IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Nanotechnology-Enhanced Delivery of Quercetin: Mechanistic Insights, Therapeutic Applications, and Translational Challenges

1Samreen Parveen, 2Shiv Dev Singh, 3Priyanka, 4Ankit Kumar Verma

1PG Scholar, 2Associate Professor, 3PG Scholar, 4PG Scholar

1MJP Rohilkhand University, Bareilly,

2MJP Rohilkhand University, Bareilly,

3MJP Rohilkhand University, Bareilly,

4MJP Rohilkhand University, Bareilly

Abstract

Quercetin is a naturally occurring flavonoid known for its antioxidant, anti-inflammatory, anticancer, cardioprotective, and neuroprotective activities. However, its therapeutic application is considerably restricted due to poor aqueous solubility, low bioavailability, rapid metabolism, and limited target-site accumulation. Recent advances in Nanotechnology have enabled the development of novel nanocarrier systems to overcome these pharmacokinetic limitations and improve the clinical potential of Quercetin. Various nanocarriers, including liposomes, solid lipid nanoparticles, polymeric nanoparticles, nanoemulsions, micelles, and inorganic nanoparticles, have demonstrated enhanced drug stability, controlled release, improved cellular uptake, and tissue-specific delivery. This review summarizes the physicochemical and pharmacokinetic challenges associated with quercetin and discusses recent progress in nanotechnology-based delivery strategies. Particular emphasis is given to targeted and stimuli-responsive nanocarriers designed for enhanced therapeutic efficacy. In addition, the molecular mechanisms of nano-quercetin, including modulation of oxidative stress, inflammatory pathways, fibrosis-related signaling, apoptosis, and tumor microenvironment regulation, are critically discussed. The therapeutic applications of quercetin nanoparticles in cancer, neurodegenerative disorders, inflammatory diseases, cardiovascular complications, and wound healing are also highlighted. Furthermore, current challenges related to nanoparticle toxicity, regulatory approval, large-scale manufacturing, and clinical translation are addressed. Overall, nano-enabled delivery systems offer a promising platform for improving quercetin therapeutics and advancing its future clinical applications.

Keywords: Quercetin; Nanotechnology; Polymeric nanoparticles; Targeted drug delivery; Oxidative stress; Cancer nanomedicine; Stimuli-responsive nanocarriers

1. Introduction

1.1 Quercetin Overview

Quercetin is a naturally occurring polyphenolic flavonoid that belongs to the flavonol subclass and is widely distributed in fruits, vegetables, medicinal herbs, and beverages. It has gained substantial scientific attention due to its broad spectrum of pharmacological activities and potential therapeutic applications in numerous chronic and degenerative diseases. Structurally, quercetin possesses five hydroxyl groups attached to its flavone backbone, which contribute significantly to its antioxidant and free radical scavenging properties. Owing to its ability to modulate multiple cellular signaling pathways, quercetin has emerged as an important bioactive molecule in pharmaceutical and biomedical research [1-5].

In recent years, increasing interest has been directed toward the therapeutic potential of quercetin in cancer, cardiovascular disorders, neurodegenerative diseases, metabolic syndrome, inflammatory conditions, and fibrotic diseases. Several in vitro and in vivo investigations have demonstrated that quercetin exerts protective effects through antioxidant, anti-inflammatory, anti-apoptotic, antimicrobial, antiviral, and immunomodulatory mechanisms. Furthermore, its natural origin and relatively low toxicity profile make it an attractive candidate for long-term therapeutic use. Despite these promising biological properties, the clinical translation of quercetin remains limited due to various physicochemical and pharmacokinetic challenges [6-11].

1.2 Sources and Chemistry

Quercetin is abundantly present in various plant-based dietary sources, including onions, apples, berries, grapes, citrus fruits, broccoli, tea, red wine, and leafy vegetables. It is also found in several medicinal plants traditionally used in herbal medicine. In nature, quercetin commonly exists in glycosylated forms, where sugar moieties are attached to its hydroxyl groups. These glycosides influence its absorption, metabolism, and biological activity within the human body. Chemically, quercetin is identified as 3,3′,4′,5,7-pentahydroxyflavone and possesses a characteristic flavonol skeleton consisting of two benzene rings linked through a heterocyclic pyrone ring [12-17]. The presence of multiple hydroxyl groups contributes to its potent reducing and metal-chelating capabilities. However, these structural characteristics also render quercetin susceptible to oxidation and degradation under physiological and environmental conditions. Quercetin exhibits poor water solubility and limited chemical stability, particularly in alkaline pH and oxidative environments, which significantly affect its therapeutic performance.

The lipophilic nature of quercetin restricts its dissolution in biological fluids, thereby limiting gastrointestinal absorption following oral administration. Moreover, the molecule undergoes extensive first-pass metabolism in the liver and intestines, resulting in rapid biotransformation into glucuronidated, sulfated, and methylated metabolites. Consequently, only a small fraction of administered quercetin reaches systemic circulation in its active form [18-25].

1.3 Pharmacological Significance

Quercetin exhibits diverse pharmacological activities that contribute to its therapeutic potential across multiple disease conditions. One of its most extensively studied properties is its antioxidant activity, which primarily arises from its ability to neutralize reactive oxygen species (ROS), inhibit lipid peroxidation, and enhance endogenous antioxidant defense systems. Quercetin can activate antioxidant signaling pathways such as nuclear factor erythroid 2-related factor 2 (Nrf2), thereby promoting the expression of antioxidant enzymes including superoxide dismutase, catalase, and glutathione peroxidase [26-30].

In addition to antioxidant effects, quercetin demonstrates potent anti-inflammatory activity through inhibition of pro-inflammatory mediators and signaling pathways such as nuclear factor-kappa B (NF-κB), cyclooxygenase (COX), and tumor necrosis factor-alpha (TNF-α). These mechanisms contribute to its protective role in inflammatory and autoimmune disorders. Quercetin also exhibits remarkable anticancer properties by regulating cell proliferation, apoptosis, autophagy, angiogenesis, and metastasis. It has been shown to modulate various molecular targets involved in tumor progression, including phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), mitogen-activated protein kinase (MAPK), and transforming growth factor-beta (TGF-β) pathways. Furthermore, quercetin has demonstrated the ability to sensitize resistant cancer cells to chemotherapeutic agents, highlighting its potential in combination therapy [31-35].

Apart from oncology applications, quercetin has shown promising neuroprotective effects in neurodegenerative diseases such as Alzheimer's and Parkinson's disease by reducing oxidative stress, neuroinflammation, and neuronal apoptosis. Cardioprotective and antidiabetic activities have also been widely reported, including prevention of endothelial dysfunction, reduction of atherosclerotic progression, and improvement of insulin sensitivity. These multifunctional therapeutic actions make quercetin a promising candidate for the management of chronic diseases [36-40].

1.4 Major Limitations

Despite extensive pharmacological potential, the clinical utility of quercetin is severely restricted by several inherent limitations. The major challenge associated with quercetin is its extremely poor aqueous solubility, which leads to inadequate dissolution and limited absorption in the gastrointestinal tract. Its low oral bioavailability further compromises therapeutic efficacy, as only a minimal concentration reaches systemic circulation after administration. Another significant limitation is rapid metabolism and elimination. Quercetin undergoes extensive enzymatic conjugation in the intestine and liver, resulting in rapid formation of inactive metabolites that reduce its biological effectiveness. Additionally, quercetin exhibits poor permeability across biological membranes and limited accumulation at target tissues[41, 42].

Chemical instability also presents a considerable challenge. Quercetin is highly susceptible to degradation upon exposure to light, oxygen, alkaline pH, and elevated temperatures. Such instability affects storage, formulation development, and therapeutic consistency. Furthermore, non-specific distribution and rapid systemic clearance hinder its ability to maintain sustained therapeutic concentrations at disease sites. These limitations collectively reduce the clinical applicability of quercetin despite encouraging preclinical evidence. Therefore, innovative formulation strategies are required to improve its pharmacokinetic profile and therapeutic performance [43-45].

1.5 Need for Nanotechnology

Recent advancements in Nanotechnology have provided promising opportunities to overcome the limitations associated with quercetin delivery. Nanotechnology-based drug delivery systems offer several advantages, including enhanced solubility, improved stability, prolonged circulation time, controlled drug release, and targeted tissue delivery. Encapsulation of quercetin within nanocarriers protects the molecule from premature degradation and metabolic inactivation while enhancing its bioavailability. Various nanocarrier systems such as liposomes, polymeric nanoparticles, solid lipid nanoparticles, nanoemulsions, micelles, dendrimers, and inorganic nanoparticles have been explored for quercetin delivery. These nanosystems can improve cellular uptake through enhanced permeability and retention effects and facilitate site-specific drug accumulation. Functionalization of nanoparticles with ligands, antibodies, peptides, or polymers further enables active targeting toward diseased tissues, thereby minimizing off-target toxicity and improving therapeutic efficacy. Stimuli-responsive nanocarriers capable of releasing quercetin in response to pH, reactive oxygen species, enzymes, or temperature have also emerged as advanced therapeutic platforms [46-48]. Such smart delivery systems enhance precision medicine approaches and improve treatment outcomes in complex diseases such as cancer and fibrosis.

2 Research Gap and Review Objective

Although numerous studies have investigated quercetin-loaded nanocarriers and their therapeutic applications, most available reviews focus only on individual aspects such as formulation development, pharmacological activity, or specific disease applications. A comprehensive and integrated review addressing the relationship between nanotechnology-based delivery systems, molecular mechanisms, targeted therapeutic applications, and translational challenges remains limited [49, 50].

Furthermore, emerging areas such as stimuli-responsive nanocarriers, hybrid co-delivery systems, tumor microenvironment modulation, and artificial intelligence-assisted nanoparticle design have not been critically discussed in a unified manner. In addition, despite extensive preclinical evidence, clinical translation of nano-quercetin systems remains inadequate due to regulatory, manufacturing, and safety-related concerns.

Therefore, the present review aims to provide a comprehensive overview of recent advances in nanotechnology-enhanced delivery of quercetin. The review critically discusses physicochemical limitations, nanocarrier systems, molecular mechanisms, therapeutic applications, targeted delivery approaches, safety considerations, and translational perspectives. Additionally, future trends and emerging strategies for improving the clinical applicability of nano-quercetin are highlighted [51].

3. Physicochemical and Pharmacokinetic Limitations of Quercetin

3.1 Chemical Structure and Stability

Quercetin is a naturally occurring flavonol chemically identified as 3,3′,4′,5,7-pentahydroxyflavone. Its molecular structure consists of two aromatic benzene rings (A and B rings) connected through a heterocyclic pyrone ring (C ring), forming the classical flavonoid backbone. The presence of five hydroxyl groups contributes significantly to its strong antioxidant and free radical scavenging activities. These hydroxyl groups are primarily responsible for hydrogen donation, metal ion chelation, and modulation of redox signaling pathways. The catechol arrangement within the B ring particularly enhances its antioxidative capacity and interaction with various biomolecular targets. Despite these favorable pharmacological characteristics, quercetin possesses several physicochemical drawbacks that limit its therapeutic applicability. One of the major concerns is its poor aqueous solubility, which is estimated to be extremely low under physiological conditions. The hydrophobic nature of quercetin restricts its dissolution in gastrointestinal fluids, thereby reducing absorption following oral administration [53-55]. Additionally, quercetin exhibits high crystallinity and strong intermolecular hydrogen bonding, further contributing to limited solubility and dissolution rate.

Chemical instability is another major limitation associated with quercetin. The molecule is highly susceptible to oxidative degradation when exposed to environmental conditions such as oxygen, heat, alkaline pH, ultraviolet radiation, and light. Under alkaline conditions, quercetin undergoes rapid oxidation and structural decomposition, resulting in loss of biological activity. Furthermore, auto-oxidation of quercetin may generate reactive quinone intermediates that can alter therapeutic efficacy and stability. Quercetin also demonstrates instability during storage and formulation processing. Factors such as temperature fluctuations, moisture exposure, and prolonged storage may accelerate degradation reactions. In biological systems, quercetin can interact with plasma proteins and enzymes, which may further influence its stability and pharmacological activity. These physicochemical limitations collectively reduce formulation efficiency and hinder the development of clinically effective conventional dosage forms[56-58].

3.2 Absorption and Metabolism

The absorption and metabolic behavior of quercetin significantly influence its pharmacokinetic profile and therapeutic effectiveness. Following oral administration, quercetin exhibits limited gastrointestinal absorption due to its low water solubility and poor membrane permeability. In dietary sources, quercetin is commonly present in glycosylated forms, which require hydrolysis before intestinal absorption. Enzymes such as lactase-phlorizin hydrolase and cytosolic β-glucosidase participate in the cleavage of sugar moieties, converting glycosides into absorbable aglycone forms.

Absorption primarily occurs in the small intestine through passive diffusion and transporter-mediated mechanisms. However, the extent of absorption remains relatively low due to poor dissolution and rapid intestinal metabolism. Once absorbed, quercetin undergoes extensive first-pass metabolism in enterocytes and hepatocytes. Phase II metabolic enzymes rapidly convert quercetin into glucuronidated, sulfated, and methylated metabolites, substantially reducing the concentration of free active quercetin in systemic circulation. Major metabolic pathways include glucuronidation by uridine diphosphate-glucuronosyltransferases (UGTs), sulfation by sulfotransferases, and methylation by catechol-O-methyltransferase (COMT). These metabolites circulate predominantly in conjugated forms rather than as free quercetin. Although some metabolites may retain partial biological activity, their pharmacological effects often differ from the parent compound [59, 60].

Additionally, quercetin demonstrates rapid elimination from the body through renal and biliary excretion. Its relatively short plasma half-life and extensive metabolic conversion result in insufficient tissue accumulation and limited therapeutic persistence. The intestinal microbiota also plays an important role in quercetin metabolism by degrading flavonoid structures into smaller phenolic acids, which may further alter pharmacological responses. Another important pharmacokinetic concern is

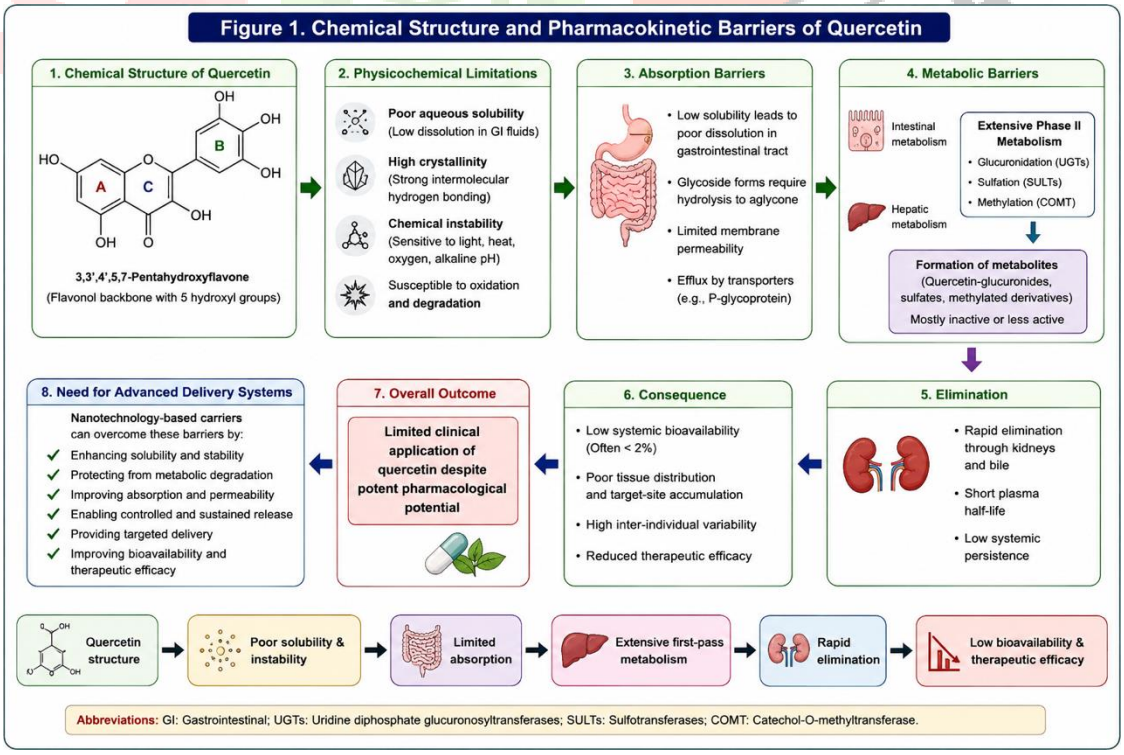
the limited ability of quercetin to cross certain biological barriers, including the blood-brain barrier (BBB), thereby restricting its effectiveness in neurological disorders. Furthermore, efflux transporters such as P-glycoprotein may reduce intracellular retention and systemic availability of quercetin in target tissues [61].

3.3 Bioavailability Challenges

Low oral bioavailability remains the most critical obstacle limiting the clinical translation of quercetin. Bioavailability refers to the proportion of an administered drug that reaches systemic circulation in an active form capable of exerting therapeutic effects. In the case of quercetin, multiple interconnected factors contribute to poor bioavailability and inconsistent pharmacological outcomes. The primary challenge arises from its poor aqueous solubility and slow dissolution rate, which significantly reduce gastrointestinal absorption. Since quercetin is highly lipophilic, only a small fraction dissolves in intestinal fluids, leading to inadequate uptake across epithelial membranes. Moreover, the crystalline nature of quercetin further impairs dissolution kinetics [62].

Extensive presystemic metabolism also substantially limits systemic bioavailability. Rapid enzymatic conjugation in the intestine and liver converts quercetin into inactive or less active metabolites before reaching circulation. Consequently, plasma concentrations of free quercetin remain extremely low even after administration of high doses. Studies have reported that the oral bioavailability of quercetin is typically below 2%, emphasizing the need for improved delivery strategies. Another major limitation is poor target-site accumulation. Conventional formulations fail to provide selective tissue distribution, resulting in non-specific biodistribution and rapid systemic clearance. In many disease conditions, therapeutic efficacy requires sustained drug concentrations at specific pathological sites, which cannot be achieved efficiently through free quercetin administration [63].

Variability in absorption among individuals further complicates therapeutic application. Factors such as dietary composition, intestinal microbiota, age, metabolic status, and co-administered drugs may influence quercetin pharmacokinetics and therapeutic response. Additionally, instability in physiological environments can cause premature degradation before reaching target tissues. To address these challenges, various advanced drug delivery systems have been explored to enhance solubility, stability, permeability, and tissue targeting of quercetin. Nanotechnology-based carriers have shown particular promise in improving pharmacokinetic behavior and therapeutic efficacy through controlled release, enhanced cellular uptake, and protection from metabolic degradation (Figure 1).



4. Nanocarrier Systems for Quercetin Delivery

The therapeutic efficacy of Quercetin is significantly restricted by poor aqueous solubility, low oral bioavailability, rapid metabolism, and limited tissue distribution. To overcome these limitations,

various nanotechnology-based delivery systems have been developed to improve quercetin stability, enhance cellular uptake, prolong systemic circulation, and enable controlled or targeted drug release. Nanocarriers can encapsulate quercetin within protective matrices, thereby minimizing degradation and enhancing therapeutic performance. Different nanosystems possess unique physicochemical properties that influence drug loading capacity, release kinetics, targeting efficiency, and biocompatibility [64].

4.1 Lipid-Based Nanoparticles

Lipid-based nanocarriers are among the most extensively explored systems for quercetin delivery because of their excellent biocompatibility, low toxicity, and enhanced drug solubilization capabilities. These systems improve membrane permeability and facilitate efficient absorption of hydrophobic compounds [65].

Liposomes

Liposomes are spherical vesicular structures composed of phospholipid bilayers surrounding an aqueous core. They can encapsulate both hydrophilic and hydrophobic drugs, making them highly versatile carriers for quercetin delivery. Liposomal encapsulation improves quercetin solubility, protects it from oxidative degradation, and prolongs circulation time in the bloodstream. Furthermore, surface modification of liposomes with polyethylene glycol (PEG) or targeting ligands enhances stability and tissue-specific accumulation. Quercetin-loaded liposomes have shown promising therapeutic outcomes in cancer therapy, inflammatory disorders, and neurodegenerative diseases. Their ability to fuse with cellular membranes facilitates efficient intracellular delivery and enhanced bioactivity. However, liposomes may exhibit limitations such as physical instability, drug leakage, and high production costs.

Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles are submicron colloidal systems composed of solid lipids stabilized by surfactants. Unlike liposomes, SLNs possess a solid lipid core that provides enhanced physical stability and controlled drug release. Encapsulation of quercetin into SLNs improves chemical stability, bioavailability, and sustained therapeutic action. SLNs offer several advantages including low toxicity, protection against enzymatic degradation, ease of large-scale production, and improved gastrointestinal absorption. These systems have demonstrated significant potential in anticancer therapy, topical formulations, and oral drug delivery applications. Nevertheless, limitations such as limited drug loading capacity and possible drug expulsion during storage remain major concerns [66, 67].

Nanostructured Lipid Carriers (NLCs)

Nanostructured lipid carriers are advanced lipid-based nanosystems developed to overcome the limitations associated with SLNs. NLCs contain a mixture of solid and liquid lipids, producing a less ordered matrix that enhances drug loading efficiency and minimizes drug leakage. Quercetin-loaded NLCs have shown improved encapsulation efficiency, better stability, prolonged release behavior, and enhanced tissue penetration. These systems are particularly useful for dermal, oral, and targeted cancer therapy applications. In addition, NLCs improve pharmacokinetic properties and increase intracellular accumulation of quercetin in diseased tissues. However, formulation complexity and optimization challenges may limit industrial scalability.

4.2 Polymeric Nanoparticles

Polymeric nanoparticles have gained considerable attention due to their tunable physicochemical properties, controlled drug release behavior, and enhanced stability. These systems are prepared using biodegradable and biocompatible polymers capable of improving therapeutic efficacy and site-specific delivery [68].

PLGA Nanoparticles

Poly(lactic-co-glycolic acid) (PLGA) nanoparticles are among the most widely investigated polymeric carriers for quercetin delivery. PLGA is a biodegradable and FDA-approved polymer that undergoes hydrolysis into non-toxic metabolites such as lactic acid and glycolic acid. Quercetin-loaded PLGA nanoparticles exhibit enhanced stability, prolonged circulation time, and sustained drug release

profiles. These systems protect quercetin from metabolic degradation and improve intracellular uptake in cancer cells. Furthermore, PLGA nanoparticles can be surface-functionalized with targeting ligands for selective delivery to tumors or inflamed tissues. Despite their advantages, PLGA formulations may occasionally show burst release effects and relatively complex preparation methods.

Chitosan Nanoparticles

Chitosan is a natural cationic polysaccharide obtained from chitin and is widely used in nanomedicine because of its biocompatibility, biodegradability, and mucoadhesive properties. Chitosan nanoparticles enhance the permeability and retention of quercetin across biological membranes.

These nanoparticles have shown promising applications in oral, nasal, and transdermal drug delivery systems. Chitosan-based carriers improve intestinal absorption and provide prolonged drug retention at mucosal surfaces. Additionally, their positive surface charge facilitates electrostatic interaction with negatively charged cellular membranes, promoting enhanced uptake. However, pH sensitivity and limited stability under physiological conditions remain potential drawbacks [69].

PEG-Based Systems

Polyethylene glycol (PEG)-based nanoparticles are extensively utilized to improve the pharmacokinetic profile of quercetin. PEGylation enhances hydrophilicity, prolongs systemic circulation, reduces immune recognition, and minimizes rapid clearance by the reticuloendothelial system. PEG-functionalized nanocarriers improve drug stability and accumulation at target tissues through enhanced permeability and retention effects. In cancer therapy, PEGylated nanoparticles can facilitate passive tumor targeting and improve therapeutic efficacy. Nevertheless, repeated administration may occasionally induce immune responses associated with accelerated blood clearance phenomena.

4.3 Inorganic Nanoparticles

Inorganic nanoparticles possess unique optical, magnetic, and physicochemical properties that make them attractive platforms for drug delivery, imaging, and theranostic applications.

Gold Nanoparticles

Gold nanoparticles exhibit excellent biocompatibility, facile surface modification, and strong optical properties. Quercetin-conjugated gold nanoparticles have demonstrated enhanced anticancer, antioxidant, and antimicrobial activities. These nanoparticles can improve cellular uptake and facilitate targeted drug delivery through ligand conjugation strategies. Gold nanoparticles are also useful in photothermal and imaging applications. However, concerns regarding long-term accumulation, toxicity, and high synthesis costs require further investigation.

Silica Nanoparticles

Mesoporous silica nanoparticles possess large surface area, tunable pore size, and high drug loading capacity. These properties make them suitable carriers for hydrophobic compounds such as quercetin. Silica-based systems provide controlled release behavior and enhanced stability while protecting quercetin from environmental degradation. Functionalized silica nanoparticles have shown improved targeting efficiency in cancer therapy and inflammatory diseases. Nonetheless, biodegradability and potential toxicity issues remain important considerations for clinical translation.

Magnetic Nanoparticles

Magnetic nanoparticles, particularly iron oxide-based systems, offer unique advantages for targeted drug delivery using external magnetic fields. Quercetin-loaded magnetic nanoparticles enable localized accumulation at diseased sites, reducing systemic toxicity and improving therapeutic precision. These nanoparticles also possess imaging capabilities useful for theranostic applications. However, challenges related to aggregation, oxidative instability, and biosafety must be carefully addressed before clinical application [70].

4.4 Nanoemulsions and Micelles

Nanoemulsions are thermodynamically or kinetically stable dispersions of oil and water stabilized by surfactants. Due to their nanoscale droplet size, nanoemulsions enhance quercetin solubility,

dissolution rate, and gastrointestinal absorption. These systems have demonstrated improved oral bioavailability and enhanced therapeutic activity in inflammatory and metabolic disorders. Polymeric micelles are self-assembled nanosystems formed from amphiphilic block copolymers containing hydrophobic cores and hydrophilic shells. The hydrophobic core efficiently encapsulates quercetin, while the hydrophilic outer shell improves aqueous stability and systemic circulation. Micellar systems exhibit excellent potential in cancer-targeted therapy due to enhanced permeability and retention effects. Despite their advantages, nanoemulsions and micelles may exhibit stability issues during long-term storage and dilution. Optimization of surfactant concentration and formulation parameters remains critical for achieving consistent therapeutic performance[71].

Table 1. Comparison of Different Quercetin Nanocarriers

Nanocarrier Type	Advantages	Limitations	Particle Size	Encapsulation Efficiency	Therapeutic Application
Liposomes	Biocompatible, improved solubility, targeted delivery	Drug leakage, physical instability	50–300 nm	High	Cancer, inflammation, neuroprotection
Solid Lipid Nanoparticles (SLNs)	Controlled release, enhanced stability	Limited drug loading	50–1000 nm	Moderate–High	Oral and topical delivery
Nanostructured Lipid Carriers (NLCs)	Improved loading capacity, sustained release	Formulation complexity	50–500 nm	High	Cancer and dermal therapy
PLGA Nanoparticles	Biodegradable, sustained release	Burst release possibility	100–300 nm	High	Targeted anticancer therapy
Chitosan Nanoparticles	Mucoadhesive, enhanced absorption	pH sensitivity	100–500 nm	Moderate	Oral and nasal delivery
PEG-Based Nanoparticles	Long circulation time, stealth effect	Possible immune response	50–200 nm	High	Tumor targeting
Gold Nanoparticles	Easy surface modification, imaging potential	High cost, accumulation risk	10–100 nm	Moderate	Cancer theranostics
Silica Nanoparticles	High loading capacity, controlled release	Biodegradability concerns	50–500 nm	High	Cancer and inflammatory disorders
Magnetic Nanoparticles	Magnetic targeting capability	Aggregation and	10–200 nm	Moderate	Targeted and imaging applications
Nanoemulsions	Enhanced solubility and absorption	Stability issues	20–200 nm	Moderate–High	Oral bioavailability enhancement
Polymeric Micelles	Improved circulation and tumor targeting	Dilution instability	10–100 nm	High	Anticancer drug delivery

5. Targeted and Functionalized Nanoparticles

Targeted and functionalized nanocarriers have emerged as advanced strategies to improve the therapeutic efficacy and site-specific delivery of Quercetin. Conventional quercetin formulations often suffer from non-specific biodistribution, rapid systemic clearance, and poor accumulation at diseased tissues. Functionalization of nanoparticles with targeting ligands, polymers, antibodies, peptides, or biomolecules enhances selective uptake by target cells while minimizing off-target toxicity. These approaches improve drug bioavailability, therapeutic precision, and controlled intracellular delivery [72].

5.1 Ligand-Mediated Targeting

Ligand-mediated targeting involves the attachment of specific ligands onto the nanoparticle surface to recognize receptors overexpressed on diseased cells. Common ligands include folic acid, transferrin, antibodies, peptides, aptamers, and carbohydrates. These ligands facilitate receptor-mediated endocytosis and improve selective cellular uptake of quercetin-loaded nanoparticles. Among various targeting strategies, folate receptor-targeted nanoparticles have shown promising results in cancer therapy because folate receptors are highly expressed in several tumor cells. Similarly, transferrin-functionalized nanoparticles enhance drug transport across the blood-brain barrier and improve delivery in neurodegenerative disorders. Ligand-mediated systems increase intracellular drug concentration, enhance therapeutic efficacy, and reduce systemic adverse effects [74, 75].

5.2 Tissue-Specific Delivery

Tissue-specific delivery systems are designed to selectively accumulate quercetin at pathological sites such as tumors, inflamed tissues, fibrotic organs, or the brain. Passive targeting mainly occurs through the enhanced permeability and retention (EPR) effect, where nanoparticles preferentially accumulate within tumor tissues due to leaky vasculature and impaired lymphatic drainage. Active targeting strategies further improve tissue specificity through surface functionalization of nanocarriers. Brain-targeted nanoparticles have been developed to overcome blood-brain barrier limitations in Alzheimer's and Parkinson's disease. Similarly, pulmonary-targeted and liver-targeted systems have shown improved outcomes in inflammatory and fibrotic disorders. Tissue-specific delivery enhances therapeutic concentration at disease sites while reducing toxicity in healthy tissues[76-78].

5.3 Cellular Uptake Mechanisms

The cellular internalization of nanoparticles significantly influences the therapeutic effectiveness of nano-quercetin systems. Cellular uptake generally occurs through endocytic pathways, including clathrin-mediated endocytosis, caveolae-mediated endocytosis, phagocytosis, and macropinocytosis. Particle size, surface charge, shape, and surface modification play critical roles in determining uptake efficiency. Positively charged nanoparticles exhibit stronger interaction with negatively charged cellular membranes, resulting in enhanced internalization. Smaller nanoparticles generally demonstrate improved tissue penetration and intracellular transport. Following internalization, nanoparticles release quercetin within intracellular compartments, enabling modulation of various molecular pathways associated with oxidative stress, inflammation, apoptosis, and fibrosis [79].

6. Stimuli-Responsive (Smart) Quercetin Nanocarriers

Stimuli-responsive or smart nanocarriers are advanced delivery systems capable of releasing quercetin in response to specific internal or external stimuli such as pH, reactive oxygen species (ROS), enzymes, temperature, or magnetic fields. These systems provide controlled and site-specific drug release, thereby improving therapeutic efficacy and minimizing systemic toxicity. Smart nanocarriers have gained considerable attention in cancer therapy, inflammatory disorders, and fibrosis management due to their ability to respond selectively to pathological microenvironments (Figure 2).

6.1 pH-Sensitive Systems

pH-sensitive nanocarriers are designed to exploit the acidic microenvironment commonly observed in tumors, inflamed tissues, and intracellular lysosomes. These systems remain stable under physiological pH but release quercetin rapidly under acidic conditions. Various polymers and acid-labile linkages are utilized to develop pH-responsive nanoparticles for controlled drug release. In cancer therapy, pH-sensitive nano-quercetin systems improve intracellular accumulation and

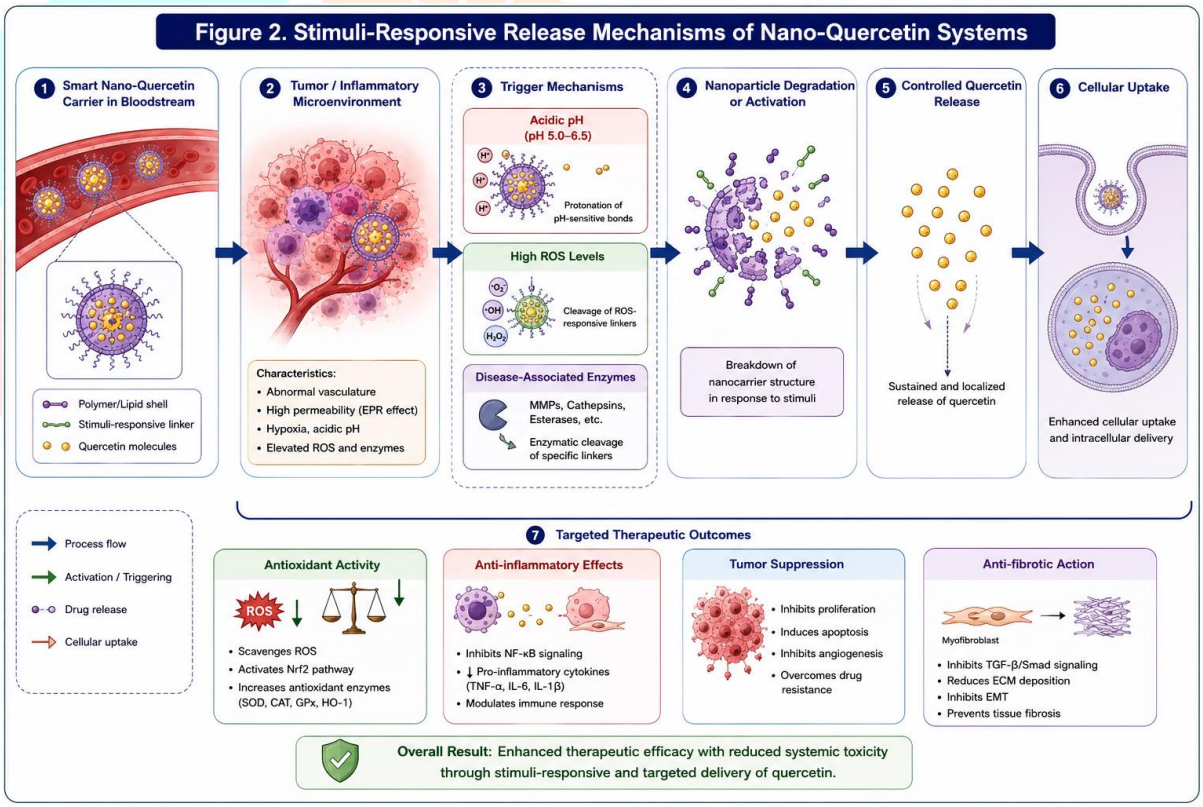
therapeutic selectivity while reducing premature drug leakage. Such systems enhance cytotoxic effects against tumor cells and improve treatment efficiency [80].

6.2 ROS-Responsive Nanoparticles

Reactive oxygen species-responsive nanoparticles are engineered to release quercetin in oxidative stress-rich environments. Since elevated ROS levels are commonly associated with cancer, inflammation, fibrosis, and neurodegenerative disorders, ROS-sensitive systems provide targeted therapeutic delivery. These nanoparticles contain ROS-cleavable bonds that undergo degradation upon exposure to oxidative conditions, leading to controlled quercetin release. ROS-responsive systems effectively reduce oxidative damage, suppress inflammatory signaling, and enhance antioxidant defense mechanisms. Such nanocarriers have demonstrated promising therapeutic outcomes in inflammatory and fibrotic diseases[81].

6.3 Enzyme-Triggered Delivery

Enzyme-responsive nanoparticles utilize disease-associated enzymes to achieve selective drug release at pathological sites. Overexpression of enzymes such as matrix metalloproteinases (MMPs), esterases, and proteases in tumors and inflamed tissues provides opportunities for enzyme-triggered nano-quercetin delivery. These systems are fabricated using enzyme-cleavable linkers or biodegradable polymer matrices that undergo degradation in the presence of target enzymes. Enzyme-responsive nanocarriers improve site-specific release, reduce systemic toxicity, and enhance therapeutic precision. Their application in cancer-targeted therapy and inflammatory disease management has shown significant potential [82,83].



7. Molecular Mechanisms of Nano-Quercetin

Nanoformulations of Quercetin enhance its cellular uptake, stability, and bioavailability, thereby improving modulation of multiple molecular signaling pathways associated with oxidative stress, inflammation, fibrosis, apoptosis, and tumor progression. Nano-quercetin systems demonstrate superior therapeutic efficacy compared to free quercetin due to targeted intracellular delivery and sustained release behavior [84-86]. (Figure 3)

7.1 Antioxidant Pathways

Nano-quercetin exerts potent antioxidant activity primarily through reactive oxygen species (ROS) scavenging and activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway. Activation of Nrf2 promotes transcription of antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, thereby reducing oxidative stress and cellular damage. Improved

intracellular accumulation of nano-quercetin enhances mitochondrial protection and prevents lipid peroxidation.

7.2 Anti-Inflammatory Signaling

Nano-quercetin suppresses inflammatory responses by inhibiting nuclear factor-kappa B (NF-κB) activation and reducing the production of pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6. These systems also inhibit cyclooxygenase (COX) and inducible nitric oxide synthase (iNOS), thereby reducing inflammation-mediated tissue injury. Enhanced bioavailability of nanoparticle formulations results in stronger anti-inflammatory activity compared to conventional quercetin formulations.

7.3 Anti-Fibrotic Pathways

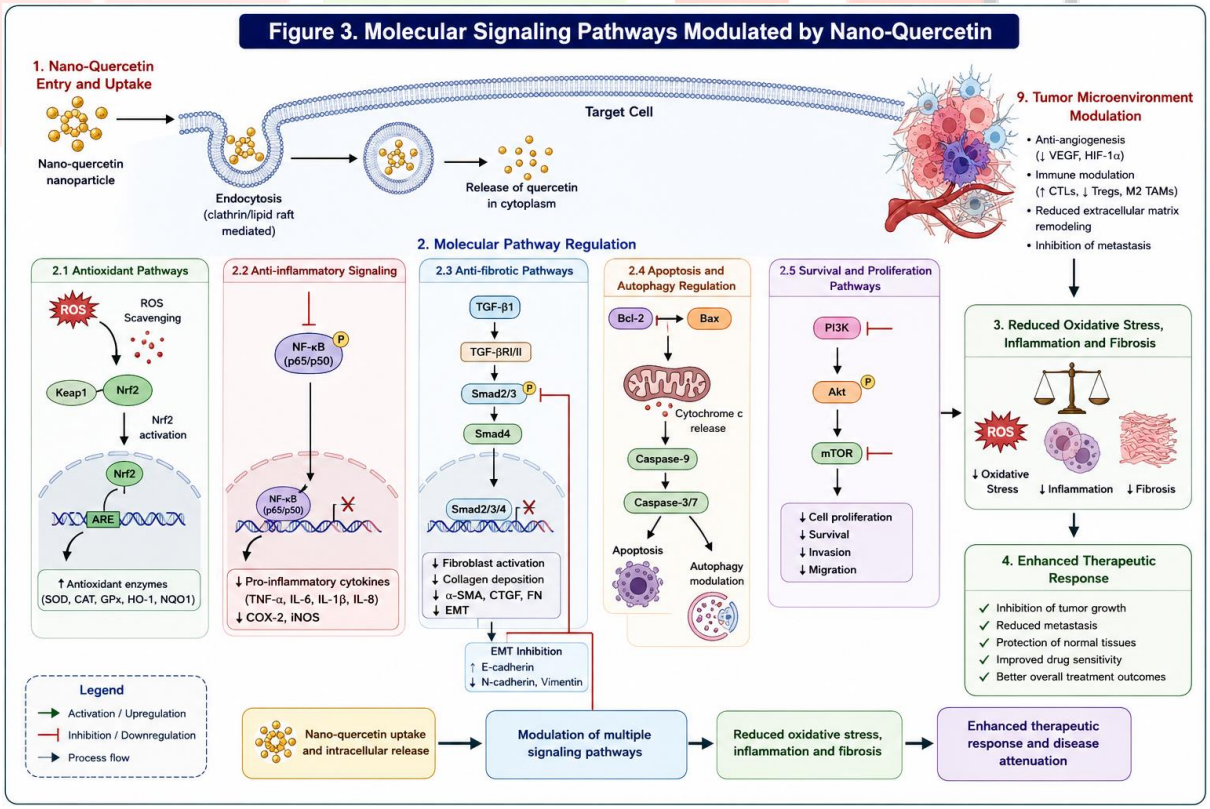
Nano-quercetin has demonstrated promising anti-fibrotic effects through regulation of transforming growth factor-beta (TGF-β)/Smad signaling and epithelial-mesenchymal transition (EMT). Suppression of these pathways inhibits fibroblast activation, extracellular matrix deposition, and tissue remodeling in renal, hepatic, and pulmonary fibrosis. Targeted nanoformulations improve tissue-specific accumulation and enhance therapeutic efficacy in fibrotic disorders.

7.4 Apoptosis and Autophagy Regulation

Nano-quercetin induces apoptosis in cancer cells through modulation of mitochondrial pathways, activation of caspases, and regulation of Bcl-2 family proteins. It also influences autophagy-related pathways involved in cell survival and stress adaptation. Controlled intracellular delivery of quercetin nanoparticles enhances programmed cell death while minimizing toxicity toward normal cells.

7.5 Tumor Microenvironment Modulation

Nano-quercetin systems can modulate the tumor microenvironment by reducing oxidative stress, inflammatory mediators, angiogenesis, and immune suppression. These effects contribute to inhibition of tumor growth, metastasis, and drug resistance. Functionalized nanoparticles additionally improve penetration into tumor tissues and enhance therapeutic selectivity.



8. Therapeutic Applications of Quercetin Nanoparticles

Nanotechnology-based quercetin delivery systems have shown promising therapeutic potential in various chronic and degenerative diseases due to improved bioavailability, targeted delivery, and enhanced pharmacological activity [87,88].

8.1 Cancer Therapy

Quercetin nanoparticles exhibit strong anticancer activity through inhibition of tumor cell proliferation, induction of apoptosis, suppression of angiogenesis, and modulation of signaling pathways such as PI3K/Akt and NF-κB. Nanoformulations improve intracellular accumulation and overcome multidrug resistance by enhancing drug retention within tumor cells.

Combination therapy involving nano-quercetin with chemotherapeutic agents such as doxorubicin and paclitaxel has demonstrated synergistic anticancer effects and reduced systemic toxicity. Although extensive preclinical studies are available, clinical trials evaluating nano-quercetin systems remain limited, highlighting the need for further translational research and immune-oncology investigations.

8.2 Neurodegenerative Diseases

Nano-quercetin systems have shown neuroprotective effects in Alzheimer's and Parkinson's disease by reducing oxidative stress, neuroinflammation, and neuronal apoptosis. Surface-functionalized nanoparticles improve transport across the blood-brain barrier (BBB), enhancing drug delivery to neural tissues. These systems may help reduce amyloid-beta aggregation and protect dopaminergic neurons.

8.3 Inflammatory and Fibrotic Diseases

Quercetin nanoparticles demonstrate significant anti-inflammatory and anti-fibrotic activities in renal, hepatic, and pulmonary fibrosis models. Targeted delivery suppresses inflammatory cytokines, oxidative damage, and extracellular matrix deposition. Nanoformulations additionally improve tissue retention and therapeutic effectiveness in chronic inflammatory conditions.

8.4 Cardiovascular and Metabolic Disorders

Nano-quercetin systems exhibit cardioprotective effects through reduction of oxidative stress, endothelial dysfunction, and atherosclerotic progression. In metabolic disorders, quercetin nanoparticles improve insulin sensitivity, reduce hyperglycemia-associated oxidative damage, and alleviate diabetic complications.

8.5 Topical and Transdermal Applications

Topical nano-quercetin formulations have shown promising results in skin disorders, wound healing, and inflammatory dermatological conditions. Nanocarriers enhance skin penetration, improve localized drug retention, and accelerate tissue repair through antioxidant and anti-inflammatory mechanisms (Table 2).

Table 2. Therapeutic Applications of Quercetin Nanoparticles in Different Diseases

Disease	Nanocarrier Used	Mechanism	Key Outcomes	Study Type
Cancer	Liposomes, PLGA nanoparticles	Apoptosis induction, anti-proliferative activity	Reduced tumor growth	In vitro/In vivo
Alzheimer's disease	PEGylated nanoparticles	BBB targeting, antioxidant activity	Neuroprotection	Preclinical
Parkinson's disease	Polymeric nanoparticles	Reduced neuroinflammation	Protection of dopaminergic neurons	Animal studies

Disease	Nanocarrier Used	Mechanism	Key Outcomes	Study Type
Renal fibrosis	Chitosan nanoparticles	TGF-β inhibition	Reduced fibrosis progression	In vivo
Liver fibrosis	Lipid nanoparticles	Antioxidant and anti-inflammatory activity	Improved hepatic function	Experimental
Pulmonary fibrosis	NLCs	EMT suppression	Reduced collagen deposition	Preclinical
Atherosclerosis	Nanoemulsions	Reduced oxidative stress	Improved endothelial function	Animal studies
Diabetes complications	Polymeric micelles	Improved insulin sensitivity	Reduced metabolic damage	In vivo
Skin disorders	Topical liposomes	Enhanced dermal penetration	Improved anti-inflammatory effects	Experimental
Wound healing	Hydrogel nanoparticles	Controlled release and antioxidant action	Accelerated wound closure	In vivo

9. Hybrid Nanoparticles and Co-Delivery Systems

Hybrid nanocarriers combining lipid, polymeric, and inorganic materials have emerged as advanced delivery platforms for quercetin. These systems improve stability, targeting efficiency, and controlled drug release. Dual-drug delivery systems co-encapsulating quercetin with anticancer or anti-inflammatory agents provide synergistic therapeutic effects and overcome multidrug resistance. Such multifunctional systems enhance therapeutic efficacy while minimizing adverse effects [89, 90].

10. Safety, Toxicity, and Regulatory Considerations

Despite promising therapeutic applications, safety concerns remain significant barriers to clinical translation of nano-quercetin systems. Nanoparticle-associated toxicity depends on particle size, composition, surface charge, and biodegradability. Certain inorganic nanoparticles may accumulate in tissues and induce oxidative stress or inflammatory responses.

Immunogenicity and long-term biosafety also require careful evaluation. Additionally, lack of standardized regulatory guidelines for nanoparticle characterization, manufacturing, and quality control complicates clinical approval. Comprehensive toxicological studies and harmonized regulatory frameworks are essential for successful therapeutic translation.

11. Translational Challenges and Clinical Perspectives

Several challenges limit the clinical advancement of quercetin nanomedicine. Large-scale manufacturing and reproducibility remain difficult due to formulation complexity and stability concerns. High production costs and regulatory requirements further restrict commercialization.

Although numerous preclinical studies demonstrate encouraging results, clinical trials investigating nano-quercetin formulations remain limited. Additional human studies evaluating long-term safety, pharmacokinetics, and therapeutic efficacy are necessary before widespread clinical adoption.

12. Future Perspectives and Emerging Trends

Future developments in Nanotechnology may significantly improve the clinical applicability of quercetin. Artificial intelligence-assisted nanoparticle design can optimize formulation parameters and targeting efficiency. Personalized nanomedicine approaches may enable patient-specific therapeutic strategies based on disease biomarkers and pharmacogenomics.

Multifunctional nanoplatforms integrating diagnostic and therapeutic functions are also emerging as promising tools for precision medicine. Stimuli-responsive and biomimetic nanoparticles may further enhance targeted delivery and therapeutic outcomes in complex diseases.

13. Conclusion

Quercetin possesses remarkable antioxidant, anti-inflammatory, anticancer, and anti-fibrotic properties; however, its therapeutic application is significantly limited by poor solubility, low bioavailability, rapid metabolism, and limited target-site accumulation. Nanotechnology-based delivery systems have emerged as promising strategies to overcome these limitations by improving stability, controlled release, cellular uptake, and tissue-specific targeting.

Various nanocarriers, including lipid-based, polymeric, inorganic, and stimuli-responsive systems, have demonstrated enhanced therapeutic efficacy in cancer, neurodegenerative disorders, fibrosis, cardiovascular diseases, and wound healing applications. Despite encouraging preclinical findings, several translational challenges related to toxicity, large-scale manufacturing, regulatory approval, and clinical validation remain unresolved.

Overall, nano-enabled quercetin delivery represents a promising direction in modern therapeutics. Continued advancements in smart nanocarriers, personalized nanomedicine, and multifunctional delivery platforms may facilitate successful clinical translation and broaden future biomedical applications of quercetin.

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