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VITAMIN C; PHARMACOKINETICS AND ITS PROPHYLACTIC APPROACH TO COMBAT ANTIMICROBIAL DISEASES

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Abstract

The role of vitamin C in the prevention and treatment of numerous illnesses and disorders has been documented for millennia. It is quite useful in the fight against microbiological infections. It has a wide-ranging effect on microorganisms. It combats harmful germs found in food. It has the ability to stimulate lymphocytes and natural killer cells, thus aiding in the battle against microorganism-caused disorders. As a result, it has pleiotropic physiological effects linked to a variety of disorders, including the common cold, sepsis, acute respiratory distress syndrome (ARDS), and, most importantly, COVID-19. It has a complex pharmacokinetic profile. Absorption and elimination are highly dose-dependent and primarily regulated by a collection of saturable sodium-dependent vitamin C transporters (SVCTs). Genetic polymorphisms, environmental influences, and lifestyle decisions all influence its homeostasis. Vitamin C dietary dose depends on different age groups, health condition and lifestyle of anybody.

Keywords: Ascorbic Acid (ASC), Vitamin C, Pharmacokinetic, Sepsis, Antimicrobial, Antiviral, Antioxidant, Common Cold, COVID-19.

1. INTRODUCTION

Vitamin C or L-Ascorbic acid (ASC) is a water-soluble vitamin that cannot be synthesized in humans and must be supplemented through diet. It was initially gleaned from the ox adrenals by the Nobel Laureate scientist, Albert Szent-Györgyi at Cambridge University and Mayo Clinic between the years of 1927 and 1930, by unraveling the function of this

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essential vitamin for the cure of physiological diseases. Vitamin C has several nutraceutical qualities; however, its deficiency causes a variety of problems such as scurvy, diabetes, cardio vascular disorders, pregnancy troubles, weakness, gum leaking, and several others (Deruelle & Baron, 2008) (**Figure 1**).

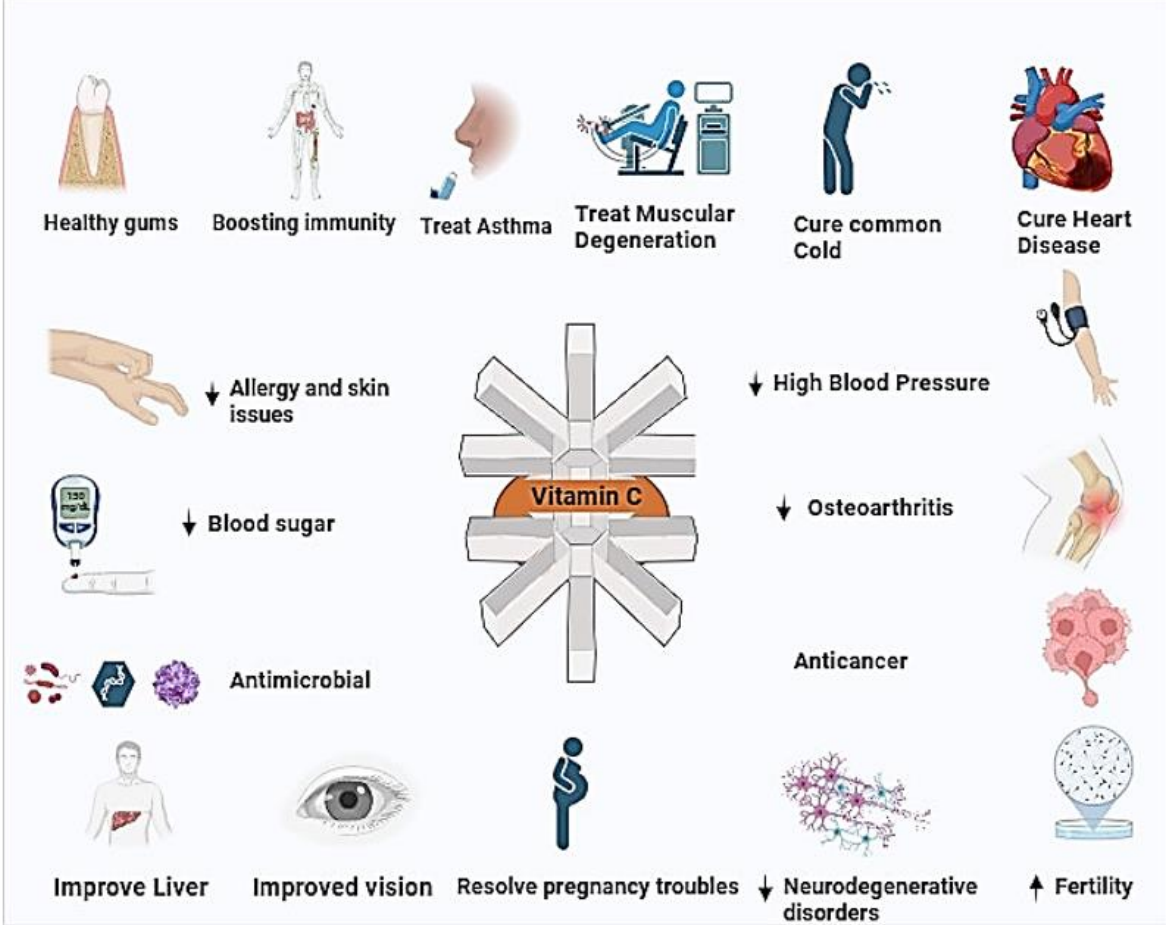

Figure 1: The Importance of Vitamin C in Human Health

These health-related difficulties can be resolved by consuming vitamin C-rich foods.

It could be found in many fruits and vegetables, although it is especially plentiful in citrus fruits, kiwi, mangoes, papaya, tomatoes, broccoli, strawberries, and pepper.

There are various additional sources of it **(Table 1)**.

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Table 1: Dietary Sources and Content of Vitamin C mg/100g- [a] Fresh Weight, [b] dry weight [c] juice; mg/100 mL of [d] juice (Doseděl *et al.,* 2021).

Family	Scientific Name	Generic Name	Vitamin C content
Fruits			
Rosaceae	*Pyrus communis* L.	Pear	7-29 [a]
Rosaceae	*Malus domestica* Borkh.	Apple	11-35 [a]
Rutaceae	*Citrus reticulata* Blanco	Mandarin	27 [a]
Rosaceae	*Fragaria virginiana* Duchesne	Strawberry	65 [a]
Rutaceae	*Citrus limon* (L.) Osbeck.	Lemons	30-31 [a]
Phyllanthaceae	*Phyllanthus emblica* L.	Emblic	469 [a]
Myrtaceae	*Psidium guajava* L.	Guava	89-980 [a]
Anacardiaceae	*Anacardium occidentale* L.	Cashew apple	555 [a]
Myrtaceae	*Myrciaria dubia* (Kunth) McVaugh	Camu-Camu	850-5000 [a]
Oxalidaceae	*Averrhoa carambola* L.	Star fruit	1626 c
Oxalidaceae	*Averrhoa bilimbi* L.	Bilimbi	2698 c
Combretaceae	*Terminalia ferdinandiana* Exell	Kakadu Plum	1360-22490 [b]
Vegetables			
Solanaceae	*Solanum tuberosum* L.	Potato	8–30 [a]
Solanaceae	*Capsicum annuum* L.	Pepper	107–154 [a]
Brassicaceae	*Brassica oleracea var*.	Broccoli	25–130 [a]
Fermented Vegetables			
Brassicaceae	*Brassica oleracea var. capitata* (L.) Alef.	Sauerkraut	103–277 [b]
Medicinal Herbs & Plants			
Apiaceae	*Coriandrum sativum* L.	Coriander	48–98 [a]
Eleagnaceae	Hippophaë *rhamnoides* L.	Sea buckthorn	70–1320 [d]

It is absorbed in the buccal cavity by passive diffusion, whereas in gastrointestinal tract absorption is by active sodium dependent vitamin C transporters (SVCT) (Nishiyama *et al.,* 2004). It is also available in the form of tablet and supplemented in many multi-vitamin formulations. U.S department of agriculture (USDA) and National cancer institute (NCI) recommended to add at least five fruits and vegetables in daily eating pattern. Food consumption according to this recommendation results in ingestion of 200-300 mg of vitamin C as per the fruit and vegetable selection pattern. Apart from the fact that vitamin C is readily available in different fruits and vegetables, but a survey conducted by National Health and Nutrition Examination Survey concluded that intake of vitamin C in diet among males and females is very low which is estimated to be around 84 mg and 73 mg, respectively (Cantin, Moreno, & Gogorcena, 2009).

Vitamin C possesses the ability to act as an antioxidant by reducing distinct molecules and can be oxidized to dehydroascorbic acid (DHA) which can be reduced back to ascorbic acid, The importance of vitamin C in human health thereby restoring its full biological activity (Umakanthan *et al.,* 2020).

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A sufficient intake of vitamin C imparts various physiological benefits and catalyzes biochemical reactions in the body. Although some animal species can integrate vitamin C in their liver and kidney but human beings have lost the gene, particularly the enzyme which imbues the final stage of the Ascorbic acid synthesis, during the evolution period by various mutations (Aliev *et al.,* 2011). However, the evolutionary period resulted in the improved capability to inhibit vitamin C deficiency by modifying the pharmacokinetics involving improved absorption, assimilation, recycling and renal uptake which is generally extremely complex. Vitamin C's transport in the intestine, its distribution in the body's tissues, and its reuptake by the kidneys is mainly carried out via a group of proteins called the sodium-reliant vitamin C transporter (SVCT) family (Wohlrab *et al.,* 2017). These proteins characteristically use the energy of sodium ions to move vitamin C across cell membranes, creating high concentrations of the vitamin in some areas of the body. This process is responsible for the unique ways that vitamin C is distributed and processed in the body at normal levels. Although, the difficulty in understanding how ASC is transported across biological membranes due to its hydrophilic nature has puzzled pharmacologists. However, studies have manifested that active transport of vit C is necessary for survival, and variations in this transport process may impact an individual's vit C level. High doses of vit C can be administered through parenteral means, such as intravenous infusion. Additionally, the recycling of vitamin C may be inadequate during disease or in smokers, requiring increased intake to maintain homeostasis. Moreover, Vitamin C executes a consequential role in collagen biosynthesis and repair, which is necessary for the integrity of connective tissues, mucosal epithelia, and basement membranes. This is crucial for adequate invigoration of wounds, bone development, and preventing devastating periodontal diseases. It also contributes in the synthesis pathway of carnitine, redox reactions, synthesis of adrenal steroids and catecholamines, digestion of amino acids and cholesterol, and iron absorption (Umakanthan *et al.,* 2020).

Vitamin C has antimicrobial properties, which can reduce the occurrence of infection, and has immunomodulatory effects, specifically at high levels. It is a promising approach to fight off and fend off bacterial infections without antibiotics. Notably, even under neutral pH circumstances, vitamin C can prevent the development of *S. aureus* and *streptococci* (Mousavi *et al*., 2019). According to Hassuna *et al*., 2023 vitamin C might significantly improve UTI in experimental mice whether used as an antibacterial and anti-biofilm agent alone or in conjunction with antibiotics. According to Majtan et al., 2020, combining honey and vitamin C may stimulate intracellular generation of reactive oxygen species in bacterial cells, but the precise biological pathways deserve additional exploration (Majtan et al., 2020).

Nevertheless, it's important to note that food storage, processing, and preparation can lead to vitamin C degradation, which highlights the need for appropriate dietary supplementation to prevent deficiency (Mousavi et al., 2019; Carr and Rowe, 2020). Bacterial biofilm may lead to secondary contamination of food during the manufacturing/processing stage, necessitating the development of innovative strategies for its efficient eradication. Food additives, such as vitamin C, which is currently utilised in the food business as an antioxidant, may be a feasible alternative. Przekwas *et al*.,

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2020 speculate that the addition of vitamin C may aid in the removal of bacterial biofilms. Thus, all of these researches demonstrate the importance of vitamin C in disease prevention (Przekwas *et al*., 2020).

The present review presents role of vitamin C in treating microbial diseases and the pharmacokinetics of vit C and its mechanism, which show how absorption, bioavailability, distribution, metabolism, and excretion start and vary depending on the route of administration.

2. BIOCHEMISTRY

Vitamin C is a six-carbon lactone, also known as 'l-ascorbic acid' or 'l-ascorbate' is a water-soluble vitamin necessary for normal growth and development. It is unique among vitamins for several reasons, abundantly present in many foods but fruits and vegetables are the rich source (Umakanthan *et al.,* 2020). Another unique aspect of this vitamin is that it is synthesized from glucose in liver but only by a few vertebrate or mammalian species, not by the humans. Oxido-reduction properties of vitamin C are responsible for biochemical functions taking part in the synthesis of collagen and carnitine as co-factor (Aliev *et al.,* 2011). Moreover, it also plays a significant role in synthesis and release of type IV collagen, while it also stimulates the growth and RNA expression of type III collagen but not the expression of type 1 collagen expression in humans' osteoblast. Collagen comprises the major portion of structural protein forming skin, vessels, bones and teeth. Gulonolactone oxidase enzyme is essential for synthesis of the ascorbic acid and is absent in mammalian species (Philips and Margaus, 2022). From a structural point of view, it acts as a free radical scavenger and electron donor due to conjugation of double bonds which results in loss of electron making semi-dehydroascorbate (SDA). It is the more stable and fairly unreactive radical with the half-life of 10^{-5}seconds. It prevents the oxidation of other compounds by donating its electrons. Sometimes it is also oxidized in the process upon loss of another electron forming dehydroascorbic acid (DDA). Formation of both SDA and DDA is mediated by various biological systems and oxidants that includes metals as copper and iron, ROS, molecular oxygen, hypochlorous acid, superoxide and hydroxyl radical. These both states can be reduced back to ascorbic acid through enzyme pathways or reducing compounds such as glutathione (Javier and Sergi, 2016). But due to the absence of gulonolactone oxidase enzyme in humans, there is only partial reduction back to ascorbic acid, therefore all the oxidized ascorbic acid is not fully recovered which ultimately results in hydrolysis of irreversible 2,3 diketogulonic acid which is further metabolized into xylose, xylonate, lyxonate and oxalate (MoustASCid *et al.,* 2022).

3. VITAMIN C AND ITS PHARMACOKINETICS

Pharmacokinetics is the study of how drugs are absorbed, distributed, metabolized, and excreted. It is built on a variety of theoretical models, each of which has certain criteria that must be met for them to be considered valid. Vitamin C is widely different than usual orally administered low molecular weight drugs in their pharmacokinetic properties

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(Lykkesfeldt, 2020). However, inadequate scrutiny to the nonlinearity of vit C pharmacokinetics has resulted in a misimpression of much of the clinical literature, as previously reappraised (Lykkesfeldt & Tveden-Nyborg, 2019).

3.1. Oral Route Administration

Oral ingestion of Vitamin C, either through food sources or by the supplements, is the primary route it is consumed. For individuals with certain medical conditions or poor Vitamin C levels, such as smokers, their dietary uptake may be inadequate to meet their needs.

I. Absorption

Vitamin C predominantly exists in two configurations in the body; i) ASC (reduced form) and ii) DHA (oxidized form), with the previous one being the most prevalent. The total available vit C in the body is made up by combined pool of ASC and DHA. There are three potential ways for vitamin C to cross the cell membrane: 1) active transport; 2) passive diffusion; and 3) facilitated diffusion.

Active transport enacts its significance in vitamin C absorption. The absorption of ASC is dose-dependent and based on saturable active transport and is sodium-reliant. The SVCT family of transporters, specifically SVCT1, is responsible for this active transport. However, the release of vitamin C into the bloodstream is not well understood and may involve unknown mediums or transporters. ASC discharge may take place via volume-susceptible anion mediums in the basolateral membranes of epithelial cells, but this has not been validated in all cell types (Frasca *et al.,* 2023).

Passive diffusion is unlikely to play a significant role in vitamin C uptake because it is highly water-soluble and predominantly in its anionic configuration at neutral pH. Facilitated diffusion occurs through carrier proteins and relies on an electrochemical gradient. DHA has been observed to contend with glucose for transmission by glucose transporters, which could explain the indistinguishable bioavailability of ASC and DHA as vitamin C sources (Malo & Wilson, 2000) (**Figure 2**).

II. Distribution

The dissemination of ascorbic acid (ASC) in the human body is highly compartmentalized and primarily occurs via active transport, rather than simple diffusion. Glucose transporters (GLUTs) are not observed to contribute a significant function in the transport of ASC over the membranes. Erythrocytes are an exception, as they do not contain the specific transporters for ASC i.e., (SVCTs) but are inadequate to uptake ASC by facilitated diffusion (Hasselholt *et al.,* 2015). Red blood cells are capable of recycling ASC to DHA and control an intracellular level resembling plasma. The recycling capability of red blood cells may account for considerable antioxidant reservoir in vivo. Recent studies concludes that ASC is significant for the structural cohesion of red blood cells and that intracellular Red blood cells ASC is important to keep up ASC plasma level in vivo (Lindblad *et al.,* 2013).

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Vitamin C uptake and distribution are mediated by two transporters: SVCT1 and SVCT2. SVCT1 has a high volume but low attraction for ASC, while SVCT2 transporter keeps low volume but high affinity. The brain is particularly dependent on SVCT2 to maintain proper function, as studies on mice without the Slc23a2 gene, which codes for SVCT2, have shown that they experience severe brain haemorrhage and high perinatal mortality. Additionally, the brain is unable to store ASC even while insufficiency and is one of the first organs to re-establish homeostasis during repletion.

Nonetheless, the level of expression of the SVCT2 transporter in the cells of each tissue contributes a pivotal function in determining the amount of vit C present (García *et al.,* 2005). However, research has shown that even within a single organ, such as the brain of guinea pigs, there can be significant variations in vitamin C levels between different regions. This suggests that other factors, such as the presence of specific cell types or post-translational modifications of the SVCT2 protein, may also play a role in determining vitamin C levels.

III. Metabolism

The antioxidant properties of ascorbic acid can be demonstrated by its metabolism in the mammals. It can be synthesized by uronic acid pathway from glucose and galactose in plants and animals. The molecule's enediol structure makes it a strong electron donor in biological reactions, allowing it to transport diminishing equal to that of a cofactor or free radical quencher. However, in this process, ASC is oxidized to the opposing stable radical intermediate, ascorbyl free radical. This intermediate can be disproportionate to DHA, which is effectively decreased intracellularly by various cell types, additionally by protecting the ascorbic acid pool (Frasca *et al.,* 2023). The yield of vitamin C is ultimately correlated to the catabolism of deoxyhexanoic acid, which takes place by hydrolysis and decarboxylation, resulting in the breakdown of the molecule and entry into the pentose phosphate channel for additional degeneration.

IV. Excretion and Reuptake

The uptake of ASC in epithelial cells is controlled through high capacity/low-attraction SVCT1 transporter, while distribution to other tissues is mainly controlled by the low capacity/high-affinity SVCT2. The paragraph also elucidate that the human brain has remarkable retention of ASC during deficiency and that the pathway(s) behind the distinctive consistent level of ASC in various tissues is still obscured. Furthermore, the metabolism of ASC is linked to its antioxidant function and is ultimately oxidized to the ascorbyl free radical state. Additionally, it is also pointed out that ASC is discharged by the route of kidneys, where the glomerulus undergoes the filtration, and concentrated in the pre-urine, but the reuptake of ASC is regulated by saturable active transmission by SVCT1.

Concerning the absorption and reabsorption of vit C in the body, the SVCT1 protein holds significance, as demonstrated by research on mice without the Slc23a1 gene which codes for SVCT1. These mice have a greatly increased excretion of vitamin C, lower levels of vitamin C in the body, and a higher mortality rate. Studies have also shown that certain

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genetic variations in the human SVCT1 gene can lead to a lifelong state of vitamin C insufficiency, regardless of how much vit C is consumed (Meydani *et al.,* 2003). The reabsorption of vitamin C by the kidneys is highly relied on the level of vit C in the body. Research has shown that the rate of discharge of vit C by the kidneys stretches from 0 to 1 relying on the individual's vit C status. The fact that the discharge ratio is about 1 for ingestion greater than 500 mg/day in healthy humans manifest that passive resorption of vitamin C does not contribute an important function in the kidneys.

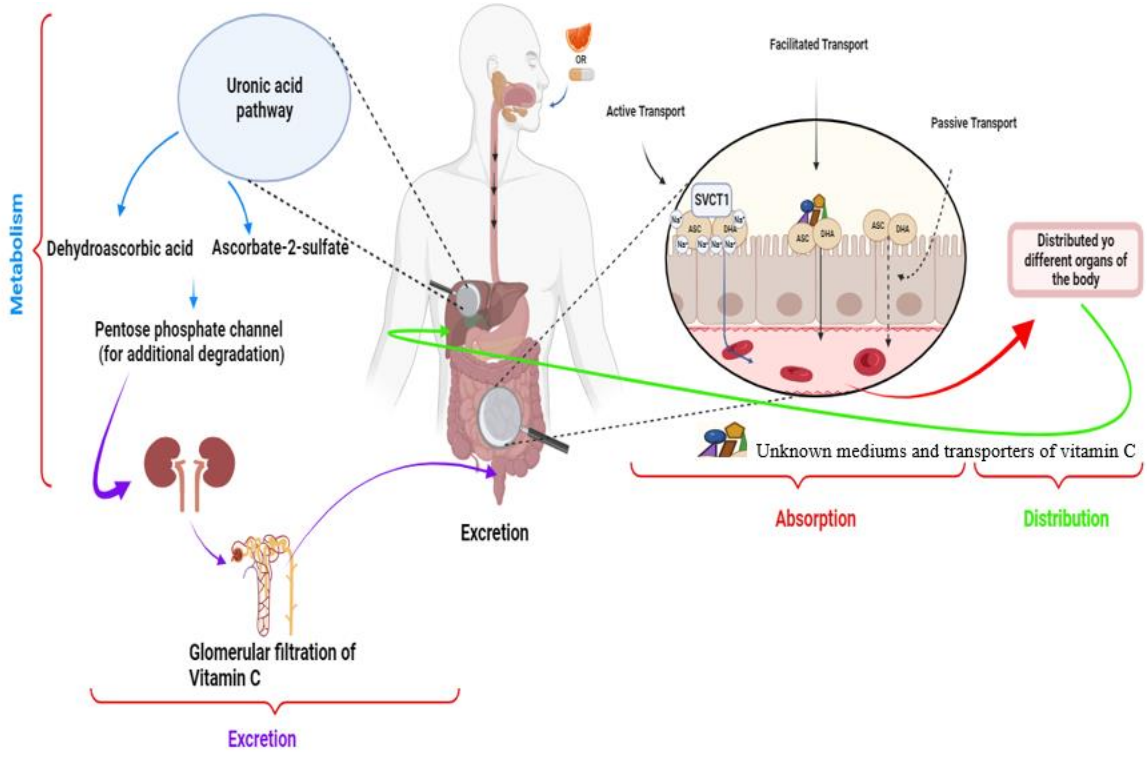

Figure 2: The Pharmacokinetics of Vitamin C Oral Administration

3.2. The Intravenous Route of Administration

I. Absorption

Administering drugs directly into the bloodstream through an IV allows for predictable and consistent plasma concentrations, as well as 100% bioavailability. This is particularly useful for Vitamin C, as IV administration allows for bypassing the absorption limitations of oral ingestion and achieving much higher plasma concentrations. Typically, Vitamin C is administered through intravenous infusion, which results in a consistent plasma level that remains equilibrated until the imbuing is stopped. Studies have manifested that there is a linear correlation between the dose of vit C and the maximum plasma concentration (Cmax) around 70 g/m^2 in human beings, resultant to a plasma level of up to 50 mM (Frasca *et al.,* 2023). However, there's still need of more research to evaluate if 50 mM is the upper limit of steady-state Vitamin C concentration in the plasma.

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II. Distribution

The distribution of Vitamin C following IV infusion is affected by the blood circulation to various tissues in the body (Lim, 2014). While normal tissues can handle millimolar plasma concentrations without issue, there is a particular interest in how Vitamin C affects poorly vascularized tumors. Studies have shown that at high levels, vit C can be injurious to cancerous cells but not to the normal cells, perhaps by a pro-oxidant role. Research using mouse models has found that daily injections of high-dose Vitamin C was significant to retard tumor proliferation and inhibit a particular transcription factor. Moreover, it was concluded that the elimination of Vitamin C from tumors was particularly suppressed as opposed to normal tissue, which may help preserve the impact of Vitamin C between imbuing. Research has used multi-layered cellular structure, which comprises over three dimensions and the pharmacokinetic model used to evaluate Vitamin C diffusion and transport measures through dense tissue in vitro, and concluded that supraphysiological level of Vitamin C, which can only be achieved by IV infusions, are necessary for efficacious transmission of Vitamin C into poorly vascularized tumors. Overall, it's known that normal body imbibition achieved by oral ingestion will not possible to diffuse to make up for the distance between vessels in typical well-perfused tissue, and thus give adequate vit C for the whole body. In comparison to that, this diffusion distance is inadequate to improve the vit C level of tumors with poor vascularization, which necessitate more than millimolar concentrations plasma level for efficacious Vitamin C diffusion. Although, there is limited information available on organ and tissue homeostasis followed by intravenous infusion of high-level Vitamin C (Frasca *et al.,* 2023).

III. Metabolism & Excretion

When ASC, is administered intravenously in high doses, it is quickly eliminated from the body through the kidneys. This results in a constant life span of about 2 hours and the elimination kinetics are first order. Studies have shown that after discontinuing the infusion, normal amount of L-ascorbic acid in the body are restored within 16 hours. However, in poorly vascularized tumor tissue, vitamin C levels may remain elevated for up to 48 hours due to the hypoxic tumor environment and the delayed clearance caused by poor blood flow in the area. This has been proposed as a possible mechanism for the potent use of high-level vitamin C in cancer ministration.

4. ANTIMICROBIAL ACTIVITY OF VITAMIN C

Vitamin C is widely known for acting as an antimicrobial agent against microbial species, i.e., *Mycobacterium tuberculosis*, which is the causative agent of tuberculosis, since the 1930s. A study from 1933 demonstrated that guinea pigs that were given tuberculosis sputum and deficient in vitamin C developed intestinal tuberculosis, while those that were treated with vitamin C-rich tomato juice did not acquire that. Initially, it was concluded that the antimicrobial properties of vit C were due to its ability to lower pH (Wohlrab *et al.,* 2017). While, a subsequent research showed that vitamin C had potent antimicrobial effects against group A bacteria, i.e., hemolytic streptococci, in a nearly neutral pH environment (Høiby *et al.,* 2010).

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Later researches investigated the antibacterial impact of vitamin C on several bacterial pathogens using microdilution assays. The results showed that vitamin C level of 0.31 mg/mL were effective in inhibiting the proliferation of *Pseudomonas aeruginosa* and 0.15 mg/mL inhibited the multiplication of *Staphylococcus aureus*. Vitamin C also efficaciously inhibited formation of biofilm by methicillin-resistant S. aureus and had antibacterial effects against *Enterococcus faecalis* at a low concentration. However, the antibacterial action of vitamin C appear to be dependent on the bacterial strain and level, as appeared by its impact on the growth of *Escherichia coli* ATTC 11775 strain (Hassuna *et al.,* 2023).

When combined with other agents, vitamin C can enhance their antibacterial effects, including epigallocatechin gallate opposed to multidrug-resistant bacteria like MRSA and deferoxamine against Gram-positive cocci and Gram-negative bacilli. Vitamin C along with lactic acid decreased the multiplication of E. coli O157:H7 in carrot juice or brain heart infusion broth. In contrary to that, another research manifested that it decreases the resistance of E. coli MG1655 to streptomycin. The combination of vitamin C along with the natural extracts like white tea and pomegranate rind also manifested improved anti-S. aureus characteristics (Umakanthan *et al.,* 2020).

4.1. Antimicrobial Influence of Vitamin C on Foodborne Gram-Negative Bacteria

4.1.1. Anti-Helicobacter Impact

A study found that 10-20 mg of vit C per ml could efficaciously inhibit the proliferation of bacteria i.e., Helicobacter pylori under low oxygen conditions. However, under regular oxygen conditions, the same concentration of vitamin C actually helped the bacteria survive. This could be because of the antioxidant characteristics of vit C, protecting bacteria from the adverse impact of reactive oxygen species (Teafatiller *et al.,* 2023). After a week of treatment with 10 mg of daily use of vit C, the amount of H. pylori bacteria in the stomachs of infected gerbils was significantly reduced. This is supported by clinical studies that found more effective eradication of H. pylori in humans treated along with vitamin C. Furthermore, vitamin C as the L-ascorbic acid-2-glucoside was able to counteract oxidative stress, induce multiplication, and decrease cellular activeness in a human gastric adenocarcinoma cell line infected with H. pylori.

4.1.2. Anti-Salmonella Impact

It has been evident by the research that vit C hadn’t imparted any specific antimicrobial action against Salmonella specie such as *Salmonella Enteritidis.* Contrary to that, vit C impart antibacterial action against *Salmonella Enteritidis* species in an in vitro experiments in which the intestine and a broiler-digestive model which includes the crop compartment, the proventriculus was employed (Hernandez-Patlan *et al.,* 2018). Coincidentally, in the crop compartment, only the vit C can efficaciously act against inhibiting *Salmonella* growth as opposed to its combination with boric acid and curcumin. While, in the case of proventriculus and intestine, the combination of vit C, curcumin and boric acid collectively exude a preventative action against proliferation of *Salmonella Enteritidis*. Moreover, recent research has unravelled the significant antibacterial action of ascorbic acid with the combination of copper and linalool. This combination was

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displayed by scanning electron microscopy employing *V. Fluvialis* on the bacterial morphology and manifested acute membrane injuries however the toxicity appraised in human embryonic kidney kidney (HEK293) cells at symbiotic congregation (16.3 μM, 8 mM, and 1.298 mM vitamin C) was found to be none (Gan *et al.,* 2020).

4.1.3. Anti-viral and Anti-pathogenic Impact

Research has indicated that vit C, particularly structured as DHA, can inhibit the proliferation of viruses such as herpes simplex virus type-1, poliovirus type-1, and influenza virus type A. Vitamin C has also been shown to inactivate the rabies virus in a laboratory setting. Furthermore, vitamin C has demonstrated anti-parasitic effects, as seen in reduced parasite counts in contaminated mice when cured with vitamin C. Additionally, vitamin C has anti-fungal properties, as demonstrated by its reduction of Hsp90-moderated morphogenesis in Candida albicans and its low-level fungistatic activities against this fungus (Umakanthan *et al.,* 2020). These characteristics of vitamin C are likely because of immunomodulatory effects as well.

4.2. Vitamin C's Anti-Sepsis Role

Sepsis proves to be fatal condition that occurs due to an uncontrolled host response to infection, followed by organ malfunctioning. The incidence of sepsis is on the rise globally, with millions of cases and deaths occurring each year (Fleischmann *et al.,* 2016). Acute respiratory distress syndrome is an acute form of sepsis-activated lung damage and is a calamitous complication that leads to higher death rates. Elderly patients with comorbidities are particularly vulnerable to sepsis. Reactive nitrogen and oxygen species generated during sepsis followed by oxidant-prompted stimulation of transcription factors that operate inflammatory cytokine and chemokine expression, endothelial disruption, and loss of microvascular barrier characteristics. Clinical experiments focusing mediators of inflammation have not appropriately decreased sepsis death rate, manifesting that a more "pleiotropic" type of therapy that can barricade multiple pathways is necessary (Umakanthan *et al.,* 2020). Currently, antibiotics, "source control," and administrating hemodynamic stability with fluid management and vasopressors are the crutch therapy for sepsis. Lately, surging indications manifests that vitamin C may be a favourable treatment for sepsis (A. C. Carr & Lykkesfeldt, 2023).

Vitamin C’s potential to regulate the neutrophil role and thwart neutrophil extracellular trap formation assistance to the avoiding of ARDS in sepsis. Regarding the sepsis, vit C has its importance as the use of high-level IV vitamin C (HDIVC) in the early stages of acute sepsis and septic shock may have potential advantages for subjects, including a decrease in organ damage, enhanced endothelial and epithelial barricade properties, increased neutrophil regulation, and a reduction in circulating cell-free DNA and syndecan-1 levels *(*Kashiouris *et al.,* 2019).

The function of HDIVC in sepsis-activated ARDS may also facilitate in diminishing the development of ARDS by regulating neutrophil potential and improving lung epithelial barricade properties.

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4.3. Oral Supplementation of Vitamin C Influencing Typical Cold

The typical cold is a viral infection that significantly influences the upper respiratory tract and can effect symptoms such as coughing, fever, sore throat, fatigue, and muscle pain (A. C. Carr & Lykkesfeldt, 2023). Although the rhinovirus is the most common pathogen responsible for the common cold, other viruses can also cause this condition.

Regarding vitamin C, Linus Pauling's speculation in the 1970s that increased ingestion of vitamin C could decreases the prevalence of colds by 45% and that the absolute daily intake should be at least 2.3 g piqued a widespread belief that vit C could fend off or treat the typical cold (Pauling, 1971). However, subsequent clinical studies failed to confirm these claims, and contemporary authors have refuted them. While high doses of vit C may not prevent viral infections in the generalized population, some people with a greater risk of viral infections, such as soldiers and athletes, may benefit from taking vitamin C supplements to support their immune system (Wohlrab *et al.,* 2017).

4.4. Effect of Vitamin C on B Lymphocytes

B lymphocytes are responsible for producing antibodies against invasive pathogens. Limited data is available on the regulation of ascorbic acid in B lymphocytes. In an earlier trial, animals subjected to 4-week ascorbic acid-free diet manifested a continuous increment in the amount of B-lymphocytes while the amount of T-lymphocytes reduced significantly. ASC-2G increased the number of viable mouse spleen B cells by about 70% and also improved the synthesis of IgM dose-dependently (Amakye-Anim *et al.,* 2000). One group manifested a slight dose-reliant increase of proliferation in murine IgM/CD40-activated B cells pre-treated with vitamin C. In human peripheral blood lymphocytes, ASC-2G increased the count of IgM and IgG-exuding cells after stimulation.

4.5. Effect of Vitamin C on Natural Killer (NK) Cells

Natural killer cells are kind of lymphocyte that plays a prominent function in the immune response in opposition to pathogens and tumours (Oh *et al.,* 2015). They are synthesized in the bone marrow and are inherent lymphoid cells, providing quick and antigen-free immunity. Natural killer cell cytotoxicity activity is focused on the non-existence of self MHC class I to segregate between typical and ailing cells (Umakanthan *et al.,* 2020). The effects of vitamin C on natural killer cell development and role have been investigated in various studies. ASC has been manifested to ameliorate the multiplication of mature natural killer cells in vitro and enhance the generation and growth of natural killer cell progenitors from hematopoietic stem cells (Huijskens *et al.,* 2015). The effect of ASC on natural killer cell function is contradictory, with some researches showing no distinction in killing capacity between natural killer cells cultivated with or without ascorbic acid, while others have shown a dose-reliant reduction or increase in natural killer cell-mediated death of target cells. ASC has also been shown to have a biphasic impact on natural killer cell cytostatic activity in healthy volunteers, with a slight decrease in accordance to a significant amelioration at 8 hours after supplementation. The impact of ASC on natural killer cell role in subjects with iron overload and β-thalassemia major may be associated to its antioxidant properties since these conditions are related with increased intracellular

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active oxygen species (Farmakis *et al.,* 2003). In a study using ASC-deficient mice, natural killer cells outlayed from ASC-depleted mice showed prominent reduction in killing capacity and decreased expression of reactive receptors and cytolytic proteins in comparison to ASC-supplemented mice and wild-type mice.

4.6. The Emerging Approach using Vitamin C in Treating COVID-19

For the previous 25 years, studies have shown that critically ill patients with conditions i.e., sepsis and conglomerate organ failure have low levels of vit C, which requires large dosage to regulate their blood levels (Migliorini *et al.,* 2022). Despite this, patients with sepsis are still given insufficient amounts of vitamin C. Clinical trials have indicated that IV ministration of high level of ascorbic acid to patients suffering from sepsis to ameliorate organ failure rate and reduces inflammation and tissue injuries hallmarks. However, vitamin C is efficacious when administered earlier in the diagnosis, and sustained administration can improve long-term outcomes. Vitamin C has been found to have several physiological functions in sepsis, including its antioxidant characteristics, acts as a cofactor for the synthesis pathway of vasopressors, and its function in leukocyte and platelet roles in human body, and endothelial and epithelial cell cohesion (Frasca *et al.,* 2023). These functions of vitamin C also associated to COVID-19-related sepsis and ARDS (**Figure 3**). Recent studies have manifested that vitamin C has several potential benefits for patients with COVID-19, including augmenting interferon levels, decreasing inflammatory markers, and preventing microthrombi formation (Tyml, 2017). Vitamin C has been identified as a complementary interruption with biological reasoning in the WHO's harmonized global research plan for COVID-19.

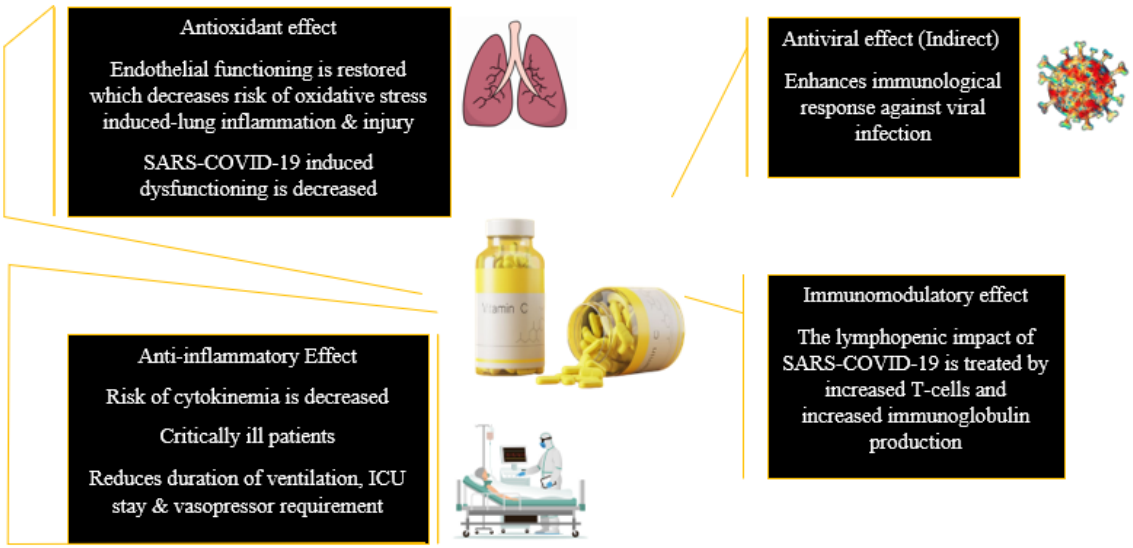

Figure 3: Probable Efficacious Activity of Vitamin C in the Administration of COVID-19 (Jouzdani *et al.,* 2021)

The possible use of high-level vitamin C as a cure of COVID-19, a viral infection that can cause acute respiratory distress syndrome (ARDS) and high death rates. The quick

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release of free radicals and cytokines leads to increased oxidative stress, which is a crucial element in ARDS. This, in turn, results in cellular damage, organ failure, and ultimately, death. (Cheng, 2020). Research has indicated that administering high doses of antioxidants, such as vitamin C, at an early stage may be a useful approach to prevent these consequences (Jouzdani *et al.,* 2021).

The key factor of fatality in Covid-19 is acute respiratory distress syndrome (ARDS). Rapid release of cytokines and free radicals can result in increased oxidative stress which is the major hallmark of ARDS and ultimately leads to organ failure, cellular injury and death. Vitamin C as an antioxidant become a effective treatment precursor for the patients suffering from viral infection. Several clinical studies confirmed the protection effect of vitamin C without any side effect (Chen *et al.,* 2020; Fowler *et al.,* 2017; Wang *et al.,* 2020) Viral infections could evoke higher oxidative stress, lung capillary endothelial cell activation and infiltration of neutrophils which leads to cytokine storm. Probably, this can be observed in both bacterial and viral infections causes high oxidative stress (Fowler *et al.,* 2017) Hypoxemia during ARDS usually damages the alveolar cappilary barrier, oxidative injury and severe inflammation (Meng *et al.,* 2019) the major factor in pulmonary injury specifically acute lung injury and ARDS that causes high mobidity and mortality is increased oxidative stress (Hecker, 2018; Yan *et al.,* 2019). Previous report suggested a huge increase in hsCrp during Covid 19, a basic marker of oxidative stress and inflammation (N. Chen *et al.,* 2020). Transcription factor, nuclear factor erythroid 2 (nfe2)-related factor 2 (nrf2), is a major regulator of antioxidant response element (ARE)-driven cytoprotective protein expression. Oxidative stress induced injury can be prevented through the activation of Nrf2. Vitamin C is the major component of cellualar antioxidant system (Q. Liu *et al.,* 2019) responsible for critical care management (Nabzdyk & Bittner, 2018). Since the prevention and management of oxidative stress could be realized by large dose of antioxidants, this approach may be applicable to COVID-19 with intravenous high-dose VC based on the outcome of three previous clinical studies involving a total of 146 patients with sepsis. Implication of high antioxidant dose could be a best strategy to prevent and manage the oxidative stress and this approach is adopted to treat Covid 19 based on the previous outcomes of clinical studies of 146 patients with sepsis (Li, 2018).

Oxidative stress plays a significant role in pulmonary injury, including ARDS, both of which are serious clinical conditions characterized by acute respiratory failure and high rates of morbidity and mortality (Kretsinger, Uversky & Permyakov, 2013). Patients with COVID-19 pneumonia have shown increased inflammation and oxidative stress. Ascorbic Acid, an important component of the cellular antioxidant system, facilitates in the management of critical care. High-level IV use of vitamin C have proved to decrease ICU stay and death rates in patients suffering from sepsis and severe influenza (Matera *et al.,* 2020). A recent report showed successful treatment of 50 mild to severe COVID-19 patients with high-level usage of vitamin C without any major adverse events (Abobaker *et al.,* 2020).

For populations at higher risk of exposure, such as healthcare workers, high level of vitamin C may be considered a preventative approach. However, to establish standard

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protocols for bedside usage, it is necessary to conduct well-designed clinical studies. The availability of effective vaccines and drugs treating viral infections may take time, and ascorbic acid other efficacious antioxidants are included in the currently available agents to diminish COVID-19 allied ARDS (A. C. Carr & Lykkesfeldt, 2023).

5. RECOMMENDED DIETARY ALLOWANCE (RDA) FOR SPECIAL POPULATION

There is a peculiar group of individuals who require special attention when it comes to their vitamin C needs. Such groups include elderly, the people who smoke and pregnant and lactating women (Table 2). Individuals with iron-rich conditions such as homozygous hemochromatosis and those who require cure for β-thalassemia may require different dosage of vitamin C. However, determining vit C requirements in acutely iron-rich individuals can be at risk by the context of safety.

5.1. Smokers

Various researches have manifested that smokers require more vit C than non-smokers (Meydani *et al.,* 2003). Vitamin C concentrations in smokers are typically lower in comparison to non-smokers and are inversely correlated with the consumption of tobacco due to increased oxidative stress. Research has suggested that vitamin C supplementation can help diminish urinary F2-isoprostanes, an index of increased oxidative stress that is usually enhanced in smokers. Vitamin E, on the other hand, has no effect on these levels. The current Recommended Dietary Allowance (RDA) for ascorbic acid uptake for smokers is 100 mg/day. However, some researchers manifest that smokers require 2-3 times the usual RDA (60 mg/day) to keep up plasma vitamin C amount in comparison to non-smokers (Nour *et al.,* 2020).

5.2. Pregnant & Lactating Women

The pregnant and lactating women also are in greater need of adequate vit C to keep up with the plasma ascorbic acid amount in correspondence to the other healthy women (A. Carr & Frei, 1999). The higher level of vit C is necessary because of active placental vit C transmission however vit C amount is greater in cord blood & in infants in contrast to mothers, and the additional vit C is lost by the lactation. The current RDAs for pregnant women are approx. 80 mg/d while for lactating ones is 100 mg/d. If smokers are in need of new Recommended Dietary Allowance then for the compromised health of lactating or pregnant women, the uptake of vit C need to be readjusted (Hassan & Onu, 2006).

5.3. Old People

The old individuals are more susceptible to vit C deficiency, due to their fluctuating dietary habits. The elderly are also required higher intake of vitamin C but there's not much research to validate this speculation. As the chances of oxidative stress is higher in adulthood therefore the activity of antioxidants may seem to have positive impact on the cognitive stability. In one cross-sectional research, there was no correlation found between the cognitive potential and intakes of the amount of vitamin C ≥160 mg/d in contrast to the previous intakes <70 mg/d. However, in another cross-sectional and

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longitudinal study, high plasma vit C levels were correlated with improved memorizing ability. A recent cohort research also manifested that intake of vitamin C additional dosage was related to a lower emergence of severe cognitive disability.

Ultimately, 2 other recent researchers found that subjects with Alzheimer's disease have low plasma vitamin C level regardless of the sufficient diet and that supplementation with vitamin C may decrease the probability of Alzheimer's disease (A. Carr & Frei, 1999).

Table 2: Population and requirement of Vitamin C

Population	Vitamin C Requirement
Smokers	≥2 to 3 times the prevailing RDA of 60 mg/day to keep up plasma vitamin C level in contrast to nonsmokers
Pregnant Women	80 mg/day
Lactating Women	100 mg/day
Elderly	Evidence is inconsistent, but vitamin C requirements may be higher

Note that these recommendations are based on current knowledge and may be subject to change as further research is conducted (Hassan & Onu, 2006; Nour *et al.,* 2020).

CONCLUSION

Vitamin C has the potential to provide benefits to those critically ill patients suffering from multiple diseases. At physiological levels, the pharmacokinetics of vitamin C are complicated and dose-dependent, but at pharmaceutical levels, they are dosage independent and first order.

It is absorbed through facilitated diffusion, active transport, and passive diffusion, with uptake and distribution occurring through SVCT1 family transporters. It possesses antimicrobial properties and strong antioxidant effects, making it significant for maintaining overall health, particularly in special populations who may have higher requirements.

People with a greater risk of viral infections may facilitate from taking vitamin C supplements to support their immune system.

Several clinical research have confirmed vitamin C's preventive effectiveness with no negative side effects. Even vitamin C has various potential advantages for COVID-19 patients, including increasing interferon levels, lowering inflammatory indicators, and avoiding micro thrombi development.

CONFLICT OF INTEREST

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