza caused by exogenous wind-heat
Tablets	Vitamin E and C chewable tablets	Vitamin C; vitamin E	Each tablet contains 100 mg of vitamin E and 200 mg of vitamin C	3	2021-10-11	Prevent and treat disease caused by vitamin E and vitamin C deficiency
Tablets	Aspirin vitamin C enteric-coated tablets	Aspirin; vitamin C	Each tablet contains 0.25 g of aspirin and 25 mg of vitamin C	10	2023-02-24	Used to relieve fever, headache, and body aches caused by cold or flu
Tablets	Compound rutin tablets	Rutin; vitamin C	Each tablet contains 20 mg of rutin and 50 mg of vitamin C	60	2022-05-09	Used for capillary hemorrhage with increased fragility, and also used for adjuvant treatment of hypertensive encephalopathy
Tablets	Diavitamin and glucuronolactone tablets	Glucuronide; vitamin C; vitamin B	Each tablet contains 5 mg of glucuronide, 10 mg of vitamin C, 110 mg of vitamin B	8	2021-03-29	Used for adjuvant treatment of liver damage in acute and chronic hepatitis and chronic poisoning such as arsenic, mercury, lead, benzene
Tablets	Vitamin C effervescent tablets	Vitamin C	0.5 g; 1g	13	2022-06-28	Infectious diseases; scurvy
Tablets	Vitamin C chewable tablets	Vitamin C	50 mg; 0.1 g	39	2021-02-26	Scurvy; infectious diseases; purpura
Tablets	Aspirin and vitamin C effervescent tablets	Aspirin; vitamin C	Each tablet contains 0.4 g of aspirin and 24 mg of vitamin C	3	2023-04-18	Used for heating, including cold caused by fever, headache, sore throat, toothache, and other pain, etc.
Tablets	Paracetamol and vitamin C dispersible tablets	Paracetamol; vitamin C	Each tablet contains 330 mg of paracetamol and 200 mg of vitamin C	2	2023-02-21	Antipyretic and analgesic

(*Continued*)

Table 2 (*Continued*)

Dosage form	Drug name	Active agent	Specification	Number of manufacturers of the same type	The most recent approval date	Indications
Tablets	Paracetamol and vitamin C effervescent tablets	Paracetamol; vitamin C	Each tablet contains 330 mg of paracetamol and 200 mg of vitamin C	3	2023-01-03	Antipyretic and analgesic
Tablets	Paracetamol vitamin C tablets	Paracetamol; vitamin C	Each tablet contains 330 mg of paracetamol and 200 mg of vitamin C	1	2022-09-14	Antipyretic and analgesic
Tablets	Compound trivitamin and calcium hydrogen phosphate tablets	Calcium hydrogen phosphate; calcium lactate; vitamin B1; vitamin B2; vitamin C	Each tablet contains 75 mg of calcium hydrogen phosphate, 45 mg of calcium lactate, 0.05 mg of vitamin B1, 0.0015 mg of vitamin B2, and 12 mg of vitamin C	5	2021-01-13	Used for calcium supplementation in children and pregnant women
Injections	Vitamin C injection	Vitamin C	2 mL: 0.5 g; 10 mL: 1 g; 5 mL: 0.5 g; 20 mL: 2.5 g; 2 mL: 0.1 g; 2 mL: 0.25 g; 5 mL: 0.5 g	214	2023-06-26	Scurvy; chronic iron poisoning; idiopathic methemoglobinemia
Injections	Vitamin C for injection	Vitamin C	0.25 g; 0.5 g; 1.0 g;	17	2022-9-14	Scurvy; chronic iron poisoning; idiopathic methemoglobinemia
Injections	Water-soluble vitamin for injection	Thiamine nitrate; riboflavin sodium phosphate; nicotinamide; pyridoxine hydrochloride; sodium pantothenate; vitamin C sodium; biotin; folic acid; vitamin B12	Each bottle contains 3.1 mg of thiamine nitrate, 4.9 mg of riboflavin sodium phosphate, 40 mg of nicotinamide, 4.9 mg of pyridoxine hydrochloride, 16.5 mg of sodium pantothenate, 113 mg of vitamin C sodium, 60 μg of biotin, 0.4 mg of folic acid, and 5.0 μg of vitamin B 12	33	2022-11-03	One of the components of parenteral nutrition
Capsules	Compound trivitamin and linolic acid soft capsules	Linoleic acid; vitamin B6; vitamin C; inositol	Each capsule contains 350 mg of linoleic acid, 2 mg of vitamin B6, 25 mg of vitamin C, and 10 mg of inositol	26	2021-03-17	Used for adjuvant treatment and prevention of atherosclerosis

Table 2 (*Continued*)

Dosage form	Drug name	Active agent	Specification	Number of manufacturers of the same type	The most recent approval date	Indications
Capsules	Vitamin C granules	Vitamin C	0.1 g	12	2021-04-25	Scurvy; chronic iron poisoning; idiopathic methemoglobinemia
Capsules	Compound trivitamin and linolic acid soft capsules I	Linoleic acid; vitamin B; vitamin C; vitamin E; inositol; soy phospholipid; methyl hesperidin	Each capsule contains 0.35 g of linoleic acid, 62 mg of vitamin B, 25 mg of vitamin C, 1.67 mg of vitamin E, 10 mg of inositol, 24 mg of soy phospholipid, and 10 mg of methyl hesperidin	2	2021-03-16	Used for adjuvant treatment and prevention of atherosclerosis
Granules	Vitamin E and C granules	Vitamin C; vitamin E	Each capsule contains 0.1 g of vitamin E and 0.2 g of vitamin C	13	2021-09-23	Used to prevent and treat diseases caused by vitamin E and vitamin C deficiency
Granules	Aurantium and vitamin C granules	Vitamin C; hesperidin	Each bag (7 g) contains 100 mg of vitamin C and 60 mg of hesperidin	13	2021-08-25	Used for diseases caused by vitamin C and hesperidin deficiency
Granules	Compound bifendate granules	Bifendate; inosine; vitamin C	Each bag (10 g) contains 15 mg of bifendate, 100 mg of inosine, and 50 mg of vitamin C	13	2021-04-30	For chronic and persistent hepatitis with elevated alanine aminotransferase
Pills	Vitamin C pills	Vitamin C	50 mg; 0.1 g	16	2021-07-27	Used to prevent and treat scurvy and various acute and chronic infectious diseases or other diseases
Powders	Oral four vitamins and glucose	Vitamin B1; vitamin B2; vitamin C; vitamin D2; glucose	Each gram contains 11.2 mg of vitamin B1, 20.8 mg of vitamin B2, 20 mg of vitamin C, 23 μg of vitamin D2, and 10 g of glucose	12	2021-08-25	For nutrition and energy supplementation for patients with vitamin deficiency
Powders	Oral five vitamins and glucose	Vitamin B1; vitamin B2; vitamin C; vitamin D2; nicotinic acid; glucose	Each gram contains 0.12 mg of vitamin B, 0.08 g of vitamin B2, 2 mg of vitamin C, 0.002 mg of vitamin D2, 1 mg of nicotinic acid, and glucose appropriate	36	2022-03-11	Used in various diseases caused by vitamin deficiency
Solutions				2	2021-03-22	

(*Continued*)

Table 2 (*Continued*)

Dosage form	Drug name	Active agent	Specification	Number of manufacturers of the same type	The most recent approval date	Indications
	Five vitamins and lysine hydrochloride oral solution	Vitamin A; vitamin D; vitamin C; vitamin B6; niacinamide; lysine hydrochloride	Each (10 mL) contains 3,000 units of vitamin A, 2,200 units of vitamin D, 50 mg of vitamin C, 2 mg of vitamin B6, 20 mg of niacinamide, and 60 mg of lysine hydrochloride			Used to prevent and treat many diseases caused by the lack of multiple vitamins in children
Solutions	Tri-vitamins and cod liver oil emulsion	Cod liver oil; vitamin A; vitamin D3; vitamin C	Each gram contains 10 mg of cod liver oil, 30 units of vitamin A, 13.5 units of vitamin D3, and 1.54 mg of vitamin C	7	2022-01-04	Used for the prevention and treatment of various diseases caused by vitamin A, D, and C deficiency in adults

Note: Data in Table 2 was acquired from the National Medical Products Administration database (https://www.nmpa.gov.cn/).

proline-rich amino acid repeats, which are essential for its structural integrity. Specifically, proline and lysine residues undergo hydroxylation and conversion to hydroxyproline and hydroxylysine, respectively. This hydroxylation process requires VC as a cofactor.[18] Collagen has a triple helix structure, and the presence of hydroxyproline is essential to stabilize this structure.[35] Without hydroxyproline, fibroblasts cannot secrete collagen properly. Hydroxylysine is necessary for collagen cross-linking, and its absence can also lead to structural instability.[37] A computer simulation experiment was conducted to study the effect of VC on amino acid sequence and interaction forces during collagen formation.[38] In the presence of VC, collagen was synthesized, while in the absence of VC, hydroxyproline dissociates from prolyl-5-hydroxylase and the reaction stops. Therefore, VC can be considered a cofactor for prolyl-5-hydroxylase, which is responsible for the conversion of proline to hydroxyproline. VC is conducive to the hydroxylation process, which facilitates the formation of a stable triple helix structure in collagen and promotes collagen formation.

VC Promotes HIF-1 Hydroxylation

Hypoxia-inducible factor-1 (HIF-1) is a nuclear protein with transcriptional activity that plays an important role in physiological processes such as erythropoiesis, cell survival, and angiogenesis.[18] HIF-1 can induce the formation of new blood vessels around hypoxic cells and tissues thus promoting cell survival. Consequently, HIF-1 exerts a significant influence on fetal development, yet it also serves as a key promoter of a range of pathological conditions, including inflammatory diseases, lung disease, heart disease, diabetes, and cancer.[39]

HIF-1 consists of an active α subunit and a structurally expressed β subunit. Proline residues on the HIF-α subunit are hydroxylated by the prolyl hydroxylase domain (PHD) and undergo rapid degradation by ubiquitin protease under normal oxygen conditions. Under hypoxia conditions, PHD is inhibited.[40] VC plays an important role in the hydroxylation of proline residues by PHD. PHD is a nonheme iron-dependent dioxygenase, its catalytic activity can be enhanced by VC.[41,42] *In vitro* experiments have shown that VC has a significant inhibition effect on HIF-1, and can block HIF-1-induced gene transcription, thereby delaying the development of the disease.[43,44] In summary, by influencing the PHD to regulate HIF-1 levels, VC can diminish symptoms and delay the progression of the disease.

VC Enhances Immune Function

VC regulates immune function by enhancing various cellular functions of both the innate and acquired immune systems, regulating redox-sensitive cell signaling pathways, or directly protecting important cellular structural components.[45] The immune system is composed of immune organs (e.g., bone marrow, spleen, and lymph), immune cells (e.g., lymphocytes, mononuclear phagocytes, and neutrophils), and immunologically active substances (e.g., antibodies and complements) that protect the host from a range of pathogens.[46] The immune system can be divided into two

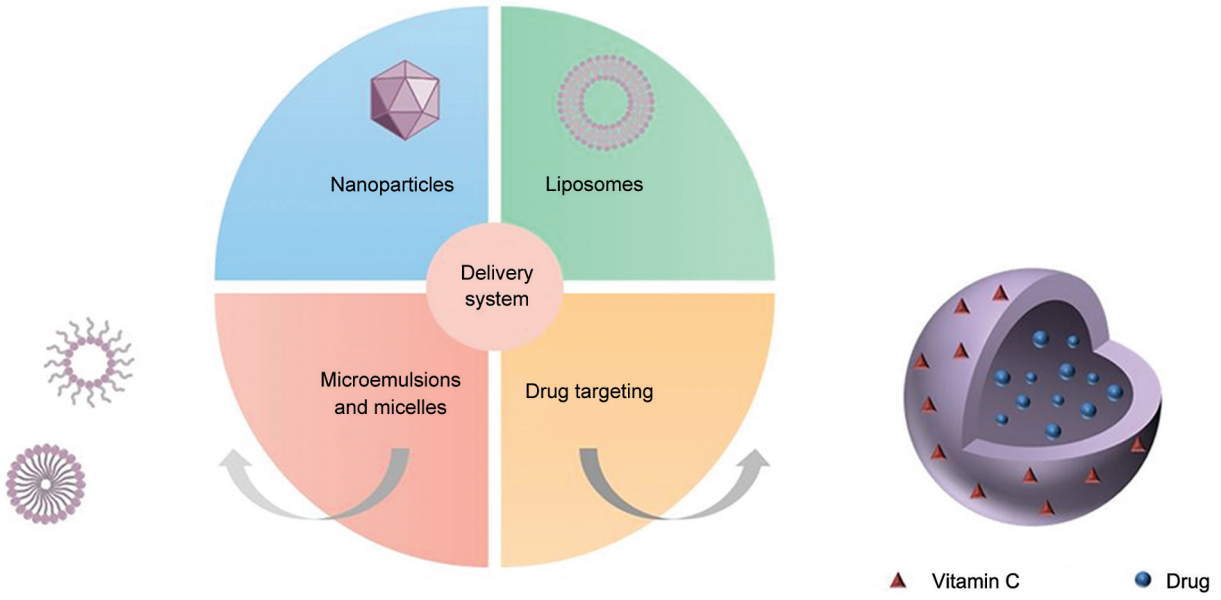

Fig. 3 The delivery system of vitamin C.

categories: nonspecific immunity and specific immunity. These categories can be further delineated into three main aspects: physical barriers such as skin and mucosa, immune cells, and antibodies.[47]

VC has been shown to protect the skin from environmental oxidative stress by promoting clearance of oxidants,[48] thereby strengthening the physical skin barrier. The infiltration of neutrophils into infected tissues is the early step of innate immunity. VC can accumulate in phagocytes such as neutrophils, enhance the chemotaxis and phagocytosis of neutrophils, produce reactive oxygen species (ROS), and eventually kill microorganisms.[45] Oxidants can activate nuclear factor κB (NF-κB), which triggers a signaling cascade that leads to the continued synthesis of oxides and other proinflammatory mediators.[49,50] VC has been shown to reduce the production of oxidants and the activation of NF-κB in dendritic cells *in vitro*.[51] In addition, research has demonstrated that VC enhances the immune system's response to infection by stimulating T lymphocyte proliferation, increasing cytokine production, and promoting immunoglobulin synthesis.[45] The Changxing team at West Lake University found that VC can facilitate plasma cell differentiation and humoral immune response by enhancing TET2/3-mediated DNA demethylation.[52]

A chronic deficiency of VC can lead to impaired immune function, rendering individuals more susceptible to infection. The inflammatory and metabolic demands associated with infection can significantly reduce the body's ability to absorb VC. Therefore, timely and appropriate supplementation of VC can help enhance the body's immune response.[53]

VC Improves Fat Metabolism

The fatty acids produced by the hydrolysis of fat in the human digestive tract are activated as fatty acyl CoA in the endoplasmic reticulum and the outer membrane of mitochondria. The enzymes that catalyze fatty acid oxidation are located within the mitochondrial matrix. Therefore, the activated fatty acyl CoA must enter the mitochondria to be oxidized. Long-chain fatty acyl CoA cannot penetrate the inner mitochondrial membrane and requires carnitine for transport into the mitochondria.[54]

Carnitine is a quaternary ammonium that exists in two stereoisomers, designated as *D*-type and *L*-type. The *D*-isomer, also known as *D*-carnitine, is physiologically inactive. The primary function of *L*-carnitine is to transfer long-chain fatty acids to the mitochondria for β-oxidation, a process by which the body derives energy.[55] Carnitine also binds to acyl residues produced by amino acid intermediate metabolism, assisting in the removal of amino acids.[54] This mechanism enables the clearance of abnormal organic acids. *L*-carnitine is synthesized from lysine and methionine, and the final step of the synthesis requires AA and iron ions to participate as cofactors.[55] Several *in vivo* experiments have proved that AA is involved in carnitine biosynthesis.[56–58] Hence, a lack of VC affects carnitine levels, which affects fat metabolism. Furthermore, Yuan et al[59] investigated the role of DNA demethylase ten-eleven translocation protein 1 (Tet1) in the development of obesity and found that VC, a cofactor of the Tet protein family, normalizes DNA methylation levels and promotes lipolysis.

VC Promotes Iron Absorption

Iron is a vital component in numerous biological processes, from oxygen transport to the synthesis of DNA. Its most important function is the transport of oxygen in hemoglobin. The primary form of dietary iron intake is iron trivalent, which is less bioavailable than ferrous iron. The absorption of iron from food is generally enhanced by the addition of iron absorption enhancers, among which AA is the most extensively studied.

The role of VC in promoting iron absorption is attributed to its ability to reduce and chelate iron. VC has the capacity to

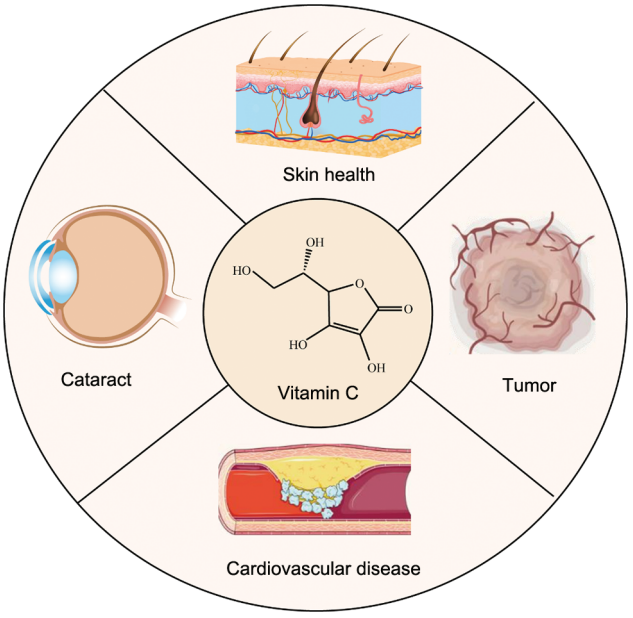

Fig. 4 The applications of vitamin C.

reduce trivalent iron to ferrous, thereby promoting the absorption and utilization of iron.[60] The extent of this reduction is influenced by the pH value. Studies have shown that in the range of pH 2.6 to 6.0, the reduction rate of VC decreases as the pH increases. At a pH range of 6.8 to 7.4, AA is unable to effectively reduce the trivalent iron.[61] Subsequent studies demonstrated that duodenal cytochrome B is an iron regulatory protein with iron-reductase activity, which plays a critical role in dietary iron absorption.[62] Several studies identified duodenal cytochrome B promoting iron reduction in a VC-dependent manner,[63–65] indicating that VC's primary role is in promoting iron dissolution. Furthermore, studies demonstrated that the administration of VC a few hours before the consumption of an iron-containing meal did not increase iron absorption, suggesting that VC must be taken with iron to promote iron absorption.[66,67]

Applications in Human Diseases

VC has many preventive and therapeutic effects in the field of medicine. This section will mainly discuss its application in cataracts, cancer, CVD, and skin disease (►**Fig. 4**).

Cataracts

Cataracts are a leading cause of vision impairment and blindness worldwide.[68] Population projections indicate that by 2025, cataracts could affect 40 million individuals.[69] The underlying mechanisms of cataract formation remain unclear, but oxidative stress is a prominent hypothesis. The free radicals generated by oxidative stress, such as glutathione (GSH), superoxide dismutase, and ROS, will damage the lens composition, resulting in lens opacity and thus lens damage.[70] Although cataract surgery is considered to be one of the safest surgeries, the prevention of cataracts has become a research focus due to the complications that can arise from the procedure, including recurrent or persistent inflammation, glaucoma, and posterior capsule opacification.[71]

The balance between antioxidants and free radicals determines the state of appropriate physiological function, if the level of free radicals rises uncontrollably, oxidative stress will appear.[72] The literature indicates that VC, as a nonenzymatic antioxidant, may have certain preventive effects on cataracts, although this is limited to nuclear cataracts.[73] Nuclear cataracts are located in the center of the lens and are usually caused by advancing age.[74] VC is present in high amounts in the aqueous humor and is therefore thought to play a role in protecting the lens from oxidative stress in the aqueous humor.[75] A statistical survey has shown that dietary intake of VC can reduce the risk of age-related cataracts.[76] Moreover, several studies and case–control studies have shown that individuals with a high dietary intake of VC exhibit a reduced risk of developing cataracts.[77–80] However, it is worth noting that the VC has the potential to generate free radicals intermediates and strong oxidizers, which can inflict damage to the biological tissue.[73] It has been demonstrated that VC can facilitate the formation of advanced glycation end products, which are responsible for the chemical aging of lens proteins.[81,82] Besides, high doses of VC have been shown to increase the prevalence of age-related cataracts in women.[73] Consequently, the effectiveness of VC for cataracts may be limited to a role in the prevention of nuclear cataracts.

Tumor Treatment

Epidemiological evidence suggests that VC or foods rich in VC may play a role in cancer prevention, as they have been shown to reduce the incidence of various tumors.[83,84] For example, Campbell et al[85] demonstrated that administering a high dose of VC daily was able to maintain optimal levels of AA within 48 hours, while simultaneously downregulating the activity of the HIF-1 pathway within tumor tissue. Nevertheless, there is a lack of consensus regarding the efficacy of VC in treating tumors. Two previous studies yielded disparate results.[86–89] Cameron and Pauling showed that high-dose VC improved the average survival rate of patients with advanced cancer. Conversely, two clinical trials by Creagan and Moertel indicated that VC did not confer a benefit in cancer treatment. A deeper examination of VC pharmacokinetics may elucidate the discrepancy in outcomes between the two administration methods. In the initial experiment, intravenous administration was used, while in the latter, oral administration alone was used. When doses of oral VC exceed 200 mg, the absorption of VC decreases, urinary excretion increases, and the bioavailability of VC decreases.[90] In contrast, intravenous administration bypasses intestinal absorption, resulting in a plasma concentration of VC that can reach pharmacological levels and thus exert efficacy.[91] Given that AA is susceptible to a pH-dependent autooxidation reaction to produce hydrogen peroxide (H_2O_2) (H_2O_2 is toxic to a variety of tumor cells[92–94]), high-dose intravenous AA can be used as a

prodrug to deliver H_2O_2 to tumors, thereby treating cancer.[95] Potential mechanisms of action for VC in cancer therapy include:

- AA is an important free-radical scavenger. The oxidation of a large dose of AA to DHA has been demonstrated to increase ROS, trigger oxidative stress, and lead to the apoptosis of tumor cells.[96] Yun et al[97] have provided evidence that human colorectal cancers carrying either KRAS or BRAF mutations are sensitive to high levels of VC. As a consequence of elevated DHA intake, the uptake of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was inhibited in cells with a high glycolytic rate and a mutation in either KRAS or BRAF.
- VC can enhance immune function, thus enhancing tumor immune surveillance during cancer initiation and progression.[98] Magrì et al found that in murine cancer models such as colorectal, breast, melanoma, and pancreatic cancers, VC potentiates adaptive immune responses against cancer cells and can be effectively combined with immune checkpoint therapy.[99]
- Outside the cell, AA autooxidation produces H_2O_2. When H_2O_2 accumulates to a certain concentration, it can diffuse across cells into tumor cells and inhibit tumor growth.[100]
- Collagen in the extracellular matrix is an important component of the physical barrier against cancer cell invasion and metastasis. AA has been proven to promote collagen formation and can inhibit cancer progression by preventing cancer cell invasion at a high dose.[100]

Additionally, alternative perspectives posit that the anticancer mechanism of VC may be classified into three distinct categories: targeting redox imbalance,[101] targeting epigenetic regulators,[102] and targeting HIF-1 signaling.[103]

Intravenous administration of VC can also be used as an adjunct to chemotherapy or radiotherapy. VC has been demonstrated to stimulate the production and activation of immune cells, thereby enhancing the immunity of patients.[84] VC has been shown to improve the therapeutic effect of certain cancer drugs. For example, Lee et al[104] applied gefitinib and AA combination therapy to non-small cell lung cancer cells, resulting in an additive effect on inhibiting cell proliferation. Meanwhile, it can also mitigate the general toxicity and cardiotoxicity of Adriamycin.[105] Combination therapy helps improve a patient's quality of life and physical function and minimizes toxicity associated with chemotherapy.[106] However, the safety of high-dose intravenous VC remains a topic of contention. Complications associated with intravenous AA administration include the formation of oxalate stones and hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.[107] Therefore, it is imperative to perform G6PD screening prior to intravenous VC administration.

Cardiovascular Disease

Several studies have shown that the incidence of coronary heart disease is inversely related to dietary VC intake, and large VC supplementation can reduce the incidence of CVD.[108–110] Nitric oxide (NO) is a potent vasodilator, mediating vascular smooth muscle relaxation and protecting endothelial function.[111,112] The current clinical trials showed that the VC plays an important role in maintaining the NO steady state in blood vessels. A single dose of VC has been demonstrated to enhance endothelial nitric oxide synthase (eNOS) activity, thereby promoting the synthesis of NO, and facilitating vasodilation.[113] Long-term supplementation of VC has been shown to mitigate the decline in vasodilation capacity associated with endothelial injury.[114] The administration of VC has been linked to beneficial outcomes in the context of vascular endothelial function as evidenced in both healthy subjects and patients with CVD.[115]

The production of NO in endothelial cells requires a variety of cofactors, including tetrahydrobiopterin (BH4).[116] Studies have shown that VC can diminish vascular oxidative stress and augment NO-mediated endothelium-dependent relaxation, which may be achieved by chemically stabilizing BH4 to enhance the activity of nitric oxide synthase (NOS).[117] Therefore, deficiency in VC affects the reduction status of BH4 and leads to decreased NO bioavailability, thereby exacerbating the progression of CVD.

Ginter proposed that the mechanism of VC in preventing CVD may also involve cholesterol metabolism, lowering blood pressure, and antioxidant effects.[118] High cholesterol and hypertension are important risk factors for the development of CVD. A deficiency in VC over an extended period will result in a reduction in the activity of cholesterol metabolic enzymes and thus reduce the conversion of cholesterol into bile acids.[119,120] This ultimately results in the accumulation of cholesterol in the body which can contribute to elevated cholesterol levels. Concurrently, long-term supplementation of VC has been demonstrated to reduce the risk of hypertension. The potential mechanism underlying this effect is that VC plays an antioxidant role, preventing the oxidation of low-density lipoprotein (LDL; oxidized LDL contributes to the vicious cycle of atherosclerosis [AS] by stimulating cell adhesion, producing ROS, and decreasing NO), and inhibits the proliferation of vascular smooth muscle involved in AS.[121–124] Furthermore, VC may also improve chronic inflammation through nonspecific antioxidant effects (chronic vascular inflammation is a part of CVD pathophysiology[125]), thereby improving the development of CVD.[111]

VC Promotes Skin Health

As the largest organ in terms of surface area in the human body, the skin serves as a protective barrier between the external environment and the body's internal tissues. The skin functions as a barrier to the invasion of the external environment, while simultaneously providing physical and chemical protection to the internal environment. VC has been demonstrated to facilitate collagen synthesis, inhibit melanin production, and protect against ultraviolet-induced oxidative damage, thereby playing an important role in maintaining optimal dermal health.[126]

VC mainly plays a role in promoting collagen synthesis in the proline and lysine hydroxylation process; the antioxidant

effect of VC is related to its structure, which can be reduced by the action of oxidants; in addition, VC can interfere with the action of tyrosinase, thereby affecting melanin production.[127] Tyrosinase is the rate-limiting enzyme in melanin synthesis, catalyzing the hydroxylation of *L*-tyrosine to form DOPA, which oxidizes to DOPA quinone. DOPA quinone is cyclized to dopamine, which is tautomerization to 5,6-dihydroxyindole-2-carboxylic acid (DHICA), and finally forms the DHICA-melanin subunit. VC interferes with melanin synthesis by reducing oxidized DOPA quinone, blocking the oxidation of DHICA, and interacting with copper ions in the active site of tyrosinase.[128]

Clinically, VC is commonly used in the treatment of atopic dermatitis, late-onset porphyrin skin disease, and a range of dermatological conditions including herpes zoster. Its primary role in cosmetics is to impart whitening and antiaging effects. The main ingredients of MAS063DP cream (Atopiclair) are grape seed extract, VC, vitamin E, hyaluronic acid, glycyrrhetinic acid, and shea butter.[129] Multiple clinical studies have demonstrated that this formulation is a safe, well-tolerated, and effective nonsteroidal therapy for the treatment of mild to moderate atopic dermatitis.[130–132] The drug is currently licensed in the United States and the European Union for the treatment of specific dermatological conditions, including dermatitis and contact dermatitis. In the treatment of other skin diseases, VC is employed in combination with other pharmaceutical agents or as an adjunct to physical therapy. Zinc, and clarithromycin combined with VC in the treatment of acne continue to demonstrate antibacterial efficacy against niacinomycin-induced acne, offering a novel avenue for the clinical use of antibiotics in acne therapy.[133] However, due to the issue of poor permeability, and stability,[1,134] the application of the VC prototype in topical skin preparations is limited. In general, it is necessary to expand the application range of applications for VC by designing VC derivatives or developing suitable dosage forms.[135,136] The emergence of microneedle technology and ion import technology has recently improved the permeability of VC, although there have been no large-scale clinical applications to date. Hence, the stability and permeability of VC must be improved to facilitate its clinical application in topical preparations.

In addition to the studies mentioned above, a joint study by the Chinese Academy of Sciences discovered that VC supplementation may impede the aging of the spinal cord.[137] By integrating transcriptomics, neurohistology, neuroelectrophysiology, and other disciplines, they identified a particular subtype of CHIT1-positive microglia in the spinal cord of older primates. These cells can activate SMAD signaling in motor neurons through paracrine CHIT1 protein, thereby contributing to the aging of the motor nerve. However, VC supplementation has been demonstrated to impede the aging and degeneration of spinal cord neurons. This study not only elucidates the potential role of VC in nervous system diseases but also indicates a novel avenue for postponing the aging of the human spinal cord and the management of geriatric diseases.

Perspectives and Conclusion

VC has a multitude of biological activities; however, its role in the field of medicine is currently in the exploratory phase, with only a limited number of large-scale clinical applications. These applications mainly focus on the role of adjuvant prevention and treatment. The primary reason for this situation lies in its extreme instability.[138] VC is easily degraded in the presence of water, oxygen, and metal ions under basic conditions, which undergoes a yellow color change.[1] Currently, the primary control measures are: controlling the oxygen content during the process, using anhydrous/nonaqueous preparations, reducing the pH value, adding antioxidants, and increasing the viscosity of the system.[134] In addition, the development of the delivery system, as well as derivatives of VC, may prove to be promising strategies to stabilize VC. The evolution of VC derivatives went through a process from binding to ionic salts to lipophilic derivatives. The structural modification improves VC's stability, but the majority of these derivatives lack direct antioxidant activity and must be converted to VC *in vivo*. As a hydrophilic esterified form of VC, magnesium ascorbate phosphate is currently the most common VC derivative with greater stability. However, the introduction of phosphate groups results in an increase in charge and a corresponding decrease in skin permeability.[127,139] Additionally, a substantial number of *in vitro* and *in vivo* experiments have been conducted with VC derivatives, yielding a multitude of contradictory results.[139] Consequently, further experimentation is necessary to comprehensively assess the overall impact of each derivative. The issue of permeability can be effectively addressed through the use of carriers, especially nanocarriers. Despite the promising potential of nanocarriers, the limitations of industrial technology and e-regulatory frameworks remain a significant challenge. Further research is needed to address these issues. By considering the *in vivo* fate of the delivery system and focusing on the composition, size, structure, and physical state of the carrier,[24] a more sophisticated carrier structure can be developed to ensure that VC has an optimal effect concentration at the treatment site.

Furthermore, consideration should be given to the compatibility of VC with other drugs. Patients with hypertension are at an elevated risk of developing cerebral hemorrhage, and as a result, the concurrent administration of antihypertensive drugs and VC has been demonstrated to exert a protective effect against cerebral hemorrhage. The combination of VC with anticoagulants has been observed to reduce the anticoagulant effect and shorten the prothrombin time, which is incompatible.[140] Therefore, although VC is a common vitamin, the use of VC should follow the advice and guidance of physicians.

In conclusion, as a multifunctional compound, VC exhibits a range of biological activities and has been demonstrated to have preventive and therapeutic effects on a variety of diseases. The stability and permeability of VC remain limitations to its clinical application. It is anticipated that further developments in the form of new applications of VC will

emerge in the future, with the potential to enhance the treatment of a range of diseases.

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Conflict of Interest
None declared.

References

1 Caritá AC, Fonseca-Santos B, Shultz JD, Michniak-Kohn B, Chorilli M, Leonardi GR. Vitamin C: one compound, several uses. Advances for delivery, efficiency and stability. Nanomedicine 2020; 24:102117
2 Levine M, Rumsey SC, Daruwala R, Park JB, Wang Y. Criteria and recommendations for vitamin C intake. JAMA 1999;281(15): 1415–1423
3 Lykkesfeldt J, Michels AJ, Frei B, Vitamin C. Vitamin C. Adv Nutr 2014;5(01):16–18
4 Kinlin LM, Weinstein M. Scurvy: old disease, new lessons. Paediatr Int Child Health 2023;43(04):83–94
5 Palmieri B, Vadalà M, Laurino C. Nutrition in wound healing: investigation of the molecular mechanisms, a narrative review. J Wound Care 2019;28(10):683–693
6 Carr AC, Lykkesfeldt J. Factors affecting the vitamin C dose-concentration relationship: implications for global vitamin C dietary recommendations. Nutrients 2023;15(07):1657
7 Wang A, Luo J, Zhang T, Zhang D. Dietary vitamin C and vitamin C derived from vegetables are inversely associated with the risk of depressive symptoms among the general population. Antioxidants 2021;10(12):1984
8 Frei B, Birlouez-Aragon I, Lykkesfeldt J. Authors' perspective: what is the optimum intake of vitamin C in humans? Crit Rev Food Sci Nutr 2012;52(09):815–829
9 Grosso G, Bei R, Mistretta A, et al. Effects of vitamin C on health: a review of evidence. Front Biosci (Landmark Ed) 2013;18(03): 1017–1029
10 Ma N, Siegfried C, Kubota M, et al. Expression profiling of ascorbic acid-related transporters in human and mouse eyes. Invest Ophthalmol Vis Sci 2016;57(07):3440–3450
11 Corpe CP, Eck P, Wang J, Al-Hasani H, Levine M. Intestinal dehydroascorbic acid (DHA) transport mediated by the facilitative sugar transporters, GLUT2 and GLUT8. J Biol Chem 2013;288 (13):9092–9101
12 Washko PW, Wang Y, Levine M. Ascorbic acid recycling in human neutrophils. J Biol Chem 1993;268(21):15531–15535
13 Subramanian VS, Sabui S, Moradi H, Marchant JS, Said HM. Inhibition of intestinal ascorbic acid uptake by lipopolysaccharide is mediated via transcriptional mechanisms. Biochim Biophys Acta Biomembr 2018;1860(02):556–565
14 Tsiaoussis GI, Christaki E, Apidianakis Y. I can C clearly now: how EPEC inhibits gut vitamin C transport by dysregulating SVCT. Dig Dis Sci 2021;66(07):2140–2142
15 Subramanian VS, Srinivasan P, Wildman AJ, Marchant JS, Said HM. Molecular mechanism(s) involved in differential expression of vitamin C transporters along the intestinal tract. Am J Physiol Gastrointest Liver Physiol 2017;312(04):G340–G347
16 Levine M, Padayatty SJ, Espey MG. Vitamin C: a concentration-function approach yields pharmacology and therapeutic discoveries. Adv Nutr 2011;2(02):78–88
17 Rivers JM. Safety of high-level vitamin C ingestion. Int J Vitam Nutr Res Suppl 1989;30:95–102
18 Padayatty SJ, Levine M. Vitamin C: the known and the unknown and Goldilocks. Oral Dis 2016;22(06):463–493
19 Gęgotek A, Skrzydlewska E. Ascorbic acid as antioxidant. Vitam Horm 2023;121:247–270
20 Ahmed TA, Aljaeid BM. Preparation, characterization, and potential application of chitosan, chitosan derivatives, and chitosan metal nanoparticles in pharmaceutical drug delivery. Drug Des Devel Ther 2016;10:483–507
21 Alishahi A, Mirvaghefi A, Tehrani MR, et al. Chitosan nanoparticle to carry vitamin C through the gastrointestinal tract and induce the non-specific immunity system of rainbow trout (Oncorhynchus mykiss). Carbohydr Polym 2011;86(01):142–146
22 Thapa Magar K, Boafo GF, Li X, Chen Z, He W. Liposome-based delivery of biological drugs. Chin Chem Lett 2022;33(02): 587–596
23 Xiao Q, Li X, Liu C, et al. Liposome-based anchoring and co-encapsulation for combinatorial cancer therapy. Chin Chem Lett 2022;33(09):4191–4196
24 Maurya VK, Shakya A, McClements DJ, et al. Vitamin C fortification: need and recent trends in encapsulation technologies. Front Nutr 2023;10:1229243
25 Wechtersbach L, Ulrih NP, Cigic B. Liposomal stabilization of ascorbic acid in model systems and in food matrices. Lebensm Wiss Technol 2012;45(01):43–49
26 Łukawski M, Dałek P, Borowik T, et al. New oral liposomal vitamin C formulation: properties and bioavailability. J Liposome Res 2020;30(03):227–234
27 Jiao Z, Wang X, Yin Y, Xia J, Mei Y. Preparation and evaluation of a chitosan-coated antioxidant liposome containing vitamin C and folic acid. J Microencapsul 2018;35(03):272–280
28 Davis JL, Paris HL, Beals JW, et al. Liposomal-encapsulated ascorbic acid: influence on vitamin C bioavailability and capacity to protect against ischemia-reperfusion injury. Nutr Metab Insights 2016;9:25–30
29 Gopi S, Balakrishnan P. Evaluation and clinical comparison studies on liposomal and non-liposomal ascorbic acid (vitamin C) and their enhanced bioavailability. J Liposome Res 2021;31 (04):356–364
30 Callender SP, Mathews JA, Kobernyk K, Wettig SD. Microemulsion utility in pharmaceuticals: implications for multi-drug delivery. Int J Pharm 2017;526(1–2):425–442
31 Sawant RR, Vaze O, D'Souza GG, Rockwell K, Torchilin VP. Palmitoyl ascorbate-loaded polymeric micelles: cancer cell targeting and cytotoxicity. Pharm Res 2011;28(02):301–308
32 Xiao W, Fu Q, Zhao Y, et al. Ascorbic acid-modified brain-specific liposomes drug delivery system with "lock-in" function. Chem Phys Lipids 2019;224:104727
33 Luo Q, Jiang M, Kou L, et al. Ascorbate-conjugated nanoparticles for promoted oral delivery of therapeutic drugs via sodium-dependent vitamin C transporter 1 (SVCT1). Artif Cells Nanomed Biotechnol 2018;46(sup1):198–208
34 Inoue Y, Hibino M, Murata I, Kanamoto I. A nanocarrier skin-targeted drug delivery system using an ascorbic acid derivative. Pharm Res 2017;35(01):1
35 Kishimoto Y, Saito N, Kurita K, Shimokado K, Maruyama N, Ishigami A. Ascorbic acid enhances the expression of type 1 and type 4 collagen and SVCT2 in cultured human skin fibroblasts. Biochem Biophys Res Commun 2013;430(02):579–584
36 Abdullah M, Jamil RT, Attia FN. Vitamin C (Ascorbic Acid). 2023 May 1. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing LLC; 2024
37 De Giorgi F, Fumagalli M, Scietti L, Forneris F. Collagen hydroxylysine glycosylation: non-conventional substrates for atypical glycosyltransferase enzymes. Biochem Soc Trans 2021;49(02):855–866
38 Chugaeva UY, Raouf M, Morozova NS, Mahdavian L. Effects of *L*-ascorbic acid ($C_6H_8O_6$: Vit-C) on collagen amino acids: DFT study. Amino Acids 2023;55(11):1655–1664
39 Dengler VL, Galbraith M, Espinosa JM. Transcriptional regulation by hypoxia inducible factors. Crit Rev Biochem Mol Biol 2014;49 (01):1–15

40 Strowitzki MJ, Cummins EP, Taylor CT. Protein hydroxylation by hypoxia-inducible factor (HIF) hydroxylases: unique or ubiquitous? Cells 2019;8(05):384
41 Fischer AP, Miles SL. Ascorbic acid, but not dehydroascorbic acid increases intracellular vitamin C content to decrease Hypoxia Inducible Factor-1 alpha activity and reduce malignant potential in human melanoma. Biomed Pharmacother 2017;86:502–513
42 Piersma B, Wouters OY, de Rond S, Boersema M, Gjaltema RAF, Bank RA. Ascorbic acid promotes a TGFβ1-induced myofibroblast phenotype switch. Physiol Rep 2017;5(17):e13324
43 Kuiper C, Dachs GU, Currie MJ, Vissers MC. Intracellular ascorbate enhances hypoxia-inducible factor (HIF)-hydroxylase activity and preferentially suppresses the HIF-1 transcriptional response. Free Radic Biol Med 2014;69:308–317
44 Vissers MC, Gunningham SP, Morrison MJ, Dachs GU, Currie MJ. Modulation of hypoxia-inducible factor-1 alpha in cultured primary cells by intracellular ascorbate. Free Radic Biol Med 2007;42(06):765–772
45 Carr AC, Maggini S. Vitamin C and immune function. Nutrients 2017;9(11):1211
46 Nikolich-Žugich J. The twilight of immunity: emerging concepts in aging of the immune system. Nat Immunol 2018;19(01):10–19
47 Netea MG, Schlitzer A, Placek K, Joosten LAB, Schultze JL. Innate and adaptive immune memory: an evolutionary continuum in the host's response to pathogens. Cell Host Microbe 2019;25(01):13–26
48 Valacchi G, Muresan XM, Sticozzi C, et al. Ozone-induced damage in 3D-Skin Model is prevented by topical vitamin C and vitamin E compound mixtures application. J Dermatol Sci 2016;82(03):209–212
49 Zhong S, Zhou Q, Yang J, et al. Relationship between the cGAS-STING and NF-κB pathways-role in neurotoxicity. Biomed Pharmacother 2024;175:116698
50 Liu ZQ. Anti-oxidant in china: a thirty-year journey. Am J Chin Med 2019;47(05):1005–1024
51 Morante-Palacios O, Godoy-Tena G, Calafell-Segura J, et al. Vitamin C enhances NF-κB-driven epigenomic reprogramming and boosts the immunogenic properties of dendritic cells. Nucleic Acids Res 2022;50(19):10981–10994
52 Qi T, Sun M, Zhang C, Chen P, Xiao C, Chang X. Ascorbic acid promotes plasma cell differentiation through enhancing TET2/3-mediated DNA demethylation. Cell Rep 2020;33(09):108452
53 Bhoot HR, Zamwar UM, Chakole S, Anjankar A. Dietary sources, bioavailability, and functions of ascorbic acid (vitamin C) and its role in the common cold, tissue healing, and iron metabolism. Cureus 2023;15(11):e49308
54 Houten SM, Wanders RJ. A general introduction to the biochemistry of mitochondrial fatty acid β-oxidation. J Inherit Metab Dis 2010;33(05):469–477
55 Pekala J, Patkowska-Sokoła B, Bodkowski R, et al. *L*-carnitine–metabolic functions and meaning in humans life. Curr Drug Metab 2011;12(07):667–678
56 Lee H, Ahn J, Shin SS, Yoon M. Ascorbic acid inhibits visceral obesity and nonalcoholic fatty liver disease by activating peroxisome proliferator-activated receptor α in high-fat-diet-fed C57BL/6J mice. Int J Obes (Lond) 2019;43(08):1620–1630
57 Conway FJ, Talwar D, McMillan DC. The relationship between acute changes in the systemic inflammatory response and plasma ascorbic acid, alpha-tocopherol and lipid peroxidation after elective hip arthroplasty. Clin Nutr 2015;34(04):642–646
58 Tragni V, Primiano G, Tummolo A, et al. Personalized medicine in mitochondrial health and disease: molecular basis of therapeutic approaches based on nutritional supplements and their analogs. Molecules 2022;27(11):3494
59 Yuan Y, Liu C, Chen X, et al. Vitamin C inhibits the metabolic changes induced by tet1 insufficiency under high fat diet stress. Mol Nutr Food Res 2021;65(16):e2100417
60 Piskin E, Cianciosi D, Gulec S, Tomas M, Capanoglu E. Iron absorption: factors, limitations, and improvement methods. ACS Omega 2022;7(24):20441–20456
61 Hsieh Y-HPHaYP. Valence state of iron in the presence of ascorbic acid and ethylenediaminetetraacetic acid. J Agric Food Chem 1997;45(04):1126–1129
62 Bergamaschi G, Di Sabatino A, Pasini A, et al. Intestinal expression of genes implicated in iron absorption and their regulation by hepcidin. Clin Nutr 2017;36(05):1427–1433
63 Ganasen M, Togashi H, Takeda H, et al. Structural basis for promotion of duodenal iron absorption by enteric ferric reductase with ascorbate. Commun Biol 2018;1:120
64 Luo X, Hill M, Johnson A, Latunde-Dada GO. Modulation of Dcytb (Cybrd 1) expression and function by iron, dehydroascorbate and Hif-2α in cultured cells. Biochim Biophys Acta 2014;1840(01):106–112
65 Lane DJ, Bae DH, Merlot AM, Sahni S, Richardson DR. Duodenal cytochrome b (DCYTB) in iron metabolism: an update on function and regulation. Nutrients 2015;7(04):2274–2296
66 von Siebenthal HK, Moretti D, Zimmermann MB, Stoffel NU. Effect of dietary factors and time of day on iron absorption from oral iron supplements in iron deficient women. Am J Hematol 2023;98(09):1356–1363
67 Cook JD, Monsen ER. Vitamin C, the common cold, and iron absorption. Am J Clin Nutr 1977;30(02):235–241
68 Lee CM, Afshari NA. The global state of cataract blindness. Curr Opin Ophthalmol 2017;28(01):98–103
69 Kupfer C. Bowman lecture. The conquest of cataract: a global challenge. Trans Ophthalmol Soc U K (1962) 1985;104(Pt 1):1–10
70 Lee B, Afshari NA, Shaw PX. Oxidative stress and antioxidants in cataract development. Curr Opin Ophthalmol 2024;35(01):57–63
71 Llop SM, Papaliodis GN. Cataract surgery complications in uveitis patients: a review article. Semin Ophthalmol 2018;33(01):64–69
72 Alkadi H. A review on free radicals and antioxidants. Infect Disord Drug Targets 2020;20(01):16–26
73 Thiagarajan R, Manikandan R. Antioxidants and cataract. Free Radic Res 2013;47(05):337–345
74 Kodera S, Hirata A, Miura F, et al. Model-based approach for analyzing prevalence of nuclear cataracts in elderly residents. Comput Biol Med 2020;126:104009
75 Ishikawa Y, Hashizume K, Kishimoto S, et al. Effect of vitamin C depletion on UVR-B induced cataract in SMP30/GNL knockout mice. Exp Eye Res 2012;94(01):85–89
76 Bejarano E, Weinberg J, Clark M, Taylor A, Rowan S, Whitcomb EA. Redox regulation in age-related cataracts: roles for glutathione, vitamin C, and the NRF2 signaling pathway. Nutrients 2023;15(15):3375
77 Lim JC, Caballero Arredondo M, Braakhuis AJ, Donaldson PJ. Vitamin C and the lens: new insights into delaying the onset of cataract. Nutrients 2020;12(10):3142
78 Wei L, Liang G, Cai C, Lv J. Association of vitamin C with the risk of age-related cataract: a meta-analysis. Acta Ophthalmol 2016;94(03):e170–e176
79 Choi JH, Lee E, Heo YR. The association between dietary vitamin A and C intakes and cataract: data from korea national health and nutrition examination survey 2012. Clin Nutr Res 2020;9(03):163–170
80 Braakhuis AJ, Donaldson CI, Lim JC, Donaldson PJ. Nutritional strategies to prevent lens cataract: current status and future strategies. Nutrients 2019;11(05):1186
81 Fan X, Xiaoqin L, Potts B, Strauch CM, Nemet I, Monnier VM. Topical application of *L*-arginine blocks advanced glycation by ascorbic acid in the lens of hSVCT2 transgenic mice. Mol Vis 2011;17:2221–2227

82 Fan X, Sell DR, Hao C, et al. Vitamin C is a source of oxoaldehyde and glycative stress in age-related cataract and neurodegenerative diseases. Aging Cell 2020;19(07):e13176
83 van Gorkom GNY, Lookermans EL, Van Elssen CHMJ, Bos GMJ. The effect of vitamin C (ascorbic acid) in the treatment of patients with cancer: a systematic review. Nutrients 2019;11 (05):977
84 Peng H, Wu X, Wen Y. Plasma circulating vitamin C levels and risk of endometrial cancer: a bi-directional mendelian randomization analysis. Front Med (Lausanne) 2022;9:792008
85 Campbell EJ, Vissers MCM, Wohlrab C, et al. Pharmacokinetic and anti-cancer properties of high dose ascorbate in solid tumours of ascorbate-dependent mice. Free Radic Biol Med 2016; 99:451–462
86 Cameron E, Pauling L. Supplemental ascorbate in the supportive treatment of cancer: prolongation of survival times in terminal human cancer. Proc Natl Acad Sci U S A 1976;73(10):3685–3689
87 Cameron E, Pauling L. Supplemental ascorbate in the supportive treatment of cancer: reevaluation of prolongation of survival times in terminal human cancer. Proc Natl Acad Sci U S A 1978;75 (09):4538–4542
88 Creagan ET, Moertel CG, O'Fallon JR, et al. Failure of high-dose vitamin C (ascorbic acid) therapy to benefit patients with advanced cancer. A controlled trial. N Engl J Med 1979;301 (13):687–690
89 Moertel CG, Fleming TR, Creagan ET, Rubin J, O'Connell MJ, Ames MM. High-dose vitamin C versus placebo in the treatment of patients with advanced cancer who have had no prior chemotherapy. A randomized double-blind comparison. N Engl J Med 1985;312(03):137–141
90 Padayatty SJ, Sun H, Wang Y, et al. Vitamin C pharmacokinetics: implications for oral and intravenous use. Ann Intern Med 2004; 140(07):533–537
91 Stephenson CM, Levin RD, Spector T, Lis CG. Phase I clinical trial to evaluate the safety, tolerability, and pharmacokinetics of high-dose intravenous ascorbic acid in patients with advanced cancer. Cancer Chemother Pharmacol 2013;72(01):139–146
92 Zhang J, Simpson CM, Berner J, et al. Systematic identification of anticancer drug targets reveals a nucleus-to-mitochondria ROS-sensing pathway. Cell 2023;186(11):2361–2379.e25
93 Heer CD, Davis AB, Riffe DB, et al. Superoxide dismutase mimetic GC4419 enhances the oxidation of pharmacological ascorbate and its anticancer effects in an H_2O_2-dependent manner. Antioxidants 2018;7(01):18
94 Chen H, He W, Guo Z. An H_2O_2-responsive nanocarrier for dual-release of platinum anticancer drugs and O_2: controlled release and enhanced cytotoxicity against cisplatin resistant cancer cells. Chem Commun (Camb) 2014;50(68):9714–9717
95 Tovmasyan A, Sampaio RS, Boss MK, et al. Anticancer therapeutic potential of Mn porphyrin/ascorbate system. Free Radic Biol Med 2015;89:1231–1247
96 Gao X, Wei K, Hu B, Xu K, Tang B. Ascorbic acid induced HepG2 cells' apoptosis *via* intracellular reductive stress. Theranostics 2019;9(14):4233–4240
97 Yun J, Mullarky E, Lu C, et al. Vitamin C selectively kills KRAS and BRAF mutant colorectal cancer cells by targeting GAPDH. Science 2015;350(6266):1391–1396
98 Guo D, Liao Y, Na J, et al. The involvement of ascorbic acid in cancer treatment. Molecules 2024;29(10):2295
99 Magrì A, Germano G, Lorenzato A, et al. High-dose vitamin C enhances cancer immunotherapy. Sci Transl Med 2020;12(532): eaay8707
100 Du J, Cullen JJ, Buettner GR. Ascorbic acid: chemistry, biology and the treatment of cancer. Biochim Biophys Acta 2012;1826(02):443–457
101 Rawal M, Schroeder SR, Wagner BA, et al. Manganoporphyrins increase ascorbate-induced cytotoxicity by enhancing H_2O_2 generation. Cancer Res 2013;73(16):5232–5241
102 Camarena V, Wang G. The epigenetic role of vitamin C in health and disease. Cell Mol Life Sci 2016;73(08):1645–1658
103 Vissers MCM, Das AB. Potential mechanisms of action for vitamin C in cancer: reviewing the evidence. Front Physiol 2018; 9:809
104 Lee KE, Hahm E, Bae S, Kang JS, Lee WJ. The enhanced tumor inhibitory effects of gefitinib and *L*-ascorbic acid combination therapy in non-small cell lung cancer cells. Oncol Lett 2017;14 (01):276–282
105 Shimpo K, Nagatsu T, Yamada K, et al. Ascorbic acid and adriamycin toxicity. Am J Clin Nutr 1991;54(6, suppl):1298S–1301S
106 Fritz H, Flower G, Weeks L, et al. Intravenous vitamin C and cancer: a systematic review. Integr Cancer Ther 2014;13(04): 280–300
107 Ausman LM. Criteria and recommendations for vitamin C intake. Nutr Rev 1999;57(07):222–224
108 Kubota Y, Iso H, Date C, et al; JACC Study Group. Dietary intakes of antioxidant vitamins and mortality from cardiovascular disease: the Japan Collaborative Cohort Study (JACC) study. Stroke 2011; 42(06):1665–1672
109 Stepaniak U, Micek A, Grosso G, et al. Antioxidant vitamin intake and mortality in three Central and Eastern European urban populations: the HAPIEE study. Eur J Nutr 2016;55(02):547–560
110 Knekt P, Ritz J, Pereira MA, et al. Antioxidant vitamins and coronary heart disease risk: a pooled analysis of 9 cohorts. Am J Clin Nutr 2004;80(06):1508–1520
111 Tveden-Nyborg P, Lykkesfeldt J. Does vitamin C deficiency increase lifestyle-associated vascular disease progression? Evidence based on experimental and clinical studies. Antioxid Redox Signal 2013;19(17):2084–2104
112 Zoulikha M, Xiao Q, Boafo GF, Sallam MA, Chen Z, He W. Pulmonary delivery of siRNA against acute lung injury/acute respiratory distress syndrome. Acta Pharm Sin B 2022;12(02): 600–620
113 Oudemans-van Straaten HM, Spoelstra-de Man AM, de Waard MC. Vitamin C revisited. Crit Care 2014;18(04):460
114 Panday S, Kar S, Kavdia M. How does ascorbate improve endothelial dysfunction? - a computational analysis. Free Radic Biol Med 2021;165:111–126
115 Brown AA, Hu FB. Dietary modulation of endothelial function: implications for cardiovascular disease. Am J Clin Nutr 2001;73 (04):673–686
116 Mortensen A, Lykkesfeldt J. Does vitamin C enhance nitric oxide bioavailability in a tetrahydrobiopterin-dependent manner? *In vitro, in vivo* and clinical studies. Nitric Oxide 2014;36:51–57
117 Yuyun MF, Ng LL, Ng GA. Endothelial dysfunction, endothelial nitric oxide bioavailability, tetrahydrobiopterin, and 5-methyltetrahydrofolate in cardiovascular disease. Where are we with therapy? Microvasc Res 2018;119:7–12
118 Ginter E. Chronic vitamin C deficiency increases the risk of cardiovascular diseases. Bratisl Lek Listy 2007;108(09):417–421
119 Zhang PY, Xu X, Li XC. Cardiovascular diseases: oxidative damage and antioxidant protection. Eur Rev Med Pharmacol Sci 2014;18 (20):3091–3096
120 Pandya V, Hunsaker JJH, La'ulu SL, et al. Excessively low cholesterol and triglyceride levels in an apparently healthy patient. Clin Biochem 2021;96:78–81
121 Das UN. Vitamin C for type 2 diabetes mellitus and hypertension. Arch Med Res 2019;50(02):11–14
122 Yuan X, Li X, Ji Z, et al. Effects of vitamin C supplementation on blood pressure and hypertension control in response to ambient temperature changes in patients with essential hypertension. Clin Exp Hypertens 2019;41(05):414–421
123 Guan Y, Dai P, Wang H. Effects of vitamin C supplementation on essential hypertension: a systematic review and *meta*-analysis. Medicine (Baltimore) 2020;99(08):e19274

124 Xu JX, Su L, Chen L, Lin JX. Protection from vascular endothelial dysfunction in acute glycemic load-induced primary hypertension by vitamin C and E. Genet Mol Res 2014;13(03):7246–7255
125 Siti HN, Kamisah Y, Kamsiah J. The role of oxidative stress, antioxidants and vascular inflammation in cardiovascular disease (a review). Vascul Pharmacol 2015;71:40–56
126 Wang K, Jiang H, Li W, Qiang M, Dong T, Li H. Role of vitamin C in skin diseases. Front Physiol 2018;9:819
127 Pullar JM, Carr AC, Vissers MCM. The roles of vitamin C in skin health. Nutrients 2017;9(08):866
128 Ebanks JP, Wickett RR, Boissy RE. Mechanisms regulating skin pigmentation: the rise and fall of complexion coloration. Int J Mol Sci 2009;10(09):4066–4087
129 Patrizi A, Raone B, Neri I. Atopiclair. Expert Opin Pharmacother 2009;10(07):1223–1230
130 Tang MB, Leong KF, Ou LS, et al. Cost-effectiveness study of pediatric atopic dermatitis in Asia: atopiclair vs. regular emollient (AD-ATOP). J Drugs Dermatol 2015;14(02):169–175
131 Copley-Merriman C, Zelt S, Clark M, Gnanasakthy A. Impact of measuring patient-reported outcomes in dermatology drug development. Patient 2017;10(02):203–213
132 Foucher C, Bisson JF, Guy M, et al. A new moisturiser improves DNCB-induced atopic dermatitis-like symptoms and restores skin barrier function in BALB/c mice. Antiinflamm Antiallergy Agents Med Chem 2023;22(01):49–57
133 Iinuma K, Noguchi N, Nakaminami H, Sasatsu M, Nishijima S, Tsuboi I. Susceptibility of Propionibacterium acnes isolated from patients with acne vulgaris to zinc ascorbate and antibiotics. Clin Cosmet Investig Dermatol 2011;4:161–165
134 Stamford NP. Stability, transdermal penetration, and cutaneous effects of ascorbic acid and its derivatives. J Cosmet Dermatol 2012;11(04):310–317
135 Lee CA, Baek JS, Kwag DG, Lee HJ, Park J, Cho CW. Enhancement of skin permeation of vitamin C using vibrating microneedles. Transl Clin Pharmacol 2017;25(01):15–20
136 Al-Niaimi F, Chiang NYZ. Topical vitamin C and the skin: mechanisms of action and clinical applications. J Clin Aesthet Dermatol 2017;10(07):14–17
137 Sun S, Li J, Wang S, et al. CHIT1-positive microglia drive motor neuron ageing in the primate spinal cord. Nature 2023;624 (7992):611–620
138 Bedhiafi T, Idoudi S, Fernandes Q, et al. Nano-vitamin C: a promising candidate for therapeutic applications. Biomed Pharmacother 2023;158:114093
139 Enescu CD, Bedford LM, Potts G, Fahs F. A review of topical vitamin C derivatives and their efficacy. J Cosmet Dermatol 2022; 21(06):2349–2359
140 Zhu YZ. Study on incompatibility of vitamin C [in Chinese]. Guide of China Medicine. 2014;12(28):398–399