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The role of vitamin C as a potent Antioxidant and Pro-oxidation in Acute Myeloid Leukemia Treatment Progress

Rabab Ali Al-Mosawi[1*], Ebtesam Mohsen Al-Azawe [2], Hisham Ali Waggiallah[3]

[1]Department of Aesthetic and Laser, Institute Najaf , Al-Furwt Al-Awsat Technical University , Iraq.

[2]The general directorate of education in Al-Najaf province, Iraq

[3]Medical Laboratory Sciences (Alkha), c)Prince Sattam bin Abdulaziz University, Saudi Arabia

[*]Corresponding Author: rababali.inj@atu.edu.iq

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Abstract:

Vitamin C has effects on cancer as both an antioxidant and a pro-oxidant. It serves as an antioxidant by reducing oxidative stressors and minimizing genetic damage. Conversely, high pharmacological doses of vitamin C can act as pro-oxidants impacts that are detrimental to cancerous cells. Moreover, vitamin C can modify the metabolomics and epigenetic profiles of cancer cells, leading to the elimination of cancer stem cells. Additionally, it can enhance immune system activity and suppress cancer transformation through various pathways.

The review included several studies that dealt with the effect of vitamin C on leukemia patients or associated it with treatment in vitro or in vivo to enhance patients' response to treatment and minimise side effects. It has been shown through previous and recent studies that the role of vitamin C is effective in treating leukemia patients. Additional researches are required to better understand the mechanistic and clinical dimensions of these effects.

Keywords: acute myeloid leukemia, antioxidant, pro-oxidant, vitamin c.

دور فيتامين سي كمضاد ومحفز للأكسدة في تقدم علاج سرطان الدم النقوي الحاد

م.د. رباب علي شناوة الموسوي [1]

م.م. ابتسام محسن العزاوي[2]

أ.د. هاشم علي وقيع الله [3]

جامعة الفرات الأوسط التقنية / المعهد التقني في النجف /قسم التجميل والليزر [1]

مديرية تربية النجف[2]

قسم المختبرات الطبية..كليه العلوم الطبية التطبيقية..جامعة الامير سطام بن عبدالعزيز..الخرج..المملكة العربية السعودية

rabab.ali.inj@atu.edu.iq

الخلاصة:

لفيتامين سي تأثيرات مضادة للأكسدة ومؤيدة للأكسدة على السرطان. فهو يعمل كمضاد للأكسدة عن طريق تقليل الجذور المؤكسدة ومنع التلف الجيني. في المقابل، يمكن للجرعات الدوائية العالية من فيتامين سي أن تمارس تأثيرات مؤيدة للأكسدة تضر بالخلايا السرطانية. علاوة على ذلك، يمكن لفيتامين سي تعديل السمات الأيضية والجينية للخلايا السرطانية، مما يؤدي إلى القضاء على الخلايا الجذعية السرطانية. بالإضافة إلى ذلك، يمكن أن يعزز نشاط الجهاز المناعي ويثبط تحول السرطان عبر مسارات مختلفة.

تضمنت الدراسة مراجعة العديد من الدراسات التي تناولت تأثير فيتامين سي على مرضى سرطان الدم أو المرتبطة بالعلاج في المختبر أو في الجسم الحي لتعزيز استجابة المريض للعلاج وتقليل الآثار الجانبية. وقد أظهرت دراسات سابقة وحديثة أن لفيتامين سي دورًا فعالًا في علاج مرضى سرطان الدم. هناك حاجة إلى أبحاث إضافية لفهم الأبعاد الميكانيكية والسريرية لهذه التأثيرات بشكل أفضل.

الكلمات المفتاحية: سرطان الدم النقوي الحاد، مضاد للأكسدة، مؤكسد، فيتامين سي.

1. Introduction:

L-ascorbic acid, often known as vitamin C (VC), is a micronutrient vital for overall human health. Ascorbic acid (AA) and dehydroascorbic acid (DHA) are its two main forms. As a potent antioxidant and enzymatic cofactor, VC is essential for many biological processes, such as metabolism of carnitine and catecholamines, dietary iron absorption, immune system support and collagen synthesis[1]. VC possesses antioxidant and pro-oxidant effects on many diseases, especially cancer. It works as an antioxidant by neutralizing reactive oxygen species and averting DNA damage. However, high pharmacological dosages of VC can have harmful pro-oxidant effects on cancer cells [2].

VC has the potential to change the metabolomics and epigenetic profiles of cancer cells, which results in the eradication of cancer stem cells. Moreover, it can boost the immune system and hinder cancer transformation through various pathways [3]. Oxidative stress, arises from an imbalance between pro-oxidant molecules and antioxidant defense systems, leading to DNA

damage and cellular alterations that drive cancer progression[4]. To reduce oxidative stress and cancer risk, antioxidant supplementation is recommended, especially with vitamin C [5].

Acute myeloid leukemia is characterized by the clonal proliferation of immature hematopoietic stem cells, or blasts, in the bone marrow. It a rare cancer that progresses rapidly. Uncontrolled expansion disrupts normal megakaryopoiesis and erythropoiesis, clinically appearing as relatively rapid bone marrow failure. The outcome is inadequate production erythrocyte and platelet [6,7]. As a result patients with AML many symptoms, such as, frequent infections, fatigue and easy bleeding or bruising, due to the insufficient production of normal blood cells. The aggressive nature of AML leads to a rapid decline in bone marrow function, making it a situation that threatens, life that, needs medical care, treatment and attention [8,9].

The review included many studies that confirm that vitamin C's pro-oxidative potential as well as its antioxidant qualities. The function of VC in cancer is discussed in the first section. The previous and recent studies highlight that VC has a therapeutic effect on Acute Myeloid Leukemia (AML) and is also advantageous for patients receiving radiation and chemotherapy when taken as a supplement. In addition,VC supplementation could be a potential combination therapy for the treatment of AML. However, the effectiveness of high-dose VC as an anticancer therapy is still debatable and requires further rigorous clinical trials for conclusive results.

2. Characteristics of Vitamin C

Organic compounds called vitamins are necessary for human metabolism. Notably, antioxidants included in vitamins A, E, and C protect against damage caused by free radicals.[10]. Ascorbic acid, is a water-soluble vitamin that is found naturally, in some foods, added to others, and sold as a nutritional supplement. Humans are dependent on food consumption because they are unable to manufacture\

VC, like most other vertebrates and are entirely reliant on food consumption. Consequently, it is a crucial nutritional component [11]. The recommended amount of VC per day ranges from 40 to 120 mg, based on factors such as physiological state, stress, and diseases. While Smokers, and those who are overweight may need up to 165 to 155 mg per day, according to recent research. [12,13].

3. Free radical

Numerous biological processes, including the intracellular bacteria elimination by phagocytic cells, especially macrophages and granulocytes, as well as some cellular signaling pathways, the mutagenic response, and redox regulation, depend on free radicals; many of these processes are necessary for life. However, excessive creation of free radicals leads to structural changes in cellular proteins that alter their activities, causing cellular dysfunction and interference with vital cellular functions. [14,15].

Increased reactive oxygen species (ROS) concentrations, a kind of free radical, can damage the integrity of various biomolecules, including proteins, lipids, and Deoxyribonucleic Acid. Specifically, ROS can damage proteins through altering amino acids at certain sites, peptide chain fragmentation, accumulation of cross-linked reaction products, alteration of electric charge, enzymatic inactivation, and proteolysis susceptibility[16]. The lipid membrane can be broken by ROS, which also increases the permeability and fluidity of the membrane. Finally, DNA damage includes deoxyribose oxidation, strand breaks, DNA-protein crosslinking, altering base, and nucleotide deletion [17].

4.Vitamin C as an antioxidant

The role of VC as an antioxidant and its effect in preventing chronic diseases associated with oxidative stress. VC works to reduce free radicals and reactive oxygen species (ROS) via two pathways. The first is by inhibiting nitrogen peroxides, blocking the formation of free radicals such as hydroxyl and proxy radicals. The second is by converting hydrogen peroxide to water through a reaction with ascorbate[18]. Additionally, vitamin C helps lower lipid peroxidation in cell membranes and increases the action of vitamin E (α-tocopherol) [19].

VC exhibits a defense against cardiovascular diseases such as hypertension and atherosclerosis, but its effects vary depending on its source and blood concentration levels[20]. Additionally, research has indicated that VC may be beneficial in preventing disorders of the nervous system such as Alzheimer's disease and depression, through its effects on nerve and brain function[21]. According to certain research, VC can affect cancerous cells, selectively killing them without affecting healthy cells, through the formation of hydrogen peroxide and free radicals. It has helped enhance the effectiveness of anti-tumor drugs like gemcitabine and adiotherapy, and reduced their side effects [22,23].

5. Vitamin C as an oxidant

VC influences several biological processes including hormone, collagen and carnitine synthesis, as well as, regulation of translation and gene transcription though a variety of mechanisms which including demethylation of DNA and histones, hydroxylation of transcription factors, tRNA, and ribosomal proteins, and tyrosine removal, Additionally, VC provides protection against free radicals, and reducing the frequency of undesired spontaneous differentiation of induced pluripotent stem cells [24] VC is particularly important for the activation of the ten-eleven translocation family (TETs) of dioxygenases, whose activity in DNA active demethylation appears to be downregulated in majority human malignancies [25]..

VC has a significant role in regulating human physiological processes, particularly cellular immune responses. It acts as an antioxidant molecule at physiological concentrations, preventing DNA damage and ultimately cancer development. Additionally, VC is involved in epigenetic regulation [12, 26]

6. Vitamin C as a Pro-oxidant

Linus Pauling and Ewan Cameron initially proposed the idea of using VC as a medicinal agent for cancer treatment in 1970 [27] High-dose VC is administered intravenously at a concentration greater than 10 g/infusion. Ascorbic acid serves a critical role in the antioxidant defense system as a nonenzymatic component. Its function is maintained by balanced dietary plasma concentrations.[28]. Even with oral supplementation, plasma ascorbate concentrations remain at micromolar levels. Ascorbate serves as an antioxidant against oxidative stress and modulates enzymes. At pharmacological doses, ascorbic acid acts as a pro-oxidant. However, at millimolar dosages and in certain clinical conditions, ascorbic acid's pro-oxidative activity can lead to DNA damage and ATP depletion [29].

7- The studies that showed the role of VC as a potential antioxidant and pro-oxidation of AMC

According to recent studies, high-dose Vitamin C may be useful in treating various tumors by targeting cancer cell growth mechanisms [30]. VC has shown specific cytotoxicity in human malignancies in preclinical studies. Its potential as an anticancer drug has been suggested. [22,31]. Intravenous high-dose VC may be used as a potential anti-cancer agent, according to pharmacological studies [32].

A study discovered that ascorbic acid can lead to apoptosis in AML cells. This is due to the build-up of H2O2 because of VC oxidizing reduced glutathione intracellularly [33].A study found that VC is cytotoxic against leukemia in vitro. It can kill most types of acute and chronic myeloid leukemia cells without harming normal cells.[34].

One study showed that VC treatment significantly stops development of leukemia in primary human leukemia patient-derived xenografts by imitates the restoration ten-eleven translocation 2 (TET_2) in Tet2-deficient mouse HSPCS. Various enzymes that are involved in DNA demethylation, including TET_2, require vitamin C to remain active [35]. The concept crucial for AML patients due to demethylase enzymes play an important role in the growth and progression of AML [36].

Research aimed to find a biomarker for VC treatment in acute myelogenous leukemia by analyzing gene expression patterns and their relation to patient survival. The study discovered that low expression of SLC2A3, a gene involved in VC uptake, was linked to lower overall survival in AML patients and reduced effectiveness of VC in AML and lymphoma cells [37].

8. VC in combination treatments

VC at high doses has been the focus of numerous research projects recently as a pro-oxidative agent in combination with chemotherapy and radiotherapy The pre-clinical and clinical literature on the use of high-dose VC in combination therapy is reviewed in this review. Other combination treatments have been studied. According to one previous study, the survival rate of mice with P388 leukemia increased upon receiving treatment with VC and vitamin B l2 [38].

Another investigation found that combining decitabine and low-level VC had a positive effect on leukemic cells and clinical results in elderly AML patients. In vitro experiments showed synergy between the two agents in inhibiting DNA methyltransferase and affecting gene expression. Patients who received the combination treatment had higher remission rates and longer survival than those who received decitabine alone. Low-dose VC improved treatment response and survival in elderly AML patients [39].

Additionally, administering Ascorbic Acid orally to patients with myeloid cancers undergoing DNMTi treatment can enhance the 5hmc/5mc ratio and normalize plasma vitamin C levels. This indicates that supplementing with VC may improve the biological impacts of DNMTis [40].

Also, the study demonstrated that in AML patients with reduced TET2 activity, VC administration could improve clinical remission and restore methylation patterns [41]. Another study examined the effect of VC on leukemia expressing the IDH1R132H mutation. The study observed that VC treatment decreased cell proliferation and increased the gene expression related to leukocyte differentiation. VC also caused changes in Histone alterations and DNA methylation, leading to the remodeling of transcription factor-binding sites and driving differentiation in the leukemia model [42].

Darwiche *et al.*'s study proposes that VC supplementation has potential using a combination of therapies to treat chronic lymphocytic leukemia. This is due to its ability to induce apoptotic cell death, enhance targeted therapies, and synergistically potentiate drug cytotoxicity in CLL B-cells targeting mitochondrial metabolism [43].

VC concentration inversely correlates with peripheral blast counts in AML patients, indicating vitamin C's potential for suppressing leukemia progression. [44].

A recent study found that ascorbic acid significantly enhances the response of leukemic cells to the histone methyl transferase inhibitor DZNep in AML by promoting apoptosis and differentiation. The enzyme D-3-phosphoglycerate dehydrogenase (PHGDH) and the anti-apoptotic gene BCL2 are downregulated by vitamin C, and the vitamin C-enhanced anti-leukemic action of DZNep is reversed by overexpression of PHGDH.[45].

9. Conclusions

Through a review of prior research, it was determined that VC possesses both pro-oxidant and antioxidant effects in relation to AML. It has a variety of effects, acting as a pro-oxidative cytotoxic agent, immunological modulator, anti-cancer epigenetic regulator, and cancer-specific agent, among other effects. Furthermore, it has a larger physiological role beyond its antioxidant properties, including involvement in hormone and carnitine synthesis, facilitation of iron absorption, and important roles in epigenetic processes. High dosages of VC function as a pro-oxidant, instead of an antioxidant. Additionally, it can act synergistically with standard therapies and reduce harmful adverse effects of chemotherapy. Strong clinical data studies are absent despite the rationale and evidence to support it., highlighting the need for more extensive awareness and research on high-dose VC as a non-toxic cancer treatment.

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