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Enhancing the Therapeutic Index of Bioactive Compounds Through Novel Delivery Systems

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The World Health Organization reports that more than 80% of the global population currently uses some form of traditional medicine.[1] In light of this, plant-derived bioactive metabolites are increasingly recognized as critical agents in preventive medicine. Natural antioxidants, in particular, have attracted considerable scientific interest due to the well-established correlation between their intake and the mitigation of chronic diseases, such as cardiovascular and renal disorders, various malignancies, neurodegenerative diseases, and diabetes mellitus. These phytochemicals exhibit a broad spectrum of biological activities, including antioxidant,[2] anti-inflammatory,[3] antifibrotic, and antibacterial properties as well as anti-atherosclerotic, anticancer, and antiaging effects.[4-7]

Such multifaceted properties underscore their substantial therapeutic potential in the prevention and management of chronic diseases. Mechanistically, these bioactive compounds exert their effects through free radical scavenging, metal chelation, mitochondrial renewal, apoptosis inhibition, fine-tuning of cellular signaling pathways, and epigenetic modulation.[4,8,9] However, despite their promise, the clinical efficacy of natural antioxidants is often limited by a persistent bioavailability paradox. This limitation is driven by suboptimal physicochemical properties, including poor aqueous solubility, chemical instability—particularly in oxidoreductase-rich environments—and extensive first-pass metabolism.[2]

To bridge the gap between biochemical potential and clinical application, addressing these delivery constraints is imperative. In this context, nano-based delivery systems offer a transformative solution by leveraging nanotechnology to enable targeted release and enhanced absorption of bioactive molecules at specific sites of action. This paradigm is increasingly applied to miRNA therapeutics, wherein nanoparticle (NP)-based platforms serve as an economically viable and non-immunogenic strategy to enhance molecular stability and achieve precise tissue targeting.[9] These platforms have emerged as one of the most extensively investigated strategies for improving the delivery efficiency of redox-active molecules.

Encapsulation of these compounds within a diverse array of delivery systems—including emulsion-based systems (micro/nano and Pickering emulsions), vesicular platforms (liposomes, niosomes, ethosomes, transferosomes, and phytosomes), lipid-based NPs such as solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), and polymeric nanocarriers—significantly enhances solubility, provides robust protection against enzymatic degradation, and facilitates intestinal absorption (Table 1).[10-12]

The nanocarrier systems summarized in the table serve as a technological foundation for overcoming the inherent pharmacological limitations of potent plant-derived antioxidants. These diverse architectures represent more than simple encapsulation strategies; they constitute a sophisticated pharmacological toolkit designed to decouple a bioactive molecule's therapeutic potential from its physicochemical constraints. While the structural advantages of NLCs, phytosomes, and polymeric shells are well documented, their clinical and therapeutic efficacy is most evident in the significant enhancement of the bioavailability of specific polyphenolic compounds. By transitioning from conventional formulations to these nanoengineered platforms, the long-standing bioavailability paradox is being systematically addressed, as these systems not only protect the antioxidant cargo but also actively redefine its pharmacokinetics.

Recent studies utilizing zein- and sodium caseinate-based NPs have demonstrated markedly increased gastrointestinal transport and bioaccessibility of curcumin and quercetin. These findings suggest that hybrid nanodelivery approaches can synergistically enhance the stability and uptake of labile bioactive compounds.[13,14]

Furthermore, systematic reviews of dietary polyphenol nanoformulations indicate that delivery systems, including nanoemulsions, micelles, and polymeric vesicles, substantially optimize the pharmacokinetic profiles of a diverse range of phenolic antioxidants.[12]

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TABLE 1. Delivery Systems for Plant-Derived Antioxidants.

System class	Nanocarrier type	Composition/structure	Advantages
Emulsion-based nanosystems	Micro/nano-emulsions	Submicron oil-in-water dispersions	Enhanced solubility and bioavailability
	Pickering emulsions	Particle-stabilized interface	High stability, low toxicity
Vesicular NPs	Liposomes	Phospholipid bilayer vesicles enclosing an aqueous core	Biocompatible, protects antioxidants
	Niosomes	Non-ionic surfactant vesicles	Stable, cost-effective
	Ethosomes	Ethanol-containing phospholipid vesicles	Enhanced skin permeation
	Transferosomes	Ultra-deformable lipid vesicles	Enhanced skin and membrane penetration
	Phytosomes	Phospholipid-polyphenol complex	Improved absorption of phenolics
Lipid-based NPs	Solid lipid NPs	Solid lipid matrix	Controlled release, degradation protection
	Nanostructured lipid carriers	Solid + liquid lipid matrix	High loading, storage stability
Polymeric and other nanocarriers	Metallic NP (Au, TiO_2)	Inorganic NPs	Photoprotection
	Polymeric NP	Zein/chitosan/polymer shells	Enhanced stability, reduced degradation

Au, gold; TiO_2, titanium oxide; NP, nanoparticle.

The progression from conventional use to contemporary clinical application of plant-derived compounds largely depends on addressing their inherent biopharmaceutical limitations. Despite the considerable therapeutic promise of many phytochemicals, their efficacy is often constrained by poor solubility and rapid degradation. Quercetin, for instance, effectively illustrates the synergy between lipid-based delivery systems and improved oral bioavailability. Despite its potent antioxidant activity and broad therapeutic potential, this flavonoid exhibits poor water solubility and undergoes extensive first-pass metabolism, thereby limiting its clinical utility. Recent reviews of nanoformulations indicate that lipid-based carriers, including liposomes and SLNs, can significantly enhance absorption, targeting, and controlled-release properties.[15] These delivery strategies not only improve systemic availability but also amplify functional activity *in vivo*, thereby opening new avenues for clinical application and functional food development. Similarly, resveratrol faces pharmacokinetic challenges, including a short biological half-life. Novel approaches, such as polymeric and lipid-based nanocarriers, as well as coencapsulation strategies, have been shown to enhance resveratrol stability, effectively prolonging systemic circulation and improving tissue distribution for both nutraceutical and clinical applications.[11]

Despite the compelling biological activities of epigallocatechin gallate (EGCG) and naringin, their clinical translation has been consistently hindered by rapid degradation following oral administration. Over the past decade, nanotechnology-driven strategies have emerged as a key focus for overcoming these barriers. A broad spectrum of nanoengineered platforms, including pH-responsive polymeric NPs and ligand-functionalized nanosystems, has demonstrated three- to five-fold improvements in EGCG bioavailability, while also enabling codelivery with chemotherapeutic agents to potentiate anticancer efficacy.[16] Research on these nanoscale matrices has elucidated how covalent and non-covalent interactions enhance physicochemical stability, thereby providing a strategic foundation for future clinical investigations. Similarly, research on naringin has increasingly incorporated nanoformulations, such as colon-targeted poly(lactic-co-glycolic acid)–polyethylene glycol NPs, to circumvent enzymatic degradation and tailor biodistribution for specific applications, including inflammatory bowel disease.[17]

Perhaps the most compelling evidence of this technological shift is observed in recent clinical trials involving silymarin. To address its notoriously low oral bioavailability, researchers have developed innovative delivery systems that markedly enhance its pharmacokinetic performance. A recent double-blind, randomized human trial demonstrated that a novel micellar silymarin formulation achieved an approximately 18.9-fold increase in maximum plasma concentration and an approximately 11.4-fold increase in bioavailability compared with standard formulations.[18] Furthermore, solid dispersion strategies and phytosome-based complexes have demonstrated relative bioavailability increases of up to 589%, significantly enhancing hepatoprotective effects.[19] Beyond the realm of polyphenols, the therapeutic potential of melatonin is similarly constrained by rapid metabolism. This limitation has prompted the exploration of lipid vesicles and polymeric NPs to prolong its half-life and facilitate targeted delivery in neuroprotective applications.[20]

The development of these advanced, multifunctional delivery platforms represents a clear paradigm shift in the field. Research

is progressing beyond simple supplementation toward precisely engineered, targeted systems designed to enhance both permeation and stability across various delivery routes. Continued advancements in NP design, together with accumulating clinical evidence, will be pivotal in translating these highly bioavailable compounds into effective, high-impact therapeutic strategies for the management of chronic diseases, ranging from metabolic disorders to neurodegenerative conditions.

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