International Journal of Nanomedicine

Dovepress
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REVIEW

A Comprehensive Review of Vitamin C for Cancer Therapy: Anti-Tumor Mechanisms and Nano-Formulation Strategies

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Abstract: The rapid advancements in nanotechnology have provided unprecedented opportunities for the clinical translation of vitamin C (VC) in cancer therapy. Although pharmacological doses of VC exhibit potent anti-tumor activities via multiple mechanisms—including selective pro-oxidative stress induction, metabolic inhibition, epigenetic modulation, and immune function enhancement—the clinical application of VC remains significantly hindered by its inherent instability, short biological half-life, and lack of tumor-specific targeting. Recent progress in the design and synthesis of VC and its derivatives combined with advanced nanocarriers has enabled precise delivery and efficient release of VC at tumor sites. In this review, we systematically summarize recent advances in nano-formulation strategies of VC, with a detailed discussion of lipid-based nanocarriers including liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), polymeric nanoparticles, as well as metal-based nanozyme delivery systems primarily composed of iron, copper, and manganese. These nano-systems not only significantly enhance the stability and circulation half-life of VC but also exploit tumor microenvironment-specific stimuli, such as pH, hydrogen peroxide (H_2O_2), and glutathione (GSH), to achieve responsive and precise drug release in cancer tissues. Notably, metal-based nanomaterials in combination with VC synergistically catalyze the Fenton reaction, markedly boosting reactive oxygen species (ROS) generation and demonstrating remarkable anti-tumor efficacy. Moreover, nanotechnology platforms have facilitated effective combination therapies involving VC with chemotherapeutic agents, photothermal catalysts, and immune agonists. Finally, this article highlights key challenges in the clinical translation of nano-formulated VC, including safety evaluation, scale-up production, and prediction of therapeutic efficacy. Future research directions in nano-drug design and exploration of synergistic mechanisms are proposed, providing theoretical guidance and practical insights for precise cancer therapy using VC-based nanomedicine.

Keywords: vitamin C, ascorbic acid, cancer therapy, nanoparticle, drug delivery, Fenton reaction

Introduction

Vitamin C (VC), chemically known as L-Ascorbic Acid (AA), is a crucial water-soluble vitamin that humans cannot synthesize endogenously and must obtain through dietary intake.[1,2] As an important electron donor and cofactor in enzymatic reactions, VC broadly participates in various physiological and biochemical processes, including collagen synthesis, immune defense, and iron metabolism regulation.[3–8] When administered at pharmacological concentrations (0.3–20 mM), VC no longer exhibits its classical antioxidant properties; instead, it demonstrates pro-oxidant effects, selectively inducing programmed cell death in cancer cells, such as apoptosis, autophagy, and ferroptosis.[9–14] Clinically, VC has shown significant synergistic effects when combined with conventional chemotherapy, radiotherapy, and immunotherapy.[15–17]

Despite its promising anti-tumor potential, VC delivery methods (primarily oral and intravenous administration) have substantial pharmacokinetic limitations. Firstly, orally administered VC exhibits very limited anticancer activity. As a small, water-soluble molecule, oral absorption of VC is constrained by saturation of sodium-dependent vitamin C transporters 1 (SVCT1) in the intestine.[18] Even with a maximum tolerated oral dosage of up to 18 grams per day, plasma peak concentration

https://doi.org/10.2147/IJN.S559426
Received: 19 September 2025
Accepted: 3 January 2026
Published: 13 January 2026

rarely exceeds approximately 220 μM.[19] Although intravenous injection can achieve pharmacological concentrations, VC is rapidly cleared by renal excretion due to its small molecular size and hydrophilic nature, resulting in a short biological half-life of merely 30 minutes to 2 hours.[20]

Furthermore, orally or intravenously administered VC lacks tumor-specific distribution and cannot preferentially accumulate in tumor tissues. To achieve and sustain therapeutically effective concentrations at the tumor site, frequent or continuous intravenous infusion is usually required, which may lead to adverse effects such as hyperoxaluria and kidney stones.[21] Moreover, VC is chemically unstable and susceptible to oxidation under environmental factors like light, heat, oxygen, and metal ions.[22] Its oxidation product, dehydroascorbic acid (DHA), exhibits a half-life of only a few minutes and rapidly undergoes irreversible hydrolysis into biologically inactive 2,3-diketogulonic acid.[23]

The advent of nanotechnology offers novel solutions to overcome the limitations associated with conventional VC therapy. Through nano-encapsulation, VC can be effectively protected from environmental degradation, significantly enhancing its chemical stability.[24] Nanocarriers can improve VC bioavailability, prolong blood circulation time, and achieve precise tumor targeting through ligand surface modifications.[25,26] Additionally, by exploiting tumor microenvironmental characteristics or external stimuli, nanocarriers enable controlled VC release specifically at the tumor site, thereby increasing therapeutic efficacy while minimizing toxicity toward healthy tissues.[27,28]

Given the promising therapeutic prospects of nano-formulated VC, this review systematically summarizes recent advancements in the application of nano-formulated VC in cancer treatment. We specifically focus on exploring its molecular anti-tumor mechanisms, diversified nano-delivery system designs, catalytic chemo-dynamic therapy, and synergistic effects with conventional chemotherapy and immunotherapy. Finally, we discuss the challenges and future perspectives of clinical translation, aiming to provide theoretical guidance and practical insights for the development of next-generation nano-formulated VC therapies.

Multiple Anti-Tumor Mechanisms of VC

The anti-tumor effects of VC do not rely on a single mechanism; rather, they involve a complex, multi-targeted, and multi-pathway network. These coordinated mechanisms collectively confer VC the ability to selectively kill cancer cells.

Selective Pro-Oxidative Stress

The selective pro-oxidative effect mediated by vitamin C at pharmacological concentrations (0.3–20 mM) is currently the most widely accepted and most extensively investigated core mechanism underlying its anti-tumor activity.

Extracellular H_2O_2 Generation and the Fenton Reaction

Under pharmacological concentrations, VC can significantly generate H_2O_2 in the extracellular fluid surrounding tumor tissues, serving as the key initiation point for VC's pro-oxidative cytotoxic effects. In vitro cell-free systems, millimolar levels of VC undergo a slow yet sustained spontaneous oxidation reaction with dissolved oxygen (O_2), producing a small amount of H_2O_2.[11] However, the presence of free transition metal ions such as Fe^{2+} or Cu^{+} in the system markedly accelerates VC's oxidation rate, resulting in a multiplied yield of H_2O_2.[29]

In in vitro experiments with human pancreatic and breast cancer cells, treatment with 0.3–20 mM VC for 10 minutes elevated the H_2O_2 concentration in the culture medium to ≥25 μM; addition of 1000 $U \cdot mL^{-1}$ catalase completely reversed the generation of reactive H_2O_2, thereby significantly alleviating cell death.[10] In a neuroblastoma mouse model, intraperitoneal injection of 4 $g \cdot kg^{-1}$ VC increased the H_2O_2 concentration in the peritumoral tissue fluid to 100–150 μM, whereas it was only approximately 10–30 μM in normal tissue fluid.[30] Due to its membrane-permeable properties, the generated H_2O_2 can rapidly diffuse from the extracellular space of tumor cells into the intracellular environment, inducing oxidative stress.[31]

In tumor cells, due to their faster proliferation rate, there is a significantly increased demand for iron. The metabolic reprogramming and iron metabolism disorders in tumor cells lead to upregulated iron uptake and downregulated ferritin expression, thereby resulting in a higher level of labile iron pool (LIP).[32] For example, in breast cancer cells, the Fe^{2+} concentration in the LIP can reach 10–15 μM, whereas in normal breast epithelial cells, it is only 5–7 μM, with the free Fe^{2+} levels being 1.5–2 times higher than in normal cells.[33]

The accumulated Fe^{2+} reacts with H_2O_2 through the intracellular Fenton reaction, generating highly reactive hydroxyl radicals (·OH) as follows:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + \cdot OH$$

The generated Fe^{3+} is reduced back to Fe^{2+} by VC, thereby forming a continuous cycle that amplifies the production of ·OH, causing severe oxidative damage to DNA, proteins, and lipids, and ultimately inducing programmed cell death in tumor cells.[34]

Iron-modulation experiments have further validated this mechanism. Pre-treatment of tumor cells with iron supplements (such as iron sucrose or transferrin-iron complexes) significantly enhances intracellular iron storage, increasing VC cytotoxicity.[35] Conversely, iron chelators (eg, deferoxamine) markedly diminish this effect, confirming intracellular iron availability as a critical determinant of VC-induced cytotoxicity.[36]

Deficiencies in Antioxidant Defense Enhance Selective Cytotoxicity of VC

Beyond differences in iron content, the selectivity of VC-induced oxidative stress primarily stems from significant variations in catalase (CAT) activity between cells. Normal cells possess high CAT activity, enabling rapid clearance of H_2O_2 and effective prevention of oxidative damage.[37] However, most solid tumor cells exhibit markedly reduced CAT expression due to chronic oxidative stress, high iron burden, and specific genetic mutations, accompanied by impaired glutathione (GSH) antioxidant systems.[38] Consequently, tumor cells are more sensitive to VC-induced H_2O_2 accumulation. The differential expression of antioxidant enzymes is also observed across distinct tumor subtypes. For instance, the proneural subtype of glioblastoma shows high levels of CAT and GPx activity, rendering it more resistant to combined VC and radiotherapy, whereas mesenchymal and classical subtypes, characterized by lower antioxidant enzyme activity, exhibit higher sensitivity.[39]

Metabolic Inhibition

To adapt to hypoxic conditions and support rapid proliferation, tumor cells undergo significant metabolic reprogramming. A hallmark of this adaptation is the Warburg effect, characterized by preferential reliance on glycolysis for ATP production even under aerobic conditions.[40] Compared with normal cells, tumor cells exhibit substantially higher glycolytic flux but generate less than 10% of the energy efficiency per glucose molecule.[41] Thus, tumor cells dramatically increase glucose uptake to meet their metabolic requirements. Particularly, tumors harboring KRAS or BRAF mutations markedly upregulate glucose transporter 1 (GLUT1, encoded by SLC2A1), increasing glucose uptake approximately 10–12-fold compared to normal tissues.[42,43] This characteristic also provides a basis for targeted intervention by VC derivatives, notably dehydroascorbic acid (DHA), which enters cells competitively through GLUT1.[44]

Under pharmacological concentrations, extracellular VC rapidly oxidizes to generate substantial amounts of H_2O_2, accompanied by conversion into DHA. The accumulated DHA efficiently enters tumor cells via overexpressed GLUT1 transporters, where it is quickly reduced back to ascorbate by intracellular GSH and NADPH. This reduction process rapidly depletes cellular NADPH and GSH stores, severely disturbing the redox balance and dramatically elevating intracellular ROS.[44,45] Excessive ROS directly oxidize and inactivate key glycolytic enzymes, notably glyceraldehyde-3-phosphate dehydrogenase (GAPDH), via thiol oxidation. Simultaneously, ROS-induced DNA damage hyperactivates poly(ADP-ribose) polymerase (PARP), rapidly consuming intracellular NAD^+. The depletion of NAD^+ further impairs GAPDH activity, severely disrupting the glycolytic pathway. Consequently, ATP synthesis declines dramatically, triggering a rapid onset of energy crisis and subsequent programmed cell death in tumor cells.[46]

In vitro studies have shown that treatment of tumor cells harboring KRAS or BRAF mutations with ≥1 mM VC initiates the aforementioned metabolic collapse.[46,47] Consistently, in vivo experiments using an Apc^−/−; Kras^G12D/+ mouse model demonstrated that daily intravenous administration of high-dose VC (4 g/kg) significantly suppressed tumor growth, whereas mice with Apc deletion alone did not show substantial responses. This evidence suggests that elevated GLUT1 expression and glycolytic dependency are critical determinants of selective anti-cancer efficacy mediated by VC.[42]

In addition to glycolytic inhibition, pharmacological concentration VC directly impacts mitochondrial functions in tumor cells. VC-induced ROS (primarily H_2O_2) readily enter mitochondria, directly impairing respiratory complexes

I and III, thereby reducing oxygen consumption rate (OCR) and ATP generation.[48] Consequently, mitochondrial membrane potential rapidly collapses, triggering the opening of mitochondrial permeability transition pores (MPTP), the release of cytochrome c, and subsequent activation of intrinsic apoptotic pathways.[49] Furthermore, elevated ROS induce aberrant mitochondrial dynamics, characterized by excessive mitochondrial fission and reduced fusion protein expression, ultimately resulting in mitochondrial fragmentation and exacerbation of mitochondrial dysfunction.[50]

Epigenetic Modulation

In addition to exerting antitumor effects through inducing oxidative stress and inhibiting energy metabolism, vitamin C can also play a significant antitumor role via epigenetic mechanisms. Its core mechanism involves VC functioning as an essential cofactor for dioxygenase enzymes such as ten-eleven translocation (TET) DNA demethylases and Jumonji C domain-containing histone demethylases (JHDM). These enzymes catalyze the oxidation of 5-methylcytosine (5mC) into intermediate products such as 5-hydroxymethylcytosine (5hmC), ultimately facilitating DNA demethylation.[51] In many cancer cells, TET enzyme activity is reduced or even absent, leading to a significant decline in 5hmC levels, which triggers abnormal DNA hypermethylation and the silencing of tumor suppressor genes. Vitamin C can reactivate inactivated TET enzymes in cancer cells, restore normal 5hmC levels, and thereby correct the abnormal epigenetic regulatory states in cancer cells.

For instance, Shenoy et al found that high-dose VC can reverse the 5hmC deficiency in kidney cancer cells, significantly elevating genomic 5hmC levels and effectively attenuating tumor growth and clonogenic potential.[52] Similarly, in hematologic malignancies, Cimmino et al demonstrated that, in a mouse model of acute myeloid leukemia (AML) induced by TET2 mutations, high-dose vitamin C can effectively restore TET2 function, block the aberrant self-renewal of tumor cells, and significantly delay leukemia progression.[53]

Recent clinical trials have also demonstrated that in lymphoma-susceptible individuals carrying TET2 truncating mutations, daily administration of 1 gram of vitamin C for one year significantly reduces whole-genome methylation levels in peripheral blood mononuclear cells, providing clinical evidence for the epigenetic regulatory effects of vitamin C.[54] Given the important role of vitamin C in epigenetic regulation, its combination with traditional epigenetic drugs has become a research hotspot. For example, the combined use of the DNA demethylating agent decitabine and vitamin C can synergistically enhance the activity of the TET family (particularly TET2 and TET3), reverse gene expression dysregulation caused by abnormal DNA methylation, and ameliorate hematopoietic abnormalities resulting from TET2 mutations. This combination strategy can improve therapeutic efficacy through multi-target synergistic effects.[55]

Modulation of the Tumor Microenvironment (TME)

Vitamin C-mediated epigenetic modifications not only directly inhibit cancer cells but also profoundly influence the tumor immune microenvironment. VC can enhance antitumor immunity and the efficacy of immune checkpoint inhibitors (ICIs) by activating TET enzymes. In studies on renal cell carcinoma, the IFN-γ signaling pathway activates STAT1, which in turn recruits TET2 to the gene locus of interferon regulatory factor 1 (IRF1). As a cofactor, vitamin C activates TET2 to maintain the demethylated state of the IRF1 promoter, thereby upregulating its expression. IRF1, as a key transcription factor, can directly induce the expression of downstream chemokines (such as CXCL9 and CXCL10) as well as the immune checkpoint molecule PD-L1, thereby promoting T-cell infiltration and sensitizing to anti-PD-L1 therapy.[56]

Furthermore, VC can enhance the function of innate immune signaling pathways by activating TET2. Within tumor cells, VC serves as a key cofactor for the demethylase TET2. Cooperating with phosphorylated STAT5A, which is activated by IL-2 signaling, VC-facilitated TET2 converts 5-methylcytosine (5mC) into 5-hydroxymethylcytosine (5hmC) at the cGAS gene promoter, relieving epigenetic repression and significantly enhancing cGAS transcription. The activated cGAS protein subsequently recognizes and binds to cytosolic DNA, catalyzing the synthesis of the pivotal signaling molecule cGAMP. cGAMP is then exported through LRRC8C channels to neighboring endothelial cells, activating the STING pathway, which promotes peripheral lymphocyte recruitment and transendothelial migration. Upon infiltration into the tumor microenvironment, these lymphocytes secrete IL-2, further activating IL-2 receptors (IL-2R) on tumor cells and subsequently re-stimulating the STAT5A signaling cascade. The reactivated STAT5A, again in cooperation with VC-assisted TET2, further amplifies the epigenetic activation of cGAS, thus creating a positive feedback loop that robustly enhances anti-tumor immune responses.[17]

Additionally, VC can directly covalently modify lysine residues in proteins, forming a novel post-translational modification—vitcylation—which in turn influences the immune microenvironment. Vitcylation at a specific lysine residue (K298) of STAT1 blocks its binding to the protein phosphatase TCPTP, preventing STAT1 dephosphorylation. Consequently, sustained phosphorylation of STAT1 (p-STAT1) promotes activation of the type-I interferon (IFN) signaling pathway and upregulates tumor cell surface MHC class I molecules, significantly enhancing anti-tumor immune responses. In vitro studies have demonstrated that VC-treated tumor cells co-cultured with dendritic cells (DCs) promote DC maturation, elevating the expression of MHC class II and co-stimulatory molecules (CD86, CD80). Co-culture with CD8+ T cells also stimulates T-cell proliferation and cytokine secretion, including IFN-γ and tumor necrosis factor-α (TNF-α). In vivo experiments consistently confirmed the efficacy of VC in suppressing tumor growth, with enhanced therapeutic effects observed when VC was combined with anti-PD-1 antibodies.[4]

In summary, Figure 1 provides an overview of the integrated mechanisms by which VC exerts broad-spectrum antitumor activity, including selective pro-oxidative stress induction, metabolic inhibition, epigenetic regulation, and reshaping of the immune microenvironment. These mechanistic insights provide a solid theoretical foundation for expanding VC's therapeutic applications across diverse cancer types.

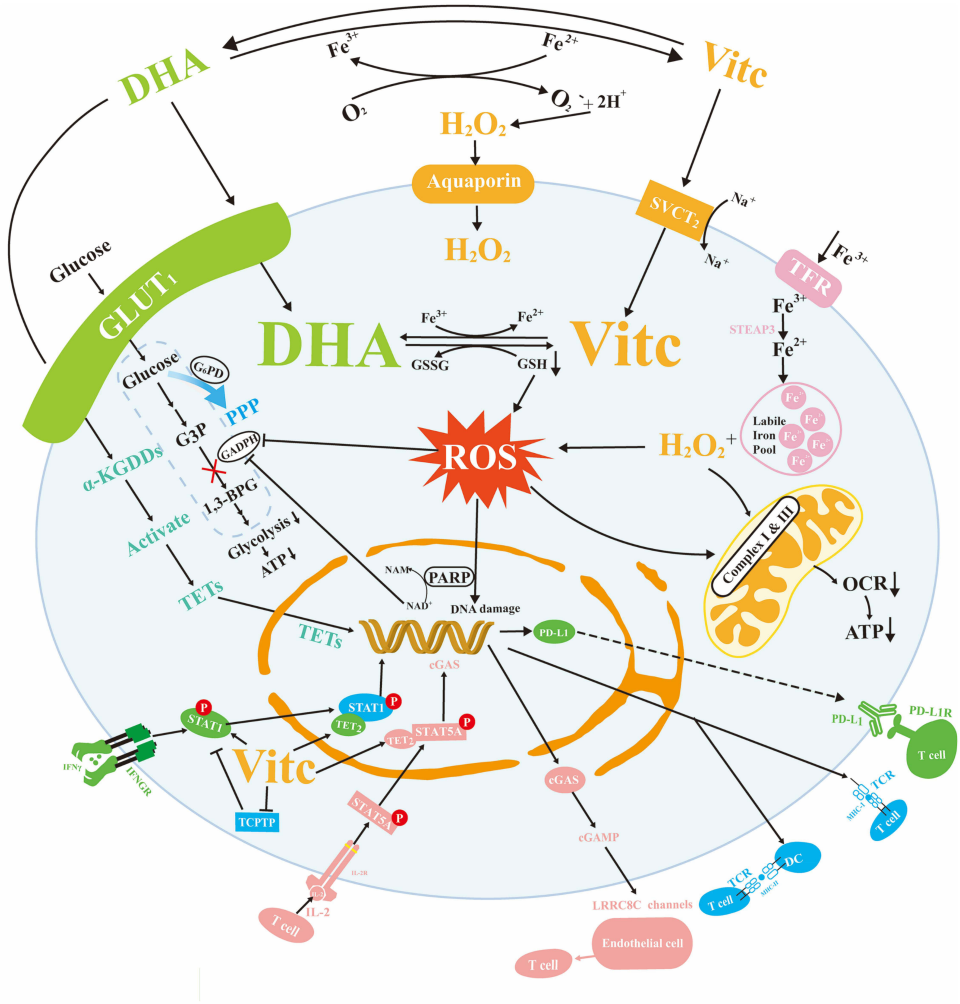


Figure 1 Schematic Overview of Vitamin C–Mediated Anti-tumor Mechanisms: Pro-oxidative Stress, Metabolic Inhibition, Epigenetic Regulation, and TME Modulation. VitC enters tumor cells via SVCT2, while DHA competitively enters through GLUT1. Extracellular VitC undergoes Fe^{3+}/Fe^{2+}-dependent oxidation to generate H_2O_2, which passes through aquaporins and reacts with the intracellular labile iron pool to produce ROS. DHA further increases ROS by disrupting redox balance through GSH/GSSG cycling, subsequently inhibiting glycolysis (red X) via GAPDH blockade and redirecting glucose flux to the pentose phosphate pathway (PPP), (blue arrows). Accumulated ROS impair mitochondria (↓OCR, ↓ATP) and induce DNA damage with PARP activation. VitC also enhances TET-dependent DNA demethylation and stimulates antitumor immunity by activating STAT1 signaling, cGAS–STING pathways, and T-cell responses.

https://doi.org/10.2147/IJN.S559426

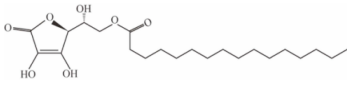
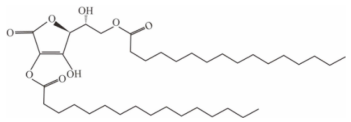
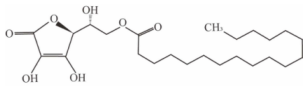
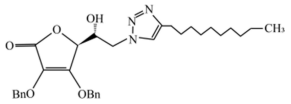
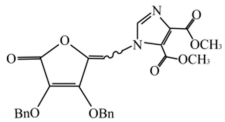
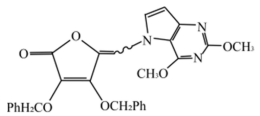
Design Strategies and Recent Advances in Nano-Delivery Systems for VC

Despite the multiple anti-tumor mechanisms described above, clinical translation of VC faces critical challenges such as inherent instability, short biological half-life, and insufficient tumor-targeting capability. To overcome these limitations, researchers have employed two main strategies in constructing various nano-delivery systems: firstly, developing VC derivatives to enhance physicochemical properties; secondly, designing diverse nanocarriers to facilitate drug protection, controlled release, and targeted delivery.

Nano-Formulation Applications of VC Derivatives

VC derivatives can be classified into lipid-soluble and water-soluble types based on their physicochemical properties, as illustrated in Table 1, with each type demonstrating unique characteristics suitable for different nano-formulation applications.

Table 1 Classification of Lipid-Soluble and Water-Soluble Vitamin C Derivatives and Their Structural Formulas

Type	VC Derivatives	Structural Formula
Lipid-soluble	Ascorbyl Palmitate AP	
Lipid-soluble	Ascorbyl-Dipalmitae ASC-DP	
Lipid-soluble	Ascorbyl stearate Asc-S	
Lipid-soluble	2,3-O,O-dibenzyl-6-deoxy-6-(4-decyl-1,2,3-triazol-1-yl)-L-ascorbic acid 1,2,3-triazole-L-ascorbic acid derivatives	
Lipid-soluble	1-[2-(3,4-Bis-benzyloxy-5-oxo-5H-furan-2-ylidene)ethyl]-1H-imidazole -4,5-dicarboxylic acid dimethyl ester 1,2,4-triazole-L-ascorbic acid derivatives	
Lipid-soluble	2,6-dimethoxy-9-deazapurine-L-ascorbic acid	

(*Continued*)

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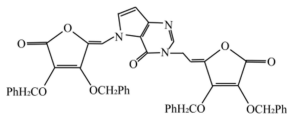
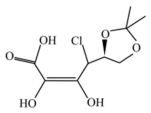
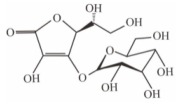
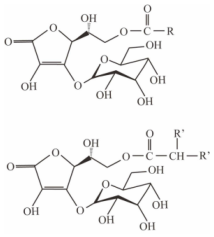
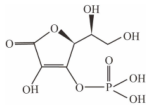
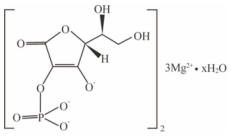
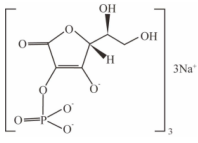
Table 1 (Continued).

Type	VC Derivatives	Structural Formula
Lipid-soluble	9-deazahypoxanthine-L-ascorbic acid	
Lipid-soluble	5,6-O-isopropylidene-L-ascorbic Acid	
Water-soluble	Ascorbic Acid 2-Glucoside AA-2G	
Water-soluble	6-sOcta-AA-2G 6-bOcta-AA-2G	
Water-soluble	Ascorbic acid-2-phosphate A2P	
Water-soluble	Magnesium ascorbyl phosphate MAP	
Water-soluble	Sodium ascorbyl phosphate SAP	

https://doi.org/10.2147/IJN.S559426

Lipid-Soluble VC Derivatives

Ascorbyl Palmitate (AP)

AP is a derivative of VC, formed via esterification of the hydroxyl group at the 6-position of ascorbic acid with the 16-carbon saturated fatty acid palmitic acid, with a molecular weight of approximately 414.5 $g \cdot mol^{-1}$. The AP molecule exhibits a typical amphiphilic structure: a hydrophobic long-chain palmitoyl moiety at one end and a hydrophilic ascorbic acid ring at the other.[57]

Under physiological conditions (pH ≈ 7.4), the ionizable acidic hydroxyl groups of AP molecules ($pK_a \approx 4.34$) are almost completely deprotonated, resulting in negatively charged ascorbate ions. Consequently, AP-assembled nanocarriers exhibit negative surface ζ-potentials (approximately –30 to –40 mV), which enhance particle stability, reduce plasma protein adsorption, and promote the enhanced permeability and retention (EPR) effect. Li demonstrated the practical utility of this feature by incorporating AP into phospholipid-based (HSPC) lipid nanoparticles (AP-PC-LNPs). They observed that as the AP content increased from 1% to 8%, the zeta potential decreased from –29.2 mV to –42.5 mV, while particle sizes remained stable within the range of 74–99 nm.[58] Sawant employed PEG-PE micelles to encapsulate AP and found that micelles containing 4 mM AP maintained a particle size of approximately 25 nm and a stable zeta potential of approximately –33 mV at 4°C for one week, demonstrating excellent stability and selective cellular uptake.[59]

In intelligent nano-delivery systems, AP uniquely exhibits dual roles as both an active "drug" and a "carrier component". As an active "drug", AP exerts therapeutic effects through multiple mechanisms. In vivo, AP undergoes gradual enzymatic hydrolysis by esterases, continuously releasing biologically active VC.[60] Additionally, under catalysis by transition metals such as Fe^{2+} or Cu^{+}, AP generates ROS, inducing DNA damage and apoptosis in cancer cells.[61] AP itself can further exert anti-tumor effects by activating Caspase-3, reducing the Bcl-2/Bax ratio, and causing cell cycle arrest in the G2/M phase.[62] As a "carrier component", the amphiphilicity of AP enables its integration into lipid bilayers or self-assembly into nano-structures. Gopinath D investigated AP liposomes (Aspasomes) and demonstrated that AP forms submicron vesicular structures capable of encapsulating hydrophilic small molecules or protein drugs for transdermal or injectable delivery.[63] Shi reported that AP could self-assemble into nanoparticles (PTX-APNPs) with a diameter of approximately 294 nm, effectively encapsulating hydrophobic drugs such as paclitaxel (PTX).[64] In addition, Shamiya (2024) developed a smart delivery system (GAP Gel) composed of AP self-assembled nanofibers synergistically integrated within a GelMA hydrogel network. AP molecules self-assembled into fibrous nanostructures with lengths of approximately 700 nm and thicknesses around 50 nm via intermolecular hydrogen bonding and van der Waals forces. These nanofibers encapsulated hydrophobic drugs such as erythromycin within their hydrophobic cores, while their hydrophilic outer surfaces formed hydrogen-bonded crosslinks with GelMA polymers, resulting in a composite hydrogel carrier with enhanced mechanical properties and sustained drug-release capabilities.[57]

Furthermore, combined nano-delivery systems co-loading AP with chemotherapeutic drugs, as illustrated in Table 2, have exhibited significant synergistic anti-tumor effects.[65–67]

Table 2 Co-Delivery of AP and Chemotherapeutic Agents via Nanocarriers for Synergistic Cancer Treatment

Carrier Type	Typical Size	Zeta Potential	Vitro Synergistic Parameters	Vivo Antitumor Effects	Reference
AP/PTXα-SLNs	223 nm	+42 mV	At an AP/PTX mass ratio of 2:1, the combination index (CI) is 0.78 ± 0.10	Significant tumor inhibition, reduced lung metastasis, stable body weight, no obvious systemic toxicity	[65]
DOC-PA200-LPs	47.2 ± 1.6 nm	−47.2 ± 0.4 mV	CI values in HepG2, MCF-7, and PC-3 cells: 0.13, 0.66, 0.28, respectively	Significant tumor inhibition, no apparent toxicity, and induction of apoptosis	[66]
DOX/PA20-LPs	113.5 ± 2.1 nm	−49.66 ± 1.14 mV	CI values in MCF-7, HepG2, A549 cells: 0.38, 0.56, 0.05, respectively	Significant tumor inhibition, reduced lung metastasis, stable body weight, alleviated toxicity, increased apoptosis, decreased Ki-67/CD31 expression	[67]

Ascorbyl Dipalmitate (ASC-DP)

ASC-DP is another significant lipid-soluble derivative of VC, formed by esterifying both the 2- and 6-hydroxyl groups of the ascorbic acid molecule with palmitic acid, further enhancing its lipophilicity.[68] ASC-DP has been utilized in the construction of formulations with unique nanostructures. Unlike AP, ASC-DP alone does not spontaneously form micelles or liposomal structures.[69] However, complexes of ASC-DP with 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-polyethylene glycol 2000 (DSPE-PEG) readily form stable nanoparticles suitable as drug carriers.

As illustrated in Table 3, Moribe first employed a thin-film hydration method to prepare ASC-DP/DSPE-PEG nanoparticles (molar ratio 1:1, size ~67 nm) in 2010. Using amphotericin B as a model drug, their study demonstrated significantly prolonged circulation time and reduced hepatotoxicity and nephrotoxicity compared to the traditional Fungizone® formulation.[69] Higashi later found that varying the molar ratio of ASC-DP to DSPE-PEG (from 0.5:1 to 2:1) transformed the nanoparticle morphology from micelle-like structures to disc- and tube-shaped structures (100–160 nm). Furthermore, ASC-DP acted as a prodrug in the TME, generating H_2O_2, and exploited the CAT deficiency in tumor cells to induce selective cytotoxicity. These nanoparticles demonstrated significant cytotoxic effects on multiple cancer cell lines (A549, LC-AI, MKN45) while exhibiting negligible toxicity to normal fibroblasts.[70] Chen increased the ASC-DP ratio further (up to 10:1), forming uniform rod-shaped nanoparticles (~100 nm diameter, ~300 nm length) with drug-loading efficiencies reaching 94.1%.[71] More recently, Chen and Higashi achieved precise control over particle morphology by adjusting PEG-lipid types: using DSPE-PEG led to rod-shaped particles, whereas cholesterol-PEG produced tubular structures. This morphological transition was attributed to differences in free energy between PEG-lipid molecules and the steric hindrance effects of PEG chains.[68]

Ascorbyl Stearate (Asc-S)

Asc-S is a lipophilic derivative of ascorbic acid formed via esterification between the hydroxyl group at the 6-position of ascorbic acid and the 18-carbon saturated fatty acid stearic acid. Owing to its markedly enhanced lipid solubility and membrane affinity, Asc-S exhibits superior anti-tumor activity compared with L-ascorbic acid. Asc-S exhibits dose-dependent antiproliferative effects across multiple cancer types—including glioblastoma, pancreatic, ovarian and cervical

Table 3 Tailoring ASC-DP Nanostructures via PEG-Lipid Composition for Enhanced Drug Delivery

Study Focus	Molar Ratio (ASC-DP: DSPE-PEG)	Key Lipids	Morphology	Key Findings	References
ASC-DP/DSPE-PEG nanocarrier for hydrophobic drug delivery	1:1	DSPE-PEG	Spherical, ~67 nm in diameter	• First successful construction of a stable carrier • Co-delivery of two agents B • Improved drug stability and circulation time	[69]
ASC-DP/DSPE-PEG Ratio-dependent structural transformation	0.5:1, 1:1, 2:1	DSPE-PEG	Transition from vesicle to tubular: 0.5:1 vesicle, 1:1 mix, 2:1 tube	• Morphology ratio-dependent • ASC-DP induces ROS in tumor microenvironment • Selective cytotoxicity & efficacy against multiple tumors	[70]
Rod-like nanoparticles characterization	10:1	DSPE-PEG	Rod-shaped 100 nm in diameter, 500 nm in length	• Successfully constructed rod-shaped particles • Superior monodispersity • Layered core–shell structure • Clinical potential (IC50<3.3)	[71]
PEG-lipid-dependent morphology modulation	10:1	DSPE-PEG, Chol-PEG	DSPE-PEG: Rod-shapedChol-PEG: Tubular	• Lipid composition governs shape • Morphology correlates with inner cavity volume and thermodynamic equilibrium	[68]

https://doi.org/10.2147/IJN.S559426

cancers, and T-cell lymphoma—while showing minimal toxicity toward normal cells, indicating a favorable safety profile.[72]

Mechanistically, the anti-tumor activity of Asc-S centers on redox disruption. By depleting intracellular glutathione (GSH) and reducing the GSH/GSSG ratio, Asc-S drives excessive ROS accumulation, resulting in mitochondrial membrane depolarization and caspase-3–dependent apoptosis. In addition, Asc-S uniquely induces glutathionylation of key oncogenic proteins such as IKK, p50-NF-κB and mutant p53, thereby blocking survival signaling at its source—an advantage not shared by unmodified vitamin C. Beyond redox regulation, Asc-S also influences membrane biophysics. For example, in cervical cancer cells it alters lipid composition and membrane fluidity, enhances permeability, and promotes autophagy–apoptosis crosstalk;[72] whereas in T-cell lymphoma, it functions as a strong radiosensitizer, augmenting apoptotic induction, reducing cancer stem-like subpopulations, lowering tumor burden in vivo, and ultimately prolonging survival.[73]

Within nano-drug delivery systems, Frungillo et al further identified Asc-S can function as a surface-functionalization ligand. PLGA nanoparticles modified with Asc-S achieved active targeting through glucose transporters (GLUTs) overexpressed on tumor cells, forming a stable sustained-release system with a particle size of approximately 100–140 nm and markedly enhancing apoptosis in HL-60 leukemia cells.[74]

Triazole-Modified Vitamin C Derivatives (Triazole-VC Derivatives)

Triazole-VC derivatives are generated by incorporating a 1,2,3- or 1,2,4-triazole ring onto the vitamin C scaffold, thereby combining the intrinsic bioactivity of vitamin C with the favorable bioisosteric and bioelectronic features of the triazole pharmacophore. This structural modification markedly improves pharmacokinetic behavior, membrane permeability, and affinity toward biological targets. In most cases, the triazole ring is introduced at the C-6 position via Cu(I)-catalyzed click chemistry, whereas side-chain tuning—using hydrocarbon spacers of variable length, electron-modulating aryl groups, sulfonamides, or purine/pyrimidine pharmacophores—enables fine control of lipophilicity, chemical stability, and anti-cancer selectivity. The use of 2,3-dibenzyl protection is particularly common, as it greatly enhances metabolic stability and facilitates cellular uptake. Accumulating evidence demonstrates that triazole modification substantially strengthens the anti-tumor activity of vitamin C and confers a high degree of selectivity. For instance, a 4-decyl-substituted 1,2,3-triazole-VC derivative exhibits nanomolar cytotoxicity against MCF-7 breast cancer cells ($IC_{50} \approx 0.08$ μM) while sparing normal fibroblasts.[75] Meanwhile, 1,2,4-triazole-VC derivatives demonstrate potent inhibition in hematologic malignancies and display potential IMPDH inhibitory features, suggesting targeting of nucleotide-metabolism pathways.[76]

Mechanistically, these derivatives not only retain the hallmarks of pharmacological-dose vitamin C— ROS elevation, mitochondrial dysfunction, and energy crisis—but also expand activity toward hypoxia-adaptation pathways. For example, the representative 4-decyl 1,2,3-triazole-6-deoxy-2,3-dibenzyl-L-ascorbate upregulates hydroxylated HIF-1α and reduces NOS2 expression, thereby impairing the hypoxia-driven proliferative adaptability of tumor cells.[75]

Nucleoside-Like Vitamin C Derivatives

Nucleoside-like vitamin C derivatives, particularly deazapurine-modified L-ascorbic acid (L-AA), represent a highly innovative design strategy. By introducing a 3-, 7-, or 9-position deazapurine ring onto the ethylene side chain of L-AA or imino-L-AA, these molecules integrate nucleoside-analogue targeting with vitamin C–mediated redox regulation, resulting in improved chemical stability, lipophilicity, membrane permeability, and overall anticancer potency. Notably, 9-deazapurine derivatives show the most promising profile: they retain the structural recognition features of nucleoside analogues while preserving the sugar-like scaffold of vitamin C, thereby enabling simultaneous interference with nucleotide metabolism and disruption of redox homeostasis. Representative compounds—such as 2,6-dimethoxy-9-deazapurine-L-ascorbic acid and 9-deazahypoxanthine-L-ascorbic acid—demonstrate potent antiproliferative activity against leukemia, cervical, colorectal, and pancreatic cancer cells in the low-micromolar range, with minimal toxicity toward normal fibroblasts, highlighting a favorable therapeutic index and tumor selectivity.[77]

5,6-O-Isopropylidene-L-Ascorbic Acid (IAA)

IAA is an acetonide-protected derivative in which the C-5 and C-6 hydroxyls of L-AA are locked to prevent oxidation. Since the C-6 primary hydroxyl is the first and most reactive oxidation site that triggers lactone-ring opening and rapid

loss of vitamin C activity, this protection critically improves oxidative stability. The isopropylidene group simultaneously increases hydrophobicity, giving IAA a combined advantage of enhanced stability, greater lipid solubility, and preserved metal-chelating capability.

As a ligand, IAA forms the Zn(II) complex [$Zn(L)Cl_2$], which shows dose-dependent cytotoxicity in PC-3, Caco-2 and MCF-7 cells and strong DPPH radical-scavenging activity, indicating redox-mediated anti-tumor effects. Zinc coordination also increases the physicochemical stability and bioavailability of IAA and may potentiate anti-proliferative activity by interfering with zinc-dependent enzymes and transcription factors.[78]

In nanosystems, IAA-functionalized silver and MnO_2 nanoparticles (Ag NPs-IAA and MnO_2 NPs-IAA) display marked antioxidant and anti-biofilm activities and induce pronounced growth inhibition and apoptosis in MCF-7 and PC-3 cells. These results suggest that IAA, when used as a surface ligand or nanoshell, improves colloidal stability and biocompatibility of metal nanomaterials while amplifying their anti-tumor efficacy through coordinated metal-ion release, ROS modulation, and membrane interactions.[79]

Water-Soluble Vitamin C Derivatives

Ascorbic Acid 2-Glucoside (AA-2G)

Ascorbic acid 2-glucoside (AA-2G) is a water-soluble VC derivatives formed by introducing a glucose moiety to the 2-position of ascorbic acid, providing exceptional stability due to its unique chemical structure. In aqueous solutions, AA-2G is highly resistant to degradation caused by temperature fluctuations, pH variations, and oxidation. In the presence of fibroblasts, over 90% of AA-2G remains intact after 60 hours, demonstrating substantially greater stability than traditional ascorbic acid.[80] This characteristic enables AA-2G preparations to avoid complex stabilization measures during storage and formulation, overcoming the limitations of traditional ascorbic acid infusion solutions that require the addition of stabilizers and must be prepared immediately prior to use.

Miura et al investigated the antitumor activities of acylated AA-2G derivatives by introducing linear and branched acyl chains of varying lengths at the 6-position of the AA-2G molecule. They found that these derivatives displayed minimal cytotoxicity to colon-26 cancer cells in vitro, whereas ascorbic acid exhibited concentration-dependent cytotoxicity. Surprisingly, in vivo experiments showed opposite results: the branched derivative, 6-bOcta-AA-2G, achieved significantly stronger antitumor effects at one-tenth the dose of ascorbic acid. The study suggested that AA-2G acts through in vivo hydrolysis to release ascorbic acid, with acyl modification enhancing bioavailability, and the branched structure potentially providing additional antitumor mechanisms.[80]

AA-2G's primary applications in nano-delivery have currently focused on antioxidant and anticancer efficacy. In vivo, AA-2G undergoes enzymatic hydrolysis to slowly release ascorbic acid, achieving sustained antioxidant effects, with 1.8% AA-2G providing an antioxidant effect equivalent to that of 15% ascorbic acid. Lamie et al developed AA-2G/Span-60 nanovesicles that achieve synergistic antitumor activity through unique oxidative stress regulation mechanisms. This system co-delivers AA-2G with itraconazole (ITZ), where AA-2G modulates oxidative balance by elevating GSH levels and reducing MDA levels in tumor tissues, thereby synergistically enhancing ITZ's antitumor efficacy, resulting in a 5.06-fold increase in cytotoxicity and a 62% tumor inhibition rate.[81]

In addition to AA-2G and its derivatives, several other water-soluble VC derivatives have shown promising effects but remain underexplored in terms of nano-delivery applications. For instance, ascorbic acid-2-phosphate (A2P), modified with a phosphate group at the second position of ascorbic acid, exhibits enhanced stability and prolonged activity. Studies have demonstrated that A2P inhibits melanoma cell invasiveness by suppressing the expression of hypoxia-inducible factor-1α (HIF-1α).[82] Additionally, magnesium ascorbyl phosphate (MAP) and sodium ascorbyl phosphate (SAP) exhibit excellent stability under neutral conditions, with MAP particularly promoting collagen synthesis and delaying the formation of UV-induced skin tumors.[83]

Overall, these diverse VC derivatives offer promising opportunities for further advancements in nano-delivery technologies, presenting valuable therapeutic prospects in cancer treatment that warrant continued exploration.

Nanocarrier-Based Vitamin C Delivery Systems

Designing diverse nanocarriers is a key strategy for overcoming the limitations of conventional VC therapy, complementing the development of VC derivatives. By encapsulating VC or its derivatives, nanocarriers can effectively protect the active ingredient from degradation, improve its bioavailability, prolong circulation time, and achieve targeted delivery to tumor tissues through surface modifications. A variety of nanocarrier systems have been developed for VC delivery, primarily including lipid-based carriers (liposomes, SLNs, NLCs), polymeric nanoparticles, metal-based nanozymes, mesoporous silica nanoparticles, and hydrogels (Figure 2). The following sections will provide a detailed overview of the design and application of these systems.

Liposomes

Liposomes are nano-sized vesicles formed by single or multiple phospholipid bilayers. Due to their structural similarity to cell membranes, excellent biocompatibility, low immunogenicity, and high drug-loading efficiency, liposomes have become a widely used and classical nanocarrier for delivering VC and its derivatives.[84] Liposomes can encapsulate water-soluble drugs within their internal aqueous compartments and lipid-soluble drugs within their lipid bilayers, making them particularly suitable for delivering lipophilic derivatives such as AP.[85] Through precise modulation of phospholipid composition, particle size, surface charge, and surface modifications, liposomes significantly enhance VC's pharmacokinetic parameters and tumor-targeted accumulation.[86] Among various surface modification strategies, polyethylene glycol (PEG) coating is essential, as it prolongs liposome circulation time in the bloodstream by reducing recognition and clearance by the mononuclear phagocyte system (MPS), thereby conferring long-circulating and immune-evasive properties.[87]

Gopinath first introduced the concept of AP liposomes (Aspasomes) in 2004.[63] Prepared using the thin-film hydration method, AP liposomes exhibited antioxidant efficiency approximately twice that of free VC and enhanced transdermal penetration by 1.5-fold. In 2010, Sawant developed a PA-modified liposomal system co-loaded with paclitaxel, demonstrating a significant synergistic anticancer effect in breast cancer cells, with a combination index (CI) of 0.3.[59]

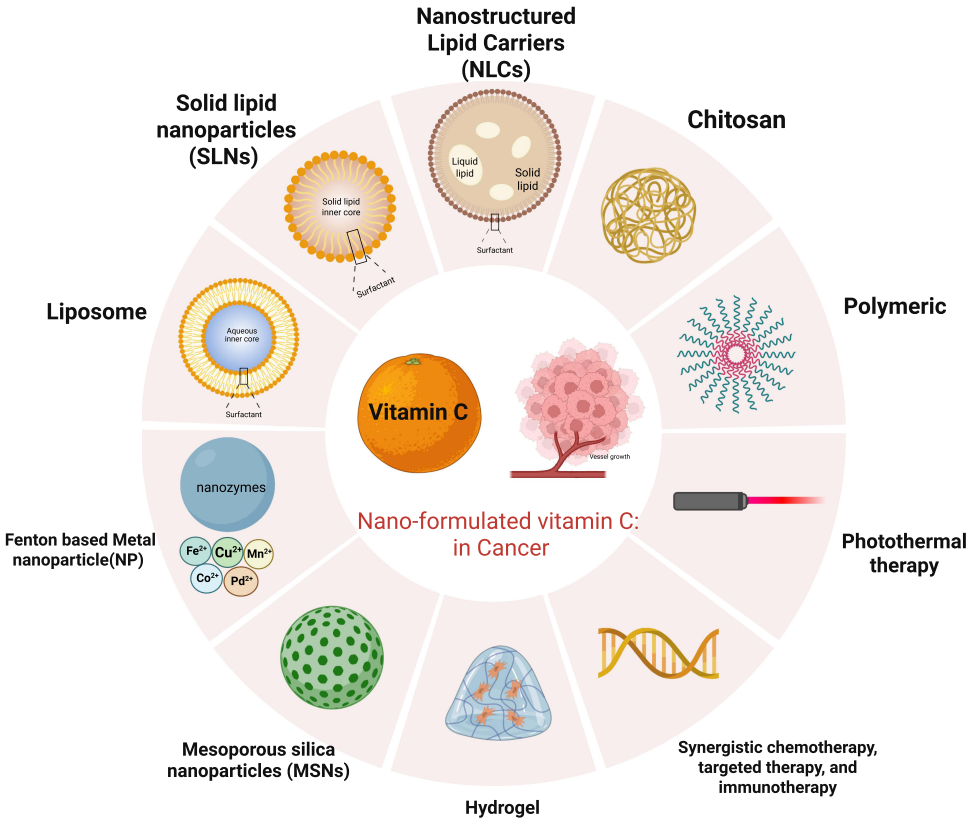


Figure 2 Diverse Nanocarrier Systems for Vitamin C Delivery in Anti-tumor Synergistic Applications. Created with BioRender.com.

The same research group compared the antitumor efficacy of PA liposomes with free VC in an animal model in 2012. They observed that PEG-modified PA liposomes achieved a tumor inhibition rate of 68%, significantly higher than the 30% inhibition observed with free VC. This enhanced therapeutic efficacy was primarily attributed to the liposomal delivery system markedly increasing localized ROS production within tumor tissues.[88] Subsequent studies by Li and Yang, using docetaxel/PA co-loaded liposomes and PA-DOX liposomes, respectively, further confirmed the advantages of liposomal carriers in VC-based anticancer applications.[65,66]

Liposomal drug delivery systems have gradually evolved towards specific delivery and stimuli-responsive release. In 2023, Ma constructed a photothermally responsive VC-loaded lipid nanoparticle system (VIP), enabling externally triggered, on-demand drug release. This system used PLGA-lecithin-PEG nanoparticles encapsulating VC and the photosensitizer indocyanine green (ICG). Under laser irradiation at specific spatial and temporal conditions, the localized thermal effect generated by ICG (temperature increased to 51.3°C) acted as a "switch", significantly accelerating VC release from the carrier (from 52.8% to 92.1% within 24 hours). Released VC subsequently exerted dual antitumor effects by concentration-dependently inducing polarization of M2 macrophages to the antitumor M1 phenotype and enhancing intracellular H_2O_2 generation, thereby achieving synergistic effects of immune modulation and direct tumor cell killing[28] (Figure 3).

Based on the responsive release strategy, researchers have further explored new ways to enhance the efficiency of cell uptake. Fox introduced ultrasonic microbubble-assisted technology, which significantly enhanced the drug uptake efficiency of PA liposomes in KRAS-mutant colorectal cancer cells using ultrasound-triggered microbubble technology, increasing the antitumor efficacy of PA liposomes by 1.7 times and 2.2 times in LS174T cells and HCT116 cells, respectively, while effectively reducing drug exposure and potential toxicity risks in non-target tissues.[89]

Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) are a class of colloidal systems composed of physiologically compatible lipids. Unlike traditional emulsions or polymer nanocarriers, the lipid core of SLNs is composed of monoglycerides, diglycerides, triglycerides, fatty acids or waxes, which have a melting point higher than body temperature and can remain solid in the body.[90] Its surface is stabilized by a surfactant and a shell supplemented by synergistic surfactants, a design that allows both the encapsulation of fat-soluble drugs and the entrapment of small amounts of hydrophilic drugs in lipid lattice defects and between layers. Since the lipids used are usually biodegradable, SLNs have low toxicity and good biocompatibility. Additionally, its fat-soluble structure improves the ability of drugs to penetrate cell membranes and enables sustained or controlled-release release by controlling the degradation of lipid cores.[91]

As illustrated in Table 4, Güney and Ledinski prepared SLNs equipped with water-soluble and lipid-soluble VC, respectively, which showed good antitumor effects.[91,92]

Nanostructured Lipid Carriers (NLCs)

Nanostructured lipid carriers (NLCs) are typically regarded as second-generation upgrades of solid lipid nanoparticles (SLNs), exhibiting superior drug-loading capacity and enhanced stability. Unlike SLNs composed exclusively of solid lipids, the core matrix of NLCs consists of a blend of solid and liquid lipids (eg, oils).[93] This composition creates an irregular internal crystal or polymorphic structure, significantly increasing the loading capacity of drug molecules and effectively preventing their expulsion from the carrier during prolonged storage, thus providing greater stability.[94]

Teeranachaideekul demonstrated that NLCs prepared with glyceryl stearate as the solid lipid and Tween 80 as the surfactant markedly improved the chemical stability of AP, maintaining a drug retention rate above 85% after 90 days of storage at 4°C.[95] Eh Suk further confirmed that Tween 80 effectively reduced NLC particle size to approximately 140 nm, with an encapsulation efficiency of over 75% for L-ascorbic acid, significantly delaying drug release.[96] Sheybani employed a response surface methodology (RSM) to optimize the formulation of AP-loaded NLCs, resulting in uniform nanoparticles with an average size of 133.4 nm, a polydispersity index (PDI) of 0.29, and encapsulation efficiency exceeding 90%; drug release kinetics followed the Korsmeyer-Peppas model.[97]

To further extend the functionality of NLCs, responsive carrier systems have been developed. Kalaycioglu introduced magnetic nanoparticles into NLCs to create magnetically sensitive carriers (~200 nm), enabling controlled drug release

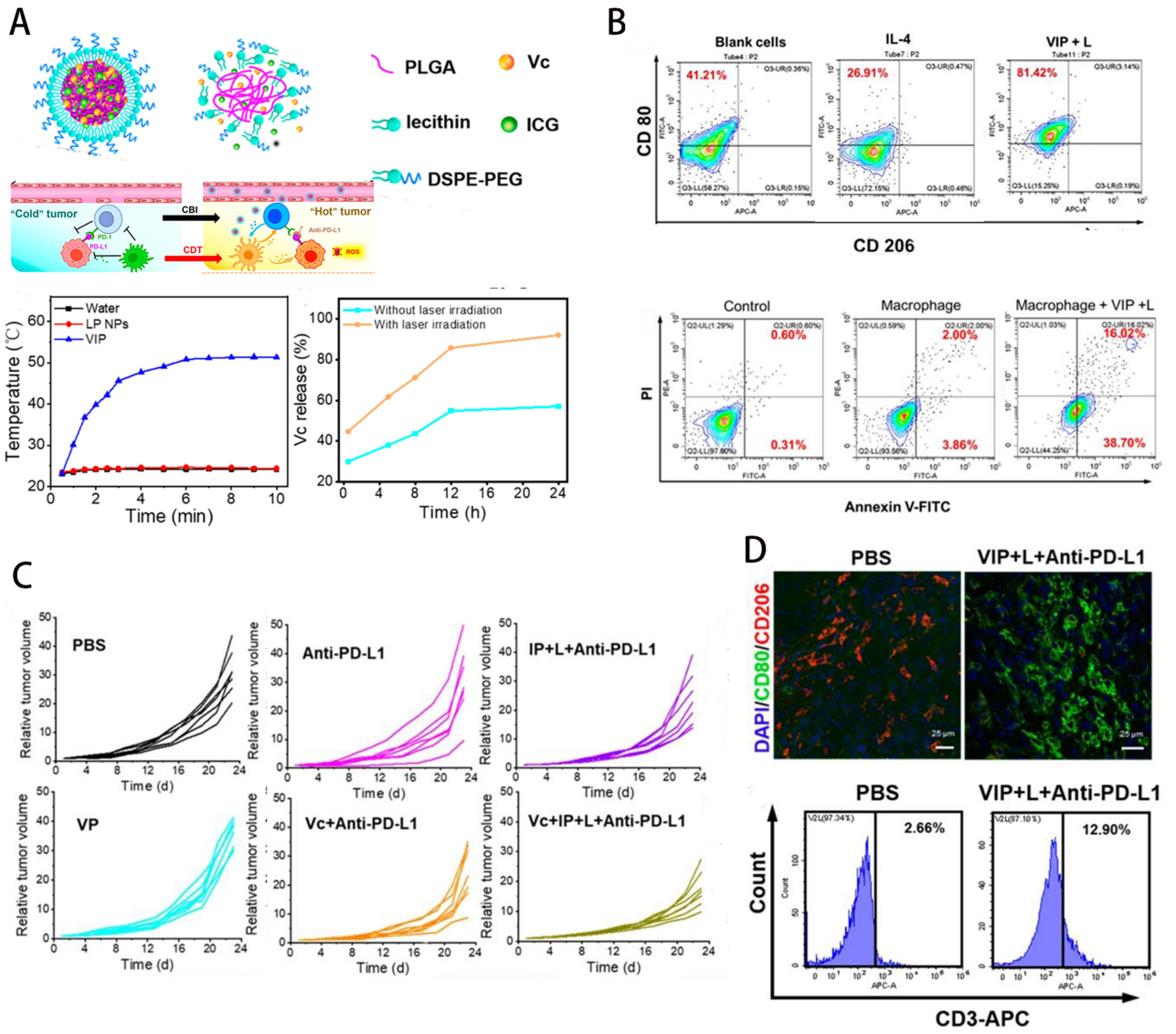


Figure 3 Photothermally Responsive Lipid Nanoparticles (VIP) for Combined Photothermal-Chemotherapy-Immunotherapy of Tumors (**A**) Schematic illustration of VIP nanoparticles and their photothermal response and vitamin C (Vc)release profiles under 808 nm laser irradiation. Laser irradiation rapidly elevates local temperature to 51.3°C, triggering 92.1% Vc release within 24 hours. (**B**) In vitro cellular experiments. Compared to the control group, VIP combined with laser irradiation (VIP+L) significantly promotes the polarization of M2 macrophages toward the M1 phenotype ($CD80^+$ cells proportion reaching 81.42%) and markedly increases apoptosis in cancer cells (late apoptosis rate reaching 38.70%). (**C**) Tumor growth curves in MB49 tumor-bearing mice. Results demonstrate that the combination of VIP and Anti-PD-L1 therapy exhibits the strongest synergistic anti-tumor effects, achieving a tumor inhibition rate of up to 90%. (**D**) Analysis of tumor immune microenvironment. Immunofluorescence and flow cytometry analyses indicate that the combined therapy significantly enhances the infiltration of M1 macrophages (green fluorescence) and $CD3^+$ T cells within tumor tissues ($CD3^+$ T cell proportion increased from 2.66% to 12.90%) (Scale bars: 25 μm). Reproduced from Ma Z, Yang M, Foda MF et al. Polarization of Tumor-Associated Macrophages Promoted by Vitamin C-Loaded Liposomes for Cancer Immunotherapy. ACS Nano. 2022;16(10):17389–17401. Copyright 2022, with permission from American Chemical Society.

through temperature elevation (43°C) induced by an alternating magnetic field.[98] Okuyucu developed a smart NLC system (~150 nm) integrating doxorubicin, verapamil, and gold nanorods for near-infrared (NIR)-triggered drug release, significantly enhancing local drug concentration and synergistic anticancer efficacy.[99]

Polymer Nanoparticles

Polymeric nanoparticles, due to their structural diversity, ease of functionalization, and controlled release properties, have become important drug delivery carriers. Polymers can be categorized into natural and synthetic types. Among natural polymers, chitosan, a cationic polysaccharide extracted from the shells of crustaceans, has garnered considerable attention due to its excellent biocompatibility, biodegradability, and mucoadhesive properties.[100] Chitosan's amino groups can undergo

Table 4 Antitumor Efficacy of Water-Soluble and Lipid-Soluble Vitamin C Formulations Based on SLNs

Nanoparticle Type	Size and Characteristics	Cell Lines	Experimental Outcomes	References
AA-SLNs	Size: 200–225 nm; Encapsulation efficiency: ~90%; 70% release over 96 h	H-Ras 5RP7 cancer cells, NIH/3T3 normal cells	Cancer cell viability: 25 μM:41% vs free AA 58.7%; Caspase-3 activity significantly increased	[91]
AP-SLN	3% Pluronic: 337 nm; 10% Pluronic: 414 nm	U2OS cancer cells, HEK293T normal cells	5 μM: Significant antioxidant effect; 50 μM: Enhanced cytotoxicity against U2OS cells	[92]

ionic cross-linking with negatively charged VC to form nanoparticles or can serve as scaffolding material to encapsulate VC and other chemotherapeutics. Sekar first systematically investigated a chitosan-VC nanocomposite system (CANs), preparing stable nanoparticles (~100 nm) via ionic gelation. The system exhibited concentration-dependent cytotoxicity (6.25–100 mg/mL) against cervical cancer HeLa cells but showed negligible toxicity toward normal fibroblasts.[101] Fahmy designed PEGylated chitosan nanoparticles loaded with VC and oxaliplatin, creating a pH-sensitive dual-drug delivery system (VC-OX/PEG-CS NPs, ~176 nm). This formulation induced 81.5% apoptosis in breast cancer MCF-7 cells, significantly outperforming the individual drugs.[102]

Synthetic polymers, prepared by polymerizing small-molecule monomers, offer advantages such as tunable structure, surface modification flexibility, and controlled drug release profiles.[103] By adjusting monomer composition, hydrophilicity/hydrophobicity and drug-loading capacity can be precisely tailored.[104] Surface modifications allow the introduction of targeting ligands to enhance specificity, and compositional adjustments facilitate controlled drug release. Early research primarily emphasized fundamental drug encapsulation and optimized release strategies. For example, Martins and Sawant demonstrated stable VC delivery using PLGA nanoparticles and PEG-PE micelles, respectively, achieving excellent tumor selectivity. Recent advancements shifted the focus toward stimuli-responsive and multifunctional systems.[59,105] Ambattu developed pullulan–PEI–VC copolymeric carriers, combining gene therapy capabilities for dual antitumor effects.[106] Yin further proposed an H_2O_2-responsive PA micelle system composed of PEG-b-PBEMA copolymers. The boronate ester groups in the PBEMA segment were responsive to H_2O_2, releasing quinone methide to consume intracellular glutathione (GSH), while PA acted as a pro-oxidant to elevate tumor H_2O_2 levels. This strategy successfully reduced intratumoral GSH by 70%, increased ROS levels by 4.2-fold, and achieved an 83% tumor suppression rate.[107] Regarding administration route optimization, Hamdi combined PLGA nanoparticles with poly(acrylic acid) hydrogels for sustained local delivery.[108] Additionally, Luo significantly improved drug intestinal absorption efficiency through AA modification on the surface of PLGA carriers. This modification strategy increased absorption efficiency by 3.4 times in the Caco-2 cell model and confirmed the efficient endocytosis mechanism mediated by the SVCT1 transporter.[109]

Metal Nanoparticles

Metal nanoparticles play diverse roles in the antitumor application of VC due to their unique physicochemical properties, including magnetism, optical properties, catalytic activity, and high specific surface area,[110] as illustrated in Table 5. These nanoparticles not only serve as passive carriers for VC but also frequently function as active components with specific roles, such as catalysts for Fenton reactions, contrast agents in medical imaging, or synergistic enhancers in combination with other therapeutic modalities like photodynamic therapy and magnetic hyperthermia.[25]

Iron-Based Nanomaterials

Iron-based nanoparticles, including iron oxide (Fe_3O_4), iron oxychloride (FeOCl), clinically approved hematite (Fe_2O_3), metastable wüstite ($Fe_{1-x}O$), and iron dextran, have drawn significant attention from researchers due to their superior magnetic responsiveness, acceptable biocompatibility, and unique enzyme-mimicking catalytic activities, notably peroxidase-like activity.[61,111–119]

https://doi.org/10.2147/IJN.S559426

Table 5 Transition Metal-Based Nanoparticles Combined with Ascorbic Acid for Anti-Tumor Applications

Nanoplatform	Particle Size	Ascorbic Acid Function	Cell Lines Studied	Main Findings and Synergistic Effects	References
Fe_3O_4@C-FA	150 nm	Induce oxidative stress, generate endogenous	Human colorectal cancer PC-3 cells; normal HEK293T cells	Low-dose AA (0.5–2 mM) synergize Fe_3O_4@C-FA triggered cell membrane rupture and cell death	[111]
AMNC	~50 nm	AA on Fe_3O_4 surface forms linkage with drug molecules	WEHI-164 (fibrosarcoma), MCF-7 (breast), A549 (lung), WI26VA4 (normal lung)	• AMNCs as effective pH-sensitive DOX carriers • Controlled release under acidic conditions • Higher selective toxicity to tumor cells	[112]
FeOCl@H-DMOS	125 nm	Precursor of H_2O_2 and activates Fenton	HeLa, L929 fibroblasts	• Efficient CDT under neutral pH • AA enhancement effect • MR imaging-guided therapy capability	[113]
Fe_3O_4 coated with VC–conjugated polyglutamic acid or polylactic acid	20 - 80 nm	Induce cell death via ROS, Fe_3O_4 enhances AA function	HeLa, KB (FR positive), CHO (control)	• Compared conjugated VC nanoparticles versus non-conjugated nanoparticles combined with exogenous VC treatment • Fe_3O_4 NPs effectively catalyze AA at pharmacological doses (minimum 0.1 mM) • Generate highly toxic ·OH intracellularly to induce tumor cell apoptosis • Significantly reduce AA effective dosage	[114]
Fe_3O_4@mSiO_2-PA	250±50 nm	AA-derived PA as H_2O_2 source	HeLa, HUVECs	• Effectively inhibits HeLa cell growth • Good biocompatibility • Effective Fenton reaction enhances oxidative damage	[61]
FHPA	140 nm	AA acts as loaded agent and reacts with iron	4T1 (mammary carcinoma), HC11 (mammary epithelium), B16 (melanoma), A9 (fibroblasts)	• TME-responsive release • Synchronized Fe3+ and AA release for synergistic OH catalysis • High efficacy and low toxicity in vitro and in vivo • Tumor inhibition rate exceeding 60% within 14 days	[115]
Fe_3O_4-LAA	20 nm	Surface modification material and therapeutic enhancer	Gastric cancer AGS cells	• LAA surface coating improves SPIONs dispersion and stability • Synergistically enhances anticancer effects • Superior cytotoxicity and gene expression responses in AGS cells compared to individual components	[116]
Fe_3O_4-AA-MIL-88B(Fe)	18.2±0.7 nm	AA loaded in MOF, enhances Fe2+/Fe3+ cycling	Not mentioned	• Magnetic field control capability • High catalytic efficiency • 3-fold higher MB degradation rate than conventional homogeneous systems • ~4.6-fold improvement in ·OH generation efficiency	[117]
Wüstite (Fe_1-xO)	8 nm	Promotes extracellular H_2O_2 (macrophages)	4T1, RAW264.7	• AA effective killing concentration reduced from 25 mM to 4 mM • Induces macrophage M1 polarization for immunomodulation • Tumor volume reduced by ~60% within 7 days	[118]
MPCF	8.4 nm	Intratumoral H_2O_2 generation, Fe3+/Fe2+ redox with GSH	4T1, 3T3	• MPCF + AA + laser synergy • Complete tumor cure in 4T/5T mice (inhibition rate >95%)	[119]

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CuO	80±20 nm	Serves as reducing agent to convert Cu^{2+} to Cu^{+}; cooperates with Cu compounds to enhance cytotoxicity	Multiple tumor cell lines: K562, MDA-MB-231, MCF-7, HCT116	• Cu^{2+} + NAC/cysteine/ascorbic acid: 2–3 orders of magnitude cytotoxicity enhancement • Effective against chemotherapy-resistant tumor cell lines • Cu^{+1} complexes generate superoxide via Fenton-like reactions • Irreversible membrane damage and caspase-independent cell death	[120]
GSH-Cu/Cu_2O nanozymes	<100 nm	Acts as nanozyme substrate; catalyzes ROS generation	Normal cells (HUVEC, SVGP12); cancer cells (PC-12, HCT116)	• 40% enhancement in ascorbate oxidase activity • Selective inhibition of cancer cell proliferation • Detection limit as low as 0.18 μM	[121]
Cu-MSN@DA	50 nm	Generates H_2O_2 via self-oxidation; facilitates Fenton-like reaction and •OH production	Breast cancer: 4T1, MCF-7; Lung cancer: A549	• Tumor inhibition rate reaches 90.4% • Synergy between chemodynamic therapy and chemotherapy • Active targeting enhances tumor site accumulation	[122]
Cu/ZIF-8@Vc-Ca/HA	90 nm	Selectively generates H_2O_2 in tumor cells; induces •OH through Fenton-like reaction	MG63 (osteosarcoma), NIH-3T3 (normal)	• pH-sensitive release • Significant tumor cell killing with low toxicity to normal cells • Significant mitochondrial membrane potential decline	[123]
$HMnO_2$-VC@mPEG-Ce_6	189.3 nm	Generates H_2O_2, drives ROS burst, alleviates tumor hypoxia	PC-3 (prostate cancer)	• Combined ultrasound therapy achieves 76.4% killing rate	[124]
Co SA–N/C	200–300 nm	Catalyzes ROS generation, depletes GSH	U87 MG (glioblastoma)	• Disrupts cellular redox balance, enhances antitumor effect	[125]
Pd CNCs	41.2 nm	Autoxidizes to produce H_2O_2 and DHA	HCT116 (colorectal cancer)	• Pd CNCs exhibit higher catalytic activity than Pd NCs • Significantly enhance H_2O_2 generation and ascorbic acid-induced oxidative stress • Anti-tumor efficacy superior to 5-FU and comparable to oxaliplatin	[126]

https://doi.org/10.2147/IJN.S559426

Early Concept Verification: Establishment of Synergistic Catalysis Mechanism

Qiao An first developed a synergistic therapeutic system using iron-based nanozymes and VC, establishing a foundational paradigm in this field. Their key contribution validated the feasibility of VC-iron nanoparticles synergistically generating hydroxyl radicals. Using folate-modified Fe_3O_4@C-FA combined with exogenous ascorbic acid, significant tumor cell killing was achieved in prostate cancer PC-3 cells at low VC concentrations (0.5–2 mM), with minimal toxicity toward normal cells. This pioneering work provided theoretical groundwork for subsequent studies while highlighting the need to improve catalytic efficiency.[111]

Pharmacological Dose Optimization: Further Synergistic Enhancement at Lower Dosages

Building upon previous research, Pal, Jana achieved significant progress by designing iron oxide nanoparticle (Fe_3O_4 NP)-based nanoplatforms to investigate the synergistic anticancer effects with VC at pharmacological concentrations (0.1–1.0 mM), thus further optimizing the required dose of AA. A major breakthrough of this study lies in the first systematic comparison of antitumor activities between Fe_3O_4-PA nanoparticles (with exogenous AA supplementation) and Fe_3O_4-PAA-PB-AA nanoparticles (AA-conjugated type). Cell experiments demonstrated that both iron-based nanosystems significantly enhanced the intracellular Fenton reaction mediated by AA. Specifically, Fe_3O_4 NPs efficiently catalyzed the conversion of low-dose AA (as low as 0.1 mM) into highly toxic hydroxyl radicals (•OH), leading to substantial apoptosis in tumor cells, whereas treatment with AA alone exhibited no noticeable cytotoxicity.[114]

Optimization of Catalytic Efficiency: Overcoming pH Limitations

The conventional Fenton reaction's narrow effective pH range (pH 2–4) contrasts sharply with the slightly acidic tumor microenvironment (pH 6.5–7.2), creating a significant technical challenge. Researchers have addressed this by designing advanced materials. Li achieved a critical breakthrough with the FeOCl@H-DMOS-VC/PEG nanosystem. Utilizing FeOCl's narrow bandgap and layered structure, they constructed a "charge storage-surface catalysis" synergistic mechanism, extending effective catalytic activity to pH 5–7, thus matching the tumor microenvironment. In a U14 tumor model, a single intravenous injection nearly completely eliminated tumors and provided integrated MRI imaging capabilities (r_2 = 34.08 $mM^{-1}s^{-1}$), effectively achieving combined diagnostic and therapeutic functions.[113] Yi et al (2024) further optimized catalytic activity through intrinsic material properties by synthesizing metastable wüstite ($Fe_{1-x}O$) nanozymes. The presence of low-valent iron (Fe^0/Fe^{2+}) markedly increased catalytic efficiency over traditional Fe_3O_4, reducing the effective AA concentration required for tumor killing from 25 mM to 4 mM. Additionally, this system induced macrophage polarization toward the pro-inflammatory M1 phenotype, resulting in approximately 60% tumor volume reduction within seven days in the 4T1 model, thereby opening a new avenue for immune modulation.[118]

Targeted Delivery Strategies: Achieving Precision and Controlled Therapy

Following enhancements in catalytic efficiency, achieving controlled drug release and precise targeting has become the subsequent critical objective. Researchers have approached this through magnetic targeting and responsive release. Regarding responsive release, Yang and Shi developed the FHPA nanomedicine, which features a sophisticated −Si−O−Fe− hybrid framework responsive to the mildly acidic tumor environment, facilitating simultaneous Fe^{3+} and $AscH^-$ release. In vivo experiments indicated tumor-targeted accumulation of 2.15% ID/g, with tumor inhibition exceeding 60% over 14 days and a blood half-life of 1.99 hours, demonstrating favorable pharmacokinetic properties.[115] Bondarenko developed the Fe_3O_4-VC-MIL-88B magnetically responsive MOF system, representing significant progress in magnetic targeting strategies. This system enabled precise manipulation under an external magnetic field (saturation magnetization of 24.6 emu/g), improving catalytic efficiency 4.6-fold compared to traditional homogeneous systems, and highlighting potential clinical application for precision therapy.[117]

Multimodal Synergistic Therapy: Overcoming Single-Modality Limitations

Single therapeutic approaches often fail to completely eradicate tumor cells, prompting increased interest in multimodal combination therapies. Zhang developed an iron dextran-based nano-platform (MPCF: M: 4T1 cell membrane; P: polydopamine; C: calcium phosphate; F: iron dextran). This platform combined ascorbic acid's pro-oxidant effects

with polydopamine-mediated photothermal therapy (PTT), achieving responsive synergistic treatment in the tumor microenvironment[119] (Figure 4).

Copper-Based Nanomaterials

Copper-based nanoparticles, including copper oxide (CuO NPs), cuprous oxide (Cu_2O NPs), metallic copper (Cu^0 NPs), Cu^{2+}-based organic frameworks (such as Cu^{2+}-doped ZIF-8), and mesoporous silica-supported copper materials (such as, Cu-MSN), exhibit significant advantages over iron-based systems in catalytic efficiency, pH adaptability, and specificity.

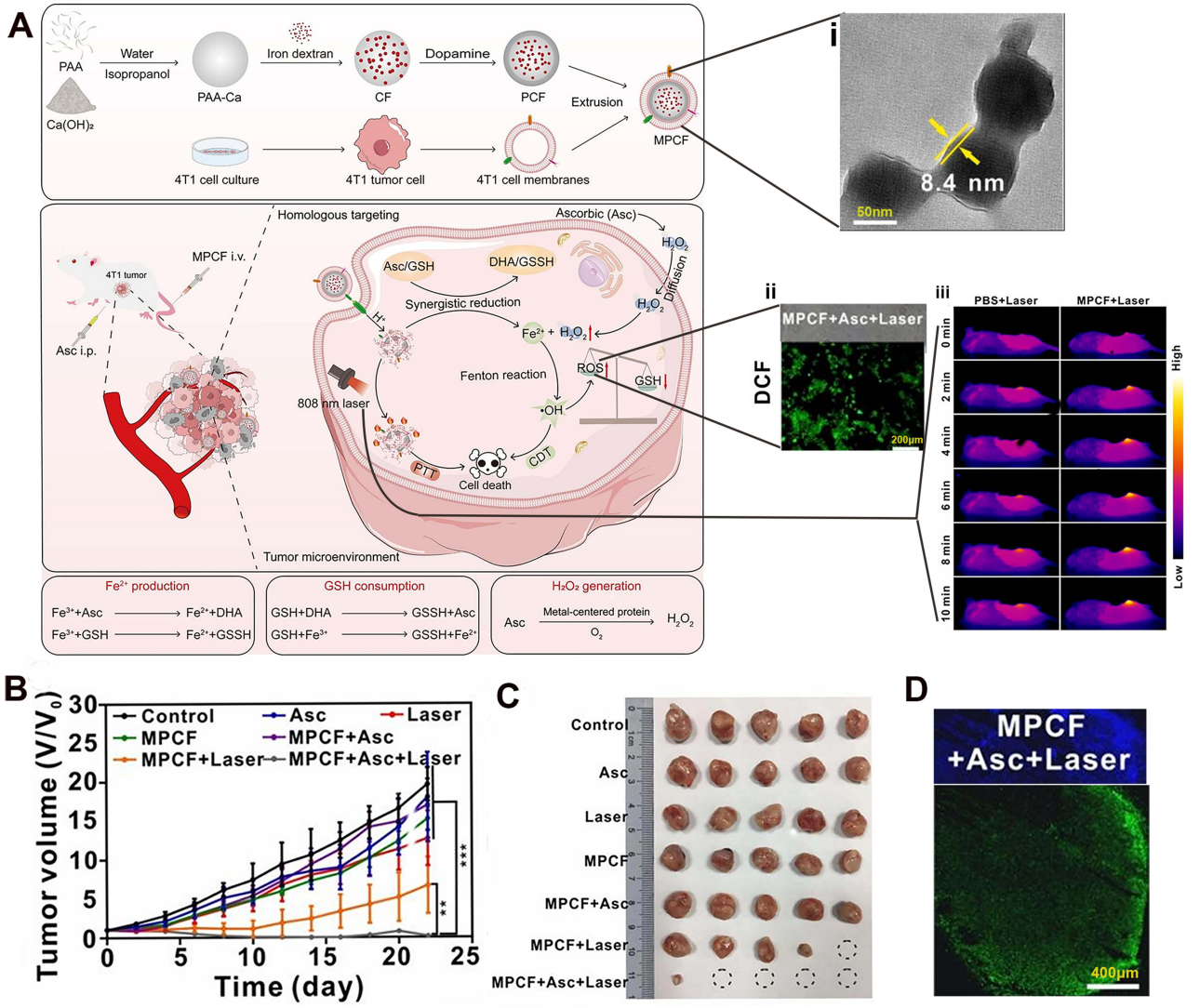

Figure 4 Iron-based Nanoplatform (MPCF) Combined with Ascorbic Acid for Photothermal–Chemodynamic Synergistic Tumor Therapy (**A**) Schematic illustration of the construction and synergistic therapeutic mechanism of the MPCF nanoplatform. MPCF is coated with a 4T1 cell membrane for homologous targeting. In the tumor microenvironment, ascorbic acid (Asc) reacts synergistically with glutathione (GSH) to reduce Fe^{3+} to Fe^{2+}, which subsequently catalyzes the Fenton reaction, producing reactive oxygen species (ROS) (The red upward arrow represents an increase). Meanwhile, 808 nm laser irradiation of the polydopamine (PDA) layer induces a photothermal effect (PTT), further amplifying the therapeutic efficacy. Insets show (i) the transmission electron microscopy (TEM) image of MPCF exhibiting a uniform core–shell structure with a cell-membrane coating. The yellow arrow indicates the approximately 8.4 nm membrane structure on the surface of MPCF (Scale bars: 50 nm) (ii)intracellular ROS fluorescence visualized by DCF (2′,7′-dichlorofluorescein) assay demonstrating markedly elevated ROS levels after MPCF + Asc + Laser treatment (Scale bars: 200μm) (iii) infrared thermal imaging of the tumor region, showing a significant temperature increase under 808 nm laser irradiation following MPCF administration, confirming efficient photothermal conversion and supporting the enhanced photothermal–chemodynamic synergistic effect (scale bar: 400μm) (**B** and **C**) In vivo antitumor evaluation in 4T1 tumor-bearing mice. (**B**) Tumor volume growth curves show that the combination treatment (MPCF + Asc + Laser) significantly suppressed tumor growth (*p < 0.05, **p < 0.01, ***p < 0.001). (**C**) Representative photographs of excised tumors confirm that the combination group achieved nearly complete tumor regression in 4 out of 5 mice, corresponding to > 95% inhibition. (**D**) Immunofluorescence staining images of tumor tissues following combination therapy. The abundant infiltration of green fluorescence-labeled $CD8^+$ T cells indicates successful activation of an effective anti-tumor immune response. Reproduced from Zhang B, Hou XL, Xie XT et al. Nanoplatforms derived from iron dextran combined with ascorbic acid for enhanced photothermal-chemodynamic therapy of tumors. Chemical Engineering Journal. 2024;496. Copyright 2024, with permission from Elsevier.

https://doi.org/10.2147/IJN.S559426

Copper ions (Cu^{2+}), with a Fenton-like reaction rate (1×10^4 $M^{-1}\cdot s^{-1}$) significantly higher than iron ions (Fe^{2+}, 76.0 $M^{-1}\cdot s^{-1}$)—more than 100-fold faster—operate effectively even in mildly acidic and neutral conditions, overcoming the strict acidic pH limitations (pH 2–4) of traditional Fenton reactions.[127–129] However, copper-based drugs alone exhibit limited cytotoxicity. Therefore, innovative strategies using AA combined with copper-based nanomaterials have been developed to enhance the pro-oxidative antitumor efficiency, addressing challenges such as insufficient H_2O_2 levels in the tumor microenvironment and targeted delivery.

Establishing Basic Catalytic Systems: Validating Synergistic Therapy

Sergey A. Tsymbal first established a synergistic treatment paradigm using CuO nanoparticles and ascorbate. Their crucial contribution was demonstrating the superior sensitizing effect of copper-based materials: CuO NPs (80±20 nm) combined with 1 mM ascorbate reduced IC_{50} values to 0.01–0.37 μg/mL, achieving sensitization factors of 12–1620-fold, effective even against drug-resistant cell lines. Mechanistic studies revealed that ascorbate reduced Cu^{2+} to Cu^{+}, triggering a Fenton-like reaction producing superoxide anions and inducing caspase-independent cell death. This study provided a foundational theoretical framework for subsequent research.[120]

Optimizing Catalytic Specificity: Enhancing Enzyme Activity and Selectivity

Although early CuO systems validated the feasibility of synergistic therapy, catalytic efficiency required improvement, and substrate selectivity was lacking. Addressing this, Zhe developed glutathione-modified Cu/Cu_2O nanozymes (GSH-Cu/Cu_2O NPs), achieving a significant breakthrough in catalytic performance. The innovation involved constructing an efficient and specific catalytic system through GSH modification: (1) AA oxidase activity increased by 40%, and the Michaelis constant optimized to 0.189 mM, approaching natural enzyme levels; (2) by tuning the redox potential of the copper center to −0.1~0.1 V, the nanozymes specifically catalyzed AA oxidation without significant activity towards other substrates such as TMB or dopamine, demonstrating high selectivity. In vitro experiments showed substantial inhibitory effects on PC-12 and HCT116 cancer cells in the presence of 1 mM AA, providing a foundation for precise therapeutic applications.[121]

Targeted Delivery Strategies: MOF Framework for Precise Controlled Release

To achieve synchronized delivery and release of copper ions and ascorbic acid, Zhang developed a multifunctional Cu/ZIF-8/Vc-Ca/HA nanoplatform. This system innovatively utilizes a MOF framework to co-load calcium ascorbate (Vc-Ca) and Cu^{2+}, with surface modification by hyaluronic acid (HA) to achieve CD44-mediated tumor targeting. Owing to the pH-responsive characteristics of the MOF, the nanoplatform precisely releases over 80% of Vc-Ca within 25 minutes under acidic tumor microenvironment (pH 6.5), compared with less than 10% under physiological conditions (pH 7.4). Released Cu^{2+} efficiently depletes intracellular glutathione (GSH), reducing itself to Cu^{+}, while Vc-Ca rapidly generates abundant H_2O_2, collectively amplifying Fenton-like reactions within tumor cells. In vitro validation demonstrated that this nanoplatform significantly induced apoptosis in MG63 tumor cells (cell viability reduced to 25%), with minimal toxicity toward normal cells, underscoring its excellent tumor specificity and biocompatibility.[122]

Intelligent Delivery and Multifunctional Integration: Advancing Towards Clinical Application

After resolving issues regarding catalytic efficiency and specificity, achieving precise drug delivery and integrating multiple therapeutic modalities have become critical for clinical translation. Tang developed Cu(II)-doped mesoporous silica nanoparticles (Cu-MSN), further constructing an active transport and charge-reversal nanoplatform (FCDC@Cu-MSN@DA) loaded with doxorubicin (DOX) and AA, and surface-modified with folic acid (FA), dimethylmaleic anhydride (DMMA), and carboxymethyl chitosan (CMC). This design employs an intelligent charge-reversal strategy for targeted delivery: under the mildly acidic conditions of the tumor microenvironment (pH 6.0–6.5), the protonation of CMC carboxyl groups and cleavage of β-carboxy amide bonds between DMMA and chitosan reverse the nanoparticle surface charge from −10.97 mV to +8.73 mV, enhancing cellular uptake. Once internalized, Cu^{2+} and AA synergistically generate hydroxyl radicals (•OH), inducing oxidative damage, while concurrently releasing chemotherapeutic DOX to trigger apoptosis, thereby achieving a dual killing mechanism. In vitro experiments demonstrated a 4T1 cell apoptosis rate of 59.39%, and in vivo tumor inhibition reached 90.4%, highlighting the advantages of multimodal synergistic therapy.[123]

Other Transition Metal Nanozymes

In addition to iron- and copper-based materials, nanozymes derived from other transition metals such as manganese (Mn), cobalt (Co), and palladium (Pd) have opened new technological avenues for synergistic treatments involving ascorbic acid, attributed to their unique electronic structures and catalytic properties. These materials not only diversify catalytic mechanisms but also provide targeted solutions to specific therapeutic challenges.

Manganese-Based Nanozymes: Overcoming Tumor Hypoxia Barriers

Hypoxia within the tumor microenvironment significantly limits the efficacy of traditional catalytic therapies. To address this, Shen developed the HMVC nanoplatform, achieving breakthrough via a triple synergistic mechanism involving oxygen supply, GSH depletion, and ferroptosis induction. The key innovation involves $HMnO_2$ efficiently catalyzing H_2O_2 decomposition to produce oxygen, approximately twice the output compared to traditional MnO_2 materials, while simultaneously consuming GSH and inhibiting GPX4 activity to induce ferroptosis. Combined with the sonosensitizer Ce6, this platform achieved multimodal sonodynamic-chemodynamic therapy, reducing PC-3 cell viability to 23.6%, thereby offering an effective strategy for hypoxic tumor treatment.[124]

Cobalt-Based Nanozymes: Precision Regulation via Single-Atom Catalysis

Single-atom catalysis represents a significant advancement in the precision of nanozyme catalysis. Ren designed Co SA-N/C nanozymes dispersing cobalt in a $Co\text{-}N_4$ coordination within a carbon matrix, enabling dual enzyme mimicry of ascorbic acid oxidase and glutathione oxidase. Through a "ROS generation and antioxidant consumption" synergistic mechanism, this system disrupts the redox balance of tumor cells. This approach demonstrated notable efficacy against U87 MG glioblastoma cells while maintaining low cytotoxicity to normal cells, highlighting the selective advantage of single-atom catalysis.[125]

Palladium-Based Nanozymes: Enhanced Catalytic Efficiency via Facet Engineering

Catalytic activity is closely associated with the surface structure of materials, and facet engineering offers new strategies to optimize catalytic performance. Yu developed high-index facet Pd nanocrystals that leverage unsaturated coordination atoms on the facet to substantially enhance catalytic activity. This material efficiently catalyzed AA conversion (DHA/AA > 4) within 5 minutes, and when combined with 1–3 mM AA, reduced the viability of HCT-116 cells to below 20%, achieving a tumor inhibition rate of 53.9%. Importantly, over 68% of Pd was excreted through intestinal pathways, demonstrating favorable biosafety profiles.[126]

Mesoporous Silica Nanoparticles (MSNs)

MSNs, characterized by their highly ordered mesoporous structures, substantial specific surface area and pore volume, adjustable pore sizes, and ease of chemical modification on both inner and outer surfaces, have emerged as an ideal platform for drug loading and controlled release.[130,131] Currently, researchers primarily incorporate catalytically active metals such as iron or other metallic elements into MSN frameworks or engineer iron-related active sites on MSN surfaces. Currently, they load VC or its lipid-soluble derivatives to design smart nanotherapeutic systems responsive to the tumor microenvironment (low pH and high H_2O_2 levels), effectively catalyzing the Fenton reaction and continuously releasing ROS.

Building upon this approach, Shuai constructed a stable $Fe\text{-}SiO_2$ catalytic carrier using iron-doped mesoporous silica, fixing Fe^{3+}/Fe^{2+} within the carrier framework via -Si-O-Fe- bonds. This innovative design enabled the stable storage and pH-responsive release of iron catalysts, synchronously releasing Fe^{3+} and AA under acidic conditions to synergistically enhance H_2O_2 concentration by 120.2%. This effectively addressed the instability issue associated with traditional free iron systems and provided a viable strategy for carrier-based applications of iron-based nanozymes.[132] Similarly, studies by Li and Tang adopted the mesoporous carrier strategy to develop iron-based and copper-based mesoporous nanotherapeutic systems, further validating the advantages of MSNs as carriers in metal-AA synergistic therapies.[113,123]

Supramolecular Hydrogels

Hydrogels are three-dimensional network materials formed by physical or chemical crosslinking of hydrophilic polymers, characterized by excellent hydrophilicity, biocompatibility, mechanical tunability, and controlled drug release, making them

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particularly suitable for localized sustained-release therapies.[133,134] To address the challenge of rapid in vivo clearance and the difficulty of maintaining effective local concentrations of VC, Zhang Han conjugated VC with hydrophobic dodecyl chains via ester bonds, forming amphiphilic molecules. These molecules self-assembled into injectable nanofiber hydrogels driven by hydrogen bonding and hydrophobic interactions. The resulting hydrogel exhibited shear-thinning and self-healing properties, was stable and biodegradable in vivo, and released VC sustainably. In vitro experiments showed that over 60% of VC was released within 7 days under esterase activity, with retention at tumor sites for up to 7 days. Studies demonstrated that the VC hydrogel alone effectively inhibited tumor growth in a CT26 colon cancer model, prolonging mouse survival to 20–26 days by upregulating IFN signaling, apoptosis pathways, and virus-recognition genes. Moreover, the VC hydrogel enhanced cancer immunotherapy efficacy when used as a delivery platform for a STING agonist (SA), outperforming either SA or VC hydrogel alone. Mechanistically, combined activation of the STING pathway and VC-mediated immunomodulation significantly promoted dendritic cell maturation and infiltration of NK and T cells, improving immune responses against both local and distant tumors. This hydrogel approach provides a safe and minimally toxic strategy, offering novel insights for VC-based antitumor therapy and synergistic immunotherapy enhancement.[135]

Targeting Strategies

To significantly enhance the specific accumulation of nano-formulated VC preparations in tumor sites while minimizing potential damage to normal tissues and organs, various innovative targeting strategies have been successfully integrated into their design and construction. These targeting strategies can be broadly classified into passive and active targeting (Figure 5).

Passive Targeting (EPR Effect)

Most nanoparticles with controlled sizes (typically ranging from tens to hundreds of nanometers) can passively accumulate and retain in tumor tissues due to the Enhanced Permeability and Retention (EPR) effect.[136] This phenomenon arises from abnormal gaps between endothelial cells in tumor vasculature and impaired lymphatic drainage in tumor regions. The EPR effect provides the physiological foundation for preliminary tumor targeting of numerous anti-tumor nanomedicines, including nano-formulated VC, although its efficiency varies across different tumor types and individuals.[137]

Active Targeting

Active targeting strategies advance further by covalently attaching or physically adsorbing ligand molecules (such as monoclonal antibodies and their fragments, aptamers, peptides, small-molecule ligands) onto nanoparticle surfaces to specifically recognize and bind to overexpressed tumor cell receptors or antigens, thus achieving precise navigation and anchoring to tumor cells.[138]

Hyaluronic acid (HA) enables precise drug delivery by specifically recognizing CD44 receptors, which are highly expressed on tumor cells. CD44 is extensively involved in cellular migration, adhesion, and cancer stem cell signaling, with notably elevated expression in various solid tumors such as breast cancer, lung cancer, pancreatic cancer, and glioblastoma.[139] As an endogenous polysaccharide with excellent biocompatibility and ease of chemical modification, HA facilitates cellular internalization through CD44-mediated caveolae or macropinocytosis pathways, subsequently releasing the encapsulated drugs following lysosomal degradation. Moreover, the overexpression of hyaluronidase in the tumor microenvironment further accelerates drug release from HA-modified nanoparticles. Although CD44 is also expressed at low levels in normal tissues, the overall tumor specificity remains high.[140] Leveraging this principle, Zhang previously developed a multifunctional Cu/ZIF-8/Vc-Ca nanoplatform modified with HA, demonstrating significantly enhanced cellular uptake efficiency in human osteosarcoma cell lines.[122]

Folic acid (FA) achieves targeted delivery due to the high overexpression of its receptor (folate receptor, FR) on the surface of various tumor cells, including ovarian, breast, and lung cancers.[141,142] Unlike CD44, FRα exhibits an extremely limited expression profile in normal tissues, primarily restricted to the brush border of proximal renal tubules, placenta, and choroid plexus epithelia, with minimal exposure on blood-facing surfaces.[143] This confers significantly higher tumor specificity to FA-based systems, enabling selective uptake by FR-positive cancer cells while minimizing

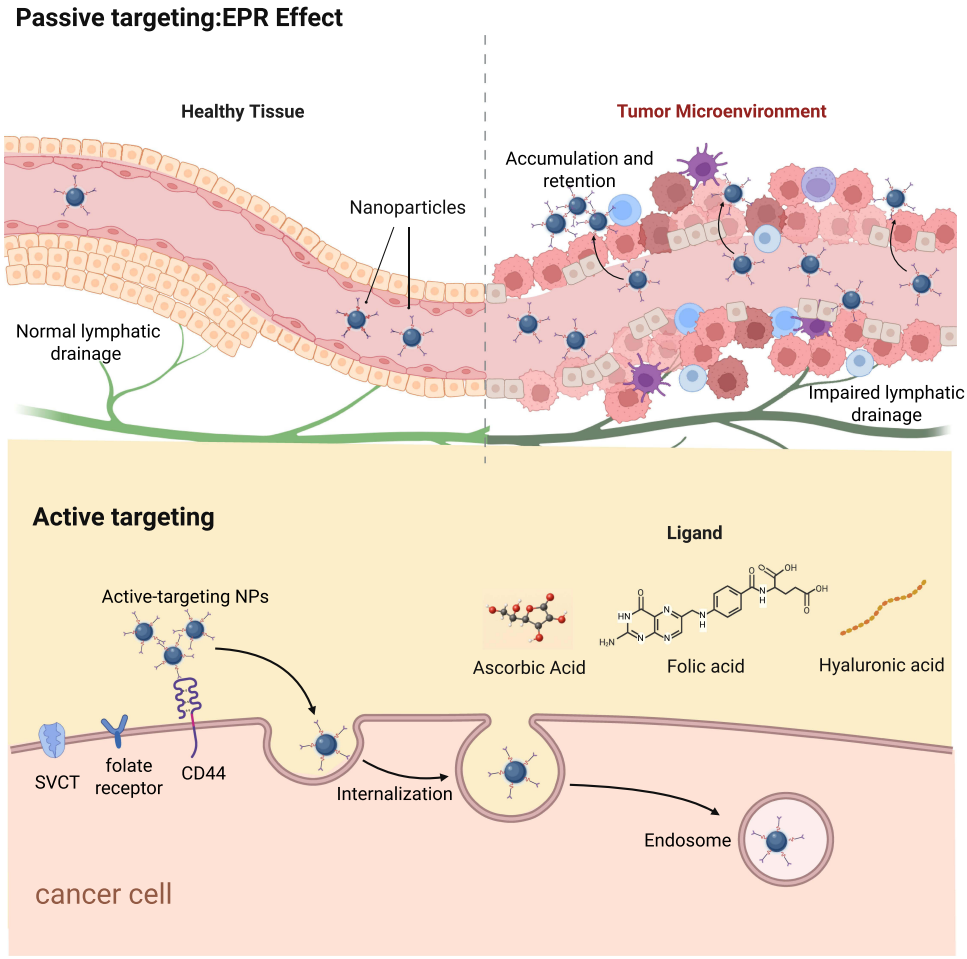

Figure 5 Schematic Illustration of Passive and Active Targeting Strategies in VC Nanomedicine. Created with BioRender.com.

systemic toxicity. Consequently, FA is frequently employed as an effective tumor-targeting ligand. For example, An previously designed core-shell Fe_3O_4@Carbon nanoparticles modified with FA to facilitate targeted delivery and enhance the cytotoxic effects of ascorbic acid on tumor cells overexpressing folate receptors.[111]

VC itself can serve as an active targeting ligand, entering cells through sodium-dependent vitamin C transporters (SVCT), classified into SVCT1 and SVCT2. Luo employed PLGA carriers with surface AA modification to enhance oral drug absorption efficiency by 3.4-fold via SVCT1-mediated endocytosis.[109] SVCT2, highly expressed in many cancer cells and minimally in normal tissues, presents an attractive target for enhancing uptake of nano-formulated VC.[144] Therefore, designing nano-formulated VC preparations recognized and efficiently transported by SVCT2 represents a promising active targeting strategy.

Challenges in Clinical Translation of Nano-Formulated VC

Nano-formulated VC faces multiple challenges in clinical translation. Firstly, from a pharmaceutical perspective, VC itself is highly susceptible to oxidation and hydrolysis, causing rapid degradation of the active ingredient and limiting formulation stability. Additionally, the large specific surface area of nanoparticles often amplifies interfacial effects, exacerbating the oxidation and leakage risks of VC, while its inherent acidity may degrade carrier materials (such as liposomes and polymers) or alter particle size. Secondly, from a manufacturing standpoint, laboratory-scale preparation methods pose significant difficulties when scaled up to continuous mass production, making consistent quality control challenging in terms of nanoparticle characteristics (particle size distribution, drug loading). Furthermore, maintaining

https://doi.org/10.2147/IJN.S559426

VC stability necessitates cold-chain logistics and specialized packaging, substantially increasing manufacturing and distribution costs. In terms of biology and toxicology, nano-carriers exhibit considerable variability in pharmacokinetics and higher toxicological risks; nanoparticles are prone to hepatic and splenic retention, reducing effective drug delivery, and co-administration with iron-based carriers could lead to nonspecific oxidative damage, iron overload, and immunotoxicity. Regulatory challenges further complicate clinical translation, as nano-formulated VC is classified as a drug-carrier combination product, requiring rigorous evaluation and comprehensive datasets on particle size, stability, and in vivo release behavior to demonstrate consistency, thus increasing the difficulty of clinical approval. Moreover, preclinical animal models often exaggerate the anticancer efficacy of nanomedicines, resulting in biases during clinical trial design and efficacy prediction. Finally, economic and market-related issues such as costly cold-chain logistics, high manufacturing expenses, and complex patent licensing significantly hinder clinical translation and commercialization prospects. Consequently, successful clinical translation of nano-formulated VC will require interdisciplinary collaboration to systematically address critical challenges in chemical stability, manufacturing controllability, biological safety, regulatory compliance, and economic accessibility.

Summary and Outlook

This review systematically analyzes recent research and development trends in nanotechnology-enhanced anti-tumor efficacy of VC across various nanomaterials. Recent studies have demonstrated that nanotechnology not only significantly improves drug delivery efficiency but also markedly enhances the therapeutic efficacy of VC through synergistic mechanisms. Specifically, metal-based nanozymes (such as, iron-, copper-, cobalt-, and manganese-based nanomaterials) synergize with VC by catalyzing in situ Fenton reactions, effectively leveraging elevated GSH levels and mildly acidic conditions within the tumor microenvironment to enhance ROS-mediated cytotoxicity, thereby significantly reducing the therapeutic threshold of VC. Additionally, the design of smart nano-delivery systems has evolved from simple encapsulation to tumor microenvironment-responsive platforms, achieving precise VC release via tumor-specific stimuli such as pH, H_2O_2, and GSH. By co-loading chemotherapeutic drugs, photosensitizers, or immunostimulants, nanocarriers further exhibit synergistic effects across multiple therapeutic modalities, demonstrating significant application potential, particularly in photothermal and immunotherapy combinations.

Notably, lipid-soluble VC derivatives, such as AP, serve dual functions as both prodrugs and carriers. Utilizing their intrinsic amphiphilic properties, these derivatives enable integrated "drug-carrier" formulations. This integrative strategy simplifies formulation design, significantly enhancing drug loading efficiency and biological stability. Furthermore, advances in targeting strategies have greatly enhanced the therapeutic precision of nano-formulated VC. Combining passive targeting via the EPR effect with active targeting through specific ligand modifications (such as, folic acid, Hyaluronic acid, and VC itself effectively improves drug accumulation in tumor sites, reduces distribution to normal tissues, significantly expands the therapeutic window, and minimizes toxic side effects.

Despite the promising potential of these strategies, several practical challenges persist. These include insufficient long-term safety evaluations of nanomaterials, stability concerns of complex systems during scale-up production, and uncertainties in pharmacokinetic and pharmacodynamic predictions, which substantially complicate clinical translation. Therefore, future research urgently needs to develop intelligent nanocarriers with enhanced biocompatibility and excellent biodegradability. Concurrently, deeper insights into the synergistic mechanisms between nanocarriers and VC are essential to accelerate the translation of nano-formulated VC therapies from the laboratory to clinical applications.

Funding

This work was supported by the National Natural Science Foundation of China (Grant No.: 82474333).

Disclosure

The authors report no conflicts of interest in this work.

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