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ADVANCES IN POLYPHENOL NANOFORMULATIONS FOR CANCER THERAPY: FROM MOLECULAR MECHANISMS TO CLINICAL APPLICATIONS

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ABSTRACT

Polyphenols are a diverse class of naturally occurring bioactive compounds that have demonstrated significant anticancer potential through their antioxidant, anti-inflammatory, ant proliferative, and pro-apoptotic properties. However, their clinical application has been limited by poor aqueous solubility, low bioavailability, rapid metabolism, and lack of target specificity. Recent advances in nanotechnology have provided innovative strategies to overcome these limitations through the development of polyphenol-based Nano formulations. This review highlights the progress in Nano engineered delivery systems, including polymeric nanoparticles, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, Nano emulsions, micelles, and hybrid Nano carriers, which enhance the stability, bioavailability, and targeted delivery of polyphenols. The review also discusses the pharmacokinetic advantages, physicochemical characterization, and synergistic potential of combining polyphenols with conventional chemotherapeutic agents. Importantly, emerging clinical studies demonstrate improved efficacy and safety profiles, supporting the translational potential of these systems. Despite existing challenges related to scalability, regulatory approval, and long-term safety, polyphenol-based Nano formulations represent a promising approach for next-generation cancer therapy, bridging the gap between molecular mechanisms and clinical applications.

Keywords: Polyphenols; Nanoformulations; Cancer therapy; Targeted drug delivery

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INTRODUCTION

Cancer remains one of the leading causes of morbidity and mortality worldwide, necessitating the continuous development of innovative and effective therapeutic strategies. In recent years, naturally occurring bioactive compounds, particularly polyphenols, have gained significant attention due to their diverse pharmacological properties, including antioxidant, anti-inflammatory, ant proliferative, and pro-apoptotic effects. Polyphenols such as curcumin, resveratrol, epigallocatechin gallate (EGCG), and quercetin have demonstrated promising anticancer potential across various in vitro and in vivo models by modulating multiple cellular signaling pathways involved in tumor initiation, progression, and metastasis. These compounds exert their effects through mechanisms such as inhibition of oxidative stress, regulation of transcription factors, induction of cell cycle arrest, and activation of intrinsic and extrinsic apoptotic pathways. Additionally, polyphenols have shown the ability to interfere with angiogenesis and metastasis, further supporting their role as multitargeted agents in cancer therapy(Vieira et al., 2023). Despite these advantages, the clinical translation of polyphenols has

been significantly limited by their poor aqueous solubility, low bioavailability, rapid metabolism, and instability under physiological conditions, which collectively reduce their therapeutic efficacy. To overcome these challenges, nanotechnology-based drug delivery systems have emerged as a promising approach to enhance the pharmacokinetic and pharmacodynamics profiles of polyphenols. Nano formulations, including polymeric nanoparticles, liposomes, solid lipid nanoparticles, Nano emulsions, and micelles, offer several advantages such as improved solubility, enhanced stability, controlled and sustained release, and targeted delivery to tumor tissues. These Nano carriers can exploit the enhanced permeability and retention (EPR) effect for passive targeting and can be further functionalized with ligands for active targeting, thereby increasing drug accumulation at the tumor site while minimizing systemic toxicity. Moreover, Nano formulations enable co-delivery of polyphenols with conventional chemotherapeutic agents, leading to synergistic anticancer effects and overcoming drug resistance mechanisms(Feng et al., 2023).

Rationale for Nano formulation of Polyphenols

The rationale for Nano formulation of polyphenols in cancer therapy arises from the need to overcome the inherent physicochemical and biopharmaceutical limitations that restrict their clinical applicability despite their potent pharmacological activities. (Khazei et al., 2021). Moreover, nanoscale carriers facilitate improved cellular uptake through endocytosis and increase circulation time by evading rapid clearance mechanisms, such as renal excretion and reticuloendothelial system uptake. One of the key advantages of Nano formulation is the ability to achieve targeted drug delivery, which enhances therapeutic efficacy while minimizing systemic toxicity. Passive targeting through the enhanced permeability and retention (EPR) effect allows nanoparticles to preferentially accumulate in tumor tissues due to leaky vasculature, whereas active targeting can be achieved by functionalizing Nano carriers with ligands such as antibodies, peptides, or small molecules that recognize tumor-specific receptors. Furthermore, Nano formulations enable the development of stimuli-responsive delivery systems that release polyphenols in response to specific tumor microenvironment conditions, including acidic pH, elevated enzyme levels, or oxidative stress, thereby ensuring site-specific drug release. Another important rationale is the potential for combination therapy, where polyphenols can be co-delivered with conventional chemotherapeutic agents within a single Nano carrier, leading to synergistic effects, dose reduction, and mitigation of drug resistance(Zhang et al., 2020).

Types of Polyphenol-Based Nano formulations

Polyphenol-based Nano formulations encompass a diverse range of nanocarrier systems designed to enhance the solubility, stability, bioavailability, and targeted delivery of polyphenolic compounds in cancer therapy. Among the most widely explored systems are polymeric nanoparticles, which are fabricated using biodegradable polymers such as PLGA, chitosan, and PEG, offering controlled and sustained drug release along with protection from enzymatic degradation. These nanoparticles can be engineered for surface modification to achieve active targeting of tumor cells. Lipid-based nanocarriers, including liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), are particularly advantageous due to their biocompatibility and ability to encapsulate both hydrophilic and lipophilic polyphenols. Liposomes, composed of phospholipid bilayers, enhance drug circulation time and reduce toxicity, while SLNs and NLCs provide improved stability and controlled release profiles(López-Rios De Castro et al., 2024). Nano emulsions and micelles represent another important class, where surfactant-based systems improve the aqueous solubility of poorly water-soluble polyphenols and facilitate efficient absorption and cellular uptake. Polymeric micelles, in particular, are effective in delivering hydrophobic compounds like curcumin and resveratrol by forming a hydrophobic core that encapsulates the drug. Dendrimers, characterized by their highly branched, tree-like structures, offer precise control over size and surface functionality, enabling high drug loading and targeted delivery through ligand attachment. Nanogels, which are hydrogel-based Nano systems, provide a unique advantage in terms of high water content, tunable swelling properties, and responsiveness to environmental stimuli such as pH and temperature, making them suitable for controlled drug release in tumor microenvironments(Verma et al., 2023).

Mechanistic Insights into Anticancer Activity

Polyphenol-based Nano formulations exert their anticancer effects through a multifaceted modulation of key cellular and molecular pathways involved in tumor initiation, progression, and metastasis, offering a comprehensive therapeutic approach beyond conventional single-target strategies. At the core of their activity is the ability to induce apoptosis in cancer cells via both intrinsic (mitochondrial) and extrinsic (death receptor-mediated) pathways. Nano encapsulated polyphenols enhance mitochondrial membrane permeabilization, leading to cytochrome c release, caspase activation, and subsequent programmed cell death, while also upregulating pro-apoptotic proteins such as Bax and downregulating anti-apoptotic proteins like Bcl-2. In addition to apoptosis, these Nano formulations effectively induce cell cycle arrest at

various checkpoints, including G0/G1, S, or G2/M phases, by modulating cyclins, cyclin-dependent kinases (CDKs), and tumor suppressor proteins such as p53, thereby inhibiting uncontrolled cellular proliferation.(M. Yang et al., 2024) Another critical mechanism involves the suppression of angiogenesis, which is essential for tumor growth and metastasis; polyphenol-loaded nanoparticles downregulate vascular endothelial growth factor (VEGF) and inhibit signaling pathways such as PI3K/Akt and MAPK, thereby impairing neovascularization. Furthermore, Nano formulated polyphenols modulate oxidative stress by regulating intracellular reactive oxygen species (ROS) levels, either by scavenging excessive free radicals or, paradoxically, inducing ROS-mediated cytotoxicity in cancer cells, leading to oxidative damage and apoptosis. They also influence key transcription factors such as NF-κB, STAT3, and AP-1, which play pivotal roles in inflammation, survival signaling, and tumor progression. By inhibiting these transcription factors, polyphenol Nano formulations reduce the expression of genes associated with proliferation, invasion, and resistance to apoptosis(Pechanova et al., 2020).

Polyphenols with Chemotherapeutic Agents

The combination of polyphenols with conventional chemotherapeutic agents represents a promising strategy in cancer therapy aimed at enhancing therapeutic efficacy, reducing drug resistance, and minimizing systemic toxicity. Polyphenols such as curcumin, resveratrol, quercetin, and epigallocatechin gal late possess intrinsic anticancer properties, including antioxidant, anti-inflammatory, and pro-apoptotic activities, and have been shown to modulate multiple signaling pathways involved in tumor growth and survival. When co-administered with standard chemotherapeutic drugs such as doxorubicin, paclitaxel, cisplatin, and 5-fluorouracil, polyphenols can exert synergistic effects by sensitizing cancer cells to these agents. One of the primary mechanisms underlying this synergy is the ability of polyphenols to inhibit drug resistance pathways, including the downregulation of efflux transporters such as P-glycoprotein (P-gp), which are often overexpressed in resistant cancer cells and limit intracellular drug accumulation. Additionally, polyphenols can modulate key survival pathways such as NF-κB, PI3K/Akt, and MAPK, thereby enhancing apoptosis and reducing cell proliferation when used in combination with chemotherapeutics.(Jakobušić Brala et al., 2023) Polyphenols also play a role in reducing chemotherapy-induced toxicity by protecting normal cells from oxidative damage and inflammation, thus improving the overall safety profile of anticancer treatment. Nano formulation further enhances this combinatorial approach by enabling the co-delivery of polyphenols and chemotherapeutic agents within a single Nano carrier system, ensuring synchronized pharmacokinetics and targeted delivery to tumor tissues. Such co-loaded nanoparticles can improve drug stability, enhance tumor accumulation through the enhanced permeability and retention (EPR) effect, and provide controlled and sustained release of both agents. This approach not only maximizes the therapeutic index but also allows for dose reduction of cytotoxic drugs, thereby minimizing adverse effects such as cardiotoxicity and nephrotoxicity. Furthermore, polyphenols can modulate the tumor microenvironment by reducing inflammation, inhibiting angiogenesis, and altering immune responses, which further supports the efficacy of chemotherapeutic agents. Emerging evidence also suggests that polyphenol-based combinations can overcome multidrug resistance and improve outcomes in difficult-to-treat cancers, including breast, lung, and colorectal cancers. Preclinical studies have demonstrated significant improvements in tumor suppression and survival rates with combination therapy compared to monotherapy(Kim et al., 2023).

Clinical Studies and Translational Potential

Clinical studies and translational potential of polyphenol-based Nano formulations represent a crucial step toward bridging the gap between promising preclinical findings and real-world cancer therapy. Although numerous in vitro and in vivo studies have demonstrated the potent anticancer effects of polyphenols such as curcumin, resveratrol, epigallocatechin gallate, and quercetin, their clinical application has historically been limited by poor bioavailability, rapid metabolism, and insufficient target specificity. Nano formulation strategies have significantly improved these limitations, leading to increased interest in clinical translation. Several Nano formulated polyphenol systems, particularly liposomal curcumin and polymeric nanoparticle-based formulations, have entered early-phase clinical trials, demonstrating enhanced systemic exposure, improved pharmacokinetics, and favorable safety profiles compared to free compounds(Pandey et al., 2024). Clinical studies have reported that Nano formulated polyphenols can achieve higher plasma concentrations, prolonged circulation time, and better tumor accumulation, which are essential for therapeutic efficacy. Importantly, these formulations have shown reduced systemic toxicity, making them suitable candidates for long-term cancer management and combination therapy. Translational research has also highlighted the potential of polyphenol Nano formulations to be integrated with existing treatment modalities, including chemotherapy, radiotherapy, and immunotherapy, thereby enhancing treatment outcomes through synergistic mechanisms. Furthermore, the ability of Nano formulations to enable targeted delivery and controlled release aligns well with the principles of precision medicine, allowing for patient-

specific therapeutic strategies based on tumor biology and molecular profiling.(B. Yang et al., 2020) .

CONCLUSION

The advances in polyphenol Nano formulations have significantly transformed the landscape of cancer therapy by addressing the long-standing limitations associated with the clinical use of naturally occurring polyphenolic compounds. Polyphenols such as curcumin, resveratrol, quercetin, and epigallocatechin gallate possess remarkable anticancer potential owing to their ability to modulate multiple molecular pathways involved in tumor initiation, progression, angiogenesis, metastasis, and resistance. Additionally, their role in epigenetic modulation, including DNA methylation, histone modification, and microRNA regulation, highlights their potential to reprogram gene expression and restore normal cellular functions in cancer cells. The ability of these Nano formulations to selectively modulate reactive oxygen species further enhances their therapeutic efficacy by exploiting the redox imbalance characteristic of tumor cells. Importantly, the incorporation of polyphenols into Nano carriers enables combination therapy strategies, where they can be co-delivered with conventional chemotherapeutic agents to achieve synergistic effects, overcome multidrug resistance, and reduce the required dosage of toxic drugs. From a pharmacokinetic perspective, Nano formulations significantly improve absorption, distribution, metabolism, and elimination profiles, resulting in enhanced bioavailability and sustained therapeutic levels. Advances in physicochemical characterization techniques have ensured the reproducibility, stability, and quality control of these Nano systems, which are essential for clinical translation. Furthermore, the development of stimuli-responsive and smart delivery systems has introduced new dimensions in precision oncology by enabling site-specific and controlled drug release in response to tumor micro environmental conditions.

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