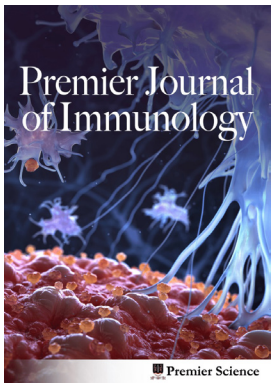

Role of Vitamin C in the Management of Immunologic Disorders

Muhammad Imran Qadir and Iqra Rasheed

Institute of Molecular Biology and Biotechnology, Bahauddin Zakariya University, Multan, Pakistan

Correspondence to: Muhammad Imran Qadir, mrimranqadir@hotmail.com

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ABSTRACT

Vitamin C was discovered in the twentieth century as a preventer of scurvy during research on guinea pigs by Albert Gyorgyi. Since then, scientists have faced many challenges in taking its beneficial claims in medical sciences. Several studies concluded that a higher intake of vitamin C, which is an antioxidant, reduces the risk of multiple diseases, such as coronary heart disease, stroke, common cold, kidney stone, and diabetes. However, some studies did not agree on the beneficial effects of vitamin C. Nowadays, many studies with advanced techniques have been accomplished to appraise the beneficial role of vitamin C. Vitamin C plays a vital role in the human body by stimulating the activity of white blood cells, and it is well known that white blood cells are the basic components of immunity. Therefore, it has been recognized through extensive research that vitamin C reduces the risk of many immunologic diseases and has a role in treating them also. Autoimmune diseases, asthma, common cold, cancer, osteoarthritis, gout, age-related macular degeneration, and cataracts are some of the diseases among them.

Keywords: Antioxidant, Coronary heart disease, Common cold, Cancer, Asthma, Diabetes, Aging, Obesity, Alzheimer's disease

Introduction

Vitamin C is water-soluble, is chemically known as ascorbic acid or specifically L-ascorbic acid, and is abundantly present in fruits, vegetables, and the adrenal glands of most animals.[1] Naturally, vitamin C is obtained from vegetables and fruits such as cauliflowers, tomatoes, and citrus fruits. In the 1920s, Albert Gyorgyi, a Hungarian biochemist and physiologist, with the assistance of his coworker, was working on the guinea pig (*Cavia porcellus*) to study scurvy which is caused by the deficiency of vitamin C. He observed scurvy symptoms as dry skin, acne on the skin, swollen and bleeding gums, delay in wound healing, and fatigue. As the result of the study, he presented vitamin C as a hexuronic acid (any uronic acid obtained from hexoses).[2] However, with the advancement in technology, it has been confirmed that vitamin C is not an hexuronic acid, but it has a fused ring instead (Figure 1).

Vitamin C is a gift of nature, richly present in plants and most animals. However, it cannot be synthesized in humans and apes due to the absence of an enzyme known as gulonolactone oxidase. Humans fulfill this need by using plants and animals which are the major source of vitamin C. Plants have a higher quantity of vitamin C usually up to 5,000 mg/100 g as compared to animals, which have a concentration less than 30–40 mg/100 g. Animals make their own vitamin C by converting D-glucose into vitamin C, a phenomenon occurring in their liver. For medicinal purposes, vitamin C is obtained from both natural and synthetic sources. Oxygen, alkali, and high temperature are the main factors that deteriorate vitamin C; therefore, medicinal vitamin C should avoid these factors. The recommended daily vitamin C intake for men is 90 mg/day and for women is 75 mg/day.[3–5]

Vitamin C is essential in supporting the immune system and overall health in humans. Vitamin C plays countless physiological roles, such as helping in the synthesis of collagen, neurotransmitters, carnitine, and folic acid. Moreover, it helps to convert cholesterol into bile acid to reduce the blood cholesterol, helps to absorb the dietary nonheme iron by reducing active iron, helps to repair wound healing,[6] acts as a preventer to reduce the hazardous functions of environmental factors such as ultraviolet (UV) radiation and free radicals (which cause skin cancer), and plays an important role in immunity. Vitamin C has its effects on immunity due to its antioxidant activity. Vitamin C has key roles in immune modulation, such as its effects on oxidative stress, inflammation, and immune cell regulation. Vitamin C increases the cellular proliferation and concentrations of interleukin-2 (IL-2), interleukin-17 (IL-17), and interferon gamma (IFNy). The mechanism behind how vitamin C modulates immune cells is given in table 1. Vitamin C behaves as a cofactor in reducing the risk of many disorders caused by reactive oxygen species (ROS) that damage important molecules of protein, lipids, and DNA by blocking the activities of ROS compounds and reducing the formation of free radicals (factors to produce ROS) causing oxidation of these molecules. Vitamin C as an antioxidant (a substance that present at low concentrations and delay the process of oxidation caused by low-density lipoprotein which enhances iron absorption)[7] reduces the risk of oxidative stress, which is considered a starting point for many disorders.[8] Vitamin C, in peripheral blood mononuclear cells, modulates gene expression, especially upon an inflammatory stimulus.

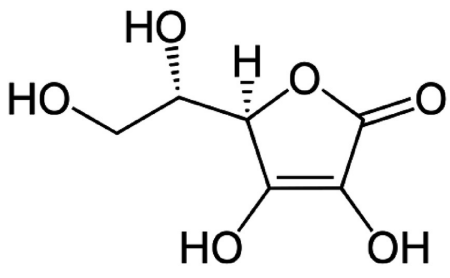

Fig 1 | The structure of vitamin C (ascorbic acid)

Immunology has been involved in the pathogenesis of many diseases, including cardiovascular diseases (CVDs), asthma, and cancer (Figure 2). Recently, vitamin C has been found to cure immunologic diseases. In addition to directly affecting immune cells, vitamin C also acts as an important antioxidant to the cells of the immune system. It can help to protect cells from both endogenously and exogenously produced ROS during an immune response.

Table 1 | How vitamin C modulates immune cells

T Cell	B Cell	Macrophage	Dendritic Cell
Increases cellular proliferation	Increases cellular proliferation	Increases antiviral factors	Increases antiviral factors
Increases cytotoxicity	Increases production of antibodies	Decreases concentrations of interleukin-1 beta (IL-1β) and interleukin-6 (IL-6)	Decreases concentrations of IL-1β and IL-6
Increases concentrations of IL-2, IL-17, and IFNγ			

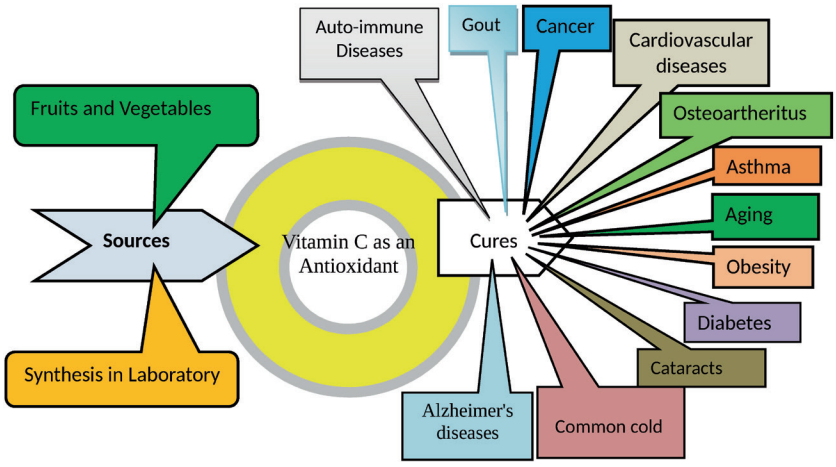

Fig 2 | Role of vitamin C in the management of different immunologic diseases

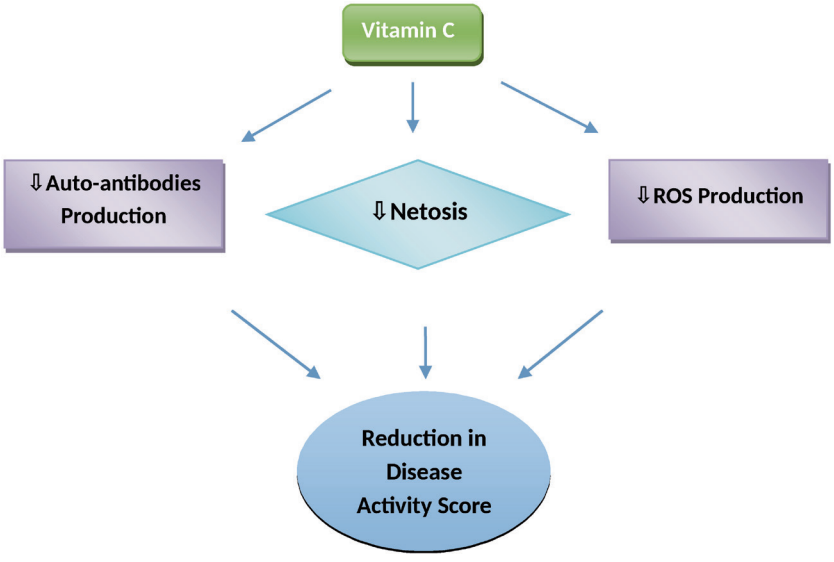

Fig 3 | Action of vitamin C in controlling autoimmune diseases

Autoimmune Diseases

In autoimmune diseases, the body produces immunity against its own body components. A large number of autoimmune diseases have been recognized, including, but not limited to, systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, type 1 diabetes, and psoriasis. Vitamin C can help in the management of autoimmune diseases by reducing inflammation and oxidative stress by decreasing the production of pro-inflammatory cytokines and free radicals. In detail deliberation, vitamin C decreases the production of autoantibodies and reduces ROS production, and also causes specific cell death of neutrophils known as NETosis. All these factors result in a reduction in the disease activity score (DAS) (Figure 3).[9]

Asthma

Asthma is known to be a multifaceted chronic disease with various symptoms, including coughing, wheezing, shortness of breath, and chest tightness. About 7% of the US population and 8% of the UK population are facing this problem.[10] Asthma is one of the most important immunologic disorders in humans. Immunologic mechanisms of asthma involve both innate immunity and adaptive immunity. Different studies conducted around the world concluded that vitamin C, as an antioxidant, plays a vital role in the treatment of asthma.[11] Vitamin C has its importance in the progression of asthma as scientific workers have established that a diet with low levels of vitamin C increases the risk for this condition.[12] The scientific workers have also confirmed that vitamin C may help to reduce symptoms of exercise-induced asthma.[13]

Cardiovascular Diseases

The role of the adaptive immune system has shown an association with CVD risk due to a sustained and chronic inflammatory state. CVD risks are considered as human health factors observed in undeveloped and developed countries, more consistently exits as a mortality factor in the United States.[14] In a report by the American Heart Association, coronary heart diseases were present in 6.2% adults and $320.1 billion were being directly or indirectly treated for CVDs in the United States.[15] Different cohort studies concluded that an intake of vitamin C inverses the risk of coronary heart diseases.[16] Recently, randomized controlled trials deliberated the association between serum vitamin C and risks of coronary heart disease by arranging a setup with a population of ages ranging from 48 to 82. The results were unexpected; vitamin C supplements surprisingly reduced the serum level of low-density lipoprotein. Similarly, epidemiological studies have proved that vitamin C decreased the risk of coronary heart diseases in those people whose diet included a sufficient amount of natural dietary vitamin C; the participants were using fresh fruits and vegetables that have a treasure of multivitamins and a better source of vitamin C. Some recent researches revealed that vitamin C is useful in avoiding a heart attack. It was

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established by a mechanism in which vitamin C has antioxidant effects, ultimately as a preventer of oxidative stress caused by the addition of iron to plasma that inhibits the proper functioning of coronary arteries resulting in a heart attack.[17] Another important function of vitamin C as an antioxidant is that it enhances the endothelial nitric oxide and vasodilatation that prevents the attachment of leukocytes with the endothelium.[13] Physicians also recommend an intake of vitamin C in the diet because of its antioxidizing ability and thereby reducing high blood pressure observed in patients.[18]

Cancer Treatment and Prevention

It has been shown that vitamin C is able to modulate the anticancer immune response and to help to overcome the resistance to immune checkpoint blockade drugs such as cytotoxic T-lymphocyte antigen 4 and programmed cell death ligand 1 inhibitors. Cancer is a collective form of cells growing abnormally due to involvement of unfavorable factors such as excess exposure to UV radiation, obesity, limited physical activity such as exercise and walk, environmental pollutants, and oxidative stress.[19] Nobel laureates Pauling and Cameron performed work on a high dose of vitamin C (10 g/day) to treat cancer. Now this work is expanded by other research institutes as randomized control trials, clinical trials, and placebo-controlled trials. Epidemiological studies and other controlled studies accepted the role of vitamin C in preventing and treating cancer (Figure 4).[16] However, prospective cohort studies did not accept its role in the prevention and treatment of cancer due to the unstable results observed during studies.[20] However, high-quality clinical trials accepted the role of vitamin C taken both orally and intravenously. Randomized controlled trials suggested that the use of vitamin C as a mega dose (2 g twice a day) regularly caused the death of cancer cells under chemotherapy and reduced the recurrence rate.[21] Alongside it, the higher dose of intravenous vitamin C enhanced the quality of life of cancer patients who faced problems during chemotherapy.[22] Other epidemiological studies concluded that a mega dose of vitamin C is helpful in the treatment of different cancer cases, such as breast cancer, esophageal cancer, lung cancer, pancreatic cancer, colorectal cancer, prostate cancer, cervical cancer, ovarian cancer, and cancer of the head and neck. Further, the scientific workers in their studies have concluded that vitamin C acts an anticancer compound that helps to enhance the collagen synthesis resulting in the prevention of the formation of kidney tumors by estradiol or diethylstilbestrol. Ascorbyl stearate, a vitamin C derivative, has a great importance in the treatment of pancreatic cancer by reducing abnormal cell's proliferation. Further studies showed that a higher intake of vitamin C limited the risk of stomach cancer by the carcinogenic N-nitroso compounds.[23] Changes in lifestyle and intake of healthy diet rich in vitamins C limit the risk of both of the two most common types of esophageal cancers: the esophageal squamous cell carcinoma and the esophageal adenocarcinoma.[24] Vitamin C also reduces the risk of breast cancer that exists in women excessively due to oxidative stress, the main environmental factor in enhancing the risk of every type of cancer.[25]

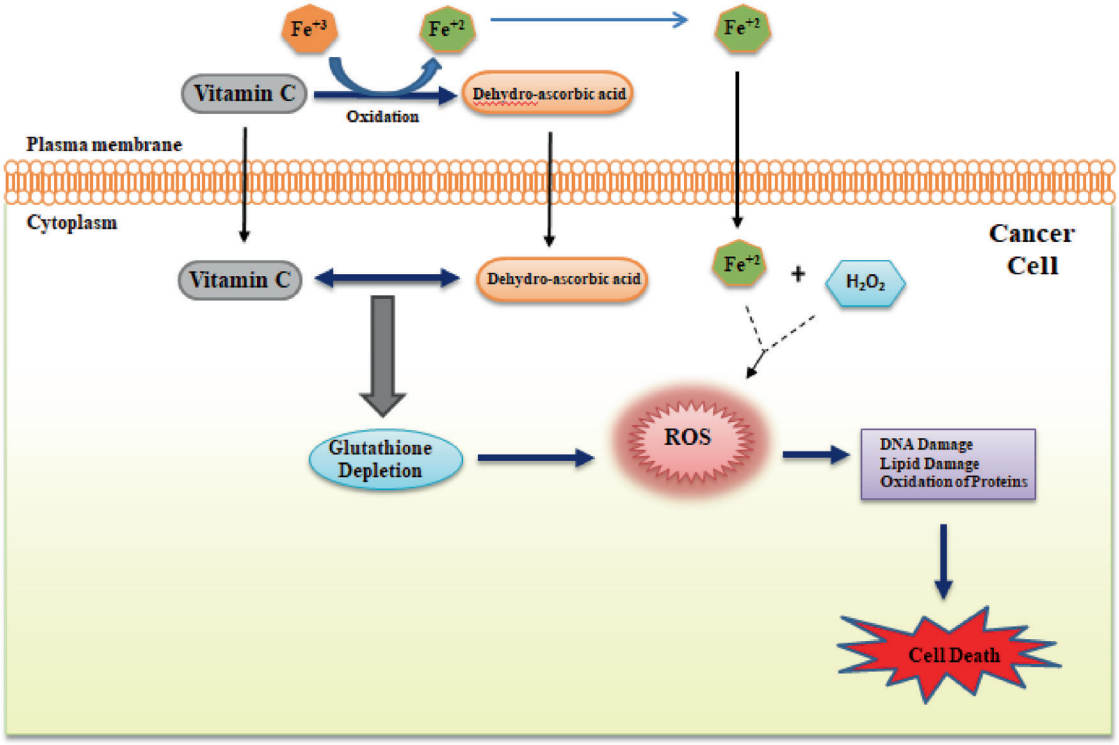

Fig 4 | Mechanism for cancer treatment by vitamin C

Vitamin C increases collagen production due to its cofactor ability, to protect against damage from ultraviolet A and ultraviolet B rays to cure pigmentation problems and inflammatory skin condition.[4] Hypoxia-inducible factor 1 (HIF-1) is a factor in human beings that causes the melanoma in which pigmentation appears on the face. In this case, vitamin C and ascorbate-2-phosphate may be used to prevent the melanoma by reducing the expression of HIF-1 to stop initiating the process of malignancies in human beings.[17] Recent studies suggested that vitamin C cannot treat the cancer alone, but need some cochemicals like vitamin E, carotenoids, and retinoic acid.[26]

Common Cold

Initially, the concept of preventing common cold by using a high dose of vitamin C was introduced by Pauling. The results were seen as inconsistent, confusing, and controversial by the majority of the scientific community.

However, interest among the general population remained so high for a longer time and eventually vitamin C became the remedy for prevention and treatment of common cold in practice. In 2007, placebo-controlled trials set between a general population and specific population, which faced physical stress conditions to observe the role of vitamin C after the attack of cold symptoms. Marathon runners, soldiers, and the general population were given 200 mg/day of vitamin C. The results of the study were unexpected. It was observed that cold symptoms reduced among marathon runners and soldiers by approximately 50%, but such reduction was not observed in the general population. The study also observed that in response to infection of cold microbes, vitamin C enhances the immune system.[27,28]

Gout and Osteoarthritis

Gout is an inflammatory arthritis characterized by red, tender, hot, and tumid joints. The development, cause, and process of gout is very complicated; recent studies, notwithstanding, have offered novel perspectives on the mechanism from an immunologic viewpoint. The pathological process of gout involves both innate and adaptive immune responses.[29]

The condition in which uric acid increases in blood to form monosodium urate crystals in joints, and as a result the patient has swelling in joints and feels severe pain during walking, is known as gout. About 4% of adults suffer from this disease. A healthy diet containing vitamin C and changes in the lifestyle may be helpful in the prevention and treatment of gout. Two cohort studies had resulted in the same results that a higher intake of supplemental vitamin C (500 mg/day) may be responsible for reducing the serum uric acid level in blood and ultimately overcoming the gout. [30]

Osteoarthritis is a major joint disease, causing the destruction of cartilage activity (the main factor to stable joint collagen), and as a result the patient facing knee pain and lower limb disability. This disease is more common in aged people as compared to younger ones. Vitamin C appeared as a preventer of osteoarthritis by acting as a cofactor in the metabolism and synthesis of collagen which is the component of cartilage. Some scientific workers concluded that vitamin C having antioxidant property is helpful in reducing osteoarthritis by decreasing the damage caused by oxidative stress.[31–33]

Age-Related Macular Degeneration and Cataracts

The role of inflammation and immunity has recently emerged as a key pathogenic factor in age-related macular degeneration (AMD). AMD patients have autoantibodies against macular tissue antigens. Similarly, cataracts have been associated with many systemic diseases, including autoimmune diseases.

AMD and cataracts are eye-related disorders caused by the breakdown of protein in the lens, causing blindness in people. In many developing countries, nutritional deficiencies are the main reason for AMD and cataract. Beside them, oxidation stress, age-related modification, and insufficient intake of vitamin C are major factors contributing to AMD and cataracts in different age groups of peoples. All advanced studies have recognized the role of vitamin C, along with other vitamins like beta-carotene and vitamin E, in the reduction of the progression of AMD and cataracts. Vitamin C acts as an antioxidant to inhibit the production of pseudoexfoliation syndrome which leads to the accumulation of extracellular material inside the ocular tissues.[34,35]

Diabetes

Diabetes is a metabolic disorder with hyperglycemia, involving a complex immunologic process. Usually, diabetes is classified into two types: type 1 diabetes and type 2 diabetes. Type 1 diabetes is an autoimmune disease, and is caused by insufficient production of insulin, resulting in the failure to control an excessive amount of blood sugar (glucose). In this situation, the patient feels severe thirst and hunger. Approximately 10% of all diabetes cases are of type 1. In type 2 diabetes, patients do not produce an adequate supply of insulin to do its proper function. Approximately 90% of all cases of diabetes worldwide are of this type. There is excessive ongoing research on type 2 diabetes, and the scientific workers have established the role of the immune system in the progression of type 2 diabetes.

Vitamin C is a vital component and its deficiency induces the risk of diabetes mellitus. Vitamin C's structural similarity to glucose makes it of interest in diabetes. Vitamin C has an antioxidant property that helps fight against oxidative stress, which destroys the activity of glucose metabolism and hyperglycemia and becomes a reason for induce the risk of diabetes. Therefore, vitamin C is of great importance in preventing the risk of diabetes.[36]

Obesity

Obesity is a state in which fat is accumulated in different parts of the body and has adverse effects on

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the health of human beings. According to the World Health Organization (WHO), in 2022, 1 in 8 people in the world were living with obesity, as reported in March 2024. (https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight) Risk factors responsible for causing obesity include genetic disorders, insufficient diet, eating habits, and environmental factors (oxidative stress). Obesity is responsible for major diseases including type 2 diabetes, inflammation, hypertension, cardiovascular diseases, and cancer. Obesity is known to impair immune function, altering leucocyte counts as well as cell-mediated immune responses. In addition, evidence has arisen that an altered immune function contributes to the pathogenesis of obesity. Different studies suggest that the addition of vitamin C to our diet is a better way to prevent obesity, through a mechanism in which vitamin C acts as an antioxidizing agent and causes the reduction of oxidative stress (caused by free radicals released in the body).[37,38]

Alzheimer's Disease

The immune system is now considered a major factor in Alzheimer's disease (AD). AD is a neurodegenerative type of dementia termed as "loss of memory due to death of brain cells." At the start of the disease, symptoms are not severe but later the symptoms become severe progressively due to the death of brain cells. Vitamin C, as an antioxidant, plays a beneficial role in curing symptoms of Alzheimer's disease mainly caused by oxidative stress. Moreover, vitamin C also reduces the activity of other factors involved in the progression of AD; for example, it reduces the β-amyloid development and acetylcholinesterase activity and exhibits the generation of endothelial dysfunction by regulating nitric oxide. Clinical trials recognize the role of vitamin C to cure Alzheimer's disease. Nowadays, vitamin C is in practice therapeutically to cure neurodegenerative disorders.[39]

Aging

Aging represents a paradox of immunodeficiency and inflammation (inflammaging) and autoimmunity. The term "aging" is defined as the progressive changes resulting in decline of age-specific fitness components, and ultimately even in the death of the human being. Vitamin C plays an important role in delaying the process of aging caused by oxidative stress that damages DNA. Vitamin C is used in medicinal creams and skin therapy to prevent skin damage, inflammation, and allergy caused by UV radiation and oxidative free radicals.[40]

Conclusion

From the above exposition, we concluded that vitamin C is an essential nutritional component for the prevention and treatment of human immunologic disorders. Therefore, vitamin C is recognized as one of the basic components that reduce the risk of many immunologic diseases and are used to treat them. CVDs, cancer, common cold, asthma, osteoarthritis, gout, AMD, and cataracts are some of the diseases among them.

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