Review Article

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Effect of Vitamin C on Cancer Process

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ABSTRACT

The diverse roles of vitamin C in combatting cancer through its antioxidative and pro-oxidative properties, as well as its immune-boosting functions, are significant. Vitamin C acts as a cofactor for oxygenase enzymes containing iron or copper, aiding in two key processes: firstly, the stimulation of reactive oxygen species production, which selectively targets cancer cells, and secondly, the regulation of cellular metabolism and epigenetic processes involving DNA and histone demethylases, thereby diminishing tumorigenesis. Although various studies highlight the potential effectiveness of vitamin C against different cancer types in laboratory and animal studies, both as a standalone treatment and in combination with traditional chemotherapy and radiation, its role in clinical or non-clinical human studies remains unclear and contentious. Recent papers of randomized clinical trials or observational studies have not yielded conclusive evidence supporting vitamin C's clinical efficacy in cancer treatment or prevention. In this review, vitamin C usage and its efficacy in cancer therapy approaches have been focused and discussed. In conclusion, it may be speculated that these complexities highlight the need for larger, high-quality randomized clinical trials to provide more definitive understanding of vitamin C's anticancer potential and to establish appropriate clinical recommendations.

Keywords: Vitamin C, Ascorbic acid, Cancer, Cancer therapy, Supplementation

1. Introduction

Vitamin C (ascorbic acid, ascorbate) is an essential nutrient vital for various biological processes but cannot be synthesized by humans due to the absence of the gluconolactone oxidase enzyme [1]. Adequate daily intake, typically ranging from 100-200 mg/day, is crucial through diet or supplements to ensure near-complete absorption, achieving plasma concentrations of 70–80 μM [2,3]. Vitamin C serves as a crucial cofactor in hydroxylation reactions for numerous enzymes, hormones, and amino acids in biochemical processes [4]. Its role includes aiding in collagen production and connective tissue synthesis by facilitating the hydroxylation of proline and lysine proteins [1]. Additionally, it is involved in the synthesis of carnitine, dopamine, and neurohormones like norepinephrine [5]. Furthermore, it regulates the degradation of hypoxia-inducible factor (HIF) under normoxic conditions and modulates the activity of dioxygenase enzymes involved in DNA and histone demethylation for epigenetic regulation [6]. Ascorbic acid enhances the bioavailability and absorption of dietary iron by converting less absorbable ferric iron (Fe^{3+}) into easily absorbable ferrous iron (Fe^{2+}) in the small intestine, thus aiding in preventing iron oxidation and improving iron storage in the form of ferritin [7,8]. Deficiency in vitamin C can lead to anemia, bleeding gums, bruising, and poor wound healing, particularly evident in conditions like scurvy, gastrointestinal issues, malnutrition, and critical illnesses such as sepsis and cancer [9,10]. While vitamin C has been attributed with therapeutic and prophylactic potential in various human diseases, including cancer, stroke, diabetes, and the coronavirus infections, the current evidence supporting its efficacy, particularly in critical illnesses remains insufficient [11].

This review aims to explore the mechanism of action and functional effects of vitamin C on cancer cells, drawing upon recent publications and meta-analyses. Despite the analysis of recent evidence, the question of whether vitamin C is efficacious in both preventing and treating cancer remains unanswered, highlighting the need for further research in this area.

2. Methodology

The study conducted an electronic search of PubMed, Scopus, and Web of Science (W*o*S) databases from January 2019 to 2023 to compile recent systematic reviews, meta-analyses, and randomized controlled trials from peer-reviewed journals, along with relevant English references. Search terms included '*vitamin C*', '*ascorbic acid*', '*ascorbate*', and '*L-ascorbic*', alongside keywords like '*cancer*', '*tumor*', or '*neoplasia*'. On the hand, background information mainly relied on articles from the past two decades, occasionally supplemented by older sources. It specifically focuses on recent randomized clinical trials (RCTs) and systematic meta-analyses (SRMA) including RCTs only to provide a high level of evidence, and sometimes with a deliberate inclusion of observational studies due to the scarcity of RCTs. Screening procedures ensured the inclusion of articles relevant to the study's subject matter, with selected ones providing evidence to support the discussion and conclusions of this review.

3. Summary of vitamin C, immune system, and cancer triangle

Vitamin C can adjust immune function by altering redox-sensitive cell signaling pathways, guarding against oxidative stress from the environment. Its strong antioxidant characteristics suggest that its function as a cofactor for various biosynthetic and gene regulatory enzymes may be crucial for its immune-regulating effects [11,12]. Vitamin C shows significant accumulation in immune cells like leukocytes, circulating lymphocytes, monocytes, and neutrophils, influences various aspects of immune response, impacting tumor progression [12]. It enhances immune function by aiding T-cell proliferation and preventing apoptosis, supporting B cells in immunoglobulin synthesis and cytokine production, and promoting neutrophil activity through improved phagocytosis and apoptosis while reducing necrosis [13]. Additionally, it has been suggested that hematopoietic and multipotent stem cells in the bone marrow have significantly higher ascorbate levels compared to differentiated cells. The elevated content is associated with increased expression of the specific ascorbate transporter, indicating an essential role for it in bone marrow stem cell differentiation [14].

Hydroxylase enzymes, part of the iron- and 2-oxoglutarate-dependent dioxygenase family, rely on ascorbate for activity and are crucial in regulating HIFs, which are essential for responding to low oxygen levels and can induce T-cell suppression within

tumors, potentially impacting tumor progression [13]. Deleting HIF-1α in myeloid cells in breast cancer and fibrosarcoma models enhances immune response and reduces tumor growth [15]. Furthermore, vitamin C enhances ten-eleven translocation enzymes (TETs, dioxygenases enzymes, histone demethylase enzymes) activities, vital for hematopoietic stem cell differentiation and epigenetic regulation, potentially influencing leukemogenesis regulating hematopoietic stem cell function, and reducing leukemia progression [16,17]. Mutations in TET2 detected in bone marrow macrophages from patients with myelodysplastic syndromes and chronic myeloid leukemia, which might influence the expression of inflammatory cytokines like interleukins [18].

4. The role of vitamin C in cancer

The ability of vitamin C as an electron donor, make it is able to scavenge and neutralize the endogenous or exogenous oxidants products which are characteristic by having single electron which contribute to the development or exacerbation of many of the most common human diseases such as not only heart attacks but also cancers [19]. Oxidant products can be free radicals, or reactive oxygen species (ROS), including hypochlorous acid, nitrosamines, nitrous acid related compounds and ozone or compounds that are formed by reaction with either of the first two classes and then react with vitamin C [20]. An example is formation of the α-tocopheroxyl radical, which is generated when exogenous radical oxidants interact with vitamin E in low-density lipoprotein [4]. Vitamin C restoring vitamin E to its active state as an antioxidant for continued cellular protection against oxidative damage [1], and inhibiting lipid oxidation via synergistic interaction with vitamin E [4]. Vitamin C readily donates an electron to potentially neutralizing and damaging oxidizing agents, and catalyzes products to hydrogen peroxide (H_2O_2), and then to water [4]. This action contributes to alleviating oxidative stress on cancer cells, thereby helping to maintain redox homeostasis [21]. Consequently, high-dose intravenous vitamin C administration triggers cytotoxicity in tumor cells by generating increased ROS leads to oxidative damage to the DNA of cancer cells [22,23]. Intracellularly, dehydroascorbic acid (DHA) undergoes reduction back to ascorbic acid through the oxidation of glutathione (GSH) and nicotinamide adenine dinucleotide phosphate (NADPH), producing glutathione disulfide (GSSG) and $NADP^+$ [22,24]. This process amplifies ROS generation, that are selectively toxic to cancer cells [23]. At higher mM concentrations, vitamin C takes on a pro-oxidant role, either through extracellular auto-oxidation or intracellular recycling of oxidized form of dehydroascorbic acid to ascorbate [25]. Extracellularly, ascorbate undergoes auto-oxidation in the presence of oxygen and transition metals. A high dose of intravenous ascorbate can reduce protein-centered transition metal ions, such as ferric and cupric (Cu^{2+}) ions to Fe^{2+}/cuprous (Cu^+) ions, oxidizing itself into ascorbate free radical (Asc^-). This property enhances iron uptake from the diet. The reduced Fe^{2+}/Cu^+ ions react with oxygen to form ROS such as superoxide radicals, which in the presence of hydrogen form H_2O_2 which induces damage in order to cancer cells [4,25]. In vitro studies demonstrated with a pharmacologic dose excess of the 1 mM threshold of ascorbate that induces significant H_2O_2, ascorbate-mediated cytotoxicity toward cancer cells, while in phase I clinical trial, data suggested that high levels of ascorbate do not induce systemic oxidative stress initiated by H_2O_2 so the evidence is still unclear that ascorbate induce the oxidative damage in tumors as a result of oxidation products formation [26].

Under conditions of low glucose, cancer cell survival is sustained by the upregulation of glycolysis, there by suggesting that disrupting glucose metabolism could be a strategy for inducing cancer cell death [27]. Upon absorption of ascorbate, cancer cells uptake DHA owing to its structural similarities to glucose, facilitated by the specific glucose transporter [25]. Subsequently, within the cell, DHA undergoes reduction back to ascorbic acid through the oxidation of GSH and NADPH to form GSSG and $NADP^+$. This process, in turn, amplifies the generation of ROS to damage the cancer cell [22,25]. *KRAS* and *BRAF* mutations are common in colorectal cancers and are associated with upregulation of the specific glucose transporter and a glycolytic phenotype. An i*n vivo* mouse model with implanted mutant *KRAS* and *BRAF* cancer cells in which tumor growth was slowed when the animals were administered high doses of vitamin C by daily intraperitoneal injection of 4 g/kg. The data in this comprehensive study clearly show that the upregulated expression of the glucose transporter can result in rapid uptake of DHA by these cancer cell lines [26].

The relationship between vitamin C and HIFs in cancer process might be mentioned as follows: Hypoxic

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condition enhances HIF activity responses to low oxygen levels (hypoxia) in tumor cell can lead to increase tumor progression. The capacity of vitamin C to enhance the activity of hydroxylase enzymes results in a reduction of HIF activity, potentially triggering cellular responses such as programmed cell death (apoptosis) can lead to decrease tumor progression [28]. Analyzing human tumor tissue retrospectively has uncovered a negative relationship between tumor ascorbate levels and markers of HIF activation in melanoma, endometrial, and colorecta cancers [29]. These findings strongly imply that ascorbate may inhibit HIF transcriptional activity, potentially slowing tumor growth. Furthermore, increasing ROS production concurrently triggers a cascade of reactions within cells, including the oxidation of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), a key enzyme in energy production. This oxidative modification of GAPDH can disrupt cellular energy metabolism, culminating in an energy deficit within the cells and subsequent cell death [29].

Epigenetics encompasses changes in gene expression that are not related to alterations in the DNA sequence itself, but rather to modifications in the structure of DNA and its associated proteins [30]. Examples of epigenetic changes include DNA and histone methylation, which are distinctive features of various cancers [31]. Vitamin C serves as an epigenetic regulator for its role in DNA demethylation, a process initiated by the TET enzymes responsible for removing methyl groups from DNA. Vitamin C is indeed part of the DNA demethylation process, enhances the enzymatic activity of TETs by acting as a co-factor promotes the recovery of Fe^{3+} to Fe^{2+} and facilitates the conversion of 5-methylcytosine to 5-hydroxymethylcytosine, and subsequent oxidation to form 5-formylcytosine and 5-carboxylcytosine [32]. Moreover, vitamin C has been observed to influence histone demethylase enzymes, which are responsible for removing methyl groups from histones, further contributing to the epigenetic modifications that impact gene regulation and chromatin structure [33].

Mutations of TET enzymes cause epigenetic dysregulation have been detected in different types of cancer, particularly hematological malignancies [34]. TET mutations cooperate with FMS-like tyrosine kinase 3 (Flt3) internal tandem duplication (ITD) ($Flt3^{ITD}$) mutations in acute myeloid leukemia, increasing the frequencies of haematopoietic progenitor cells and some of the myeloid progenitors to cause acute myeloid leukemia [12]. As ascorbate deficiency related with TET mutation, there is also a study investigated ascorbate depletion cooperates with $Flt3^{ITD}$ mutations in bone marrow cells of mice. TET2 or $Flt3^{ITD}$ restoration suppresses hematopoietic stem cell frequency and leukemogenesis while promote myelopoiesis [13]. Recently, more ongoing research aims to understand specific genes and pathway influenced by vitamin C in different biological contexts [35].

Vitamin C's impact on cancer cells is hypothesized to be multifaceted, involving roles as an antioxidant, pro-oxidant, epigenetic regulator, down-regulator of HIFs, and an agent impairing glucose metabolism. These mechanisms collectively lead to cell death.

5. Use of vitamin C in cancer

There has recently been a surge of interest in the use of vitamin C in the treatment and prevention cancer risk.

5.1. Vitamin C and cancer prevention

It has been recognized that diet and nutrients play an important role in the development and progression of cancer, and many components of the diet are associated with the risk of cancer [36,37]. However, the association between dietary vitamin C intake and supplemental and different types of cancer risk is still inconsistent.

Three comprehensive reviews incorporating multiple systematic reviews and meta-analyses, involving both observational and RCTs, were conducted to evaluate the correlation between vitamin C and cancer risk. The initial review focused on examining the association between vitamin C intake or supplements and diverse health outcomes. The analysis of 29 meta-analysis of all observational studies, revealed a connection between higher vitamin C dietary or intake and a reduced risk of cancers, particularly in breast, gastric, bladder, colorectal, pancreatic, prostate, and esophageal cancers. However, there seemed to be a possible relationship between vitamin C supplementation and breast, bladder, pancreatic, colorectal cancer and non-Hodgkin lymphoma, with only one study on breast cancer reporting statistically significant benefits associated with vitamin C supplementation. Dose–response analysis also

demonstrated that an increase in daily consumption of vitamin C by 50–100 mg was associated with reduced risk of esophageal cancer, gastric cancer, cervical cancer and lung cancer. However, despite these discoveries, most clinical trials, as revealed in four meta-analyses examining cancer outcomes (n = 3) and cancer mortality (n = 1), failed to show protective effects of vitamin C supplements against various types of cancers, including lung and pancreatic cancers. The median number of studies included in each meta-analysis was 2 [38].

In other review by Chen et al., which involved 57 meta-analyses, the results indicated that dietary vitamin C intake was associated with a lower risk of several types of cancers such as bladder, breast, cervical, esophageal, gastric, glioma, lung, pancreatic, prostate, and renal cell cancers, and endometrial carcinoma. Vitamin C intake was linked to a reduced risk of breast cancer prognosis, including recurrence, cancer-specific mortality, and all-cause mortality. However, no significant association was observed between dietary vitamin C intake and the incidence of colon or colorectal cancers. Similarly, there was no significant relationship found between supplementary vitamin C intake and the risk of non-Hodgkin lymphoma, breast cancer, or bladder cancer when considering supplementary intake alone or in combination with dietary intake. Dose-response analysis revealed that higher vitamin C intake was linked to lower risks of several cancers. For instance, every 50 mg increase was associated with 15% lower risk of endometrial carcinoma, 13% lower risk of esophageal cancer, and 8% lower risk of cervical neoplasm. Additionally, each 100 mg/day increment was linked to 26% lower risk of gastric cancer and 7% lower risk of lung cancer. Moreover, a daily dietary intake of 150 mg was associated with 9% lower risk of prostate cancer [39]. It's important to note some potential limitations when interpreting these research results, particularly that most of the included studies were observational, carrying a lower level of evidence. Moreover, in Mendelian randomization (MR) investigation, an extensive examination of the connections between genetically forecasted circulating vitamin C and specific site-related cancers was carried out through a meta-analysis of prospective cohort studies and randomized controlled trials. The data were derived from genetic instruments and genome-wide association study data involving up to 1,992,894 participants. The MR analysis did not find any support for an association between dietary or supplementary vitamin C intakes and the risk of breast, prostate, colon, rectal, and digestive cancers. Intriguingly, the study proposed that a higher intake of dietary vitamin C, rather than vitamin C supplementation, was associated with a reduced risk of lung cancer [40,41]. In a recent MR study, it was discovered that there was an insignificant correlation between vitamin C intake and lung cancer [42,43].

5.2. Vitamin C and cancer treatment

Ascorbate exhibits the potential to enhance the efficacy of various chemotherapeutic drugs and radiation therapy when used in neoadjuvant, concomitant, or adjuvant treatment settings. Examples of studies include the use of oral Vitamin C supplementation in combination with neoadjuvant chemoradiation for esophageal adenocarcinoma, demonstrating a mild protective effect in inflammation and modulation of carcinogenesis [44]. Another study involving advanced-stage non-small cell lung cancer (NSCLC) patients receiving 75 g of intravenous ascorbate twice per week concomitantly with standard treatment showed improved tumor response in advanced-stage NSCLC [45]. Furthermore, in the Phase I Clinical Trial administering intravenous L-ascorbic acid after salvage chemotherapy for relapsed non-Hodgkin's lymphoma, a dose of 75 g was deemed both safe and sufficient to achieve effective serum concentrations [46].

In the 1970s, Nobel Prize Pauling and Cameron conducted the first known study where they administered high-dose intravenous ascorbate for the treatment of cancer patients and the results revealed the beneficial effects of high-dose vitamin C [47-50]. Other studies performed afterwards, while research found no advantages in using oral ascorbate, certain RCTs have yielded promising outcomes with intravenous ascorbate treatment [51]. Extensive research efforts have been dedicated to examining the potential of high-dose intravenous vitamin C in the mitigation of oxidative stress, all in pursuit of enhancing the overall clinical condition and health outcomes of cancer patients [52]. However, the efficacy of intravenous vitamin C as a monotherapy or in combination with cancer treatment is inconsistent.

The latest systematic review in 2019, evaluating the effectiveness of vitamin C in treating cancer patients, encompassed 19 studies, including 4 randomized

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controlled trials and various observational studies. Vitamin C was administered either intravenously or orally, with varying doses and time intervals. The conclusions of RCT studies drawn from that review are inconclusive in establishing a significant and beneficial impact of vitamin C on the overall survival, clinical condition, quality of life, and performance status of the majority of cancer patients. However, one RCT reported positive outcomes when vitamin C was used intravenously in elderly acute myeloid leukemia patients, especially those deficient in vitamin C and treated with decitabine. The synergy between vitamin C and decitabine is attributed to the essential role of vitamin C in supporting TET enzymes crucial for DNA demethylation [53].

Since the latest review in March 2019, no updated review has been conducted to assess the effectiveness of vitamin C in cancer treatment. However, new findings from four randomized controlled trials have emerged. The VITALITY Study, a phase 3 RCT conducted in 2022 with patients diagnosed with metastatic colorectal cancer, high-dose vitamin C combined with chemotherapy [administered at 1.5 g/kg/day intravenously for 3 hours from D1 to D3 alongside FOLFOX ± bevacizumab] did not demonstrate improved progression-free survival (PFS) compared to chemotherapy alone (median PFS, 8.6 vs. 8.3 months for the control group, $p = 0.10$). However, subgroup analyses revealed that patients with metastatic colorectal cancer harboring RAS mutations experienced significantly longer PFS (median PFS, 9.2 vs. 7.8 months, $p = 0.01$) when vitamin C was added to chemotherapy compared to chemotherapy alone. Additionally, the objective response rate (ORR) and overall survival (OS) between the experimental and control groups were similar (ORR, 44% vs. 42%; $p = 0.90$; median OS, 20.7 vs. 19.7 mo; $p = 0.70$) [54]. In another study performed by van Gorkom et al., involving 44 patients undergoing autologous stem cell transplantation for hematological cancer, intravenous 70 mg/kg vitamin C supplementation showed no significant impact on neutrophil recovery ($p = 0.96$), hospital stay duration (19.7 vs. 19.1 days, $p = 0.80$), incidence of neutropenic fever (57% vs. 78%, $p = 0.20$), or 3-month overall survival (90.5% vs. 100%, $p = 0.13$). However, it did lead to a reduction in the rates of bacteremia (10% vs. 35%, $p = 0.07$) [55]. In contrast, Park et al.'s study showed that 1 g of intravenous vitamin C reduced bladder discomfort (CRBD) in bladder cancer patients after transurethral resection. The vitamin C group reported higher satisfaction scores than the control group (5.0 ± 1.3 vs. 4.4 ± 1.4, $p = 0.009$) and a significantly lower incidence of moderate or severe CRBD immediately post-operation (29% vs. 68%, $p < 0.001$). The difference in CRBD incidence decreased over time (17% vs. 42% at 1 h, $p = 0.003$; and 8.5% vs. 27% at 2 h, $p = 0.008$), but no significant difference was observed 6 hours postoperatively [56]. Furthermore, Gillberg et al.'s study on Danish myeloid cancer patients receiving azacytidine treatment for 3 cycles revealed that plasma vitamin C deficiency (< 23 μM) was observed in the majority of patients. After oral supplementation with 500 mg of vitamin C daily during the last 2 cycles, plasma vitamin C levels returned to normal, leading to an increase in the 5-hydroxymethylcytosine/5-methylcytosine ratio (0.04% vs — 0.03%, $p = 0.041$). This ratio represents the initial phase of DNA demethylation [57].

6. Conclusion

Vitamin C is a crucial micronutrient, and its varied functions in fighting cancer are noteworthy, through its antioxidative, pro-oxidative, and immune-boosting properties, vitamin C acts as a cofactor for iron or copper oxygenases. This aids in stimulating reactive oxygen species production, targeting cancer cells selectively, and regulating cellular metabolism and epigenetic processes. Comprehensive reviews suggest a potential protective role of vitamin C intake against cancer development; however, umbrella reviews present lower evidence levels due to heterogeneity when combining systematic reviews, particularly as most studies are epidemiological with limited RCTs and evidence levels. Considering that fruits and vegetables are the primary sources of vitamin C, individuals rarely consume it as the only antioxidant or essential nutrient in their daily diet. The combined intake of these micronutrients may influence the impact of ascorbic acid on cancers, although subgroup analyses in the included meta-analyses did not assess these factors. Epidemiological findings suggest improved cancer outcomes and reduced incidence with dietary vitamin C intake but not with supplements alone for cancer prevention. Furthermore, RCTs have not established the protective effects of vitamin C supplements across various cancer types. The ef-

ficacy of vitamin C in cancer treatment, either alone or in combination with standard anti-cancer therapies such as chemotherapy and radiotherapy, is still controversy. Notably, studies examining the role of vitamin C in cancer treatment show significant heterogeneity in outcome measures, study populations, and treatment modalities, such as doses, schedules, and delivery methods. The random-effects inverse-variance-weighted method is commonly used in analyzing such data. Recent RCTs have shown that intravenous vitamin C does not significantly impact progression-free survival or the length of hospital stay. Nevertheless, intravenous vitamin C or oral supplementation in patients with myeloid cancer has been suggested a synergistic inhibition of cancer cell proliferation when combined with DNA demethylation inhibitor agents. This effect is likely attributed to enhanced DNA demethylation through the activation of TET-induced conversion of 5-methylcytosine to 5-hydroxymethylcytosine. The overall quality of evidence is poor by the lack of double-blinded randomized controlled trials. The results did not demonstrate a clinically significant positive effect of vitamin C on cancer patients' overall survival, clinical status, quality of life, or performance status. Therefore, further exploration of ascorbate's potential advantages in cancer process requires more rigorous and controlled studies. Consequently, larger, high-quality randomized controlled trials are imperative to offer more definitive understandings regarding the effectiveness of vitamin C in managing severe medical conditions.

Conflict of Interest

The authors have no conflicts of interest, financial or otherwise, to declare.

Statement of Contribution of Researchers

Concept – T.B.; Design – O.A.M.H., G.G.; Supervision – T.B.; Data Collection and/or Processing – O.A.M.H.; Literature Search – O.A.M.H.; Writing – O.A.M.H., G.G.; Critical Reviews – T.B.

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