

REVIEW PAPER

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Vitamin C biochemistry: From scurvy to COVID-19 treatment

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HISTORY OF VITAMIN C

Although its importance in human biology has been known ever since the emersion of scurvy, it was not until the 20th century that vitamin C was discovered. Scurvy is a disease caused by severe vitamin C deficiency, which was very common among sailors on long sea journeys during the early modern period [1–3]. In 1753 Scottish naval surgeon James Lind identified citrus fruits as an effective cure for scurvy in the first-ever controlled clinical study [1,3,4]. Still, the reason why the citrus fruits had a therapeutic effect was yet to be discovered. The reducing agent responsible for preventing and curing the disease was first found in 1928 by Hungarian scientist Albert Szent-Györgyi. The off-white crystalline substance that he isolated from plant juices and animal tissues (adrenal glands) and that he named hexuronic acid was thought to be a new hormone similar to simple sugars [5]. Still, a few years later, Svrbely and Szent-Györgyi confirmed that hexuronic

Abstract

The story of vitamin C (L-ascorbic acid) as an antioxidant and a cofactor in numerous biochemical reactions is a part of its long history and it is well known today. However, many questions of its mechanism of action and the benefits that it has on human health are still emerging. This applies not only to the recommended doses but also to the route of its administration. Besides, there are numerous questions about the therapeutic efficacy of vitamin C in various human (infectious) diseases, as well as its immune system function and antiviral potential. The fact that vitamin C can act as a reductant (antioxidant) and a prooxidant further emphasizes its oxidation-reduction (redox) potential in real physiological conditions. Today, the question of the intravenous administration of vitamin C effect in patients with SARS-CoV-2 requires special attention. This review aims to showcase known facts about vitamin C and its mechanisms of action to better understand the current new challenges related to vitamin C.

Key words: Vitamin C; Metabolism; Antioxidant; Mechanism of action; Physiological function; Immune function; Cancer; Common cold; SARS-CoV-2; COVID-19.

acid was, in fact, vitamin C [6]. At the same time, W. A. Waugh and C. G. King isolated a crystalline vitamin C from lemon juice and reported that it had similar physical and chemical properties as hexuronic acid, including the antiscorbutic quality, and that it was identical with the hexuronic acid, which was indeed later confirmed [7]. In 1933 a team led by British chemist Walter N. Haworth defined the molecular structure of vitamin C (i.e., hexuronic acid), renaming it to the ascorbic acid [8]. Albert Szent-Györgyi and Walter N. Haworth were awarded the Nobel Prize in Physiology or Medicine and Chemistry, respectively, for their work on vitamin C.

VITAMIN C BIOCHEMISTRY

Vitamin C, also known as L-ascorbic acid, is a white, water-soluble crystalline powder. Ascorbate coexists in two main forms – reduced (L-ascorbic acid or vitamin C) and oxidized (Dehydroascorbic acid, DHA) (**Figure 1**). The biological functions of ascorbate depend on

its ability to donate electrons. Ascorbate can serve as a biologically relevant reducing agent in both plasma and tissues. As a result of one-electron oxidation of ascorbate, ascorbyl radical (i.e., monodehydroascorbate) is formed. Ascorbyl radical is an unusually stable, but not very reactive molecule, making it a biologically relevant electron donor. However, dismutation of two molecules of the ascorbyl radical is preferable, forming ascorbate and DHA [9–11]. DHA is then imported into cells, where it can be quickly restored back to ascorbate by NADH-dependent, NADPH-dependent, or glutathione-dependent systems [11–14]. Otherwise, DHA is irreversibly hydrolyzed since it is a relatively unstable molecule at physiological pH, thus the need for efficient DHA reduction to ascorbate in the cells [15].

Ascorbate is synthesized *de novo* from D-glucose through a cascade of enzyme-catalyzed reactions. The key step which drives the biosynthetic pathway towards ascorbate synthesis is the conversion of UDP-glucuronate to D-glucuronate. Otherwise, UDP-glucuronate can be used for the biosynthesis of specific polysaccharides [11,14]. Unlike plants and most other vertebrates, humans do not synthesize ascorbate due to the accumulation of mutations in the *Gulo* gene, which encodes for the last enzyme in the pathway, L-gulono- γ -lactone oxidase [14,16]. Since vitamin C is an essential micro-nutrient for humans, it needs to be supplied through dietary sources and supplements [17].

VITAMIN C METABOLISM

Vitamin C metabolism is regulated by respective mechanisms – intestinal absorption, transport to tissue, renal reuptake, and urine excretion [18]. After the intake through food or supplementation, vitamin C is then ingested along the gastrointestinal tract (GIT) via specific transporters in both reduced and oxidized forms [19–21]. Ascorbate is directly absorbed by active transport via the sodium-dependent vitamin C transporter 1 (SVCT1). SVCT1 is also expressed in the proximal kidney tubule, where it is involved in the reabsorption of vitamin C. Furthermore, vitamin C can either carry out its function in the blood and extracellular fluid or it can be imported into the cells via SVCT2, a transporter present in nearly every cell type. Plasma vitamin C is filtered by renal glomeruli, but most of it is reabsorbed in the proximal tubule via SVCT1 [21–23]. On the other hand, DHA is absorbed in GIT and imported into cells by facilitated diffusion via GLUT transporters [24,25]. Glucose is considered to be a competitive inhibitor of DHA because it is also transported via GLUTs, which can cause vitamin C deficiency in obese and diabetic individuals [21,26].

Numerous endogenous and exogenous factors have an impact on vitamin C bioavailability in the body. The recommended dietary allowance (RDA) for vitamin C varies from 45 mg/day (World Health Organization)

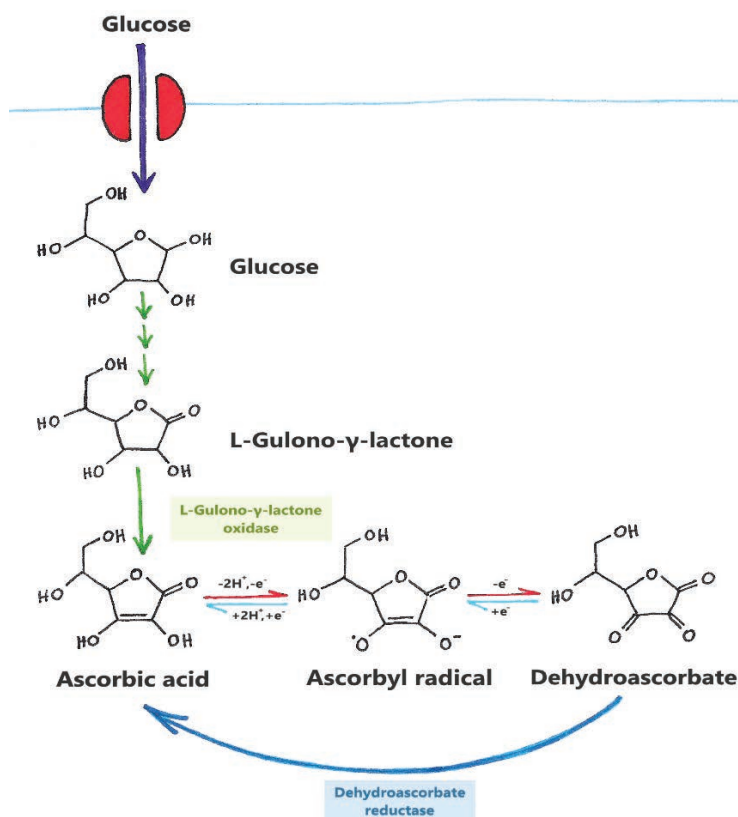


Figure 1. Simplified schematic view of vitamin C biosynthesis from glucose and redox-dependent interconversion between ascorbic acid and its oxidized form dehydroascorbic acid, with the ascorbyl radical as an intermediate.

to 90 mg/day (National Academy of Sciences) [9,27]. Saturation of tissues and plasma requires a higher dosage than recommended, 100 mg and over 500 mg per day, respectively [9,28]. Doses over 500 mg/day cannot cause any harm since half of the absorbed vitamin C is eliminated from the body unmetabolized. Moreover, single doses up to 10 g/day in adults did not show any adverse or toxic effects in most of the studies [29]. Still, it has been known for hypersensitivity, oxalate urolithiasis, iron overload in haemochromatosis and anemia etc. to happen, but on very rare occasions [17]. However, adequate doses cannot be established since the need for vitamin C changes during both pathological and physiological conditions [30,31].

VITAMIN C PHYSIOLOGICAL FUNCTION

Maintaining sufficient vitamin C concentration is necessary for the occurrence of many biological processes since vitamin C functions as an enzyme cofactor, a potent antioxidant, and it also has an immune function. The reducing potential of vitamin C enabled its role as a cofactor of several enzymes that contain a metal ion (Fe^{2+} and Cu^{+}) in their active site, such as monooxygenases and dioxygenases. Particularly, it maintains metal ions in a reduced ferrous (Fe^{2+}) and cuprous (Cu^{+}) state, which are needed for enzyme activity. These enzymes have a role in the synthesis of collagen, carnitine, different neurotransmitters and hormones, including dopamine, norepinephrine, calcitonin, oxytocin, vasopressin, and cholecystokinin [11,32,33]. Recent studies have shown that vitamin C also has an important role in the epigenetic regulation as methylcytosine dioxygenases ten-eleven translocation (TET) and JmJc

domain-containing histone demethylases cofactor. By contributing to the methylation/demethylation balance of histones and DNA, vitamin C is involved in the regulation of embryonic and postnatal development, aging, as well as in pathological conditions [34,35]. Ever since the role of vitamin C in the prevention of scurvy has been established, numerous clinical studies have investigated its effects on human health. There has been some evidence of its protective role in cardiovascular diseases and several cancers, as well as in respiratory tract infections [9].

The fact that vitamin C has a high reducing ability also makes it a potent antioxidant [36–40]. It can act directly by scavenging reactive oxygen and nitrogen species (ROS/RNS), including free radicals – hydroxyl radical, superoxide anion [41] and nitrogen dioxide [42], and nonradical species – singlet oxygen [43], hydrogen peroxide, and peroxyxynitrite [40,44]. Moreover, vitamin C activity can lead to decreasing ROS/RNS levels by inhibiting different prooxidative enzymes, including NADPH oxidase [40] and xanthine oxidase activity [41], inducible nitric oxide synthase expression [40], or by regenerating other small molecule antioxidants, like vitamin E [39,45,46] and glutathione (GSH) [47]. Even though vitamin C is a water-soluble molecule it has a role in preventing lipid peroxidation by reducing lipid-soluble vitamin E radical to its active form, vitamin E (Figure 2) [45,48,49]. Since phospholipids build plasma membranes and membranes surrounding organelles, it is clear that vitamin C is essential for maintaining cell structure. Besides its antioxidative role, vitamin C may have a prooxidative effect [39,50,51]. However, *in vivo* studies showed that vitamin C predominantly acts as an antioxidant in physiological conditions [36].

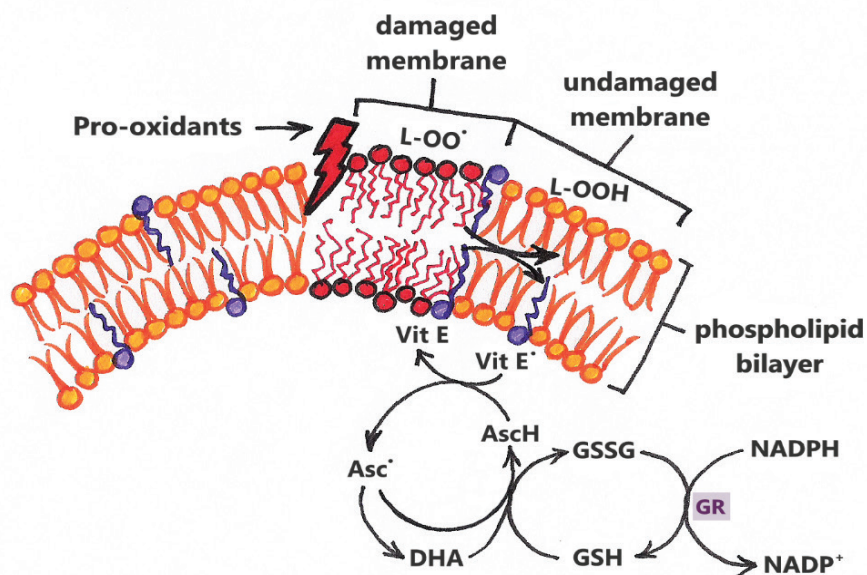


Figure 2. The cooperation between vitamin C and vitamin E in the prevention of lipid peroxidation. *L-OO•* - lipid peroxyl radical; *L-OOH* - lipid peroxide; *Vit E* - vitamin E; *Vit E•* - vitamin E radical; *AscH* - ascorbate; *Asc•* - ascorbyl radical; *DHA* - dehydroascorbate; *GR* - glutathione reductase.

VITAMIN C IMMUNE FUNCTION

Even though vitamin C acts as a powerful antioxidant protecting tissues from various pathogens, it mainly affects components of innate and acquired immunity, acting as a cofactor for many biosynthetic enzymes and enzymes regulating gene expression [52–55]. It has been demonstrated that vitamin C positively affects production [56–58] and function of leukocytes *in vitro* (especially lymphocytes, neutrophils, and mononuclear phagocytes), acting on cellular motility [59,60], chemotaxis [61,62] and phagocytosis [55,63–66]. Moreover, vitamin C has cell-specific functions – ROS generation in neutrophils [65,67], caspase-dependent apoptosis of neutrophils in macrophages [68,69], thus promoting resolution of the inflammatory response, and antibody generation in lymphocytes [55,70,71]. Vitamin C also has a role in the maintenance of epithelial barriers in skin [72,73] and lungs [74] due to its contribution to collagen synthesis [75–77], wound healing [78–80], protection against ROS-induced damage [73,81,82], as well as the regulation of cytoskeletal rearrangements and gene expression of tight junction proteins [74]. Additionally, vitamin C supports immune function by modulating cytokine production [57,83–85]. Although there are many benefits from increased vitamin C intake on the immune system, its role in preventing or curing diseases has not been established yet.

VITAMIN C AND THE COMMON COLD

The work of Linus Pauling put back in focus the benefits that vitamin C has on human health. He suggested that vitamin C mega-dose supplementation could be used to lower the incidence and severity of a condition known as the common cold [29,86]. The term “the common cold” is used to describe a complex condition with a large number of symptoms that do not relate to any specific disease. It is, however, usually caused by the viruses affecting different parts of the respiratory system (also known as chest, throat, and nose colds) [87,88]. As a response to Pauling’s statement, there has been a large number of clinical studies concerning the role of vitamin C in human health. Even though its beneficial effects on the duration and severity of the common cold are indisputable, it has not been proven yet that vitamin C can, in fact, be used as a preventive or therapeutic agent for the common cold [89–91]. *Hemila* suggested that supplemental vitamin C may lead to neutralization of reactive species in the respiratory tract generated during virus-mediated neutrophil activation, thus supporting the immune response associated with the common cold [92,93]. Furthermore, its antihistamine property [94] may be beneficial in reducing cold severity since histamine is responsible for the symptoms of the cold. Some clinical studies have

proven that vitamin C supplementation ameliorates leukocyte motility (chemotaxis) [62,95], therefore also reducing the severity of cold symptoms. In addition, vitamin C might also have an effect on some other respiratory infections appearing as complications of colds or independently of colds [96].

Even though meta-analysis confirmed that regular supplementation with vitamin C (0.25 to 2 g/day) did not reduce the common cold incidence in the general population, in six of the trials, the common cold incidence was halved in individuals experiencing short periods of extreme physical stress (e.g., marathon runners, skiers). A benefit of regular vitamin C supplementation was also demonstrated regarding the duration of colds, with a greater benefit in children than in adults. Public interest in this topic continues to expand and vitamin C is still being extensively used as an antiviral drug. Nevertheless, it must be noted that vitamin C does not prevent nor treat the common cold [89,90].

SARS-COV-2 INFECTION

Antiviral properties of vitamin C have once again come into question with the immersion of a novel virus from the beta coronavirus family named SARS-CoV-2. Coronaviruses of the beta genus (β -CoVs) are enveloped, positive-sense, single-stranded RNA viruses. They predominantly infect bats, but other mammals like rodents and humans can also be their hosts [97]. Beta coronaviruses that have caused human epidemics include the Middle East Respiratory Syndrome coronavirus (MERS-CoV) [98] and Severe Acute Respiratory Syndrome coronaviruses SARS-CoV-1 [99] and SARS-CoV-2 [100]. The infection caused by the virus SARS-CoV-2 has been identified as Coronavirus Disease 2019 (COVID-19) [101].

SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptor via Spike Glycoprotein (S), thus infecting lung endothelial cells (ECs) [102]. ACE2 receptors are not only present in cardiopulmonary tissues, but also in some hematopoietic cells, kidneys, and intestines [103,104]. This is supported by the fact that SARS-CoV-2-infected ECs were found in several organs of deceased patients [103]. Infected ECs are characterized by dysfunction, lysis, and finally, death. Moreover, ECs promote inflammation in damaged tissues by expressing leukocyte adhesion molecules [105], thus causing accumulation and extravasation of leukocytes. As a result of leukocytes activation cytokine storm occurs [106,107]. After being recruited to the lungs, activated neutrophils and macrophages also generate excessive reactive oxygen and nitrogen species. On the one hand, ROS and RNS regulate immune response by oxidant-induced activation of transcription factors responsible for the expression of inflammatory cytokines and chemokines. On the other hand, ROS can act as

oxidants, damaging both virus cells and lung (heart) cells, hence further promoting ECs malfunction and finally lung tissue damage [108,109].

In the cases of severe endothelial cell damage, the loss of microvascular barrier function occurs in the lungs resulting in enhanced vascular permeability. In addition, the binding of SARS-CoV-2 to the ACE2 receptor prevents ACE2 from degrading angiotensin II, thus affecting the angiotensin-vasopressor system. Reduced ACE2 activity also leads to increased vascular permeability [110]. Furthermore, immune cells, inflammatory cytokines, and vasoactive molecules promote enhanced EC contractility. As a consequence of these events, fluid leaks and fills alveolar sacks [105]. Finally, the cytokines IL-1 β and TNF stimulate fluid retention (pulmonary edema) in the lungs. All of these symptoms – ECs malfunction, inflammation, vasodilatation, forming of the blood clots are being amplified by the high levels of cytokines, which are constantly being produced as a response to the virus infection [110].

Clinical manifestations of the COVID-19 can vary from asymptomatic to severe pneumonia [111–113]. When the body's response to infection causes injury to its own tissues and organs, sepsis occurs. The most common infectious source of sepsis is indeed pneumonia [114]. Alveolar dysfunction and consequential severe lung injury lead to acute respiratory distress syndrome (ARDS) and septic shock, followed by multiple organ failure and very often death [112,115]. ARDS as a form of fluid accumulation in the lungs prevents necessary oxygen from entering the lungs, ultimately causing hypoxic respiratory failure [116]. Hence, ARDS and septic shock are the main cause of ICU care and mortality in COVID-19 patients, as well as concurrent pathological conditions, including hypertension, cardiovascular and cerebrovascular diseases, and diabetes [111,112,115].

COVID-19 TREATMENT

Being that SARS-CoV-2 is genetically similar to SARS-CoV-1 [117], previously described pathological symptoms in patients suffering from COVID-19 are also similar to the one of SARS [111,118]. However, in comparison to SARS-CoV-1, SARS-CoV-2 has higher transmissibility and infectivity. Moreover, patients with COVID-19 have a longer incubation period, therefore explaining the rapid expansion of the SARS-CoV-2 virus [119,120]. The COVID-19 pandemic has been spreading to many continents and countries since it was first reported in December of 2019, henceforth causing a public health emergency [101,121]. Numerous clinical trials concerning COVID-19 are in effect. However, an effective cure for the disease is yet to be found, with the main current treatment being the symptomatic one. Besides oxygen therapy, some of the treatments for severe cases of

COVID-19 also include several antiviral drugs, normally used against other viruses, in combination with interferon [113,116,122,123]. Nonetheless, further studies concerning vaccines and/or antiviral drugs are necessary since these are all temporary solutions with no confirmed competence in the treatment of COVID-19.

The hypothesis that vitamin C may be beneficial in the treatment of COVID-19 is supported by the data showing its well-established role as an imperative medicament against various viral infections [91,124]. What is more important, vitamin C is a very safe biomolecule, and it can be used in massive dosages with the exception of those suffering from glucose-6-phosphate dehydrogenase (G6PD) deficiency [125,126], hemochromatosis [127], or renal insufficiency [128,129]. As previously mentioned, multiple placebo-controlled trials have shown that the duration and severity of common cold were reduced in the vitamin C groups, suggesting that the viral respiratory infections in humans are affected by vitamin C levels. There is also data from controlled trials with human subjects suggesting that vitamin C may lower susceptibility to pneumonia [91,130]. Despite the well-known beneficial effect of vitamin C in viral infections, there is still no solid clinical data confirming the *in vivo* virucidal activity of vitamin C. Considering the possibility that vitamin C may affect severe viral respiratory tract infections as well, there are currently many ongoing studies examining its effect and possible applications against COVID-19.

Normal vitamin C plasma level of around 50 $\mu\text{mol/l}$ in adults is not enough to prevent viral infections and physiological stress. Moreover, in hospitalized patients suffering mostly from acute respiratory infections, sepsis or severe COVID-19 metabolic consumption of vitamin C is increased, and its plasma level drastically declines ($\leq 11 \mu\text{mol/l}$) [131–135]. This occurs as a consequence of highly enhanced inflammation and oxidation caused by ROS/RNS, which is why these patients require high dosage vitamin C supplementation [83,136]. Due to the limited enteral absorption of vitamin C by oral intake (maximum plasmatic levels around 220 $\mu\text{mol/l}$) [137], therapeutic effects can be achieved only by high dosage intravenous administration of vitamin C (HD-IVC), leading to its rapid increase in the blood (plasmatic levels up to 20–49 mmol/l) [138]. The results of one study [139] suggest that the early use of HD-IVC in combination with hydrocortisone and thiamine (HAT therapy) may prevent progressive organ dysfunction and reduce the mortality of patients with severe sepsis and septic shock. Studies have shown that the therapeutic effect of vitamin C here is based on its immunosuppressive capacity through down-regulation of the production of the proinflammatory cytokines, enabling protection of alveolar epithelial barrier from inflammatory damage, and through the increase of the α/β interferon production [85,116,140–142]. Inhibition

of the cytokine storm progression is achieved by attenuation of nuclear factor kappa-B (NFκB) activation [143–145]. This is confirmed in a study examining the levels of IL-6 and tumor necrosis factor alpha (TNF-α) production in hospitalized patients suffering from pneumonia [83]. Furthermore, it has been shown that vitamin C suppresses acute lung injury by multiple mechanisms, including enhancement of the epithelial barrier function and regulation of the alveolar fluid clearance through increased synthesis and/or activity of ion channels and pumps [74]. Meta-analyses also demonstrated that vitamin C may have a vasopressor sparing effect and that it may shorten the duration of mechanical ventilation [146]. The CITRIS-ALI Randomized Clinical Trial [147] has shown that HD-IVC can successfully reduce mortality and ICU stay in patients with sepsis and ARDS. What is more important, it has been reported that HD-IVC was generally well tolerated in clinical trials with no adverse effect [89,129,148].

Based on all of these observations, numerous clinical trials examining the effect of HD-IVC administration as a treatment for COVID-19 were highly encouraged. Although oral vitamin C supplementation does not help in the critical COVID-19 cases, it has been suggested that oral dose (2-8 g/day) may attenuate the conversion from mild to the critical COVID-19 infection [149]. On the other hand, HD-IVC administration was shown to have a beneficial effect in the critical COVID-19 cases. There is an urgent need to examine the uses of HD-IVC pre-, post-, and during different stages of the COVID-19 infection. The following preliminary results were reported: HD-IVC seems to significantly reduce the inflammation, ICU, and hospital stays of COVID-19 patients [150]. Nevertheless, more research is needed to confirm the clinical efficacy and safety of HD-IVC administration in the treatment of COVID-19 before its official approval as an applicable medicament.

POSSIBLE MECHANISMS OF VITAMIN C ACTION IN COVID-19

Vitamin C has been extensively used against many other diseases like the common cold [90], and other viral infections, cancer [151,152], diabetes [153,154], heart disease [155], etc. Several proven mechanisms underlying the role of vitamin C in the treatment and/or prevention of previously mentioned diseases include enhancement of the immune system, prevention of the free radical damage (antioxidant role), inhibition of the excessive activation of the immune system, and consequential prevention of tissue damage, the formation of the epithelial and endothelial barrier. Vitamin C, along with other micronutrients (zinc, selenium, magnesium, vitamin A, D, and E) [156–158], glutathione [159,160], and omega-3 fatty acids [161], is considered to be one of the leading antiviral co-therapy targeting SARS-CoV-2. While the positive effects of vitamin C were recognized, its mechanism of action remains unknown. An important question has been raised here – does HD-IVC act as a therapeutic agent against SARS-CoV-2 in some of the previously described ways or does it act in some other way? In the case of HD-IVC, its mechanism of action is usually carried out by H_2O_2 . There are two potential pathways – one of them involves the cytotoxic effect of H_2O_2 , as seen in tumor cells induced by HD-IVC, and the other one suggests changes in metabolism and energetic homeostasis, again via increase in H_2O_2 level (**Figure 3**).

A similar therapeutic approach, i.e., HD-IVC in cancer therapy, may point to the prooxidant property of vitamin C as a potential mechanism of vitamin C action in SARS-CoV-2. Parenteral administration of HD-IVC neglects tight control, leading to H_2O_2 formation in a distinct point of time [151,152,162,163]. H_2O_2 in the blood is immediately eliminated by catalase [164,165], while

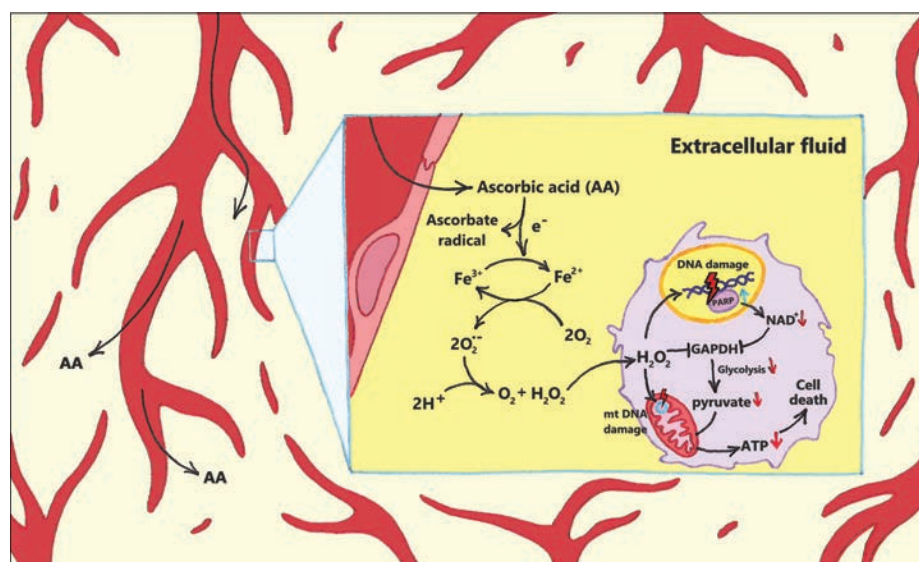


Figure 3. Proposed mechanisms of HD-IVC effect through hydrogen-peroxide-dependent pathway. GAPDH – Glyceraldehyde 3-phosphate dehydrogenase; PARP – poly (ADP-ribose) polymerase. Adapted from [151,152].

H₂O₂ present in extracellular fluid enters the cells. Due to different preferential energetic metabolism known as Warburg effect [166–168] H₂O₂ displays cell-dependent cytotoxicity. Oxidative stress induced by pharmacological concentrations of vitamin C causes DNA damage and inhibits glycolysis in susceptible cancer cells, leading to their death [151,152]. That is because cancer cells highly depend on glycolysis for their ATP production. Unlike cancer cells, the main source of ATP production in normal cells is mitochondrial oxidative phosphorylation, hence explaining why glycolysis inhibition does not affect them as much [151]. One of the proposed mechanisms of glycolysis inhibition is through DNA damage induced by H₂O₂, which in turn activates poly (ADP-ribose) polymerase (PARP). PARP depletes NAD⁺, and depletion of NAD⁺ leads to inhibition of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) activity [169]. Being that GAPDH is a crucial glycolytic enzyme, glycolysis is inhibited and ATP levels are reduced [151,152]. Another possible way of ATP depletion is direct damage of mitochondrial ATP synthase by H₂O₂ and/or degradation of H₂O₂ by concurrent oxidation of GSH to GSSG [170,171].

Considering glycolysis is also thought to be the main energy source for the immune effector cells [166], HD-IVC administration might also have a prooxidant effect on the immune effector cells, thus downregulating proinflammatory mediator expression and improving alveolar fluid clearance during SARS-CoV-2 infection [172]. Moreover, lung ECs, just like any other normal cell type, mostly depend on mitochondrial oxidative phosphorylation for ATP production, which is why HD-IVC should act as an antioxidant in the lung ECs, enhancing their function [74]. Still, intravenous glucocorticoid treatment is proposed to be taken together with HD-IVC to reduce possible inflammation caused by osmotic death of the immune effector cells [172]. Nevertheless, there is currently no evidence pointing to the cytotoxic effect of vitamin C pharmacological concentrations in the treatment of COVID-19 infection.

CONCLUSION AND PERSPECTIVE

In the paper from 1996 [39] Barry Halliwell, after an extraordinary analysis of the biological effects of vitamin C and its antioxidant and prooxidant effects, postulates: "Ascorbate is essential in the human diet, but many unanswered questions remain." Further, the website of the Linus Pauling Institute, which promotes his work and healthy nutrition, states: "There is currently no data available to show that vitamin C can prevent or successfully treat COVID-19 infections" (<https://lpi.oregonstate.edu/COVID19/vitamin-c-and-COVID-19>).

On the other hand, we have witnessed for a long time, and even today, that vitamin C is the most frequently used supplement. Historically, just like aspirin.

In health and disease. Even today in the epidemic of COVID-19, regardless of the method, amount, and duration of supplementation. We could say it is reborn as a Phoenix, or perhaps it is more correct to say that vitamin C is continuously a Phoenix. A redox Phoenix, used even before we knew about it, and always before discovering the mechanisms of its action *in vivo*.

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Biohemija vitamina C: Od skorbuta do COVID-19 tretmana

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Kratak sažetak

Priča o vitaminu C (L-askorbinska kiselina), antioksidansu i kofaktoru u brojnim biohemijskim reakcijama, deo je njegove duge istorije danas dobro poznata. Međutim, mnoga pitanja o mehanizmima njegovog delovanja i koristi koja on ostvaruje po ljudsko zdravlje se kontinuirano nameću. Ovo se odnosi ne samo na preporučene doze vitamina C, već i na način njegove primene. Pored toga, postoje brojna pitanja o efikasnosti vitamina C u terapiji različitih humanih infektivnih bolesti, njegovom antivirusnom potencijalu, kao i ulozi u funkcionisanju imunskog sistema. Činjenica da vitamin C može delovati kao redukciono sredstvo (antioksidant) i pro-oksidativno, dodatno naglašava njegov oksidaciono-redukcioni (redoks) potencijal u fiziološkim uslovima. Danas posebnu pažnju zahteva pitanje efekta intravenske primene vitamina C kod pacijenata sa SARS-CoV-2. Ovaj pregled ima za cilj da prikaže poznate činjenice o vitaminu C i njegovim mehanizmima delovanja kako bi se bolje razumeli novi izazovi povezani sa vitaminom C.

Ključne reči: Vitamin C; Metabolizam; Antioksidant; Mehanizam delovanja; Fiziološka funkcija; Imuna funkcija; Kancer; Prehlada, SARS-CoV-2; COVID-19.