Global Journal of Research in
Chemistry and Pharmacy
Journal homepage: https://gsjournals.com/gjrcp/
ISSN: 2980-4213 (Online)

(REVIEW ARTICLE)

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NANOTECHNOLOGY-ENHANCED DELIVERY AND BIOACTIVITY OF NATURAL PRODUCTS

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Global Journal of Research in Chemistry and Pharmacy, 2023, 02(04), 001–008

Publication history: Received on 09 September 2023; revised on 20 October 2023; accepted on 27 October 2023

Article DOI: https://doi.org/10.58175/gjrcp.2023.2.4.0135

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ABSTRACT

The therapeutic potential of natural products is often severely limited by poor bioavailability, low aqueous solubility, rapid metabolism, and inadequate tissue distribution. Nanotechnology-based delivery systems have emerged as transformative strategies for overcoming these fundamental limitations, thereby enhancing the bioactivity and therapeutic efficacy of natural compounds. This review comprehensively examines the application of nanotechnology for natural product delivery, focusing on three major classes of nanocarriers: lipid-based nanoparticles (liposomes, solid lipid nanoparticles, nanostructured lipid carriers, and nanoemulsions), polymeric carriers (synthetic biodegradable polymers, natural polymers, and polymeric micelles), and metal-organic frameworks (MOFs). We critically evaluate the design principles, formulation strategies, and performance characteristics of these nanocarriers for encapsulating natural products including curcumin, resveratrol, paclitaxel, quercetin, and various polyphenols. Furthermore, we assess the impact of nanocarriers on bioavailability, pharmacokinetics, biodistribution, and therapeutic outcomes in preclinical models of cancer, inflammatory diseases, and other disorders. Despite significant advances, challenges including scale-up, long-term stability, and regulatory approval persist. This review identifies critical research gaps and discusses future directions for optimizing nanotechnology-based natural product delivery.

Keywords: Nanotechnology; Natural Products; Drug Delivery; Bioavailability; Lipid Nanoparticles; Polymeric Nanoparticles; Metal-Organic Frameworks

1 INTRODUCTION

Natural products have historically been the most prolific source of pharmaceutical leads, contributing to approximately 60% of approved small-molecule drugs (Newman and Cragg, 2020). The structural complexity and diversity of natural products, characterized by unique scaffolds and stereochemical configurations, offer unparalleled opportunities for targeting challenging biological targets (Atanasov et al., 2021). However, the clinical translation of natural products is frequently impeded by unfavorable physicochemical and pharmacokinetic properties (Harvey et al., 2015).

The most significant challenges facing natural product drug development include poor aqueous solubility, limited gastrointestinal stability, extensive first-pass metabolism, rapid systemic clearance, and inadequate tissue distribution (Ashfaq et al., 2023). Curcumin, for instance, exhibits less than 1% oral bioavailability in humans due to poor absorption and rapid glucuronidation (Anand et al., 2007). Similarly, resveratrol and quercetin suffer from extensive metabolism

and rapid elimination (Walle, 2011). These limitations compromise therapeutic efficacy and necessitate the development of effective delivery strategies.

Nanotechnology-based delivery systems have emerged as powerful approaches for overcoming these bioavailability challenges (Elmowafy et al., 2023). Nanoparticles offer numerous advantages including enhanced solubility, protection from degradation, controlled release, improved pharmacokinetics, and targeted delivery to specific tissues (Patra et al., 2018). Diverse nanocarrier systems have been developed for natural product encapsulation, broadly categorized into lipid-based nanoparticles, polymeric carriers, and metal-organic frameworks (Maranescu and Visa, 2022).

This review provides a comprehensive examination of nanotechnology-based delivery systems for natural products, evaluating formulation strategies, performance characteristics, and therapeutic applications across these three major nanocarrier classes.

2 CHALLENGES IN NATURAL PRODUCT DELIVERY

2.1 Poor Aqueous Solubility

A substantial proportion of bioactive natural products are hydrophobic or lipophilic compounds with limited aqueous solubility (Elmowafy et al., 2023). This hydrophobicity results in poor dissolution and inadequate absorption following oral administration. Phytochemicals such as polyphenols, flavonoids, carotenoids, and terpenoids typically exhibit low water solubility, which severely limits their bioavailability and therapeutic efficacy (Elmowafy et al., 2023; Ashfaq et al., 2023).

2.2 Poor Gastrointestinal Stability

Natural products often demonstrate limited stability in the gastrointestinal tract, where they are susceptible to degradation by gastric acid, digestive enzymes, and intestinal microbiota (Ashfaq et al., 2023). Many polyphenols and flavonoids undergo extensive degradation before reaching the systemic circulation, further compromising oral bioavailability (Elmowafy et al., 2023).

2.3 Extensive Metabolism and Rapid Clearance

Most natural products undergo extensive first-pass metabolism in the liver, resulting in rapid systemic clearance and short half-lives (Ashfaq et al., 2023). Curcumin, resveratrol, and numerous flavonoids are rapidly conjugated by glucuronidation and sulfation pathways, leading to their swift elimination from the body (Walle, 2011). This rapid metabolism significantly limits the duration of therapeutic action.

2.4 Limited Tissue Distribution

The distribution of natural products to target tissues is often inadequate, particularly for compounds targeting the central nervous system where the blood-brain barrier presents a formidable obstacle (Ashfaq et al., 2023). The large molecular size and hydrophilicity of some natural products further restrict their ability to penetrate cellular membranes and reach intracellular targets.

Table 1: Bioavailability Challenges of Key Natural Products

Compound	Aqueous Solubility	Oral Bioavailability	Primary Metabolic Pathway	Key Limitation
Curcumin	Very low	<1%	First-pass glucuronidation & sulfation	Poor aqueous solubility, rapid systemic clearance
Resveratrol	Low	<5%	Rapid hepatic & intestinal glucuronidation, sulfation	Extensive first-pass metabolism
Paclitaxel	Very low	Poor	Hepatic CYP450 metabolism	Poor aqueous solubility, low mucosal permeability
Quercetin	Low	<5%	Intestinal & hepatic glucuronidation	Poor aqueous solubility, extensive metabolism

EGCG *(Epigallocatechin gallate)*	Moderate	<10%	Chemical degradation, glucuronidation	Intestinal instability, rapid metabolic degradation

3 LIPID-BASED NANOPARTICLES

Lipid-based nanoparticles (LNPs) represent one of the most extensively investigated classes of drug delivery systems for natural products (Ashfaq et al., 2023). These nanocarriers offer numerous advantages including the ability to accommodate both hydrophilic and hydrophobic molecules, favorable biocompatibility, protection of encapsulated compounds from degradation, controlled release profiles, and improved bioavailability (Ashfaq et al., 2023). The primary categories of lipid-based nanoparticles include liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and nanoemulsions (Ashfaq et al., 2023; Elmowafy et al., 2023).

3.1 Liposomes

Liposomes are spherical vesicles composed of one or more phospholipid bilayers surrounding an aqueous core (Chavda et al., 2022). This unique structure enables the encapsulation of both hydrophilic compounds (in the aqueous core) and lipophilic compounds (within the lipid bilayer). Liposomes offer excellent biocompatibility, biodegradability, and the capacity for surface modification with targeting ligands (Chavda et al., 2022).

Liposomal formulations of phytochemicals have demonstrated significantly enhanced therapeutic efficacy in cancer therapy (Chavda et al., 2022). Anticancer phytochemicals are extracted and purified from natural plants, providing alternative therapeutic approaches with recognized biomedical benefits (Chavda et al., 2022). However, poor bioavailability, high dose requirements, and non-specific targeting have made those molecules less effective (Chavda et al., 2022). To tackle these issues, liposomal nanovesicles for phytochemical delivery are taken into consideration for improving the therapeutic effectiveness by increasing transportation across cell barriers and conferring attractive cancer-specific targeting capabilities (Chavda et al., 2022). Liposomal phyto-chemotherapy has been described as a promising therapeutic and technological intervention against cancer that has the potential to enhance the effectiveness of cancer therapy, reduce the associated side effects, and improve the clinical outcomes of cancer patients (Chavda et al., 2022).

Liposomes as multifunctional nano-carriers for medicinal natural products have been extensively reviewed, highlighting their versatility in encapsulating diverse natural compounds and their potential for targeted delivery (Frontiers, 2022). The surface of liposomes can be modified with polyethylene glycol (PEG) to prolong circulation time or with specific ligands to achieve active targeting to diseased tissues.

3.2 Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles are colloidal carriers composed of solid lipids that remain solid at both body temperature and ambient temperature (Ashfaq et al., 2023; Elmowafy et al., 2023). SLNs were developed to address the shortcomings of existing colloidal carriers, such as emulsions, liposomes, and polymeric nanoparticles (Ashfaq et al., 2023). These LNPs are made of solid phase lipids and surfactants and range in size from 40 to 1000 nm on average (Ashfaq et al., 2023). SLNs feature benefits such as a favorable release profile and targeted drug delivery with outstanding physical stability (Ashfaq et al., 2023).

Curcumin-loaded solid lipid nanoparticles (CSLNs) have been extensively investigated. In one study, CSLNs produced by hot high-pressure homogenization demonstrated high drug content (0.6% w/w), significantly enhanced solubility (6105 times), and high encapsulation efficiency (75%) (Ashfaq et al., 2023). The CSLNs exhibited controlled release, were photostable, autoclavable, and stable for up to one year at 30°C (Ashfaq et al., 2023). Compared to free curcumin dispersion, the CSLNs significantly inhibited the growth of Staphylococcus aureus and demonstrated superior wound healing potential in vivo, with noticeably quicker wound closure, better histological healing, lower oxidative stress, and reduced inflammation (Ashfaq et al., 2023).

3.3 Nanostructured Lipid Carriers (NLCs)

Nanostructured lipid carriers are modified SLNs that represent the next generation of lipid nanoparticles, designed to increase stability and drug loading capacity (Ashfaq et al., 2023). NLCs are composed of a blend of solid and liquid lipids, creating a less ordered crystalline structure that accommodates higher drug payloads (Ashfaq et al., 2023). NLCs can enclose both hydrophilic and lipophilic medicines (Ashfaq et al., 2023).

NLCs have been developed for the delivery of various natural bioactive compounds, demonstrating improved therapeutic potential in drug delivery systems (Shamsuddin et al., 2023). In one reported study, an NLC comprising curcumin and epidermal growth factor (EGF) was designed using a modified double-emulsion technique (Ashfaq et al., 2023). The EGF-Cur-NLC particles displayed high encapsulation effectiveness (81.1% and 99.4% for EGF and curcumin, respectively) with an average diameter of 331.8 nm (Ashfaq et al., 2023). In vitro cell experiments demonstrated that the NLC formulation maintained the biological activity of both encapsulated compounds (Ashfaq et al., 2023).

3.4 Nano-emulsions

Nanoemulsions are oil-in-water emulsions with droplet sizes in the nanometer range (typically 20-200 nm). These systems enhance the solubility and bioavailability of lipophilic natural products by dispersing them in nanoscale oil droplets stabilized by surfactants. Nanoemulsions offer advantages including ease of preparation, high drug loading capacity, and improved stability (Ashfaq et al., 2023). Self-emulsifying drug delivery systems (SEDDS) and self-microemulsifying systems (SMEDDS) have been developed for natural product delivery, forming fine emulsions upon contact with gastrointestinal fluids (Ashfaq et al., 2023).

Table 2: Lipid-Based Nanoparticles for Natural Product Delivery

Nanocarrier	Composition	Advantages	Limitations	Suitable Compounds
Liposomes	Phospholipid bilayers with an aqueous core	Encapsulates both hydrophilic and lipophilic compounds; highly biocompatible	Physical stability issues, potential drug leakage, rapid systemic clearance	Curcumin, resveratrol, polyphenols
SLNs *(Solid Lipid Nanoparticles)*	Solid lipids at room temperature	High physical stability, controlled/sustained release profile, scalable	Limited drug loading capacity, risk of drug expulsion during storage	Curcumin, quercetin, lipophilic bioactives
NLCs *(Nanostructured Lipid Carriers)*	Spatially incompatible solid and liquid lipids (oils)	Higher drug loading capacity, improved long-term storage stability	Complex formulation optimization and characterization	Curcumin, EGCG, various lipophilic compounds
Nanoemulsions	Oil, water, and surfactant/co-surfactant mixture	Ease of preparation, thermodynamic/kinetic stability, high loading capacity	Long-term stability concerns *(e.g., Ostwald ripening, coalescence)*	Highly lipophilic compounds, essential oils

4 POLYMERIC NANOCARRIERS

Polymeric nanoparticles have been reported to offer proficient delivery of various natural bioactive agents with good entrapment potential and stability, efficiently controlled release, improved bioavailability, and fascinating therapeutic efficacy (Elmowafy et al., 2023). These nanocarriers are fabricated from either synthetic biodegradable polymers or natural polymers, each offering distinct advantages for natural product delivery (Elmowafy et al., 2023). Surface decoration and polymer functionalization have opened the door to improving the characteristics of polymeric nanoparticles and alleviating the reported toxicity (Elmowafy et al., 2023).

4.1 Synthetic Biodegradable Polymers

Poly(lactic-co-glycolic acid) (PLGA) and polylactic acid (PLA) are the most widely employed synthetic biodegradable polymers for natural product delivery (Elmowafy et al., 2023). PLGA nanoparticles have been developed to incorporate many active agents, including quercetin, pelargonidin, and various phytochemicals (Elmowafy et al., 2023). These polymers offer excellent biocompatibility, tunable degradation rates, and the capacity for controlled release over extended periods (Elmowafy et al., 2023).

PLGA-based formulations of curcumin, epigallocatechin gallate (EGCG), and resveratrol have demonstrated enhanced anticancer potential compared to free compounds (Elmowafy et al., 2023). Curcumin encapsulation in functional PLGA nanoparticles has been identified as a promising strategy for cancer therapies (Feltrin et al., 2022). The PLGA matrix protects encapsulated natural products from degradation while enabling sustained release, thereby improving bioavailability and therapeutic efficacy (Elmowafy et al., 2023).

4.2 Natural Polymers

Natural polymers, including chitosan, alginate, gelatin, and hyaluronic acid, offer inherent biocompatibility, biodegradability, and often bioactivity (Elmowafy et al., 2023). Chitosan, a mucoadhesive, non-toxic, and biodegradable polysaccharide, is considered one of the best nanoplatforms for the oral delivery of phytochemicals (Elmowafy et al., 2023). Chitosan nanoparticles have been extensively investigated for the delivery of herbal bioactives, demonstrating improved bioavailability and bioactivity (Recent development in nanoencapsulation, 2022).

Chitosan nanoparticles are characterized by their mucoadhesive properties, which prolong gastrointestinal residence time and enhance absorption of encapsulated natural products (Elmowafy et al., 2023). Recent developments in nanoencapsulation through chitosan scaffolds for various biological applications have been summarized, with an emphasis on the encapsulation of natural bioactives (Recent development in nanoencapsulation, 2022).

4.3 Polymeric Micelles

Polymeric micelles are self-assembled nanostructures formed by amphiphilic block copolymers above their critical micelle concentration (Elmowafy et al., 2023). These nanocarriers offer excellent solubilization capacity for hydrophobic natural products, with a hydrophobic core for drug loading and a hydrophilic shell for steric stabilization (Elmowafy et al., 2023). Polymeric micelles with inherent stability and ease of formulation are ideal for tumor targeting via the enhanced permeation and retention (EPR) effect (Farhoudi et al., 2022).

Curcumin delivery using polymeric micelles for various cancers has been extensively reviewed, discussing recent developments in this approach (Farhoudi et al., 2022). Polymeric micelles have demonstrated the ability to significantly enhance the aqueous solubility and bioavailability of curcumin while enabling passive targeting to tumor tissues through the EPR effect (Farhoudi et al., 2022).

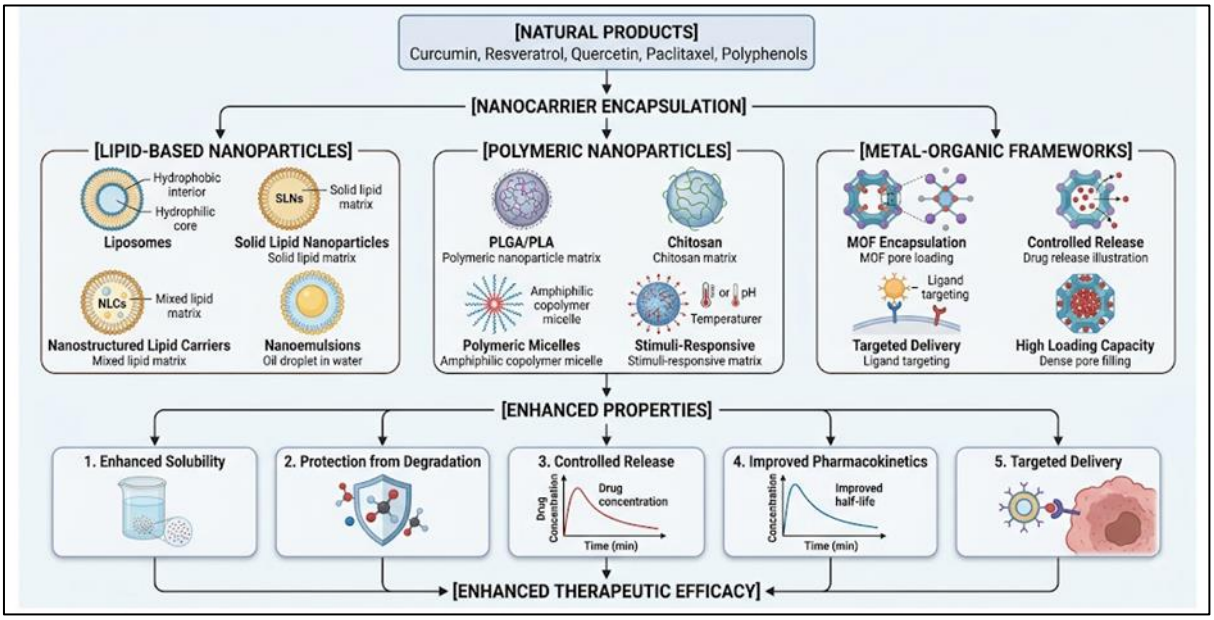

Figure 1: Schematic Representation of Nanocarrier Systems for Natural Product Delivery

5 METAL-ORGANIC FRAMEWORKS (MOFS)

Metal-organic frameworks are a relatively newer class of porous crystalline materials created by combining metal clusters and organic linkers (Chen et al., 2023). MOFs have enormous applications, particularly in the biomedical field, due to their ability for pre-functional design and post-functional modification (Chen et al., 2023). In the last decade, MOFs have shown great prospective as new drug delivery systems due to their unique porous structure, high surface area, tunable pore size, and versatile functionalization capabilities (Maranescu and Visa, 2022).

MOFs offer several distinct advantages for natural product delivery. Their high porosity enables exceptional drug loading capacities, often surpassing those of traditional nanocarriers (Maranescu and Visa, 2022). The tunable pore size allows for the encapsulation of molecules of varying dimensions, while the ability to modify surface chemistry facilitates targeted delivery and controlled release (Chen et al., 2023). Furthermore, certain MOFs exhibit intrinsic biodegradability, releasing non-toxic byproducts upon degradation (Maranescu and Visa, 2022).

Recent advancements in combining MOFs with natural compounds for cancer therapy have been summarized, highlighting the potential of this approach (Chen et al., 2023). Natural compounds such as functional food factors have demonstrated great potential for cancer therapy due to their low cost, mild side effects, and common raw materials (Chen et al., 2023). However, their short half-life period, easy decomposition, and lack of targeting severely limit their further development (Chen et al., 2023). MOFs offer a solution to these limitations by providing protection from degradation, sustained release, and targeted delivery capabilities (Chen et al., 2023).

Precision release systems of food bioactive compounds based on MOFs have been developed, with principles and mechanisms summarized in detail (Lv et al., 2022). MOF-based controlled release systems enable the spatiotemporal regulation of bioactive compound release, enhancing therapeutic efficacy while minimizing side effects (Lv et al., 2022). MOF-based nanomedicines inspired by structures of natural active components represent an emerging area of research, where the structural features of natural compounds inform the design of MOF-based delivery systems (MOF-based nanomedicines, 2022).

6 THERAPEUTIC APPLICATIONS

6.1 Cancer Therapy

Nanotechnology-based natural product delivery has demonstrated significantly enhanced anticancer efficacy across numerous preclinical models (Chavda et al., 2022; Elmowafy et al., 2023). Paclitaxel nanoparticle formulations (Abraxane) are clinically used for cancer therapy, representing a successful translation of nanotechnology for natural product delivery (Newman and Cragg, 2020). Curcumin and resveratrol nanoparticle formulations have shown enhanced efficacy in preclinical cancer models, with improved bioavailability translating to superior antitumor activity (Ashfaq et al., 2023; Farhoudi et al., 2022).

Liposomal phytochemical formulations have demonstrated particular promise in cancer therapy. Phytochemical-loaded liposomes for anticancer therapy have been extensively reviewed, with liposomal approaches of anticancer phytochemicals discussed in detail (Chavda et al., 2022). The liposomal delivery of phytochemicals improves therapeutic effectiveness by increasing transportation across cell barriers and conferring attractive cancer-specific targeting capabilities (Chavda et al., 2022).

MOF-based natural product delivery has shown promising results in cancer therapy. The combination of MOFs with natural compounds for anti-cancer performance has been summarized, providing new insights for future research in the biomedical field (Chen et al., 2023).

6.2 Inflammatory and Metabolic Disorders

Nanotechnology-based natural product delivery has been extensively investigated for inflammatory and metabolic disorders. The improved bioavailability of natural products through nanoencapsulation translates to enhanced anti-inflammatory and metabolic regulatory effects (Ashfaq et al., 2023). Lipid nanoparticles have been identified as effective tools to improve the bioavailability of nutraceuticals, encompassing a wide range of research aimed at encapsulating natural therapeutic molecules (Ashfaq et al., 2023).

6.3 Neurodegenerative Disorders

Nanotechnology-based delivery has been investigated for neuroprotective natural products targeting the central nervous system. Nanoparticle formulations of curcumin and other neuroprotective compounds have demonstrated enhanced brain delivery and neuroprotective effects (Ashfaq et al., 2023). The ability of lipid nanoparticles to cross the blood-brain barrier through various transport mechanisms makes them particularly attractive for delivering neuroprotective natural products.

6.4 Wound Healing

Curcumin-loaded lipid nanoparticles have demonstrated significant potential for wound healing applications (Ashfaq et al., 2023). CSLNs integrated into hydrogels showed noticeably quicker wound closure, better histological and immune-histochemical healing, lower oxidative stress, reduced inflammation, and increased angiogenesis in animal models (Ashfaq et al., 2023). The antibacterial activity of CSLNs against Staphylococcus aureus, including biofilm disruption, further supports their utility in wound healing applications (Ashfaq et al., 2023).

7 CHALLENGES AND RESEARCH GAPS

7.1 Scale-Up and Manufacturing

The scale-up of nanoparticle production for clinical applications remains a significant challenge (Ashfaq et al., 2023). Batch-to-batch variability, reproducibility issues, and the complexity of manufacturing processes present substantial hurdles for commercialization (Elmowafy et al., 2023). Developing scalable, reproducible, and cost-effective manufacturing processes is essential for translating nanotechnology-based natural product formulations to clinical use.

7.2 Long-Term Stability

The long-term stability of nanoparticle formulations is a critical concern (Ashfaq et al., 2023). Physical instability, including aggregation, Ostwald ripening, and drug leakage, can compromise product quality and shelf life (Elmowafy et al., 2023). Stabilization strategies, including lyophilization and the use of appropriate excipients, are being developed to address these stability concerns (Ashfaq et al., 2023).

7.3 Regulatory Approval

The regulatory approval of nanoparticle-based natural product formulations presents unique challenges (Ashfaq et al., 2023). Establishing safety, efficacy, and quality requires extensive preclinical and clinical studies, often at significant cost (Elmowafy et al., 2023). The regulatory framework for nanoparticle-based products continues to evolve, with harmonized guidelines needed to facilitate clinical translation (Ashfaq et al., 2023).

7.4 Toxicity and Biocompatibility

While many nanocarrier materials are considered biocompatible, the potential for toxicity at the nanoscale requires careful evaluation (Elmowafy et al., 2023). The long-term accumulation of nanoparticles in tissues, potential immunogenicity, and the toxicity of degradation products must be thoroughly investigated (Elmowafy et al., 2023).

8 FUTURE PERSPECTIVES

The future of nanotechnology-based natural product delivery lies in the development of multifunctional systems that combine targeting, imaging, and therapeutic functions. The integration of personalized medicine approaches, including patient stratification and biomarker identification, promises to enhance therapeutic outcomes. The exploration of novel nanocarrier systems, including extracellular vesicles and biomimetic nanoparticles, may offer enhanced biocompatibility and delivery efficiency. The development of stimuli-responsive systems that release their cargo in response to specific biological triggers represents an emerging frontier. Continued investment in translational research, scale-up technologies, and regulatory science is essential for realizing the full potential of nanotechnology-based natural product delivery.

9 CONCLUSION

Nanotechnology-based delivery systems offer transformative approaches for enhancing the bioavailability, pharmacokinetics, and therapeutic efficacy of natural products. Lipid-based nanoparticles, including liposomes, SLNs, NLCs, and nanoemulsions, have demonstrated success in encapsulating and delivering diverse natural compounds with improved bioavailability and controlled release. Polymeric carriers, encompassing synthetic biodegradable polymers (PLGA, PLA), natural polymers (chitosan), and polymeric micelles, provide versatile platforms for natural product delivery with good entrapment potential, stability, and controlled release. Metal-organic frameworks represent an emerging class of nanocarriers offering exceptionally high drug loading capacities and tunable release profiles. The enhanced therapeutic efficacy of nanoparticle formulations has been demonstrated across diverse disease models, including cancer, inflammatory disorders, and wound healing. Despite significant advances, challenges including scale-up, long-term stability, regulatory approval, and toxicity evaluation persist. Continued research and development, focusing on scalable manufacturing, regulatory compliance, and clinical translation, are essential for realizing the full potential of nanotechnology-based natural product delivery.

REFERENCES

[1] Anand, P., Kunnumakkara, A. B., Newman, R. A., & Aggarwal, B. B. (2007). Bioavailability of curcumin: Problems and promises. *Molecular Pharmaceutics*, *4*(6), 807–818. https://doi.org/10.1021/mp700113r

[2] Ashfaq, R., Rehman, A., Mushtaq, A., Rauf, A., Al-Asmari, F., & Al-Ghamdi, S. (2023). Lipid nanoparticles: An effective tool to improve the bioavailability of nutraceuticals. *International Journal of Molecular Sciences*, *24*(21), Article 15764. https://doi.org/10.3390/ijms242115764

[3] Atanasov, A. G., Zotchev, S. B., Dirsch, V. M., & Supuran, C. T. (2021). Natural products in drug discovery: Advances and opportunities. *Nature Reviews Drug Discovery*, *20*(3), 200–216. https://doi.org/10.1038/s41573-020-00114-z

[4] Chavda, V. P., Vihol, D., Mehta, B., Shah, D., Patel, M., Vora, L. K., Pereira-Silva, M., & Paiva-Santos, A. C. (2022). Phytochemical-loaded liposomes for anticancer therapy: An updated review. *Nanomedicine*, *17*(8), 547–568. https://doi.org/10.2217/nnm-2021-0422

[5] Chen, B., Zhang, L., & Jiang, K. (2023). Recent advancements in combining MOFs and natural compounds for cancer therapy. *Zeitschrift für Anorganische und Allgemeine Chemie*, *649*(18), Article e202300085. https://doi.org/10.1002/zaac.202300085

[6] Cheng, X., Yan, H., Pang, S., Ya, M., Qiu, F., Qin, P., Zeng, C., & Lu, Y. (2022). Liposomes as multifunctional nano-carriers for medicinal natural products. *Frontiers in Chemistry*, *10*, Article 963004. https://doi.org/10.3389/fchem.2022.963004

[7] Elmowafy, M., Shalaby, K., & Mostafa, E. M. (2023). Polymeric nanoparticles for delivery of natural bioactive agents: Recent advances and challenges. *Polymers*, *15*(5), Article 1123. https://doi.org/10.3390/polym15051123

[8] Farhoudi, L., Kesharwani, P., Majeed, M., Johnston, T. P., & Sahebkar, A. (2022). Polymeric nanomicelles of curcumin: Potential applications in cancer. *International Journal of Pharmaceutics*, *617*, Article 121622. https://doi.org/10.1016/j.ijpharm.2022.121622

[9] Feltrin, F. S., Soane, M. M., do Carmo, F. A., de Sousa, V. P., & Cabral, L. M. (2022). Curcumin encapsulation in functional PLGA nanoparticles: A promising strategy for cancer therapies. *Advances in Colloid and Interface Science*, *300*, Article 102582. https://doi.org/10.1016/j.cis.2021.102582

[10] Garg, U., Sharma, S., & Singh, R. (2022). Recent development in nanoencapsulation and delivery of natural bioactives through chitosan scaffolds for various biological applications. *International Journal of Biological Macromolecules*, *218*, 410–425. https://doi.org/10.1016/j.ijbiomac.2022.07.120

[11] Harvey, A. L., Edrada-Ebel, R., & Quinn, R. J. (2015). The re-emergence of natural products for drug discovery in the genomics era. *Nature Reviews Drug Discovery*, *14*(2), 111–129. https://doi.org/10.1038/nrd4510

[12] Lv, M., Sun, D. W., Cheng, J. H., & Pu, H. (2022). Precision release systems of food bioactive compounds based on metal-organic frameworks: Synthesis, mechanisms and recent applications. *Critical Reviews in Food Science and Nutrition*, *62*(15), 3991–4009. https://doi.org/10.1080/10408398.2020.1868461

[13] Maranescu, B., & Visa, A. (2022). Applications of metal-organic frameworks as drug delivery systems. *International Journal of Molecular Sciences*, *23*(8), Article 4458. https://doi.org/10.3390/ijms23084458

[14] Newman, D. J., & Cragg, G. M. (2020). Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. *Journal of Natural Products*, *83*(3), 703–721. https://doi.org/10.1021/acs.jnatprod.9b01285

[15] Patra, J. K., Das, G., & Fraceto, L. F. (2018). Nano based drug delivery systems: Recent developments and future prospects. *Journal of Nanobiotechnology*, *16*, Article 71. https://doi.org/10.1186/s12951-018-0392-8

[16] Shamsuddin, N. A. M., Salim, N., & Abdullah, R. (2023). Nanostructured lipid carriers for the delivery of natural bioactive compounds. *Current Drug Delivery*, *20*(2), 145–160. https://doi.org/10.2174/1567201819666220418101230

[17] Sharma, V., & Kumar, P. (2022). Improved activity of herbal medicines through nanotechnology. *Nanomaterials*, *12*(22), Article 4073. https://doi.org/10.3390/nano12224073

[18] Singla, M., Smriti, Gupta, S., Behal, P., Singh, S. K., Preetam, S., Rustagi, S., Bora, J., Mittal, P., Malik, S., & Slama, P. (2022). Nanotechnology: An approach to overcome bioavailability challenges of nutraceuticals. *Journal of Drug Delivery Science and Technology*, *72*, Article 103418. https://doi.org/10.1016/j.jddst.2022.103418

[19] Walle, T. (2011). Bioavailability of resveratrol. *Annals of the New York Academy of Sciences*, *1215*(1), 9–15. https://doi.org/10.1111/j.1749-6632.2010.05842.x

[20] Xu, B., Huang, Z., & Huang, Y. (2023). MOF-based nanomedicines inspired by structures of natural active components. *Nano Today*, *48*, Article 101735. https://doi.org/10.1016/j.nantod.2022.101735