

Immunomodulatory and Antimicrobial Effects of Vitamin C

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Humans have lost their vitamin C-synthesizing capacities during evolution. Therefore, the uptake of this essential compound from external sources is mandatory in order to prevent vitamin C-deficient conditions resulting in severe morbidities such as scurvy. The potent antioxidant, immunomodulatory, and anti-infectious effects of vitamin C are known since the 1930s. We here (i) review the impact of vitamin C on innate and adaptive immune functions, (ii) provide an overview of its antimicrobial, antibacterial, antiviral, antiparasitic, and antifungal properties, and finally, (iii) discuss vitamin C as an adjunct treatment option for the combat of human infections by bacteria, particularly by emerging multidrug-resistant species.

Keywords: vitamin C, ascorbic acid, immunomodulatory properties, anti-microbial synergy, antibacterial effects

Introduction

In the 1920s, vitamin C was first identified by the prospective Nobel laureate Albert Szent-Györgyi from Szeged University in Hungary, who unraveled the role of this essential vitamin for the treatment and prevention of scurvy resulting from vitamin C deficiency [1–5]. Vitamin C is the generic term for L-threo-hexo-2-enono-1,4-lactone [6], which constitutes a low molecular weight carbohydrate [1, 7]. Chemically, vitamin C is a gluconic acid lactone derived from glucuronic acid and water-soluble ketolactone with 2 ionizable hydroxyl groups with prominent antioxidant properties [1, 6]. In nature, the 2 essential isomeric molecules of vitamin C are found in equal parts, namely the reduced form D-ascorbic acid and the chemically active and oxidized form L-ascorbic acid [8], which are mutually interchangeable [1, 6, 9, 10]. Vitamin C has a strong potential to reduce distinct molecules while being reversibly oxidized to dehydroascorbic acid (DHA), which can be reduced back to vitamin C exhibiting full biological activity [1, 6, 11]. The intracellular transport of vitamin C takes place in every kind of cells as DHA through glucose transporters (GLUT) following a concentration gradient due to the structure similarity to glucose [8, 12] or actively as ascorbic acid via the sodium-dependent vitamin C transporters (SVCT)-1 and -2 [13, 14] in specific organs such as the small intestines, liver, kidneys, adrenal glands, brain, and retina [15]. Inside the cell, DHA is subsequently reduced to ascorbic acid [16]. Due to these characteristics, vitamin C is involved in several vital processes such as energy metabolism and gene transcription, as well as in regulation of hormonal and epigenetic pathways [17].

The natural sources of vitamin C are citrus fruits, kiwi, mango, strawberries, papaya, tomatoes, green leafy vegetables, and broccoli, for instance [1, 7, 10, 18–20]. Interestingly, the

vast majority of vertebrates can synthesize vitamin C from glucose, but a few mammals including guinea pigs and humans have lost this ability due to a lack of L-glucono- γ -lactone oxidase, which is necessary for the synthesis of vitamin C *in vivo* [1, 2, 7, 8, 10, 18, 21, 22]. Therefore, humans need to acquire vitamin C from a diet that supplies 100 to 200 mg of vitamin C per day to cover the general human needs [23, 24] and to decrease the risk of vitamin C-deficient conditions resulting in scurvy, which might be fatal if left untreated [7]. In order to prevent scurvy, a low daily dose of 10 mg is needed [25]. Individuals with scurvy exhibit down-regulated immune responses [26] and are hence highly susceptible towards infections [2, 17]. Given that vitamin C is essentially involved in collagen biosynthesis and repair, the lack of ascorbic acid impairs integrity of basement membranes, mucosal epithelia, and connective tissues, which is causative for the devastating periodontal disease observed in scurvy. Furthermore, the vitamin is required for proper wound healing and bone development, both of which linked to the role of ascorbic acid in collagen synthesis. Other biochemical functions of vitamin C include carnitine synthesis, redox-reactions, production of adrenal steroids and catecholamines, metabolism of amino acids and cholesterol, and iron absorption [5, 27, 28].

Several studies revealed that vitamin C possesses antimicrobial properties, thus reducing the risk of infections, and have immunomodulatory functions, particularly in high concentrations [8]. However, one needs to take into consideration that inappropriate storage, processing and preparation procedures of food might result in vitamin C degradation [7], further supporting the demand of appropriate dietary supplementation of this essential vitamin in order to reduce the risk of deficiency. Furthermore, given that vitamin C is water-soluble, intoxication upon excess intake is virtually impossible since vitamin C in concentrations exceeding the daily demands will be excreted via the kidneys [29]. Given its anti-infectious and immunomodulatory properties on one side and the lack of unwanted side effects on the other, vitamin C constitutes a promising antibiotic-independent strategy to combat and/or prevent bacterial (including enteropathogenic) infections.

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Therefore, this review will focus on the immunomodulatory and antimicrobial effects of vitamin C.

Immunomodulatory Properties of Vitamin C

A critical basal concentration of vitamin C is essential for a normal and well-functional host defense mechanism, and pharmacological application of vitamin C is believed to enhance immune function [30]. Several studies revealed that experimentally induced vitamin C deficiency reduces cellular [31–33] and humoral immune responses [33, 34]. Furthermore, the effect of vitamin C on different immune cell populations has been shown in both experimental *in vivo* models and in humans [35–38]. In clinical studies, vitamin C treatment of healthy subjects promoted and enhanced natural killer cell activities, lymphocyte proliferation, and chemotaxis [30, 39]. Furthermore, high doses of vitamin C not only stimulated murine immune cells, primarily dendritic cells, to more distinct interleukin (IL)-12 secretion [40], but also activated T and B cell functions [34, 41].

In addition, the observations that vitamin C concentrations in immune cells such as leukocytes are 10- to 100-fold higher than those measured in the plasma [6] and the fact that these cells accumulate vitamin C against a concentration gradient further underline the immunological importance of vitamin C [42, 43] and support its role as crucial player in various aspects of immune cell functions, such as immune cell proliferation and differentiation [17, 44–46], besides its anti-inflammatory properties [47, 48]. Moreover, the newly characterized hydroxylase enzymes, which regulate the activity of the hypoxia-inducible factors (HIF), gene transcription, and cell signaling of immune cells, require vitamin C as a cofactor for optimal activity [49–52].

In the gastrointestinal tract, vitamin C plays an important role as essential micronutrient and antioxidant protecting intestinal cells from inflammatory stimuli [1, 53]. However, in the inflamed mucosa of patients suffering from chronic inflammatory bowel disease (IBD) such as Crohn's disease and ulcerative colitis [54, 55], the mucosal vitamin C concentrations are highly reduced [56]. Furthermore, when applying vitamin C to duodenal explants derived from patients suffering from coeliac disease due to a hypersensitivity reaction to wheat gliadin and similar proteins from rye and barley [57], a decreased secretion of pro-inflammatory mediators in response to gluten could be assessed [58]. In addition, in a small study cohort, intravenous high dose vitamin C application was found to be beneficial as an adjunct treatment option of colorectal cancer [59]. Hence, vitamin C has been shown to exhibit potent immunomodulatory activity in the course of distinct gastrointestinal inflammatory morbidities. In the following paragraph, we will focus on the effect of vitamin C on distinct immune cell populations.

Monocytes and Macrophages

As pivotal components of the innate immune system, monocytes and macrophages are the first line of defense against invading pathogens [60]. The high vitamin C concentrations measured in monocytes [17, 26, 61] underline the regulatory role of this vitamin in monocyte and macrophage functions. In support, an *in vitro* study revealed that intracellular accumulation of pharmacologic vitamin C concentrations could effectively inhibit apoptotic pathways in human monocytes [16]. Vitamin C may also regulate distinct genes expressed in human macrophages, which are induced by lipopolysaccharide (LPS) via nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) activation [62]. Moreover, vitamin C

application to monocytes derived from human whole blood diminished secretion of pro-inflammatory cytokines such as IL-6 and tumor necrosis factor (TNF)- α [63]. In addition, vitamin C treatment was shown to stimulate and enhance phagocytosis and clearance of macrophages *in vitro* [17, 33]. Taken together, these findings underline the important role of vitamin C in host defense against pathogens.

Neutrophils

The exposure of neutrophils to oxidants inhibits their motility, which is related to oxidation of membrane lipids and affecting cell membrane fluidity [17]. As a potent water-soluble antioxidant, vitamin C can neutralize reactive oxidants and also regenerate cellular and membrane antioxidants such as glutathione and vitamin E (tocopherol) [64]. In order to protect themselves from oxidative damage, neutrophils accumulate millimolar (mM) concentrations of vitamin C [65], resulting in improved cellular motility and migration in response of chemotactic stimuli [66] and, subsequently, in enhanced phagocytosis of microbes and generation of reactive oxygen species (ROS) [17].

In support, oral administration of vitamin C has been shown to enhance neutrophilic functions and to result in increased serum immunoglobulin levels in aging patients [67]. Interestingly, neutrophils isolated from sepsis patients exhibited compromised functional capabilities regarding chemotaxis and the generation of ROS [68, 69]. These phenomena might be associated with decreased vitamin C concentrations in the plasma and leukocytes during infectious diseases and stress conditions [6, 33], which is related to the oxidation of ascorbic acid to DHA, the active form of vitamin C [6, 70].

T Lymphocytes

T lymphocytes as key players in acquired (adaptive) immunity are impacted by vitamin C, as shown by both *in vitro* [40, 41] and *in vivo* studies [8]. The development and maturation of murine [37, 71] and human [72] T cells are enhanced in the presence of vitamin C in physiological concentrations, whereas proliferation and viability of T lymphocytes are also affected [37]. In a clinical study with elderly patients who received vitamin C (500 mg/day) versus placebo for one month, an increased T cell proliferation could be assessed in the serum as compared to the placebo group [73]. These results are supported by several *in vitro* studies with human and murine T cells. In human peripheral lymphocytes, vitamin C application promoted T cell proliferation [72, 74]. In another report, however, a decreased number of human IL-2 producing T cells could be assessed in the presence of vitamin C, whereas TNF- α and interferon (IFN)- γ expressing T lymphocytes were not affected [63]. In murine splenic T cell cultures, only high vitamin C levels (0.25–0.5 mM) have been shown to decrease T cell viability and secretion of pro- and anti-inflammatory cytokines such as TNF- α , IFN- γ , and IL-4 by activated T cells, which was not the case following incubation with lower vitamin C concentrations [41]. In support, a recent *in vivo* study revealed that vitamin C administration during sepsis modified regulatory T cell activity by directly enhancing cell proliferation and by inhibiting the expression of distinct transcription factors, cytokines, and antigens directed against regulatory T cells [75].

Furthermore, T cell activation has been shown to increase expression of SCVT2 [8, 17], which is directly related to a more pronounced cellular uptake of ascorbic acid, further underlining the pivotal role of vitamin C during T cell activation. Given that ROS are formed during T cell activation and

act as a second messenger [76–78], it is highly likely that vitamin C affects T cell activation as an antioxidant [8].

B Lymphocytes

B lymphocytes are the main components of adaptive humoral immunity and control the antigen-specific immunoglobulin (Ig) production [37]. Like T cells, B lymphocytes are capable of accumulating vitamin C, whereas in the absence of vitamin C, the viability of B cells derived from murine spleens was shown to be decreased [79], further underlining the essential role of vitamin C in proliferation, viability, and function also of B cells. Interestingly, an *in vitro* study revealed a slight dose-dependent apoptosis induction in vitamin C-pretreated murine IgM/CD40-activated B cells, whereas lower vitamin C concentrations promoted antioxidant properties in activated B cells and did not affect cell proliferation and expression of distinct surface molecules, such as CD80 and CD86 [34].

Further studies addressed the effect of vitamin C on antibody production by B cells. To investigate if vitamin C might be beneficial for vaccination strategies directed against infectious bursal disease, specific pathogen-free (SPF) chickens received 1 g/mL vitamin C supplementation and showed higher immunoglobulin levels as compared to placebo controls [80, 81]. In support, a clinical trial with healthy male university students revealed that vitamin C supplementation was associated with a significant increase in the serum IgA and IgM concentrations [82]. Thus, these results underline the regulatory effects of vitamin C in B cell proliferation and function.

Natural Killer Cells

Natural killer (NK) cells are arising from the same lymphoid progenitors as T and B lymphocytes [37] and play important roles in the elimination of pathogens including viruses [83]. Proliferation of human NK cells derived from peripheral blood mononuclear cells could be accelerated by co-incubation with vitamin C resulting in higher cell numbers with accurate functional capacity [84]. Furthermore, the cytotoxic capabilities of NK cells could be blocked via platelet aggregation around migrating tumor cells, whereas *in vitro* vitamin C application increased the cytotoxic activity of NK cells directed against tumor cells [85]. Patients suffering from β -thalassemia major are known to display compromised cytotoxic activity of NK cells [86], which could be rescued by vitamin C application [87]. In healthy subjects, however, the cytotoxic capacities of NK cells could not be further enhanced by vitamin C stimulation [87]. Future *in vivo* trials need to further unravel the vitamin C related effects on NK cell functions.

Antimicrobial Properties of Vitamin C

As early as the 1930s, vitamin C has been known for its antimicrobial effects directed against *Mycobacterium tuberculosis*, the infectious agents of human tuberculosis [88–91]. An *in vivo* study from 1933 revealed that administration of tuberculosis sputum to vitamin C-deficient guinea pigs led to intestinal tuberculosis, whereas the guinea pigs that had received vitamin C-containing tomato juice did not suffer from the disease [92]. Initially it was hypothesized that the antimicrobial properties of vitamin C were due to its pH lowering effect [93]. Another study, however, could prove potent antimicrobial effects of vitamin C directed against group A hemolytic streptococci, even in a nearly pH-neutral environment [94].

Further studies assessed the antibacterial effects of vitamin C against distinct bacterial (opportunistic) pathogens, in more detail, applying microdilution assays. Vitamin C concentrations of 0.31 mg/mL could effectively inhibit *Pseudomonas*

aeruginosa growth *in vitro* [95]. In addition, vitamin C application at low concentration (0.15 mg/mL) was shown to inhibit the growth of *Staphylococcus aureus* [95]. Furthermore, vitamin C could even effectively counteract biofilm formation by methicillin-resistant *S. aureus* (MRSA), displaying low-level resistance to vitamin C (8 to 16 μ g/mL) [96]. Interestingly, pH-neutralized vitamin C had only a minor inhibitory effect on *S. aureus* growth [97]. Furthermore, low concentration of vitamin C (0.15 mg/mL) was shown to have antibacterial effects directed against *Enterococcus faecalis* [95]. These results are contrasted by another study revealing that the *E. faecalis* growth was not affected upon co-incubation with 0.22 mg/mL of vitamin C [98]. Thus, the antibacterial effects of vitamin C might be both, bacterial strain and concentration dependent. In support, vitamin C had only a marginal effect on the growth of *Escherichia coli* ATTC 11775 strain [97]. In combination with lactic acid, however, vitamin C inhibited replication of *E. coli* O157:H7 strain when incubated in brain heart infusion broth or in carrot juice [99], whereas another study reported that vitamin C even reduced the sensitivity of *E. coli* MG1655 to streptomycin [100].

Notably, the co-administration of vitamin C could sufficiently enhance the antibacterial effects of other agents such as epigallocatechin gallate directed even against multidrug-resistant bacterial species such as MRSA [101], which also held true for vitamin C in combination with deferoxamine against Gram-positive cocci, such as *S. aureus* and *S. epidermidis*, as well as against Gram-negative bacilli, including *E. coli*, *Klebsiella pneumoniae* and *Proteus mirabilis* [102]. Synergistic antibacterial effects could also be observed upon co-administration of vitamin C and quercetin [97], whereas the combination of vitamin C with natural extracts such as pomegranate rind extracts [103] and white tea [104] resulted in enhanced anti-*S. aureus* properties of the latter.

In the following paragraph, we will focus on the antimicrobial effect of vitamin C on distinct food-borne Gram-negative bacterial pathogens causing frequent human diseases – some leading to prominent morbidity.

Anti-Helicobacter Effects of Vitamin C

In an *in vitro* study, 10 to 20 mg vitamin C per ml could effectively inhibit *Helicobacter pylori* growth under microaerobic conditions, whereas in an aerobic milieu, vitamin C even promoted *H. pylori* survival in concentrations ranging from 2 to 20 mg/mL [105]. These observations might be explained by the antioxidant properties of vitamin C, protecting microaerophilic bacteria against toxic effects of ROS. Following one-week treatment of *H. pylori*-infected Mongolian gerbils with 10 mg vitamin C daily, gastric pathogen loads could be significantly lowered [106]. In support, several clinical studies reported more effective *H. pylori* eradication upon vitamin C application to infected humans [107–109]. In addition, oxidative stress, apoptotic responses, and decreased cellular viability that had been induced in an *H. pylori*-infected human gastric adenocarcinoma cell line could be counteracted by vitamin C application in its L-ascorbic acid-2-glucoside form [110].

Anti-Salmonella Effects of Vitamin C

It was reported that vitamin C did not exhibit significant antibacterial activity against *Salmonella enterica* in cantaloupe puree [111]. In contrast, vitamin C exhibited antibacterial effects against *Salmonella* Enteritidis in an *in vitro* study using a broiler-digestive model including the crop compartment, the proventriculus, and the intestine [112]. Interestingly, in the

crop compartment, vitamin C alone could even more effectively inhibit *Salmonella* growth inhibition, as compared to a combination with curcumin and boric acid, whereas conversely, in the proventriculus and intestine, only the combination of vitamin C, curcumin and boric acid exhibited significant antibacterial activity against *S. Enteritidis* [112]. Furthermore, a recent study revealed that the antibacterial effect of vitamin C against *S. enterica subsp. enterica* serovar Typhi and *Vibrio fluvialis* could be enhanced when applied in a combination with linalool and copper [113]. The effect of this triple combination on bacterial morphology was demonstrated by scanning electron microscopy using *V. fluvialis*, which showed severe membrane damage, whereas no toxicity could be assessed in human embryonic kidney (HEK293) cells at synergistic concentrations (16.3 μ M, 8 mM, and 1.298 mM vitamin C) [113].

Anti-Campylobacter Effects of Vitamin C

Supported by several *in vitro* studies in the 1980s, vitamin C in a combination with linalool and copper was shown to exhibit synergistic activities against *Campylobacter jejuni* [113]. Fletcher et al. demonstrated the inhibitory effect of vitamin C (0.5 mg/mL) on *C. jejuni* growth *in vitro*, mainly caused by vitamin C oxidation products such as L-dehydroascorbic acid or L-diketogulonic acid [114]. Interestingly, vitamin C in concentrations below 1 mM even stimulated *C. jejuni* growth, whereas 5 mM of vitamin C killed the bacterial cells [115]. This bactericidal effects of vitamin C was further confirmed on *C. jejuni*-contaminated turkey meat, given that *C. jejuni* death rates increased in vitamin C treated samples (5 mmol/kg) [116]. To date studies addressing potential anti-*C. jejuni* effects of vitamin C *in vivo* are missing, however.

Anti-Viral, Anti-Parasitic and Anti-Fungal Effects of Vitamin C

The antimicrobial properties of vitamin C are not restricted to bacterial cells. Several studies reported that vitamin C, especially in form of DHA, inhibited the replication of herpes simplex virus type 1, poliovirus type 1 [117], and influenza virus type A [117, 118]. Moreover, vitamin C effectively inactivated the rabies virus *in vitro* [119]. Also, anti-parasitic effects of vitamin C could be demonstrated. A previous *in vivo* study revealed reduced parasite counts in *Trypanosoma cruzi* [120] and *Plasmodium yoelii* 17XL [22]-infected mice, when treated with vitamin C as compared to placebo control animals, which might also be due to the immunomodulatory properties of vitamin C. In support, another study demonstrated that high doses of vitamin C application (i.e., 8.56 mg/kg body weight) can dampen malarial parasitaemia in infected mice, but surprisingly, the co-administration of vitamin C and the anti-malaria drug artemether [121] reduced parasitic clearance in *Plasmodium berghei* malaria infected mice as compared to artemether application alone [122]. In addition, anti-fungal effects of vitamin C have also been reported. One study showed vitamin C-associated inhibition of Hsp90-mediated morphogenesis in *Candida albicans*, whereas in another study, vitamin C exhibited low-level fungistatic activities against *C. albicans* [95]. Thus, vitamin C possesses potent antimicrobial properties reducing pathogenicity of bacteria, viruses, parasites, and fungi.

Summary and Conclusions

For a few vertebrate species including humans having lost their capacities to synthesize vitamin C themselves during evolution, the uptake of this essential compound from external

sources is mandatory in order to prevent from vitamin deficient conditions resulting in severe morbidities such as scurvy. However, vitamin C supplementation is well tolerated and safe, given a virtual absent risk of intoxication upon uncompromised renal function. The biological role of vitamin C is related to its reversibly oxidized form and is involved in a multitude of both enzymatic and non-enzymatic processes. Additionally, vitamin C is a powerful antioxidant compound directed against free radicals and ROS. Leukocytes including lymphocytes can actively accumulate vitamin C against a concentration gradient, which underlines not only vitamin C dependent functional but also developmental immune cell features. In fact, vitamin C has a pivotal impact on both innate and adaptive immune responses. Vitamin C is also involved in bacterial metabolism. It is known that several bacteria can ferment vitamin C, whereas the presence of this vitamin exposes others to oxidative stress, which may result in bacterial growth inhibition. The potent antibacterial effects of vitamin C are, at least in part, due to its low pH and thus milieu-modifying properties. Notably, vitamin C is able to inhibit the growth of *S. aureus* and streptococci even under neutral pH conditions. Potent growth-inhibitory effects against multi-drug resistant (MDR) bacteria such as MRSA and proven synergistic effects with natural or synthetic antibiotic compounds open novel avenues for the combat of infections with emerging MDR bacterial species. However, both *in vitro* and *in vivo* (experimental and clinical) studies are needed to better understand the molecular mechanism of antimicrobial synergies. This applies not only to bacterial, but also to viral, parasitic, and fungal infections.

List of Abbreviations:

CFU: colony-forming units
 DHA: dehydroascorbic acid
 GLUT: glucose transporter
 HIF: hypoxia-inducible factors
 IBD: inflammatory bowel disease
 IFN: interferon
 Ig: immunoglobulin
 IL: interleukin
 LPS: lipopolysaccharide
 MDR: multi-drug resistant
 MRSA: methicillin-resistant *Staphylococcus aureus*
 NF- κ B; nuclear factor kappa-light-chain-enhancer of activated B cells
 NK cell: natural killer cell
 ROS: reactive oxygen species
 SPF: specific pathogen-free
 SVCT: sodium-dependent vitamin C transporter
 TNF: tumor necrosis factor

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S.M. wrote the paper. S.B. and M.M.H. co-edited paper.

Conflicts of Interest

S.B. and M.M.H. are Editorial Board members.

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