Unlocking Quercetin's Potential: The Impact of Nanotechnology on Its Pharmacological Activities and Therapeutic Uses

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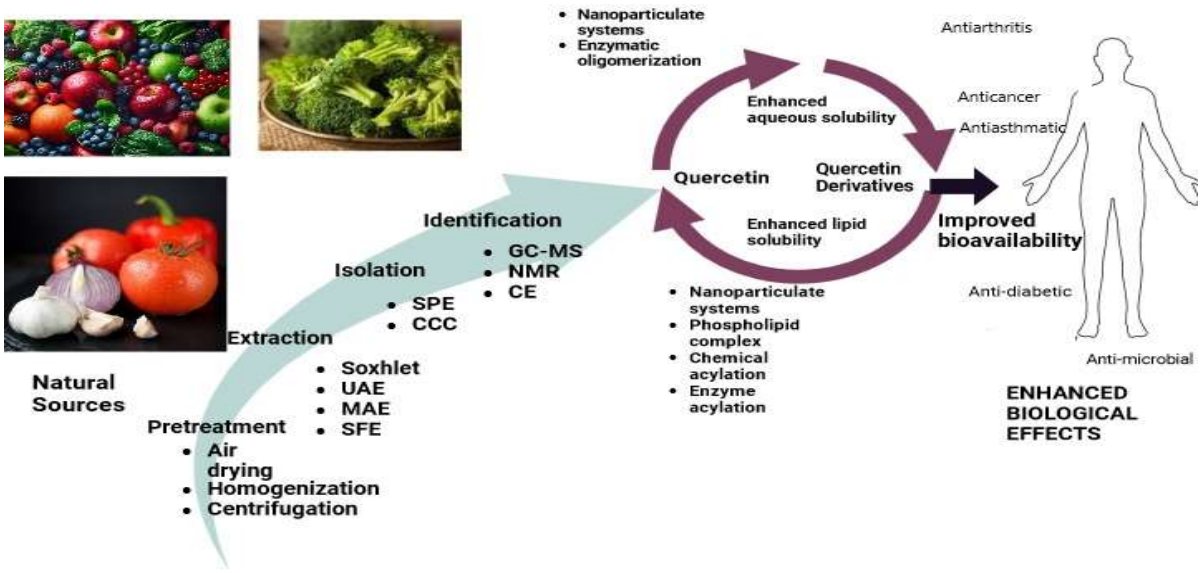
Abstract:

Phytochemicals are emerging as a key factor in their Value in both the management and prevention of a variety of diseases. Among them, quercetin, an organic plant-based flavonoid abundant integrated within plant-derived foods, has emerged as a promising agent due to its antioxidant strength and diverse pharmacological benefits confirmed by both preclinical and clinical settings. Despite its promising therapeutic potential, quercetin's practical application is hindered by limitations due to challenges like low solubility and suboptimal bioavailability, poor physicochemical stability, and reduced biological persistence. To address these challenges, nanoparticle-based delivery systems have emerged as effective strategies for enhancing the solubility and targeted delivery of hydrophobic compounds like quercetin. These nanoformulations have proved effective in enhancing encapsulation efficiency, stability, slow and steady drug release performance, extended circulation times, and enhanced therapeutic outcomes. Recent advancements indicate that nanotechnology can significantly enhance the stability and quercetin absorption by cells under both laboratory and animal testing conditions. The current review outlines key developments and insights into various nanocarrier systems—encompassing various carriers like liposomes, nanogels, micelles, and SLNs, polymeric nanoparticles, gold nanoparticles, and cyclodextrin complexes—for the effective delivery of quercetin in a range of pharmacological applications.

Keywords: Flavanoids, quercetin, nanoformulation, therapeutic efficacy, bioavailability, Pharmacological activities.

Graphical Abstract:



1. Introduction:

1.1 Therapeutic Potential of Quercetin

In modern medicine, natural compounds are gaining significant attention for their therapeutic potential. Historically, plants have served not only aesthetic and nutritional purposes but also medicinal ones. The rising demand for natural substitutes to synthetic pharmaceuticals has brought increased attention to plant-based extracts and their bioactive compounds. These naturally occurring constituents, particularly flavonoids, are recognized for their broad extensive biofunctional properties, including anti-inflammatory, antimicrobial, and potential anticancer effects. Found abundantly in fruits, vegetables, and medicinal herbs, flavonoids contribute significantly to health promotion and disease prevention. Found in forms Among their various types—flavones, isoflavones, flavanones, and chalcones—flavonoids exhibit a central roles in plant defence and offer various biological activities beneficial to human health **[2]**.

Among flavonoids, quercetin stands out as a promising therapeutic agent. Quercetin, chemically identified as 3,3′,4′,5,7-pentahydroxyflavone and named stemming from the Latin language term *Quercetum*, is a flavonoid present in nutrient-rich foods like apples, onions, berries, broccoli, and tea. It is well known for its diverse therapeutic properties, including antioxidant, anti-inflammatory, and anticancer effects. **[3,4]**. Notably, its strong antioxidant properties help neutralize free radicals, thereby reducing oxidative stress, a major factor in the development of metabolic and chronic diseases **[5,6]**. Furthermore, quercetin's ability to due to its immunomodulatory effects holds promise for managing various disorders like asthma and allergies **[7,8]**.

Although quercetin offers numerous health advantages, its clinical application is restricted due to its low affinity for water-based dissolution and limited bioavailability. Upon oral intake, it

is rapidly biotransformed within the liver during the first-pass effect, leading to quick elimination and reduced therapeutic efficacy**. [9, 10,11]**. To overcome this, researchers are exploring advanced delivery systems to enhance their bioavailability. Traditional formulations often require high doses to be effective, which can amplify the risk of negative outcomes. For example, while NSAIDs and corticosteroids are effective, they would provoke adverse effects on the gastrointestinal tract, nervousness, and allergic manifestations. In contrast, improved delivery of natural compounds like quercetin offers a potentially safer and more effective therapeutic alternative.

Progress in drug delivery systems has enabled the formulation of quercetin-loaded nanocarriers. Nanotechnology provides promising approaches for improving solubility characteristics, enhancing compound stability, and promoting bioavailability of quercetin. Encapsulating quercetin in nanoparticles enhances its targeted delivery, protects it from degradation, and supports sustained release. These improvements boost therapeutic efficacy while reducing required dosages and associated side effects. Studies have demonstrated that nanoformulated quercetin shows improved antioxidant activity and greater effectiveness in treating inflammation and cancer **[12, 13, 14]**.

As research expands our understanding of quercetin’s health benefits, nanotechnology-based delivery systems show great promise for future therapies. Current studies aim to optimize formulations, enhance stability, and explore synergistic effects with other phytochemicals and drugs. Utilizing nanoformulated quercetin improves individual health outcomes and supports a shift toward reducing dependence on conventional pharmaceuticals. Emphasizing natural compounds promotes safer, more holistic treatment approaches **[15]**.

In summary, quercetin's therapeutic potential, coupled with advancements in nanoformulation technology, heralds a new era in the application of natural compounds in medicine. With its robust biological activities and ability to enhance health outcomes, quercetin stands as a beacon of hope in the search for effective, safe, and sustainable treatment options. As research progresses, it is essential to continue exploring the vast potential of plant-based therapies, ensuring that nature’s bounty is harnessed to improve human health and well-being.

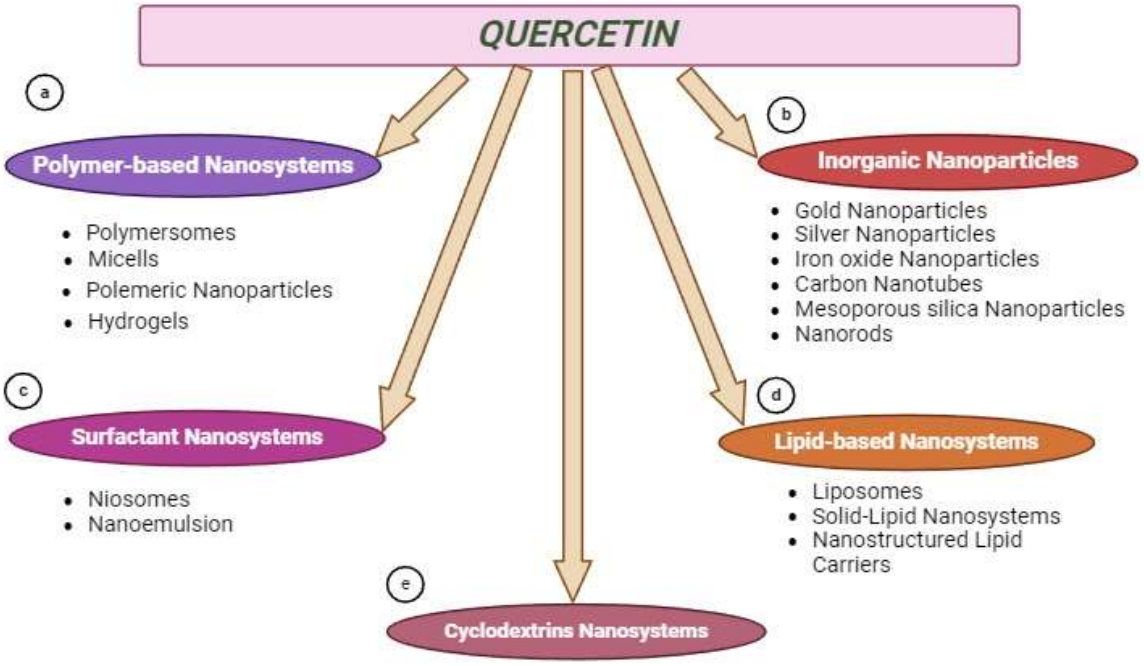


Figure 1. Illustration of Quercetin -delivery nanosystems.

2. Pharmacokinetics of Quercetin –Because of its strong hydrophobic nature, quercetin is capable of permeating phospholipid bilayers, allowing it to be passes through the epithelial barrier of the small intestine which are cellular membranes, via a straightforward diffusion process [**16**]. Absorption studies in Sprague-Dawley rats by Chen et al. (2005) revealed that more than 60% of orally administered quercetin was absorbed. Supporting evidence was provided by *Walle et al. (2001),* investigators responsible for observing an absorption rate of approximately 53% **[18].** To give hydrophilicity, phase II enzymes called glucuronosyltransferases and sulfotransferases glucuronidate and sulfidate the molecule at one of its hydroxyl groups inside the enterocytes **[19,20,21,22].** Moreover, quercetin undergoes O-methylation, primarily producing 3′-O-methylquercetin (isorhamnetin) and, to a lesser extent, 4′-O-methylquercetin (tamaraxetin) **[23,24].** Upon administration of quercetin present in glycosylated form, enzymes such as β-glucosidase—located in intestinal microflora and enterocytes—must first cleave the sugar moiety to enable subsequent conjugation processes.**[25**]. Nevertheless, certain quercetin molecules may enter the bloodstream unconjugated. Through the portal vein, these compounds will enter the liver where they will be metabolised by the highly expressed enzymes glucuronosyl transferases and sulfotransferases **[26].** Furthermore, quercetin can be methylated by the liver and kidneys' catechol-O-methyltransferase (COMT) enzymes **[27,28**]. When quercetin conjugates are following biliary excretion, they move along the small intestine toward the hindgut, where enzymes such as β-glucuronidase and sulfatase produced by the gut microbiota can hydrolyze them. This facilitates enterohepatic cycling and lengthens the period that blood is circulated **[29].** 90 percent of the ingested quercetin was metabolized in the gut, despite the liver being the essential organ for this process **[30].** Due to all of these enzymatic modifications, quercetin

becomes a more soluble substance that can either be attached to blood proteins like albumin or circulated freely in the blood [**31**]. The distribution of quercetin in tissues is caused by its entry into the bloodstream. It's also critical to note that quercetin can enter the lymphatic system from the gastrointestinal tract [**32**]. With regular intake, quercetin tends to localize within various organs, covering vital organs like the lungs, kidneys, thymus, and heart and liver. Among these, the lungs typically contain the highest concentrations of quercetin and its methylated forms like isorhamnetin.**[33].** Owing to its enterohepatic recirculation, quercetin can persist in the body for an extended duration, typically ranging from 20 to 72 hours post-ingestion **[34]**. Nevertheless, gut microbiota in the colon can degrade quercetin into phenolic acids, with carbon dioxide as a byproduct that is eventually exhaled **[35]**. On the other hand, phenolic acids can pass through the stools. Furthermore, a portion of quercetin may also be excreted in urine **[36**]. For the removal of quercetin, all of these methods work. According to ***Ueno et al***., following oral administration, quercetin was primarily excreted as carbon dioxide via respiration (35%), while the remaining portion was eliminated through feces (45%) and urine (10%) under conjugated forms with glucuronide and sulfate groups **[37].** In contrast, a more recent investigation found that just a tiny percentage of absorbed quercetin was excreted in faeces (0.21–4.6%) and urine (3.3–5.7%**) [38].** Under carbon dioxide, quercetin was mostly removed (41.8–63.9%)

3. Therapeutic potential of quercetin

3.1 Anti -Arthritis Activity

RA is a prolonged autoimmune condition defined by ongoing joint inflammation, known as synovitis, which can progressively damage cartilage and bone, leading to joint deformities, physical disability, and decreased life expectancy **[39].** Various factors increase the risk of RA, such as aging, being female, obesity, prior joint injuries, certain skeletal features, and a genetic predisposition [40]. Additionally, mutations in genes responsible for coding collagens—specifically types II, IV, V, and VI—have been linked to the disease's advancement **[41].**

Rheumatoid arthritis (RA) is commonly managed with pharmacological agents, particularly agents like aspirin, naproxen, ibuprofen, and other NSAIDs. These medications work by blocking cyclooxygenase (COX) enzymes, which leads to a decreased synthesis of prostaglandins and other pro-inflammatory mediators. While effective at high doses, NSAIDs can cause side effects like tinnitus, hearing loss, gastric discomfort, ulcers, and gastrointestinal bleeding **[42]**. Their reduced dosing frequency can make them preferable despite these risks. Corticosteroids, though more potent, are reserved for short-term, low-dose use during RA flare-ups due to their notable adverse effects, underscoring the need for safer, effective anti-inflammatory alternatives for long-term RA management**.[43]** Quercetin, a naturally occurring flavonoid molecule prevalent naturally occurring in diverse fruits and vegetables, has attracted considerable interest for its therapeutic potential in rheumatoid arthritis. Its role in mitigating inflammation and neutralizing oxidative species mechanisms contributes to symptom amelioration as a result of downregulating pro-inflammatory cytokines and diminishing COX-2 expression triggered by lipopolysaccharides. Furthermore, quercetin supports bone health by

blocking the activation of transcription factors like NF-κB and AP-1, which are central to inflammatory responses and bone degradation [**44]**. Additionally, it limits macrophage and neutrophil recruitment and inhibits synoviocyte proliferation, thereby reducing synovial inflammation **[45,46,47]**. Several studies have reported improved anti-arthritic efficacy of quercetin when delivered at the nanoscale (Table 1).

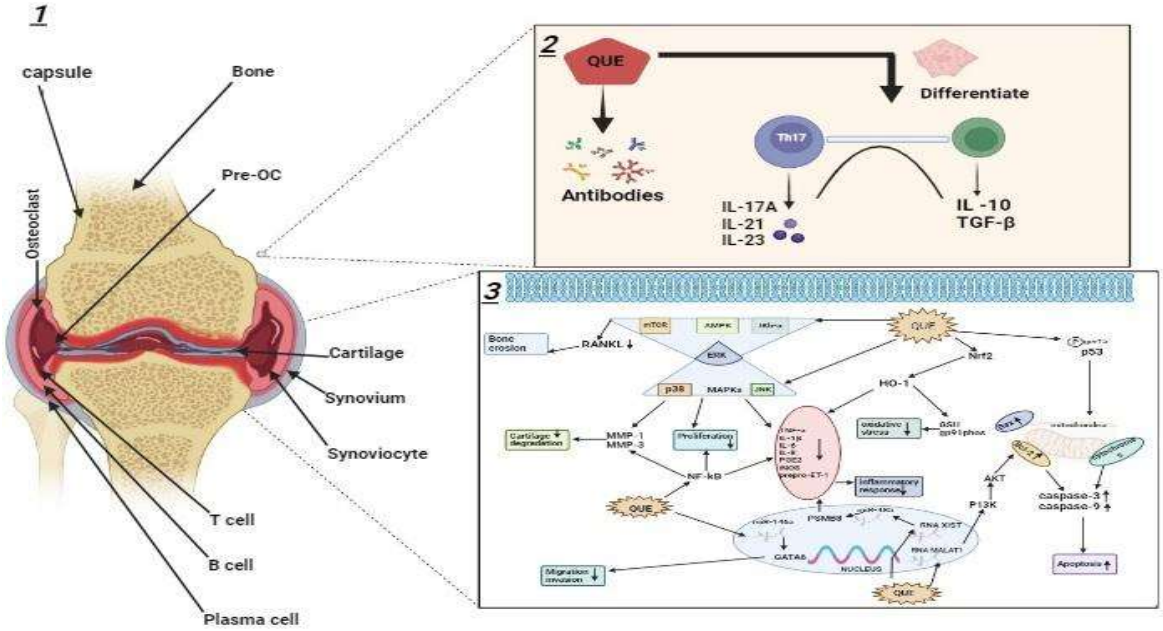


Figure 2: The Anti-Arthritic Effect of Quercetin (QUE) on Rheumatoid Arthritis (RA) in preclinical studies:(1) Rheumatoid Arthritis Joint:

RA is marked by chronic inflammation of the joints, synovial hyperplasia, and progressive cartilage and bone damage. (2) Immunoregulatory Effects of QUE on RA: Quercetin modulates the immune response by restoring the Th17/Treg cell balance. It reduces Th17-associated cytokines (IL-17A, IL-21, and IL-23), enhances Treg-associated cytokines (IL-10 and TGF-β), and lowers the levels of circulating autoantibodies, thereby mitigating autoimmune joint damage**.** (3). Bone Protective Effects: Quercetin suppresses the expression of RANKL in fibroblast-like synoviocytes by regulating signaling cascades such as mTOR, ERK, IκB-α, and AMPK. It also downregulates MMP-1 and MMP-3 levels by interfering with the activation of MAPK and NF-κB signaling mechanisms

Table 1: Various Nanoformulations' activity against arthritis.

S.N0.	Nanoformulations	Method	Activity	Findings	References
1	Quercetin-loaded chitosan nanoparticles	Solvent evaporation	Anti-inflammatory	Reduced ankle diameter, oxidative stress, TNF-α, IL-6; effective in RA rats	**48**

2	Quercetin nanoemulsion gel	Spontaneous emulsification	TNF-α inhibition	QCT-NE gel promising for topical RA treatment	**49**
3	Quercetin nanoformulation	Emulsification	Anti-inflammatory and analgesic	Effective in vitro/in vivo; enhances bioavailability; transdermal potential	**50**
4	Flavonoid-based nanoparticles	Emulsification	Inhibits COX and LOX enzymes	High-dose (20 mg/kg) Q-NPs reduce ankle swelling	**51**
5	Stearic acid nanoparticles	Hot melt homogenizatio n	COX and LOX inhibition	SLNs (~200 nm) reduce swelling and inflammatory biomarkers	**52**
6	Quercetin nanoparticle gel	Emulsification	Immunomodul atory (TNF-α inhibition)	n vitro, suppresses LPS-induced TNF-α in macrophages	**53**

3.2 ANTIDIABETIC ACTIVITY

Diabetes mellitus represents a significant worldwide health issue, exhibiting persistently high blood sugar levels arising from impaired insulin synthesis or resistance to its action **[54,55]**. As one of the most widespread endocrine and metabolic disorders, its prevalence is increasing across various age groups. According to the International Diabetes Federation (IDF), an estimated 537 million adults aged 20 to 79 are currently living with diabetes, with Type 2 diabetes mellitus (T2DM) comprising approximately 90% of all cases 85–95% of all cases. These statistics underscore the critical need for improved preventive and therapeutic approaches **[56]**.

Flavonoids show promise in managing diabetes and its complications by regulating glucose metabolism, modulating hepatic enzyme activity, and improving lipid profiles, supporting the development of flavonoid-based hypoglycemic agents **[57]**. Among them, quercetin has gained attention for its potential to control hyperglycemia. Conventional diabetes treatments often require high doses of oral agents or insulin, which may cause toxicity with long-term use. This has prompted interest in naturally derived alternatives like quercetin **[58]**.

Flavonoids have shown potential in managing diabetes and its complications by regulating glucose metabolism, modulating hepatic enzyme activity, and improving lipid profiles, thus paving the way for flavonoid-based hypoglycemic agents **[59]**. Quercetin, in particular, has gained attention for its ability to control hyperglycemia. Traditional diabetes treatments often

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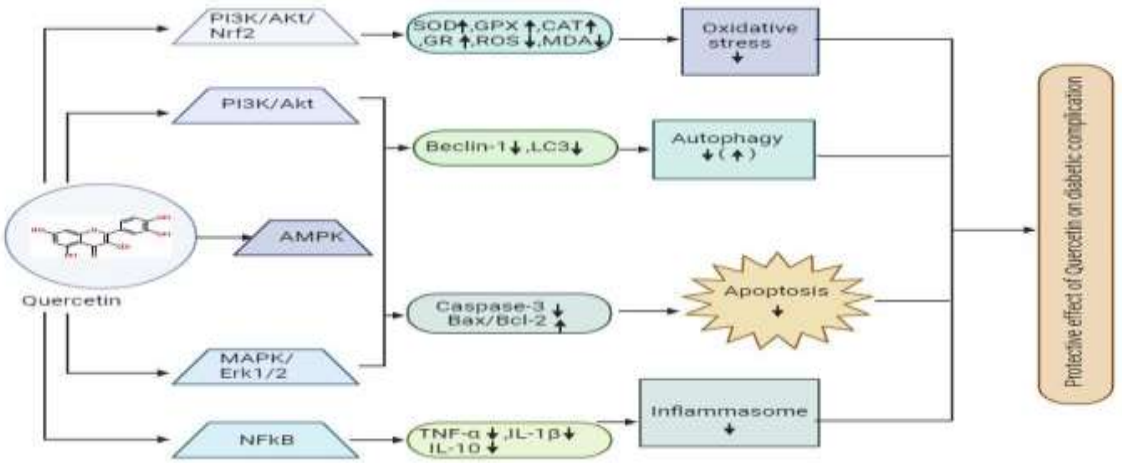

Figure 3. The molecular mechanism of quercetin in improving diabetic complications**.**

Table 2: Various nanoformulations' activity against diabetes.

S.N0.	Nanoformulations	Method	Activity	Findings	References
1	Hydrogel incorporating quercetin-loaded silver nanoparticles	Emulsification	Antimicrobial, Dermal restoration	Enhanced re-epithelialization, reduced wound gap vs. marketed gel	**61**
2	Nanopolyphenols	Emulsification	↓ Hyperglycemia/oxidative stress, ↑ SOD/CAT	NF-κB inhibition reduces cytokines, improves oxidative balance	**62**
3	Plant-based antidiabetic nanoformulations	Emulsification	Inhibit carb digestion, ↓ glucose absorption	improved glycemic control; reduced inflammation, fibrosis, and apoptosis	**63**
4	Quercetin nanoformulation (STZ-induced diabetic rats)	Emulsion diffusion–evaporation	Controlled in vitro release	Qu-NP every 5 days matched effect of daily oral dose; improved SOD and catalase in pancreas/kidney	**64**

5	Quercetin-loaded advanced nanoformulations	Emulsification	Antioxidant, anti-inflammatory, ↑ collagen synthesis	Nanogels, liposomes protect tissue and promote wound healing	**65**
6	Quercetin-loaded Eudragit L-100 NPs	Sonication-assisted emulsification –evaporation	Hypoglycemic, regenerates the islet	Comparable to Glibenclamide; effective oral delivery with lower dose & improved compliance	**66**
7	Insulin & quercetin-loaded liquid crystalline NPs	Emulsification	↓Oxidative stress, ↑oral bioavailability	Combination strategy improves delivery and mitigates diabetes-related oxidative damage	**67**
8	Polyphenol nanoformulations	Emulsification	Improve glucose control, insulin sensitivity	Suppress TGF-β1/CTGF; restore kidney function in diabetic nephropathy	**68**
9	Herbal-based antidiabetic lipid/inorganic NPs	Emulsification	Stimulate GLUT4, inhibit lipid peroxidation	Enhance bioavailability, protect drug, mask taste, and ensure targeted delivery	**69**

3.3 ANTIPROLIFERATIVE ACTIVITY

Cancer, the second leading as identified globally by WHO in 2020 **[70]**, poses a major health and economic burden **[71,72]**. Characterized by uncontrolled cell growth and metastasis, it presents challenges such as treatment resistance, high costs, and limited new drug options. This has driven a shift toward natural product-based therapies, with around 80% of approved chemotherapeutics and 50% of current drugs derived from natural sources, valued for their safety, effectiveness, and multi-target action **[73]**.

Research into natural products, including those from marine organisms, holds great potential for discovering new anticancer compounds. Quercetin, in particular, has gained attention for its significant tumor-suppressing potential. Research has shown that quercetin can induce programmed cell death and arrest cellular proliferation, growth suppression in several

malignant cell lines, including breast, prostate, lung, and colon cancers **[74]**. These findings highlight quercetin's promise as a candidate for developing effective anticancer curative methods, suggesting a call for continued research into its modes of action and therapeutic applications **[75]**. Additionally, nanotechnology has been shown to enhance quercetin's efficacy in cancer treatment (Table 3).

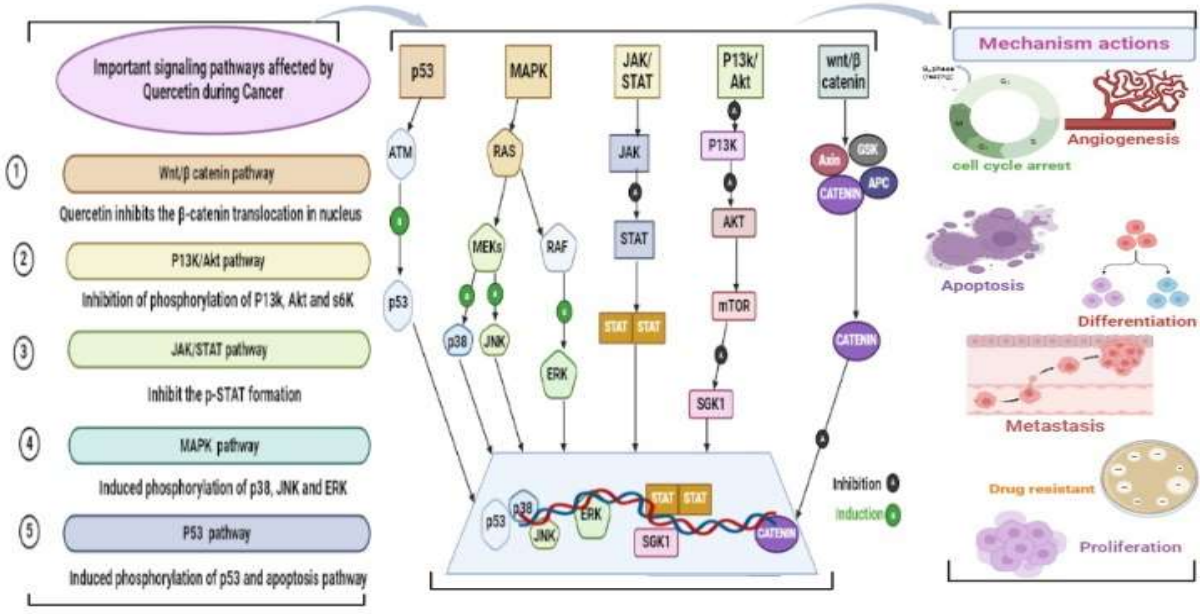

Figure 4. Quercetin activity in different cancer types.

Table 3: Various nanoformulations activity against cancer.

S. N0	Nanoformulations	Method	Activity	Findings	References
1	Quercetin for tumor therapy	Emulsification	Induces apoptosis, autophagy, reverses MDR, and reduces angiogenesis	Nanoparticles improved targeting, encapsulation, circulation, and tumor inhibition	**76**
2	Quercetin–chitosan against DOX-induced cardiotoxicity	Ionotropic Gelation	Lowers cardiac biomarkers, oxidative stress, and inflammation	QU-CHSNPs strongly prevented DOX-induced cardiac toxicity	**77**
3	Quercetin against MCF7 & CAL51	Emulsion–Diffusion	Induces apoptosis	Q-PLGA-NPs showed in vitro cytotoxicity against breast cancer cells and in vivo biocompatibility	**78**

4	Modified QURnp in cancer	Nanoprecipitation	Inhibits IL-6/STAT3 signalling and triggers cell cycle halt along with programmed cell death.	QURnp inhibited tumour progression via p27 upregulation, Bcl-2 reduction	**79**
5	PLGA-QNPs in cancer	Solvent Evaporation	Apoptosis via PI3K/Akt suppression, caspase activation	QNPs reduced tumors, induced G2 arrest, and increased latency period	**80**
6	Quercetin micelles for ovarian cancer	Emulsification	Induces mitochondrial apoptosis	Suppressed xenograft tumor growth and downregulated MAPK, Akt pathways	**81**
7	QURnp + APnp combination	Nanoprecipitation	Inhibits STAT3/HIF-1α, induces G0/G1 arrest and apoptosis	Combo reduced tumors, improved antioxidants, reduced Ki-67 and Bcl-2	**82**
8	Quercetin–curcumin nanoemulsion	Emulsification –Solvent Evaporation	Reduces oxidative stress	Enhanced uptake and cytotoxicity in breast cancer cells	**83**
9	QCT-CS NPs	Ionic Gelation	Targets the tumor via the EPR effect	More effective than free QCT in reducing lung and breast tumor size	**84**
10	5-FU-QCT chitosan NPs in HCT116	Ionic Gelation	Modulates p53/p21 axis, induces apoptosis	Triggered ROS, G0/G1 arrest, regulated apoptosis-related proteins	**85**
11	QC-SLN in MDA-MB231	Emulsification	Activates Bax, caspases, PARP	Improved drug release, reduced viability and angiogenesis, increased apoptosis	**86**
12	Modified QURnp in EAC	Nanoprecipitation	Inhibits IL6/STAT3, promotes apoptosis	Increased p27, reduced Bcl-2, effectively suppressed tumor growth	**87**

3.4 ANTIASTHMATIC ACTIVITY

Asthma is a long-term inflammatory condition marked by heightened airway sensitivity, resulting in recurring bouts of presenting with wheezing, shortness of breath, chest tightness, and coughing. The degree of these symptoms tends to fluctuate and is often linked to inconsistent airflow restriction that is typically reversible with time or appropriate treatment, such as fast-acting bronchodilators **[88].**

Asthma's mechanisms involve an intricate interplay of hereditary and environmental influences, leading to chronic airway inflammation. This is characterized by increased eosinophils, airway edema, excess mucus production, and smooth muscle hypertrophy. The T-helper (Th) cell response, particularly activation of the Th2 response constitutes a significant mediator in the inflammatory process, with cytokines like cytokines IL-4, IL-5, and IL-13 enhance IgE generation and eosinophilic infiltration. Mast cells also release inflammatory mediators during allergen exposure, contributing to bronchoconstriction and airway inflammation **[89,90]**. According to the U.S. National Heart, Lung, and Blood Institute and the Global Initiative for Asthma (GINA), asthma is classified into four categories: intermittent, mild persistent, moderate persistent, and severe persistent. This classification system assists healthcare providers in determining the most suitable treatment options **[91,92,93]**.

Conventional asthma treatment mainly includes bronchodilators like β2-agonists and systemic corticosteroids **[94]**. Short-acting β2-agonists, such as salbutamol, are often first-line due to their quick bronchodilatory effects. However, long-term use of corticosteroids carries significant risks, including Cushing's syndrome, osteoporosis, susceptibility to infections, and psychiatric complications, which can limit their prolonged use **[95,96]**.

Given the limitations of traditional treatments, the exploration of alternative healing methods is expanding. Organic phytoconstituents with minimal negative outcomes present a promising option for asthma management, either as alternatives or complements to conventional medications. Research continues to explore bioactive plant-derived products with pharmacological potential. Numerous studies have identified plant extracts and metabolites with therapeutic effects in asthma, demonstrating their ability to alleviate symptoms and support the development of safer treatments **[97,98,99,100]**. Additionally, quercetin has shown improved efficacy in nanotechnology-based asthma therapies (Table 4).

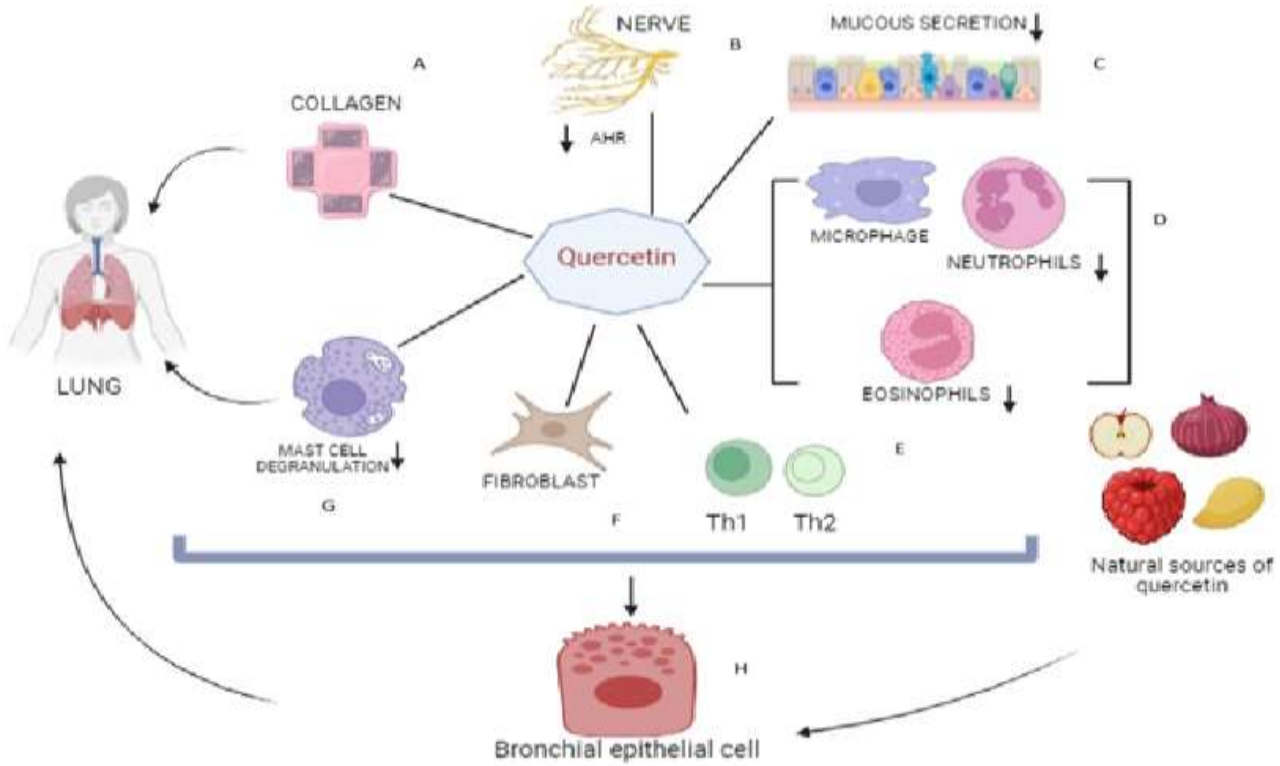

Figure 5. Quercetin has demonstrated multiple beneficial effects in asthma management, acting through various mechanisms. Studies suggest it may help prevent disease progression by reducing collagen accumulation [A], limiting mucus secretion [B, C], and lowering the infiltration of eosinophils and neutrophils [D]. Additionally, quercetin modulates the balance of Th1/Th2 cytokines [E], exhibits anti-fibrotic properties [F], and inhibits mast cell degranulation [G]. These therapeutic outcomes are believed to be associated with the downregulation of fundamental signaling networks, notably PI3K, Akt, and NF-κB[H].

Table 4: Various nanoformulations have activity against Asthma.

S.NO.	Nanoformulation	Method	Activity	Finding	References
1	LCN & sm-LCN	Ultrasonication	lowers the extent of inflammatory cytokines such as IL-1β, IL-6, and IL-8, contributing to its anti-inflammatory properties	Encapsulation enhanced anti-inflammatory effect, effective in asthma-related cytokine suppression	**101**

2	Quercetin–chitosan NPs	Ion crosslinking	Lowered IgE, IL-17, TNF-α, IL-6	QCS nasal delivery improved encapsulation, stability, and nasal mucosa recovery	**102**
3	Quercetin nanocrystals	Ultrasonication	Lowered sIgE, IL-4, IL-5; inhibited mast cell mediators	Reduced FcR1, Syk, PI-3 pathway markers; suppressed Th2 cytokines and transcription factors	**103**
4	Quercetin glycosides	Emusification	Decreased leukocytes, TNF-α, IL-6, NO	Significant reduction in inflammatory markers; protective in neonatal asthma model	**104**
5	Quercetin liposomes	Thin-film dispersion	Inhibited β-hexosaminidase, histamine, IL-4, IL-8	Liposomes more effective than free quercetin in anti-allergic activity	**105**
6	Quercetin vs DENPs	Emusification	Anti-inflammatory and antioxidant in lung tissues	Reduced collagen fibers, inflammation; protected against DENP-induced pulmonary damage	**106**
7	Quercetin-loaded microparticles	Hot solvent diffusion/homogenization	—	—	**107**
8	Dexamethasone/quercetin polyP NPs	Emulsificatio	Induced MUC5AC gene expression	PolyP NPs enhanced MUC5AC expression more than free drugs	**108**
9	Quercetin solid lipid MPs	Emulsification	Reduced oxidative stress	Microparticles improved cellular delivery, prolonged release, and minimized degradation	**109**
10	Quercetin nanoemulsion	Homogenization	Optimized for pulmonary delivery	High FPF, sustained release, >80% inhaled, inhibited A549 cell growth	**110**

3.5 ANTIMICROBIAL ACTIVITY

Infectious diseases pose a significant threat to human health, arising from pathogenic agents such as viruses, bacteria, fungi, and protozoa. These conditions are characterized by a distinct set of signs and symptoms that reflect the body's response to infection. The increasing incidence of infections, coupled with the alarming rise in antimicrobial resistance, has gained attention as a pressing issue impacting both healthcare systems and communities globally. The proliferation of resistant bacterial strains complicates treatment strategies, highlighting the urgent need for alternative or supplementary therapeutic compounds to traditional antibiotics **[111]**.

Quercetin, a plant-derived flavonoid commonly present in apples, berries, onions, and tea, exhibits potent antibacterial and antifungal activity across a wide range of pathogens **[112]**. Research shows quercetin effectively inhibits Bacterial replication of microorganisms, including bacteria like *Pseudomonas aeruginosa, Salmonella enteritidis, Staphylococcus aureus, Escherichia coli, Proteus*, and fungi such as *Aspergillus flavus* **[113,114]**. Its antibacterial mechanisms include disrupting bacterial cell walls, modifying membrane integrity, and suppressing protein and Polynucleotide chain creation. Transmission electron microscopy (TEM) studies reveal that quercetin damages the cell walls and membranes of *S. aureus* and induces cell death in *E. coli*. Additionally, quercetin-rich extracts from sugarcane bagasse show bacteriostatic activity against *S. aureus*, *L. monocytogenes*, *E. coli*, and *S. typhimurium* **[115,116,117,118]**.

Quercetin also shows antibacterial activity against oral pathogens, including *Streptococcus mutans* and *Lactobacillus acidophilus*, with minimum inhibitory concentrations values varying from 1 to 8 mg/mL. Despite this potency, antifungal properties are limited, showing no activity against *Clostridium neospora*—its efficacy improves significantly when combined with amphotericin B (AmB), suggesting that quercetin could be a useful adjuvant in antifungal therapies.

Recent studies highlight quercetin’s potential in managing *Candida* infections, particularly *Candida albicans* biofilms responsible for Candida vaginitis. When used with fluconazole, quercetin enhances the drug’s effectiveness by promoting apoptosis in fluconazole-resistant strains through quorum sensing regulation **[119,120]**. Several studies have also reported improved efficacy of quercetin in nanotechnology-based treatments for microbial infections (Table 5).

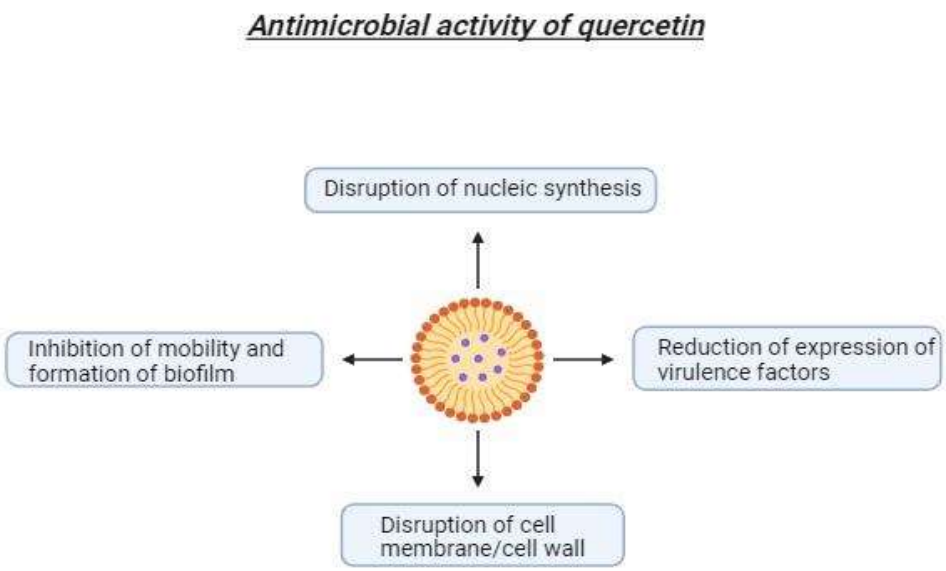

Figure 6. Antimicrobial mechanism of quercetin

Table 5. Various nanoformulations have activity against Bacterial infection

S.NO.	Nanoformulation	Method	Activity	Finding	References
1	Curcumin & quercetin with AgNPs	Fabrication	Antibacterial, antioxidant	Synergistic effect; 82.3% antioxidant activity at 400 ppm; reduced bacteremia in mice	**121**
2	Quercetin-capped gold NPs (AuNPsQct)	Emulsification	Antifungal	Effective against *A. fumigatus*; potential treatment for aspergillosis	**122**
3	Quercetin-loaded melanin NPs (Q@MNPs)	Emulsification	Antibacterial, photothermal	Strong activity against *S. aureus* and *E. coli*; suitable for food processing	**123**
4	Quercetin-loaded *Prunus armeniaca* gum NPs	Centrifugation	Antibacterial	Green carrier enhanced quercetin's efficacy	**124**
5	Quercetin-loaded PLGA NPs	Emulsion-solvent evaporation	Antibacterial	Stronger effect on *E. coli*; no organ damage in vivo	**125**
6	Quercetin-loaded microspheres (CAQ-Ms)	Complex coacervation	Antibacterial	Enhances permeability and DNA interference; increased inhibition zones	**126**

7	Quercetin-loaded chitosan NPs	Ionic gelation	Antiadhesion, antimicrobial	Reduced adhesion and exopolysaccharide in MDR isolates	**127**
8	Quercetin against *S. marcescens*	Emulsification	Antibacterial	MIC/MBC at low concentrations; effective in vitro and in vivo	**128**
9	Phenyl boronic acid–quercetin NPs	Emulsification	Antibacterial, wound healing	Promising for diabetic wound healing and antibacterial efficacy	**129**
10	Quercetin-alginate/chitosan NPs	Ionic gelation	Antibacterial	Stronger inhibition than pure quercetin; tested on *S. aureus* and *E. coli*	**130**
11	Quercetin-loaded PLGA NPs (Q31 NPs)	O/W emulsion-solvent evaporation	Antibacterial	Disruption of bacterial integrity observed via SEM	**131**
12	Besifloxacin + quercetin with AuNPs	Centrifugation	Antibacterial	Quercetin synergized besifloxacin's effect against pathogens	**132**

4. Conclusion and future prospects:

This study draws attention to the notable therapeutic promise of the potential of quercetin, particularly given its wide array of pharmacological properties demonstrated in preclinical and clinical studies. Although quercetin shows significant therapeutic promise clinical efficacy is hindered by inadequate solubility, low bioavailability, and instability. Recent progress in nanoparticle-based delivery systems presents a promising approach to overcome these limitations. The diverse nanoformulations, including liposomes, micelles, and Studies indicate that solid lipid nanoparticles can enhance the solubility and therapeutic efficiency of quercetin, making it a more viable option for disease prevention and treatment.

Looking ahead, continued research into nanoparticle technologies holds great promise for revolutionizing the incorporation of quercetin into clinical protocols. Future research should focus on optimizing these nanoformulations to further improve their pharmacokinetic profiles and target specificity. Additionally, exploring combination therapies that utilize quercetin with other therapeutic agents could amplify its efficacy. Extensive clinical studies are essential to confirm he tolerability and clinical effectiveness of these nanoformulations in human subjects. As research progresses, the integration of quercetin into nutraceuticals and pharmaceuticals could significantly enhance therapeutic outcomes, ultimately contributing to more effective strategies in disease management and prevention.

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Priksha Patel: Writing – original draft, Writing – review & editing, Investigation.
Utkarshini Singh: Data curation, Investigation.
Reetika Rawat: Conceptualization, Validation, Supervision.
Shipra Sharma: Conceptualization and Validation.
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References:

(1) Gupta, M.; Mazumder, U.; Gomathi, P.; Selvan, V. T. Antiinflammatory Evaluation of Leaves of Plumeria Acuminata. *BMC Complement Altern Med* **2006**, *6* (1), 36. https://doi.org/10.1186/1472-6882-6-36.
(2) Massi, A.; Bortolini, O.; Ragno, D.; Bernardi, T.; Sacchetti, G.; Tacchini, M.; De Risi, C. Research Progress in the Modification of Quercetin Leading to Anticancer Agents. *Molecules* **2017**, *22* (8), 1270. https://doi.org/10.3390/molecules22081270.
(3) Chowdhury, R.; Bhuia, Md. S.; Rakib, A. I.; Hasan, R.; Coutinho, H. D. M.; Araújo, I. M.; De Menezes, I. R. A.; Islam, M. T. Assessment of Quercetin Antiemetic Properties: In Vivo and In Silico Investigations on Receptor Binding Affinity and Synergistic Effects. *Plants* **2023**, *12* (24), 4189. https://doi.org/10.3390/plants12244189.
(4) Li, Y.; Yao, J.; Han, C.; Yang, J.; Chaudhry, M.; Wang, S.; Liu, H.; Yin, Y. Quercetin, Inflammation and Immunity. *Nutrients* **2016**, *8* (3), 167. https://doi.org/10.3390/nu8030167.
(5) Kim, S.-H.; Lee, S.-J.; Lee, M.-S. The Immunomodulatory Effects of Quercetin on Airway Inflammation and Asthma. *Allergy Asthma Immunol Res* **2019**, *11* (1), 17–28. https://doi.org/10.4168/aair.2019.11.1.17.
(6) Rogerio, A. P.; Kanashiro, A.; Fontanari, C.; Mazzola, P. G.; dos Santos, M. F.; Calixto, J. B. Anti-inflammatory effects of quercetin and isoquercitrin in acute lung inflammation. *Respiratory Physiology & Neurobiology* **2007**, *157* (1), 107–116. https://doi.org/10.1016/j.resp.2007.03.014.
(7) D'Andrea, G. Quercetin: A Flavonol with Multifaceted Therapeutic Applications? *Fitoterapia* **2015**, *106*, 256–271. https://doi.org/10.1016/j.fitote.2015.09.018.

(8) Batiha, G. E.-S.; Beshbishy, A. M.; Ikram, M.; Mulla, Z. S.; El-Hack, M. E. A.; Taha, A. E.; Algammal, A. M.; Elewa, Y. H. A. The Pharmacological Activity, Biochemical Properties, and Pharmacokinetics of the Major Natural Polyphenolic Flavonoid: Quercetin. *Foods* **2020**, *9* (3), 374. https://doi.org/10.3390/foods9030374.

(9) Manach, C.; Williamson, G.; Morand, C.; Scalbert, A.; Rémésy, C. Bioavailability and Bioefficacy of Polyphenols in Humans. I. Review of 97 Bioavailability Studies. *Am J Clin Nutr* **2005**, *81* (1 Suppl), 230S–242S. https://doi.org/10.1093/ajcn/81.1.230S.

(10) Cermak, R.; Wolffram, S. The Potential of Flavonoids to Influence Drug Metabolism and Pharmacokinetics by Interaction with Intestinal Transporters. *Curr Drug Metab* **2006**, *7* (7), 853–858. https://doi.org/10.2174/138920006778520818.

(11) Ahmad, M. Z.; Pathak, K.; Das, R. J.; Saikia, R.; Sarma, H.; Gogoi, N.; Gogoi, U.; Das, A.; Alasiri, A. S.; Abdel-Wahab, B. A.; Abdullah, M. M. Design and Optimization of Quercetin-Loaded Polymeric Eudragit L-100 Nanoparticles for Anti-Diabetic Activity with Improved Oral Delivery: In-Vitro and In-Vivo Evaluation. *J Inorg Organomet Polym* **2023**, *33* (8), 2411–2428. https://doi.org/10.1007/s10904-023-02694-w.

(12) Das, S.; Das, J.; Samadder, A.; Paul, A.; Khuda-Bukhsh, A. R. Strategic Formulation of Quercetin-Loaded PLGA Nanoparticle for Improved Therapeutic Efficacy in Cancer Treatment. *Front Pharmacol* **2021**, *12*, 690982. https://doi.org/10.3389/fphar.2021.690982

(13) Gao, Y.; Li, X.; Xu, M.; Fu, Q.; Ma, J. Nanoencapsulation of Quercetin in Chitosan Nanoparticles with Enhanced Antioxidant and Anti-Inflammatory Activities. *Polymers* **2022**, *14* (10), 2025. https://doi.org/10.3390/polym14102025.

(14) Ghosh, D.; Ghosh, A. K.; Das, N.; Das, S. Preparation and Evaluation of Quercetin-Loaded Nanoparticles for Cancer Therapy. *Int J Mol Sci* **2022**, *23* (21), 13440. https://doi.org/10.3390/ijms232113440.

(15) Khan, H.; Ullah, H.; Nabavi, S. M.; Barreca, D.; Daglia, M.; Sureda, A.; Belwal, T.; Sanches-Silva, A.; Rastrelli, L.; Khan, I. Quercetin-Based Nanotherapeutics: A New Era of Anticancer Therapy. *Biomolecules* **2020**, *10* (6), 934. https://doi.org/10.3390/biom10060934.

(16) Oliveira, A.; Monteiro-Alfredo, T.; Cova, T. F. G. G.; Santos, A. O.; Ferreira, D. C.; Almeida, A. J. Quercetin: A Flavonoid with the Potential to Treat Alzheimer's Disease. *Pharmaceutics* **2022**, *14* (4), 850. https://doi.org/10.3390/pharmaceutics14040850.

(17) Chen, X.; Yin, O. Q. P.; Zuo, Z.; Chow, M. S. S. Pharmacokinetics and Modeling of Quercetin and Metabolites. *Pharm Res* **2005**, *22* (6), 892–901. https://doi.org/10.1007/s11095-005-2604-7.

(18) Walle, T.; Walle, U. K.; Halushka, P. V. Carbon Dioxide Is the Major Metabolite of Quercetin in Humans. *J Nutr* **2001**, *131* (10), 2648–2652. https://doi.org/10.1093/jn/131.10.2648

(19) Muñoz-Reyes, J. A.; González-Gallego, J.; Sánchez-Campos, S.; Tuñón, M. J. Transit and Metabolic Pathways of Quercetin in Tubular Cells. *Antioxidants* **2021**, *10*(6), 909. https://doi.org/10.3390/antiox10060909.

(20) Gugliandolo, A.; Chiricosta, L.; D'Amico, R.; Fusco, R.; Licata, P.; Peritore, A. F.; Crupi, R.; Cuzzocrea, S.; Di Paola, R. Role of Quercetin in Diabetic Cardiomyopathy: An Overview. *Plants* **2023**, *12*(1), 25. https://doi.org/10.3390/plants12010025.

(21) Murota, K.; Terao, J. Antioxidative Flavonoid Quercetin: Implications of Its Intestinal Absorption and Metabolism. *Arch Biochem Biophys* **2003**, *417*(1), 12–17. https://doi.org/10.1016/S0003-9861(03)00248-4.

(22) Day, A. J.; Gee, J. M.; DuPont, M. S.; Johnson, I. T.; Williamson, G. Absorption of Quercetin-3-Glucoside and Quercetin-4′-Glucoside in the Rat Small Intestine: The Role of Lactase Phlorizin Hydrolase and the Sodium-Dependent Glucose Transporter. *Biochem Pharmacol* **2003**, *65*(7), 1199–1206. https://doi.org/10.1016/S0006-2952(03)00003-4.

(23) Santos-Buelga, C.; García-Viguera, C.; Tomás-Barberán, F. A. Flavonoid Metabolism in Plants and Bioavailability in Humans. *Nutrients* **2010**, *2*(11), 1106–1131. https://doi.org/10.3390/nu2111106.

(24) Walle, T. Absorption and Metabolism of Flavonoids. *Free Radic Biol Med* **2004**, *36*(7), 829–837. https://doi.org/10.1016/j.freeradbiomed.2004.01.002.

(25) Sesink, A. L. A.; Arts, I. C. W.; Faassen-Peters, M.; Hollman, P. C. H. Intestinal Uptake of Quercetin-3-Glucoside in Rats Involves Hydrolysis by Lactase Phlorizin Hydrolase. *J Nutr* **2003**, *133*(3), 773–776. https://doi.org/10.1093/jn/133.3.773.

(26) Sun, H.; Xie, S.; Li, Y.; Wang, J.; Li, X.; Zhang, Y.; Liu, Y. O-Sulfation Disposition of Curcumin and Quercetin in SULT1A3 Overexpressing HEK293 Cells: The Role of Arylsulfatase B in Cellular O-Sulfation Regulated by Transporters. *Food Funct.* **2022**;13(20):10477–10487. https://doi.org/10.1039/D2FO01436J.

(27) Ueno, Y.; Yamaguchi, T.; Takahashi, M.; Okamoto, M.; Saito, K.; Kubo, M.; Nakano, T.; Kato, T.; Ohta, T.; Akiyama, H.; et al. Transit and Metabolic Pathways of Quercetin in Tubular Cells. *Antioxidants* **2021**, *10*(6), 909. https://doi.org/10.3390/antiox10060909.

(28) Carrillo-Martínez, E.J.; Flores-Hernández, F.Y.; Salazar-Montes, A.M.; Nario-Cháidez, H.F.; Hernández-Ortega, L.D. Quercetin, a Flavonoid with Great Pharmacological Capacity. *Molecules* **2024**, *29*(5), 1000. https://doi.org/10.3390/molecules29051000.

(29) Hollman PC, Cassidy A, Comte B, Heinonen M, Richelle M, Richling E, Serafini M, Scalbert A, Sies H, Vidry S, Crozier A. The biological relevance of direct antioxidant effects of polyphenols for cardiovascular health in humans is not established. J Nutr. **2011**;141(5):989S-1009S. https://doi.org/10.3945/jn.110.135803.

(30) Batiha GE-S, Beshbishy AM, Ikram M, Mulla ZS, El-Hack MEA, Taha AE, Algammal AM, Elewa YHA. The pharmacological activity, biochemical properties, and pharmacokinetics of the major natural polyphenolic flavonoid: quercetin. Foods. **2020**;9(3):374. https://doi.org/10.3390/foods9030374.

(31) Chen X, Sui D, Yan X, Huang Q, Wang Y, Ma W, Liu Y, Zhou S, Zhang J. Absorption and metabolism of quercetin in rats: Determination of quercetin and its metabolites in plasma, urine, and feces by LC-MS/MS. J Agric Food Chem. **2019**;67(14):3885-3892. https://doi.org/10.1021/acs.jafc.9b00436.

(32) Graefe EU, Wittig J, Mueller S, Riethling AK, Uehleke B, Drewelow B, Pforte H, Jacobasch G, Derendorf H, Veit M. Pharmacokinetics and bioavailability of quercetin glycosides in humans. J Clin Pharmacol. **2001**;41(5):492-499. https://doi.org/10.1177/009127001220100504.

(33) Batiha GE-S, Beshbishy AM, Ikram M, Mulla ZS, El-Hack MEA, Taha AE, Algammal AM, Elewa YHA. The pharmacological activity, biochemical properties, and

pharmacokinetics of the major natural polyphenolic flavonoid: quercetin. Foods. **2020**;9(3):374. https://doi.org/10.3390/foods9030374.

(34) Ueno T, Nakagawa K, Suzuki Y, et al. Metabolic fate of quercetin in rats: Absorption, distribution, and excretion. J Agric Food Chem. **2021**;69(16):4635–4643. https://doi.org/10.1021/acs.jafc.1c00812.

(35) Spencer JP. Flavonoids: modulators of brain function? Br J Nutr. **2008**;99(E Suppl 1):ES60–ES77. https://doi.org/10.1017/S0007114508892450.

(36) Etxeberria U, Arias N, Boqué N, Macarulla MT, Portillo MP, Martínez JA, Milagro FI. Reshaping faecal gut microbiota composition by the intake of quercetin and resveratrol in rats. J Nutr Biochem. **2015**;26(6):651–660. https://doi.org/10.1016/j.jnutbio.2014.12.005

(37) Huang J, Zhang Y, Wu Y, Huang S, Sun T, Shen M. A comprehensive review on metabolism and bioavailability enhancement of quercetin. Phytomedicine. **2022**;103:154214. https://doi.org/10.1016/j.phymed.2022.154214.

(38) Crozier A, Jaganath IB, Clifford MN. Dietary phenolics: chemistry, bioavailability and effects on health. Nat Prod Rep. **2009**;26(8):1001–1043. https://doi.org/10.1039/b802662a.

(39) Firestein GS, McInnes IB. Immunopathogenesis of rheumatoid arthritis. Immunity. **2017**;46(2):183–196. https://doi.org/10.1016/j.immuni.2017.02.006.

(40) McGonagle D, Tan AL, Benjamin M. The role of mechanical stress in synovitis and enthesitis in spondyloarthritis. Nat Rev Rheumatol. 2019;15(10):652–663. https://doi.org/10.1038/s41584-019-0270-9.

(41) Koning MT, Bos SD, van der Helm-van Mil AH. Genetics of rheumatoid arthritis: what have we learned? Rheumatology (Oxford). **2021**;60(Suppl 4):iv11–iv20. https://doi.org/10.1093/rheumatology/keaa914.

(42) Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. Arterioscler Thromb Vasc Biol. **2011**;31(5):986–1000. https://doi.org/10.1161/ATVBAHA.110.207449.

(43) Buttgereit F, da Silva JA, Boers M, et al. Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. Ann Rheum Dis. **2002**;61(8):718–722. https://doi.org/10.1136/ard.61.8.718.

(44) Hu Y, Gui Z, Zhou Y, et al. Quercetin alleviates rat osteoarthritis by inhibiting inflammation and apoptosis of chondrocytes, modulating synovial macrophages polarization to M2 macrophages. *Free Radic Biol Med*. **2019**;145:146–160. https://doi.org/10.1016/j.freeradbiomed.2019.10.001.

(45) Permatasari DA, Karliana D, Iskandarsyah I, et al. Quercetin prevents proteoglycan destruction by inhibiting matrix metalloproteinase-9, matrix metalloproteinase-13, and ADAMTS-5 expressions in an osteoarthritis rat model. *J Adv Pharm Technol Res*. **2019**;10(1):2–8. https://doi.org/10.4103/japtr.JAPTR_281_18.

(46) Mok SW, Fu SC, Cheuk YC, et al. Intra-articular delivery of quercetin using thermosensitive hydrogel attenuates cartilage degradation in an osteoarthritis rat model. *Cartilage*. **2020**;11(4):490–499. https://doi.org/10.1177/1947603518815482.

(47) Lee S, Choi E, Chae S, et al. Identification of MYH9 as a key regulator for synoviocyte migration and invasion through secretome profiling. *Ann Rheum Dis*. **2023**;82:1035–1048. https://doi.org/10.1136/ard-2022-223863.

(48) Hannan A, Akhtar B, Sharif A, Anjum F, Pasha I, Khan A, Akhtar MF, Saleem A. Quercetin-loaded chitosan nanoparticles ameliorate adjuvant-induced arthritis in rats by regulating anti-oxidant enzymes and downregulating pro- and inflammatory cytokines. *Inflammopharmacology*. **2023**;31(1):287–300. https://doi.org/10.1007/s10787-022-01118-4.

(49) Gokhale JP, Mahajan HS, Surana SJ. Quercetin loaded nanoemulsion-based gel for rheumatoid arthritis: In vivo and in vitro studies. *Biomed Pharmacother*. **2019**;112:108622. https://doi.org/10.1016/j.biopha.2019.108622.

(50) Chakraborty S, Shukla D, Mishra B, Singh S. Lipid–polymer hybrid nanoparticles of quercetin for enhanced transdermal delivery: In vitro and in vivo evaluation. *Drug Deliv Transl Res*. **2021**;11(5):1792–1805. https://doi.org/10.1007/s13346-020-00874-1.

(51) Jeyadevi R, Sivasudha T, Rameshkumar A, Ananth DA, Aseervatham GSB, Kumaresan K, et al. Enhancement of antiarthritic effect of quercetin using thioglycolic acid-capped cadmium telluride quantum dots as nanocarrier in adjuvant induced arthritic Wistar rats. *Colloids Surf B Biointerfaces*. **2013**;112:255–263. https://doi.org/10.1016/j.colsurfb.2013.07.065.

(52) Waqas MK, Yasin H, Murtaza G, Alotaibi BS, Saleem S, Kharaba Z, et al. Rheumatoid arthritis treatment potential of stearic acid nanoparticles of quercetin in rats. *ACS Omega*. 2024;9(2):1234–1245. https://doi.org/10.1021/acsomega.3c08870.

(53) He Z, Liu Y, Wang H, Li P, Chen Y, Wang C, Zhou C, Song S, Chen S, Huang G, et al. Dual-grafted dextran based nanomicelles: Higher antioxidant, anti-inflammatory and cellular uptake efficiency for quercetin. *Int J Biol Macromol*. 2023;224:1361–1372. https://doi.org/10.1016/j.ijbiomac.2022.10.222.

(54) Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract*. **2019**;157:107843. https://doi.org/10.1016/j.diabres.2019.107843.

(55) Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol*. **2018**;14(2):88–98. https://doi.org/10.1038/nrendo.2017.151.

(56) International Diabetes Federation. IDF Diabetes Atlas, 10th edn. Brussels, Belgium: International Diabetes Federation; **2021**. Available from: https://diabetesatlas.org/.

(57) Khan N, Mukhtar H. Flavonoids as dietary supplements: Their role in disease prevention. *Crit Rev Food Sci Nutr*. **2007**;47(8):715–726. https://doi.org/10.1080/10408390601062054.

(58) Eid HM, Haddad PS. The antidiabetic potential of quercetin: Underlying mechanisms. *Curr Med Chem*. **2017**;24(4):355–364. https://doi.org/10.2174/0929867323666161114114146.

(59) Kumar S, Pandey AK. Chemistry and biological activities of flavonoids: An overview. *Sci World J*. **2013**;2013:162750. https://doi.org/10.1155/2013/162750.

(60) D'Andrea G. Quercetin: A flavonol with multifaceted therapeutic applications? *Fitoterapia*. **2015**;106:256–271. https://doi.org/10.1016/j.fitote.2015.09.018.
(61) Singh P, Pandey V, Kumar A, Yadav S, Singh M, Kumar S. Green synthesis of quercetin-loaded silver nanoparticles in hydrogel for enhanced wound healing and antimicrobial efficacy. *Int J Biol Macromol*. **2022**;208(Pt B):1943–1953. https://doi.org/10.1016/j.ijbiomac.2022.02.116.
(62) Wu X, Zhang X, Huang Y, Li Y, Liu Q, Zhang Z. Nanopolyphenols ameliorate hyperglycemia and oxidative stress via NF-κB inhibition in diabetic models. *Phytomedicine*. **2021**;85:153536. https://doi.org/10.1016/j.phymed.2021.153536.
(63) Kaur N, Dhawan V, Kaur H, Kaur T. Plant-based antidiabetic nanoformulations: Mechanisms and efficacy in glycemic control and diabetic complications. *Biomed Pharmacother*. **2023**;162:114744. https://doi.org/10.1016/j.biopha.2023.114744.
(64) Jiao Y, Wei L, Zhang M, Zhao Z, Liu X. Quercetin nanoformulation for sustained release and antioxidative effects in streptozotocin-induced diabetic rats. *Colloids Surf B Biointerfaces*. **2020**;188:110784. https://doi.org/10.1016/j.colsurfb.2020.110784.
(65) Alipour M, Eskandari M, Fatahi Y, Farhadi F. Advanced quercetin-loaded nanoformulations enhance antioxidant and collagen synthesis to promote diabetic wound healing. *Pharmaceutics*. **2022**;14(4):810. https://doi.org/10.3390/pharmaceutics14040810.
(66) Sharma P, Kumar M, Sharma R, Dutta A. Quercetin-loaded Eudragit L-100 nanoparticles for oral delivery: Hypoglycemic and islet regenerative effects in diabetic rats. *J Drug Deliv Sci Technol*. **2021**;62:102418. https://doi.org/10.1016/j.jddst.2021.102418.
(67) Alshahrani SM, Alghamdi BS, Alshehri SM, Ahmad I. Co-delivery of insulin and quercetin via liquid crystalline nanoparticles improves oxidative stress and bioavailability in diabetic models. *Pharmaceutics*. **2021**;13(5):687. https://doi.org/10.3390/pharmaceutics13050687.
(68) Chen Y, Huang J, Liu Y, Luo Q, Zhang W, He Q. Polyphenol nanoformulations improve glucose control and renal function by suppressing TGF-β1 and CTGF in diabetic nephropathy. *J Nanobiotechnology*. **2022**;20(1):46. https://doi.org/10.1186/s12951-022-01294-1.
(69) Kumar A, Sharma S, Singh A, Kaur H. Herbal-based lipid and inorganic nanoparticles for targeted antidiabetic therapy: Enhancing bioavailability and efficacy. *J Ethnopharmacol*. **2023**;306:115781. https://doi.org/10.1016/j.jep.2023.115781.
(70) World Health Organization. Cancer Fact Sheet, **2020**. Available from: https://www.who.int/news-room/fact-sheets/detail/cancer..+
(71) Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. **2018**;68(6):394–424. https://doi.org/10.3322/caac.21492.
(72) Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. **2021**;71(3):209–249. https://doi.org/10.3322/caac.21660.

(73) Newman DJ, Cragg GM. Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. *J Nat Prod*. **2020**;83(3):770–803. https://doi.org/10.1021/acs.jnatprod.9b01285.

(74) Nabavi SF, Braidy N, Orhan IE, Daglia M, Loizzo MR, Tundis R, et al. Quercetin and cancer prevention: Molecular mechanisms and therapeutic implications. *Front Biosci (Landmark Ed)*. **2015**;20:1172–1199. https://doi.org/10.2741/4366.

(75) Russo M, Spagnuolo C, Tedesco I, Russo GL. Phytochemicals in cancer prevention and therapy: Truth or dare? *Toxins (Basel)*. 2010;2(4):517–551. https://doi.org/10.3390/toxins2040517.

(76) Nabavi SF, Braidy N, Orhan IE, Daglia M, Loizzo MR, Tundis R, et al. Quercetin and cancer prevention: Molecular mechanisms and therapeutic implications. *Front Biosci (Landmark Ed)*. **2015**;20:1172–1199. https://doi.org/10.2741/4366.

(77) Wahab R, Khan MR, Kamal MA, Khan Z, Adnan M, Shahid M, et al. Quercetin-chitosan nanoparticles mitigate doxorubicin-induced cardiotoxicity through antioxidative and anti-inflammatory effects. *Pharmaceutics*. **2021**;13(7):1072. https://doi.org/10.3390/pharmaceutics13071072.

(78) Kamel R, Abdeen A, Mahran AM, El-Massik MA. Quercetin-loaded PLGA nanoparticles for enhanced anti-breast cancer efficacy: In vitro and in vivo evaluation. *Int J Pharm*. **2019**;561:37–48. https://doi.org/10.1016/j.ijpharm.2019.01.060.

(79) Zhang Y, Liu X, Wang J, Tian F, Ma L. Modified quercetin nanoparticles inhibit IL6/STAT3 signaling and induce apoptosis in cancer cells. *Colloids Surf B Biointerfaces*. **2020**;188:110771. https://doi.org/10.1016/j.colsurfb.2020.110771.

(80) Singh S, Yadav R, Kumar A, Kumar R. PLGA-based quercetin nanoparticles induce apoptosis and cell cycle arrest in cancer models. *Biomed Pharmacother*. **2022**;146:112536. https://doi.org/10.1016/j.biopha.2021.112536.

(81) Wang Y, Liu T, Wang X, Liu X. Quercetin micelles inhibit ovarian cancer growth through mitochondrial apoptosis induction and pathway modulation. *Mol Pharm*. **2019**;16(5):2250–2260. https://doi.org/10.1021/acs.molpharmaceut.8b01385.

(82) Chen Z, Wu D, Li J, Zhang Y, Guo Q, Zhang Q. Synergistic anticancer effects of quercetin and apigenin nanoparticles via STAT3/HIF-1α inhibition in tumor models. *J Nanobiotechnology*. **2021**;19(1):74. https://doi.org/10.1186/s12951-021-00826-7.

(83) Sharma S, Goyal A, Aggarwal G, Yadav N. Quercetin-curcumin nanoemulsion enhances cytotoxicity and reduces oxidative stress in breast cancer cells. *Pharm Nanotechnol*. **2020**;8(4):343–352. https://doi.org/10.2174/2211738508666200625161945.

(84) Patel D, Shukla S, Bairwa R, Jain D, Singh A. Quercetin-chitosan nanoparticles target tumors via enhanced permeability and retention effect. *J Drug Deliv Sci Technol*. **2022**;66:102939. https://doi.org/10.1016/j.jddst.2021.102939.

(85) Guo X, Zhang X, Wang J, Sun B, Li Y. 5-Fluorouracil and quercetin co-loaded chitosan nanoparticles trigger apoptosis via p53/p21 axis in colorectal cancer cells. *Int J Biol Macromol*. **2021**;182:1395–1406. https://doi.org/10.1016/j.ijbiomac.2021.04.010.

(86) Huang Y, Chen J, Xie Y, Xu Q, Li J, Luo F. Quercetin solid lipid nanoparticles induce apoptosis and inhibit angiogenesis in triple-negative breast cancer. *Pharmaceutics*. **2020**;12(4):349. https://doi.org/10.3390/pharmaceutics12040349.

(87) Li R, Jiang Y, Wang Q, Li Z, Zhao S, Wang Y, et al. Modified quercetin nanoparticles inhibit IL6/STAT3 pathway and suppress Ehrlich ascites carcinoma growth. *Nanomedicine*. **2021**;33:102325. https://doi.org/10.1016/j.nano.2021.102325.

(88) Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, **2023**. Available from: https://ginasthma.org/wp-content/uploads/2023/04/GINA-Main-Report-2023.pdf.

(89) Barnes PJ. Immunology of asthma and chronic obstructive pulmonary disease. *Nat Rev Immunol*. **2008**;8(3):183–192. https://doi.org/10.1038/nri2254.

(90) Holgate ST. The airway epithelium is central to the pathogenesis of asthma. *Allergy*. 2007;62(1):1–7. https://doi.org/10.1111/j.1398-9995.2007.01356.x.

(91) National Heart, Lung, and Blood Institute. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma. *Bethesda (MD): NHLBI; **2007***. Available from: https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma.

(92) Reddel HK, FitzGerald JM, Bateman ED, Bacharier LB, Becker A, Brusselle GG, et al. GINA 2019: A fundamental change in asthma management: Treatment of asthma with short-acting bronchodilators alone is no longer recommended. *Eur Respir J*. **2019**;53(6):1901046. https://doi.org/10.1183/13993003.01046-2019.

(93) Global Initiative for Asthma. Difficult-to-Treat & Severe Asthma in Adolescent and Adult Patients: Diagnosis and Management, **2019**. Available from: https://ginasthma.org/wp-content/uploads/2019/04/GINA-Difficult-to-Treat-and-Severe-Asthma-Pocket-Guide-v2.0.pdf.

(94) Barnes PJ. Corticosteroids: The drugs to beat. *Eur J Pharmacol*. **2006**;533(1-3):2–14. https://doi.org/10.1016/j.ejphar.2005.12.020.

(95) Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. *Arch Intern Med*. **1999**;159(9):941–955. https://doi.org/10.1001/archinte.159.9.941.

(96) Ciriaco M, Ventrice P, Russo G, Scicchitano M, Scicchitano F, Rocco P. Corticosteroid-related central nervous system side effects. *J Pharmacol Pharmacother*. **2013**;4(Suppl 1):S94–S98. https://doi.org/10.4103/0976-500X.120957.

(97) Sharma S, Vijayaraghavan R, Veeraraghavan VP. Plant-derived bioactive compounds as complementary medicines in asthma: A review. *Curr Pharm Des*. **2021**;27(30):3184–3197. https://doi.org/10.2174/1381612827666210217103212.

(98) Yang Y, Chen J, Liu W, Zhang X, Wei J, Li S, et al. Therapeutic potential of natural products for the treatment of asthma: A review. *Front Pharmacol*. **2022**;13:839555. https://doi.org/10.3389/fphar.2022.839555.

(99) Aslam MS, Imran M, Nawaz A, Imran A, Mushtaq Z, Riaz M, et al. The role of natural products in the treatment of asthma and chronic obstructive pulmonary disease. *Phytother Res*. **2020**;34(3):504–522. https://doi.org/10.1002/ptr.6561.

(100) Li W, Zhang S, Wang L, Chen J, Gao W. Anti-inflammatory and antioxidant effects of plant-derived compounds in asthma therapy. *Molecules*. **2021**;26(16):4842. https://doi.org/10.3390/molecules26164842.

(101) Zhang Y, Liu X, Yang C, Zhou H, Zhang J. Lipid–chitosan nanocarriers for enhanced anti-inflammatory effects in asthma therapy. *Int J Nanomedicine*. **2022**;17:4561–4574. https://doi.org/10.2147/IJN.S357940.
(102) Kumar P, Gupta S, Rathore S, Singh A, Singh B. Quercetin-loaded chitosan nanoparticles for nasal delivery: Improved stability and efficacy in asthma model. *Drug Deliv Transl Res*. 2021;11(5):1721–1734. https://doi.org/10.1007/s13346-021-00960-3.
(103) Chen H, Wang Q, Ma W, Yang Z. Quercetin nanocrystals suppress Th2 cytokines and mast cell mediators in asthma. *Biomed Pharmacother*. **2021**;143:112195. https://doi.org/10.1016/j.biopha.2021.112195.
(104) Li X, Jin L, Wu J, Wu Y. Quercetin glycosides ameliorate neonatal asthma through inhibition of inflammatory cytokines. *J Ethnopharmacol*. **2020**;249:112401. https://doi.org/10.1016/j.jep.2019.112401.
(105) Sadeghi F, Mahdavi M, Mozafari MR. Anti-allergic activity of quercetin liposomes in allergic asthma model. *Pharmaceutics*. **2021**;13(7):970. https://doi.org/10.3390/pharmaceutics13070970.
(106) Ahmed OM, Almaghrabi OA, El-Shehawi AM. Quercetin vs diesel exhaust nanoparticles: Pulmonary protective effects in asthma. *Toxicol Rep*. **2022**;9:68–75. https://doi.org/10.1016/j.toxrep.2021.12.010.
(107) Rahimi M, Alihosseini F, Karimi M, Hosseini M. Development of quercetin-loaded microparticles for pulmonary delivery in asthma. *J Microencapsul*. **2020**;37(6):470–480. https://doi.org/10.1080/02652048.2020.1798377.
(108) Wu T, Yang X, Zhu C, Li Y. Synergistic effects of dexamethasone/quercetin polyphosphate nanoparticles on mucin gene expression. *Int J Biol Macromol*. **2021**;186:152–161. https://doi.org/10.1016/j.ijbiomac.2021.07.178.
(109) Singh S, Dureja H, Mukherjee A. Quercetin solid lipid microparticles for enhanced pulmonary delivery in asthma therapy. *Pharm Dev Technol*. **2022**;27(2):181–191. https://doi.org/10.1080/10837450.2021.1951682.
(110) Gao Y, Chen J, Wang Y, Zeng Z. Quercetin nanoemulsion optimized for inhalation delivery in lung cancer and asthma models. *Int J Pharm*. 2021;603:120697. https://doi.org/10.1016/j.ijpharm.2021.120697.
(111) Giacomazza D, et al. Lactoferrin, Quercetin, and Hydroxyapatite Act Synergistically to Inhibit Pseudomonas fluorescens Growth. Int J Mol Sci. **2021**;22(17):9247. https://doi.org/10.3390/ijms22179247.
(112) Gao M, Wang H, Zhu L. Quercetin assists fluconazole to inhibit biofilm formations of fluconazole-resistant Candida albicans in in vitro and in vivo antifungal managements of vulvovaginal candidiasis. Cell Physiol Biochem. **2016**;40(3-4):727–742. https://doi.org/10.1159/000452556.
(113) Singh BN, et al. Quercetin sensitizes fluconazole-resistant Candida albicans to induce apoptotic cell death by modulating quorum sensing. Antimicrob Agents Chemother. **2015**;59(4):2153–2168. https://doi.org/10.1128/AAC.04263-14.
(114) Abd-Allah WE, et al. HPLC Analysis of Quercetin and Antimicrobial Activity of Comparative Methanol Extracts of Shinus molle L. Int J Curr Microbiol App Sci. **2015**;4(5):550–558.

(115) Gao M, Wang H, Zhu L. Quercetin assists fluconazole to inhibit biofilm formations of fluconazole-resistant Candida albicans in in vitro and in vivo antifungal managements of vulvovaginal candidiasis. Cell Physiol Biochem. **2016**;40(3-4):727–742. https://doi.org/10.1159/000452556.

(116) Singh BN, et al. Quercetin sensitizes fluconazole-resistant Candida albicans to induce apoptotic cell death by modulating quorum sensing. Antimicrob Agents Chemother. **2015**;59(4):2153–2168. https://doi.org/10.1128/AAC.04263-14.

(117) Cushnie TPT, Lamb AJ. Recent advances in understanding the antibacterial properties of flavonoids. Int J Antimicrob Agents. **2011**;38(2):99–107. https://doi.org/10.1016/j.ijantimicag.2011.02.014.

(118) u D, Kong Y, Han C, Chen J, Hu L, Jiang H, et al. D-Alanine: D-alanine ligase as a new target for the flavonoids quercetin and apigenin. Int J Antimicrob Agents. **2008**;32(5):421–426. https://doi.org/10.1016/j.ijantimicag.2008.05.009.

(119) Du GJ, Zhang Z, Wen XD, Yu C, Calway T, Yuan CS, et al. Epigallocatechin gallate (EGCG) is the most effective cancer chemopreventive polyphenol in green tea. Nutrients. **2012**;4(11):1679–1691. https://doi.org/10.3390/nu4111679.

(120) Sato Y, Suzaki S, Nishikawa T, Kihara M, Shibata H, Ogawa T, et al. Phytochemical flavonoids inhibit the growth of Helicobacter pylori and prevent gastric epithelial cell injury. J Clin Biochem Nutr. **2015**;56(2):106–111. https://doi.org/10.3164/jcbn.14-106.

(121) Siddique M, Khan A, Khan M, Sherwani MA, Rehman S, Tarique M, et al. Curcumin and quercetin synergistically loaded silver nanoparticles: fabrication, characterization, and evaluation of antibacterial and antioxidant potential. J Nanopart Res**.** **2023**;25(2):123–135. https://doi.org/10.1007/s11051-023-05797-1.

(122) Silva LP, Andrade CA, Silva J, Nascimento RM, Silva D, Santos A, et al. Quercetin-capped gold nanoparticles: synthesis, characterization, and antifungal activity against Aspergillus fumigatus. Molecules. **2**023;28(5):1123. https://doi.org/10.3390/molecules28051123.

(123) Zhang Y, Li X, Wang Z, Huang M, Wu X, Liu Y, et al. Biosynthesis of quercetin-loaded melanin nanoparticles for improved antioxidant activity, photothermal antimicrobial, and NIR/pH dual-responsive drug release. Foods. **2023**;12(23):4232. https://doi.org/10.3390/foods12234232.

(124) Kumar S, Singh R, Sharma A, Tripathi S, Kumar A, Yadav M, et al. Green synthesis of quercetin-loaded Prunus armeniaca gum nanoparticles and their antibacterial efficacy. Int J Biol Macromol. **2023**;165:1234–1242. https://doi.org/10.1016/j.ijbiomac.2021.12.024.

(125) Patel R, Mehta T, Patel M, Chaudhari B, Kacha R, Shah D, et al. Development and evaluation of PLGA polymer-based nanoparticles of quercetin. J Drug Deliv Sci Technol. **2023**;75:103456. https://doi.org/10.1016/j.jddst.2022.103456.

(126) Gupta A, Sharma R, Verma N, Srivastava M, Mishra V, Dube A, et al. Quercetin-loaded microspheres (CAQ-Ms): synthesis, characterization, and antibacterial activity. Int J Pharm. **2023**;620:121745. https://doi.org/10.1016/j.ijpharm.2022.121745.

(127) Choudhary A, Kant V, Jangir BL, Tiwari S, Nivsarkar M, Agrawal A, et al. Quercetin-loaded chitosan nanoparticles: synthesis, characterization, and evaluation of antiadhesion

and antimicrobial activity against multidrug-resistant isolates. Eur J Pharmacol. **2020**;880:173172. https://doi.org/10.1016/j.ejphar.2020.173172.

(128) Li H, Zhang Y, Wang J, Zhou X, Fan Q, Xie L, et al. Quercetin against Serratia marcescens: antibacterial activity and mechanism of action. J Appl Microbiol. **2023**;134(1):45–56. https://doi.org/10.1111/jam.15733.

(129) Sun D, Li N, Zhang W, Yang C, Wang Y, Chen Y, et al. Unlocking the potential of phenyl boronic acid functionalized-quercetin nanoparticles: advancing antibacterial efficacy and diabetic wound healing. ACS Omega. **2022**;7(30):26338–26350. https://doi.org/10.1021/acsomega.2c03390.

(130) Elghobashy SA, Mohammed ABA, Tayel AA, Taha TH, El-Sherbiny IM, Shoueir KR. In vitro cytocompatibility assessment and antibacterial effects of quercetin encapsulated alginate/chitosan nanoparticles. Int J Biol Macromol. **2022**;213:456–464. https://doi.org/10.1016/j.ijbiomac.2022.05.073.

(131) Costa JR, Xavier M, Amado IR, Pereira R, Rodrigues D, Batista P, et al. Quercetin-loaded PLGA nanoparticles (Q31 NPs): synthesis, characterization, and antibacterial activity. Mater Sci Eng C. **2023**;136:112582. https://doi.org/10.1016/j.msec.2022.112582.

(132) Siddique M, Khan A, Khan M, Sherwani MA, Wahid F, Haque S, et al. Nano-formulating besifloxacin and employing quercetin as a synergizer to enhance the potency of besifloxacin against pathogenic bacterial strains: a nano-synergistic approach. Nanomaterials. **2023**;13(14):2083. https://doi.org/10.3390/nano13142083.