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Review on Effect of Vitamin C on Immune System

By Dr. Abel Abraham Thomas, Ms. Layana Roy & Ms. Fphamin. P. Philipose

Nazareth College of Pharmacy

Abstract- Vitamin C is a water-soluble vitamin that is naturally present in some foods also available as dietary supplement. It's an essential vitamin, and so the body synthesizes vitamin c endogenously. Besides being involved in the biosynthesis of collagen, neurotransmitters, and protein metabolism, it is a potent antioxidant. Its role in immune-boosting is widely studied for various disease conditions. Vitamin c provide immune defense by supporting the innate and adaptive immune system. Vitamin c provides epithelial barrier function against pathogens and promotes the antioxidant activity of the skin, and thus protecting against environmental oxidative stress. Considering the immense organic, physiological capacities and remedial part of nutrient, this audit is an endeavor, to sum up confirmations in this unique circumstance. Understanding the various physiological pathways and effects of vitamin c is essential due to the ever-increasing number of infectious disease.

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Review on Effect of Vitamin C on Immune System

Dr. Abel Abraham Thomas ^α, Ms. Layana Roy ^σ & Ms. Fphamin. P. Philipose ^ρ

Abstract- Vitamin C is a water-soluble vitamin that is naturally present in some foods also available as dietary supplement. It's an essential vitamin, and so the body synthesizes vitamin c endogenously. Besides being involved in the biosynthesis of collagen, neurotransmitters, and protein metabolism, it is a potent antioxidant. Its role in immune-boosting is widely studied for various disease conditions. Vitamin c provide immune defense by supporting the innate and adaptive immune system. Vitamin c provides epithelial barrier function against pathogens and promotes the antioxidant activity of the skin, and thus protecting against environmental oxidative stress. Considering the immense organic, physiological capacities and remedial part of nutrient, this audit is an endeavor, to sum up confirmations in this unique circumstance. Understanding the various physiological pathways and effects of vitamin c is essential due to the ever-increasing number of infectious disease.

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I. INTRODUCTION

The immune system is a multifaceted network of specialized organs, tissues, cells, proteins, and chemicals, which protects the host from a range of pathogens, such as bacteria, viruses, fungi, and parasites. It is divided into epithelial barriers and cellular and humoral constituents of either innate or acquired immunity. More than half a century of research has shown vitamin C to be a crucial player in various aspects of the immune system ^[2]. Vitamin C is an essential nutrient that cannot be synthesized by humans due to the loss of an important enzyme in the biosynthetic pathway ^[3]. Severe vitamin C deficiency results in the potentially fatal disease scurvy. Scurvy is characterized by the weakening of collagenous structures, resulting in poor wound healing and impaired immunity. Individuals with scurvy are highly susceptible to potentially fatal infections such as pneumonia. In turn, infections can significantly impact vitamin C levels due to enhanced inflammation and metabolic requirements^[1]

Vitamin C has several activities that could contribute to its immune-modulating effects. It is a highly effective antioxidant due to its ability to readily donate electrons, thus protecting bio molecules (proteins, lipids,

carbohydrates, and nucleic acids) from damage by oxidants generated during normal cell metabolism and through exposure to toxins and pollutants ^[3]. Vitamin C is also a cofactor for a family of biosynthetic and gene regulatory monooxygenase and dioxygenase enzymes. Vitamin C is also a cofactor for the hydroxylase enzymes involved in the synthesis of catecholamine hormones, e.g., norepinephrine, and amidated peptide hormones, e.g. vasopressin, which are central to the cardiovascular response to severe infection. Vitamin C possesses antimicrobial properties, reducing the risk of infections ^[4], and has immunomodulatory functions, particularly in high concentrations ^[3]. However, one needs to take into consideration that inappropriate storage and preparation procedures of food might result in vitamin C degradation, further supporting the demand for appropriate dietary supplementation of this essential vitamin to reduce the risk of deficiency.

Furthermore, given that vitamin C is water-soluble, intoxication upon excess intake is virtually impossible since vitamin C concentrations exceeding the daily demands will be excrete via the kidneys^[1]. 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 prevent bacterially(including enter pathogenic) infections^[3]

II. IMMUNOMODULATORY PROPERTIES OF VITAMIN C

An optimum concentration of vitamin C is essential for a well-functional host defense mechanism. Several studies revealed that experimentally induced vitamin C deficiency reduces cellular and humoral immune responses. In clinical studies, vitamin C treatment in healthy subjects promoted and enhanced natural killer cell activities, lymphocyte proliferation, and chemotaxis. Furthermore, high doses of vitamin C stimulate murine immune cells, primarily dendritic cells, to more interleukin (IL)-12 secretions but also activated T and B cell functions ^[1]. Also, the observations that vitamin C concentrations in immune cells such as leukocytes are 10- to 100-fold higher than those measured in the plasma and the fact that these cells accumulate vitamin C against a concentration gradient further underline the immunological importance of vitamin C and support its role as a crucial player in

Author α: Assistant Professor, Department of Pharmacy Practice, Nazareth college of Pharmacy, Kerala, India
e-mail: abelthomas119@gmail.com

Author σ ρ: Fifth Year Pharm.D, Department of Pharmacy Practice, Nazareth college of Pharmacy, Kerala, India.

various aspects of immune cell functions, such as immune cell proliferation and differentiation, besides its anti-inflammatory properties^[2]. 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 action. In the gastrointestinal tract, vitamin C plays a role as an essential micronutrient and antioxidant, protecting intestinal cells from inflammatory stimuli. However, in the inflamed mucosa of patients suffering from chronic inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, the mucosal vitamin C concentrations are highly reduced. Also in a small study cohort intravenous high-dose vitamin C application was beneficial as an adjunct treatment option for colorectal cancer. Hence, vitamin C has shown to exhibit potent immunomodulatory activity in the course of distinct gastrointestinal inflammatory morbidities^[3].

III. ROLE OF VITAMIN C IN BARRIER INTEGRITY & WOUND HEALING

The skin has numerous essential functions, the primary of which is to act as a barrier against external agents, including pathogens. The epidermal layer is highly cellular, comprising primarily keratinocytes, while the dermal layer comprises fibroblasts, which secrete collagen fibers, the major component of the dermis. The skin contains millimolar concentrations of vitamin C, with higher levels found in the epidermis than the dermis^[1]. Vitamin C is actively accumulated into the epidermal and dermal cells via the two sodium-dependent vitamin C transporter (SVCT) isoforms one and two, indicating that the vitamin has crucial functions within the skin...

Examples pointing on the role of vitamin C in the skin come from the symptoms of the vitamin C deficiency disease scurvy, which is characterized by bleeding gums, bruising, and impaired wound healing. These symptoms are thought to be a result of vitamin C as a co-factor for the prolyl and lysyl hydroxylase enzymes that stabilize the tertiary structure of collagen. Research has shown that vitamin C can also increase collagen gene expression in fibroblasts^[3]. Vitamin C intervention studies in humans have pointed that enhanced vitamin C uptake into skin cells and enhanced oxidant scavenging activity of the skin. The elevated antioxidant status of the skin following vitamin C supplementation could protect against oxidative stress induced by environmental pollutants^[2]. The antioxidant effects of vitamin C are likely to be enhanced in combination with vitamin E. Vitamin C supplementation of keratinocytes in culture increases differentiation and barrier function via modulating signaling and biosynthetic pathways, with resultant elevations in barrier lipid synthesis^[4]

Dysfunctional epithelial barrier function in the lungs of animals with a serious infection can be restored by administration of vitamin C. It attribute to enhanced expression of tight junction proteins and the prevention of cyto skeletal rearrangements. Vitamin C appears to be particularly essential during wound healing, decreasing the expression of pro-inflammatory mediators and enhancing the expression of various wound healing mediators. Fibroblast cell culture experiments have also indicated that vitamin C can alter gene expression profiles within dermal fibroblasts, promoting fibroblast proliferation and migration, which is essential for tissue remodeling and wound healing. Following surgery, patients require relatively high intakes of vitamin C to normalize their plasma vitamin C status, and administration of antioxidant micronutrients, including vitamin C, to patients with disorders in wound healing, can shorten the time to wound closure. Leukocytes, mainly neutrophils and monocyte-derived macrophages, are main players in wound healing^[3].

During the initial inflammatory stage, neutrophils migrate to the wound site to sterilize it via the release of reactive oxygen species (ROS) and antimicrobial proteins^[2]. The neutrophils eventually undergo apoptosis and are cleared by macrophages, resulting in the resolution of the inflammatory response. However, in chronic, non-healing wounds, such as those observed in diabetics, the neutrophils persist and instead undergo necrotic cell death, which can perpetuate the inflammatory response and hinder wound healing.^[3]

IV. EFFECT OF VITAMIN C ON DISTINCT IMMUNE CELLS: MONOCYTES & MACROPHAGES

The major component of the innate immune system, monocyte and macrophages are the first-line of defense against invading pathogens. The high vitamin C concentrations measured in monocytes underline the regulatory role of this vitamin in monocyte and macrophage functions.^[3] An in vitro study revealed that intracellular accumulation of pharmacologic vitamin C concentrations could effectively inhibitapoptotic pathways in human monocytes. Vitamin C may also regulate distinct genes expressed in human macrophages, which are induced by lipopolysaccharide via nuclear factor kappa-light-chain-enhancer of activated B cells activation. Moreover, vitamin C application to monocytes derived from whole human blood diminished secretion of pro-inflammatory cytokines such as IL-6 and TNF- α ^[2]

a) Neutrophils

The exposure of neutrophils to oxidants inhibits their motility, which is related to oxidation of membrane lipids and affecting cell membrane fluidity. As a potent water-soluble antioxidant, vitamin C can neutralize

reactive oxidants and regenerate cellular and membrane antioxidants such as glutathione and vitamin E (tocopherol)^[3]. To protect themselves from oxidative damage, neutrophils accumulate vitamin C, resulting in improved cellular motility and migration in the response to chemotactic stimuli and, subsequently, in enhanced phagocytosis of microbes and generation of reactive oxygen species.

b) *T Lymphocytes*

T lymphocyte, as major players in acquired immunity, has impact by vitamin C. The development and maturation of murine and human T cells are enhanced in vitamin C in physiological concentrations, where the proliferation and viability of T lymphocytes are also affected. In human peripheral lymphocytes, vitamin C application promotes

T cell proliferation. However, a decreased number of human IL-2 producing T cells could be assessed in the presence of vitamin C. In contrast TNF- α and interferon (IFN)- γ expressing T lymphocytes were not affected. In murine splenic T cell cultures, only high vitamin C levels (0.25–0.5 mM) has shown to decrease T cell viability and secretion of 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. Vitamin C administration during sepsis modify 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.^[3]

c) *B Lymphocytes*

B lymphocytes are the main component of adaptive humoral immunity and control the antigen-specific immunoglobulin (Ig) production. 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, further underlining the essential role of vitamin C in proliferation, viability, and function also of B cells

d) *Natural Killer Cells*

Natural killer (NK) cells are arising from the same lymphoid progenitors as T and B lymphocytes and play important roles in the elimination of pathogens, including viruses^[2]. The proliferation of human NK cells derived from peripheral blood mononuclear cells can be accelerated by co-incubation with vitamin C resulting in higher cell numbers with accurate functional capacity.

Furthermore, the cytotoxic capabilities of NK cells can block via platelet aggregation around migrating tumor cells, whereas in vitro vitamin C application increased the cytotoxic activity of NK cells directed against tumor cells. Patients suffering from β -thalassemia major are known to display compromised

cytotoxic activity of NK cells, which could be rescued by vitamin C application^[3].

V. THE ROLE OF ASCORBATE IN THE HYPOXIC RESPONSE & IMPLICATIONS FOR IMMUNE CELL FUNCTION

The hydroxylase enzymes that regulate the activity of the hypoxia-inducible factors (HIF)s require ascorbate for optimal action. The HIFs are controlled by hydroxylation of proline and asparagine residues on the regulatory alpha subunit and, in response to changes in oxygen availability, direct the transcription of hundreds of genes via the hypoxia response element^[1]. The dependence of the hydroxylases on ascorbate as a cofactor has been demonstrated in cell-free systems, with other reducing agents such as glutathione being very much less effective as a recycler of the hydroxylase active site. Depleted intracellular ascorbate levels have been shown to contribute to the up-regulation of HIF activation, particularly under conditions of mild or moderate hypoxia. The interaction between ascorbate and the HIFs is relevant to the function of immune cells in both inflammation and cancer. Inflammatory sites are known to be under hypoxic stress, potentially due to the increased oxidative metabolism of inflammatory cells. Growing tumors are also well characterized as being hypoxic tissues due to rapid proliferation and outgrowth of the established blood supply^[2]. The resulting up-regulation of the HIFs is the main reason for the activation of glycolysis, angiogenesis, resistance to chemotherapy, and the promotion of a stem cell phenotype, thereby promoting tumor growth and metastasis. At inflammatory sites and in tumor tissue, the hypoxic environment affects immune cell function and, given the interdependence between the HIFs and cellular ascorbate^[3].

VI. ANTIMICROBIAL PROPERTIES OF VITAMIN C

Vitamin C is known for its antimicrobial effects directed against *Mycobacterium tuberculosis*, the infectious agent of human tuberculosis. An in vivo study revealed that administration of tuberculosis sputum to vitamin C-deficient guinea pigs led to intestinal tuberculosis. In contrast, the guinea pigs that had received vitamin C-containing tomato juice did not suffer from the disease^[1]. Initially, it was hypothesized that the antimicrobial properties of vitamin C were due to its pH lowering effect. Another study, however, could prove potent antimicrobial effects of vitamin C directed against group a hemolytic streptococci, even in a nearly pH-neutral environment. Further studies assessed the antibacterial effects of vitamin C against distinct bacterial (opportunistic) pathogens in more detail, applying microdilution assays^[1]. Vitamin C

concentrations of 0.31 mg/mL could effectively inhibit *Pseudomonas aeruginosa* growth in vitro. Also, vitamin C application at low concentration (0.15 mg/ml) to inhibit the growth of *Staphylococcus aureus*. The antibacterial effects of vitamin C might be both bacterial strain and concentration dependent.

VII. REVIEW OF STUDIES CONDUCTED

Anitra. C. C. and Silvia. M did a review on the topic "Vitamin C and Immune function." They point out that vitamin C appears to exert a multitude of beneficial effects on cellular functions of both the innate and adaptive immune system. Even though vitamin C have potent antioxidant activity in the body against both endogenous and exogenous oxidative reactions, likely its action as a cofactor for numerous biosynthetic and gene regulatory enzymes plays a critical role in its immune - modulating effects. Vitamin C stimulates neutrophil migration to the infection site, enhances phagocytosis and oxidant generation, and microbial killing. At the same time, it protects host tissue from excessive damage by increasing neutrophil apoptosis and clearance by macrophages, and decreasing neutrophil necrosis. Thus, it is apparent that vitamin C is necessary for the immune system to mount and sustain an adequate response against pathogens, while avoiding further damage to the host. Vitamin C helps in preventing and treating respiratory and systemic infections by various immune cell functions alterations. Prophylactic prevention of malaria requires dietary vitamin C intakes that provide at least adequate, if not saturating plasma levels, which optimize cell and tissue levels

Abel. A, Juliet. P. M, Margaret. C.J and Margreet. C.D did a review on the topic "Vitamin C and immune cell function in inflammation and cancer." They explain that Vitamin C (ascorbate) when maintained at peak levels in most immune cells and can alter many aspects of the immune response. At intracellular levels generally it responds to variations in plasma ascorbate availability and imbalance during severe stress can result in low plasma ascorbic acid status. Intracellular ascorbate is essential, in particular, acts as an enzyme cofactor for Fe- or Cu-containing oxygenases. The demonstrated dependency of the Fe-containing 2-oxoglutarate-dependent di oxygenase family on ascorbate availability and the involvement of members of this family of enzymes on many immune cell functions provide a rational basis for the belief that ascorbate supports the immune system. Ascorbate availability will influence HIF activation and immune cell function in hypoxic inflammatory and tumor environments, affecting the resolution of inflammation..

Soraya. M, Stefan. B and Markus. H.M studied the topic "Immune modulatory and antimicrobial effects of Vitamin C." 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. Vitamin C has a good impact on both innate and adaptive immune responses. Vitamin C is also involved in bacterial metabolism. It is proven 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 due to its low pH where bacterial growth is inhibited. Notably, vitamin C can 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.

Benjamin. S.V did a study on the topic "Vitamin C and the immune response in health and disease." Vitamin C can affect various aspects of the immune process. Its concentration in leukocytes and rapid utilization during infection, and its depression in clinical situations associated with reduced immunologic function have suggested a role for the vitamin in the immune response.

Ascorbic acid affect other facets of the immune response, including delayed hypersensitivity and monocyte-macrophage reactivity. The introduction of ascorbic acid as an antiviral and antibacterial agent needs further stimulated study on the possible immunologic mechanisms involved in its protective role. Vitamin C has also been used to treat several 254 immunology associated blood disorders, including rheumatic and allergic diseases. In patients with neutrophilic dysfunctions such as Chediak-Higashi syndrome, chronic granulomatous disease, and recurrent infections, vitamin C has been administered and shows some immunologic and clinical benefit.

Nilashi M, Samad S, Shahmoadi I, Ahmadi Hossein, Akbari Elnaz, Rashid T A did a study on "The COVID-19 infection and the immune system: The role of complementary and alternative medicines". The study was conducted at Department for Management of Science and Technology Development, Ton Duc Thang University, Ho Chi Minh City, Vietnam, School of Engineering, University of California, Merced, USA, Health Information Management Department, School of Allied Medical Sciences, Tehran University of Medical Sciences, Tehran, Iran. This study investigates the efficacy of Complementary and Alternative Medicines (CAMs) in boosting immune response against COVID-19. As per the study due to the wide spread universal impact of the COVID -19 and as there is no clinically

approved antiviral introduction or vaccination exits it is critical to analyze the nature of the disease and relation with human immune system and to develop immunity boosting measures against COVID-19. Recognizing the disease and its consequences on the immune system will support its better management providing preferred treatment strategies and more effective prevention. It is found that CAMs are effective in boosting immune response and diseases. Several cases of CAMs proposed for prohibiting and curing diseases are identified. An example for CAM is CURCUMIN which is found to improve the immune function against many disease conditions. It acts by modulating the response of T cells. It has been demonstrated that Vitamin C, Vitamin D and zinc boost the immune system versus viruses. It is guaranteed that the Covid pandemic can be fundamentally brought down by utilization of high use of vitamin C. Antiviral action of nutrient C has been perceived and affirmed in the past, however it's generally less communicated and specifically, there exist lack of data on its impact on Covid. Vitamin C can be directed with expected meds to treat the malady in intense conditions. Early administration of vitamin C as IV is found to be effective in the treatment of COVID-19.

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perceived and affirmed in the past. However, it's generally less communicated, and specifically, there exists a lack of data on its impact on Covid. Vitamin C can be directed with expected meds to treat the disease in intense conditions. Early administration of vitamin C as IV was found to be effective in the treatment of COVID-19. Sorice A, Guerriero E, Capone F, Colonna G, Castello Giuseppe, Costantini studied "Ascorbic Acid: Its Role in Immune System and Chronic Inflammation Diseases" at Centro Ricerche Oncologiche di Mercogliano, Istituto Nazionale Per Lo Studio E La Cura Dei Tumori "Fondazione Giovanni Pascale." IRCCS, Italy; Biochemistry, Biophysics and General Pathology Department, Second University of Naples, Italy. According to the study, Ascorbic acid (AA) or Vitamin C, was initially identified as the factor preventing scurvy; it is well known for its antioxidant properties. Being co-substrate of a large class of enzymes, regulates gene expression by acting with main transcription factors. AA is also linked to inflammatory processes and involves immunity. AA is essential to stimulate the immune system by increasing the strength and protection of the organism. Therefore, its immune stimulant inflammatory, antiviral and antibacterial roles are well known. We can conclude that AA, due to its effects and diversity of regulated pathways, is suitable for use in various fields of medicine. AA is not preferable to be used as an isolated mode of treatment. Still, it can be used as an adjuvant to regulate immunity, gene expression, and other main physiological processes. Besides these properties, vitamin C is cost-effective and chances of toxicities, and its simple administration techniques increase the compliance of the drug. In conclusion, it is very significant to understand the synergistic actions, interactions, counteraction of vitamin c, and thus, extensive research is essential on this subject.

Bendich A did a study on "Physiological Role of Antioxidants in the Immune System." According to this in order to tackle the large number of free radicals that generates in our body, it is critical eradicating them with antioxidants. There is much strong evidence that suggests that supplementation with vitamins A, C provides a safe and effective means to enhance immune functions. Vitamin A supplementation significantly effective in measles in children.

The protective effects of vitamin c were associated with an enhancement in immune responses and reduced the rate of secondary infections. Supplementation with vitamin C is co-related with the enhancement of immune responses in several population groups. Many of the immune response modulations destroys cancer cells. The antioxidant micronutrients protected immune responses from the immunosuppressive effects. Thus, antioxidant vitamins enhance immune responses that are involved in protection from infection and malignancies.

The data strongly suggest that the intake is needed to improve immune responses.

VIII. DISCUSSION

Vitamin c has many beneficial effects on cellular function of the innate and adaptive immune system. Vitamin c is a potent antioxidant give protection against endogenous and exogenous oxidative reactions, it act as a cofactor for numerous biosynthetic and gene regulatory process and plays a crucial role in its immune-modulation. Vitamin C activate neutrophil migration to the infection site, improve phagocytosis and provide antimicrobial activity. Vitamin c can be used to and treat respiratory and foundational contaminations by improving different resistant cell capacities. Prophylactic counteraction of contamination requires dietary nutrient c admissions that give at any rate sufficient, if not soaking plasma levels (i.e., 100–200 mg/day), which upgrade cell and tissue levels. Conversely, treatment of set up diseases requires essentially higher (gram) portions of the nutrient to make up for the expanded metabolic interest. Vitamin c has a number of activities that could contribute to its immune-modulating effects. It is a highly effective antioxidant, due to its ability to readily donate electrons, thus protecting important bio molecules (proteins, lipids, carbohydrates, and nucleic acids) from damage by oxidants generated during normal cell metabolism and through exposure to toxins and pollutants

IX. CONCLUSION

In clinical studies, vitamin c treatment in healthy subjects promoted and enhanced natural killer cell activities, lymphocyte proliferation, and chemotaxis. Furthermore, high doses of vitamin c not only stimulate murine immune cells, primarily dendritic cells, to more distinct interleukin-12 secretion, but also activated T and B cell functions. Overall there is large body of evidence supporting that maintaining healthy vitamin c level can have a protective function against age related cognitive decline but avoiding vitamin c deficiency is likely to be more beneficial than taking supplements on top of normal healthy diet. Study on the topic “immuno modulatory and antimicrobial effects of vitamin c” conducted by M.soraya, B.stefan and H.M.markus explains well about the biological pathway of vitamin c. Thus, it is apparent that vitamin c is necessary for the immune system to mount and sustain an adequate response against pathogens, whilst avoiding excessive damage to the host.

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Abbreviations

CFU: colony-forming units
 DHA: dehydroascorbic acid
 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*
 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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