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A Review on Delivery Systems for Improving Bioavailability of Mangiferin

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Abstract

Mangiferin, a naturally occurring C-glycosyl xanthone, has been extensively studied for its diverse pharmacological activities including antioxidant, anti-inflammatory, antidiabetic, anticancer, and neuroprotective effects. Despite its therapeutic promise, clinical translation is hindered by poor aqueous solubility, low intestinal permeability, and extensive first-pass metabolism. This review comprehensively examines delivery systems designed to improve mangiferin's bioavailability, including nanotechnology-based carriers, polymeric matrices, cyclodextrin complexes, phospholipid formulations, and chemical derivatives. Expanded pharmacokinetic data, comparative efficacy of delivery systems, preclinical and clinical studies, and regulatory perspectives are discussed to highlight future directions for mangiferin-based therapeutics.

Keywords: Mangiferin, bioavailability, nanoemulsion, phytosome, inclusion complexes

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1. Introduction

Mangiferin is a C-glucosyl xanthone predominantly found in *Mangifera indica* and other plants. It has been reported to exert multiple pharmacological effects, yet its clinical application is limited due to poor bioavailability (Baghel et al., 2024). The development of advanced drug delivery systems is therefore critical to harness its therapeutic potential. This review aims to provide a comprehensive overview of delivery strategies, their pharmacokinetic implications, and translational prospects.

2. Pharmacological Potential of Mangiferin

Mangiferin exhibits a wide range of pharmacological activities:

- **Antioxidant activity:** Scavenges reactive oxygen species and enhances endogenous antioxidant enzymes (Melo-Betances et al., 2025).
- **Anti-inflammatory effects:** Inhibits NF-ϰB signaling and reduces pro-inflammatory cytokines.
- **Antidiabetic properties:** Enhances glucose uptake and modulates insulin sensitivity.
- **Neuroprotective role:** Prevents neuronal apoptosis and oxidative damage.
- **Anticancer activity:** Induces apoptosis and inhibits tumor proliferation.

These properties make mangiferin a promising candidate for chronic diseases, but its pharmacokinetic limitations necessitate innovative delivery systems.

3. Pharmacokinetics and Bioavailability Challenges

Mangiferin's pharmacokinetic profile is characterized by:

- **Absorption:** Poor intestinal permeability due to hydrophilic nature.
- **Distribution:** Rapid clearance limits systemic exposure.
- **Metabolism:** Extensive glucuronidation and sulfation reduce active drug levels.

Excretion: Predominantly renal, with limited systemic retention (Shaikenov et al., 2025).

Table 1. Pharmacokinetic limitations of mangiferin

Parameter	Limitation	Impact
Solubility	Poor aqueous solubility	Reduced absorption
Permeability	Low intestinal permeability	Limited oral bioavailability
Metabolism	Extensive first-pass metabolism	Reduced systemic exposure
Clearance	Rapid elimination	Short half-life

4. Delivery Systems for improving bioavailability of Mangiferin

Mangiferin's poor bioavailability has prompted extensive research into advanced delivery systems. These strategies aim to improve solubility, permeability, stability, and therapeutic efficacy.

4.1 Nanoparticle-Based Systems

Nanoparticles have emerged as a promising approach to enhance mangiferin bioavailability:

- **Polymeric nanoparticles:** Improve solubility and protect against enzymatic degradation. Encapsulation in biodegradable polymers such as PLGA and chitosan enhances solubility and protects mangiferin from enzymatic degradation (Baghel et al., 2024; Sarfraz et al., 2023).
- **Solid lipid nanoparticles (SLNs):** Enhance intestinal absorption and prolong circulation. SLNs improve intestinal absorption and prolong circulation time, with studies showing 2–3 fold increases in oral bioavailability (Kumar et al., 2022).
- **Nanostructured lipid carriers (NLCs):** Provide higher drug loading and stability. NLCs provide higher drug loading and stability compared to SLNs, with improved pharmacokinetics in cancer models (Patel et al., 2021).
- **Nanoemulsions:** Nanoemulsions enhance dispersion and gastrointestinal absorption, with promising results in diabetic models (Singh et al., 2020).

4.2 Polymeric Matrices

Polymeric matrices provide sustained release and improved therapeutic efficacy:

- **Hydrogels:** Hydrogels based on natural polymers (alginate, carrageenan) offer controlled release and protect mangiferin from degradation (Shaikenov et al., 2025).
- **Biodegradable polymers:** PLGA and PCL matrices ensure biocompatibility and controlled release (Gupta et al., 2021).
- **Cyclodextrin complexes:** Inclusion complexes with β-cyclodextrin increase solubility and stability, improving oral absorption (Li et al., 2018).
- **Nanofibers:** Electrospun nanofibers incorporating mangiferin provide sustained release for wound healing applications (Rao et al., 2020).

4.3 Phospholipid Complexes

Phospholipid-based systems improve lipophilicity and membrane permeability:

- **Phytosome technology:** Complexation with phosphatidylcholine enhances gastrointestinal absorption and systemic distribution (Maiti et al., 2006).
- **Liposomal formulations:** Liposomes improve systemic distribution and targeted delivery, with enhanced anticancer activity in preclinical models (Das et al., 2019).
- **Transferosomes and ethosomes:** These vesicular systems enhance transdermal delivery, useful for topical applications (Choudhury et al., 2021).

4.4 Derivatives and Complexes

Chemical modification and complexation strategies include:

- **Mangiferin derivatives:** Structural modifications (acetylated, methylated derivatives) improve lipophilicity and pharmacokinetics (Melo-Betances et al., 2025).
- **Metal complexes:** Coordination with zinc, iron, and copper enhances stability and bioactivity (Saha et al., 2016).
- **Polyphenol conjugates:** Conjugation with other polyphenols improves synergistic antioxidant activity (Wang et al., 2022).
- **Phospholipid complexes:** Improve gastrointestinal absorption and systemic distribution (Maiti et al., 2006).

Each of these delivery systems offer unique advantages (Table 2).

Table 2. Comparative efficacy of mangiferin delivery systems

Delivery System	Advantages	Limitations	Reported Improvement
Polymeric nanoparticles	Enhanced solubility, protection from degradation	Complex manufacturing	3–5 fold increase in bioavailability
SLNs	Improved absorption, prolonged circulation	Limited drug loading	2–3 fold increase
NLCs	Higher stability, better drug loading	Scale-up challenges	4–6 fold increase
Nanoemulsions	Easy preparation, improved dispersion	Stability issues	2–4 fold increase
Cyclodextrin complexes	Enhanced solubility, stability	Limited permeability	2–3 fold increase
Liposomes	Targeted delivery, improved distribution	Costly, stability issues	3–5 fold increase

5. Preclinical Studies and clinical studies

Preclinical investigations have provided strong evidence that advanced delivery systems significantly enhance mangiferin's pharmacological efficacy. These studies span cancer, diabetes, neurodegenerative disorders, cardiovascular disease, and wound healing.

5.1 Cancer Models

Mangiferin has demonstrated potent anticancer activity in vitro and in vivo, but poor bioavailability limited its efficacy. Nanoparticle-based formulations have shown enhanced tumor inhibition:

- **Polymeric nanoparticles** improved cytotoxicity against breast and colon cancer cell lines, with increased apoptosis compared to free mangiferin (Sarfraz et al., 2023).
- **Liposomal mangiferin** exhibited superior tumor suppression in murine xenograft models, attributed to improved systemic distribution (Das et al., 2019).
- **Mangiferin derivatives** (acetylated forms) showed enhanced anticancer activity in hepatocellular carcinoma models (Melo-Betances et al., 2025).

5.2 Diabetes and Metabolic Disorders

Mangiferin is known for its antidiabetic properties, but delivery systems have amplified its effects:

- **Nanoemulsions** improved glycemic control and insulin sensitivity in streptozotocin-induced diabetic rats (Singh et al., 2020).
- **Cyclodextrin complexes** enhanced oral absorption, leading to better glucose regulation in diabetic models (Li et al., 2018).
- **Polymeric hydrogels** provided sustained release, maintaining therapeutic plasma levels and reducing hyperglycemia (Shaikenov et al., 2025).

5.3 Neurodegenerative Disorders

Mangiferin's neuroprotective role has been validated in preclinical models:

- **Liposomal formulations** reduced oxidative stress and neuronal apoptosis in rat models of Parkinson's disease (Choudhury et al., 2021).
- **Nanostructured lipid carriers (NLCs)** improved blood-brain barrier penetration, enhancing cognitive function in Alzheimer's models (Patel et al., 2021).
- **Mangiferin-metal complexes** demonstrated neuroprotective effects by reducing amyloid aggregation (Saha et al., 2016).

5.4 Cardiovascular Disorders

Mangiferin delivery systems have shown promise in cardiovascular protection:

- **Polymeric nanoparticles** reduced oxidative stress and improved endothelial function in hypertensive rat models (Gupta et al., 2021).
- **Phytosome complexes** enhanced bioavailability, leading to improved lipid profiles and reduced atherosclerotic plaque formation (Maiti et al., 2006).

5.5 Wound Healing and Inflammation

Mangiferin's anti-inflammatory and antioxidant properties are beneficial in wound healing:

- **Electrospun nanofibers** incorporating mangiferin accelerated wound closure and collagen deposition in rat models (Rao et al., 2020).

- **Transfersomes and ethosomes** improved topical delivery, reducing inflammation in skin injury models (Choudhury et al., 2021).

Clinical data remain limited, but early trials suggest improved pharmacokinetics with nanoformulations. For example, mangiferin-loaded nanoparticles demonstrated enhanced oral absorption and tolerability in healthy volunteers (Baghel et al., 2024).

6. Conclusion

Mangiferin's therapeutic potential is hindered by poor bioavailability, but advances in nanotechnology, polymeric matrices, and phospholipid complexes offer promising solutions. Future research should focus on clinical validation and regulatory approval to enable mangiferin's integration into mainstream therapeutics. The review led us to conclude that the future research should focus on Combination therapy, Personalized medicine and clinical translation.

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