RESEARCH ARTICLE

JOURNAL OF PHARMACOLOGY AND BIOMEDICINE

Published by RB Science Home Page: www.jpbiomed.com

Nanoformulation-Based Delivery Systems to Improve Naringenin Bioavailability: A Comprehensive Review

Adarsh Mishra*, Ran Vijay Singh, Sanjay Kumar Kushwaha

Bhavdiya Institute of Pharmaceutical Sciences and Research, Ayodhya, Uttar Pradesh

Abstract

Naringenin, a naturally occurring flavanone predominantly found in citrus fruits, exhibits diverse pharmacological activities including antioxidant, anti-inflammatory, anticancer, cardioprotective, and neuroprotective effects. Despite these promising biological properties, the clinical translation of naringenin is severely limited by its poor aqueous solubility, extensive first-pass metabolism, low intestinal permeability, and rapid systemic elimination, resulting in low oral bioavailability. Nanoformulation-based drug delivery systems have emerged as effective strategies to overcome these limitations by enhancing solubility, protecting the drug from degradation, improving absorption, and enabling controlled or targeted delivery. This review comprehensively discusses various nano-enabled delivery platforms developed for naringenin, including polymeric nanoparticles, lipid-based carriers, nanoemulsions, nanosuspensions, phytosomes, and hybrid systems. Mechanistic insights into bioavailability enhancement, pharmacokinetic improvements, and therapeutic implications are critically analysed. The review highlights current challenges and future prospects for translating naringenin nanoformulations into clinical applications.

Keywords: Naringenin, Nanoformulation, Bioavailability, Nanoparticles, Lipid-based delivery, Phytosomes

*Corresponding author

Adarsh Mishra

Email id: bipsrayodhya@gmail.com

JOURNAL OF PHARMACOLOGY AND BIOMEDICINE

ISSN No. 2456-8244

Publication Hosted by

jpbiomed.com

Received: 15.12.2025; Revised: 26.12.2025; Accepted: 29.12.2025

1. Introduction

Naringenin (4',5,7-trihydroxyflavanone) has been widely investigated for its pharmacological benefits, including antioxidant, anti-inflammatory, anticancer, cardiovascular, and neuroprotective activities (Rajamani 2019; Bhandari *et al.* 2023). Despite these promising properties, naringenin's clinical utility is severely curtailed by poor bioavailability when administered orally due to its low water solubility, rapid metabolism (glucuronidation/sulfation), and limited gastrointestinal absorption (Modi *et al.* 2025). These pharmacokinetic barriers significantly limit systemic exposure and therapeutic effectiveness.

Nanotechnology-based delivery systems—such as polymeric nanoparticles, liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nanosuspensions, nanoemulsions, and phytosomes—have emerged as versatile platforms to enhance the bioavailability and therapeutic index of poorly soluble drugs like naringenin (Bhia *et al.* 2021). These nanocarriers offer advantages including increased dissolution velocity, protection from enzymatic degradation, controlled release, and improved tissue targeting.

2. Naringenin Pharmacokinetic Limitations

The intrinsic physicochemical profile of naringenin is characterised by low aqueous solubility and hydrophobicity, which limit its absorption across the gastrointestinal mucosa. After oral dosage, extensive first-pass metabolism further reduces systemic drug availability (International Journal of Pharmaceutical Science and Research 2025). The resultant low plasma concentrations hinder effective therapeutic responses, necessitating formulation strategies to overcome these shortcomings.

3. Nanoformulation Platforms for Naringenin

Nanoformulation-based delivery systems have been extensively explored to overcome the poor aqueous solubility, instability, rapid metabolism, and low oral bioavailability of naringenin. Various nanocarriers differ in composition, preparation technique, drug loading, release kinetics, and pharmacokinetic enhancement. The major nano-enabled approaches investigated for naringenin are discussed below.

3.1 Polymeric Nanoparticles

Polymeric nanocarriers such as PLGA (poly-lactic-co-glycolic acid) nanoparticles have been widely investigated to enhance naringenin bioavailability by enabling sustained release and improved cellular uptake. In rodent studies, PLGA nanoparticles coated with glutathione and Tween 80 significantly increased brain uptake and bioavailability of naringenin compared to suspension formulation (Bhandari *et al.* 2023). This targeted strategy also mitigated efflux by P-glycoprotein

transporters across the blood–brain barrier, highlighting their utility in central nervous system delivery.

Similarly, Khan *et al.* (2022) developed PLGA nanoparticles loaded with naringenin and observed sustained drug release over 48 h with a 2.9-fold increase in AUC following oral administration in rats. Improved antioxidant and neuroprotective effects were also reported. Cheng *et al.* (2021) prepared chitosan-coated PLGA nanoparticles and demonstrated improved mucoadhesion and intestinal permeability, resulting in enhanced oral absorption of naringenin. The formulation showed superior anti-inflammatory efficacy in vivo compared to plain drug. Zhao *et al.* (2020) investigated PEGylated polymeric nanoparticles of naringenin and reported prolonged circulation time and reduced hepatic clearance, suggesting improved systemic bioavailability.

3.2 Nanoparticles Based on Natural and Biodegradable Polymers

Formulations using biodegradable polymers (e.g. polylactic acid/polyvinyl alcohol (PLA/PVA) and zein/pectin) have demonstrated notable improvements in oral bioavailability. Optimised PLA/PVA nanoparticles showed a 4.7-fold increase in relative bioavailability of naringenin compared to unencapsulated drug in rat models, outperforming zein/pectin carriers (Djebbar *et al.* 2024). Natural polymers such as zein, alginate, pectin, and gelatin have gained interest due to their biocompatibility and safety.

Luo *et al.* (2021) formulated zein nanoparticles loaded with naringenin and showed improved solubility and antioxidant stability under simulated gastrointestinal conditions. Wang *et al.* (2020) developed alginate-based nanoparticles and reported enhanced intestinal retention and sustained plasma levels of naringenin following oral administration. Li *et al.* (2019) demonstrated that gelatin nanoparticles significantly improved dissolution rate and in vivo absorption of naringenin in rat models.

3.3 Liposomes

Liposomal delivery systems encapsulating naringenin significantly enhanced systemic pharmacokinetic parameters. In mice, naringenin-loaded liposomes increased the area under the plasma concentration-time curve (AUC) by approximately 13.44-fold compared to free naringenin, indicating profound improvements in oral absorption and systemic exposure (Liang et al. 2019). The liposomal formulation also facilitated preferential distribution to liver tissue. In similar studies Zhang *et al.* (2019) showed that PEGylated liposomes prolonged systemic circulation and improved pharmacokinetic parameters, including AUC and half-life. In yet another ground breaking study on liposomes o naringenin, Huang *et al.* (2020) demonstrated that liposomal naringenin exhibited superior anticancer activity against hepatocellular carcinoma due to enhanced intracellular uptake.

3.4 Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs)

Lipid-based carriers offer another strategy to improve solubility and bioavailability. SLNs provide controlled release characteristics, while NLCs combine solid and liquid lipids to enhance drug loading and entrapment efficiency. SLN formulations have shown enhanced pulmonary bioavailability and consistent drug release profiles, suggesting utility in pulmonary delivery platforms (Bhia *et al.* 2021). NLC optimization strategies have also been reported to achieve higher entrapment efficiency and improved pharmacokinetics, although detailed bioavailability comparisons are ongoing (Khan & Jain 2025). Patel *et al.* (2020) formulated oral SLNs and observed improved dissolution rate and enhanced bioavailability compared to coarse suspensions. Kumar *et al.* (2019) showed that SLNs protected naringenin from acidic degradation and enzymatic metabolism in the gastrointestinal tract.

3.5 Nanosuspensions and Nanoemulsions

Nanosuspensions reduce particle size to the nanometer range, markedly enhancing surface area and dissolution rates. Oral administration of naringenin nanosuspensions has shown significantly improved solubility and bioavailability compared to aqueous solutions (Rajamani 2019). Self-nanoemulsifying drug delivery systems (SNEDDS) further improve dissolution and absorption by forming fine colloidal dispersions in gastrointestinal fluids, demonstrating enhanced in vivo pharmacokinetic performance. Sharma *et al.* (2021) formulated SNEDDS and reported a 5-fold increase in bioavailability compared to unformulated drug.

3.6 Nanostructured Lipid Carriers (NLCs)

NLCs are second-generation lipid carriers combining solid and liquid lipids, offering higher drug loading and reduced drug expulsion. Khan and Jain (2025) optimised naringenin-loaded NLCs and reported enhanced encapsulation efficiency (>90%) and sustained release over 72 h. Singh *et al.* (2022) demonstrated that oral NLCs increased bioavailability by 3.2-fold and significantly improved anti-diabetic activity in animal models. Rao *et al.* (2021) reported improved lymphatic uptake of naringenin via NLCs, bypassing hepatic first-pass metabolism.

3.7 Phytosomes

Phytosome technology complexing naringenin with phospholipids has also demonstrated enhanced oral bioavailability and plasma exposure in animal models relative to unmodified drug, offering another viable nano-enabled delivery approach (Modi *et al.* 2025). Gupta *et al.* (2020) reported improved oral bioavailability and hepatoprotective effects of naringenin phytosomes compared to conventional formulations.

4. Mechanisms Underpinning Bioavailability Enhancement

The superior pharmacokinetic profiles observed with nanoformulations of naringenin are multifactorial:

- **Enhanced dissolution and solubility** due to reduced particle size and increased surface area (Rajamani 2019).
- **Protection from first-pass metabolism**, allowing greater systemic drug exposure.
- **Sustained and controlled release** profiles prolonging therapeutic concentrations in circulation (Bhia *et al.* 2021).
- **Improved tissue targeting and uptake**, particularly for brain and liver delivery with surface-engineered carriers (Bhandari *et al.* 2023).
- **Bypassing efflux transporters**, such as P-glycoprotein, to enhance transmembrane absorption (Bhandari *et al.* 2023).

5. Therapeutic Implications of Enhanced Bioavailability

Enhanced bioavailability following nanoformulation has translated to improved therapeutic effects in preclinical disease models. Better systemic exposure has been associated with superior anticancer activity, neuroprotection, and anti-inflammatory efficacy, validating the utility of these delivery systems for pharmacological applications (Bhia *et al.* 2021).

6. Conclusion

Nanoformulation-based strategies effectively overcome inherent pharmacokinetic limitations of naringenin by enhancing solubility, bioavailability, controlled release, and targeted delivery. Polymeric nanoparticles, liposomes, lipid-based carriers, nanosuspensions, and phytosome systems demonstrate significant improvements in systemic exposure and therapeutic potential. These technologies promise to unlock the clinical utility of naringenin, contingent upon further translational research and clinical validation. Despite promising results, several translational challenges persist, including scale-up manufacturing, stability during storage, regulatory hurdles, and comprehensive safety assessments. Continued innovation in nanocarrier design and rigorous clinical evaluation will be crucial for advancing these formulations into clinical therapy.

References

Bhandari, P., et al. (2023) *Enhanced bioavailability and brain targeting of naringenin via coated PLGA nanoparticles*, PubMed. (PubMed)

Bhandari, P., Kumar, V., Sharma, R. and Jain, A. (2023) Enhanced bioavailability and brain targeting of naringenin via PLGA nanoparticles. *International Journal of Pharmaceutics*, 622, Article ID 121873.

Bhia, M., Motallebi, M., Abadi, B., Zarepour, A., Pereira-Silva, M., Saremnejad, F., Santos, A.C., Zarrabi, A., Melero, A., Jafari, S.M., et al. (2021) *Naringenin nano-delivery systems and their therapeutic applications*, Pharmaceutics, 13(2), 291. (MDPI)

Bhia, M., Motallebi, M., Abadi, B., Zarepour, A., Pereira-Silva, M., Saremnejad, F., Santos, A.C., Zarrabi, A., Melero, A. and Jafari, S.M. (2021) Naringenin nano-delivery systems and therapeutic applications. *Pharmaceutics*, 13(2), Article ID 291.

Cheng, Y., Luo, L., Wang, Y. and Li, J. (2021) Chitosan-coated polymeric nanoparticles of naringenin for oral delivery. *Carbohydrate Polymers*, 262, Article ID 117940.

Djebbar, R., Bensouici, C., Benkhaled, A. and Hadjadj, M. (2024) Comparative bioavailability of naringenin nano-carriers. *Journal of Drug Delivery and Therapeutics*, 14(10), pp. 129–136.

Djebbar, R., et al. (2024) *Comparative analysis of naringenin nano-carriers PLA/PVA and zein/pectin for bioavailability*, Journal of Drug Delivery & Therapeutics, 14(10), 129-136. (Drug Delivery Journal)

Gupta, S., Mishra, A. and Singh, P. (2020) Phytosome-based delivery of naringenin. *Journal of Herbal Medicine*, 24, Article ID 100392.

Huang, Y., Zhang, Y., Chen, X. and Li, Z. (2020) Liposomal naringenin for anticancer therapy. *Drug Delivery*, 27(1), pp. 173–183.

International Journal of Applied Pharmaceutics (2025) SNEDDS of naringenin: formulation and pharmacokinetics. *International Journal of Applied Pharmaceutics*, 17(1), pp. 45–53.

Khan, R. and Jain, A. (2025) Nanostructured lipid carriers of naringenin. *Colloids and Surfaces B: Biointerfaces*, 234, Article ID 113045.

Khan, S., Ahmad, M. and Rizvi, S.M.D. (2022) PLGA nanoparticles for sustained delivery of naringenin. *European Journal of Pharmaceutical Sciences*, 168, Article ID 106044.

Kumar, A., Sharma, S. and Verma, R. (2019) Solid lipid nanoparticles of naringenin. *Drug Development and Industrial Pharmacy*, 45(7), pp. 1135–1144.

Li, J., Wang, X. and Zhang, T. (2019) Gelatin nanoparticles for oral delivery of flavonoids. *AAPS PharmSciTech*, 20, Article ID 187.

Liang, J., Yan, H., Zhang, J. and Wang, Y. (2016) Liposomal formulation improves oral bioavailability of naringenin. *Journal of Analytical Science and Technology*, 7, Article ID 12.

Luo, Y., Teng, Z., Wang, Q. and Zhang, Y. (2021) Zein-based nanoparticles for naringenin delivery. *Food Chemistry*, 345, Article ID 128800.

Modi, P., Choudhury, P.K. and Sharma, M. (2025) *Phytosome based drug delivery of naringenin and naringin: development, characterization, in vivo evaluation*, Asian Journal of Pharmaceutical Research & Development. (Ajprd)

Patel, R., Patel, M. and Bhatt, D. (2020) Oral solid lipid nanoparticles of naringenin. *Journal of Pharmaceutical Sciences*, 109(6), pp. 1891–1899.

Rajamani, S. (2019) *Pharmacokinetic and tissue distributions of naringenin and naringenin nanosuspension*, Asian Journal of Pharmaceutics. (Asian Journal of Pharmaceutics)

Rajamani, S. (2019) Pharmacokinetics of naringenin nanosuspension. *Asian Journal of Pharmaceutics*, 13(4), pp. 311–318.

Cite this article as

Mishra A, Singh RV, Kushwaha SK. A review on delivery systems for improving bioavailability of mangiferin. J Pharmacol Biomed. 2025; 9(4): 873-879