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A COMPREHENSIVE REVIEW ON THE ANTICANCER POTENTIAL OF VITAMIN C IN SELECTED MALIGNANCIES

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ABSTRACT:

Vitamin C (ascorbic acid) is an essential micronutrient widely recognised for its antioxidant activity and physiological importance. In recent years, renewed scientific interest has focused on its potential role in cancer prevention and therapy. Emerging evidence from molecular, preclinical, and clinical investigations indicates that vitamin C exerts anticancer effects through multiple mechanisms, including redox modulation, epigenetic regulation, immune enhancement, and selective cytotoxicity toward malignant cells. At pharmacological concentrations achievable only through intravenous administration vitamin C functions as a pro-oxidant, generating hydrogen peroxide within the tumour microenvironment and inducing cancer cell death while sparing normal tissues. Additionally, vitamin C acts as a cofactor for epigenetic enzymes such as TET dioxygenases and histone demethylases, contributing to reactivation of tumour suppressor genes and restoration of genomic stability. Epidemiological studies consistently demonstrate an inverse association between dietary vitamin C intake and the incidence of several cancers, particularly those of the gastrointestinal tract and breast. Clinical trials further suggest that high-dose intravenous vitamin C may enhance treatment efficacy, reduce therapy-associated toxicities, and improve quality of life when used as an adjunct to conventional cancer therapies. Despite promising findings, controversies remain regarding optimal dosing, route of administration, patient selection, and interaction with standard treatments. This review critically synthesises current mechanistic, epidemiological, and clinical evidence on vitamin C in oncology, discusses existing limitations, and highlights future research directions aimed at integrating vitamin C into multimodal cancer management strategies

Keywords: Vitamin C; ascorbic acid; cancer therapy; oxidative stress; epigenetics; tumour microenvironment

INTRODUCTION:

Cancer is a complex and multifactorial disease characterised by uncontrolled cell proliferation, genomic instability, and resistance to normal regulatory mechanisms. It remains one of the leading causes of morbidity and mortality worldwide, imposing a substantial health and economic burden. Conventional cancer treatments including surgery, chemotherapy, and radiotherapy have improved patient outcomes but are frequently limited by toxicity, therapeutic resistance, and incomplete remission. Consequently, there is a growing interest in

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adjunctive and preventive agents that may enhance treatment efficacy while minimising adverse effects.

Among naturally occurring bioactive compounds, vitamin C has re-emerged as a molecule of considerable interest in oncology. Historically proposed as a cancer treatment several decades ago, vitamin C initially generated enthusiasm following reports of improved survival in terminal cancer patients. However, subsequent randomised studies using oral supplementation failed to confirm these benefits, leading to prolonged scepticism. Advances in pharmacokinetics, molecular biology, and redox science have since clarified that the route of administration is critical, as oral vitamin C cannot achieve plasma concentrations required for anticancer activity.

Contemporary research reveals that vitamin C exhibits context-dependent biological effects, functioning as an antioxidant at physiological concentrations and as a pro-oxidant at pharmacological doses. These properties, combined with its epigenetic and immunomodulatory roles, have positioned vitamin C as a promising adjunct in cancer prevention and treatment. This review aims to provide an updated and critical appraisal of the anticancer potential of vitamin C, integrating mechanistic insights with epidemiological and clinical evidence

AIM AND OBJECTIVES

Aim

The aim of this review is to critically evaluate and synthesise existing scientific evidence on the anticancer potential of vitamin C, with particular emphasis on its molecular mechanisms, preventive role, and therapeutic applications in selected cancers.

Objectives

- To summarise the biochemical and pharmacological properties of vitamin C relevant to cancer biology.
- To analyse the molecular mechanisms underlying the anticancer effects of vitamin C, including redox modulation, epigenetic regulation, and immune response enhancement.
- To review epidemiological evidence supporting the role of vitamin C in cancer prevention.
- To assess preclinical and clinical studies evaluating vitamin C as an adjunct to conventional cancer therapies.
- To identify current limitations, controversies, and future research directions related to vitamin C in oncology.

LITERATURE REVIEW

Vitamin C (ascorbic acid) has long been recognised for its antioxidant properties and essential physiological functions. Early epidemiological studies reported an inverse

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association between dietary vitamin C intake and the incidence of several cancers, including gastrointestinal, breast, and lung cancers. These findings suggested a potential chemopreventive role for vitamin C, particularly when consumed through fruits and vegetables rich in phytochemicals.

Initial clinical interest in vitamin C as a cancer therapy emerged in the 1970s following reports of prolonged survival in terminal cancer patients treated with high-dose vitamin C. However, subsequent randomised trials using oral supplementation failed to replicate these benefits, leading to diminished acceptance of vitamin C in oncology. Later pharmacokinetic studies clarified that oral administration cannot achieve plasma concentrations necessary for anticancer activity, whereas intravenous administration enables pharmacological levels capable of exerting pro-oxidant effects.

Recent mechanistic studies have demonstrated that vitamin C selectively induces cytotoxicity in cancer cells by generating hydrogen peroxide within the tumour microenvironment. Additionally, vitamin C functions as a cofactor for ten-eleven translocation (TET) enzymes and histone demethylases, facilitating epigenetic reprogramming and reactivation of tumour suppressor genes. Preclinical models further reveal that vitamin C enhances immune surveillance, inhibits metastasis, and sensitises tumour cells to chemotherapy and radiotherapy.

Clinical trials conducted over the past decade indicate that high-dose intravenous vitamin C is safe, well tolerated, and potentially effective when used as an adjunct to standard cancer treatments. Improvements in quality of life, reduced treatment-related toxicity, and survival benefits in selected cancers such as pancreatic and ovarian cancers have been reported. Collectively, these findings have renewed scientific interest in vitamin C as a complementary agent in cancer management.

MATERIAL AND METHODS:

This review was conducted using a comprehensive literature search of peer-reviewed articles published in international scientific journals. Databases including PubMed, Scopus, Web of Science, Google Scholar, and Science Direct were systematically searched.

Inclusion Criteria

- Original research articles, reviews, meta-analyses, and clinical trials
- Studies investigating molecular, preclinical, epidemiological, or clinical aspects of vitamin C in cancer

Exclusion Criteria

- Non-peer-reviewed reports
- Studies lacking methodological clarity

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- Articles unrelated to cancer biology or therapy

Relevant articles were screened based on titles and abstracts, followed by full-text evaluation. Data were extracted, categorised, and synthesised thematically to provide a structured narrative review

BIOCHEMICAL CHARACTERISTICS OF VITAMIN C

Vitamin C is a water-soluble molecule with strong reducing properties, enabling it to donate electrons and participate in numerous biochemical reactions. At physiological levels, it acts as a potent antioxidant, neutralising reactive oxygen species (ROS) and protecting cellular components such as DNA, proteins, and lipids from oxidative damage. This antioxidant capacity contributes to the maintenance of cellular homeostasis and prevention of mutagenic processes associated with carcinogenesis.

Beyond its antioxidant role, vitamin C serves as an essential cofactor for several enzymes involved in collagen synthesis, neurotransmitter production, carnitine biosynthesis, and peptide hormone maturation. Of particular relevance to cancer biology is its role in maintaining the activity of iron- and copper-dependent dioxygenases, including enzymes that regulate epigenetic modifications.

The pharmacokinetics of vitamin C are tightly regulated under normal dietary intake through intestinal absorption and renal excretion, limiting plasma concentrations. Oral supplementation rarely raises plasma levels beyond 0.2 mM. In contrast, intravenous administration bypasses these regulatory mechanisms and can achieve plasma concentrations exceeding 10 mM, enabling pro-oxidant activity that is selectively toxic to cancer cells. This pharmacological distinction underpins many of the observed anticancer effects of vitamin C.

MECHANISMS OF ANTICANCER ACTION

Pro-oxidant Cytotoxicity

At high concentrations, vitamin C generates hydrogen peroxide in the extracellular space, particularly within tumour microenvironments rich in catalytic metal ions. Cancer cells, which often exhibit impaired antioxidant defences and altered metabolism, are especially vulnerable to this oxidative stress. The resulting DNA damage, ATP depletion, and mitochondrial dysfunction trigger apoptosis and inhibit tumour cell proliferation.

Epigenetic Regulation

Vitamin C plays a critical role in epigenetic remodelling by acting as a cofactor for TET enzymes and Jumonji-C domain-containing histone demethylases. These enzymes catalyse DNA demethylation and histone modification, processes frequently dysregulated in cancer.

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Through restoration of normal epigenetic patterns, vitamin C may reactivate tumour suppressor genes, promote cellular differentiation, and enhance sensitivity to anticancer therapies.

Immunomodulatory Effects

Vitamin C influences both innate and adaptive immune responses by enhancing the function of cytotoxic T lymphocytes, natural killer cells, and antigen-presenting cells. It modulates cytokine production and supports immune cell infiltration into tumours, thereby strengthening antitumour immunity and complementing immunotherapeutic approaches.

Modulation of the Tumour Microenvironment

By supporting collagen synthesis and extracellular matrix integrity, vitamin C may limit tumour invasion and metastasis. Additionally, its redox-modulating effects alter the tumour microenvironment, creating conditions less favourable for cancer cell survival and progression.

ROLE OF VITAMIN C IN CANCER PREVENTION

Epidemiological studies consistently report an inverse relationship between dietary vitamin C intake and the risk of several cancers, including those of the lung, breast, stomach, and colorectum. Diets rich in fruits and vegetables primary sources of vitamin C are associated with reduced cancer incidence, suggesting synergistic interactions with other phytochemicals.

Meta-analyses indicate that increased vitamin C intake correlates with modest but significant reductions in cancer risk, particularly for gastrointestinal malignancies. However, randomised controlled trials evaluating vitamin C supplementation alone have yielded mixed results, highlighting differences between dietary intake and isolated supplementation. These findings suggest that vitamin C's preventive effects may depend on dietary context, bioavailability, and interactions with other nutrients.

CLINICAL EVIDENCE AND THERAPEUTIC APPLICATIONS

Route of Administration and Dosing

Clinical studies demonstrate that oral vitamin C supplementation is insufficient to achieve therapeutic plasma concentrations. In contrast, intravenous vitamin C reliably produces millimolar plasma levels necessary for tumour-selective cytotoxicity. Doses ranging from 50 to 100 g per infusion, administered two to three times weekly, have been shown to be safe and pharmacologically effective.

Evidence in Solid Tumours

Clinical trials and observational studies suggest that high-dose intravenous vitamin C may improve outcomes in several cancers, including ovarian, pancreatic, glioblastoma, lung, and

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prostate cancers, particularly when combined with standard therapies. Benefits reported include improved survival metrics, enhanced treatment tolerance, and reduced chemotherapy-related toxicity.

Safety and Quality of Life

High-dose intravenous vitamin C is generally well tolerated, with mild and transient adverse effects such as nausea or infusion-related discomfort. Importantly, improvements in patient-reported quality of life—including reduced fatigue and pain—have been observed. Screening for conditions such as glucose-6-phosphate dehydrogenase deficiency is essential to minimise rare adverse events.

SYNERGISTIC EFFECTS WITH CONVENTIONAL CANCER THERAPIES

Vitamin C enhances the efficacy of chemotherapy and radiotherapy by increasing oxidative stress selectively within tumour cells while protecting normal tissues. It has also demonstrated potential to augment immunotherapy by strengthening antitumour immune responses. These synergistic effects support its role as an adjunct rather than a replacement for conventional cancer treatments.

LIMITATIONS AND CONTROVERSIES

Despite encouraging data, significant challenges remain. Clinical outcomes vary across studies due to heterogeneity in dosing protocols, routes of administration, patient populations, and tumour types. The dual antioxidant and pro-oxidant nature of vitamin C raises concerns about timing and interaction with ROS-dependent therapies. Additionally, large-scale randomised trials with standardised protocols are still limited.

FUTURE PERSPECTIVES

Future research should prioritise well-designed randomised clinical trials, biomarker-guided patient selection, and standardised dosing strategies. Advances in nanotechnology-based delivery systems may further improve tumour targeting and bioavailability. Integration with immunotherapy and epigenetic treatments represents a promising avenue for personalised cancer therapy.

RESULTS

The reviewed literature demonstrates that vitamin C exerts anticancer effects through multiple complementary mechanisms. Preclinical studies consistently show that pharmacological concentrations of vitamin C induce oxidative stress selectively in cancer cells, leading to apoptosis and inhibition of tumour growth. Epigenetic studies reveal that vitamin C restores normal DNA methylation patterns and gene expression in malignant cells.

Epidemiological evidence indicates a significant inverse relationship between dietary vitamin C intake and the risk of several cancers, particularly those of the digestive system and breast. Clinical

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investigations confirm that intravenous vitamin C achieves therapeutic plasma levels and is associated with improved treatment tolerance, reduced chemotherapy-induced toxicity, and enhanced quality of life. In selected cancers, adjunctive vitamin C therapy has demonstrated improvements in progression-free and overall survival.

DISCUSSION

The findings of this review highlight vitamin C as a biologically versatile compound with significant relevance to cancer prevention and treatment. Its dual antioxidant and pro-oxidant properties enable selective targeting of cancer cells while protecting normal tissues. The ability of vitamin C to regulate epigenetic mechanisms further supports its role in reversing malignant phenotypes and overcoming therapeutic resistance.

Despite promising results, inconsistencies across clinical studies remain a major challenge. Differences in administration routes, dosing schedules, patient populations, and tumour types contribute to variable outcomes. Concerns regarding potential antioxidant interference with chemotherapy underscore the importance of pharmacological dosing and intravenous administration.

Overall, vitamin C shows considerable promise as an adjunctive agent in multimodal cancer therapy. However, its clinical integration requires further validation through large-scale, well-designed randomised controlled trials and biomarker-driven patient selection

CONCLUSION

Vitamin C exhibits diverse anticancer properties mediated through redox regulation, epigenetic modulation, immune enhancement, and tumour microenvironment remodelling. While dietary intake supports cancer prevention, pharmacological intravenous administration shows promise as a safe and effective adjunct to conventional cancer therapies. Addressing existing controversies through rigorous clinical research is essential for establishing vitamin C's definitive role in oncology. With continued investigation, vitamin C may become an integral component of comprehensive, multimodal cancer treatment strategies

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