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FLAVONOID-BASED NANOTHERAPEUTICS: RECENT ADVANCES IN DELIVERY SYSTEMS, PHARMACOKINETICS, THERAPEUTIC APPLICATIONS, AND CLINICAL TRANSLATION

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Graphical Abstract



LIST OF ABBREVIATIONS

Quercetin (QTN), curcumin (CUR), baicalin (BCL), luteolin (LUT), kaempferol (KMF), apigenin (APN), naringenin (NRG), hesperidin (HSP), Fisetin (FIS), epigallocatechin gallate (EGCG), phloretin (PHL) polymeric nanoparticles (PNPs), inorganic nanoparticles (INPs) nanostructured lipid carriers (NLCs), solid lipid nanoparticles (SLNs), nanoemulsion (NE), entrapment efficiency (EE), quality by design (QbD)

Abstract

Flavonoids are a group of structurally diverse bioactive compounds with high therapeutic potential for diverse pathological conditions; however, their clinical translation is often limited by poor aqueous solubility, chemical instability, extensive metabolism, rapid elimination, and low systemic bioavailability. As such, nanotechnology has emerged as a promising approach to overcome these physicochemical and pharmacokinetic limitations by enabling controlled drug loading and release, improved solubility and stability, enhanced absorption, prolonged circulation, and targeted or tissue-specific delivery. This review critically surveys recent progress in flavonoid nanotherapeutics, covering lipid-based, polymeric, vesicular, biomimetic, inorganic and hybrid nanocarrier systems with an emphasis on formulation-property-performance relationships. The available evidence is evaluated in terms of physicochemical characterization, in vitro biological activity, animal pharmacokinetics and efficacy, human pharmacokinetic studies, and clinical investigations to distinguish between formulation feasibility and meaningful therapeutic benefit. In particular, the discussion focuses on changes of important pharmacokinetic parameters like systemic exposure, maximum plasma concentration, half-life, and bioavailability, realizing that better pharmacokinetic performance does not necessarily mean better clinical efficacy. The review also discusses nano-bio

interactions, biodistribution, immunological and organ-specific safety, manufacturing and scale-up challenges, critical quality attributes and regulatory considerations that currently prevent clinical translation. Future progress relies on standardized characterization, reproducible manufacturing, robust long-term safety assessment, human-relevant pharmacokinetic and efficacy studies, and well-designed clinical trials. The translation of flavonoid nanotherapeutics from promising experimental systems into clinically viable therapeutic products may be enabled by the integration of formulation science and pharmacology, artificial intelligence, quality by design (QbD) principles, and regulatory science.

KEYWORDS: Flavonoids: nanoformulations; drug delivery systems; bioavailability; clinical translation; regulatory challenges

INTRODUCTION

Flavonoids constitute a large family of polyphenolic compounds ubiquitously distributed in plants, fruits, vegetables, and beverages such as tea and wine. These bioactive molecules have garnered substantial scientific and clinical interest due to their diverse pharmacological properties, including potent antioxidant, anti-inflammatory, anticancer, neuroprotective, cardioprotective, and antimicrobial activities [1,2]. Flavonoids such as QTN, CUR, EGCG, BCL, KMF, LUT, APN, NRG, HSP, FIS, and resveratrol have demonstrated remarkable therapeutic potential in preclinical studies and epidemiological investigations [3,4]. Despite their promising biological activities, the clinical translation of flavonoid therapeutics has been severely hampered by inherent physicochemical and pharmacokinetic limitations. Most flavonoids exhibit poor aqueous solubility (typically<10 μg/mL), resulting in limited dissolution in gastrointestinal fluids and, consequently, poor oral bioavailability (often<5%) [5,6]. Additionally, flavonoids undergo extensive first-pass metabolism in the liver and intestinal mucosa, rapid systemic clearance, and chemical instability under physiological conditions, leading to short plasma half-lives and subtherapeutic concentrations at target sites [7,8]. These challenges have necessitated the development of innovative delivery strategies to unlock the full therapeutic potential of flavonoids (**Fig. 1**).

Nanotechnology-based drug delivery systems have emerged as a transformative approach to overcome the bioavailability barriers associated with flavonoid therapeutics [9–11]. Nanocarriers including polymeric NPs, liposomes, SLNs, NLCs, NEs, cyclodextrin complexes, and various hybrid systems-offer multiple advantages: enhanced solubility through encapsulation in lipophilic or amphiphilic matrices, protection from degradation and metabolism, prolonged circulation time, improved cellular uptake, and the potential for targeted delivery to specific tissues or cells [12,13]. These platforms can be further functionalized with targeting ligands (e.g., folic acid, antibodies, and peptides) to achieve site-specific accumulation, thereby maximizing therapeutic efficacy while minimizing systemic toxicity [14,15].

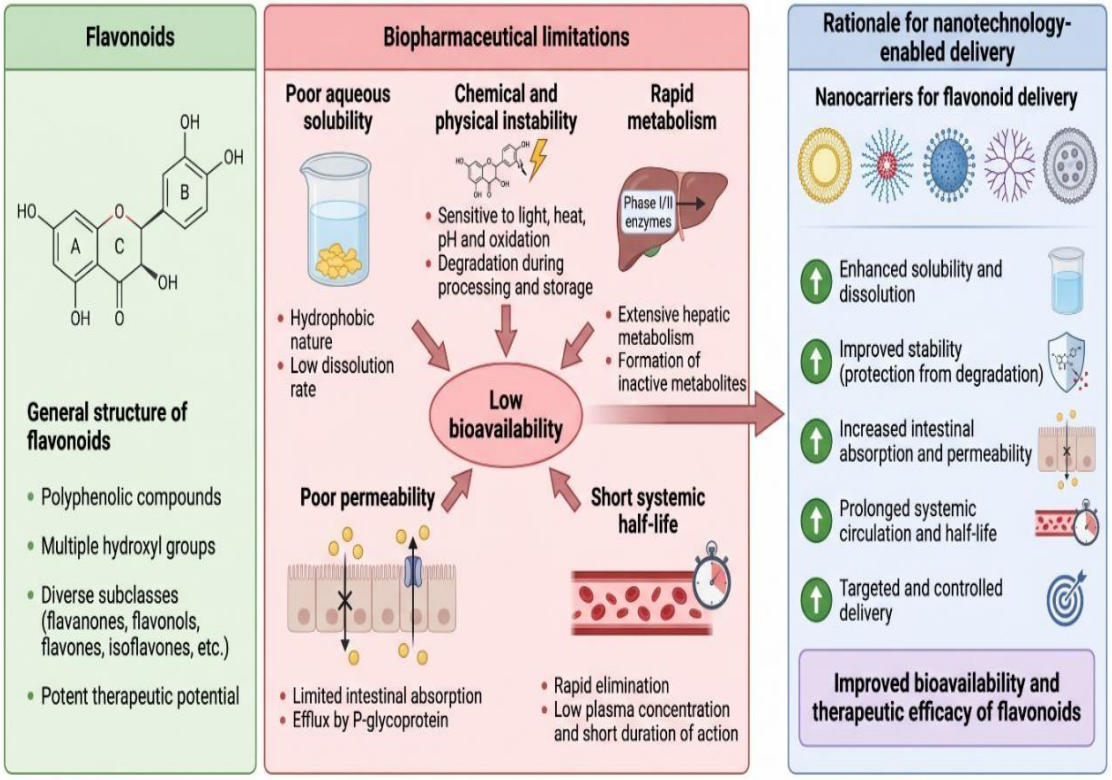


Fig. 1. Biopharmaceutical limitations of flavonoids and rationale for nanotechnology-enabled delivery (Created

with BioRender.com. Adapted by the authors).

Recent advances in nanotechnology have enabled the development of sophisticated flavonoid delivery systems with controlled release kinetics, stimuli-responsive behaviour (pH, temperature, or enzyme-triggered release), and co-delivery capabilities for synergistic therapeutic effects [16,17]. The integration of nanotechnology with flavonoid therapeutics represents a convergence of natural product pharmacology and advanced materials science, offering unprecedented opportunities for treating complex diseases such as cancer, neurodegenerative disorders, inflammatory conditions, and metabolic diseases [18–20]. This systematic literature review was designed to comprehensively evaluate the current state of nanotechnology-based formulation strategies for flavonoid therapeutics. Specifically, the review aims to compare nanotechnology-based formulation strategies, including NPs, liposomes, NEs, solid lipid NPs, polymeric NPs, and NLCs, with conventional flavonoid formulations or free flavonoids in terms of enhanced bioavailability, improved pharmacokinetics, and therapeutic efficacy for flavonoid compounds such as QTN, BCL, CUR, KMF, LUT, APN, NRG, HSP, EGCG, FIS, and resveratrol related bioactive molecules.

Furthermore, this review critically examines the evidence from including both preclinical and clinical investigations, to assess the pharmacological activities of nano formulated flavonoids. In particular emphasis on their anticancer, anti-inflammatory, antioxidant, neuroprotective, cardioprotective, and antimicrobial effects in comparison with non-nano-formulated flavonoids, standard therapeutic agents, placebo, or appropriate control groups. Finally, the review discusses the current status of clinical translation and therapeutic application of flavonoid nanoformulations, highlighting emerging clinical opportunities while critically evaluating the major translational challenges, safety considerations associated with their human application in comparison with existing clinical standards.

METHODOLOGY

This study is a comprehensive review of the literature that includes recent information collected to get better insights on flavonoid therapeutics through nanotechnology and get insights on therapeutic potential, nanoformulations, clinical translation, regulatory approvals, safety, and exclusion of AI in flavonoid-based nanoformulations. To gather the data, the scientific literature was searched in various databases, including PubMed, ScienceDirect, Taylor & Francis Online, WILEY Online Library, Springer Nature Link, and MDPI. In searching the scientific literature published during 2021-2026, a multi-layered searching approach was adopted using keywords like “flavonoid”, “dietary flavonoid”, “polyphenol”, “therapeutic potential”, “pharmacological activity”, “health benefit” for a broader review. Then, for searching nano-delivery-related literature, keywords like “flavonoid”, “QTN”, “BCL”, “nanoparticle”, “nanocarrier”, “nano-formulation”, “liposome”, “solid lipid nanoparticle”, and “polymeric nanoparticle” were used. Then with respect to clinical translation, keywords like “flavonoid”, “nanocarrier”, “preclinical”, “in vitro”, “pharmacokinetic”, “biodistribution”, “clinical translation” for searching related safety and regulatory literature. Keywords like “flavonoid”, “nano-formulation”, “flavonoid nanoparticle”, “toxicity”, “safety”, “biocompatibility”, “regulatory”, “CMC”, and “quality by design” (QbD) were used. For AI-related literatures keywords like “flavonoid”, “nano-formulation”, were used. The total number of cumulative literatures from all the above six databases was around 13390, and that collected from other methods was 225; these were summarized and critically discussed to provide a consistent overview (Fig. 2). This meta-analysis was performed according to the PRISMA guidelines 2020 [21,22].

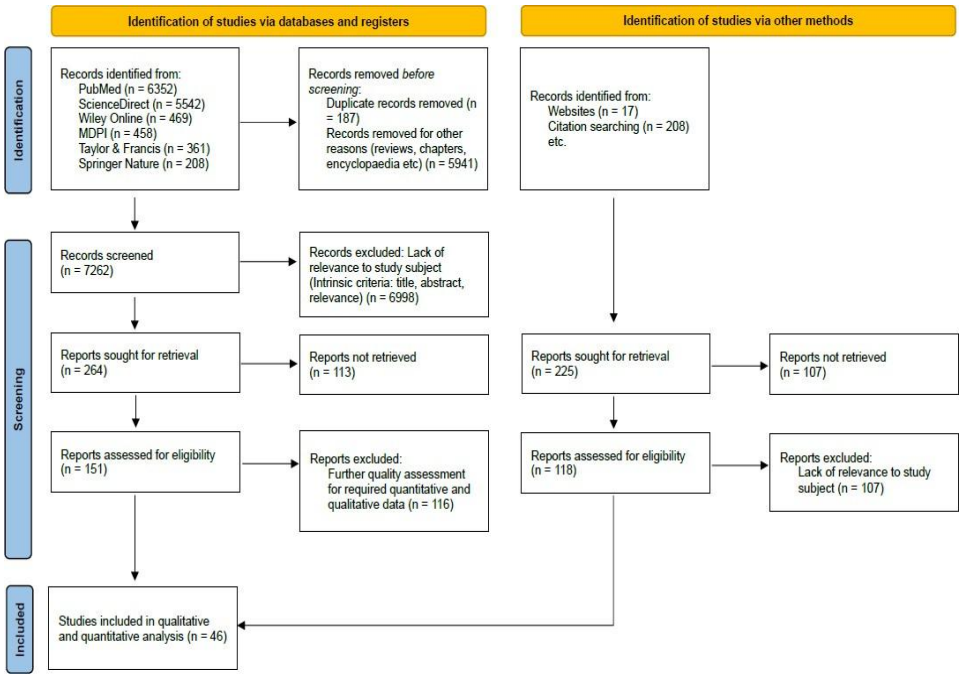


Fig. 2. PRISMA 2020 flow diagram for identification and screening of suitable resources.

The coloured cloud depicted in **Fig. 3** was obtained by VOS viewer software (version 1.6.21,

www.vosviewer.com, accessed on 28 July 2026) using the ScienceDirect online database. During the bibliographic search (n=1861 documents), the main keywords used were flavonoids, nanotechnology, nanoformulations, and nano-carriers. We conducted co-occurrence (map) analysis based on the text data from the title, abstract, and keyword of the documents found. **Fig. 3a** illustrates the co-occurrence network between keywords (indicated by the curved lines), which refers to the frequency (indicated by the size of the circles) of their occurrence in a document. In our analysis, the minimum occurrence of a keyword was defined as fifteen, and a total of seven clusters were obtained. According to density visualization map results, the colour of a keyword can be used to indicate its occurrence, with lighter colours indicating increased research activity and faded colours indicating decreased activity (**Fig. 3b**).

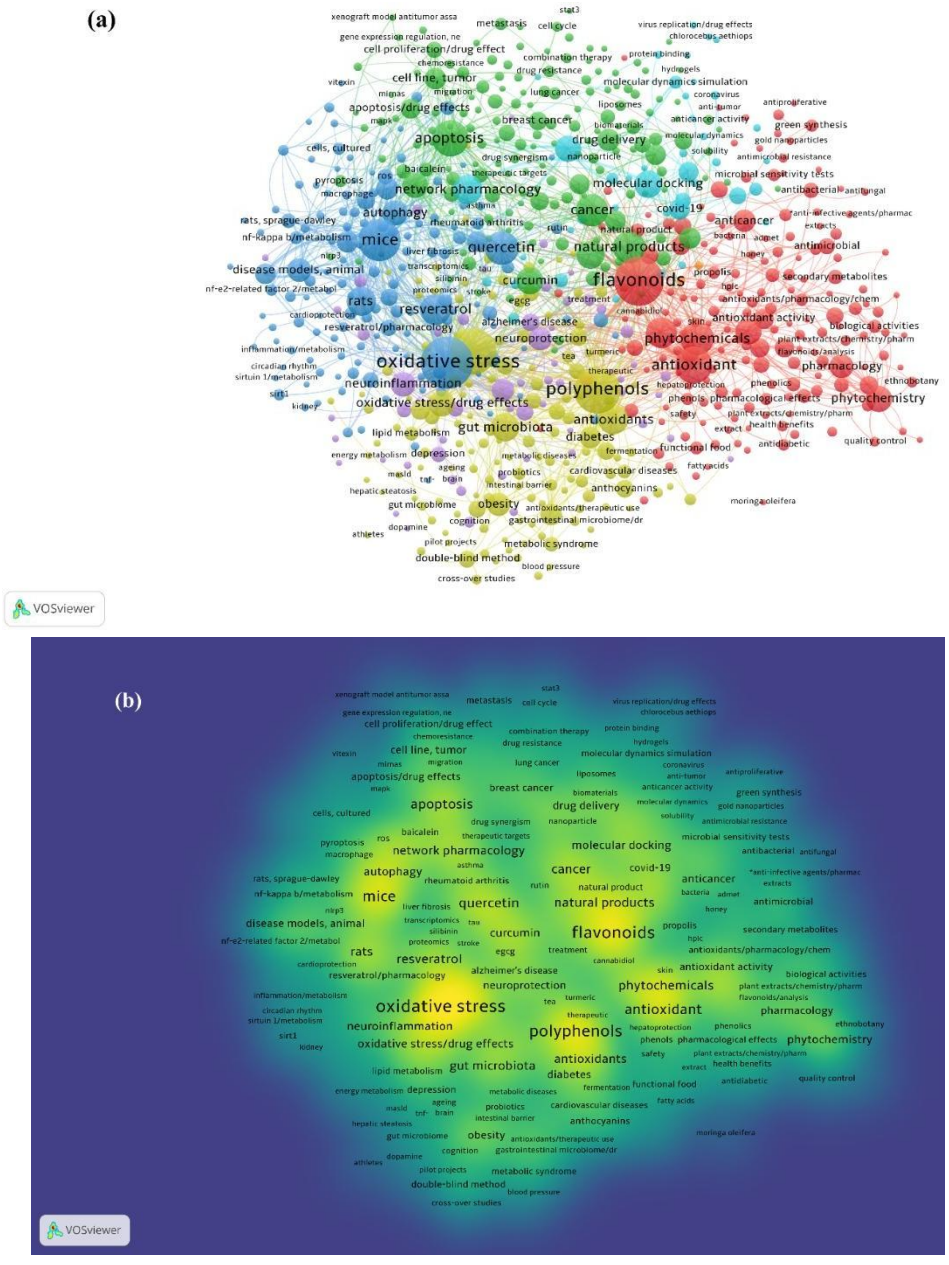


Fig. 3. VOS viewer keywords co-occurrence analysis: (a) Network visualization map and (b) Density visualization map.

CLASSIFICATION OF FLAVONOIDS

Flavonoids are phenolic compounds found in plants structurally consisting of two six-carbon aromatic rings (A and B), which are interconnected by a three-carbon chain known as the C-ring (Fig. 4). The fundamental structure of nearly all flavonoids is a carbon skeleton based on the flavan system (C6-C3-C6). Based on their chemical structure, oxidation level, and chain-linked unsaturation, flavonoids can be categorized into seven main

groups: flavone, flavonol, flavanone, flavan-3-ol (flavanol), anthocyanin, isoflavone, and chalcone [23–26]. The basic structural features, examples, and main sources of all the flavonoid classes are mentioned in **Table 1** [27-33].

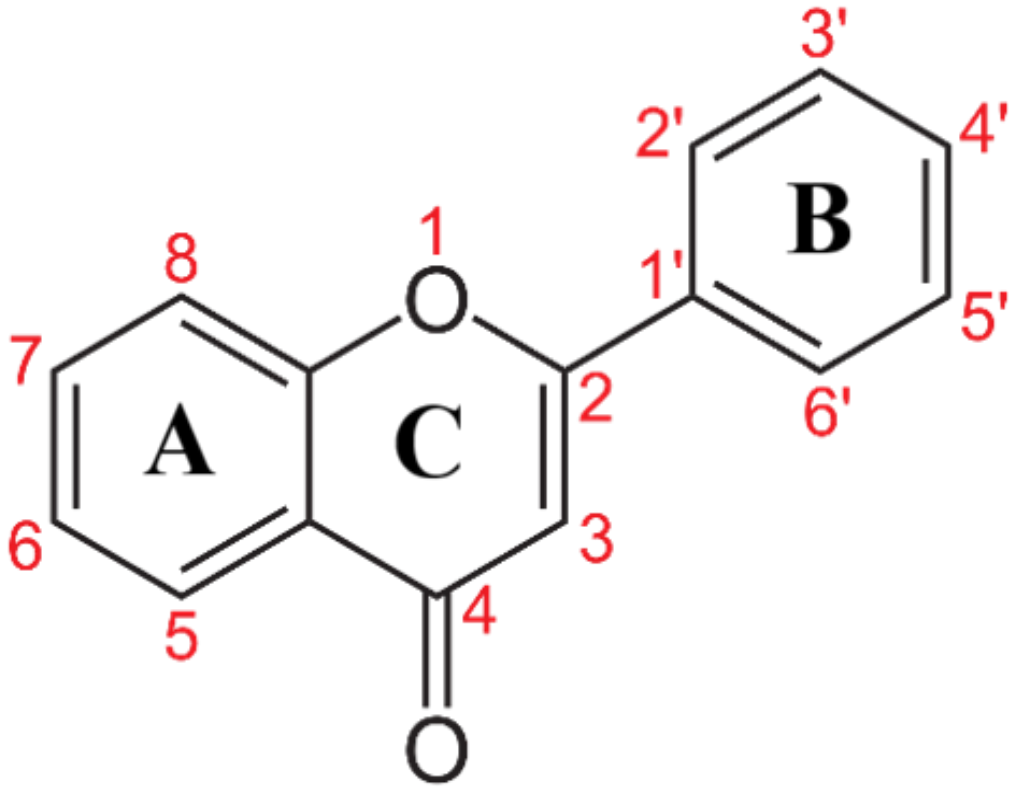


Fig. 4. Basic chemical structure of flavonoid.

Table 1: Classification of flavonoids with structural features, examples and main source.

Flavonoid Class	Structural features	Common examples	Main source
Flavone	Double bond between C2–C3 and a ketone at C4; typical substitution at positions 5, 7 (A ring) and 3′,4′ (B ring)	APN, LUT, Chrysin	Parsley, celery, chamomile, herbs and peppers
Flavonol	Hydroxyl group at C3, C2–C3 double bond and C4 carbonyl	QTN, KMF, MYR, RUT	Onions, apples, berries, tea and citrus peels
Flavanone	Saturated C2–C3 bond (no double bond), ketone at C4 (flavanone nucleus)	NRG, Hesperetin, HSP	Citrus fruits and herbs
Flavan-3-ol (Flavanol)	No C4 carbonyl (no C4=O), saturated C2–C3 single bond, hydroxyl group at C3	Catechin, Epicatechin, EGCG	Green and black tea, cocoa, apples and grapes
Anthocyanin	Flavylium cation core (positively charged oxygen at position 1), conjugated system responsible for red/blue/purple pigments	Cyanidin, Delphinidin, Pelargonidin, Malvidin	Berries, red grapes and cabbage, purple corn and black rice
Isoflavone	B ring attached at C3 of the heterocyclic ring (isomeric position)	Genistein, Daidzein, Glycitein	Soybean, red clover and legumes
Chalcone	Open-chain flavonoids without heterocyclic C ring; two aromatic rings joined by an α, β-unsaturated carbonyl	PHL, Xanthohumol	Apples, hops, spices and medicinal plants

system

NANO-DELIVERY PLATFORMS FOR FLAVONOIDS

Currently research on all types of nanocarrier systems has become a central focus in pharmaceutical sciences because nanoscale design can improve solubility, circulation, and site-specific delivery relative to conventional dosage forms [27,28]. Early nanomedicine efforts emphasized liposomes and other submicron carriers, but subsequent work broadened the landscape to polymeric, lipid-based, inorganic, and biomimetic architectures, enabling controlled and responsive release strategies [29,30]. Fig. 5 depicted nanocarrier platforms for flavonoid and selected polyphenols delivery. Clinically validated examples and expanding investigational pipelines have reinforced the translational relevance of nanocarriers, particularly lipid nanoparticles (LNPs), which have enabled clinically successful mRNA delivery and several approved nucleic-acid and vaccine formulations [31,32]. Meanwhile, cross-barrier delivery requirements have increased demand for platform-level comparisons across physicochemical properties, targeting strategies, and manufacturability. [33,34]. Despite extensive literature on individual nanocarrier classes, comparative synthesis across chemically and biologically distinct platforms remains fragmented, particularly when vesicular and polymeric nanoparticles are considered alongside metallic, carbon-based, and extracellular-vesicle-derived systems [35]. Knowledge gaps also remain around how nanomaterial type, formulation technique, and targeting strategy jointly determine bioavailability,
biodistribution, and therapeutic outcomes. Competing perspectives persist on which platforms best balance efficacy with biosafety and regulatory feasibility, with ongoing concerns about toxicity, immune interactions, and scalability, while other reviews emphasize their precision potential when design constraints are matched to biological barriers [36–38]. These gaps hinder the evidence synthesis needed to guide clinically reliable selection among carrier classes rather than individual formulations. Conceptually, nanocarriers can be viewed as material platforms engineered through formulation and surface functionalization to tune key physicochemical determinants, including size, surface chemistry, morphology, and drug-loading capacity, thereby modulating biodistribution, passive or active targeting, and stimuli-responsive drug release [37,39,40]. These determinants govern interactions with biological barriers, including immune-mediated clearance and organ- and cell-level uptake, thereby shaping the pharmacokinetic, biodistribution, and safety profiles of nanomedicines. [37,41].

Liposomes are spherical vesicles composed of one or more phospholipid bilayers enclosing an aqueous core, enabling the encapsulation and delivery of both hydrophilic and hydrophobic compounds. Kumar et al. demonstrated the potential of QTN-loaded liposomes to mitigate oxidative stress in red blood cells during aging, as evidenced by reduced malondialdehyde levels and enhanced glutathione levels, highlighting their potential as antioxidant nanocarriers [42].

SLNs are colloidal drug delivery systems composed of nano-sized lipid particles, conventionally prepared by dispersing a solid lipid matrix in an aqueous phase containing a surfactant as a stabilizing agent [2,43]. Pareek et al. have developed a new inhaled swellable microsphere system for the dual delivery of NRG-loaded solid lipid NPs and doxofylline for the treatment of asthma [44]. In another study Al-sayadi et al. have enhanced the neuroinflammation potential of QTN by developing and optimizing QTN-loaded TPGS (D-α-tocopheryl polyethylene glycol 1000 succinate, a novel stabilizer) coated SLNs by QbD [45].

NLCs are lipid-based nanocarriers composed of a mixture of solid and liquid lipids, generating a less-ordered lipid matrix that can accommodate therapeutic molecules. This structure can provide higher drug-loading and entrapment efficiencies than conventional SLNs, while potentially improving drug stability, permeation, and bioavailability [46,47]. Costa et al. in their recent study have enhanced the skin delivery and bioavailability of QTN, using NLCs embedded within sodium alginate/poly(vinyl alcohol) hydrogels [48]. Joshi et al. developed a nanostructured lipid carrier (NLC)-based topical gel for the co-delivery of cyclosporine A and QTN, designed to simultaneously target immune dysregulation and oxidative stress in psoriasis. In an imiquimod-induced murine model, the optimized cyclosporine A–QTN NLC gel enhanced dermal drug deposition and markedly reduced psoriatic severity and inflammatory changes, supporting its potential as a localized, synergistic therapeutic strategy [49].

Polymeric nanoparticles (NPs) are nanoscale drug-delivery systems composed of natural or synthetic polymers, generally ranging from approximately 10 to 1000 nm depending on their formulation and classification, and can be engineered to control drug encapsulation, release, stability, and cellular or tissue targeting [50,51]. Keturakis et al. encapsulated CUR within biodegradable polymeric NPs to enhance solubility, protect against premature degradation, and, critically, enable controlled drug release kinetics of CUR to explore its cardioprotective potential [52]. Abraham et al. developed NRG-loaded chitosan nanoparticles (NRG/CS-NPs) incorporated into a topical gel for diabetic wound management. The optimized NRG/CS-NPs exhibited nanoscale size, high entrapment efficiency, sustained drug release, and favorable biocompatibility, while the NRG/CS-NP gel demonstrated enhanced wound-site retention and promoted in-vitro cell migration, supporting its potential for diabetic wound healing [53]. Göl et al. developed QTN-loaded PLGA nanoparticles using a nanoprecipitation method and functionalized their surfaces with two distinct triphenyl phosphonium (TPP)-containing conjugates, TPP–Tween 80 (TT80) and PLGA–PEG–TPP (PPT), to achieve mitochondria-targeted delivery. The targeted nanoparticles exhibited high cellular viability and significantly reduced ROS production under inflammatory conditions, while JC-1 analysis supported improved mitochondrial membrane potential, highlighting their potential for mitigating oxidative stress-associated inflammation [54].

Micelles are self-assembled colloidal structures formed by amphiphilic surfactant molecules in aqueous media,

typically above their critical micelle concentration. Their hydrophilic segments orient toward the aqueous phase, whereas hydrophobic segments associate within the micellar core, creating a hydrophobic domain capable of solubilizing poorly water-soluble compounds. These properties make micelles attractive nanocarriers for flavonoids, which often exhibit limited aqueous solubility and bioavailability [55,56]. Singla et al. investigated Pluronic (poloxamer)-based polymeric nanomicelles for the encapsulation of the hydrophobic phytocompounds NAR and BCL. Pluronics are amphiphilic triblock copolymers composed of poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide) (PEO–PPO–PEO), which can self-assemble into micelles with a hydrophobic PPO core and hydrophilic PEO corona. Among the investigated formulations, Pluronic P84 exhibited superior encapsulation of both phytocompounds, while the solvent evaporation method provided substantially higher drug solubilization than the direct dissolution method. The authors therefore identified solvent evaporation as a more convenient and efficient approach for preparing NAR- and BCL-loaded Pluronic micelles [57].

Dendrimers are highly branched, three-dimensional synthetic macromolecules characterized by a central core, successive generations of regularly branched monomeric units, and a functionalized peripheral surface. Their well-defined molecular architecture, nanoscale dimensions, and tunable internal cavities and surface functionalities make them attractive nanocarriers for drug encapsulation, controlled release, and targeted delivery [58–60]. Zhang et al. developed a hybrid dendrimer-based micellar delivery system for the co-delivery of PARP-1 siRNA and QTN for cataract management. The system incorporated poly(amidoamine) (PAMAM) dendrimer units within an amphiphilic DSPE–PEG-based architecture, enabling electrostatic complexation of PARP-1 siRNA with the dendrimer moieties and encapsulation of hydrophobic QTN within the micellar lipid core. Surface modification with cyclic RGD further enhanced corneal retention and transcorneal delivery. In a selenite-induced cataract rat model, the formulation improved antioxidant responses, reduced PARP-1 expression and lipid peroxidation, and attenuated cataract-associated inflammatory responses, highlighting its potential as a multifunctional ocular nanocarrier [61].

NEs are kinetically stable colloidal dispersions of two immiscible liquids, typically oil and water, with nanoscale droplets commonly ranging from approximately 20 to 200 nm. Depending on the dispersed and continuous phases, they may exist as oil-in-water (O/W) or water-in-oil (W/O) systems and are generally stabilized by surfactants and/or co-surfactants to minimize droplet coalescence and phase separation [62,63]. Juan Li et al. developed a dihydroMYR (DMYR)-loaded stiff–soft hybrid biomimetic NEs (DMYR-hNE) for oral liver-targeted delivery and treatment of early nonalcoholic fatty liver disease. The system comprised a DMYR-loaded PLA nanoparticle as a stiff core surrounded by a biomimetic lipid-based soft shell. DMYR-hNE enhanced gastrointestinal absorption, hepatic accumulation, and systemic exposure of DMYR and improved hepatic lipid accumulation and inflammation in an early NAFLD mouse model, demonstrating its potential as a biomimetic nanocarrier for liver-targeted delivery [64]. The findings of Zadeh et al. suggested that the nano-emulsion containing EGCG has significant anticancer activity and may be a suitable treatment option for the management of squamous cell carcinoma of the head and neck [65].

Niosomes are self-assembled, nanoscale or submicron vesicular drug-delivery systems formed primarily from non-ionic surfactants, often in combination with cholesterol or other membrane-stabilizing lipids. Their amphiphilic bilayer structure enables the encapsulation and delivery of both hydrophilic and lipophilic therapeutic agents, making niosomes versatile carriers for drug delivery and other biomedical applications [66,67]. Riazi et al. in their study evaluated the anti-cancer activities of MYR-loaded PEGylated niosomes [68]. Alsaidan et al. developed the APN-loaded noisome gel to improve transdermal delivery and got significantly higher antioxidant activity compared to pure APN [69].

Ethosomes are deformable vesicular nanocarriers composed primarily of phospholipids, ethanol, and water. The presence of ethanol imparts high membrane flexibility and enhances vesicle deformability, facilitating penetration across the stratum corneum and improving the cutaneous and transdermal delivery of active pharmaceutical ingredients. Depending on the formulation and drug properties, ethosomes can enhance localized skin deposition or facilitate systemic delivery following transdermal administration [70,71]. Zhang et al. developed PHL-loaded propylene glycol-based ethosomes to enhance the physicochemical stability, skin permeation, and antioxidant performance of PHL. The incorporation of propylene glycol and ethanol into the vesicular system improved the deformability and skin-delivery characteristics of the formulation, highlighting its potential as a topical nanocarrier for enhancing the dermal delivery and antioxidant activity of poorly water-soluble phytoconstituents. [72] [57]. Raghav et al. developed KMF-loaded ethosomes and evaluated their potential for the treatment of diabetic foot ulcers. The ethosomal formulation was prepared using the cold method and systematically optimized using a Box–Behnken design to identify critical formulation variables and optimize the physicochemical characteristics of the vesicles. The optimized KMF-loaded ethosomes demonstrated favorable characteristics for topical delivery, supporting their potential as a vesicular nanocarrier for diabetic wound management. [73].

Transfersomes are highly deformable phospholipid-based vesicular nanocarriers containing edge activators, typically surfactants such as sodium cholate or Tween 80, which impart high membrane flexibility and facilitate passage through the skin barrier. Wang et al. evaluated PHL-loaded transfersomes and their gel formulations using in vitro skin permeation and preliminary antioxidant studies. The results demonstrated enhanced transdermal penetration and antioxidant activity of the PHL-loaded formulations, supporting their potential as flexible vesicular systems for transdermal delivery of poorly water-soluble phytoconstituents [74,75]. Hsieh et al. developed and characterized catechin-loaded transfersomes to enhance the topical delivery and skin permeability of catechin. The optimized transfersomal formulation improved cutaneous penetration and exhibited enhanced photoprotective and antioxidant effects against ultraviolet radiation-induced oxidative damage, highlighting its potential as a vesicular nanocarrier for topical skin protection [76].

Exosomes are small extracellular vesicles of endosomal origin, typically ranging from approximately 30–150 nm in

diameter, that are generated within multivesicular endosomes and released into the extracellular environment through fusion of multivesicular bodies with the plasma membrane. They contain diverse biomolecular cargo, including proteins, lipids, and nucleic acids, and play important roles in intercellular communication and emerging nanomedicine applications [77–79]. Zhao et al. developed a QTN-loaded exosome delivery system (Exo-QTN) to enhance the aqueous solubility, ocular bioavailability, and corneal permeability of QTN for myopia prevention. The Exo-QTN formulation prolonged precorneal retention and exhibited significant efficacy in a form-deprivation myopia guinea-pig model, reducing refractive-error progression and axial elongation. Mechanistically, Exo-QTN alleviated scleral extracellular-matrix remodelling by suppressing endoplasmic-reticulum stress and ferroptosis-related pathways, highlighting its potential as an exosome-based nanocarrier for ocular delivery of QTN [80]. He et al. developed a dissolving microneedle-based co-delivery system incorporating human umbilical cord mesenchymal stem cell-derived exosomes (hUMSC-Exo) and EGCG for the treatment of UV-induced skin damage. The hUMSC-Exo/EGCG-loaded microneedles enabled efficient transdermal co-delivery and enhanced local retention of both therapeutic agents. In vitro and in vivo studies demonstrated synergistic antioxidant and anti-inflammatory effects, with reduced oxidative stress and DNA damage and enhanced tissue regeneration, highlighting the potential of this platform for mitigating UV-induced skin injury and photoaging [81].

Inorganic nanoparticles (INPs) are nanoscale materials composed predominantly of inorganic elements or compounds, including metals, metal oxides, metal sulfides, silica, and semiconductor materials. Their distinctive physicochemical properties, such as tunable size, morphology, surface chemistry, optical characteristics, and catalytic activity, make them versatile platforms for drug delivery, imaging, biosensing, phototherapy, and other biomedical applications [82–84]. Milanezi et al. developed and characterized QTN-capped gold nanoparticles (AuNPsQct) and evaluated their antioxidant, antimicrobial, and cytotoxic properties. The AuNPsQct exhibited enhanced nitric oxide radical-scavenging activity compared with free QTN and demonstrated strong antifungal activity against Aspergillus fumigatus, while showing no cytotoxicity toward L929 fibroblast cells. These findings highlight the potential of QTN-functionalized gold nanoparticles as multifunctional inorganic nanocarriers for biomedical applications [85].

Phytosomes are phyto-phospholipid molecular complexes in which plant-derived bioactive constituents or standardized extracts interact with phospholipids, typically phosphatidylcholine, to form lipid-compatible complexes. This molecular association can enhance the solubility, membrane permeability, absorption, and systemic bioavailability of poorly absorbed phytoconstituents, thereby improving their pharmacokinetic and therapeutic potential [86,87]. Talaat et al. developed FIS-loaded cholephytosomes to enhance its antitumor activity against breast cancer. Stearylamine-bearing cationic cholephytosomes (mPHY) were designed to promote interaction with negatively charged, externally exposed phosphatidylserine on breast cancer cells, while further surface decoration with hyaluronic acid generated CD44-targeted cholephytosomes (HPHY). Both modified systems improved FIS complexation, aqueous–lipid partitioning, and sustained drug release, and exhibited enhanced cytotoxicity against MDA-MB-231 breast cancer cells compared with free FIS and conventional FIS–phospholipid complexes. These findings highlight the potential of surface-engineered cholephytosomes for targeted phytochemical delivery in breast cancer [88]. Sabzichi et al. developed LUT-loaded nanophytosomes to improve the bioavailability of LUT and facilitate passive delivery to breast cancer cells. In MDA-MB-231 cells, co-treatment with LUT nanophytosomes and doxorubicin produced greater cytotoxicity than doxorubicin alone, accompanied by suppression of Nrf2 and its downstream genes, including HO-1 and MDR1. These findings suggest that LUT nanophytosomes may enhance the chemosensitizing potential of Lut and improve the therapeutic efficacy of doxorubicin against breast cancer [89].

A comparative analysis of major nanocarrier systems based on composition, encapsulation efficiency (EE), stability, biocompatibility, targeting capability, scalability, cost considerations, toxicity, regulatory considerations, and biological applications is presented in **Table 2** [90–97]. Various flavonoids have been incorporated into diverse nanoformulations to overcome their intrinsic limitations, including poor aqueous solubility, limited permeability, chemical instability, and low bioavailability, thereby improving their therapeutic performance. The selection of an appropriate nanocarrier depends on the physicochemical properties of the flavonoid, intended route of administration, target site, and desired release profile. In **Table 3** presented comparative summary of representative flavonoid-based nanoformulations with respect to particle size, EE, release characteristics, advantages, limitations, and biological applications [98–103]. The pharmacokinetic profiles of selected flavonoids in their free and nano formulated forms are summarized in **Table 4**.

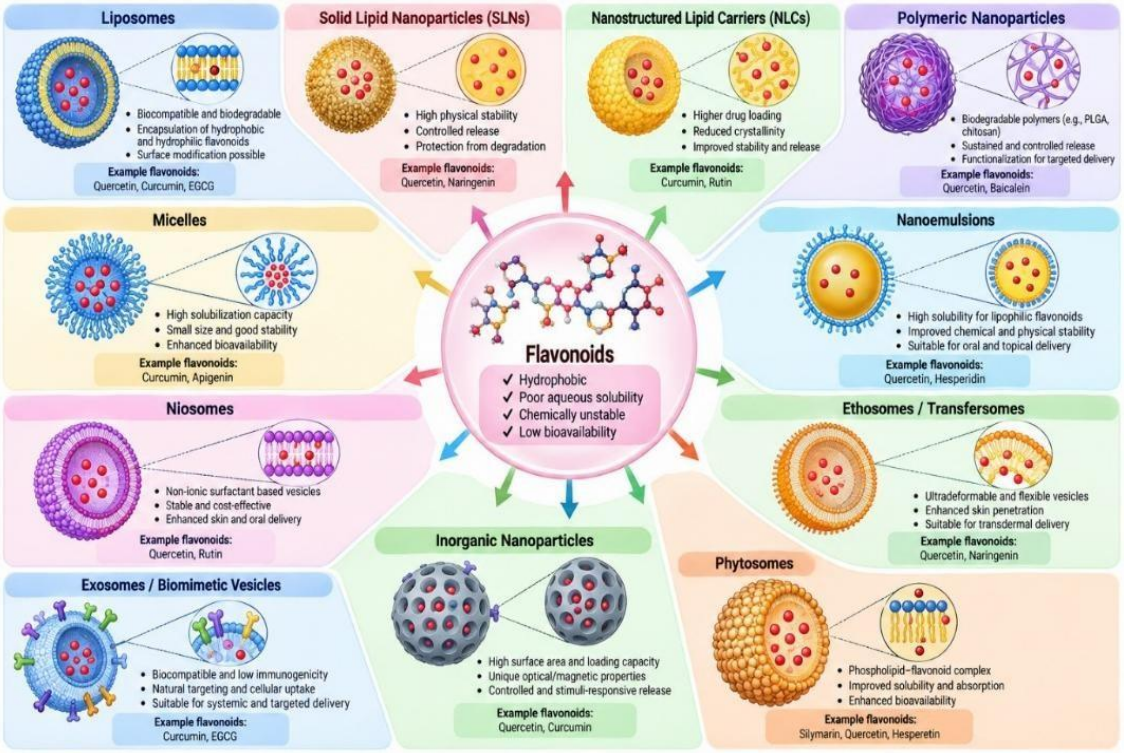


Fig. 5. Nanocarrier platforms for flavonoid and selected polyphenols delivery. (Created with BioRender.com. Adapted by the authors).

Table 2: Comparative characteristics, translational potential, and biomedical applications of major nanocarrier systems.

Nano-carrier system	Composition	Encapsulation efficiency	Stability	Biocompatibility	Targeting ability	Scale-up potential & Overall cost	Toxicity	Regulatory approval	Applications
Liposomes	Phospholipid bilayer vesicles; Phospholipids, cholesterol, and hydration medium	high for hydrophilic and amphiphilic drugs	Moderate; can face leakage, oxidation, fusion, and storage instability	High, especially with approved phospholipid excipients	Good surface functionalization potential	Good to moderate; manufacturing is relatively mature but scale-up can still be challenging. Overall cost: Moderate to high	Usually low to moderate, but depends on composition	Yes; several liposomal products are approved, including amikacin liposome inhalation suspension	Cancer, antifungals, antibiotics, vaccines, transdermal and parenteral delivery
SLNs	Solid lipids stabilized by surfactants and cosurfactants	High for lipophilic drugs and Moderate for some hydrophilic drugs	Good physical stability, but may show polymorphic transitions and drug expulsion on storage	High to good	Moderate; can be surface-modified	Good; uses scalable lipid-processing methods. Overall cost: Low to moderate	Generally low, though excipient choice matters	Limited approved products compared with liposomes	Oral, dermal, pulmonary, and controlled-release delivery
NLCs	Mixture of solid and liquid lipids along with surfactants and cosurfactants	higher than SLN because the imperfect lipid matrix accommodates more drug	Improved and better stability compared to other lipid systems, but still formulation-sensitive	High to good	Moderate; can be ligand-functionalized	Good; more scalable than complex biomimetic carriers. Overall cost: Moderate	Low to moderate	Few approved products relative to liposomes	Oral, dermal, ocular, and tumor delivery
PNPs	Natural or synthetic polymers such as chitosan, PLGA,	Variable; can be high, especially for hydrophobic drugs and controlled-	Good if polymer is stable; degradation rate can be tuned	High to Good when biocompatible/ biodegradable polymers are	Good, especially with ligand conjugation	Moderate; reproducible large-scale production can be	Low for biodegradable polymers, but cationic systems can	Some polymeric systems and excipients are clinically	Gene delivery, cancer therapy, protein/peptide delivery,

	Eudragit with crosslinking agents	release systems		used		difficult for some methods. Overall cost: moderate	be more toxic	used, but fewer are marketed as stand-alone nano drugs than liposomes	sustained release
Micelles	Amphiphilic surfactant or block-copolymer self-assemblies	Moderate to high for hydrophobic drugs, but often lower payload retention than vesicles under dilution	Sensitive to dilution because of critical micelle concentration; low CMC improves stability	Good, but depends on surfactant/ polymer	Moderate to good with surface engineering	Good; but stability during storage and dilution is a challenge. Overall cost: Low to moderate	Low to moderate	Limited approved products compared with liposomes	Solubilization of poorly soluble drugs, cancer therapy, intravenous delivery
Dendrimers	Highly branched macromolecules with internal cavities and surface groups; synthetic polymers and surface modifiers	Very High for some drugs due to internal voids and multivalent binding	Good structural control, but surface charge can affect colloidal stability	Moderate; depends strongly on generation and terminal groups	Very good due to precise surface functionalization	Moderate; synthesis is complex and costly. Overall cost: High	Can be significant for cationic dendrimers	Very limited clinical approval	Gene delivery, imaging, anticancer delivery, diagnostics
NEs	Oil-in-water or water-in-oil nano scale emulsions stabilized by surfactants, cosurfactants	Moderate to high; Good for lipophilic drugs; less suitable for hydrophilic drug without special design	Thermodynamically unstable, though kinetically stable if well formulated	Good if excipients are biocompatible	Moderate; can be surface-modified	Good; comparatively easy to manufacture at scale. Overall cost: Low	Low to moderate	Some NE-based products and excipients are in use, but fewer than liposomes	Oral, topical, ocular, vaccine, and antimicrobial delivery
Niosomes	Non-ionic surfactant	Moderate; Good for hydrophilic	Better chemical stability than	Good, though less established	Moderate to good	Good; cheaper	Low to moderate	Very limited approved	Transdermal, ocular, oral,

	vesicles, often with cholesterol and hydration medium	and hydrophobic drugs and formulation-dependent	liposomes	than liposomes		materials make scaling attractive. Overall cost: Low to moderate		products	and vaccine delivery
Ethosomes	Phospholipids plus high ethanol content and water	High for dermal/transdermal delivery	Good short-term performance; ethanol can affect long-term stability	Good for topical use, but ethanol limits some systemic uses	Strong skin-targeting/ permeation enhancement	Moderate; composition is simple but ethanol handling matters. Overall cost: Moderate	Low for topical use, but irritation is possible	No major FDA-approved systemic products highlighted in the sources	Transdermal vaccines, peptides, anti-inflammatory and cosmetic delivery
Transfersomes	Flexible phospholipid vesicles with edge activators (surfactants), and water	High especially for skin delivery	Flexible; less stable than liposomes; stability dependent on surfactant load	Good	Strong deformability helps penetration through skin	Moderate; formulation control is important. overall cost: moderate	Low to moderate	Very limited approval history	Transdermal drug delivery
Exosomes	Natural extracellular vesicles secreted by cells	Lower and variable with complex loading methods	Very stable biologically, but manufacturing consistency is difficult	Excellent natural biocompatibility	Very good intrinsic targeting and cell communication properties	Poor to moderate; isolation and standardization are major barriers. Overall cost: Very high	Low intrinsic toxicity, but source-dependent risks exist	No routine FDA-approved exosome drug products in the cited source	Gene delivery, regenerative medicine, immunotherapy, diagnostics
Inorganic NPs	Metal and Metal oxides, Silica, Carbon nanotubes, Graphene oxide, Fullerenes, Quantum dots, etc.	Variable; depends on surface chemistry and pore design	High physicochemical stability	Lower than many lipid/polymer systems unless surface-engineered	Excellent for imaging and multimodal targeting	Moderate; synthesis can be reproducible, but regulatory barriers are high. Overall cost:	Can be higher, especially if non-biodegradable or cationic	Few approved therapeutic products; more common in diagnostics	Imaging, theranostics, photothermal therapy, biosensing

Phytosome	Formed by non-covalent interaction between phytochemicals and phospholipids, with cholesterol, stabilizer or penetration enhancer	High for lipophilic phytochemicals	Short to medium term stability and oxidation/hydrolysis of phospholipids and phytochemical degradation major concerns	High, especially with approved or food grade phospholipids	Moderate; can be surface-modified	Moderate to high Moderate; solvent handling, removal and lipid oxidation main scale-up issues. Overall cost: Moderate to high	Usually low to moderate, but depends on composition	No routine FDA-approved Phytosome drug products, but some phytochemical phospholipid complexes have progressed to marketed nutraceuticals or cosmetic products	Oral, Topical/dermal delivery, Parenteral and targeted therapy, food or nutraceuticals

Table 3: Comparative characteristics, advantages, limitations, and applications of representative flavonoid-based nanoformulations.

Flavonoids based-Nano formulation	Typical size (nm)	EE (%)	Release profile	Advantages	Limitations	Applications
Liposomes; (QTN, RUT, LUT, APN)	50 to 500	Moderate to high; (50 to 95)	Fast to sustained release	Biocompatible, versatile for hydrophilic and lipophilic drugs	Physical instability, leakage, oxidation, costlier sterilization and scale-up	Oral, topical, transdermal, targeted delivery
SLNs (QTN, NRG, HSP, KMF)	50 to 300	Moderate; (30 to 90)	Sustained release; matrix diffusion controlled	Good stability, scalable, protects labile drugs	Drug expulsion during storage, limited loading due to solid matrix	Oral, topical, parenteral
NLCs (QTN, LUT, APN, chrysin)	50 to 300	Higher than SLNs; (30 to 95)	Sustained release with reduced burst effect	Better loading than SLNs, improved stability, less drug leakage	Formulation complexity; lipid selection is critical	Oral, topical, transdermal
PNPs; (QTN, BCL, catechin, FIS)	10 to 1000	High; (70 to 94)	Controlled, prolonged, sometimes stimuli-responsive	Strong control over release, surface functionalization possible	Residual solvent concerns, polymer toxicity, scale-up issues	Oral, parenteral, targeted delivery
Micelles; (QTN, genistein, LUT, KMF)	10 to 100	Low to moderate; (variable by system)	Faster release unless specially stabilized	Excellent solubilization of poorly soluble drugs	Low dilution stability, possible premature dissociation	Oral, intravenous, solubilization-based delivery
Dendrimers; (QTN, RUT, APN, BCL)	Less than 100	Moderate to high; (Variable)	Highly tuneable, controlled release	Precise structure, many surface groups, high targeting potential	Expensive synthesis, possible cytotoxicity with cationic surfaces	Targeted, parenteral, diagnostic delivery
NE; (QTN, hesperetin, NRG, daidzein)	20 to 200	Moderate to high; (Variable)	Rapid release and absorption	Easy to prepare, improve solubility and bioavailability	Thermodynamic instability, limited sustained release	Oral, topical, transdermal

Niosomes; (QTN, catechin, RUT, APN)	100 to 1000	Moderate to high; (40 to 95)	Controlled to sustained release	Stable, cost-effective, non-ionic surfactants improve safety	Vesicle aggregation, leakage, batch variability	Oral, topical, transdermal
Ethosomes; QTN, RUT, HSP, NRG)	100 to 400	Moderate; (50 to 70)	Sustained transdermal release	Excellent skin permeation, flexible vesicles	High ethanol content can cause irritation and instability	Transdermal, topical
Transfersomes; (QTN, LUT, APN, catechin)	100 to 400	Moderate; (50 to 70)	Sustained and enhanced permeation	Very deformable, crosses skin barriers well	Sensitive to composition, leakage under stress	Transdermal, topical
Exosomes; (QTN, KMF, APN, LUT)	30 to 150	Highly variable; (not standardized like synthetic systems)	Biological, targeted, cell-dependent kinetics	Natural origin, good biocompatibility, intrinsic targeting	Isolation and loading are complex, expensive, and difficult to standardize	Targeted delivery, biologics, gene and drug delivery
INPs; (QTN, KMF, RUT, catechin)	1 to 100	Not usually expressed as classical EE%; (often surface-loaded)	Rapid to medium; can be engineered for controlled release	Strong imaging and theranostic utility, robust chemistry	Potential toxicity, limited biodegradability for some materials	Targeted delivery, imaging, theranostics
Phytosome; (QTN, silymarin, RUT, LUT)	100 to 500	Variable; (improved complexation of phytoconstituents)	Moderately sustained release	Enhances solubility, absorption, and oral bioavailability of herbal drugs	Limited to suitable phytoconstituents; formulation optimization is needed	Oral phytopharmaceutical delivery

Table 4: Comparative pharmacokinetic parameters of selected flavonoids following administration as free and nano-formulated preparations.

Nano-formulation	Species/study type	AUC		Cmax		Tmax		t1/2		Bioavailability*	MRT
		FRF	NFF	FRF	NFF	FRF	NFF	FRF	NFF		FRF
Micelles	Human; double-blind, randomized, crossover study	456.9 (ng·h/mL)	914.8 (ng·h/mL)	42.1 (ng/mL)	87.3 (ng/mL)	4.2 (h)	4.8 (h)	11.0 (h)	25.3 (h)	2-fold increase	17.2 (h)
LipoMicel (Micelles)	Human; open-label, crossover study	77.3 (ng·h/mL)	543.1 (ng·h/mL)	6.8 (ng/mL)	52.5 (ng/mL)	3.0 (h)	5.9 (h)	NR	NR	7-fold increase	NR
Phytosome	Human; randomized crossover studies	4774.93 (ng·min/mL)	96,163.87 (ng·min/mL)	10.93 (ng/mL)	223.10 (ng/mL)	290 (min)	202.50 (min)	375.63 (min)	226.84 (min)	20-fold increase	410.41 (min)
Micelles	Sprague Dawley rats	40.99 (µg·h/mL)	123.79 (µg·h/mL)	1.38 (µg/mL)	6.32 (µg/mL)	1.34 (h)	1.56 (h)	3.45 (h)	4.89 (h)	3-fold increase	5.42 (h)
Micelles	Male Sprague Dawley rats	350.5 (ng·h/mL)	934.7 (ng·h/mL)	49.6 (ng/mL)	239.2 (ng/mL)	3.67 (h)	0.67 (h)	4.73 (h)	4.32 (h)	2.6-fold increase	NR
Lipid based nano-formulation	Male Sprague Dawley rats	NR	NR	4.20 (µg/mL)	9.48 (µg/mL)	3 (h)	1 (h)	NR	NR	2.24-fold increase	NR
Poly (lipoic acid) nanoparticles	Male Sprague Dawley rats	19 (ng·h/mL)	710 (ng·h/mL)	8.2 (ng/mL)	130 (ng/mL)	0.083 (h)	2.1 (h)	0.22 (h)	1.7 (h)	37-fold increase	0.32 (h)
NE against suspension	Male New Zealand white rabbits	992 (ng·h/mL)	4337 (ng·h/mL)	122.56 (ng/mL)	286.51 (ng/mL)	2 (h)	2 (h)	11.09 (h)	9.05 (h)	4-fold increase	8.79 (h)
Nano cochleates	Male Wistar albino rats	95.96 (µg·h/mL)	179.55 (µg·h/mL)	22.0 (µg/mL)	38.8 (µg/mL)	6 (h)	8 (h)	6.12 (h)	11.1 (h)	2-fold increase	NR
Hybrid-hydrogel	Human; randomized, double-blinded crossover design	27.44 (ng·h/mL)	510.86 (ng·h/mL)	14.48 (ng/mL)	112.41 (ng/mL)	1.12 (h)	3.38 (h)	1.91 (h)	4.74 (h)	18.6-fold increase	NR
Nanocrystals	Male Sprague Dawley rats	35.92 (µg·h/mL)	72.19 (µg·h/mL)	2.51 (µg/mL)	4.43 (µg/mL)	3.33 (h)	2.92 (h)	12.57 (h)	15.43 (h)	2-fold increase	9.29 (h)

AUC: Area under the curve, which quantifies total drug exposure over the time by measuring the area under the plasma concentration-time curve; **Cmax:** maximum plasma concentration; **Tmax:** time taken to reach C_{max}; $t_{1/2}$: elimination half-life is the time required for the amount or concentration of a drug to decrease by half; **MRT:** mean residence time**; FRF:** Free or non-nano formulated Flavonoids; **NFF:** Nano-formulated Flavonoids; *Increase in bioavailability of flavonoid in nano formulations (NFF) compared to free or non-nano formulated form of flavonoids (FRF); **NR**: Not reported.

Applications of flavonoid-based Nano formulations in therapeutics

The selection of nanocarriers for flavonoid delivery is largely governed by the physicochemical properties of the flavonoid, intended administration route, biological barriers, target site, and desired release profile. Liposomes, SLNs, NLCs, micelles, PNPs, and dendrimers are widely investigated to improve flavonoid solubility, physicochemical stability, permeability, bioavailability, controlled release, and, where appropriate, targeted delivery, with their therapeutic performance generally evaluated against the corresponding free flavonoid. Lipid-based systems such as NEs, niosomes, ethosomes, and transfersomes are particularly attractive when enhanced solubilization, membrane interaction, skin or mucosal permeation, and controlled topical or systemic delivery are required. Exosomes and inorganic nanoparticles provide additional opportunities for biologically mediated targeting, imaging, combined therapeutic–diagnostic applications, and multifunctional delivery, although their translational development remains subject to formulation, safety, manufacturing, and regulatory challenges. Phytosomes, in contrast, are primarily employed to enhance the absorption and systemic exposure of poorly bioavailable flavonoids through formation of phospholipid–phytoconstituent complexes [102,115–120]. **Table 5** summarizes representative flavonoid-based nanoformulations developed using the nanocarrier platforms discussed above, with emphasis on particle size, encapsulation efficiency (EE), release characteristics, and key therapeutic outcomes, thereby illustrating the potential of nanocarrier engineering to enhance the delivery and biological

performance of flavonoids. Also, in **Fig. 6** depicted some therapeutic applications of flavonoid-based nanoformulations.

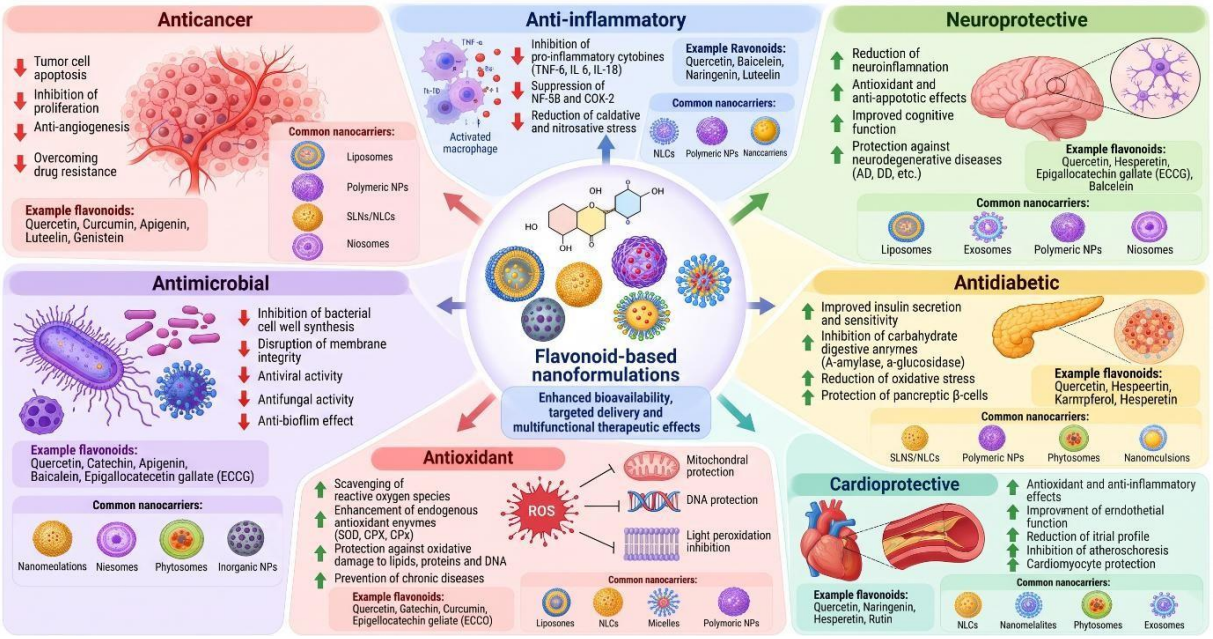


Fig. 6. Some therapeutic applications of flavonoid-based nanoformulations (Created with BioRender.com. Adapted by the authors).

Table 5: Comparative overview of representative flavonoid-based nanoformulations: particle size, encapsulation efficiency, release characteristics, and key therapeutic findings.

Flavonoid	Nano formulation	Size (nm)	EE (%)	Release	Major findings	Ref.
Antioxidant activity						
LUT	Liposomes	412.8	86.6	90% in 24h (Controlled release)	Significant improvement in cognitive function and reduces the pathology of Alzheimer's disease	[121]
MYR	NLCs	89.7	80.81	biphasic release pattern	Improved behaviour and neurotransmitter levels	[122]
KMF and CUR	Phytosomes	167.1 to 497.3	94.12	90.52% (KMF) and 94.67% (CUR) in 12h	Increased antioxidant potential from the combined impact of flavonoids	[123]
QTN	Niosomes	195	82.77	87.16% in 24h (Sustained release)	Improved bioavailability and performance in laboratory and animal investigations	[124]
QTN	SLNs	183.3	97.49	91.65% in 48h (Sustained release)	Improved antioxidant properties, degradation resistance, and overall stability	[125]
Anti-inflammatory activity						
Rhoifolin	PNPs	204	45	Sustained release for 96h	Nanoparticles superior in mitigating the histopathological changes	[126]
FIS	Lipid polymer hybrid nanoparticles	125.39	61.76	Sustained release over 48h	Significant reduction in NF-κB activity, NLRP3, TNF-α, IL-1β, IL-6, and C-reactive protein (CRP) levels in pancreatic tissue	[127]
NRG	Nano-emulsions	220	80	Steady release profile	Reduction in the mRNA levels of inflammatory mediators	[128]
LUT	NLCs	202 to 538	84.21 to 96.53	Sustained drug release up to 24h	Enhanced skin deposition resulting in improved anti-psoriatic efficacy	[129]
Xanthorrhizol and CUR	NLCs	130	83	Sustained release profile	Enhanced anti-inflammatory activity through modulated prostaglandin and mitogen-activated protein kinase pathways in a dose-dependent manner	[130]

Anticancer/Cytotoxic activity						
FIS	NLCs	135	78.16	74.79% in 96h (Sustained release)	Substantial inhibition of melanoma-associated metastasis both in lungs and liver	[131]
QTN	SLNs	132.16	97.8	41.12% in 48h (Delayed release)	Greater cytotoxic action of nanoparticles compared to free QTN, with an IC50 of approximately 49 µM/mL on Caco-2 cells, compared to 128 µM/mL for free QTN	[132]
NRG	PNPs	44.14	77.72	78.46% (At pH 5.8)	Higher cytotoxic efficacy in MCF-7 cells, with an IC50 of 31.51 µg/mL	[133]
QTN	Micelles	107.16	77.46	92.78% in 72h (Sustained release)	Micelles showed 1.7 times higher cytotoxicity against C6 and U87MG cells compared to pure QTN	[134]
CUR and QTN	Liposomes	327	82.30 (CUR) and 83.28 (QTN)	77.19% (CUR) and 80.23% (QTN)	Synergistic effect on inhibiting cancer cells	[135]
Neuroprotective activity						
QTN	PNPs	161.4	86.74	98 % over 48h (Sustained release)	Enhanced intestinal permeability, absence of hippocampal toxicity, and effective blood-brain barrier (BBB) transport	[136]
QTN	Liposome	116–124	89.9	Slow Sustained release	Enhanced brain target ability allowed liposomes to deliver more QTN to neuronal cells	[137]
QTN	Transferosomes	171.4	78.2	61.3% in 3h	Effective brain targeting via the intranasal route was achieved	[138]
LUT	Bile-salt-based nano-vesicles (Bilosomes)	153.2	70.4	92.8 to 98.7% in 24h	Preservation of intact and well-organized hippocampal CA3 regions with intact neurons and minimal neuronal degenerative changes were achieved with LUT-bilosomes	[139]
KMF	SLNs	451.2	84.92	93.24% (Controlled release)	Decreased level of ROS and some mediators like NF-κB and p-STAT3	[140]
Antidiabetic activity						
QTN	PNPs	130.1	79.72	86.10 % in 24h (Sustained release)	Fasting blood glucose decreased from 292.9 to 107.7 mg/dL, along with improved lipid profiles	[141]
CUR	Nano CUR (micronization process)	119.9 (CURF) and 117 (CURA)	75 (CURA) and 85 (CURF)	75% in 180 min and 82.5% in 210 min (Controlled release)	Substantial reduction in fasting blood sugar levels (from 392 to 187 mg/mL)	[142]
LUT and Diosmin	Selenium NPs	47.84	86.1	70% in 40h (Initially fast then slow)	Significantly restored blood glucose, lipid profile, glycogen, glycosylated hemoglobin, and insulin levels	[143]
QTN	NE	153.1	73.25	91.10 % in 12h	Significant bioavailability enhancement (5.38-fold) exhibited potential therapeutic benefits	[144]
NRG	PNPs	163.4	93.2	91.60% in 24h (Sustained release)	Pharmacokinetic results suggested high absorption profile (AUC_{0-24}) and antidiabetic activity for nanoparticles compared to pure NRG	[145]
Cardioprotective activity						

PHL	Polymeric NCs	105.8	92.36		Reduction of myocardial infarct size by 46%, compared to just a 13% reduction with free PHL	[146]
QTN	PNPs	150.7	64.01	biphasic release maximum at pH 5.5	Significant decrease in indicators of cardiac injury (troponin I and CK-MB). Also reduced cardiac histopathological damage and inflammation	[147]
NRG	Lignin NPs	138.24	91.53	88.75% in 24h	Significant reduction in cardiac injury markers like CK-MB, LDH, AST and MDA. Restoration of cardiac tissue damage and improved size of the cardiac infarction was observed	[148]
BCL	NPs	102.21	26.43	Slow and sustained release (pH 5.5)	Reduced infarct size, ameliorated cardiac fibrosis, and improved overall heart function	[149]
RUT	Nanoparticles	179 to 209	45	Sustained release in 96h	Proinflammatory cytokines and levels of intracellular NLRP3 and MyD-88 were significantly lowered in the cells	[150]
Antimicrobial activity						
NRG	PNPs	85	89.5	90% in 48h (Sustained and prolonged release)	Co-delivered ciprofloxacin and NRG significantly enhanced antimicrobial activity compared to CIP alone against E. coli and S. aureus	[151]
QTN	Nanostructured lipid carrier (NLCs)	<200	>99	36.3% in 72h (Slow and sustained release)	Enhanced antibacterial activity against Staphylococcus aureus and NLCs were capable of transporting QTN to an intranuclear location within HaCaT cells	[152]
NRG	SLNs	50	97.9	55% in 24h	Antibacterial activity against S. aureus strains which was the result of interaction between surfactant-coated SLNs with the bacterial surface	[153]
QTN	Niosome	57.4 (QCT) and 178.9 (QCT-SA)	75.9 (QCT) and 59.6 (QCT-SA)	36% (QCT) and 25% (QCT-SA) in 24h	Niosomal drug delivery system for QTN to combat Pseudomonas aeruginosa infections, particularly drug-resistant strains and biofilms	[154]
NRG	Hybrid PNPs	246	83.5	89.62% in 24h	Enhanced antibacterial activity against Escherichia coli and Staphylococcus aureus with lower MIC values and larger zones of inhibition	[155]

Antioxidant activity

Flavonoids are important naturally occurring antioxidants that can attenuate oxidative stress through multiple complementary mechanisms. Their antioxidant activity involves direct scavenging of reactive oxygen species and reactive radicals, chelation of redox-active metal ions such as Fe^{2+} and Cu^{2+}, and modulation of endogenous antioxidant defenses, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). These mechanisms contribute to the ability of flavonoids to mitigate oxidative damage and may underlie their protective effects against a range of oxidative stress-associated disorders [156–161]. Abbas et al. developed LUT-loaded chitosan-decorated nanoparticles (LUT-CHS) as a non-invasive intranasal delivery system for the management of cognitive dysfunction associated with Alzheimer's disease (AD). In a sporadic AD mouse model, intranasal administration of LUT-CHS improved short- and long-term spatial memory, enhanced neuronal survival, and reduced amyloid plaque burden. The formulation also enhanced antioxidant activity and attenuated pro-inflammatory responses, while reducing Aβ aggregation and hyperphosphorylated tau levels by approximately 50% compared with the disease-model control. These findings highlight the potential of LUT-CHS as a brain-targeted nanocarrier for mitigating multiple pathological features of AD [162]. Halder et al. developed and optimized MYR-loaded nanostructured lipid carriers (MYR-NLCs) to enhance brain bioavailability and mitigate cognitive impairment in an amyloid-β ($Aβ_{1–42}$)-induced rat model of Alzheimer's disease (AD). The optimized MYR-NLCs exhibited a particle size of 89.7 ± 26.0 nm and an entrapment efficiency of 80.81 ± 10.39%. Compared with free MYR, MYR-NLCs increased systemic exposure and demonstrated enhanced brain targeting. In $Aβ_{1–42}$-induced AD rats, MY-NLC treatment significantly improved cognitive and behavioral performance and modulated brain neurotransmitter levels, supporting its potential as a lipid-based nanocarrier for brain delivery of MYR in AD [163]. Kumar et al. successfully developed and characterized flavonosomes loaded with KMF and CUR, demonstrating improved bioavailability and stability and enhanced antioxidant activity compared to the individual flavonoids. The IC_{50} values were 228.20 μg/mL for KMF, 175.51 μg/mL for CUR, and 158.19 μg/mL for the flavonosome, indicating enhanced antioxidant potential due to the combined effect of the flavonoids [164]. The research conducted by Revankar et al. resulted in the successful formulation development of QTN-loaded niosomes with favourable properties for Parkinson's disease. The enhanced bioavailability and efficacy observed in both laboratory and animal studies position this novel delivery system as a promising therapeutic strategy, although further optimization and clinical validation are necessary [124]. Shang et al. focused on developing a novel glyceryl monostearate-based solid lipid nanocomplex to overcome the poor solubility and instability of QTN. The oleic acid modification significantly improved the antioxidant properties, degradation resistance, and overall stability of the QTN nanocomplex [165].

Anti-inflammatory activity

Flavonoids exert anti-inflammatory effects through multiple complementary mechanisms, including suppression of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and lipoxygenase (LOX) expression or activity, together with attenuation of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). These effects are mediated, at least in part, through modulation of key inflammatory signaling pathways, particularly nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) signaling, thereby limiting the production of inflammatory mediators and downstream tissue damage [166–169]. Al-Shalabi et al. investigated the antioxidant and anti-inflammatory potential of rhoifolin-loaded PLGA NPs using both in vitro macrophage assays and an in vivo formalin-induced rat paw edema model. In the animal model, rhoifolin-loaded PLGA NPs were more effective than free rhoifolin in reducing paw edema and mitigating histopathological alterations in inflamed paw tissues. The nanoformulation also normalized nitric oxide levels and modulated the expression of pro-inflammatory cytokines, including TNF-α and IL-1β. These findings suggest that PLGA-based nanoencapsulation can enhance the anti-inflammatory performance of rhoifolin compared with the free flavonoid [170]. Awadeen et al. developed FIS-LPHNPs as a prophylactic nanotherapeutic strategy against severe acute pancreatitis and associated multiple-organ injury. In an L-arginine-induced SAP rat model, oral pretreatment with FIS-loaded LPHNPs attenuated pancreatic inflammation and tissue injury more effectively than free FIS and unloaded LPHNPs. The nanoformulation reduced NF-κB and NLRP3 expression and decreased the levels of pro-inflammatory mediators, including TNF-α, IL-1β, IL-6, and C-reactive protein. These findings suggest that FIS-loaded LPHNPs may enhance the anti-inflammatory and organ-protective effects of FIS in experimental SAP [171]. Fuior et al. investigated NRG-loaded lipid nanoemulsions, including VCAM-1-targeted formulations, as a nanocarrier-based approach for modulating acute inflammation. In an LPS-induced murine model of acute inflammation, treatment with NRG-loaded NEs reduced the mRNA expression of several inflammatory mediators, including TNF-α, IL-1β, MCP-1, VCAM-1, and ICAM-1, in selected organs. These findings indicate that NRG-loaded NEs possess anti-inflammatory potential and may facilitate targeted delivery of naringenin to inflamed tissues [172]. The research conducted by Hatem et al. developed NLCs of LUT to enhance its skin deposition and anti-inflammatory potential for treating psoriasis. The NLCs significantly enhanced LUT's skin deposition by 3.4-fold in the stratum corneum, epidermis, and dermis compared to a LUT suspension, with minimal transdermal delivery. In vitro studies on an imiquimod-induced psoriasis rat model, assessed morphologically, histopathologically, and biochemically, revealed a significant augmentation of LUT's anti-psoriatic efficacy when encapsulated in NLCs compared to free LUT suspension [173]. Lee et al. developed nanostructured lipid carriers loaded with standardized Curcuma xanthorrhiza extract (CXE-NLCs) to enhance the oral delivery and bioactivity of its major bioactive constituents, xanthorrhizol and CUR. The optimized CXE-NLCs exhibited improved gastrointestinal stability, sustained release, and enhanced intestinal permeability compared with free CXE. In a carrageenan-induced paw edema model, oral administration of CXE-NLCs produced a dose-dependent reduction in inflammation and modulated prostaglandin E1/E2 production and eicosanoid- and MAPK-associated pathways, with greater anti-inflammatory activity than free CXE. These findings support the potential of CXE-NLCs as an oral nano-delivery

system for overcoming the poor aqueous solubility and limited bioavailability of C. xanthorrhiza constituents and enhancing their anti-inflammatory activity [174].

Anticancer and cytotoxic activity

Flavonoids exhibit anticancer and cytotoxic potential through multiple, often interconnected mechanisms. These include induction of apoptosis through caspase activation and mitochondrial signaling, modulation of cell-cycle progression with arrest at the G1/S or G2/M checkpoints, and suppression of tumor-cell proliferation, migration, invasion, and angiogenesis. Flavonoids can also modulate key oncogenic signaling pathways, including PI3K/Akt, MAPK, and Wnt/β-catenin, thereby influencing apoptosis, cell survival, epithelial–mesenchymal transition, and metastatic progression. Collectively, these pleiotropic effects highlight flavonoids as promising multi-target phytoconstituents for cancer chemoprevention and therapeutic development, although their clinical translation remains limited by issues including bioavailability, target selectivity, and variability among individual flavonoid [117,166,175,176]. Kumar et al. developed and optimized FIS-NLCs to enhance the anticancer efficacy of fisetin against advanced and metastatic melanoma. The optimized FIS-NLCs exhibited enhanced cellular uptake and cytotoxicity compared with free fisetin, accompanied by G1/S cell-cycle arrest and activation of pro-apoptotic signaling. In vivo, FIS-NLC treatment markedly suppressed melanoma-associated metastasis, with approximately 5.9-fold and 10.7-fold greater inhibition of metastatic burden in the lungs and liver, respectively, compared with free fisetin. These findings support the potential of FIS-NLCs as a nanocarrier-based strategy for improving the therapeutic performance of fisetin against metastatic melanoma [177]. Mohamed et al., focused on optimizing and characterizing QTN-SLNs for their potential application in colorectal cancer treatment. QTN-SLNs demonstrated greater cytotoxic action than free QTN, with an IC_{50} of approximately 49 μM/mL on Caco-2 cells, compared to 128 μM/mL for free QTN. Apoptosis was identified as the primary mode of cell death induced by QTN-SLNs, with minimal necrosis [132]. Pandi et al. formulated NAR-encapsulated PLA/neem gum (NAR-NPs) to enhance their anticancer potency against breast cancer cells. The MTT assay showed that NAR-PLA/NNAR NPs had a significantly higher cytotoxic efficacy than free-NRG in Michigan Cancer Foundation 7 (MCF-7) cells, with an IC_{50} of 31.51 μg/mL. The IC_{50} concentration of NAR-PLA/NAR NPs significantly elevated the intracellular ROS level and caspase-3 and -9 activity and triggered apoptosis in MCF-7 cells. Apoptotic indicators, such as membrane blebbing and nuclear disintegration, have been observed in cancer cells treated with NRG-PLA/NEG NPs. These findings suggested that NRG-PLA/NEG NPs, which target NRG delivery into MCF-7 cells and promote endocytosis, could have potent anticancer activity against breast cancer cells [178]. Paranthaman et al., developed and evaluated QTN -loaded polymeric mixed micelles as an enhanced therapeutic strategy against rat C6 and human U87MG glioma cells. QTN-PMMs showed 1.7 times higher cytotoxicity against C6 and U87MG cells compared to pure QTN [179]. Tilawat et al., formulated CUR-and QTN-loaded nanocochleates and converted them into a gel for localized application to enhance the breast cancer treatment. The in vitro drug release behaviour of gel is controlled compared to plain QTN and QTN nanocochleates. The release of QTN and CUR from nanocochleates gel was 78.19%, and 77.19%, respectively. The MTT assay results showed QTN-and CUR-loaded nanocochleates have maximum inhibition compared to the control, pristine QTN, QTN liposomes, and QTN nanocochleates. Resulted in QTN and CUR combination nanocochleates gel formulation could be a better option for the localized application in breast cancer treatment [180].

Neuroprotective activity

Emerging preclinical evidence indicates that flavonoids may exert neuroprotective effects through multiple complementary mechanisms, including attenuation of neuroinflammation and oxidative stress within the central nervous system, inhibition of acetylcholinesterase and butyrylcholinesterase, and modulation of amyloid-β (Aβ) aggregation and tau hyperphosphorylation. In addition, several flavonoids have been reported to promote neurogenesis, enhance synaptic plasticity and neuronal survival, and modulate neurotransmission and related signaling pathways. Collectively, these pleiotropic actions suggest potential utility of flavonoids in mitigating cognitive dysfunction and neurodegenerative processes; however, limitations related to bioavailability, blood–brain barrier penetration, and limited clinical evidence remain important translational challenges [160,167,181–183]. Bhadane et al. developed a modified polymeric nanocarrier for targeted brain delivery of QTN, in which polyethyleneimine (PEI) was conjugated with polyethylene glycol (PEG) and further functionalized with phenylalanine to reduce PEI-associated toxicity and enhance brain-targeting efficiency. The optimized QTN-PEI-PEG-S-S-AA nanoparticles demonstrated sustained QTN release, enhanced intestinal permeability, and effective transport across the BBB, while showing no evident hippocampal toxicity. These findings support the potential of the modified polymeric nanocarrier for improving quercetin delivery to the brain and its application in neurotherapeutic development [184]. Chen et al., developed a novel glucose-modified QTN liposome (QTN-Glu-Lip) to address QTN's poor water solubility and bioavailability. The primary goal was to enhance QTN delivery to brain tissue to boost its neuroprotective effects against neurodegenerative diseases, which are often induced by oxidative stress. QU-Glu-Lip significantly attenuated hydrogen peroxide-induced oxidative damage in PC12 cells. It resulted in higher cell viability (88.42%) and lower intracellular ROS levels compared to free QTN. The enhanced brain target ability of QTN-Glu-Lip allowed it to deliver more QTN to neuronal cells, thereby effectively exerting its antioxidative neuroprotection effect [185]. Elkomy et al. focused on developing and evaluating an intranasal nanotransferosomal gel containing QTN for brain targeting, aiming to overcome QTN's low oral bioavailability and improve brain delivery. Computed tomography scan of rat brains revealed a build-up of gold NPs in all treatment groups, with a greater level observed in rats given the transferosomal gel. This suggests effective brain targeting via the intranasal route [186]. Elsheikh et al., investigated the use of intranasally delivered LUT-loaded nanobilosomes as a brain-targeted approach to improve memory disorders in a sporadic AD mouse model. Histopathological studies showed that LUT-loaded nanobilosomes preserved almost intact and well-organized hippocampal CA3 regions with abundant intact neurons and minimal neuronal degenerative changes, significantly better than the streptozotocin (STZ) control and LUT suspension groups. They also significantly reduced Glial

fibrillary acidic protein immunohistochemical expression and activated microglial cell counts compared to the alzheimer's disease model [187]. Ghosh et al., investigated the development and efficacy of KMF-SLNs as a vehicle for brain delivery in a focal cerebral ischemic rat model. After oral administration, fluorescently labelled KMF-SLNs accumulated in the brain cortex, confirming their ability to penetrate the brain. KMF-SLNs significantly reduced neurological deficit and infarct volume and decreased the level of ROS. It also lowered the levels of pro-inflammatory mediators like NF-κB and p-STAT3. Improvements were observed in damaged neurons and overall brain texture [188].

Antidiabetic activity

Flavonoids may contribute to improved glycemic regulation through multiple complementary mechanisms, including inhibition of carbohydrate-hydrolyzing enzymes such as α-amylase and α-glucosidase, enhancement of insulin secretion and peripheral insulin sensitivity, and protection of pancreatic β-cells against oxidative and inflammatory damage. Several flavonoids also modulate glucose uptake by promoting insulin-dependent GLUT4 translocation and influencing downstream insulin-signaling pathways. Collectively, these actions may reduce postprandial hyperglycemia, improve glucose utilization, and preserve pancreatic β-cell function, supporting the potential of flavonoids as complementary candidates for the management of metabolic disorders [166,167,189]. Ahmad et al., developed the QTN-loaded chitosan-lecithin NPs (QTN/LCHS-NPs) to enhance its therapeutic profile. The bioavailability of QTN/LCHS-NPs (AUC: 167.22 h·µg/mL) exceeded free QTN (AUC: 26.2 h·µg/mL). Fasting blood glucose decreased from 292.9 to 107.7 mg/dL, along with improved lipid profiles [190]. Ferradj et al. developed nanoCUR-based formulations encapsulated in corn starch and fenugreek mucilage to enhance the delivery and bioactivity of CUR for the management of oxidative stress and diabetes. The formulations exhibited improved dissolution and antioxidant activity compared with crude CUR. In an in vivo antidiabetic evaluation using Wistar rats, the fenugreek-mucilage-based nanoCUR formulation significantly reduced fasting blood glucose levels from 392 to 187 mg/dL. These findings support the potential of biopolymer-encapsulated nanocurcumin as a nano-enabled approach for improving the antidiabetic and antioxidant effects of curcumin [191]. Gutiérrez et al. developed gum Arabic-stabilized selenium nanoparticles conjugated with LUT and diosmin (GA/LU/DIO-SeNPs) and evaluated their antidiabetic potential in STZ-induced type 2 diabetic C57BL/6 mice. Following six weeks of treatment, GA/LU/DIO-SeNPs significantly improved blood glucose and insulin levels and ameliorated diabetes-associated alterations in lipid profile, hepatic glycogen, and glycosylated hemoglobin (HbA1c). The formulation also improved insulin sensitivity and exhibited antioxidant activity in hepatic and renal tissues. These findings suggest that GA/LU/DIO-SeNPs may enhance the antidiabetic effects of luteolin and diosmin through the combined actions of flavonoids and selenium [192]. Mahadev et al. developed and optimized an ultrasonically fabricated β-carotene nanoemulsion (βC-NE) and evaluated its antidiabetic potential alone and in combination with QTN-NEs in a STZ-induced diabetic rat model. The optimized βC-NE exhibited a 5.38-fold higher in vivo bioavailability than standard βC. In diabetic rats, combined βC-NE and QU-NE treatment improved body-weight maintenance and reduced blood glucose and lipid levels, while attenuating tissue injury and oxidative-stress markers and preserving pancreatic and hepatic tissue architecture. These findings suggest that the combined nanoemulsion system may enhance the therapeutic potential of β-carotene and quercetin for managing diabetes [193]. Zafar et al., formulated, and optimized the NRG-loaded NPs designed to enhance the therapeutic efficacy of NRG. Pharmacokinetic studies indicated a significantly higher absorption profile for NRG-NPs compared to pure NRG dispersion, and demonstrated significantly enhanced antidiabetic activity compared to pure NRG dispersion. Furthermore, the biochemical profile showed remarkable improvement in altered biochemical parameters [194].

Cardioprotective activity

Flavonoids may exert cardioprotective effects through multiple complementary mechanisms, including preservation of endothelial function and nitric oxide (NO) bioavailability, inhibition of low-density lipoprotein (LDL) oxidation, attenuation of vascular inflammation and atherosclerotic lesion development, and modulation of platelet activation and thrombotic processes. Several flavonoids also influence vascular tone and blood pressure through enhancement of endothelium-dependent vasodilation and, for specific flavonoids, inhibition of angiotensin-converting enzyme activity. Collectively, these actions may contribute to improved vascular function and reduced cardiovascular risk, although the magnitude and clinical relevance of these effects vary among individual flavonoids and remain influenced by their bioavailability and metabolism [25,160,195–198].Sharma et al. developed PHL-loaded biodegradable polymeric nanocomposites using an ionic-gelation approach to enhance the oral bioavailability and cardioprotective efficacy of PHL. The optimized nano-PHL formulation exhibited enhanced antioxidant activity and, in both in vitro and in vivo ischemia models, provided greater cardioprotection than free PHL. In the in vivo rat model of myocardial ischemia, nano-PHL reduced myocardial infarct size by approximately 46%, compared with approximately 13% for free PHL, accompanied by enhanced cardiomyocyte protection and suppression of oxidative stress and ROS generation. These findings support the potential of polymeric nanoencapsulation to improve the cardioprotective performance of PHL [199]. Chahardori et al., developed QTN loaded PLGA NPs using a microfluidic approach and further functionalized them with the cardiac-targeting cyclic peptide. Treatment with QTN-NPs, particularly at doses of 25 mg/kg and 50 mg/kg, markedly attenuated doxorubicin-induced cardiotoxicity by restoring antioxidant defence systems, preserving mitochondrial membrane potential, and reducing oxidative stress. Furthermore, QTN-NPs upregulated the Nrf2/HO-1 antioxidant signalling pathway, while the higher-dose formulation significantly lowered serum troponin I and CK-MB levels. Histopathological analyses further confirmed reduced myocardial inflammation and structural damage, highlighting the enhanced cardioprotective efficacy of targeted QTN nano delivery [200]. Jaiswal et al. developed NRG-loaded lignin NPs (NRG-LGNPs) to improve the therapeutic efficacy of NRG against isoproterenol-induced myocardial infarction. Intravenous administration of NRG-LGNPs (10 mg/kg) significantly decreased serum levels of cardiac injury biomarkers, including CK-MB, LDH, AST, and malondialdehyde. Histopathological examination demonstrated substantial restoration of myocardial architecture and a marked reduction in infarct size, confirming the superior cardioprotective potential of the nanoformulation over free NRG

in mitigating myocardial injury [201]. Chen et al. developed baicalin (BCL)-loaded polydopamine (PDA)-modified zeolitic imidazolate framework-8 (ZIF-8) nanoparticles (PZB-NPs) as a nanocarrier system for cardioprotection against myocardial ischemia/reperfusion (I/R) injury. The PZB-NPs exhibited sustained BCL release under acidic conditions and enhanced recovery of H/R-injured H9c2 cells, accompanied by reduced apoptosis and ROS generation and activation of the Nrf2/HO-1 pathway. In a rat model of myocardial I/R injury, PZB-NPs significantly reduced myocardial infarct size and fibrosis and improved cardiac function compared with free BCL. These findings suggest that PDA-modified ZIF-8 nanoencapsulation can enhance the cardioprotective potential of BCL through improved delivery and modulation of oxidative-stress-related pathways [202]. Serri et al., focused on developing and evaluating hyaluronic acid-based NPs loaded with RUT to protect endothelial cells from damage induced by anthracyclines, such as epirubicin. Levels of the intracellular NLRP3 and MyD-88 were significantly lower in cells treated with epirubicin+LicpHA RUT compared to epirubicin-only groups. Proinflammatory cytokines were also significantly reduced in the epirubicin+LicpHA+RUT-exposed cells. The study concluded that hyaluronic acid-based nanoparticles loaded with RUT exhibit significant vasculo-protective properties against anthracycline-induced damage RUT-exposed [203].

Antimicrobial activity

Flavonoids exhibit antimicrobial activity against bacteria, fungi, and viruses by disrupting microbial membranes and interfering with nucleic acid, protein, and energy metabolism. They may also inhibit biofilm formation and efflux pumps, thereby enhancing the activity of conventional antibiotics and potentially overcoming antimicrobial resistance [166,175,204–206]. Almeleebia et al., designed novel composite system, ciprofloxacin (CIP), NRG, carboxymethyl chitosan (CM-CS), alginate (AG)-NPs, which co-delivered CIP and NRG encapsulated within an oleic acid lipid core. This was achieved using a nonsolvent ionic gelation technique. The NRG displayed good antioxidant capacity, which contributed to improving the antimicrobial activity of CIP. The developed CIP+NRG-CM-CS/AG-NPs formulation significantly enhanced antimicrobial activity compared to CIP alone against E. coli and S. aureus [207]. de Barros et al., focused on developing and evaluating QTN-loaded natural plant-oil-based NLCs (QTN-NPO-NLCs) for topical treatment of bacterial skin infections. The research highlighted the synergistic potential of combining QTN's antibacterial properties with the drug delivery capabilities of NLCs. The systems containing QTN exhibited enhanced antibacterial activity specifically against Staphylococcus aureus. QTN-NPO-NLCs were capable of transporting QTN to an intranuclear location within HaCaT cells, and suggested potential for controlled topical drug delivery [208]. De Gaetano et al., prepared NRG-loaded SLNs using a solvent emulsification/diffusion and ultrasonication method. NRG10-SLNs showed bacteriostatic activity against S. aureus (including methicillin-resistant S. aureus or MRSA) and E. coli strains. Notably, an improvement in antibacterial activity was observed for NRG-loaded SLNs compared to free NRG, particularly against S. aureus strains. This enhancement was attributed to the interaction of the surfactant-coated SLNs with the bacterial surface. A similar positive trend was also noted for biofilm inhibition [209]. Hemmati et al., has investigated a surface-modified niosomal drug delivery system for QTN to tackle Pseudomonas aeruginosa infections, specifically drug-resistant strains and biofilms. The study emphasizes the efficacy of QTN-niosome and QTN-stearyl amine-niosome as therapeutic agents against P. aeruginosa infections. The modified QTN-niosome with cationic lipids displayed strong antibacterial and anti-biofilm activity, enhanced stability, and good biocompatibility, indicated that it may efficiently target P. aeruginosa cells with minimal toxicity [210]. Imam et al. focused on designing and optimizing NRG hybrid nanoparticles (NRG-HNs) for oral delivery, as well as defining and assessing their biological activity. NRG-HNs showed much higher antibacterial activity against E. coli and S. aureus than pure NRG, with lower MIC values and broader zones of inhibition. This was attributable to the reduced particle size, longer disintegration, and enhanced permeability through the cell wall [211].

CLINICAL TRANSLATION OF FLAVONOID-BASED NANO FORMULATIONS

Figure 7 illustrates an integrated bench-to-bedside translational roadmap for flavonoid-based nanotherapeutics, outlining the sequential stages required to advance bioactive flavonoids toward clinically relevant nanoformulations. The process begins with flavonoid identification and characterization based on bioactivity, physicochemical properties, therapeutic relevance, and structure–activity relationships.

Flavonoids represent a major class of naturally occurring polyphenols with diverse therapeutic potential, including antioxidant, anti-inflammatory, anticancer, neuroprotective, and cardioprotective activities [99,212]. Over the past two decades, research has progressed from conventional pharmacological characterization toward the development of advanced nanocarrier systems designed to overcome the intrinsic limitations of flavonoids, particularly poor aqueous solubility, chemical instability, extensive metabolism, limited absorption, and low systemic exposure [115,213–216]. The increasing global burden of chronic diseases, including cancer, cardiovascular disorders, and neurodegenerative diseases, has further stimulated interest in nanotechnology-enabled delivery strategies [217]. Accumulating preclinical evidence indicates that nanoformulation can substantially improve flavonoid solubility, physicochemical stability, cellular uptake, systemic exposure, and tissue delivery, thereby enhancing pharmacokinetic and pharmacodynamic performance compared with free flavonoids. However, the magnitude of these improvements is highly dependent on the flavonoid, nanocarrier composition, formulation characteristics, administration route, and experimental model [214,215,217,218].

Despite these advances, the clinical translation of flavonoid-based nanoformulations remains constrained by substantial technical, biological, manufacturing, and regulatory challenges, including formulation stability, batch-to-batch reproducibility, scalable manufacturing, long-term safety, pharmacokinetic variability, limited clinical evidence, and regulatory standardization [7,36,219,220]. A critical knowledge gap exists between successful preclinical outcomes and human clinical application, primarily due to challenges in large-scale manufacturing, batch-to-batch consistency, and the absence of standardized regulatory guidelines [36,221,222]. While some researchers argue that current regulatory frameworks are sufficient for nanomedicines, others contend that the unique physicochemical properties of these systems

necessitate tailored evaluation methods [223]. This disconnects between laboratory innovation and commercial viability results in a limited number of products reaching the market, leaving the therapeutic potential of many flavonoid-loaded systems largely unrealized [36,224,225].

Safety of Flavonoid-based Nano formulations

A central challenge in nanomedicine translation is the persistent gap between laboratory-scale innovation and clinical adoption, partly arising from an incomplete understanding of how nanoparticle physicochemical properties govern their biological interactions, cellular behavior, biodistribution, and ultimately in vivo performance [36,221,226]. A critical knowledge gap exists regarding the standardization of toxicological assessments, as current regulatory frameworks often rely on conventional guidelines that fail to address nano-specific risks [227,228]. While regulatory authorities generally recognize the need for product-specific, case-by-case safety assessment because nanomedicines can exhibit distinct physicochemical and biological properties, there is growing emphasis on harmonizing characterization methods, safety assays, and mechanistically informed testing frameworks to improve reproducibility, comparability, and regulatory decision-making. This lack of consensus creates significant regulatory uncertainty, potentially delaying the development of safe, clinically viable flavonoid-based nanotherapeutics [229–234].

Nanotoxicity represents a major safety concern for flavonoid-based nanoformulations because physicochemical characteristics such as particle size, surface area, surface charge, and surface coating can substantially influence cellular uptake, reactive oxygen species generation, inflammatory responses, biodistribution, and organ accumulation. Consequently, the safety profile of a flavonoid nanoformulation cannot be assumed to be equivalent to that of the corresponding free flavonoid and requires formulation-specific evaluation. Following systemic administration, nanoparticles rapidly interact with plasma proteins and other biomolecules, forming a dynamic protein corona that can confer a new biological identity to the nanoparticle. This corona may alter cellular recognition, targeting efficiency, uptake, circulation and clearance, pharmacokinetics, and tissue distribution, potentially modifying the biological performance of the nanoformulation. [235–240]. Recent studies indicate that nanoparticle surface chemistry and physicochemical properties, including particle size, surface charge, hydrophobicity, and surface functionalization, strongly influence the composition and dynamics of the adsorbed protein corona. The resulting corona can confer a new biological identity to nanoparticles and subsequently modulate cellular recognition, immune interactions, systemic clearance, biodistribution, and therapeutic performance [240–243] [167–169]. Conversely, deliberate engineering of nanoparticle surfaces, including the use of hydrophilic coatings, functional ligands, or protein pre-coating, can modulate corona formation and composition to improve circulation behavior, targeting, safety, and therapeutic outcomes [243–245].

Another safety issue with nanoformulations is that nanoparticle surfaces can activate complement, resulting in faster clearance or infusion responses. According to certain research studies, complement activation is a key mechanism for fast nanoparticle sequestration and clearance [246,247]. Complement activation represents an important but often underappreciated safety consideration in nanomedicine and may not be adequately captured by conventional preclinical toxicity assessments. Nanoparticle-induced complement activation can promote opsonization, phagocytic clearance, inflammatory responses, and altered biodistribution, thereby influencing both safety and therapeutic performance. Surface engineering provides an opportunity to modulate these interactions; for example, ginsenoside-modified lipid-coated perfluorocarbon nanodroplets have been shown to reduce C3 adsorption and complement activation, decrease phagocytic uptake, and prolong blood circulation in vivo [248–250]. Hemocompatibility is an important safety consideration for parenterally administered nanoformulations and encompasses assessment of hemolysis, coagulation, platelet activation or aggregation, hematological alterations, and complement activation. Although several preclinical studies of flavonoid-loaded nanoformulations have monitored hematological parameters and organ histopathology, these endpoints alone may not adequately capture nanoparticle–blood interactions. In particular, systematic concentration-dependent assessment of hemolysis, platelet responses, coagulation, and complement activation remains insufficiently standardized for many nanocarrier systems. Consequently, formulation-specific hemocompatibility testing should be incorporated alongside systemic toxicity and histopathological evaluation during preclinical development, particularly for formulations intended for parenteral administration [251–253]. A robust preclinical safety package for flavonoid nanocarriers should integrate comprehensive physicochemical characterization with in vitro release, cytotoxicity, hemocompatibility, complement activation, protein-corona characterization, immune-response assessment, biodistribution, and appropriate repeat-dose toxicity studies. The selection of these endpoints should be tailored to the nanocarrier composition, administration route, intended target, and anticipated biological interactions. FDA guidance emphasizes the importance of characterizing nanomaterial attributes, including particle size and size distribution, surface characteristics, morphology, composition, and stability, and establishing their relationships with product quality, safety, and efficacy. Changes in these critical quality attributes may influence the biological performance and clinical risk profile of nanomedicines and therefore require appropriate control and characterization during product development [229,251,252,254].

From a regulatory perspective, no single ICH guideline is dedicated specifically to nanomedicines. Instead, the development of nanomaterial-containing drug products generally follows applicable ICH quality, nonclinical, and clinical principles, supplemented by product- and nanomaterial-specific considerations to address unique physicochemical properties and associated safety, quality, and efficacy risks. FDA guidance similarly indicates that standard nonclinical frameworks, including ICH M3 and, where applicable, ICH S9 and S6, should be considered alongside nanomaterial-specific characterization and risk assessment [229,254–256].

There is an emerging consensus that existing immunotoxicity frameworks may require complementary nanomedicine-specific endpoints, particularly for phenomena such as complement activation-related pseudo-allergy (CARPA), hypersensitivity, and other immune-mediated effects that are not fully addressed by ICH-S8 [227,257]. The International Organization for Standardization (ISO) provides additional guidance through ISO/TR 10993-22:2017 for the biological

evaluation of nanomaterials in the medical-device context, including nanomaterial characterization, release of nano-objects, toxicokinetics, biological evaluation, and risk assessment [258]. For pharmaceutical products, the U.S. Food and Drug Administration (FDA) recommends a product-specific, risk-based approach encompassing detailed physicochemical characterization, critical quality attribute (CQA) control, appropriate nonclinical evaluation, and assessment of biodistribution, pharmacokinetics, immunogenicity, and other nanomaterial-specific biological interactions [229,254].

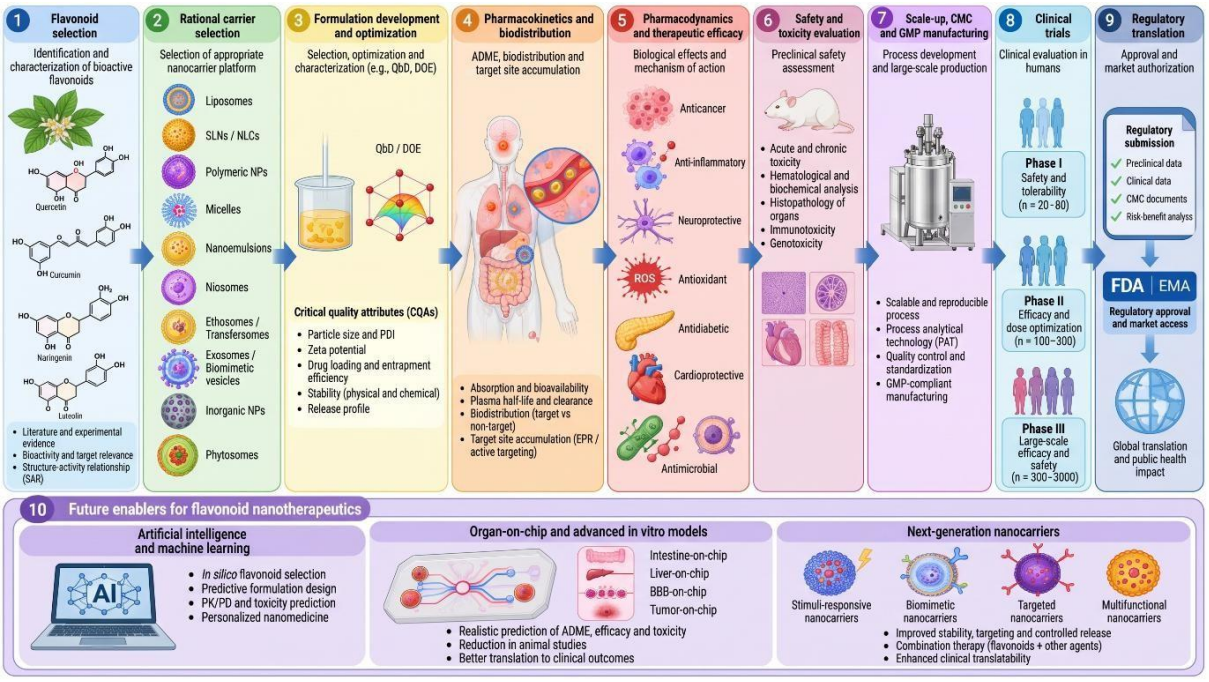


Fig. 7. Integrated bench-to-bedside translational roadmap for flavonoid-based nanotherapeutics. (Created with BioRender.com. Adapted by the authors).

LIMITATIONS OF THE REVIEW

This review is limited by the substantial heterogeneity among flavonoids, nanocarriers, particle characteristics, doses, administration routes, experimental models, and reported endpoints, which restricts direct comparison across studies. The available evidence is also predominantly preclinical, with relatively limited robust human pharmacokinetic, efficacy, and safety data. In addition, differences in reporting of stability, biodistribution, nano–bio interactions, and long-term toxicity may limit comprehensive assessment of clinical translation. The literature search was focused on selected databases and recent publications; therefore, relevant studies outside the defined scope may not have been captured.

FUTURE PERSPECTIVES

Future research should move beyond proof-of-concept studies toward clinically relevant formulation property pharmacokinetic and pharmacodynamic relationships, and standardized critical quality attributes. QbD-based development and scalable manufacturing should be integrated early to improve reproducibility and regulatory readiness. Human-relevant models, systematic biodistribution and immunotoxicity assessment, and adequately designed clinical trials comparing nanoformulations with conventional formulations are particularly important. AI/ML can help in formulation optimization when high quality and standardized datasets are available. Targeted, stimuli-responsive, biomimetic and co-delivery systems are promising, but their added complexity should be justified by a demonstrable therapeutic benefit. Ultimately, successful translation will be a balance of formulation performance, manufacturability, safety, regulatory feasibility and meaningful clinical benefit.

CONCLUSION

Flavonoid-based nanotherapeutics offer a promising strategy to overcome the poor aqueous solubility, instability, rapid metabolism, and limited bioavailability of many flavonoids. Lipid- polymer, vesicular, biomimetic, inorganic, and hybrid nanocarriers can improve formulation stability, drug loading, release, pharmacokinetic exposure, and tissue delivery, with encouraging preclinical therapeutic outcomes. However, improved pharmacokinetic performance does not necessarily translate into superior clinical efficacy. The field remains predominantly supported by preclinical evidence, while standardized characterization, reproducible manufacturing, long-term safety data, and well-designed clinical studies remain limited. Future translation therefore requires stronger formulation property pharmacokinetic and pharmacodynamic relationships, harmonized critical quality attributes, scalable manufacturing, systematic nano–bio interaction and toxicity assessment, and rigorous clinical validation. Integration of QbD, artificial intelligence, and regulatory science may further accelerate the development of clinically meaningful flavonoid nanomedicines.

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CONFLICT OF INTEREST
The authors declare that there is no conflict of interests.

DECLARATION OF AI-ASSISTED TECHNOLOGIES
During the preparation of this manuscript, the authors used an AI-assisted tool (s) to improve the language and no data, results or scientific conclusions were generated by AI. All analyses, interpretations and conclusions are the authors' own. The authors reviewed and edited the content and take full responsibility for the published work.

REFERENCES
[1] P.R.F. Lalong, C.W. Refdi, S. Une, M. Sayuti, D. Iswadi, Bioavailability of Curcumin in Various Nanoformulations: A Critical Review, AJARCDE (Asian J. Appl. Res. Community Dev. Empower. 9 (2025) 409–416. https://doi.org/10.29165/ajarcde.v9i3.861.
[2] S. Jacob, R. Rao, B. Gorain, S.H.S. Boddu, A.B. Nair, Solid Lipid Nanoparticles and Nanostructured Lipid Carriers for Anticancer Phytochemical Delivery: Advances, Challenges, and Future Prospects, Pharmaceutics. 17 (2025) 1079. https://doi.org/10.3390/pharmaceutics17081079.
[3] R.F.E.-S. Baiomy, Quercetin nanoparticles as a therapeutic approach: pharmacological actions and potential applications in therapy, BioTechnologia. 105 (2024) 377–393. https://doi.org/10.5114/bta.2024.145258.
[4] S. Ahmad, M.K. Sahu, D.S. Chaturvedi, J. Kushwaha, Enhanced oral bioavailability of baicalein using phospholipid-coated nanoparticles: A novel drug delivery system, World J. Biol. Pharm. Heal. Sci. 23 (2025) 475–484. https://doi.org/10.30574/wjbphs.2025.23.3.0842.
[5] S. Egba, M. Edeh, N. Uchenna, M. Igwe, J. Ogbodo, Nasal Delivery of Phytochemicals Using Nanocarriers: Therapeutic Opportunities and Translational Challenges, Int. J. Nanomedicine. Volume 20 (2025) 15017–15041. https://doi.org/10.2147/IJN.S564106.
[6] S. Yadav, R.K. Harwansh, R. Mazumder, Recent Updates on Novel Carrier Systems for the Delivery of Herbal Bioactives with Poor Bioavailability and their Clinical Trial Status, Curr. Nanomedicine. 15 (2025) 523–545. https://doi.org/10.2174/0124681873305117240627172050.
[7] D.R. Srivastava, Nanoencapsulation of Herbal Extracts for Enhanced Bioavailability, Int. J. Pharmacogn. Herb. Drug Technol. (2025) 86–102. https://doi.org/10.64063/3049-1630.vol.2.issue7.8.
[8] E.-M. Tomou, P. Papakyriakopoulou, E.-M. Saitani, G. Valsami, N. Pippa, H. Skaltsa, Recent Advances in Nanoformulations for Quercetin Delivery, Pharmaceutics. 15 (2023) 1656. https://doi.org/10.3390/pharmaceutics15061656.
[9] M. Bhia, M. Motallebi, B. Abadi, A. Zarepour, M. Pereira-Silva, F. Saremnejad, A.C. Santos, A. Zarrabi, A. Melero, S.M. Jafari, M. Shakibaei, Naringenin Nano-Delivery Systems and Their Therapeutic Applications, Pharmaceutics. 13 (2021) 291. https://doi.org/10.3390/pharmaceutics13020291.
[10] R. Verma, S. Bahadur, A Comprehensive Review of Naringin Loaded Nano Drug Delivery System in Treatment of CNS Disorders, Curr. Pharm. Des. 32 (2026). https://doi.org/10.2174/0113816128407188251116030341.
[11] S. Kaur, A. Goyal, A. Rai, A. Sharma, K.C. Ugoeze, I. Singh, Quercetin nanoformulations: recent advancements and therapeutic applications, Adv. Nat. Sci. Nanosci. Nanotechnol. 14 (2023) 033002. https://doi.org/10.1088/2043-6262/acedaa.
[12] C.N. Wong, Y.M. Lim, K. Bin Liew, Y.-L. Chew, A.-L. Chua, S.-K. Lee, EGCG as a therapeutic agent: a systematic review of recent advances and challenges in nanocarrier strategies, J. Zhejiang Univ. B. 26 (2025) 633–656. https://doi.org/10.1631/jzus.B2400040.
[13] K. Wadhwa, V. Kadian, V. Puri, B.Y. Bhardwaj, A. Sharma, R. Pahwa, R. Rao, M. Gupta, I. Singh, New insights into quercetin nanoformulations for topical delivery, Phytomedicine Plus. 2 (2022) 100257. https://doi.org/10.1016/j.phyplu.2022.100257.
[14] I.A. Rodríguez Martínez, P.S. Londoño-Ruíz, M.R. Serafini, I.A. Alves, D.M. Aragon Novoa, Trends in Oral Flavonoid Drug Delivery Systems Based on Current Pharmaceutical Strategies. A Systematic Patent Review (2011–2023), J. Herb. Med. 43 (2024) 100828. https://doi.org/10.1016/j.hermed.2023.100828.
[15] P. Patel, K. Garala, S. Singh, B.G. Prajapati, C. Chittasupho, Lipid-Based Nanoparticles in Delivering Bioactive Compounds for Improving Therapeutic Efficacy, Pharmaceuticals. 17 (2024) 329. https://doi.org/10.3390/ph17030329.
[16] B. Martinez, P. V. Peplow, Amelioration of behavioral and neural deficits in animal models of neurodegenerative disease by nanoformulations of curcumin and quercetin, Neural Regen. Res. 21 (2026) 3311–3322. https://doi.org/10.4103/NRR.NRR-D-25-00343.
[17] M.D. Ansari, H. Majid, S. Mahmood, Z.M. Sofian, A. Husain, Y. Sultana, F. Shakeel, Nanotechnology-enabled delivery of phytoconstituents: Recent developments, applications, and regulatory considerations, Asian Pac. J. Trop. Biomed. 16 (2026) 1–23. https://doi.org/10.4103/apjtb.apjtb_491_25.
[18] V. Murade, A. Waghmare, D. Pakhare, S. Dichayal, R. Patil, M. Wanjari, S. Gurav, D. Hase, A plausible involvement of GABAA/benzodiazepine receptor in the anxiolytic-like effect of ethyl acetate fraction and quercetin isolated from Ricinus communis Linn. leaves in mice, Phytomedicine Plus. 1 (2021) 100041. https://doi.org/10.1016/j.phyplu.2021.100041.

[19] S. Yeo, M.J. Kim, Y.K. Shim, I. Yoon, W.K. Lee, Solid Lipid Nanoparticles of Curcumin Designed for Enhanced Bioavailability and Anticancer Efficiency, ACS Omega. 7 (2022) 35875–35884. https://doi.org/10.1021/acsomega.2c04407.
[20] A. Tiwari, V. Tiwari, Nanotechnology for Polyphenol Delivery and Applications, in: Explor. Synth. Ethnopharmacol. Ther. Appl. Bioact. Polyphenols, CRC Press, Boca Raton, 2026: pp. 184–194. https://doi.org/10.1201/9781003564300-15.
[21] M.J. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, L. Shamseer, J.M. Tetzlaff, E.A. Akl, S.E. Brennan, R. Chou, J. Glanville, J.M. Grimshaw, A. Hróbjartsson, M.M. Lalu, T. Li, E.W. Loder, E. Mayo-Wilson, S. McDonald, L.A. McGuinness, L.A. Stewart, J. Thomas, A.C. Tricco, V.A. Welch, P. Whiting, D. Moher, The PRISMA 2020 statement: An updated guideline for reporting systematic reviews, Int. J. Surg. 88 (2021) 105906. https://doi.org/10.1016/j.ijsu.2021.105906.
[22] R. Jeyavelkumaran, S. Panneerselvam, S.H. Jeya, L. Kumar, K. Ganesan, J. Kumaran, Prenylated flavonoids in cancer therapy: Structural determinants, multilay mechanisms, and translational potential, Pharmacol. Res. - Nat. Prod. 12 (2026) 100826. https://doi.org/10.1016/j.prenap.2026.100826.
[23] C. Yang, Q. Gong, R. Zhu, Y. Fan, Q. Wang, G. Ge, P. Wang, Flavonoids as promising drug leads: Structural diversity, synthetic strategies, and drug-likeness optimization, Eur. J. Med. Chem. 305 (2026) 118549. https://doi.org/10.1016/j.ejmech.2025.118549.
[24] M. Huang, X. Xie, R. Yuan, Q. Xin, S. Ma, H. Guo, Y. Miao, C. Hu, Y. Zhu, W. Cong, The multifaceted anti-atherosclerotic properties of herbal flavonoids: A comprehensive review, Pharmacol. Res. 211 (2025) 107551. https://doi.org/10.1016/j.phrs.2024.107551.
[25] A.N. Panche, A.D. Diwan, S.R. Chandra, Flavonoids: an overview, J. Nutr. Sci. 5 (2016) 1–15. https://doi.org/10.1017/jns.2016.41.
[26] G. Drețcanu, I. Știrbu, N. Leoplold, D. Cruceriu, C. Danciu, A. Stănilă, A. Fărcaș, I.M. Borda, C. Iuhas, Z. Diaconeasa, Chemical Structure, Sources and Role of Bioactive Flavonoids in Cancer Prevention: A Review, Plants. 11 (2022) 1117. https://doi.org/10.3390/plants11091117.
[27] D.S.K.V. S.K. Verma, R.S. Ritu Suryavanshi, D.K.K.D. Dr K.K. Daryani, Nanotechnology-Based Drug Delivery: A Modern Approach in Pharmaceutical Sciences, Int. J. Pharm. Res. Appl. 10 (2025) 82–86. https://doi.org/10.35629/4494-10058286.
[28] J. Madhusudhanan, S. Gundu, K. Kavitha, D. Abirami, R. Manickam, N.M.I. Ahamed, Role of nanomaterials with special reference to pharmaceutical technology, Int. J. Health Sci. (Qassim). (2022) 7210–7227. https://doi.org/10.53730/ijhs.v6nS3.7736.
[29] D. Bobo, K.J. Robinson, J. Islam, K.J. Thurecht, S.R. Corrie, Nanoparticle-Based Medicines: A Review of FDA-Approved Materials and Clinical Trials to Date, Pharm. Res. 33 (2016) 2373–2387. https://doi.org/10.1007/s11095-016-1958-5.
[30] Y.S. Rhee, H.M. Mansour, Nanopharmaceuticals I: nanocarrier systems in drug delivery, Int. J. Nanotechnol. 8 (2011) 84. https://doi.org/10.1504/IJNT.2011.037172.
[31] X. Hou, T. Zaks, R. Langer, Y. Dong, Lipid nanoparticles for mRNA delivery, Nat. Rev. Mater. 6 (2021) 1078–1094. https://doi.org/10.1038/s41578-021-00358-0.
[32] P.R. Cullis, M.J. Hope, Lipid Nanoparticle Systems for Enabling Gene Therapies, Mol. Ther. 25 (2017) 1467–1475. https://doi.org/10.1016/j.ymthe.2017.03.013.
[33] A.B. Uzakova, E.M. Yergaliyeva, A. Yerlanuly, Z.S. Mukatayeva, A Systematic Review of Advanced Drug Delivery Systems: Engineering Strategies, Barrier Penetration, and Clinical Progress (2016–April 2025), Pharmaceutics. 18 (2025) 11. https://doi.org/10.3390/pharmaceutics18010011.
[34] R. Hocaoğlu, K. Zıkşahna, M. Ihlamur, Selecting nanocarrier platforms for drug delivery: a criteria-based, translational review integrating CQA/CMC and immune interactions, Heal. Nanotechnol. 2 (2026). https://doi.org/10.1186/s44301-026-00026-8.
[35] S. Gressler, C. Hipfinger, F. Part, A. Pavlicek, C. Zafiu, B. Giese, A systematic review of nanocarriers used in medicine and beyond — definition and categorization framework, J. Nanobiotechnology. 23 (2025) 90. https://doi.org/10.1186/s12951-025-03113-7.
[36] P. Joyce, C.J. Allen, M.J. Alonso, M. Ashford, M.S. Bradbury, M. Germain, M. Kavallaris, R. Langer, T. Lammers, M.T. Peracchia, A. Popat, C.A. Prestidge, C.J.F. Rijcken, B. Sarmento, R.B. Schmid, A. Schroeder, S. Subramaniam, C.R. Thorn, K.A. Whitehead, C.-X. Zhao, H.A. Santos, A translational framework to DELIVER nanomedicines to the clinic, Nat. Nanotechnol. 19 (2024) 1597–1611. https://doi.org/10.1038/s41565-024-01754-7.
[37] H. Cabral, J. Li, K. Miyata, K. Kataoka, Controlling the biodistribution and clearance of nanomedicines, Nat. Rev. Bioeng. 2 (2023) 214–232. https://doi.org/10.1038/s44222-023-00138-1.
[38] M. Balash, H. Boucetta, W. He, Factors affecting drug delivery system translation: A focus on advanced technologies, biological barriers, and regulatory challenges, J. Control. Release. 387 (2025) 114167. https://doi.org/10.1016/j.jconrel.2025.114167.
[39] Y. Sun, E. Davis, Nanoplatforms for Targeted Stimuli-Responsive Drug Delivery: A Review of Platform Materials and Stimuli-Responsive Release and Targeting Mechanisms, Nanomaterials. 11 (2021) 746. https://doi.org/10.3390/nano11030746.
[40] J. Gao, Z. Xia, S. Gunasekar, C. Jiang, J.M. Karp, N. Joshi, Precision drug delivery to the central nervous system using engineered nanoparticles, Nat. Rev. Mater. 9 (2024) 567–588. https://doi.org/10.1038/s41578-024-00695-w.
[41] M.J. Saadh, M.A. Mustafa, A. Kumar, H.T.A. Alamir, A. Kumar, S.A. Khudair, A. Faisal, M.H.S. Alubiady, S.S. Jalal, S.S. Shafik, I. Ahmad, F.A.F. Khry, M.K. Abosaoda, Stealth Nanocarriers in Cancer Therapy: a Comprehensive

Review of Design, Functionality, and Clinical Applications, AAPS PharmSciTech. 25 (2024) 140. https://doi.org/10.1208/s12249-024-02843-5.
[42] A. Kumar, S. Bhagat, K. Moar, S. Singh, P.K. Maurya, Mitigating oxidative stress in red blood cells with quercetin-loaded liposomes: a promising strategy, RSC Pharm. 2 (2025) 1471–1478. https://doi.org/10.1039/D5PM00112A.
[43] R.H. Müller, K. Mäder, S. Gohla, Solid lipid nanoparticles (SLN) for controlled drug delivery - A review of the state of the art, Eur. J. Pharm. Biopharm. 50 (2000) 161–177. https://doi.org/10.1016/S0939-6411(00)00087-4.
[44] A. Pareek, R. Kothari, A. Pareek, Y. Ratan, P. Kashania, V. Jain, P. Jeandet, P. Kumar, A.A. Khan, A.M. Alanazi, M.M. Gupta, Development of a new inhaled swellable microsphere system for the dual delivery of naringenin-loaded solid lipid nanoparticles and doxofylline for the treatment of asthma, Eur. J. Pharm. Sci. 193 (2024) 106642. https://doi.org/10.1016/j.ejps.2023.106642.
[45] G.M.H. Al-sayadi, G. Garg, A. Singh, P. Patel, G. Das Gupta, B. Das Kurmi, Development of QCT loaded TPGS coated solid lipid nanoparticles for improved in vivo neuroprotective activity in LPS administered adult zebrafish model: A QbD-based approach, OpenNano. 17 (2024) 100206. https://doi.org/10.1016/j.onano.2024.100206.
[46] R.H. Müller, M. Radtke, S.A. Wissing, Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations, Adv. Drug Deliv. Rev. 54 (2002) S131–S155. https://doi.org/10.1016/S0169-409X(02)00118-7.
[47] J. Pardeike, A. Hommoss, R.H. Müller, Lipid nanoparticles (SLN, NLC) in cosmetic and pharmaceutical dermal products, Int. J. Pharm. 366 (2009) 170–184. https://doi.org/10.1016/j.ijpharm.2008.10.003.
[48] R. Costa, C. Nunes, S.A.C. Lima, P. Gameiro, S. Reis, Nanostructured lipid carrier-embedded hydrogels for enhanced skin delivery of quercetin: Optimized formulation with pomegranate oil for UVB protection, Int. J. Pharm. 681 (2025) 125894. https://doi.org/10.1016/j.ijpharm.2025.125894.
[49] R. Joshi, B. Sukumaran, Topical co-delivery of cyclosporine A and quercetin via nanostructured lipid carriers attenuates imiquimod-induced psoriatic inflammation in a murine model, J. Drug Deliv. Sci. Technol. 123 (2026) 108566. https://doi.org/10.1016/j.jddst.2026.108566.
[50] Y. Duan, A. Dhar, C. Patel, M. Khimani, S. Neogi, P. Sharma, N. Siva Kumar, R.L. Vekariya, A brief review on solid lipid nanoparticles: Part and parcel of contemporary drug delivery systems, RSC Adv. 10 (2020) 26777–26791. https://doi.org/10.1039/d0ra03491f.
[51] A. Kumari, S.K. Yadav, S.C. Yadav, Biodegradable polymeric nanoparticles based drug delivery systems, Colloids Surfaces B Biointerfaces. 75 (2010) 1–18. https://doi.org/10.1016/j.colsurfb.2009.09.001.
[52] V. Keturakis, O. Gok, D. Puzinovė, Z. Balion, M. Kairytė, I. Žukauskaitė, D. Kulakauskienė, D. Gol, E. Pilnikovaitė, R. Benetis, E. Stankevičius, V. Lesauskaitė, D. Benyamin, A. Jekabsone, pH-responsive PLGA nanoparticles enable sustained curcumin release and preserve mitochondrial bioenergetics in cardiomyocytes, J. Drug Deliv. Sci. Technol. 118 (2026) 108075. https://doi.org/10.1016/j.jddst.2026.108075.
[53] N. Abraham, T. Kolipaka, G. Pandey, D.K. Arya, A. Sharma, G. Vambhurkar, R. Kumar, P.S. Rajinikanth, S. Srivastava, Quality by Design (QbD) accredited naringenin-loaded chitosan nanoparticles impregnated gel for diabetic wound healing: Formulation, optimization, In silico and In vitro characterization, J. Drug Deliv. Sci. Technol. 114 (2025) 107418. https://doi.org/10.1016/j.jddst.2025.107418.
[54] D. Gol, O. Gok, Development of mitochondria-targeted and quercetin-loaded PLGA nanoparticles for reducing ROS production†, J. Drug Deliv. Sci. Technol. 104 (2025) 106577. https://doi.org/10.1016/j.jddst.2024.106577.
[55] V.P. Torchilin, Micellar Nanocarriers: Pharmaceutical Perspectives, Pharm. Res. 24 (2006) 1–16. https://doi.org/10.1007/s11095-006-9132-0.
[56] O.V. Obayomi, G.I. Edo, A.O. Dada, M. Dokouhaki, Advanced encapsulation technologies for functional foods: Enhancing stability, bioavailability, and controlled release of nutraceuticals and bioactives, Appl. Food Res. 6 (2026) 101622. https://doi.org/10.1016/j.afres.2025.101622.
[57] P. Singla, G. Parokie, S. Garg, S. Kaur, I. Kaur, R.D. Crapnell, C.E. Banks, U. Rinner, C. Wills, M. Peeters, Enhancing encapsulation of hydrophobic phyto-drugs naringenin and baicalein in polymeric nano-micelles, J. Drug Deliv. Sci. Technol. 83 (2023) 104403. https://doi.org/10.1016/j.jddst.2023.104403.
[58] A.R. Menjoge, R.M. Kannan, D.A. Tomalia, Dendrimer-based drug and imaging conjugates: design considerations for nanomedical applications, Drug Discov. Today. 15 (2010) 171–185. https://doi.org/10.1016/j.drudis.2010.01.009.
[59] A. PATRI, J. KUKOWSKALATALLO, J. BAKERJR, Targeted drug delivery with dendrimers: Comparison of the release kinetics of covalently conjugated drug and non-covalent drug inclusion complex, Adv. Drug Deliv. Rev. 57 (2005) 2203–2214. https://doi.org/10.1016/j.addr.2005.09.014.
[60] E. Abbasi, S.F. Aval, A. Akbarzadeh, M. Milani, H.T. Nasrabadi, S.W. Joo, Y. Hanifehpour, K. Nejati-Koshki, R. Pashaei-Asl, Dendrimers: synthesis, applications, and properties, Nanoscale Res. Lett. 9 (2014) 247. https://doi.org/10.1186/1556-276X-9-247.
[61] J. Zhang, Z. Zou, Y. He, N. Filipczak, S.S.K. Yalamarty, X. Li, V.P. Torchilin, Hybrid micellar preparations for co-delivery of PARP-1 siRNA and quercetin for cataract treatment, J. Control. Release. 382 (2025) 113700. https://doi.org/10.1016/j.jconrel.2025.113700.
[62] Y. Yousefpoor, S.S. Esnaashari, H. Baharifar, M. Mehrabi, A. Amani, Current challenges ahead in preparation, characterization, and pharmaceutical applications of nanoemulsions, WIREs Nanomedicine and Nanobiotechnology. 15 (2023). https://doi.org/10.1002/wnan.1920.
[63] N. Mishra, N. Kaushik, P.K. Sharma, M.A. Alam, Nano Emulsion Drug Delivery System: A Review, Curr. Nanomedicine. 13 (2023) 2–16. https://doi.org/10.2174/2468187313666230213121011.
[64] J. Li, M. Yin, M. Tian, J. Fang, H. Xu, Stiff-Soft Hybrid Biomimetic Nano-Emulsion for Targeted Liver Delivery

and Treatment of Early Nonalcoholic Fatty Liver Disease, Pharmaceutics. 16 (2024) 1303. https://doi.org/10.3390/pharmaceutics16101303.
[65] Z. Khatib Zadeh, S. Arab, S. Kazemi, M. Arabhalvaei, E.S. Afraz, M. Bahraminasab, In vitro anticancer effect of epigallocatechin gallate nano-emulsion on head and neck cancers, Clin. Transl. Oncol. 27 (2025) 3745–3762. https://doi.org/10.1007/s12094-025-03886-1.
[66] S. Moghassemi, A. Hadjizadeh, Nano-niosomes as nanoscale drug delivery systems: An illustrated review, J. Control. Release. 185 (2014) 22–36. https://doi.org/10.1016/j.jconrel.2014.04.015.
[67] T. Nasu, M. Sasaki, Effect of Mn2+ on the Development of Tension Induced in Guinea-pig Taenia Coli by Bay K 8644, J. Pharm. Pharmacol. 50 (1998) 311–315. https://doi.org/10.1111/j.2042-7158.1998.tb06866.x.
[68] H. Riazi, M.T. Goodarzi, M.H. Tabrizi, M. Mozaffari, A. Neamati, Preparation of the Myricetin-Loaded PEGylated Niosomes and Evaluation of their in vitro Anti-Cancer Potentials, Chem. Biodivers. 21 (2024). https://doi.org/10.1002/cbdv.202301767.
[69] O.A. Alsaidan, A. Zafar, R.H. Al-Ruwaili, M. Yasir, S.I. Alzarea, A.A. Alsaidan, L. Singh, M. Khalid, Niosomes gel of apigenin to improve the topical delivery: development, optimization, ex vivo permeation, antioxidant study, and in vivo evaluation, Artif. Cells, Nanomedicine, Biotechnol. 51 (2023) 604–617. https://doi.org/10.1080/21691401.2023.2274526.
[70] E. Touitou, N. Dayan, L. Bergelson, B. Godin, M. Eliaz, Ethosomes - Novel vesicular carriers for enhanced delivery: Characterization and skin penetration properties, J. Control. Release. 65 (2000) 403–418. https://doi.org/10.1016/S0168-3659(99)00222-9.
[71] A. Ascenso, C. Batista, P. Cardoso, T. Mendes, F. Praça, V. Bentley, S. Raposo, S. Simões, Development, characterization, and skin delivery studies of related ultradeformable vesicles: transfersomes, ethosomes, and transethosomes, Int. J. Nanomedicine. (2015) 5837. https://doi.org/10.2147/IJN.S86186.
[72] M. Zhang, X. Zhuang, S. Li, Y. Wang, X. Zhang, J. Li, D. Wu, Designed Fabrication of Phloretin-Loaded Propylene Glycol Binary Ethosomes: Stability, Skin Permeability and Antioxidant Activity, Molecules. 29 (2023) 66. https://doi.org/10.3390/molecules29010066.
[73] S.S. Raghav, B. Kumar, N.K. Sethiya, S. Pahwa, Development and optimization of kaempferol loaded ethosomes using <scp>Box–Behnken</scp> statistical design: In vitro and ex-vivo assessments, J. Biomed. Mater. Res. Part B Appl. Biomater. 112 (2024). https://doi.org/10.1002/jbm.b.35394.
[74] S.A.T. Opatha, V. Titapiwatanakun, R. Chutoprapat, Transfersomes: A Promising Nanoencapsulation Technique for Transdermal Drug Delivery, Pharmaceutics. 12 (2020) 855. https://doi.org/10.3390/pharmaceutics12090855.
[75] J. Wang, Y. Zhao, B. Zhai, J. Cheng, J. Sun, X. Zhang, D. Guo, Phloretin Transfersomes for Transdermal Delivery: Design, Optimization, and In Vivo Evaluation, Molecules. 28 (2023) 6790. https://doi.org/10.3390/molecules28196790.
[76] W.-C. Hsieh, C.-W. Fang, M. Suhail, Q. Lam Vu, C.-H. Chuang, P.-C. Wu, Improved skin permeability and whitening effect of catechin-loaded transfersomes through topical delivery, Int. J. Pharm. 607 (2021) 121030. https://doi.org/10.1016/j.ijpharm.2021.121030.
[77] C. Théry, K.W. Witwer, E. Aikawa, M.J. Alcaraz, J.D. Anderson, R. Andriantsitohaina, A. Antoniou, T. Arab, F. Archer, G.K. Atkin-Smith, D.C. Ayre, J. Bach, D. Bachurski, H. Baharvand, L. Balaj, S. Baldacchino, N.N. Bauer, A.A. Baxter, M. Bebawy, C. Beckham, A. Bedina Zavec, A. Benmoussa, A.C. Berardi, P. Bergese, E. Bielska, C. Blenkiron, S. Bobis-Wozowicz, E. Boilard, W. Boireau, A. Bongiovanni, F.E. Borràs, S. Bosch, C.M. Boulanger, X. Breakefield, A.M. Breglio, M.Á. Brennan, D.R. Brigstock, A. Brisson, M.L. Broekman, J.F. Bromberg, P. Bryl-Górecka, S. Buch, A.H. Buck, D. Burger, S. Busatto, D. Buschmann, B. Bussolati, E.I. Buzás, J.B. Byrd, G. Camussi, D.R. Carter, S. Caruso, L.W. Chamley, Y. Chang, C. Chen, S. Chen, L. Cheng, A.R. Chin, A. Clayton, S.P. Clerici, A. Cocks, E. Cocucci, R.J. Coffey, A. Cordeiro-da-Silva, Y. Couch, F.A. Coumans, B. Coyle, R. Crescitelli, M.F. Criado, C. D'Souza-Schorey, S. Das, A. Datta Chaudhuri, P. de Candia, E.F. De Santana, O. De Wever, H.A. del Portillo, T. Demaret, S. Deville, A. Devitt, B. Dhondt, D. Di Vizio, L.C. Dieterich, V. Dolo, A.P. Dominguez Rubio, M. Dominici, M.R. Dourado, T.A. Driedonks, F. V Duarte, H.M. Duncan, R.M. Eichenberger, K. Ekström, S. EL Andaloussi, C. Elie-Caille, U. Erdbrügger, J.M. Falcón-Pérez, F. Fatima, J.E. Fish, M. Flores-Bellver, A. Försönits, A. Frelet-Barrand, F. Fricke, G. Fuhrmann, S. Gabrielsson, A. Gámez-Valero, C. Gardiner, K. Gärtner, R. Gaudin, Y.S. Gho, B. Giebel, C. Gilbert, M. Gimona, I. Giusti, D.C. Goberdhan, A. Görgens, S.M. Gorski, D.W. Greening, J.C. Gross, A. Gualerzi, G.N. Gupta, D. Gustafson, A. Handberg, R.A. Haraszti, P. Harrison, H. Hegyesi, A. Hendrix, A.F. Hill, F.H. Hochberg, K.F. Hoffmann, B. Holder, H. Holthofer, B. Hosseinkhani, G. Hu, Y. Huang, V. Huber, S. Hunt, A.G. Ibrahim, T. Ikezu, J.M. Inal, M. Isin, A. Ivanova, H.K. Jackson, S. Jacobsen, S.M. Jay, M. Jayachandran, G. Jenster, L. Jiang, S.M. Johnson, J.C. Jones, A. Jong, T. Jovanovic-Talisman, S. Jung, R. Kalluri, S. Kano, S. Kaur, Y. Kawamura, E.T. Keller, D. Khamari, E. Khomyakova, A. Khvorova, P. Kierulf, K.P. Kim, T. Kislinger, M. Klingeborn, D.J. Klinke, M. Kornek, M.M. Kosanović, Á.F. Kovács, E. Krämer-Albers, S. Krasemann, M. Krause, I. V Kurochkin, G.D. Kusuma, S. Kuypers, S. Laitinen, S.M. Langevin, L.R. Languino, J. Lannigan, C. Lässer, L.C. Laurent, G. Lavieu, E. Lázaro-Ibáñez, S. Le Lay, M. Lee, Y.X.F. Lee, D.S. Lemos, M. Lenassi, A. Leszczynska, I.T. Li, K. Liao, S.F. Libregts, E. Ligeti, R. Lim, S.K. Lim, A. Linē, K. Linnemannstöns, A. Llorente, C.A. Lombard, M.J. Lorenowicz, Á.M. Lörincz, J. Lötvall, J. Lovett, M.C. Lowry, X. Loyer, Q. Lu, B. Lukomska, T.R. Lunavat, S.L. Maas, H. Malhi, A. Marcilla, J. Mariani, J. Mariscal, E.S. Martens-Uzunova, L. Martin-Jaular, M.C. Martinez, V.R. Martins, M. Mathieu, S. Mathivanan, M. Maugeri, L.K. McGinnis, M.J. McVey, D.G. Meckes, K.L. Meehan, I. Mertens, V.R. Minciacchi, A. Möller, M. Møller Jørgensen, A. Morales-Kastresana, J. Morhayim, F. Mullier, M. Muraca, L. Musante, V. Mussack,

D.C. Muth, K.H. Myburgh, T. Najrana, M. Nawaz, I. Nazarenko, P. Nejsum, C. Neri, T. Neri, R. Nieuwland, L. Nimrichter, J.P. Nolan, E.N. Nolte-'t Hoen, N. Noren Hooten, L. O'Driscoll, T. O'Grady, A. O'Loghlen, T. Ochiya, M. Olivier, A. Ortiz, L.A. Ortiz, X. Osteikoetxea, O. Østergaard, M. Ostrowski, J. Park,
D.M. Pegtel, H. Peinado, F. Perut, M.W. Pfaffl, D.G. Phinney, B.C. Pieters, R.C. Pink, D.S. Pisetsky, E. Pogge von Strandmann, I. Polakovicova, I.K. Poon, B.H. Powell, I. Prada, L. Pulliam, P. Quesenberry, A. Radeghieri, R.L. Raffai, S. Raimondo, J. Rak, M.I. Ramirez, G. Raposo, M.S. Rayyan, N. Regev-Rudzki, F.L. Ricklefs, P.D. Robbins, D.D. Roberts, S.C. Rodrigues, E. Rohde, S. Rome, K.M. Rouschop, A. Rughetti, A.E. Russell, P. Saá, S. Sahoo, E. Salas-Huenuleo, C. Sánchez, J.A. Saugstad, M.J. Saul, R.M. Schiffelers, R. Schneider, T.H. Schøyen, A. Scott, E. Shahaj, S. Sharma, O. Shatnyeva, F. Shekari, G.V. Shelke, A.K. Shetty, K. Shiba, P.R. Siljander, A.M. Silva, A. Skowronek, O.L. Snyder, R.P. Soares, B.W. Sódar, C. Soekmadji, J. Sotillo, P.D. Stahl, W. Stoorvogel,
S.L. Stott, E.F. Strasser, S. Swift, H. Tahara, M. Tewari, K. Timms, S. Tiwari, R. Tixeira, M. Tkach, W.S. Toh, R. Tomasini, A.C. Torrecilhas, J.P. Tosar, V. Toxavidis, L. Urbanelli, P. Vader, B.W. van Balkom, S.G. van der Grein,
J. Van Deun, M.J. van Herwijnen, K. Van Keuren-Jensen, G. van Niel, M.E. van Royen, A.J. van Wijnen, M.H. Vasconcelos, I.J. Vechetti, T.D. Veit, L.J. Vella, É. Velot, F.J. Verweij, B. Vestad, J.L. Viñas, T. Visnovitz, K. V Vukman, J. Wahlgren, D.C. Watson, M.H. Wauben, A. Weaver, J.P. Webber, V. Weber, A.M. Wehman, D.J. Weiss, J.A. Welsh, S. Wendt, A.M. Wheelock, Z. Wiener, L. Witte, J. Wolfram, A. Xagorari, P. Xander, J. Xu, X. Yan, M. Yáñez-Mó, H. Yin, Y. Yuana, V. Zappulli, J. Zarubova, V. Žėkas, J. Zhang, Z. Zhao, L. Zheng, A.R. Zheutlin, A.M. Zickler, P. Zimmermann, A.M. Zivkovic, D. Zocco, E.K. Zuba-Surma, Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines, J. Extracell. Vesicles. 7 (2018). https://doi.org/10.1080/20013078.2018.1535750.

[78] D.M. Pegtel, S.J. Gould, Exosomes, Annu. Rev. Biochem. 88 (2019) 487–514. https://doi.org/10.1146/annurev-biochem-013118-111902.

[79] R. Kalluri, V.S. LeBleu, The biology , function , and biomedical applications of exosomes, Science (80-.). 367 (2020). https://doi.org/10.1126/science.aau6977.

[80] L. Zhao, X. Dong, B. Guo, J. Song, H. Bi, Quercetin-loaded exosomes delivery system prevents myopia progression by targeting endoplasmic reticulum stress and ferroptosis in scleral fibroblasts, Mater. Today Bio. 32 (2025) 101896. https://doi.org/10.1016/j.mtbio.2025.101896.

[81] C. He, Z. Wang, Z. Jiang, Y. Zhou, X. Chen, J. Zhang, B. Wang, Q. Wang, T. Wu, C. Li, Z. Jian, Microneedles combining delivery of hUMSC-derived exosomes and EGCG mitigate UV-induced skin damage, J. Nanobiotechnology. 23 (2025) 643. https://doi.org/10.1186/s12951-025-03735-x.

[82] J.M. Rosenholm, C. Sahlgren, M. Lindén, Towards multifunctional, targeted drug delivery systems using mesoporous silica nanoparticles – opportunities & challenges, Nanoscale. 2 (2010) 1870. https://doi.org/10.1039/c0nr00156b.

[83] E. Boisselier, D. Astruc, Gold nanoparticles in nanomedicine: preparations, imaging, diagnostics, therapies and toxicity, Chem. Soc. Rev. 38 (2009) 1759. https://doi.org/10.1039/b806051g.

[84] J. Gao, H. Gu, B. Xu, Multifunctional Magnetic Nanoparticles: Design, Synthesis, and Biomedical Applications, Acc. Chem. Res. 42 (2009) 1097–1107. https://doi.org/10.1021/ar9000026.

[85] F.G. Milanezi, L.M. Meireles, M.M. de Christo Scherer, J.P. de Oliveira, A.R. da Silva, M.L. de Araujo, D.C. Endringer, M. Fronza, M.C.C. Guimarães, R. Scherer, Antioxidant, antimicrobial and cytotoxic activities of gold nanoparticles capped with quercetin, Saudi Pharm. J. 27 (2019) 968–974. https://doi.org/10.1016/j.jsps.2019.07.005.

[86] A. Semalty, M. Semalty, M.S.M. Rawat, F. Franceschi, Supramolecular phospholipids–polyphenolics interactions: The PHYTOSOME® strategy to improve the bioavailability of phytochemicals, Fitoterapia. 81 (2010) 306–314. https://doi.org/10.1016/j.fitote.2009.11.001.

[87] M. Lu, Q. Qiu, X. Luo, X. Liu, J. Sun, C. Wang, X. Lin, Y. Deng, Y. Song, Phyto-phospholipid complexes (phytosomes): A novel strategy to improve the bioavailability of active constituents, Asian J. Pharm. Sci. 14 (2019) 265–274. https://doi.org/10.1016/j.ajps.2018.05.011.

[88] S.M. Talaat, Y.S.R. Elnaggar, M.A. Gowayed, S.O. El-Ganainy, M. Allam, O.Y. Abdallah, Novel PEGylated cholephytosomes for targeting fisetin to breast cancer: in vitro appraisal and in vivo antitumoral studies, Drug Deliv. Transl. Res. 14 (2024) 433–454. https://doi.org/10.1007/s13346-023-01409-5.

[89] M. Sabzichi, H. Hamishehkar, F. Ramezani, S. Sharifi, M. Tabasinezhad, M. Pirouzpanah, P. Ghanbari, N. Samadi, Luteolin-loaded Phytosomes Sensitize Human Breast Carcinoma MDA-MB 231 Cells to Doxorubicin by Suppressing Nrf2 Mediated Signalling, Asian Pacific J. Cancer Prev. 15 (2014) 5311–5316. https://doi.org/10.7314/APJCP.2014.15.13.5311.

[90] S.Z. Alshawwa, A.A. Kassem, R.M. Farid, S.K. Mostafa, G.S. Labib, Nanocarrier Drug Delivery Systems: Characterization, Limitations, Future Perspectives and Implementation of Artificial Intelligence, Pharmaceutics. 14 (2022) 883. https://doi.org/10.3390/pharmaceutics14040883.

[91] X. Zhang, S. Tu, J. Tian, Y. Liang, Y. An, T. Zhang, H. Guan, B. Xiong, L. Qin, Y. Li, L. Gong, Liposome-Based Nanoparticle Delivery Systems for Lung Diseases: Opportunities and Challenges, Int. J. Nanomedicine. Volume 20 (2025) 12485–12509. https://doi.org/10.2147/IJN.S538382.

[92] S.S. Marques, M.A. Segundo, Nanometrics goes beyond the size: Assessment of nanoparticle concentration and encapsulation efficiency in nanocarriers, TrAC Trends Anal. Chem. 174 (2024) 117672. https://doi.org/10.1016/j.trac.2024.117672.

[93] B.T. Sanika Kadam, S. Kadam, B. Tare, Advances in Nanocarriers for the Encapsulation of Phytochemicals: A Comparative Review, Int. J. Pharm. Sci. 04 (2026) 3083. https://doi.org/10.5281/zenodo.18700610.

[94] Y.Y. Uzuner, H. Sevinç, Z. Kanlidere, Ethosomal Nanocarriers for Hydrophilic Peptide Encapsulation: Formulation

Optimization, Stability, and In Vitro Release Performance, Molecules. 31 (2026) 744. https://doi.org/10.3390/molecules31040744.
[95] Z. Xu, Y. Xie, W. Chen, W. Deng, Nanocarrier-Based Systems for Targeted Delivery: Current Challenges and Future Directions, MedComm. 6 (2025). https://doi.org/10.1002/mco2.70337.
[96] Y. Zhang, W. Ng, X. Feng, F. Cao, H. Xu, Lipid vesicular nanocarrier: Quick encapsulation efficiency determination and transcutaneous application, Int. J. Pharm. 516 (2017) 225–230. https://doi.org/10.1016/j.ijpharm.2016.11.011.
[97] A. Mokhtarzadeh, A. Alibakhshi, H. Yaghoobi, M. Hashemi, M. Hejazi, M. Ramezani, Recent advances on biocompatible and biodegradable nanoparticles as gene carriers, Expert Opin. Biol. Ther. 16 (2016) 771–785. https://doi.org/10.1517/14712598.2016.1169269.
[98] A.R. Bilia, B. Isacchi, C. Righeschi, C. Guccione, M.C. Bergonzi, Flavonoids Loaded in Nanocarriers: An Opportunity to Increase Oral Bioavailability and Bioefficacy, Food Nutr. Sci. 05 (2014) 1212–1327. https://doi.org/10.4236/fns.2014.513132.
[99] P. Uniyal, A. Akhtar, R. Rawat, Flavonoid-Based Combination Therapies and Nano-Formulations: An Emerging Frontier in Breast Cancer Treatment, Pharmaceuticals. 18 (2025) 1486. https://doi.org/10.3390/ph18101486.
[100] A. Ullah, S. Munir, S. Lal Badshah, N. Khan, L. Ghani, B.G. Poulson, A.-H. Emwas, M. Jaremko, molecules Important Flavonoids and Their Role as a Therapeutic Agent, (n.d.). https://doi.org/10.3390/molecules25225243.
[101] K. Agarawal, Y. Anant Kulkarni, S. Wairkar, Nanoformulations of flavonoids for diabetes and microvascular diabetic complications, Drug Deliv. Transl. Res. 13 (2023) 18–36. https://doi.org/10.1007/s13346-022-01174-x.
[102] K. Dwivedi, A.K. Mandal, O. Afzal, A.S.A. Altamimi, A. Sahoo, M.A. Alossaimi, W.H. Almalki, A. Alzahrani, M.A. Barkat, T.M. Almeleebia, S.N. Mir Najib Ullah, M. Rahman, Emergence of Nano-Based Formulations for Effective Delivery of Flavonoids against Topical Infectious Disorders, Gels. 9 (2023) 671. https://doi.org/10.3390/gels9080671.
[103] J.C. Stevens Barrón, C. Chapa González, E. Álvarez Parrilla, L.A. De la Rosa, Nanoparticle-Mediated Delivery of Flavonoids: Impact on Proinflammatory Cytokine Production: A Systematic Review, Biomolecules. 13 (2023) 1158. https://doi.org/10.3390/biom13071158.
[104] A. Ibi, C. Chang, Y.C. Kuo, Y. Zhang, P. Do, M. Du, Y.S. Roh, R. Gahler, M. Hardy, J. Solnier, Comparative Pharmacokinetics and Safety of a Micellar Chrysin–Quercetin–Rutin Formulation: A Randomized Crossover Trial, Antioxidants. 14 (2025) 1313. https://doi.org/10.3390/antiox14111313.
[105] J. Solnier, Y. Zhang, K. Roh, Y.C. Kuo, M. Du, S. Wood, M. Hardy, R.J. Gahler, C. Chang, A Pharmacokinetic Study of Different Quercetin Formulations in Healthy Participants: A Diet-Controlled, Crossover, Single- and Multiple-Dose Pilot Study, Evidence-Based Complement. Altern. Med. 2023 (2023). https://doi.org/10.1155/2023/9727539.
[106] A. Riva, M. Ronchi, G. Petrangolini, S. Bosisio, P. Allegrini, Improved Oral Absorption of Quercetin from Quercetin Phytosome®, a New Delivery System Based on Food Grade Lecithin, Eur. J. Drug Metab. Pharmacokinet. 44 (2019) 169–177. https://doi.org/10.1007/s13318-018-0517-3.
[107] H. Shen, Y. Liu, H. Zhang, P. Ding, L. Zhang, L. Zhang, J. Ju, Enhancing the oral bioavailability of baicalein via Solutol® HS15 and Poloxamer 188 mixed micelles system, J. Pharm. Pharmacol. 71 (2019) 765–773. https://doi.org/10.1111/jphp.13058.
[108] I.S. Song, J.S. Cha, M.K. Choi, Enhanced oral bioavailability of naringenin administered in a mixed micelle formulation with Pluronic F127 and Tween 80 in rats, J. Pharm. Investig. 45 (2015) 633–640. https://doi.org/10.1007/s40005-015-0216-x.
[109] D. Chen, Y. Liu, P. Liu, Y. Zhou, L. Jiang, C. Yuan, M. Huang, Orally delivered rutin in lipid-based nano-formulation exerts strong antithrombotic effects by protein disulfide isomerase inhibition, Drug Deliv. 29 (2022) 1824–1835. https://doi.org/10.1080/10717544.2022.2083726.
[110] S. Banik, K. Yamada, H. Sato, S. Onoue, Development of Poly(lipoic acid) Nanoparticles with Improved Oral Bioavailability and Hepatoprotective Effects of Quercetin, Mol. Pharm. 19 (2022) 1468–1476. https://doi.org/10.1021/acs.molpharmaceut.2c00009.
[111] S.S. Das, P.R.P. Verma, V. Sekarbabu, S. Mohanty, A.K. Pattnaik, J. Ruokolainen, K.K. Kesari, S.K. Singh, Liquid Chromatography–Electrospray Ionization Tandem Mass Spectrometry Estimation of Quercetin-Loaded Nanoemulsion in Rabbit Plasma: In Vivo – In Silico Pharmacokinetic Analysis Using GastroPlus, ACS Omega. 8 (2023) 12456–12466. https://doi.org/10.1021/acsomega.3c00429.
[112] H.S. Kapare, N. Patil, M. Bhosale, D. Kulkarni, R. Bhole, Nanocochleate-based delivery of quercetin with enhanced therapeutic potential: formulation, cytotoxicity and pharmacokinetics study, Futur. J. Pharm. Sci. 10 (2024) 165. https://doi.org/10.1186/s43094-024-00732-z.
[113] A. Joseph, P. Shanmughan, A. Balakrishnan, B. Maliakel, K.I. M, Enhanced Bioavailability and Pharmacokinetics of a Natural Self-Emulsifying Reversible Hybrid-Hydrogel System of Quercetin: A Randomized Double-Blinded Comparative Crossover Study, ACS Omega. 7 (2022) 46825–46832. https://doi.org/10.1021/acsomega.2c05929.
[114] Z. Wang, B. Dai, X. Tang, Z. Che, F. Hu, C. Shen, W. Wu, B. Shen, H. Yuan, Fabrication and In Vitro/Vivo Evaluation of Drug Nanocrystals Self-Stabilized Pickering Emulsion for Oral Delivery of Quercetin, Pharmaceutics. 14 (2022) 897. https://doi.org/10.3390/pharmaceutics14050897.
[115] H.M. Morsy, M.Y. Zaky, N.Y.S. Yassin, A.Y.Z. Khalifa, Nanoparticle-based flavonoid therapeutics: Pioneering biomedical applications in antioxidants, cancer treatment, cardiovascular health, neuroprotection, and cosmeceuticals, Int. J. Pharm. 670 (2025) 125135. https://doi.org/10.1016/j.ijpharm.2024.125135.
[116] S. Dewanjee, P. Chakraborty, H. Bhattacharya, S.K. Singh, K. Dua, A. Dey, N.K. Jha, Recent advances in flavonoid-based nanocarriers as an emerging drug delivery approach for cancer chemotherapy, Drug Discov. Today. 28

(2023) 103409. https://doi.org/10.1016/j.drudis.2022.103409.
[117] N. Kaushal, M. Singh, R. Singh Sangwan, Flavonoids: Food associations, therapeutic mechanisms, metabolism and nanoformulations, Food Res. Int. 157 (2022) 111442. https://doi.org/10.1016/j.foodres.2022.111442.
[118] Y.F. Zverev, A.Y. Rykunova, Modern Nanocarriers as a Factor in Increasing the Bioavailability and Pharmacological Activity of Flavonoids, Appl. Biochem. Microbiol. 58 (2022) 1002–1020. https://doi.org/10.1134/S0003683822090149.
[119] N. Hussain, S.K. Dubey, C.K. Katiyar, R. P, M. Agrawal, A. Alexander, Harnessing potential of liposomal drug carriers for enhanced pharmacokinetic profile of flavonoids, J. Drug Deliv. Sci. Technol. 109 (2025) 106978. https://doi.org/10.1016/j.jddst.2025.106978.
[120] I.A. Khabarov, S.D. Sergazy, A. Amanzhan, A.S. Maikenova, A.N. Zhabayeva, S.M. Adekenov, Polyphenolic phytosomes for targeted drug delivery, Fitoterapia. 187 (2025) 106920. https://doi.org/10.1016/j.fitote.2025.106920.
[121] H. Abbas, N.S. El Sayed, N.A.H.A. Youssef, P. M. E. Gaafar, M.R. Mousa, A.M. Fayez, M.A. Elsheikh, Novel Luteolin-Loaded Chitosan Decorated Nanoparticles for Brain-Targeting Delivery in a Sporadic Alzheimer's Disease Mouse Model: Focus on Antioxidant, Anti-Inflammatory, and Amyloidogenic Pathways, Pharmaceutics. 14 (2022) 1003. https://doi.org/10.3390/pharmaceutics14051003.
[122] T. Halder, B. Patel, N. Acharya, Design and optimization of myricetin encapsulated nanostructured lipid carriers: In-vivo assessment against cognitive impairment in amyloid beta (1–42) intoxicated rats, Life Sci. 297 (2022) 120479. https://doi.org/10.1016/j.lfs.2022.120479.
[123] P. Kumar, P. Kumar, N.P. Jain, Preparation, Characterization and Evaluation of Antioxidant Flavonosomes, J. Drug Deliv. Ther. 14 (2024) 114–120. https://doi.org/10.22270/jddt.v14i6.6626.
[124] A.A. Revankar, A.S. Patil, R. Karishetti, K.R. Chougule, P. Patil, A. Salokhe, Enhanced bioavailability of Quercetin-loaded niosomal in situ gel for the management of Parkinson's disease, Front. Pharmacol. 15 (2025). https://doi.org/10.3389/fphar.2024.1519649.
[125] X. Shang, F. Hu, Oleic Acid-Shelled Solid Lipid Nanocomplexes for Enhanced Quercetin Delivery with Improved Antioxidant and Stability Properties, ACS Omega. 10 (2025) 32424–32432. https://doi.org/10.1021/acsomega.5c04754.
[126] E. Al-Shalabi, S. Abusulieh, A.M. Hammad, S. Sunoqrot, Rhoifolin loaded in PLGA nanoparticles alleviates oxidative stress and inflammation in vitro and in vivo, Biomater. Sci. 10 (2022) 5504–5519. https://doi.org/10.1039/D2BM00309K.
[127] R.H. Awadeen, M.F. Boughdady, R.A. Zaghloul, W.M. Elsaed, I.I. Abu Hashim, M.M. Meshali, Formulation of lipid polymer hybrid nanoparticles of the phytochemical Fisetin and its in vivo assessment against severe acute pancreatitis, Sci. Rep. 13 (2023) 19110. https://doi.org/10.1038/s41598-023-46215-8.
[128] E.V. Fuior, C.A. Mocanu, M. Deleanu, G. Voicu, M. Anghelache, D. Rebleanu, M. Simionescu, M. Calin, Evaluation of VCAM-1 Targeted Naringenin/Indocyanine Green-Loaded Lipid Nanoemulsions as Theranostic Nanoplatforms in Inflammation, Pharmaceutics. 12 (2020) 1066. https://doi.org/10.3390/pharmaceutics12111066.
[129] S. Hatem, M. El-Kayal, Novel anti-psoriatic nanostructured lipid carriers for the cutaneous delivery of luteolin: A comprehensive in-vitro and in-vivo evaluation, Eur. J. Pharm. Sci. 191 (2023) 106612. https://doi.org/10.1016/j.ejps.2023.106612.
[130] E.Y. Lee, J. Choi, Y.M. Kim, K. Yang, A. Jang, H.K. Shin, H.R. Kim, K. Nam, J.K. Hwang, J. Park, W.J. Park, .H. Roh, Plant derived extract loaded nanostructured lipid carriers with enhanced oral delivery for the treatment of acute inflammation, Sci. Rep. 15 (2025) 34551. https://doi.org/10.1038/s41598-025-17898-y.
[131] H. Kumar, P. Chand, S. Pachal, S. Mallick, R. Jain, S. V. Madhunapantula, V. Jain, Fisetin-Loaded Nanostructured Lipid Carriers: Formulation and Evaluations against Advanced and Metastatic Melanoma, Mol. Pharm. 20 (2023) 6035–6055. https://doi.org/10.1021/acs.molpharmaceut.3c00309.
[132] J.M.M. Mohamed, F. Ahmad, M. El-Sherbiny, M.A. Al Mohaini, K. Venkatesan, Y.B.A. Alrashdi, M.B. Eldesoqui, A.E. Ibrahim, A.F. Dawood, A.M. Ibrahim, S. El Deeb, Optimization and characterization of quercetin-loaded solid lipid nanoparticles for biomedical application in colorectal cancer, Cancer Nanotechnol. 15 (2024) 16. https://doi.org/10.1186/s12645-024-00249-3.
[133] J.S. Pandi, P. Pavadai, T. Panneerselvam, M. Sankaranarayanan, S. Kunjiappan, Enhanced anticancer activity of naringenin-encapsulated poly (lactic acid)/neem gum nanoparticles for breast cancer cells, Biomed. Mater. 21 (2026) 015017. https://doi.org/10.1088/1748-605X/ae3411.
[134] S. Paranthaman, C.A. Uthaiah, R.A.M. Osmani, U. Hani, M. Ghazwani, A.H. Alamri, A. Al Fatease, S. V. Madhunapantula, D.V. Gowda, Anti-Proliferative Potential of Quercetin Loaded Polymeric Mixed Micelles on Rat C6 and Human U87MG Glioma Cells, Pharmaceutics. 14 (2022) 1643. https://doi.org/10.3390/pharmaceutics14081643.
[135] M. Tilawat, S. Bonde, Curcumin and quercetin loaded nanocochleates gel formulation for localized application in breast cancer therapy, Heliyon. 9 (2023) e22892. https://doi.org/10.1016/j.heliyon 2023.e22892.
[136] P. Bhadane, A. Khairnar, K. Pandya, A. Naha, D. Kumar, K.A. Abutwaibe, J. Desai, N. Bombatkar, P. Rajput, D. Kumar, Targeted Delivery of Quercetin to the Brain via a Modified Polymeric Nanocarrier, Macromol. Biosci. 26 (2026). https://doi.org/10.1002/mabi.202500503.
[137] J. Chen, J. Chen, P. Yu, C. Yang, C. Xia, J. Deng, M. Yu, Z. Xiang, L. Gan, B. Zhu, Y. Wu, X. Yang, A Novel Quercetin Encapsulated Glucose Modified Liposome and Its Brain-Target Antioxidative Neuroprotection Effects, Molecules. 29 (2024) 607. https://doi.org/10.3390/molecules29030607.
[138] M.H. Elkomy, R.M. Zaki, O.A. Alsaidan, M. Elmowafy, A. Zafar, K. Shalaby, M.A. Abdelgawad, F.I. Abo El-Ela,

M.E. Rateb, I.A. Naguib, H.M. Eid, Intranasal Nanotransferosomal Gel for Quercetin Brain Targeting: I. Optimization, Characterization, Brain Localization, and Cytotoxic Studies, Pharmaceutics. 15 (2023) 1805. https://doi.org/10.3390/pharmaceutics15071805.
[139] M.A. Elsheikh, Y.A. El-Feky, M.M. Al-Sawahli, M.E. Ali, A.M. Fayez, H. Abbas, A Brain-Targeted Approach to Ameliorate Memory Disorders in a Sporadic Alzheimer's Disease Mouse Model via Intranasal Luteolin-Loaded Nanobilosomes, Pharmaceutics. 14 (2022) 576. https://doi.org/10.3390/pharmaceutics14030576.
[140] A. Ghosh, N. Khanam, D. Nath, Solid lipid nanoparticle: A potent vehicle of the kaempferol for brain delivery through the blood-brain barrier in the focal cerebral ischemic rat, Chem. Biol. Interact. 397 (2024) 111084. https://doi.org/10.1016/j.cbi.2024.111084.
[141] M.Z. Ahmad, K. Pathak, A. Alam, B.A. Abdel-Wahab, M.B. Bakir, A. Das, M.P. Pathak, M.M. Abdullah, K.A. Ahmed, M.Y. Alasmary, A.A. Alqahtani, H. Sarma, Improved antidiabetic potential of quercetin-loaded chitosan–lecithin nanoparticles for effective glycaemic control, J. Drug Target. 33 (2025) 1591–1606. https://doi.org/10.1080/1061186X.2025.2511837.
[142] S. Ferradj, M.M. Yahoum, M. Rebiha, I. Nabi, S. Toumi, S. Lefnaoui, A. Hadj-Ziane-Zafour, N. Touzout, H. Tahraoui, A. Mihoub, M.F. Seleiman, N. Ali, J. Zhang, A. Amrane, Nanocurcumin-Based Sugar-Free Formulation: Development and Impact on Diabetes and Oxidative Stress Reduction, Nanomaterials. 14 (2024) 1105. https://doi.org/10.3390/nano14131105.
[143] R. Gutiérrez, J. Gómez, R. Urby, J. Soto, H. Parra, Evaluation of Diabetes Effects of Selenium Nanoparticles Synthesized from a Mixture of Luteolin and Diosmin on Streptozotocin-Induced Type 2 Diabetes in Mice, Molecules. 27 (2022) 5642. https://doi.org/10.3390/molecules27175642.
[144] M. Mahadev, A. Dubey, A. Shetty, Ultrasonically Fabricated Beta-Carotene Nanoemulsion: Optimization, Characterization and Evaluation of Combinatorial Effect with Quercetin on Streptozotocin-Induced Diabetic Rat Model, Pharmaceutics. 15 (2023) 574. https://doi.org/10.3390/pharmaceutics15020574.
[145] A. Zafar, O.A. Alsaidan, M.H. Elkomy, S.S. Imam, M. Yasir, K.S. Alharbi, M. Khalid, Formulation and optimization of Naringin polymeric nanoparticles: Optimization to in vivo evaluation, J. Drug Deliv. Sci. Technol. 88 (2023) 104978. https://doi.org/10.1016/j.jddst.2023.104978.
[146] P. Sharma, T. Bal, S.K. Singh, N. Sharma, Biodegradable polymeric nanocomposite containing phloretin for enhanced oral bioavailability and improved myocardial ischaemic recovery, J. Microencapsul. 41 (2024) 754–769. https://doi.org/10.1080/02652048.2024.2418608.
[147] M. Chahardori, R. Yazdian-Robati, M. Seyedabadi, M. Shokrzadeh, H. Mohammadi, Cardiac-Targeted Quercetin-Loaded PLGA Nanoparticles Attenuate Doxorubicin-Induced Cardiotoxicity via Nrf2/HO-1 Pathway Activation in Mice, J. Appl. Toxicol. 46 (2026) 2528–2543. https://doi.org/10.1002/jat.70044.
[148] S. Jaiswal, M.M. Anjum, S. Thakur, P. Pandey, D.K. Arya, A. Kumar, A.S. Kaushik, P.S. Rajinikanth, Evaluation of cardioprotective effect of naringin loaded lignin nanoparticles against isoproterenol induced myocardial infarction, J. Drug Deliv. Sci. Technol. 89 (2023) 105076. https://doi.org/10.1016/j.jddst.2023.105076.
[149] C. Chen, W. Liu, X. Gu, L. Zhang, X. Mao, Z. Chen, L. Tao, Baicalin-loaded Polydopamine modified ZIF-8 NPs inhibits myocardial ischemia/reperfusion injury in rats, J. Biomater. Sci. Polym. Ed. 35 (2024) 1863–1878. https://doi.org/10.1080/09205063.2024.2358640.
[150] C. Serri, V. Quagliariello, I. Cruz-Maya, V. Guarino, N. Maurea, P. Giunchedi, G. Rassu, E. Gavini, Hyaluronic Acid-Based Nanoparticles Loaded with Rutin as Vasculo-Protective Tools against Anthracycline-Induced Endothelial Damages, Pharmaceutics. 16 (2024) 985. https://doi.org/10.3390/pharmaceutics16080985.
[151] T. Almeleebia, M., M.H. Akhter, H. Khalilullah, M.A. Rahman, S. Ahmad, N. Alam, M.S. Ali, G. Khan, I.M. Alanazi, M., N. Shahzad, A. Alalmaie, Co-Delivery of Naringin and Ciprofloxacin by Oleic Acid Lipid Core Encapsulated in Carboxymethyl Chitosan/Alginate Nanoparticle Composite for Enhanced Antimicrobial Activity, ACS Omega. 9 (2024) 6845–6860. https://doi.org/10.1021/acsomega.3c08200.
[152] D.P.C. de Barros, R. Santos, P. Reed, L.P. Fonseca, A. Oliva, Design of Quercetin-Loaded Natural Oil-Based Nanostructured Lipid Carriers for the Treatment of Bacterial Skin Infections, Molecules. 27 (2022) 8818. https://doi.org/10.3390/molecules27248818.
[153] F. De Gaetano, F. Caridi, N. Totaro, C. Celesti, V. Venuti, G. Ginestra, A. Nostro, S. Tommasini, C.A. Ventura, R. Stancanelli, Naringenin-Loaded Solid Lipid Nanoparticles: Physical–Chemical Characterization and In Vitro Antibacterial Activity, Pharmaceuticals. 18 (2025) 232. https://doi.org/10.3390/ph18020232.
[154] J. Hemmati, M. Chiani, Z. Chegini, A. Seifalian, M.R. Arabestani, Surface modified niosomal quercetin with cationic lipid: an appropriate drug delivery system against Pseudomonas aeruginosa Infections, Sci. Rep. 14 (2024) 13362. https://doi.org/10.1038/s41598-024-64416-7.
[155] S. Imam, S. Gilani, A. Zafar, M. Jumah, R. Ali, M. Ahmed, S. Alshehri, Preparation and Optimization of Naringin Oral Nanocarrier: In Vitro Characterization and Antibacterial Activity, Coatings. 12 (2022) 1230. https://doi.org/10.3390/coatings12091230.
[156] K. Jomova, S.Y. Alomar, R. Valko, J. Liska, E. Nepovimova, K. Kuca, M. Valko, Flavonoids and their role in oxidative stress, inflammation, and human diseases, Chem. Biol. Interact. 413 (2025) 111489. https://doi.org/10.1016/j.cbi.2025.111489.
[157] P.-G. Pietta, Flavonoids as Antioxidants, J. Nat. Prod. 63 (2000) 1035–1042. https://doi.org/10.1021/np9904509.
[158] S. Chen, X. Wang, Y. Cheng, H. Gao, X. Chen, A Review of Classification, Biosynthesis, Biological Activities and Potential Applications of Flavonoids, Molecules. 28 (2023) 4982. https://doi.org/10.3390/molecules28134982.
[159] S. Kumar, A.K. Pandey, Chemistry and Biological Activities of Flavonoids: An Overview, Sci. World J. 2013

(2013). https://doi.org/10.1155/2013/162750.
[160] S. Safe, A. Jayaraman, R.S. Chapkin, M. Howard, K. Mohankumar, R. Shrestha, Flavonoids: structure–function and mechanisms of action and opportunities for drug development, Toxicol. Res. 37 (2021) 147–162. https://doi.org/10.1007/s43188-020-00080-z.
[161] M.C. Dias, D.C.G.A. Pinto, A.M.S. Silva, Plant Flavonoids: Chemical Characteristics and Biological Activity, Molecules. 26 (2021) 5377. https://doi.org/10.3390/molecules26175377.
[162] H. Abbas, N.S. El Sayed, N.A.H.A. Youssef, P. M. E. Gaafar, M.R. Mousa, A.M. Fayez, M.A. Elsheikh, Novel Luteolin-Loaded Chitosan Decorated Nanoparticles for Brain-Targeting Delivery in a Sporadic Alzheimer's Disease Mouse Model: Focus on Antioxidant, Anti-Inflammatory, and Amyloidogenic Pathways, Pharmaceutics. 14 (2022) 1003. https://doi.org/10.3390/pharmaceutics14051003.
[163] T. Halder, B. Patel, N. Acharya, Design and optimization of myricetin encapsulated nanostructured lipid carriers: In-vivo assessment against cognitive impairment in amyloid beta (1–42) intoxicated rats, Life Sci. 297 (2022) 120479. https://doi.org/10.1016/j.lfs.2022.120479.
[164] P. Kumar, P. Kumar, N.P. Jain, Preparation, Characterization and Evaluation of Antioxidant Flavonosomes, J. Drug Deliv. Ther. 14 (2024) 114–120. https://doi.org/10.22270/jddt.v14i6.6626.
[165] X. Shang, F. Hu, Oleic Acid-Shelled Solid Lipid Nanocomplexes for Enhanced Quercetin Delivery with Improved Antioxidant and Stability Properties, ACS Omega. 10 (2025) 32424–32432. https://doi.org/10.1021/acsomega.5c04754.
[166] A. Ullah, S. Munir, S.L. Badshah, N. Khan, L. Ghani, B.G. Poulson, A.H. Emwas, M. Jaremko, Important flavonoids and their role as a therapeutic agent, Molecules. 25 (2020). https://doi.org/10.3390/molecules25225243.
[167] H. Hasnat, S.A. Shompa, M.M. Islam, S. Alam, F.T. Richi, N.U. Emon, S. Ashrafi, N.U. Ahmed, M.N.R. Chowdhury, N. Fatema, M.S. Hossain, A. Ghosh, F. Ahmed, Flavonoids: A treasure house of prospective pharmacological potentials, Heliyon. 10 (2024) e27533. https://doi.org/10.1016/j.heliyon.2024.e27533.
[168] M.M. Jucá, F.M.S. Cysne Filho, J.C. de Almeida, D. da S. Mesquita, J.R. de M. Barriga, K.C.F. Dias, T.M. Barbosa, L.C. Vasconcelos, L.K.A.M. Leal, J.E. Ribeiro, S.M.M. Vasconcelos, Flavonoids: biological activities and therapeutic potential, Nat. Prod. Res. 34 (2020) 692–705. https://doi.org/10.1080/14786419.2018.1493588.
[169] Z. Wu, T. Zhang, X. Ma, S. Guo, Q. Zhou, A. Zahoor, G. Deng, Recent advances in anti-inflammatory active components and action mechanisms of natural medicines, Inflammopharmacology. 31 (2023) 2901–2937. https://doi.org/10.1007/s10787-023-01369-9.
[170] E. Al-Shalabi, S. Abusulieh, A.M. Hammad, S. Sunoqrot, Rhoifolin loaded in PLGA nanoparticles alleviates oxidative stress and inflammation in vitro and in vivo, Biomater. Sci. 10 (2022) 5504–5519. https://doi.org/10.1039/D2BM00309K.
[171] R.H. Awadeen, M.F. Boughdady, R.A. Zaghloul, W.M. Elsaed, I.I. Abu Hashim, M.M. Meshali, Formulation of lipid polymer hybrid nanoparticles of the phytochemical Fisetin and its in vivo assessment against severe acute pancreatitis, Sci. Rep. 13 (2023) 19110. https://doi.org/10.1038/s41598-023-46215-8.
[172] E.V. Fuior, C.A. Mocanu, M. Deleanu, G. Voicu, M. Anghelache, D. Rebleanu, M. Simionescu, M. Calin, Evaluation of VCAM-1 Targeted Naringenin/Indocyanine Green-Loaded Lipid Nanoemulsions as Theranostic Nanoplatforms in Inflammation, Pharmaceutics. 12 (2020) 1066. https://doi.org/10.3390/pharmaceutics12111066.
[173] S. Hatem, M. El-Kayal, Novel anti-psoriatic nanostructured lipid carriers for the cutaneous delivery of luteolin: A comprehensive in-vitro and in-vivo evaluation, Eur. J. Pharm. Sci. 191 (2023) 106612. https://doi.org/10.1016/j.ejps.2023.106612.
[174] E.Y. Lee, J. Choi, Y.M. Kim, K. Yang, A. Jang, H.K. Shin, H.R. Kim, K. Nam, J.K. Hwang, J. Park, W.J. Park, Y.H. Roh, Plant derived extract loaded nanostructured lipid carriers with enhanced oral delivery for the treatment of acute inflammation, Sci. Rep. 15 (2025) 34551. https://doi.org/10.1038/s41598-025-17898-y.
[175] A. Roy, A. Khan, I. Ahmad, S. Alghamdi, B.S. Rajab, A.O. Babalghith, M.Y. Alshahrani, S. Islam, M.R. Islam, Flavonoids a Bioactive Compound from Medicinal Plants and Its Therapeutic Applications, Biomed Res. Int. 2022 (2022). https://doi.org/10.1155/2022/5445291.
[176] S. Shah, R. Narang, V.J. Singh, G. Pilli, S.K. Nayak, A Review on Anticancer Profile of Flavonoids: Sources, Chemistry, Mechanisms, Structure-activity Relationship and Anticancer Activity, Curr. Drug Res. Rev. 15 (2023) 122–148. https://doi.org/10.2174/2589977515666230120144852.
[177] H. Kumar, P. Chand, S. Pachal, S. Mallick, R. Jain, S. V. Madhunapantula, V. Jain, Fisetin-Loaded Nanostructured Lipid Carriers: Formulation and Evaluations against Advanced and Metastatic Melanoma, Mol. Pharm. 20 (2023) 6035–6055. https://doi.org/10.1021/acs.molpharmaceut.3c00309.
[178] J.S. Pandi, P. Pavadai, T. Panneerselvam, M. Sankaranarayanan, S. Kunjiappan, Enhanced anticancer activity of naringenin-encapsulated poly (lactic acid)/neem gum nanoparticles for breast cancer cells, Biomed. Mater. 21 (2026) 015017. https://doi.org/10.1088/1748-605X/ae3411.
[179] S. Paranthaman, C.A. Uthaiah, R.A.M. Osmani, U. Hani, M. Ghazwani, A.H. Alamri, A. Al Fatease, S. V. Madhunapantula, D.V. Gowda, Anti-Proliferative Potential of Quercetin Loaded Polymeric Mixed Micelles on Rat C6 and Human U87MG Glioma Cells, Pharmaceutics. 14 (2022) 1643. https://doi.org/10.3390/pharmaceutics14081643.
[180] M. Tilawat, S. Bonde, Curcumin and quercetin loaded nanocochleates gel formulation for localized application in breast cancer therapy, Heliyon. 9 (2023) e22892. https://doi.org/10.1016/j.heliyon 2023.e22892.
[181] A. Calderaro, G.T. Patanè, E. Tellone, D. Barreca, S. Ficarra, F. Misiti, G. Laganà, The Neuroprotective Potentiality of Flavonoids on Alzheimer's Disease, Int. J. Mol. Sci. 23 (2022) 14835. https://doi.org/10.3390/ijms232314835.
[182] M. Ramezani, A.Z. Meymand, F. Khodagholi, H.M. Kamsorkh, E. Asadi, M. Noori, K. Rahimian, A.S.

Shahrbabaki, A. Talebi, H. Parsaiyan, S. Shiravand, N. Darbandi, A role for flavonoids in the prevention and/or treatment of cognitive dysfunction, learning, and memory deficits: a review of preclinical and clinical studies, Nutr. Neurosci. 26 (2023) 156–172. https://doi.org/10.1080/1028415X.2022.2028058.
[183] K. Wang, X. Chen, Protective effect of flavonoids on oxidative stress injury in Alzheimer's disease, Nat. Prod. Res. 39 (2025) 1272–1299. https://doi.org/10.1080/14786419.2024.2345760.
[184] P. Bhadane, A. Khairnar, K. Pandya, A. Naha, D. Kumar, K.A. Abutwaibe, J. Desai, N. Bombatkar, P. Rajput, D. Kumar, Targeted Delivery of Quercetin to the Brain via a Modified Polymeric Nanocarrier, Macromol. Biosci. 26 (2026). https://doi.org/10.1002/mabi.202500503.
[185] J. Chen, J. Chen, P. Yu, C. Yang, C. Xia, J. Deng, M. Yu, Z. Xiang, L. Gan, B. Zhu, Y. Wu, X. Yang, A Novel Quercetin Encapsulated Glucose Modified Liposome and Its Brain-Target Antioxidative Neuroprotection Effects, Molecules. 29 (2024) 607. https://doi.org/10.3390/molecules29030607.
[186] M.H. Elkomy, R.M. Zaki, O.A. Alsaidan, M. Elmowafy, A. Zafar, K. Shalaby, M.A. Abdelgawad, F.I. Abo El-Ela, M.E. Rateb, I.A. Naguib, H.M. Eid, Intranasal Nanotransferosomal Gel for Quercetin Brain Targeting: I. Optimization, Characterization, Brain Localization, and Cytotoxic Studies, Pharmaceutics. 15 (2023) 1805. https://doi.org/10.3390/pharmaceutics15071805.
[187] M.A. Elsheikh, Y.A. El-Feky, M.M. Al-Sawahli, M.E. Ali, A.M. Fayez, H. Abbas, A Brain-Targeted Approach to Ameliorate Memory Disorders in a Sporadic Alzheimer's Disease Mouse Model via Intranasal Luteolin-Loaded Nanobilosomes, Pharmaceutics. 14 (2022) 576. https://doi.org/10.3390/pharmaceutics14030576.
[188] A. Ghosh, N. Khanam, D. Nath, Solid lipid nanoparticle: A potent vehicle of the kaempferol for brain delivery through the blood-brain barrier in the focal cerebral ischemic rat, Chem. Biol. Interact. 397 (2024) 111084. https://doi.org/10.1016/j.cbi.2024.111084.
[189] T.-P. Lam, N.-V.N. Tran, L.-H.D. Pham, N.V.-T. Lai, B.-T.N. Dang, N.-L.N. Truong, S.-K. Nguyen-Vo, T.-L. Hoang, T.T. Mai, T.-D. Tran, Flavonoids as dual-target inhibitors against α-glucosidase and α-amylase: a systematic review of in vitro studies, Nat. Products Bioprospect. 14 (2024) 4. https://doi.org/10.1007/s13659-023-00424-w.
[190] M.Z. Ahmad, K. Pathak, A. Alam, B.A. Abdel-Wahab, M.B. Bakir, A. Das, M.P. Pathak, M.M. Abdullah, K.A. Ahmed, M.Y. Alasmary, A.A. Alqahtani, H. Sarma, Improved antidiabetic potential of quercetin-loaded chitosan–lecithin nanoparticles for effective glycaemic control, J. Drug Target. 33 (2025) 1591–1606. https://doi.org/10.1080/1061186X.2025.2511837.
[191] S. Ferradj, M.M. Yahoum, M. Rebiha, I. Nabi, S. Toumi, S. Lefnaoui, A. Hadj-Ziane-Zafour, N. Touzout, H. Tahraoui, A. Mihoub, M.F. Seleiman, N. Ali, J. Zhang, A. Amrane, Nanocurcumin-Based Sugar-Free Formulation: Development and Impact on Diabetes and Oxidative Stress Reduction, Nanomaterials. 14 (2024) 1105. https://doi.org/10.3390/nano14131105.
[192] R. Gutiérrez, J. Gómez, R. Urby, J. Soto, H. Parra, Evaluation of Diabetes Effects of Selenium Nanoparticles Synthesized from a Mixture of Luteolin and Diosmin on Streptozotocin-Induced Type 2 Diabetes in Mice, Molecules. 27 (2022) 5642. https://doi.org/10.3390/molecules27175642.
[193] M. Mahadev, A. Dubey, A. Shetty, Ultrasonically Fabricated Beta-Carotene Nanoemulsion: Optimization, Characterization and Evaluation of Combinatorial Effect with Quercetin on Streptozotocin-Induced Diabetic Rat Model, Pharmaceutics. 15 (2023) 574. https://doi.org/10.3390/pharmaceutics15020574.
[194] A. Zafar, O.A. Alsaidan, M.H. Elkomy, S.S. Imam, M. Yasir, K.S. Alharbi, M. Khalid, Formulation and optimization of Naringin polymeric nanoparticles: Optimization to in vivo evaluation, J. Drug Deliv. Sci. Technol. 88 (2023) 104978. https://doi.org/10.1016/j.jddst.2023.104978.
[195] R. Logesh, P. Parasuraman, G. Jebarsan, Flavonoids as potential modulators targeting lipoprotein lipase in combating cardiovascular disorders: Mechanistic insights, pharmacological activity and drug delivery approaches, Curr. Probl. Cardiol. 51 (2026) 103400. https://doi.org/10.1016/j.cpcardiol.2026.103400.
[196] M. Jaganjac, N.N. Orie, Modulation of Redox Balance by Phytochemicals: Implications for Cardiovascular Health, Nutrients. 18 (2026) 1204. https://doi.org/10.3390/nu18081204.
[197] F.J. Olatoye, A.J. Akindele, O. Awodele, The role of Kolaviron, a bioflavonoid from Garcinia kola, in the management of cardiovascular diseases: A systematic review, Heliyon. 10 (2024) e27333. https://doi.org/10.1016/j.heliyon.2024.e27333.
[198] M. Sakuda, K. Ito, Y. Adaniya, N. Watanabe, L. Han, M. Natsume, K. Nakamura, Impact of cocoa flavanols on blood pressure and vascular function: an updated systematic review and meta-analysis of randomized controlled trials, J. Nutr. Heal. Aging. 30 (2026) 100966. https://doi.org/10.1016/j.jnha.2026.100966.
[199] P. Sharma, T. Bal, S.K. Singh, N. Sharma, Biodegradable polymeric nanocomposite containing phloretin for enhanced oral bioavailability and improved myocardial ischaemic recovery, J. Microencapsul. 41 (2024) 754–769. https://doi.org/10.1080/02652048.2024.2418608.
[200] M. Chahardori, R. Yazdian-Robati, M. Seyedabadi, M. Shokrzadeh, H. Mohammadi, Cardiac-Targeted Quercetin-Loaded PLGA Nanoparticles Attenuate Doxorubicin-Induced Cardiotoxicity via Nrf2/HO-1 Pathway Activation in Mice, J. Appl. Toxicol. 46 (2026) 2528–2543. https://doi.org/10.1002/jat.70044.
[201] S. Jaiswal, M.M. Anjum, S. Thakur, P. Pandey, D.K. Arya, A. Kumar, A.S. Kaushik, P.S. Rajinikanth, Evaluation of cardioprotective effect of naringin loaded lignin nanoparticles against isoproterenol induced myocardial infarction, J. Drug Deliv. Sci. Technol. 89 (2023) 105076. https://doi.org/10.1016/j.jddst.2023.105076.
[202] C. Chen, W. Liu, X. Gu, L. Zhang, X. Mao, Z. Chen, L. Tao, Baicalin-loaded Polydopamine modified ZIF-8 NPs inhibits myocardial ischemia/reperfusion injury in rats, J. Biomater. Sci. Polym. Ed. 35 (2024) 1863–1878. https://doi.org/10.1080/09205063.2024.2358640.

[203] C. Serri, V. Quagliariello, I. Cruz-Maya, V. Guarino, N. Maurea, P. Giunchedi, G. Rassu, E. Gavini, Hyaluronic Acid-Based Nanoparticles Loaded with Rutin as Vasculo-Protective Tools against Anthracycline-Induced Endothelial Damages, Pharmaceutics. 16 (2024) 985. https://doi.org/10.3390/pharmaceutics16080985.
[204] J. Luo, J. Luo, Z. Sheng, Z. Fang, Y. Fu, N. Wang, B. Yang, B. Xu, Latest research progress on anti-microbial effects, mechanisms of action, and product developments of dietary flavonoids: A systematic literature review, Trends Food Sci. Technol. 156 (2025) 104839. https://doi.org/10.1016/j.tifs.2024.104839.
[205] V. Sharma, D. Sharma, M. Saini, A. Jain, J. Chaudhary, N. Kaur, S. Sahoo, S.K. Singh, K. Goyal, A. Rekha, H. Ali, S. Gupta, M.S. Hussain, G. Gupta, Flavonoids as Antimicrobial Agents: A Comprehensive Review of Mechanisms and Therapeutic Potential, Curr. Pharm. Biotechnol. 26 (2025). https://doi.org/10.2174/0113892010384002250628163849.
[206] T.P.T. Cushnie, A.J. Lamb, Antimicrobial activity of flavonoids, Int. J. Antimicrob. Agents. 26 (2005) 343–356. https://doi.org/10.1016/j.ijantimicag.2005.09.002.
[207] T.M. Almeleebia, M.H. Akhter, H. Khalilullah, M.A. Rahman, S. Ahmad, N. Alam, M.S. Ali, G. Khan, I.M.M. Alanazi, N. Shahzad, A. Alalmaie, Co-Delivery of Naringin and Ciprofloxacin by Oleic Acid Lipid Core Encapsulated in Carboxymethyl Chitosan/Alginate Nanoparticle Composite for Enhanced Antimicrobial Activity, ACS Omega. 9 (2024) 6845–6860. https://doi.org/10.1021/acsomega.3c08200.
[208] D.P.C. de Barros, R. Santos, P. Reed, L.P. Fonseca, A. Oliva, Design of Quercetin-Loaded Natural Oil-Based Nanostructured Lipid Carriers for the Treatment of Bacterial Skin Infections, Molecules. 27 (2022) 8818. https://doi.org/10.3390/molecules27248818.
[209] F. De Gaetano, F. Caridi, N. Totaro, C. Celesti, V. Venuti, G. Ginestra, A. Nostro, S. Tommasini, C.A. Ventura, R. Stancanelli, Naringenin-Loaded Solid Lipid Nanoparticles: Physical–Chemical Characterization and In Vitro Antibacterial Activity, Pharmaceuticals. 18 (2025) 232. https://doi.org/10.3390/ph18020232.
[210] J. Hemmati, M. Chiani, Z. Chegini, A. Seifalian, M.R. Arabestani, Surface modified niosomal quercetin with cationic lipid: an appropriate drug delivery system against Pseudomonas aeruginosa Infections, Sci. Rep. 14 (2024) 13362. https://doi.org/10.1038/s41598-024-64416-7.
[211] S. Imam, S. Gilani, A. Zafar, M. Jumah, R. Ali, M. Ahmed, S. Alshehri, Preparation and Optimization of Naringin Oral Nanocarrier: In Vitro Characterization and Antibacterial Activity, Coatings. 12 (2022) 1230. https://doi.org/10.3390/coatings12091230.
[212] S. Hassanizadeh, G. Askari, P. Kesharwani, M. Bagherniya, A. Sahebkar, Clinical trials, patents, and marketed products of nanocurcumin-based anticancer drug delivery systems, in: Curcumin-Based Nanomedicines as Cancer Ther., Elsevier, 2024: pp. 431–442. https://doi.org/10.1016/B978-0-443-15412-6.00004-0.
[213] H. Teng, Y. Zheng, H. Cao, Q. Huang, J. Xiao, L. Chen, Enhancement of bioavailability and bioactivity of diet-derived flavonoids by application of nanotechnology: a review, Crit. Rev. Food Sci. Nutr. 63 (2023) 378–393. https://doi.org/10.1080/10408398.2021.1947772.
[214] T.F. Rambaran, A patent review of polyphenol nano-formulations and their commercialization, Trends Food Sci. Technol. 120 (2022) 111–122. https://doi.org/10.1016/j.tifs.2022.01.011.
[215] A. Antonelli, F. Palma, Nanocarrier-Based Delivery Systems for Natural Compounds Across Research Stages, Materials (Basel). 18 (2025) 4960. https://doi.org/10.3390/ma18214960.
[216] S.M. Saleh, R.A. Khan, L.M. Aroua, H.A. Mohammed, Nanotechnology-Enhanced Delivery and Bioactivity of Dietary Flavonoids: Overcoming Bioavailability Barriers for Targeted Antimicrobial and Antiviral Therapies-A Comprehensive Review, Int. J. Nanomedicine. Volume 21 (2026) 1–33. https://doi.org/10.2147/IJN.S630746.
[217] H. Wahnou, Y. Limami, M. Oudghiri, Flavonoids and Flavonoid-Based Nanoparticles for Osteoarthritis and Rheumatoid Arthritis Management, BioChem. 4 (2024) 38–61. https://doi.org/10.3390/biochem4010003.
[218] X. Wu, Pharmaceutical Design and Clinical Translation Challenges of Baicalein Anti-Tumor Nano-Preparations in Traditional Chinese Medicine, Theor. Nat. Sci. 131 (2025) 74–79. https://doi.org/10.54254/2753-8818/2025.SH26311.
[219] S. Jacob, F. Kather, M. Morsy, S. Boddu, M. Attimarad, J. Shah, P. Shinu, A. Nair, Advances in Nanocarrier Systems for Overcoming Formulation Challenges of Curcumin: Current Insights, Nanomaterials. 14 (2024) 672. https://doi.org/10.3390/nano14080672.
[220] V. Agrahari, V. Agrahari, Facilitating the translation of nanomedicines to a clinical product: challenges and opportunities, Drug Discov. Today. 23 (2018) 974–991. https://doi.org/10.1016/j.drudis.2018.01.047.
[221] S. Đorđević, M.M. Gonzalez, I. Conejos-Sánchez, B. Carreira, S. Pozzi, R.C. Acúrcio, R. Satchi-Fainaro, H.F. Florindo, M.J. Vicent, Current hurdles to the translation of nanomedicines from bench to the clinic, Drug Deliv. Transl. Res. 12 (2022) 500–525. https://doi.org/10.1007/s13346-021-01024-2.
[222] D. Tripathi, P. Pandey, M. Sabir, V.K. Gupta, N. Bou-Chacra, Naringenin in Melanoma: Mechanistic Insights and Nanodelivery Strategies for Clinical Translation, Mol. Pharm. 22 (2025) 6430–6455. https://doi.org/10.1021/acs.molpharmaceut.5c00556.
[223] S. Sharma, Himanshi, J. Jwala, Khusbu, K. Sharma, S. Debnath, D. Agrawal, R. Gupta, B. Ghosh, Regulatory, Ethical and Current Status (Clinical trials & Patents) in Nano-Brain Drug Delivery, in: Nano-Brain Revolut. Alzheimer's Dis. A New Era Brain Drug Deliv., Deep Science Publishing, 2025: pp. 238–266. https://doi.org/10.70593/978-93-7185-149-7_10.
[224] C.A. Ligarda-Samanez, M.L. Huamán-Carrión, J.M. Romero Plasencia, D.F. Calderón Huamaní, B. Vivanco Garfias, J.C. Muñoz-Saenz, M.M. Bautista Gómez, J.A. Martinez-Hernandez, W.C. Calsina-Ponce, Innovations in the Delivery of Bioactive Compounds for Cancer Prevention and Therapy: Advances, Challenges, and Future Perspectives, Pharmaceuticals. 19 (2025) 60. https://doi.org/10.3390/ph19010060.
[225] S. Vishwas, R. Kumar, R. Khursheed, A.K. Ramanunny, R. Kumar, A. Awasthi, L. Corrie, O. Porwal, M.F.

Arshad,
M.K. Alshammari, A.A. Alghitran, A.N. Qumayri, S.M. Alkhaldi, A.K. Alshammari, D.K. Chellappan, G. Gupta,
T. Collet, J. Adams, K. Dua, M. Gulati, S.K. Singh, Expanding Arsenal against Neurodegenerative Diseases Using Quercetin Based Nanoformulations: Breakthroughs and Bottlenecks, Curr. Neuropharmacol. 21 (2023) 1558–1574. https://doi.org/10.2174/1570159X20666220810105421.
[226] J.-B. Coty, C. Vauthier, Characterization of nanomedicines: A reflection on a field under construction needed for clinical translation success, J. Control. Release. 275 (2018) 254–268. https://doi.org/10.1016/j.jconrel.2018.02.013.
[227] C. Giannakou, M.V.D.Z. Park, I.E.M. Bosselaers, W.H. de Jong, J.W. van der Laan, H. van Loveren, R.J. Vandebriel, R.E. Geertsma, Nonclinical regulatory immunotoxicity testing of nanomedicinal products: Proposed strategy and possible pitfalls, WIREs Nanomedicine and Nanobiotechnology. 12 (2020). https://doi.org/10.1002/wnan.1633.
[228] F. Stucchi, M. Li, G. Castellano, F. Cellesi, Regulatory framework for polymer-based nanotherapeutics in clinical translation, Front. Bioeng. Biotechnol. 14 (2026). https://doi.org/10.3389/fbioe.2026.1735885.
[229] D. Administration, Guidance for industry considering whether an FDA-regulated product involves the application of nanotechnology, Biotechnol. Law Rep. 30 (2011) 613–616. https://doi.org/10.1089/blr.2011.9814.
[230] S. Jesus, M. Schmutz, C. Som, G. Borchard, P. Wick, O. Borges, Hazard Assessment of Polymeric Nanobiomaterials for Drug Delivery: What Can We Learn From Literature So Far, Front. Bioeng. Biotechnol. 7 (2019). https://doi.org/10.3389/fbioe.2019.00261.
[231] B. Mangla, P. Kumar, S. Javed, T. Pathan, W. Ahsan, G. Aggarwal, Regulating nanomedicines: challenges, opportunities, and the path forward, Nanomedicine. 20 (2025) 1911–1927. https://doi.org/10.1080/17435889.2025.2533107.
[232] L.G. Powell, S. Gillies, T.F. Fernandes, F. Murphy, E. Giubilato, V. Cazzagon, D. Hristozov, L. Pizzol, M. Blosi,
A.L. Costa, A. Prina-Mello, H. Bouwmeester, H. Sarimveis, G. Janer, V. Stone, Developing Integrated Approaches for Testing and Assessment (IATAs) in order to support nanomaterial safety, Nanotoxicology. 16 (2022) 484–499. https://doi.org/10.1080/17435390.2022.2103470.
[233] L. Mude, G. Kuppusamy, V.V.S. Reddy Karri, R. Arun, N. Kumar, M. Thanzim, Regulatory Aspects of Herbal Nanoformulations, in: Nanophytomedicine, CRC Press, Boca Raton, 2022: pp. 255–264. https://doi.org/10.1201/9781003231745-23.
[234] A. Ahmad, M. Imran, N. Sharma, Precision Nanotoxicology in Drug Development: Current Trends and Challenges in Safety and Toxicity Implications of Customized Multifunctional Nanocarriers for Drug-Delivery Applications, Pharmaceutics. 14 (2022) 2463. https://doi.org/10.3390/pharmaceutics14112463.
[235] R. Kumar, A. Kumar, S. Bhardwaj, M. Sikarwar, S. Sriwastaw, G. Sharma, M. Gupta, Nanotoxicity unveiled: Evaluating exposure risks and assessing the impact of nanoparticles on human health, J. Trace Elem. Miner. 13 (2025) 100252. https://doi.org/10.1016/j.jtemin.2025.100252.
[236] M. Mahmoudi, M.P. Landry, A. Moore, R. Coreas, The protein corona from nanomedicine to environmental science, Nat. Rev. Mater. 8 (2023) 422–438. https://doi.org/10.1038/s41578-023-00552-2.
[237] D. Knowland, A. Arac, K.J. Sekiguchi, M. Hsu, S.E. Lutz, J. Perrino, G.K. Steinberg, B.A. Barres, A. Nimmerjahn,
D. Agalliu, Stepwise Recruitment of Transcellular and Paracellular Pathways Underlies Blood-Brain Barrier Breakdown in Stroke, Neuron. 82 (2014) 603–617. https://doi.org/10.1016/j.neuron.2014.03.003.
[238] U. Havelikar, K.B. Ghorpade, A. Kumar, A. Patel, M. Singh, N. Banjare, P.N. Gupta, Comprehensive insights into mechanism of nanotoxicity, assessment methods and regulatory challenges of nanomedicines, Discov. Nano. 19 (2024) 165. https://doi.org/10.1186/s11671-024-04118-1.
[239] W.-C. Chou, Z. Lin, Impact of protein coronas on nanoparticle interactions with tissues and targeted delivery, Curr. Opin. Biotechnol. 85 (2024) 103046. https://doi.org/10.1016/j.copbio.2023.103046.
[240] T. Zhao, M. Ren, J. Shi, H. Wang, J. Bai, W. Du, B. Xiang, Engineering the protein corona: Strategies, effects, and future directions in nanoparticle therapeutics, Biomed. Pharmacother. 175 (2024) 116627. https://doi.org/10.1016/j.biopha.2024.116627.
[241] F. Fu, D. Crespy, K. Landfester, S. Jiang, In situ characterization techniques of protein corona around nanomaterials, Chem. Soc. Rev. 53 (2024) 10827–10851. https://doi.org/10.1039/D4CS00507D.
[242] F. Guo, S. Luo, L. Wang, M. Wang, F. Wu, Y. Wang, Y. Jiao, Y. Du, Q. Yang, X. Yang, G. Yang, Protein corona, influence on drug delivery system and its improvement strategy: A review, Int. J. Biol. Macromol. 256 (2024) 128513. https://doi.org/10.1016/j.ijbiomac.2023.128513.
[243] J. Wang, Y. Xu, Y. Zhou, J. Zhang, J. Jia, P. Jiao, Y. Liu, G. Su, Modulating the toxicity of engineered nanoparticles by controlling protein corona formation: Recent advances and future prospects, Sci. Total Environ. 914 (2024) 169590. https://doi.org/10.1016/j.scitotenv.2023.169590.
[244] M. Barz, W.J. Parak, R. Zentel, Concepts and Approaches to Reduce or Avoid Protein Corona Formation on Nanoparticles: Challenges and Opportunities, Adv. Sci. 11 (2024). https://doi.org/10.1002/advs.202402935.
[245] C. Marques, G. Borchard, O. Jordan, Unveiling the challenges of engineered protein corona from the proteins' perspective, Int. J. Pharm. 654 (2024) 123987. https://doi.org/10.1016/j.ijpharm.2024.123987.
[246] H.B. Haroon, E. Dhillon, Z.S. Farhangrazi, P.N. Trohopoulos, D. Simberg, S.M. Moghimi, Activation of the complement system by nanoparticles and strategies for complement inhibition, Eur. J. Pharm. Biopharm. 193 (2023) 227–240. https://doi.org/10.1016/j.ejpb.2023.11.006.
[247] T.M. Ramos, L.M.R. Alencar, E. Ricci-Junior, P.B.A. Fechine, R. Santos-Oliveira, Enhancing the Safety of Nanoparticles in Medicine: Highlights of Progress and Critical Objectives, Int. J. Nanomedicine. Volume 21 (2026) 1–70. https://doi.org/10.2147/IJN.S559584.
[248] J. Zhou, B. Gao, H. Zhang, R. Yang, J. Huang, X. Li, Y. Zhong, Y. Wang, X. Zhu, Y. Luo, F. Yan, Ginsenoside

modified lipid-coated perfluorocarbon nanodroplets: A novel approach to reduce complement protein adsorption and prolong in vivo circulation, Acta Pharm. Sin. B. 14 (2024) 1845–1863. https://doi.org/10.1016/j.apsb.2023.11.016.
[249] J. Xia, C. Chen, M. Dong, Y. Zhu, A. Wang, S. Li, R. Zhang, C. Feng, X. Jiang, X. Xu, J. Wang, Ginsenoside Rg3 endows liposomes with prolonged blood circulation and reduced accelerated blood clearance, J. Control. Release. 364 (2023) 23–36. https://doi.org/10.1016/j.jconrel.2023.10.023.
[250] Z. Wang, E.D. Hood, J. Nong, J. Ding, O.A. Marcos-Contreras, P.M. Glassman, K.M. Rubey, M. Zaleski, C.L. Espy, D. Gullipali, T. Miwa, V.R. Muzykantov, W. Song, J.W. Myerson, J.S. Brenner, Combating Complement's Deleterious Effects on Nanomedicine by Conjugating Complement Regulatory Proteins to Nanoparticles, Adv. Mater. 34 (2022). https://doi.org/10.1002/adma.202107070.
[251] P. Urbán, N.J. Liptrott, S. Bremer, Overview of the blood compatibility of nanomedicines: A trend analysis of in vitro and in vivo studies, WIREs Nanomedicine and Nanobiotechnology. 11 (2019). https://doi.org/10.1002/wnan.1546.
[252] A. Tkachenko, Hemocompatibility studies in nanotoxicology: Hemolysis or eryptosis? (A review), Toxicol. Vitr. 98 (2024) 105814. https://doi.org/10.1016/j.tiv.2024.105814.
[253] S. Guo, Y. Shi, Y. Liang, L. Liu, K. Sun, Y. Li, Relationship and improvement strategies between drug nanocarrier characteristics and hemocompatibility: What can we learn from the literature, Asian J. Pharm. Sci. 16 (2021) 551–576. https://doi.org/10.1016/j.ajps.2020.12.002.
[254] Center for Drug Evaluation and Research, Drug Products, Including Biological Products, that Contain Nanomaterials - Guidance for Industry, U.S. Food Drug Adm. (2022). https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-products-including-biological-products-contain-nanomaterials-idance-industry.
[255] Manheng, Nonclinical Perspective on Development of Drug Products Containing Nanomaterials, (2022). www.fda.gov.
[256] U.S. Food and Drug Administration, Guidance for Industry: Questions and Answers, Fda.Gov. (2017). https://www.fda.gov/media/102650/download.
[257] J. Szebeni, Complement activation-related pseudoallergy: A stress reaction in blood triggered by nanomedicines and biologicals, Mol. Immunol. 61 (2014) 163–173. https://doi.org/10.1016/j.molimm.2014.06.038.
[258] T.S. Preview, TECHNICAL REPORT ISO / TR Nanotechnologies — Guidance on iTeh STANDARD PREVIEW iTeh STANDARD PREVIEW, 2012 (2012).