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REVIEW ARTICLE

Nano Drug Delivery Strategies for an Oral Bioenhanced Quercetin Formulation

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Abstract

Quercetin, a naturally occurring flavonoid, has been credited with a wide spectrum of therapeutic properties. However, the oral use of quercetin is limited due to its poor water solubility, low bioavailability, rapid metabolism, and rapid plasma clearance. Quercetin has been studied extensively when used with various nanodelivery systems for enhancing quercetin bioavailability. To enhance its oral bioavailability and efficacy, various quercetin-loaded nanosystems such as nanosuspensions, polymer nanoparticles, metal nanoparticles, emulsions, liposomes or phytosomes, micelles, solid lipid nanoparticles, and other lipid-based nanoparticles have been investigated in in-vitro cells, in-vivo animal models, and humans. Among the aforementioned nanosystems, quercetin phytosomes are attracting more interest and are available on the market. The present review covers insights into the possibilities of harnessing quercetin for several therapeutic applications and a special focus on anticancer applications and the clinical benefits of nanoquercetin formulations.

Key Points

Quercetin is a plant flavonoid used mainly as an anticancer agent due to its antioxidant properties, but also as an anti-microbial agent, anti-osteoporotic agent, anti-fungal agent, anti-psoriatic agent, anti-neurodegenerative agent, anti-inflammatory agent, and in the treatment of cardiovascular diseases.

The bioavailability and therapeutic efficacy of quercetin are limited by its low water solubility, limited permeability, high enzymatic degradation, and the lack of bioenhanced formulations on the market.

Among various approaches, the nanodrug delivery strategy provides significant improvements in the solubilization and bioenhancement of quercetin, with the added advantage of targeted delivery whenever desired.

Marketed quercetin nanoformulations and quercetin phytosomes have attracted huge attention around the world.

1 Introduction

Quercetin is a plant flavonoid obtained from vegetables, grains, and fruits. It has attained immense importance in the past few years due to its multifarious therapeutic applications [1, 2]; for example, it can be used as an anti-microbial agent, anti-osteoporotic agent, anticancer agent, anti-fungal, anti-psoriatic, and anti-neurodegenerative, and anti-inflammatory agent, as well as in the treatment of cardiovascular diseases [3]. The potential use of quercetin in the treatment of viral infections such as COVID-19 has also proposed [3, 4]. The various mechanisms of action and possible applications of quercetin are depicted in Fig. 1 [5].

2 Challenges Associated with the Conventional Administration of Quercetin

The structure of quercetin is shown in Fig. 2. Quercetin is classified as a BCS class IV drug based on its poor solubility (0.00215 g/L at 25 °C) in aqueous media and limited permeability through the gastrointestinal epithelium [6]. Quercetin is unstable in the presence of heat and oxygen and also undergoes photolytic degradation [7, 8]. Another challenge to delivering quercetin is its rapid metabolization into glucuronide and sulfate conjugates, which limits systemic circulation and therapeutic efficacy [9]. Studies were

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carried out by administering quercetin either via intraperitoneal injection or orally (via the gavage method or drinking water) and the intravenous injection route at various doses ranging from 100 µg to 200 mg/kg/day for between 10 and 90 days [10]. The suggested reviews [11–14] provide additional details on routes of administration of quercetin. Gastrointestinal factors are reported to influence the delivery of quercetin. Oral bioavailability is influenced significantly by food and in particular fat intake, as well as the gastrointestinal tract pH [15]. Collectively, factors including its low water solubility, high metabolic rate, inactive metabolic products, and rapid clearance from plasma [16–18] limit the bioavailability and therapeutic efficacy of quercetin, implying the need to develop nanoformulation strategies to improve quercetin's bioavailability and efficacy.

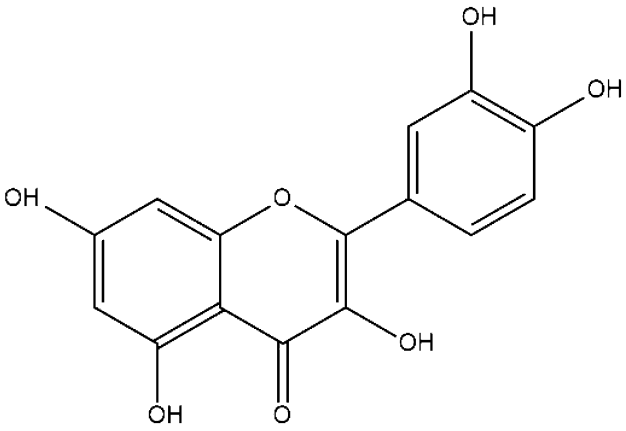

Fig. 2 Chemical structure of quercetin

3 Bioenhancement Strategies for Quercetin

Various approaches have been evaluated for quercetin bioenhancement [12]: for instance, coadministration with piperine [19] or chemical modification (e.g., esterification) or the design of prodrugs [20]. Nevertheless, an important focus has been the development of solid dispersions using various carriers. An amorphous solid dispersion (ASD) generally comprises emulsifying components with drug particles less than 1000 nm in size [21]. Using an ASD is an exciting approach for improving enhancement due to its rapid dissolution and simplicity of preparation [22–24]. An ASD of quercetin in a 1:1 weight ratio with combination carriers of Pluronic F-127 and polyvinylpyrrolidone K30 (5:95)

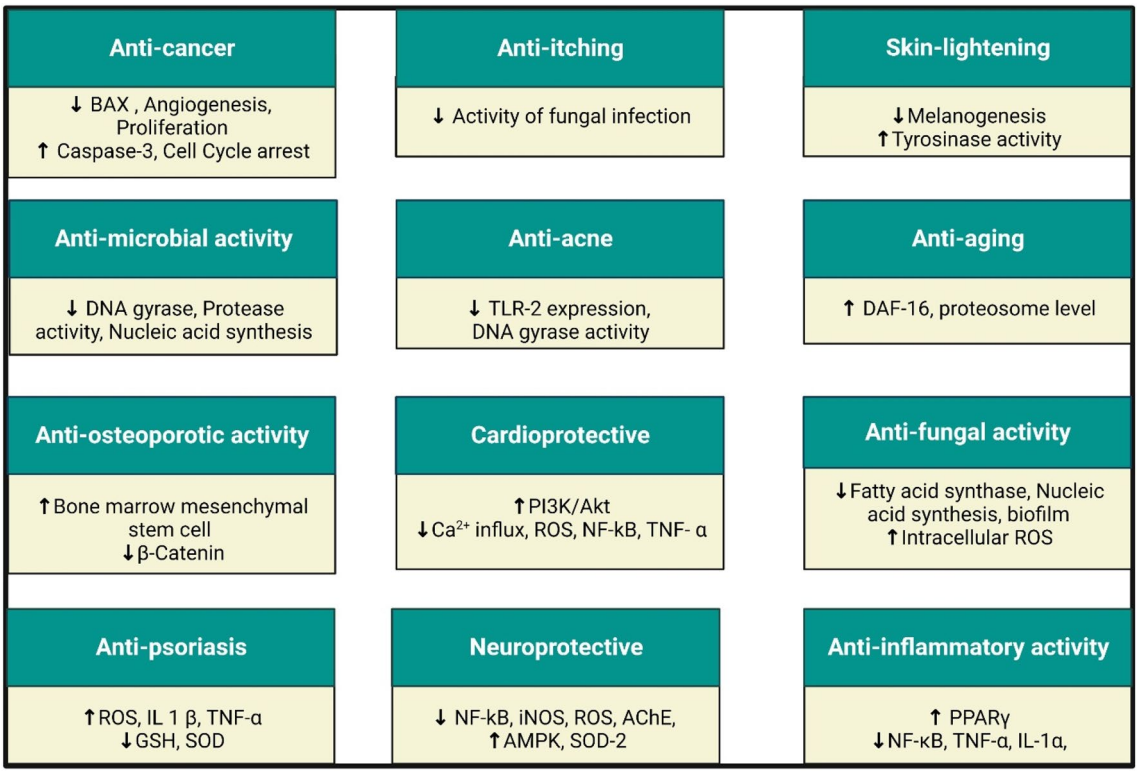

Fig. 1 Various uses and mechanisms of action of quercetin. *BAX* Bcl-2-associated X protein, *TLR* toll-like receptor, *DAF* abnormal Dauer formation, *PI3K* phosphoinositide 3-kinase, *Akt* protein kinase B, *ROS* reactive oxygen species, *NF-κB* nuclear factor kappa B, *TNF-α* tumor necrosis factor α, *IL* interleukins, *GSH* glutathione, *SOD* superoxide dismutase, *iNOS* inducible nitric oxide synthase, *AChE* acetylcholinesterase, *AMPK* adenosine monophosphate-activated protein kinase, *PPAR-γ* PPAR peroxisome proliferator-activated receptor

significantly improved quercetin solubility with its enhanced dissolution performance [25]. Chitosan oligosaccharide (amorphous) was reported as a promising hydrophilic matrix for a quercetin ASD. The ASD formulation showed enhanced in vitro dissolution performance and oral bioavailability compared to pure quercetin [26]. Further, a quercetin solid dispersion with hydrophilic carriers of hydroxypropyl methylcellulose along with poloxamer 188 as a surfactant exhibited an enhanced dissolution rate with a 61-fold higher oral bioavailability than the pure drug [27]. Other polymers explored for the design of quercetin solid dispersions with rapid dissolution and/or enhanced bioavailability include polyvinylpyrrolidone [28], cellulose esters [29], polyethylene glycol 1000 [30], hydroxypropyl methylcellulose [31], polyvinylpyrrolidone K30 [32], poloxamer 188 [33], and combination of polyvinylpyrrolidone or hydroxypropyl methylcellulose with Pluronic F-127 [34, 35].

4 Nanoformulation Approaches for Oral Bioenhancement

Nanoparticles (NPs) are small particles 1–1000 nm in size [36] which exhibit significantly enhanced dissolution rates due to their large surface area and also the bioavailability of water-insoluble drugs [37]. These nanosystems can be prepared from many materials, including lipids, polymers, metals, proteins [38, 39], and combinations [11, 40]. All of these materials display good chemical stability, enhanced drug loading, controlled drug release, enhanced bioavailability, and excellent biocompatibility [41]. Figure 3 shows nanodrug delivery strategies for oral bioenhanced quercetin formulations. These NPs can encapsulate drug molecules and carry them to various target sites in the body, as their nanosize permits them to cross biological barriers and target specific cells and tissues [42]. Another strategy that could particularly target the lung and breast is lymph-mediated oral uptake [43, 44]. Moreover, NPs can protect drugs from degradation and metabolism, thereby improving their bioavailability [45]. Among various approaches, nano approaches present significant advantages in solubilization and bioenhancement, with the added advantage of targeted delivery whenever desired. This review focuses on various nano approaches for quercetin bioenhancement, which could also have targeting applications. Table 1 summarizes the physicochemical properties and other outcomes of quercetin nanoformulations, whereas Table 2 represents a summary of oral pharmacokinetic parameters of quercetin nanoformulations.

4.1 Nanosuspensions

Nanosuspensions are dispersions of active hydrophobic substances that are nanometrically dispersed in water using stabilizers (surfactants) and produced by various methods [70]. Generally, nanosuspensions are prepared by either the top-down or the bottom-up process [71]. In the bottom-up process, the active moiety with or without carrier(s) is solubilized in an organic solvent. It is then precipitated by addition to an aqueous phase acting as an anti-solvent along with a stabilizer to enable precipitation at a nanosize [72]. This is followed by the elimination of organic solvents. This process is simple, cost-effective, and requires a low energy

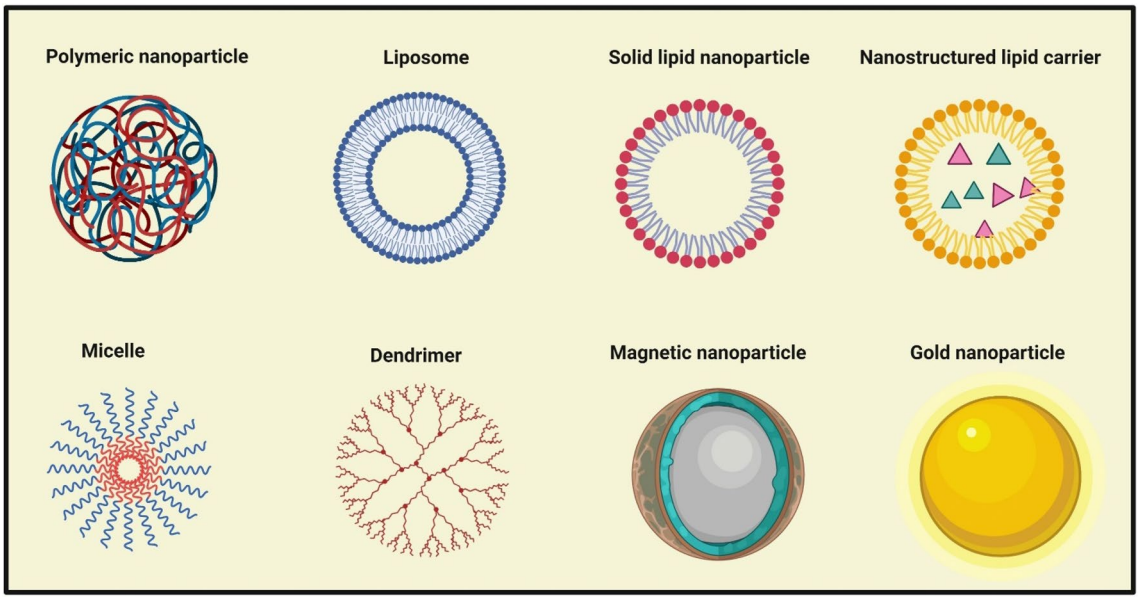

Fig. 3 Schematic representation of oral bioenhanced quercetin nano drug delivery systems

input [73]. The top-down process involves breaking down the bulk material into NPs in the presence of a high-energy input such as high-pressure homogenization [74].

Improved solubility of quercetin nanosuspensions—nine times higher than that of quercetin—is reported. This improved solubility is attributed to the reduced particle size and enhanced surface area available for dissolution [75]. Quercetin nanosuspensions prepared by evaporative precipitation in an aqueous solution (EPAS, a bottom-up technique) and by high-pressure homogenization (HPH, a top-down process) were compared. The nanosuspension produced by the EPAS process displayed an improved solubility and dissolution rate when compared with the HPH process. These observations were related to the unchanged crystalline state of quercetin during the top-down manufacturing process, whereas a crystalline to amorphous phase change was induced during the bottom-up process, implying the role of the preparation method in the properties of the nanosuspension [76, 77]. Nanosuspensions of quercetin prepared by wet milling combined with lyophilization displayed a 26-fold improvement in dissolution as well as a 3.35-fold enhancement in quercetin permeability [78]. Quercetin nanosuspensions prepared by a solvent displacement method were studied for efficacy against *A. aegypti* larvae. A high and concentration-dependent larvae mortality was reported for nanosuspensions of quercetin at 100 ppm (44%) and 500 ppm (100%) at 48 h. Pure quercetin showed a maximum mortality of ~ 50% irrespective of concentration [79]. A quercetin nanosuspension formulation revealed a 70-fold solubility enhancement, a 7-fold reduction in clearance rate, and a > 10-fold increase in $AUC_{0-\infty}$ compared with a control suspension in a rat model [80]. In another study, the enhanced cellular uptake of a quercetin nanosuspension was attributed to the small particle size, which facilitated high cellular uptake and bioavailability [81]. Further, quercetin nanosuspensions have shown significantly higher anticancer activity against human breast cancer cells [82, 83].

4.2 Liposomes

Liposomes are phospholipid-based vesicular systems [84]. Phospholipids, which have hydrophobic and hydrophilic portions, align as lamellar structures, which form liposomes [85]. These can protect active pharmaceutical ingredients from their external surroundings, increase water solubility, and facilitate targeted delivery due to their morphology, which resembles cellular membranes [86]. Liposomes are classified based on size, preparation method, and lamellarity [87]. The manufacturing method dictates the formation of unilamellar, multilamellar, or multivesicular vesicles [88]. The lipid film hydration and ether/ethanol injection, solvent dispersion, mechanical dispersion, and detergent removal methods are the most common techniques used to load both hydrophilic and hydrophobic drugs into liposomes. Extensive details are provided in the reviews [89–92]. Due to their safety and efficacy, liposomes are the most commonly used nanoformulations [93].

Liposomal quercetin prepared by the ethanol injection method displayed extended drug release and suppressed the levels of reactive oxygen species induced by UVB irradiation [94]. Lecithin, cholesterol, and PEG containing flexible liposomes generated by a simple solid dispersion method induced apoptosis by arresting the cell cycle in A2780s and A2780cp cells [47]. Liposomal quercetin formulations prepared by thin-film hydration revealed effective accumulation in tumor tissues, suppression of tumor growth, and prolonged survival time in tumor-bearing mice. This demonstrated the application of quercetin liposomes for tumor-targeted drug delivery in vivo [95]. Poloxamer 188, tween 80, cholesterol, soy lecithin, and glyceryl behenate (ATO)-containing liposomes generated by low-temperature emulsification evaporation exhibited a prolonged in vivo circulation time [65].

Quercetin is loaded into peptide-functionalized liposomes by the thin-film hydration method. These targeted formulations showed a threefold increase in cell toxicity, higher apoptosis, and S-phase cell-cycle arrest in A549 cell lines. When targeted to the lungs by pulmonary administration, they exhibited significantly increased anticancer activity in orthotopic lung tumor-bearing mice as well as an increase in the lifespan of mice [96]. Quercetin liposomes of phosphatidylcholine and cholesterol also exhibited oral hepatoprotective activity in rats and 50 times more antioxidant activity compared to plain quercetin [48]. Further, the superior therapeutic effect of quercetin PEGylated liposomes seen in streptozotocin-induced diabetic nephropathy was attributed to the higher quercetin concentrations in plasma compared to quercetin [97]. In another study, quercetin liposomes of phosphatidylcholine and cholesterol demonstrated cognition-enhancing and anxiolytic effects [98].

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

SLNs are an example of a colloidal lipid carrier delivery system; they are prepared using biodegradable, physiological, and biocompatible solid lipids [99]. SLNs display good chemical stability, enhanced drug loading, controlled drug release, enhanced bioavailability, and excellent biocompatibility [41]. The reviews [100–102] detail the various techniques utilizing SLN formulations. However, a major concern with SLNs is the expulsion of encapsulated drugs from the carrier over time; this challenge led to the development of NLCs [103].

NLCs are made of solid lipids combined with liquid lipids acting as the matrix [104]. The combination of solid and liquid lipids gives imperfections that can entrap more

Table 1 Physico-chemical properties and other outcomes of quercetin nanoformulations

Nanosystem	Physico-chemical properties and outcomes	Reference
Liposomes	Particle size: 130 ± 20 nm Effectively accumulate in tumor tissues Lengthen circulation time of quercetin in vivo Effectively inhibit multiple kinds of tumor growth and prolong the survival time of tumor-bearing mice Inhibition of tumor angiogenesis and induction of tumor cell apoptosis	[46]
	Particle size: 163 ± 10 nm Induced apoptosis by arresting the cell cycle in A2780s and A2780cp cells Suppressed tumor growth in ovarian xenografted nude mice models	[47]
	Particle size: 271 ± 32.34 nm Drug loading: 81.82 ± 1.30% Oral hepatoprotective activity in rats 50-fold enhancement in antioxidant activity compared to plain quercetin	[48]
NLCs	Drug loading: 11% Enhanced solubility and stability Enhanced apoptosis in MDA-MB-231and MCF-7 cells	[49]
	Particle size: 200 nm Entrapment efficiency: 80–90% Zeta potential: − 30 mV Promoted neuroprotective effects an in vitro model of Alzheimer's disease Inhibited fibril formation	[50]
Microemulsions	Reduced IL-4 and IL-5 levels Reduced P-selectin expression and mucus secretion in the lung	[51]
Nanoemulsion	Particle size: 219.7 ± 2.1 nm Encapsulation efficiency: 98.12 ± 0.07% Improved quercetin bioavailability (12.70 ± 0.12%) Improved cell permeability ($4.93 \pm 0.01 \times 10^{-6}$ cm/s)	[52]
	Improved in vitro permeability and in vivo oral bioavailability Artificial intestinal membrane: 188-fold Caco-2 cell monolayer: 3.37-fold In vivo oral bioavailability: 33.51-fold	[53]
Polymeric NPs	Particle size: ~ 300 nm Zeta potential: – 45 mV Drug release followed zero-order kinetics Relative oral bioavailability in rats: ~ 60% Attenuated endotoxic symptoms induced by lipopolysaccharides	[54]
	Particle size: 300–400 nm Content: 110 ± 3 to 335 ± 4 mg/ml Controlled release in simulated gastric fluid (80% after 3h) Prevented quercetin degradation Increased oral bioavailability Strong antioxidant activity	[55]
	Encapsulation efficiency: 87.9 ± 1.5 to 93.0 ± 2.6% Slower in vitro gastro-intestinal release after 240 min	[56]
	Particle size: 198.4 ± 7.8 nm Drug loading: 8.1 ± 0.4% Significant growth and metastasis inhibition in TNBC Oral gavage in 4T1-bearing mice Tumor inhibition: 67.88% Fewer lung metastatic colonies	[57]
	Particle size: < 200 nm Encapsulation efficiency: 79.78% In vitro drug release at pH 7.4: 67.28% Significantly reduced IC_{50} value Significant inhibition of tumor volume in A549 Reduced tumor inhibition in an MDA-MB-468 xenografted mice model	[58]
	Particle size: 150 nm Encapsulation efficiency: 70.52% Significantly greater antiproliferative and cytotoxic effects Apoptotic potential and cellular arrest of cancer cells	[59]

Table 1 (continued)

Nanosystem	Physico-chemical properties and outcomes	Reference
Micelles	Drug loading: 8.75 ± 0.41% Stable in aqueous media Markedly improved solubility Exhibited sustained release	[60]
	Particle size: 31.18 nm Drug loading: 11.2 ± 1.6% Improved anticancer efficacy in HepG2 and H9c2 cell lines	[61]
	Particle size: 36 nm Drug loading: 6.9% Inhibition of ovarian cancer by apoptosis	[60]
	Particle size: 87.5 nm Encapsulation efficiency: 63 − 77% Exhibited significantly lower glucose levels Higher SOD and higher catalase levels highlighted an enhanced anti-diabetic effect	[40]
	Particle size: 31 ± 2 nm Drug loading: 14.81 ± 0.07% Zeta potential: − 0.21 ± 0.07 mV In vitro release of 56.5 ± 7.8% in 7 days Increased cellular uptake and apoptosis Inhibitory effects on migration, the proliferation of 4T1 cells	[47]
	Particle size: < 100 nm Zeta potential: − 8.25 ± 1.26 mV Higher intracellular uptake Greater inhibitory effect against cell proliferation Improved therapeutic efficacy in lung carcinoma	[34]
	Particle size: 92.2 ± 0.35 nm Drug loading: 4.72% Orally relative bioavailability increased to 360% Increased antitumor activity Efficient growth inhibition in BALB/c mice	[59]
Dendrimers	Improved solubility Induced anti-inflammatory activity in RAW 264.7 Improved migration of AGS epithelial cells Potential in treatment of gastric ulcers by wound healing	[32]
	Particle size: 34.39–100.3 nm In vitro release displayed a biphasic pattern with Korsmeyer–Peppas kinetics Anti-inflammatory activity (45%) within 1 h	[62]
	Particle size: 225.5 ± 16.31 nm Encapsulation efficiency: 88 ± 1.52% Zeta potential: − 28.9 ± 1.9 mV Controlled and sustained drug release MIC of encapsulated quercetin decreased to 136 mg/mL compared to quercetin (500 mg/mL) Antibacterial efficacy against multidrug-resistant *S. aureus*; showed complete distortion of the cell surface morphology	[63]
	Particle size: > 100 nm Encapsulation efficiency: 82% Zeta potential: − 28.9 ± 1.9 mV Improved drug release at pH 5.8 (80%) compared to pH 7.4 (65%) with Korsmeyer–Peppas and Higuchi release kinetics	[64]

IL interleukins; *IC* inhibitory concentration, *TNBC* triple-negative breast cancer, *SOD* superoxide dismutases, *AGS* human gastric adenocarcinoma cells, *MIC* minimum inhibitory concentration

molecules than SLNs, thus enabling a high entrapment efficiency. NLCs overcome the challenge presented by drug expulsion from SLNs, thereby providing a major advantage [105]. Both SLNs and NLCs provide solubility enhancement, improved bioavailability and permeability, a prolonged

Table 2 Oral pharmacokinetic parameters of quercetin nanoformulations

Nanoformulations	Pharmacokinetic parameters	Reference
Liposomes	K_e (1/h): 0.3993 Half-life (h): 1.7355 AUC (mg·h/L): 77.72 V_d (l/kg): 0.0806 CL (l/h): 0.0322	[65]
	C_{max} (nmol/mL): 19.20 AUC (μmol·h/mL): 604.16 $t_{1/2}$ (h): 14.20 CL (mL/h): 0.01 MRT_{last} (h): 9.22 V_d (mL/g): 0.08	[66]
SLNs	AUC (μg·h/mL): 14.22 ± 2.15 K_e (1/h): 0.04 ± 0.01 K_a (1/h): 0.32 ± 0.11 Lag time (h): 0.02 ± 0.01 $t_{1/2Ka}$ (h): 2.16 ± 0.38 $t_{1/2Ke}$ (h): 17.96 ± 2.22 T_{max} (h): 8.00 ± 1.38 C_{max} (μg/mL): 12.22 ± 2.15 $AUC_{(0\rightarrow4-8h)}$ (μg·h/mL): 324.18 ± 41.35 CL (L/h): 0.04 ± 0.01 V_c (L): 1.04 ± 0.02 MRT (h): 27.48 ± 3.42	[67]
NLCs	C_{max} (μg/mL): 1.662 AUC (μg·h/g): 3.54 MRT (h): 18.7	[68]
Micelle	T_{max} (h): 0.25 C_{max} (μg/ml): 1.52 ± 1.31 $AUC_{(0\text{-inf})}$ (μg·h/ml): 0.90 ± 0.26 V_d (l/kg): 19.76 ± 14.05	[59]
	$AUC_{(0\text{-}24)}$ (ng·h/mL): 1477.27 ± 25.57 C_{max} (ng/mL): 182.85 ± 106.64 T_{max} (h): 0.5 ± 0.02 $t_{1/2}$ (h): 8.29 ± 0.49	[52]
Polymeric NPs	T_{max} (h): 5 ± 2.7 C_{max} (μg/mL): 3.4 ± 0.59 $t_{1/2}$ (h): 24.6 ± 8.41 AUC (μg·h/mL): 94.51 ± 18.71 V_d (mL): 837 ± 159 CL (mL/h): 24.4 ± 3.55 MRT (h): 25.4 ± 2.99	[54]
Solid dispersion	K_e (1/h): 0.1124 K_a (1/h): 1.3592 T_{max} (h): 0.63 C_{max} (ng/ml): 419.02 $AUC_{(0-t)}$ (ng·h/ml): 2841.63 $MRT_{(0-t)}$ (h): 4.6633 $CL/F_{(s)}$ (ng/h/(ng/ml)): 0.0038	[33]
	C_{max} (ng/mL): 2833.78 ± 537.64 T_{max} (h): 0.61 ± 0.31 $t_{1/2}$ (h): 8.68 ± 4.58 $AUC_{(0-24)}$ (ng·h/mL): 23252.76 ± 2475.90 $AUC_{(0-\infty)}$ (ng·h/mL): 27569.59 ± 6112.24	[69]

K_e elimination rate constant, *AUC* area under the curve, V_d volume of distribution, *CL* serum drug concentration at a steady state, C_{max} peak plasma concentration, $t_{1/2}$ half-life, *MRT* mean residence time, K_a absorption rate constant, t_{max} peak plasma time, V_c volume of the central compartment

half-life, fewer adverse effects, and targeted tissue delivery [106].

Quercetin SLNs prepared by emulsification followed by low-temperature solidification with glyceryl monostearate as the solid lipid displayed increased quercetin gastrointestinal absorption in rats [67]. Quercetin SLNs prepared using an ultrasonication method with a combination of tripalmitin and lecithin as the lipid core coated with chitosan allowed a faster release than pure quercetin, with enhanced uptake in Caco-2 cells [107]. Quercetin NLCs prepared using soya lecithin, medium-chain triglyceride, and glyceryl monostearate showed higher solubility, good stability, and enhanced apoptosis in MCF-7 and MDA-MB-231 cells [49]. NLCs of quercetin promoted neuroprotective effects in vitro in a model of Alzheimer's disease by inhibiting fibril formation [50].

4.4 Microemulsions (MEs), Nanoemulsions, and Self-microemulsifying Drug Delivery Systems (SMEDDS)

Microemulsions are thermodynamic stable, optically isotropic clear systems [108] comprising oil, a surfactant, a cosurfactant, and an aqueous phase [109, 110]. The ability of microemulsions to increase the solubility of water-insoluble BCS class II and IV drugs as well as enhance absorption facilitates bioavailability enhancement [111, 112]. ME can also be prepared by the phase-inversion temperature method [113, 114]. MEs provide manifold advantages like easy preparation, transparency, protection from degradation, low viscosity, and a high solubilization capacity.

Nanoemulsions—also known as ultrafine emulsions, submicron emulsions, and mini-emulsions—are kinetically stable nanodispersions of two immiscible liquids which are stabilized by surfactant(s) to form a single phase [115–118]. A nanoemulsion offers various merits such as improved dissolution and enhanced oral bioavailability [119]. Yet another very effective approach for enhancing the solubility and bioavailability of hydrophobic moieties utilizes SMEDDS [120]. These are microemulsions without an aqueous phase, which improves the stability of the formulation. SMEDDS are isotropic mixtures of surfactant, oil, and cosurfactant that spontaneously form microemulsions in GIT fluid/aqueous media with gastric motility/mixing [121, 122]. SMEDDSs can be added to finished dosage forms such as capsules or other solid dosage forms [123, 124].

The significantly increased solubility of another quercetin ME in comparison with plain quercetin in aqueous media with good ileum absorption was demonstrated [125]. Reduced IL-4 and IL-5 levels, reduced P-selectin expression, and decreased mucus secretion in the lung have also been demonstrated with a quercetin ME [51]. Nanoemulsions showed improved quercetin bioavailability and permeability [52]. A quercetin nanoemulsion prepared by aqueous-phase titration showed improved in vitro permeability through artificial intestinal membranes as well as enhanced oral bioavailability [53]. Co-delivery of pemetrexed and a quercetin-based nanoemulsion improved oral bioavailability and exhibited superior tumor growth inhibition in A549 tumor-bearing mice models compared with controls [126]. Quercetin SMEDDS showed rapid in vitro release, with a ninefold increase in AUC compared to free quercetin [127]. They also provided significantly enhanced solubility and 1-month stability at 25 °C along with enhanced transport across the Caco-2 cell monolayer [128].

4.5 Polymeric NPs

Natural and synthetic polymers that are biodegradable are used to prepare polymeric NPs of size <1000 nm [129]. They are classified as either nanocapsules, wherein the drug is present in the core, or as nanospheres, where the drug is distributed uniformly in the polymeric matrix [130, 131]. Polymeric NPs may show increased reactivity, sensitivity, and stability compared to liposomes. Their enhanced membrane permeability (attributed to their nanosize) and an ability to target a specific organ by attaching ligands to their surfaces make polymeric NPs attractive drug carriers [132].

Nanoprecipitation is considered the simplest approach for preparing drug-loaded NPs; in this, drug-loaded polymeric particles are precipitated out of organic solvents following addition to aqueous media. Other approaches for the fabrication of drug-loaded polymeric NPs include crosslinking, homogenization, solvent evaporation/diffusion, and spray drying. Other green techniques based on microwaves and aqueous solvents are also reported [133, 134]. Various polymers used for quercetin polymeric NPs include polylactic acid [135], poly(lactic-*co*-glycolic acid) (PLGA), chitosan [58], fucoidan [55], zein [56], zein-hydroxypropyl-β-cyclodextrin [54], and PEGylated PLGA conjugated with folic acid [136].

Quercetin-loaded polylactic acid NPs with high drug encapsulation efficiency exhibited controlled release, suggesting promise in terms of their utilization in newer therapies [137]. pH-sensitive NPs were synthesized that displayed high drug release in acidic media, leading to proposed applications in cancer therapy, considering the acidic environment of the tumor site [138]. Using cholate-modified polymer-lipid hybrid NPs (cPLNs), a bile salt transport pathway was evaluated for the oral delivery of quercetin. Quercetin cPLNs exhibited a 375.12% bioenhancement compared to quercetin suspensions [139]. PLGA-TPGS (D-α-tocopheryl polyethylene glycol 1000 succinate) quercetin NPs developed for oral delivery exhibited superior inhibition of triple-negative breast cancer

cells. Remarkable anti-tumor efficacy was observed in 4T1-bearing mice, and fewer lung metastatic colonies were detected [57].

4.6 Micelles

Micelles are drug delivery systems with a size range of 5–100 nm wherein a surfactant or block copolymer forms self-assembled aggregates [140, 141]. They are aqueous dispersions in which the block copolymer concentration is greater than the critical micelle concentration [142]. Micelles can be prepared by dissolution, emulsion technique, dialysis, solvent evaporation, as well as lyophilization [143]. Micelles are small in size and can facilitate an increased cellular uptake, improved therapeutic potential, and sustained drug release [144, 145].

Pluronic P123/TPGS mixed micelles enabled improved solubility and bioactivity of quercetin [146]. PEG-modified quercetin micelles demonstrated enhanced solubility and K562 (human erythromyelogenous leukemia) cells were arrested at the G2/M phase [147] Quercetin micelles of γ-benzyloxy-substituted poly(ε-caprolactone) have proven to have anticancer and antioxidative activity against HepG2 and H9c2 [60, 61]. Quercetin-loaded mixed micelles showed high uptake inside the cells and exhibited sustained drug release. Results indicated that TPGS facilitated enhanced apoptosis, which resulted in an improvement in lung cancer treatment [34].

Quercetin-loaded sodium taurocholate-Pluronic P123 micelles demonstrated sustained release in both simulated gastric and intestinal fluids. This formulation displayed 1.8-fold and 1.6-fold higher C_{max} and $AUC_{0–24}$ values compared to the free quercetin, respectively [148]. Quercetin-loaded LipoMicel® (liquid micelle matrix) exhibited a ninefold enhancement in C_{max} and an eightfold increase in $AUC_{0–24}$ compared to free quercetin [149]. In another pharmacokinetic study, orally administered lecithin-stabilized polymeric micelles significantly increased the relative bioavailability by 360% and showed an absolute bioavailability of 5.13% compared to quercetin [59]. While most studies have evaluated the anticancer efficacy of quercetin, Brahmeshwar Mishra et al. developed quercetin-loaded bio-enhanced and prolonged-release Soluplus® micelles for the management of diabetes and demonstrated an enhanced anti-diabetic effect [40].

4.7 Dendrimers

Dendrimers are especially recognized for their monodispersity, hyperbranched nature, polyvalence, nanoscale size, biocompatibility, and stability [150]. Dendrimers comprise a hydrophobic cavity that acts as an initiator, surrounding interior generations of repeating units, and outermost exterior terminal functional groups [151]. Convergent and divergent methods are the two common approaches for dendrimer synthesis [152]. Polyamidoamine (PAMAM) was the first family of dendrimers to be commercialized, and they are the most commonly exploited [153]. Due to their nanoscale size, dendrimers can adapt paracellular or transcellular pathways to cross cell barriers, making them attractive carriers for nanodrug delivery [154]. Investigations proved that the solubility of quercetin improved when PAMAM was used as a carrier [155]. Quercetin magnetite/poly-aminoester dendrimer with poly(ε-caprolactone) improved the release of quercetin at pH 5.8 (80%) when compared with pH 7.4 (65%) [64]. Quercetin with linear PEG-PLGA polymer caused significantly increased cancer cell death in 66 GB cell lines [156]. Dendrimeric quercetin formulations were also found effective in terms of anti-inflammatory [62], anti-bacterial [63], and neuroprotective [157] activity.

4.8 Magnetic NPs

Due to their magnetic properties, magnetic NPs are readily targeted to the target sites with the help of an externally applied magnetic field [158]. Magnetic NPs are less than 10–20 nm in size, exhibit the properties of a giant paramagnetic atom, and exhibit a rapid response to external magnetic fields. They also exhibit only trace residual magnetism and coercivity [159]. This is crucial to prevent agglomeration [160].

A quercetin-loaded pH-sensitive superparamagnetic drug carrier (Fe_3O_4) surface coated with polyamidoamine-*b*-PEG-folate (hyperbranched) demonstrated high aqueous solubility [161]. Iron oxide was functionalized with folic acid to target overexpressed folic acid receptors on brain adenocarcinoma cells (U87). Results of MTT assay and cell uptake studies confirmed that these magnetic NPs are useful for cancer therapy [162]. Similarly, quercetin-loaded PLGA-MNPs demonstrated anticancer activity against viable A549 cells and were safe after being injected into mice [163]. In another study, superparamagnetic quercetin Fe_3O_4 NPs were also found to be cytotoxic to MCF-7 breast cancer cell lines, which was confirmed by morphological changes observed under a fluorescence microscope [164].

4.9 Gold NPs

Quercetin was effectively harnessed to prepare gold NPs of size 20–45 nm by reduction [165]. High anticancer activity was exhibited by the quercetin-functionalized gold NPs, with an anti-angiogenic effect demonstrated in a chorioallantoic membrane assay [166]. However, these NPs exhibited no cytotoxicity to human fibroblasts (L929 cells) [167]. An in-vivo reduction in tumor volume seen in the 4T1 tumor mouse model was attributed to altered expression of genes

related to apoptosis [168]. Furthermore, quercetin gold NPs demonstrated higher antioxidant activity compared to free quercetin [167]. Quercetin-conjugated gold NPs were also studied for their efficacy against leishmaniasis [169].

4.10 Miscellaneous Quercetin Nanosystems

Silver nanocubes prepared using extract of the leaf of *Peltophorum pterocarphum* relied on quercetin-3-*O*-β-*d*-galactopyranoside to act as the reducing agent. They showed promising antifungal activity compared to the commercial antifungal agent fluconazole [170]. Quercetin mesoporous silica NPs anchored with folic acid caused apoptosis due to cell cycle arrest in breast cancer cell lines [171, 172]. In melanoma cells, the activity of titanium dioxide nanotubes containing quercetin on melanoma cells was ascribed to enhanced cleaved caspase-3 levels and enhanced apoptosis compared to titanium dioxide nanotubes or quercetin alone [173]. Quercetin-poly(lactide-*co*-glycolide)-folic acid targeted nanocapsules showed selective uptake and cytotoxicity towards cancer cells where folate was over-expressed. High accumulation at tumors and active targeting were confirmed following intravenous administration in IGROV-1 or HeLa tumor-bearing mice [136]. Treatment with quercetin was effective at overcoming the harmful effects of multi-walled carbon nanotubes, which included inflammatory and oxidative as well as immunotoxic effects [174]. On the other hand, quercetin-loaded protein NPs based on natural proteins (albumin, gelatin, hemoglobin) are an attractive alternative to synthetic polymers in drug delivery applications due to their safety, biodegradability, biocompatibility, unique self-assembly, and hydrophobic interaction properties [38, 39, 175].

5 Quercetin Clinical Trials

Clinical trials investigating the therapeutic effects of quercetin are on the rise. Inflammation is a major contributor to the progress of many chronic diseases, namely, cancer, diabetes, and heart disease [148]. Several clinical trials have investigated the anti-inflammatory properties of quercetin. One randomized controlled trial (RCT) involving 50 participants with rheumatoid arthritis found that supplementation with quercetin reduced inflammatory markers and improved joint mobility compared to a placebo (NCT05371340).

Quercetin has also been studied for its potential to improve cardiovascular health [176]. A meta-analysis of 17 RCTs found that quercetin supplementation significantly reduced blood pressure, especially in those with high blood pressure (NCT01839344). Another RCT involving obese individuals with type 2 diabetes found that quercetin supplementation improved blood lipid profiles compared to a placebo (NCT00065676).

Cancer is a key cause of mortality and morbidity worldwide [177]. Quercetin nanoformulations have been extensively evaluated for anticancer efficacy. Importantly, while free quercetin has demonstrated some activity against various anticancer cell lines, quercetin nanoformulations have demonstrated superior activity. This application of quercetin nanoformulations for the treatment of a variety of cancers is evident from Table 3, which lists the cell lines evaluated for various cancers. Quercetin has been studied for its potential anticancer effects, given its ability to affect cancer cell death and inhibit the growth of tumors. Several clinical trials have investigated quercetin as an adjuvant therapy for cancer treatment (NCT03493997, NCT05456022, NCT03476330, NCT01538316, NCT05724329, NCT01912820). A pilot RCT involving patients with sarcoidosis and idiopathic pulmonary fibrosis found that quercetin supplementation improved quality of life and reduced inflammation markers compared to a placebo (NCT00512967). Another RCT involving 40 patients with prostate cancer found that quercetin supplementation improved oxidative stress markers and inflammation compared to a placebo (NCT03493997). Quercetin has also been studied for its potential to improve immune function. One RCT study with quercetin supplementation showed increased natural killer cell activity and attenuated the incidence of COVID-19 infection compared to a placebo (NCT04853199).

In summary, quercetin has been studied for its possible therapeutic effects in a variety of health conditions. Clinical trials have provided evidence that quercetin supplementation may have anti-inflammatory, cardiovascular, anticancer, and immune-enhancing effects. However, further research is important to fully harness quercetin as a therapeutic and to arrive at optimal dosages of quercetin for different health conditions [257].

6 Marketed Products of Quercetin Nanoformulations

Quercefit® is a lecithin-based water-soluble quercetin formulation that produced a 20-fold-increase in plasma levels of quercetin without any notable side effects after oral administration of the quercetin nanoformulation in human volunteers [258]. On the same note, each tablet of Quevir®, a dietary supplement, contains 500 mg of quercetin phytosome. Here, quercetin is in a food-grade delivery system with sunflower phospholipids, which increases its oral absorption up to 20-fold [259]. Other marketed formulations are Thorne's Quercetin Phytosome® [260], Codeage's Quercetin Phytosome® [261], One Planet Nutrition's Nano Quercetin® [262], and Quercetin LipoMicel® [149].

Table 3 Summary of the half-maximal effective dose (IC_{50}) of quercetin for different cancer cell lines

Cancer type	Cancer cell line	IC_{50}	References
Ovarian	A2780s	30 µg/mL	[178]
	CAOV3	100 µM	[179]
	CRL11731	–	[180]
	CRL1978	–	[180]
	OV2008, OV2008, and its resistant variant C13	–	[181, 182]
	OVCAR-5	66 µM	[183]
	PA-1	75 µM	[184]
	SKOV-3	22 µM	[185]
Breast	4T1	50 µM	[186]
	AU565	20 µM	[187, 188]
	BT-20		[187]
	HCC1937		[189]
	MCF-7	100 µM	[187, 190–197]
	MCF-7Ca/TAM-R	100 µM	[198]
	MDA-MB-231	125 µM	[190, 198–201]
	MDA-MB-453	–	[199, 200, 202]
	MDA-MB-468	7 µg/ml	[203]
Cervical	C-33A	8 mM	[204]
	Caski	–	[205]
	CC cells	100 µM	[206]
	HeLa	100 µM	[205, 207]
	SiHa	13.3 µM	[205, 207]
Gastric	AGS cells	40 µM	[208–211]
	EBV(−) MKN74	150 µM	[212]
	GES-1	40 µM	[213]
	HCG-27		[214]
	MGC-803 Cells	23.35 µM	[215]
	SNU719	60 µM	[216]
Lung	A-549	80 µM	[217–224]
	H1299	50 µM	[225]
	H460	100 µM	[225]
	HTB-182/R	–	[226]
	Radiation-resistant GLC-82/R	–	[226]
Blood	232B4 CLL	20 µM	[227]
	DLBCL TMD8	50 µM	[228] [229]
	U 937	45 µM	[228]
	MVA-11	36.3 µM	[228]
	HL-60	12.5 µM	[228, 230–232]
	HSB2	25 µM	[233]
	Jurkat	75 µM	[228]
	K562	12.5 µM	[228]
	K562/ADR	100 µM	[234]
	KG-1 cells	100 µM	[235]
	THP-1	40 µM	[228]
	MOLT4	50 µM	[236]
	Nalm6	25 µM	[237]
	PEL	30 µM	[238–240]
	T-ALL	10 µM	[230]
	CEM	50 µM	[228]
	U-937	50 µM	[241]

Table 3 (continued)

Cancer type	Cancer cell line	IC_{50}	References
Prostate	DU145	50 µM	[242–244]
	LNCaP	100 µM	[236, 242, 243, 245–247]
	PC-3 cells	100 µM	[236, 242–244, 246–251]
Miscellaneous			
Colon	HT-29	30 µM	[252]
Brain	Glioma A172, LN229, U87-MG, U251	200 µM	[253]
Skin	Melanoma A375SM	40 µM	[231, 254]
	Melanoma A375P	>200 µM	[231, 254]
	Melanoma A2058	60 µM	[231, 254]
Bone	Osteosarcoma HOS	160 µM	[255, 256]]
	Osteosarcoma U20S	50 µM	[249]

7 Future Perspective and Conclusion

Clinical trials to date have employed free quercetin, which, despite serious solubility and bioavailability limitations, exhibits great promise. Nanoformulations of quercetin shown great promise for anticancer activity compared with free quercetin and combinations of drugs. Through their inherent targeting property, nanoformulations could provide a remarkable improvement in therapy, possibly even at lower doses. Considering the high dose of quercetin, the oral route appears to be the most practical. Among all the nanoformulations, quercetin phytosomes—which are available on the market—are attracting the most interest because of the enhanced plasma concentration levels of quercetin (20-fold more bioavailable compared to free quercetin) after the oral administration of a single dose in humans. However, more clinical safety and efficacy studies are needed to study the safety and effectiveness of quercetin nanoformulations. Targeting organs like the lung and breast through lymph-mediated uptake increases the oral bioavailability. Quercetin-loaded nanosystems could be one more opportunity to harness the beneficial effects of quercetin nanoformulations for breast cancer as well as various lung afflictions. More research into quercetin nanoformulations is imperative to harness the various applications of this wonderful nutraceutical.

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Declarations

Conflict of Interest Esha S. Attar, Vanashree H. Chaudhari, Chaitanya G. Deokar, Sathish Dyawanapelly, and Padma V. Devarajan report that they have no conflict of interest to declare.

Author Contributions Esha S. Attar and Vanashree H. Chaudhari: conceptualization, writing—original draft, writing—review, and editing. Chaitanya G. Deokar: writing—original draft. Sathish Dyawanapelly: visualization, writing—review, and editing. Padma V. Devarajan: conceptualization, supervision, writing—review, and editing.

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