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REVIEW

Quercetin and Nano-Derivatives: Potential and Challenges in Cancer Therapy

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Abstract: Quercetin, a prevalent flavonol compound, has gained attention for its multifaceted mechanisms of action against various cancers, highlighting its potential as an adjunctive therapy in cancer treatments. This review aims to systematically evaluate the structural optimization, mechanisms of action, and clinical applications of quercetin and its nano-derivatives in cancer treatment. Employing a bibliometric analysis of 6231 articles from the Web of Science Core Collection, we observed a notable increase in annual publications, particularly from the USA and China, indicating a growing interest in quercetin's therapeutic potential. Our findings reveal that quercetin enhances the efficacy of conventional therapies by modulating critical signaling pathways, thereby increasing cancer cell sensitivity while simultaneously protecting normal tissues from therapy-induced damage. Structural modifications, including glycosylation, methylation, sulfation, and glucuronidation, alongside nanoparticle formulation, significantly improve the stability, solubility, and bioavailability of quercetin, enabling targeted drug delivery. Despite the promising preclinical outcomes, the clinical translation of quercetin remains nascent, necessitating further rigorous research to validate its safety and efficacy in human subjects. In conclusion, while quercetin exhibits substantial anticancer properties and therapeutic potential, future studies should focus on expanding sample sizes, elucidating metabolic pathways, and conducting comprehensive clinical trials to inform its application in oncology.

Keywords: quercetin, nano-derivatives, cancer therapy, mechanisms of action, drug safety

Introduction

In 1857, the flavonol compound quercetin was named after Quercus as a natural plant compound. It is one of the most abundant flavonoids among flavonol compounds.[1] Quercetin (molecular formula: $C_{15}H_{10}O_7$) consists of two benzene rings and a benzopyran ring. The International Union of Pure and Applied Chemistry (IUPAC) chemical name of Quercetin (QUE) is 3,3′,4′,5,7-pentahydroxyflavone. QUE is widely found in botanical drugs, such as *Ginkgo biloba, Lonicerae Japonicae Flos, Scutellariae Radix, Puerariae Radix*, and *Buglossoides Radix*, with the highest content found in *sophora flower*.[2] (Figure 1). The medical active structures of quercetin include QUE Glycosides, Methylated QUE, Sulfated QUE, QUE glucuronides, and QUE-nanoparticle composites such as Metal-QUE Complexes, QUE Nanoparticles, QUE Liposomes, and QUE Nano-micelles.[3–5] In recent years, researchers have created innovative intelligent systems that integrate synthetic materials with flavonoid compounds,[6–9] like QUE-magnetoliposome (Q-MLs), for use in magnetic hyperthermia and smart drug delivery for breast cancer. In vitro experiments indicate that Q-MLs have significant cytotoxic effects on MCF-7 breast cancer cells at various concentrations. Additionally, the application of a magnetic field significantly increases both the release rate of QUE and the cell death rate. Q-MLs effectively generate heat when subjected to an alternating magnetic field, thereby enhancing the anticancer effect of quercetin. However, because quercetin is a polyphenolic compound, it often produces non-specific effects. Existing in vivo studies have demonstrated that quercetin and its nano-derivatives can serve as adjuvant therapies for cancer, yielding significant therapeutic effects. However, the reliability of these studies requires further verification.[10–12] This

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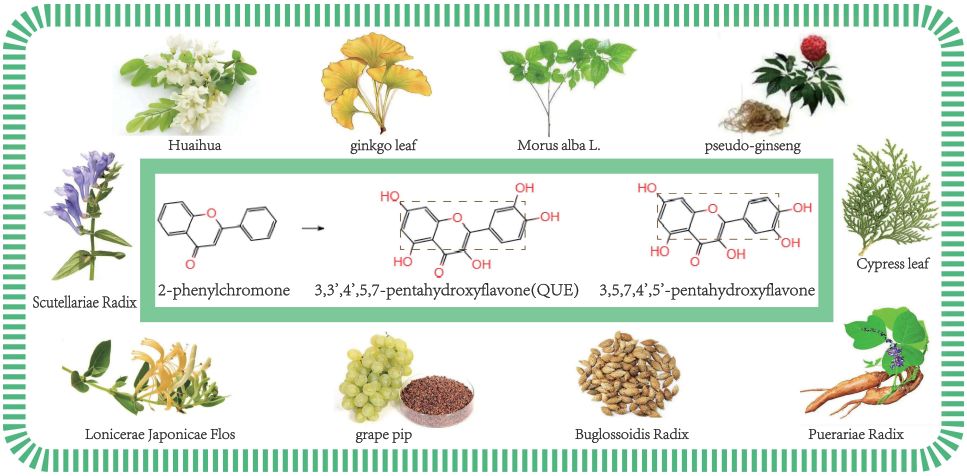

Figure 1 QUE molecular structure and medicinal plants. Adapted from Institute of Botany, Chinese Academy of Sciences. Plant photo bank of china (PPBC). https://ppbc.iplant.cn. Accessed Dec 15, 2024.[13]

review analyzes the research progress on QUE and its nano-derivatives in cancer treatment worldwide from 2004 to 2024 through bibliometric. Based on the latest research hotspots, it explores the mechanism of action of QUE and its nano-derivatives in cancer treatment, and evaluates their safety and effectiveness as adjuvant therapy. QUE nano-derivatives have enhanced the bioavailability and targeted delivery of quercetin, exhibiting significant clinical application potential. It is recommended to expand the sample size in in vivo studies in future research, comprehensively explore the metabolic mechanisms and biological activities of QUE under various physiological conditions, and rigorously assess its long-term efficacy and safety.

The Physiochemical Properties of QUE

QUE has hydroxyl groups at positions 3, 5, 7, 3′ and 4′. Both QUE and its isomeric molecules belong to the flavonoid compounds with the basic nucleus of 2-phenylchromen. The molecule of QUE is a pentahydroxyflavone obtained by substituting the hydrogen atoms at the 3, 5, 7, 3′, and 4′ positions of the skeleton structure with hydroxyl groups (–OH). The various phenolic hydroxyl groups on this skeleton structure have certain activity and belong to active sites. The activity of –OH groups in the structure of QUE follows the sequence of 4′-, 3′-, 7-, 3-. Changing the positions of phenolic hydroxyl groups on QUE molecule alters the properties of the generated 14 isomeric molecules.[14] Lower total energy of the molecule is associated with more stable structure. However, the B-ring of QUE molecule exhibits the strongest activity and the highest medicinal value.

QUE possesses certain inherent characteristics, such as low water-solubility (2.2 μg/mL), extensive first-pass metabolism, and low oral bioavailability.[15] Previous research has revealed that QUE primarily binds to plasma proteins in the body, with albumin accounting for 99.4% of this binding, thereby reducing its cellular bioavailability.[16] Additionally, QUE and its derivatives demonstrate stability in gastric acid and are absorbed in the upper segment of the small intestine. Following absorption, they undergo metabolism in various organs, including the small intestine, colon, liver, and kidneys. The highest accumulation of QUE's metabolites has been observed in the lungs (in rats) and the liver and kidneys (in pigs), with the kidneys serving as a major excretory organ.[17] Therefore, to optimize the clinical application of QUE, it is necessary to make structural modifications to enhance its efficacy and reduce potential toxic side effects.

Common Structural Modifications of QUE

QUE Glycosides

QUE glycosides, also known as flavonoid glycosides, can be isolated from a variety of plants, including *Scutellar*ia Radix,[18,19] *Astragalus membranaceus*,[20,21] *Salvia miltiorrhiza Hedyotis diffusa*,[22,23] and *Pueraria lobata*.[24,25] Common isolation techniques encompass solvent extraction and chromatographic separation methods.

Hydroxyl groups (–OH) in QUE are replaced by glycosyl groups (–O–glycosyl). These are natural compounds formed by the combination of QUE with sugar molecules and represent the main form of QUE in human blood. Among them, QUE glucoside exhibits improved water-solubility, increasing its bioavailability and stability. Its absorption rate ranges from 3% to 17%, making it a potent antioxidant.[2] Isomers of QUE glycosides, also known as isoquercitrin, possess better stability and water-solubility, making them more readily absorbed and utilized in the body.[26,27]

Methylation

Methylated QUE can be isolated from various plants, including *Sorbaria sorbifolia* and *Jatropha curcas*,[28,29] through commonly employed separation techniques such as organic solvent extraction, chromatographic separation, and spectroscopic identification.

Methoxy groups are introduced onto the hydroxyl groups of QUE, resulting in the formation of methylated QUE derivatives. Previous research has shown that strong methylation occurs in the liver for 90–95% of QUE derivatives, which enhances their solubility and stability. In vitro experiments have demonstrated that methylated QUE, such as 3,4′,7-o-trimethylquercetin (34'7TMQ), can inhibit the migration and invasion of ovarian cancer cells without affecting cell proliferation.[30]

Sulfation

Sulfated QUE can be isolated from various plants, including Echinacea purpurea and Echinacea angustifolia,[31–33] using conventional techniques such as organic solvent extraction, chromatographic separation, and spectroscopic identification.

Compounds formed by esterification of QUE molecules with sulfate groups ($–SO_4$) are known as sulfated QUE derivatives. Sulfated QUE exhibits better water-solubility and facilitates the preparation of water-soluble drugs. Compared with pure QUE, it is easily absorbed and utilized by the human body.

Glucuronidation

QUE glucuronides can be isolated from plants such as Uncarina through conventional techniques, including organic solvent extraction, chromatographic separation, and spectroscopic identification. Hydroxyl groups on QUE molecules undergo chemical reactions with glucuronic acid molecules, resulting in the formation of QUE glucuronides. This esterification process involves the binding of QUE to glucuronic acid, leading to the formation of QUE glucuronide. Glucuronidation increases the solubility and water-solubility of QUE, facilitating its excretion and metabolism[34] (Figure 2).

Sulfonation and glucuronidation have been shown to reduce the ability of QUE to induce cell cycle arrest in tumor cells to a certain extent.[14] Previous studies have revealed that the metabolites Q3S and Q3G, similar to the parent compound QUE, exhibit significant antiproliferative and cytotoxic effects on MCF-7 breast cancer cells, with a dose-dependent relationship and potency in the order of QUE > Q3S > Q3G.[35] Therefore, it can be concluded that sulfonation and glucuronidation of QUE can attenuate its inherent anticancer effects.

QUE -Cyclodextrin Inclusion Complexes

To address the issue of low bioavailability of QUE, researchers have employed various strategies in recent years to enhance its solubility. For example, using cyclodextrins as carriers to form inclusion complexes has been shown to significantly improve the water solubility of QUE. Studies indicate that the inclusion complex formed between quercetin and β-cyclodextrin can increase its solubility up to 20 times the original level.[36] Additionally, nanotechnology, such as nano-emulsions and nanoparticles, has also been widely applied to enhance the solubility and bioavailability of QUE.[37,38]

Properties and Classification of Cyclodextrins

Cyclodextrins are a class of cyclic oligosaccharides formed by glucose units linked by α-1,4-glycosidic bonds. Due to their unique molecular structure and properties, they have been widely used in drug delivery, the food industry, and biomedicine. Based on the number of glucose units in the cyclic structure, cyclodextrins can be classified into α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin. These different types of cyclodextrins exhibit significant differences in

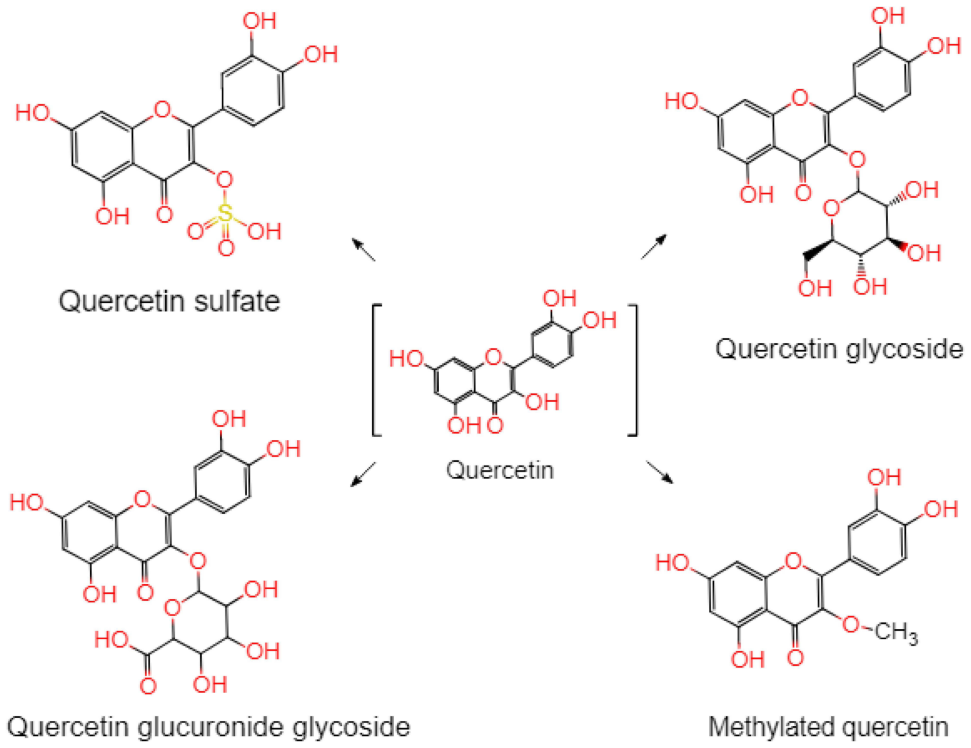

Figure 2 Common Structural Modifications of QUE.

physicochemical properties, inclusion capacity, and biocompatibility, allowing them to play their respective advantages in various application scenarios.

α-Cyclodextrin

α-Cyclodextrin (α-CD) consists of six glucose units, with a molecular weight of approximately 972 daltons. The exterior of α-cyclodextrin is hydrophilic, while the interior is hydrophobic, allowing it to encapsulate small molecular compounds such as drug molecules and fragrances. Research shows that α-CD exhibits good biocompatibility and biodegradability in drug delivery systems, effectively enhancing the solubility and stability of drugs. For example, the inclusion complex formed between α-CD and certain drugs can significantly improve the bioavailability of the drugs, thereby enhancing their therapeutic effects.[39] Additionally, α-CD has important application value in the food industry, as it can improve the taste of food and extend shelf life, while also serving as a carrier for nutritional components to help enhance the nutritional value of food. Studies have found that α-CD can effectively encapsulate fat-soluble vitamins, thereby increasing their solubility and bioavailability in aqueous phases.

β-CD

β-Cyclodextrin (β-CD) consists of seven glucose units, with a molecular weight of approximately 1135 daltons. β-CD is the most widely used type of cyclodextrin, known for its strong inclusion capacity, allowing it to encapsulate various drug molecules and bioactive components. Due to its larger cavity, β-CD can effectively encapsulate compounds with larger molecular weights, enhancing their solubility and stability. Studies indicate that the inclusion complex formed between β-CD and drugs can significantly improve the solubility and bioavailability of the drugs, thereby enhancing their pharmacological effects.[40] In the field of biomedicine, β-CD is widely used in the preparation of drug carriers and nano drug delivery systems. For instance, the complex formed between β-CD and anticancer drugs can improve the distribution and targeting of the drugs in the body, thereby enhancing the antitumor effects.[36] Additionally, β-CD is also used to improve the sensory characteristics of food and extend shelf life, showing good application prospects.[41]

γ- CD

γ-Cyclodextrin (γ-CD) consists of eight glucose units, with a molecular weight of approximately 1290 daltons. The larger cavity of γ-CD allows it to encapsulate larger molecular compounds, thus holding great potential for applications in drug delivery and biomedicine. Research has shown that γ-CD can effectively encapsulate various bioactive components, improving their solubility and stability, thereby enhancing their biological activity. In the food industry, γ-CD is used as a food additive to improve the taste and flavor of food while extending shelf life.[42] Its good biocompatibility and low toxicity make γ-CD promising for applications in both food and pharmaceuticals.[43] Furthermore, γ-CD also shows good application potential in the preparation of functional foods and health products, effectively enhancing the bioavailability and stability of nutritional components.[44]

Formation of QUE Inclusion Complexes with Different Types of Cyclodextrins

QUE is a natural flavonoid widely found in plants, gaining significant attention due to its good biological activity. However, the low solubility of QUE in water limits its effectiveness in drug development and clinical applications. Cyclodextrins, as a class of carbohydrate compounds with unique molecular structures, can form inclusion complexes, significantly enhancing the solubility and bioavailability of QUE. The following sections will explore the interactions between QUE and different types of cyclodextrins and the formation of their inclusion complexes.

Interaction with α-CD

α-CD is a cyclic oligosaccharide composed of six glucose units, with a smaller cavity suitable for encapsulating small molecules. Studies have shown that the inclusion complex formed between quercetin and α-CD is stable, primarily relying on hydrogen bonding and hydrophobic interactions. The interaction between the phenyl ring of quercetin and the cavity of α-CD allows quercetin to effectively embed into the structure of α-CD, thereby improving its solubility and stability.[39] In one study, through nuclear magnetic resonance (NMR) and molecular dynamics simulations, researchers found that the binding energy between quercetin and α-CD was high, indicating good inclusion capacity. This inclusion not only improved the water solubility of quercetin but also enhanced its bioavailability, thereby increasing its efficacy in the body.[40] Additionally, the QUE-α-CD inclusion complex demonstrated better antioxidant activity and cell protection in in vitro experiments, indicating its potential application value in drug delivery systems.

Interaction with β-CD

β-Cyclodextrin (β-CD) consists of seven glucose units and has a relatively larger cavity suitable for encapsulating larger molecules. The inclusion reaction between quercetin and β-CD is achieved through both physical adsorption and chemical bonding. Studies indicate that the inclusion complex formed between quercetin and β-CD significantly improves both solubility and bioavailability, especially showing superiority in drug delivery and targeted therapy.[45] In one study, the QUE-β-CD inclusion complex was characterized using high-performance liquid chromatography (HPLC) and Fourier-transform infrared spectroscopy (FT-IR), with results showing that the formation of the complex significantly increased the solubility of quercetin and exhibited good stability under different pH conditions.[41] Furthermore, the quercetin-β-CD inclusion complex demonstrated enhanced anticancer activity in cell experiments, suggesting its potential application in cancer treatment.

Interaction with γ-CD

γ-CD consists of eight glucose units, with a larger cavity suitable for encapsulating more complex molecules. The inclusion reaction between quercetin and γ-CD also exhibits good inclusion capacity. Research shows that the inclusion complex formed between quercetin and γ-CD has higher solubility and bioavailability in water, with significantly enhanced antioxidant activity.[46] In one study, the formation of the quercetin-γ-CD inclusion complex was confirmed through X-ray diffraction (XRD) and thermogravimetric analysis (TGA), with results indicating that the thermal stability and structural integrity of the complex were significantly improved.[42] Additionally, the quercetin-γ-CD inclusion complex demonstrated excellent cytotoxicity and antitumor effects in in vitro experiments, indicating its potential application prospects in cancer treatment.[43]

Pharmacokinetics of QUE-Cyclodextrin Inclusion Complexes

QUE-cyclodextrin inclusion complexes also exhibit advantages in pharmacokinetics. Compared to free QUE, the inclusion complexes have a faster absorption rate in the body and higher peak blood concentrations, indicating a significant improvement in their bioavailability. This phenomenon may be related to the structural characteristics of cyclodextrins, which allow for better penetration of cell membranes, facilitating the absorption of QUE.[47]

It is noteworthy that cyclodextrin inclusion complexes can extend the half-life of QUE in the body, thereby enhancing its therapeutic effects. An increasing number of clinical trials are beginning to focus on the use of QUE -cyclodextrin inclusion complexes. For example, clinical studies targeting breast cancer patients have shown that QUE -cyclodextrin inclusion complexes can significantly improve patients' quality of life and reduce side effects caused by chemotherapy.[48]

However, there are still some controversies and differing viewpoints. For instance, some studies indicate that the stability and biocompatibility of the inclusion complexes may vary under different environmental conditions, posing challenges to the reliability of their clinical applications. Therefore, balancing the viewpoints from different studies, especially regarding the actual application effects and mechanisms of the inclusion complexes, has become an important task for future research.

Nanoparticle Structures of QUE and Their Therapeutic Applications

The combination of QUE with nanomaterials forms QUE–nanoparticle composites, which can enhance the solubility and stability of QUE. Additionally, functionalized nano-carriers can achieve controlled release and targeted delivery of QUE, increasing its drug concentration in tumor tissues and reducing toxic side effects on normal tissues.[49]

Metal–QUE Complexes

QUE has the ability to bind with metal ions, particularly transition metal ions such as iron and copper. These complexes may facilitate the formation of ROS through involvement in oxidation–reduction reactions. Previous research has shown that QUE-conjugated gold nanoparticles (AuNPs-Qu-5), when applied to MCF-7 and MDA-MB-231 cells, exhibit a reduction in cancer cell EMT, migration, invasion, and angiogenesis capabilities.[50] Furthermore, they strongly inhibit the PI3K/AKT pathway, which may be associated with decreased EGFR activity.[51] Additionally, AuNPs-Qu-5 promote the repair and regeneration of mammary gland-like epithelial structures.[52]

Nanomaterials formed by the combination of metal oxide zinc oxide (ZnO) with QUE, known as ZnO@Quercetin, possess a larger surface area and stronger electrochemical properties, which are key features for the generation of ROS. In vitro experiments have confirmed that ZnO@Quercetin effectively induces apoptosis in human ovarian cancer cells by generating ROS and permeating mitochondrial membranes.[53]

QUE-Loaded Nanoparticles

QUE's solubility and stability can be enhanced through encapsulation in nanoparticles. Nanoparticles facilitate the passive accumulation of drugs at tumor sites, thereby enhancing drug penetration and retention through the enhanced permeability and retention (EPR) effect.[54–56] Additionally, the larger surface area of nanoparticles enables high drug payloads and selective control of drug concentration and distribution within the tumor.[57,58] Furthermore, their surface properties can be chemically modified to achieve active drug targeting.[58]

Nanoparticle-based drug delivery systems offer improved safety, cost-effectiveness, fewer side effects, and the ability to provide stronger activity with lower doses.[59] Examples of such nanoparticles include polyethylene glycol nanoparticles, polymer nanoparticles, zinc oxide nanoparticles, and poly (lactic-co-glycolic acid) (PLGA) nanoparticles. It has been shown that QUE encapsulated in polymer nanoparticles exhibits enhanced stability, activity, and higher bioavailability.[60,61] Previous research has confirmed that nanoparticle-based drug delivery systems effectively increase cellular uptake of drugs, thereby enhancing therapeutic effects and reducing toxicity.[62,63]

QUE Liposomes

Liposomes are composed of phospholipids and cholesterol, forming a bilayer membrane structure that can encapsulate QUE for targeted delivery and release, thereby increasing its solubility and bioavailability. QUE embedded in solid lipid nanoparticles increases the stability of the complex in the bloodstream and possesses high drug-loading capacity.[64] In vitro experiments have demonstrated that polyethylene glycol liposomes loaded with QUE can induce apoptosis and cell cycle arrest in ovarian cancer cells sensitive or resistant to platinum compounds, showing significant inhibitory effects compared with free QUE.[65]

QUE Nano-Micelles

Nano-micelles are self-assembled structures that can encapsulate QUE, thereby enhancing its solubility and stability. They can also achieve targeted drug delivery by modulating their surface properties and incorporating targeting ligands.[15] In vivo experiments have shown that HA-QU polymer micelles can downregulate the expression of p-gp in liver cancer cells, thereby reducing multidrug resistance. Additionally, they can target PTX-loaded micelles to liver cancer cells and enhance their antitumor effects.[66]

QUE nanocarriers can be synthesized using various preparation methods and have the potential to improve drug performance and enhance drug effects (Table 1). However, further research, evaluation, and clinical trials are required before the clinical application of these nanocarriers to ensure their safety, efficacy, and stability. Furthermore, nanocarrier technology is still in a stage of continuous development and exploration, and there may be emerging novel nanocarriers for QUE in the future.

Overview of Articles on QUE in Cancer Therapy

Using bibliometric analysis,[67] we summarized QUE in cancer therapy literature from the Web of Science (WoS) Core Collection over the last decade. The search strategy was as follows: TS= (Quercetin OR Quercetin Nano-Derivatives) AND TS= (cancer OR tumor OR malignancy OR carcinoma OR neoplasm). A total of 4066 articles on QUE and Nano-Derivatives in cancers were retrieved on November 23, 2024 (excluding reviews and irrelevant article).

Table 1 The Comparative of Physicochemical Properties and Applications of Various QUE Nanomaterials

QUE Nanomaterials	Physicochemical Properties	Advantages	Disadvantages
Metal-QUE Complexes	Formation of complexes with metal ions effectively generates ROS	This reduces the transformation, migration, invasion, and angiogenesis capabilities of cancer cells and promotes the repair and regeneration of mammary gland-like epithelial structures.	The preparation process is complex and there may be potential toxicity associated with metal ions.
QUE-loaded Nanoparticles	Enhancing the solubility and stability of QUE enables passive accumulation of the drug and allows for selective drug release and targeted delivery.	This approach improves drug permeability and retention and has a large drug loading capacity.	The preparation process is complex and the release rate may be slow.
QUE Liposomes	Forming a bilayer liposome structure enhances the solubility and bioavailability of QUE and enables controlled drug release and targeted delivery.	This approach allows for targeted drug delivery, improves the bioavailability of QUE, and increases the stability of the complex.	The preparation process is complex and there may be stability issues.
QUE Nano-Micelles	Self-assembled structures enhance the solubility and stability of QUE and enable controlled drug release and targeted delivery.	This approach allows for targeted drug delivery and precise control of drug release.	The preparation process is complex and there may be issues with drug stability.

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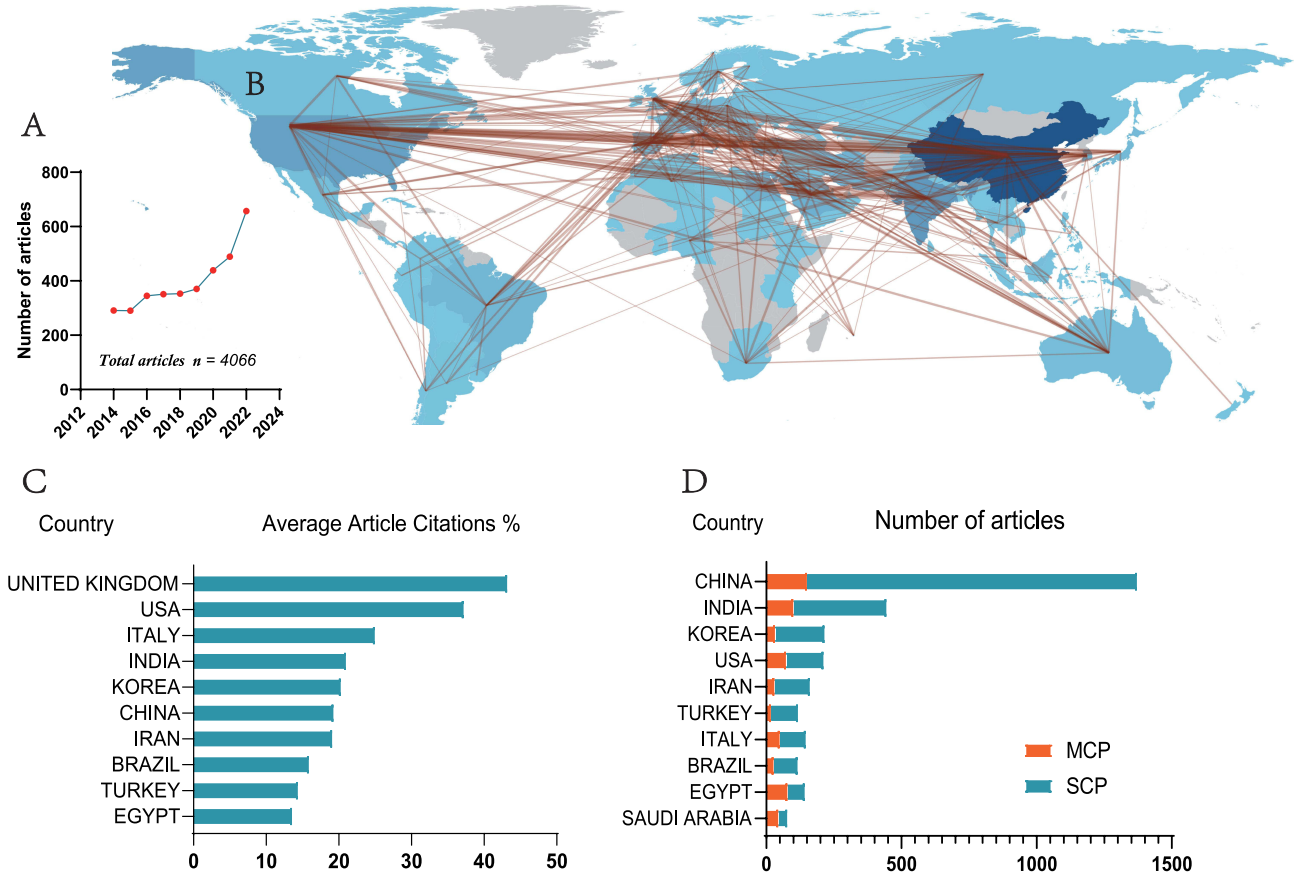

Figure 3 Global trends in publications on the application of QUE in cancer therapy over the last decade: (**A**) the annual publications over the past decade; (**B**) world map showing collaboration between different countries in this field; (**C**) top 10 countries with the highest total number of citations of related articles; (**D**) top 10 countries with the highest number of articles. The figures were plotted automatically using the bibliometrix package in R version 4.3.2 based on the retrieved articles.
Abbreviations: SCP, Single-country publications; MCP, Multi-country publications.

The number of published articles has increased year by year, with annual growth rate of 33.64% (Figure 3A). World collaborations between the USA and China were the most frequent, followed by those between Saudi Arabia and Egypt (Figure 3B). Studies from the United Kingdom had the highest number of citations, followed by those from USA (Figure 3C). China contributed the most articles and single-country publications (SCP; Figure 3D), and exhibited the highest multiple-country publications (MCP; Figure 3D).

The global increase in QUE-related articles indicates its crucial biological significance. Reviewing the 10 most cited articles (Table 2), we found that QUE has a broad impact on various aspects of tumor biology, including apoptosis and autophagy,[68–74] tumor microenvironment,[75] and tumor metastasis and migration.[52,76] Among the retrieved articles, the five words that appeared most frequently in Keywords Plus were “quercetin”, “apoptosis”, “cancer”, “expression”, and “flavonoids” (Figure 4A). The thematic map in Figure 4B shows that QUE (1849 occurrences), apoptosis (1083 occurrences), cancer (1006 occurrences), flavonoids (931 occurrences) and expression (917 occurrences) were the most popular research topics. We analyzed the main effects and interactions of various factors, and observed that these thematic words were concentrated in studies on lung and breast cancer, anti-apoptosis, and research at the cellular level in vitro. We will discuss the research progress of QUE in cancer from these aspects (Figure 4C and D).

Table 2 Top 10 Articles with the Highest Citations of QUE and Nano-Derivatives Articles

Rank	Title	First Authors, years	Source	Normalized Total Citations
1	Identification of a novel senolytic agent, navitoclax, targeting the Bcl-2 family of anti-apoptotic factors	SOOBRATTEE MA, 2005	AGING CELL	17.99
2	A combination of quercetin and resveratrol reduces obesity in high-fat diet-fed rats by modulation of gut microbiota	SRIVASTAVA S, 2016	FOOD FUNCT	10.41
3	Phenolics as potential antioxidant therapeutic agents: mechanism and actions	HASHEMZAEI M, 2017	MUTAT RES-FUND MOL M	9.95
4	Quercetin, a Natural Flavonoid Interacts with DNA, Arrests Cell Cycle and Causes Tumor Regression by Activating Mitochondrial Pathway of Apoptosis	LI HL, 2009	SCI REP-UK	9.17
5	Anticancer and apoptosis-inducing effects of quercetin in vitro and in vivo	PAPADOPOULOU A, 2005	ONCOL REP	8.72
6	Enhancement of gastrointestinal absorption of quercetin by solid lipid nanoparticles	MARTINEZ-OUTSCHOORN UE, 2010	J CONTROL RELEASE	8.05
7	Interaction of flavonoids with bovine serum albumin: a fluorescence quenching study	WANG K, 2011	J AGR FOOD CHEM	7.95
8	Oxidative stress in cancer associated fibroblasts drives tumor-stroma co-evolution: A new paradigm for understanding tumor metabolism, the field effect and genomic instability in cancer cells	TANIGAWA S, 2007	CELL CYCLE	6.57
9	Quercetin induces protective autophagy in gastric cancer cells: involvement of Akt-mTOR- and hypoxia-induced factor 1α-mediated signaling	SOOBRATTEE MA, 2005	AUTOPHAGY	6.22
10	Action of Nrf2 and Keap1 in ARE-mediated NQO1 expression by quercetin	SRIVASTAVA S, 2016	FREE RADICAL BIO MED	6.05

The Mechanisms of Action of QUE in Cancer Therapy

Apoptosis and Autophagy

Oxidative Stress

QUE induces production of reactive oxygen species (ROS) in tumor cells through various mechanisms. In general, the antioxidative activity of QUE is thought to be substantially due to its catechol moiety.[77] It activates NADPH oxidase (NOX), leading to ROS generation. QUE-3′-sulfate and QUE-3-glucuronide inhibits antioxidases such as superoxide dismutase (SOD), thereby increasing ROS accumulation and promoting tumor cell death.[14] Furthermore, QUE glucuronides disrupts the mitochondrial respiratory chain, leading to increased ROS production.[78] QUE Nanoparticles also acts as a radical scavenger, reducing ROS accumulation and preserving normal mitochondrial function.[79,80]

Mitochondrial-Mediated Signaling Pathway

The mitochondrial-mediated pathway is one of the primary mechanisms through which QUE induces apoptosis in tumor cells.[30,81,82] 3′-Methoxy QUE induces apoptosis in tumor cells through the upregulation of proapoptotic proteins (Bax and Bad) and downregulation of antiapoptotic proteins (Bcl-2 and Bcl-xL).[83,84] This leads to increased mitochondrial membrane permeability, release of cytochromec, and activation of caspase family proteins, initiating cell death.[85] Apoptosis induced by QUE occurs through both intrinsic mitochondrial pathways and caspase-dependent pathways.[86] QUE also activates proapoptotic molecules such as caspase-3 and caspase-9, and down-regulates antiapoptotic molecules.[87–89] It induces DNA damage in mitochondrial genome, triggering ROS production and enhancing oxidative stress.[90,91] Moreover, QUE inhibits signaling pathways related to mitochondria, suppressing tumor-cell proliferation and invasion. QUE also disrupts protein folding and maintenance functions, inducing apoptosis in tumor cells.[92,93] It effectively binds to pyruvate dehydrogenase kinase 3 (PDK3), inhibiting its kinase

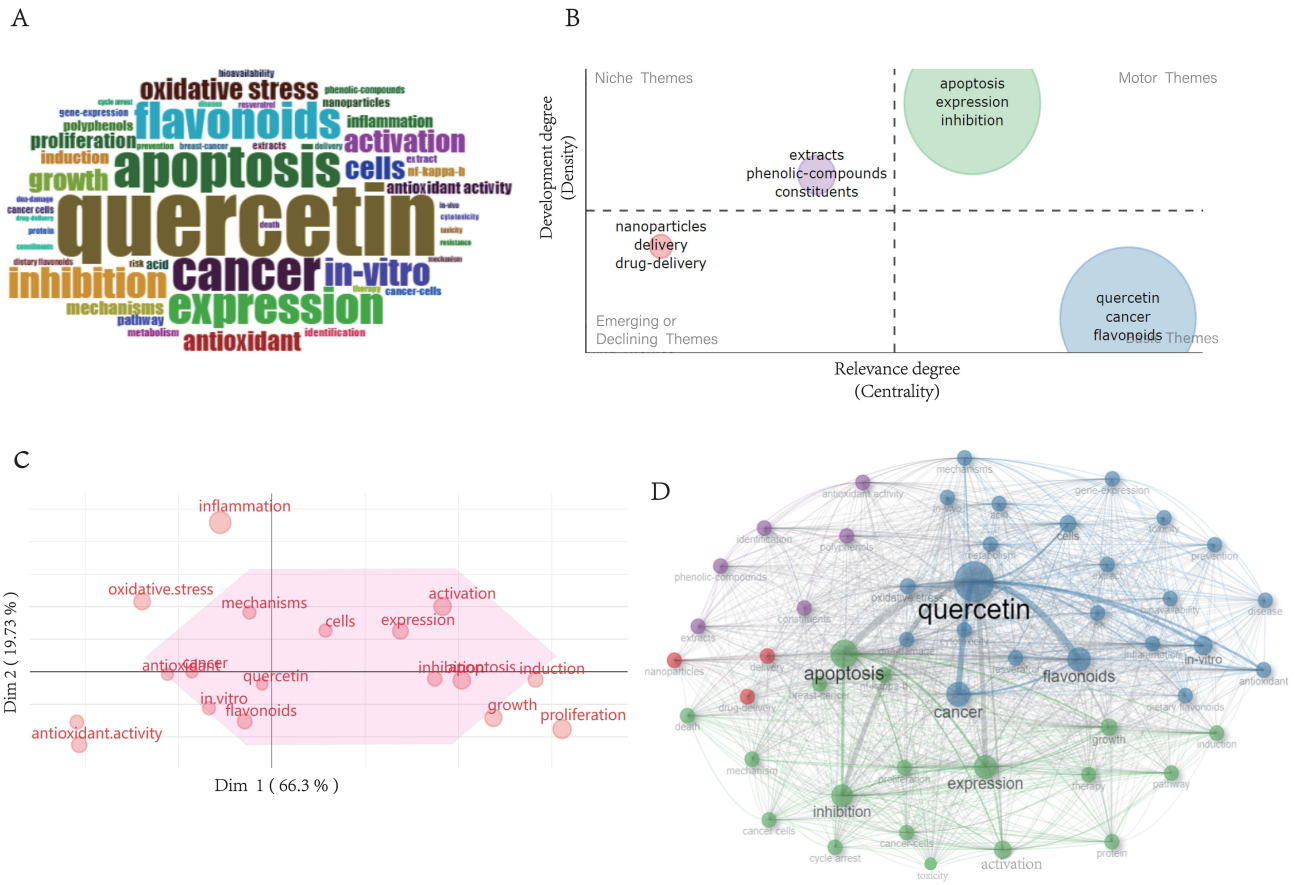

Figure 4 Keywords and topics analysis of articles about QUE and Nano-Derivatives: (**A**) WordCloud showed the top 50 most frequent words. The frequency of keywords determined the font type; (**B**) Thematic map plotted by the authors keywords; (**C**) Cause analysis chart drawn by title keywords, where the proximity of keywords to the centre represents the popularity of the research area, and keywords around the centre are highly focused on by the research community; (**D**) Contribution network chart of title keywords, where the contribution degree of keywords determines the font type. The figures were plotted automatically using the bibliometrix package in R version 4.3.2 based on the retrieved articles.

activity and eradicating tumor cells.[94] At high doses, QUE can induce apoptosis in various cancer cells via death domain pathways.[95]

MAPK Signaling Pathway

The mitogen-activated protein kinase (MAPK) pathway is a well-known extracellular signal–regulated pathway. QUE inhibits the MAPK pathway, reducing cell proliferation and inducing apoptosis.[96,97] This pathway plays a role in promoting cell proliferation through the phosphorylation of mTORC1, ULK1, and autophagy-related proteins. Inhibition of the MAPK pathway by QUE-loaded nanoparticles leads to reduced cell proliferation and transcriptional activity, ultimately inducing apoptosis.[98]

PI3K/AKT Signaling Pathway

QUE inhibits the PI3K/AKT pathway, promoting apoptosis and reducing cancer-cell proliferation and invasion, such as Pentahydroxyflavone dihydrate-quercetin.[99–102] It also acts on the TLR4–MyD88–PI3K complex, suppressing downstream signaling pathways and inhibiting the expression of inflammatory factors and apoptosis inhibitory proteins.[103] By directly binding to tubulin, QUE causes cell cycle arrest.[104] It also promotes tumor-cell death and increases chemosensitivity through the RAGE/PI3K/AKT/mTOR signaling axis.[100]

The Regulatory Effect on the Immune System

QUE regulates immune cells, promoting extracellular signal–regulated kinase 2 (Erk2) and mitogen-activated protein (MAP) kinases in PBMCs and T lymphocytes.[2] It blocks the tyrosine phosphorylation of JAK2, TYK2, STAT3, and

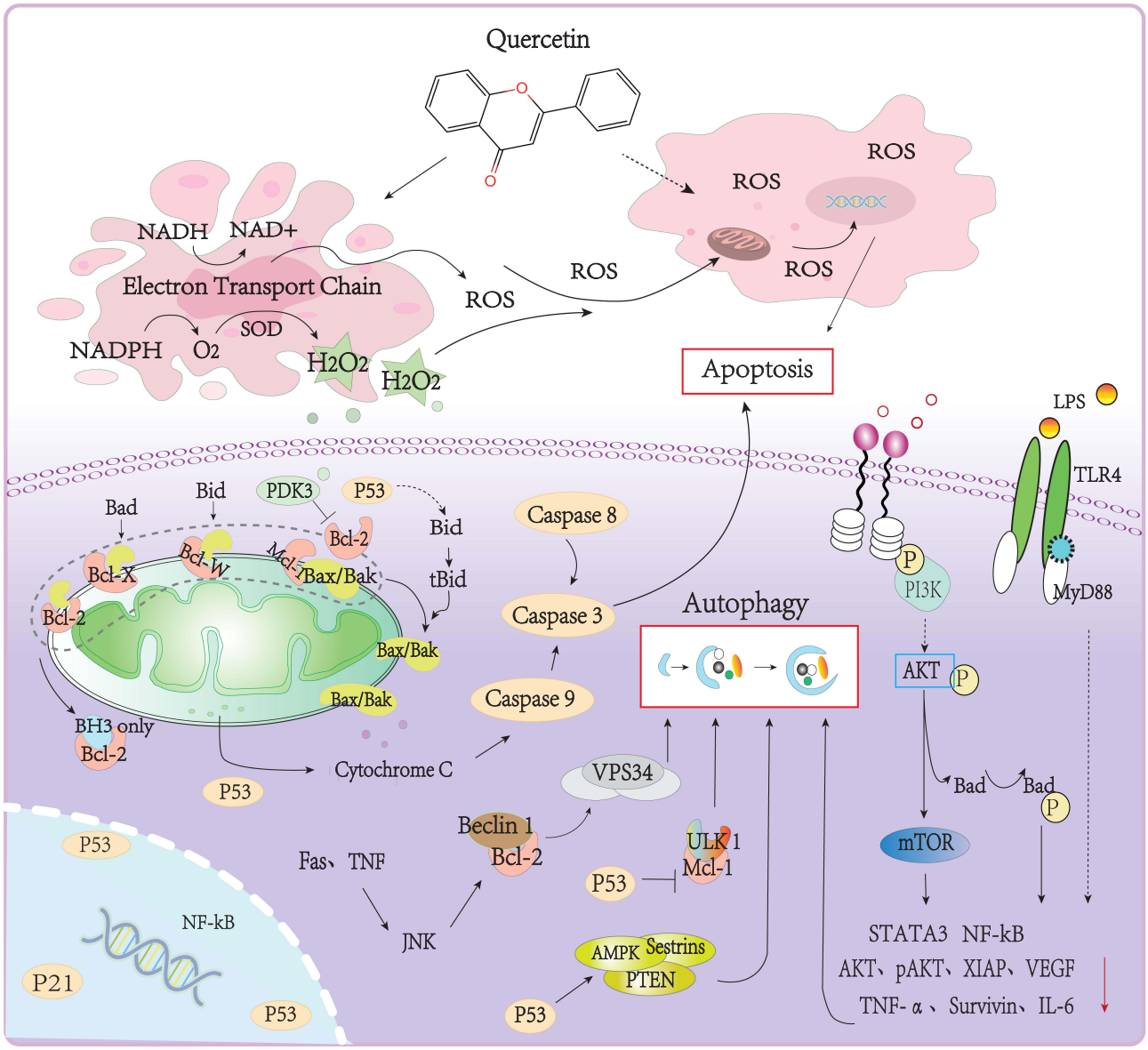

Figure 5 QUE regulates tumor apoptosis and autophagy.

STAT4 induced by IL-12, reducing T-cell proliferation and Th1 differentiation.[105] QUE enhances the immune system's ability to kill tumor cells by regulating cell signaling pathways and protein expression, such as PD-L1 and interferon-γ. It also synergizes with recombinant human tumor necrosis factor–related apoptosis-inducing ligand (rhTRAIL), enhancing its proapoptotic action.[106] QUE glycosides influencing the immune system and inflammatory responses by acting on leukocytes and targeting intracellular kinases and phosphatases.[107] Figure 5

Tumor Metastasis and Migration

Blocking the Cell Cycle Progression

G1/S Phase

QUE inhibits G1-phase cyclin-dependent kinases (CDKs), specifically CDK4 and CDK6, leading to G1/S cell-cycle arrest. It also downregulates cyclin D1/CDK4 and E/CDK2 and upregulates p21, inducing G1 cell-cycle arrest. Moreover, QUE induces DNA damage, inhibiting DNA synthesis and arresting cells in the S phase.[14,108]

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G2/M Phase

QUE glucuronides interferes with M-phase CDKs (CDK1 and Cyclin B1), upregulates kinase inhibitors (p21, p27, and p53), and prevents cells from entering mitosis.[108,109] It also decreases the levels of survivin protein, causing growth arrest in the G2/M phase.[110–112] Significant growth inhibition of G2/M-phase tumor cells is observed at a concentration of 7 μg/mL, with an IC_{50} determined for cancer cells.[1,113] QUE also blocks the progression of the G2/M phase in prostate cancer cells.[84]

Inhibition of Extracellular Matrix Degradation

The overexpression of proteolytic enzymes such as matrix metalloproteinases (MMPs) and urokinase-type plasminogen activator (uPA) are associated with tumor tissue remodeling and metastasis. Dual docetaxel/QUE-loaded nanoparticles inhibit the production and release of MMPs in tumor cells, such as MMP-2 and MMP-9.[98] By inhibiting these proteases, QUE reduces degradation of the surrounding matrix, thereby weakening migration and invasion abilities of tumor cells.[114]

Regulation of Epithelial–Mesenchymal Transition (EMT)

EMT promotes tumor progression by enhancing the invasive capabilities of epithelial-derived tumors.[115] It involves a reduction in epithelial markers (E-cadherin and ZO-1) and an increase in mesenchymal markers (α-SMA and vimentin).[116] Transforming growth factor-β1 (TGF-β1) upregulates mesenchymal marker transcription factors and downregulates E-cadherin transcription.[117] Additionally, EMT can contribute to chemo-resistance, reducing sensitivity to epidermal growth factor receptor (EGFR) inhibitors.[118,119]

QUE regulates the expression of transcription factors, such as the Snail superfamily and Twist, to inhibit tumor-cell migration and invasion.[120] It also inhibits the increase of p-Smad2, associated with methotrexate-induced EMT, and has antiproliferative effects in various cancer types.[114,121] In prostate cancer, QUE downregulates TGF-β–induced vimentin and N-cadherin, promotes E-cadherin expression, and regulates Wnt signaling to target EMT.[84] In lung cancer, QUE inhibits metastasis through modulation of the Akt/MAPK/β-catenin signaling pathway and inhibits β-catenin nuclear translocation.[122] In nasopharyngeal carcinoma, QUE activates the Hippo pathway by suppressing Yes-associated protein (YAP) expression, thereby suppressing EMT.[123] In pancreatic cancer, QUE reduces TGF-β1 levels and regulates SHH and TGF-β/Smad signaling to inhibit EMT.[124–126] In glioblastoma, Schiff base QUE derivatives inhibits the migration and invasion of glioma cells by targeting the GSK3-β/β-catenin/ZEB1 signaling pathway, associated with mesenchymal transition.[127] Receptor-gamma (PPAR-γ) activation by quantum dots can counteract EMT partially, and QUE regulates the TGF-β1–induced EMT pathway by partially activating PPAR-γ.[117]

However, it should be noted that the combination of QUE with the epidermal growth factor receptor (EGFR) inhibitor erlotinib may counteract the antitumor effect of erlotinib.[128]

Inhibition of Angiogenesis

Angiogenesis plays a crucial role in tumor growth and metastasis. Tumor cells produce various growth factors that promote angiogenesis and metastasis, including vascular endothelial growth factor (VEGF), EGFR, fibroblast growth factor receptor (FGFR) and chemokines.[114] QUE inhibits angiogenesis by reducing the production of angiogenic factors such as VEGF, EGFR, FGFR, and chemokines. It inhibits VEGF expression and NF-κB signaling pathway activity in nasopharyngeal carcinoma, exerting antitumor effects.[129] Figure 6

The Efficacy and Safety of QUE in vivo Studies

QUE exerts anti-tumor effects through mechanisms such as antioxidant activity, anti-inflammatory properties, and inhibition of tumor cell proliferation. However, as a polyphenolic compound, QUE is prone to exhibiting non-specific effects. Consequently, in vitro experiments or computer simulations often result in false positive outcomes, rendering the research findings meaningless. We have conducted a statistical and analytical review of in vivo and clinical studies (Table 3). Among these studies, the pharmacokinetics of QUE in animals demonstrated that different administration methods have an impact on the characteristics of QUE metabolites. Gastric tube administration was found to be more effective in enhancing the bioavailability of QUE, whereas free feeding may lead to high binding and methylation of QUE, thereby reducing its antioxidant activity. Furthermore, the metabolic process of QUE is likely to involve multiple enzymes, including glucuronosyltransferase and sulfotransferase, and the activities of these enzymes may vary across

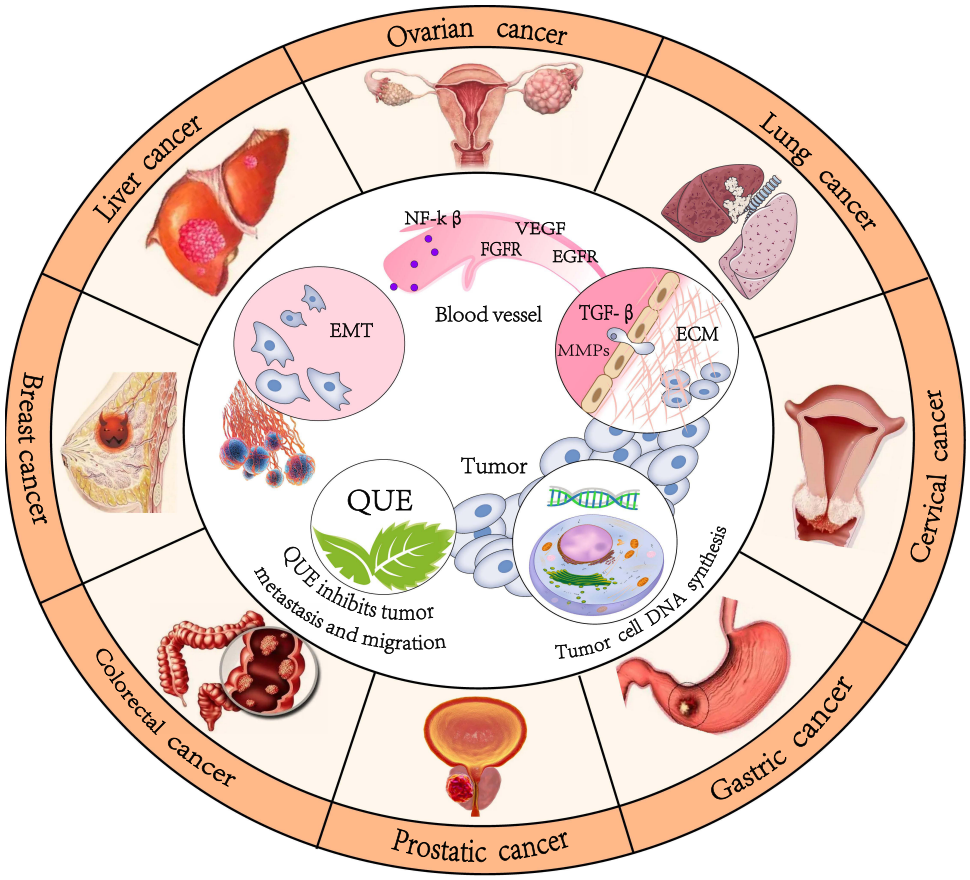

Figure 6 QUE inhibits tumor metastasis and migration.

different tissues.[77] In human studies, it was shown that QUE concentrations significantly increased within 30 minutes of ingestion, indicating significant absorption in the human duodenum and exhibiting two peaks of absorption. However, it is excreted in large quantities within 24 hours, indicating that quercetin has a rapid clearance rate in the blood, a short

Table 3 In Vivo and Clinical Studies of QUE

Rank	Quercetin	Method to Induce Cancer in Selected Models	Control Drug	Route of Administration	Minimum Effective Concentration	Maximum Dose	Tumor size Reduction Rate	Safety	References
1	Que-loaded star nano-carriers	4T1 cell lines (breast cancer mice)	Free QUE	Administered orally	N/A	2000 mg/kg	43%	Good	[131]
2	PBA-ZnO- Que	EAC cells (breast cancer mice)	Free QUE	Intravenously	N/A	33 mg/kg	50%	Good	[132]
3	Self-nanoemulsifying formulation of Que	DMBA breast cancer rats	Free QUE	Administered orally	50 mg/kg	100 mg/kg	60%	Good	[133]
4	Que-loaded nanomicelles	PC-3 cells (Prostate cancer mice)	Physiological saline	Intravenously	200 ng/mL	30 mg/kg	89%	Good	[134]
5	Que-M–hydrogel composites	SKOV-3 cells (ovarian cancer mice)	QUE-M/QUE	Intraperitoneal injection	N/A	50 mg/kg	81%	Good	[135]
6	PLGA-Que Nano-Formulation	DMBA breast cancer Rats	QUE	Intraperitoneal injection	N/A	128 mg/kg	45%	Good	[136]

(*Continued*)

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Table 3 (Continued).

Rank	Quercetin	Method to Induce Cancer in Selected Models	Control Drug	Route of Administration	Minimum Effective Concentration	Maximum Dose	Tumor size Reduction Rate	Safety	References
7	Que-7-rhamnoside	HepG2 cells (liver cancer zebrafish)	N/A	Administered orally	80μg/mL	80μg/mL	N/A	N/A	[137]
8	Que-3-glycoside	Rats	30-methylquercetin	Oral zonde needle	N/A	50 mg/kg	N/A	Good	[77]
9	Que aglycone	Healthy volunteers	Rutin	Administered orally	N/A	93.5mg	N/A	Good	[130]

half-life, and is quickly metabolized in the liver, circulating in the form of methylated, glucuronide, and sulfate metabolites. Therefore, when using quercetin, special attention should be paid to liver and gastrointestinal toxicity. The absorption of QUE was not affected by gender or contraceptives, and the clinical study dosage of QUE was close to the dosage in drug formulations, within the range of 2.6mg-38.3mg daily dietary intake, demonstrating good safety.[130]

The potential for in vivo toxicity has always been a great concern in the development of nanomedicines. To study any potential changes in organ morphology of tumor-bearing mice, we have systematically gathered and analyzed the histopathological characteristics of the heart, liver, spleen, lung, and kidney following treatment across all pertinent articles. These results provide evidence that the QUE nanomedicines in vivo cancer treatment induced no significant side effects in the treated mice. The low in vivo toxicity of QUE nanomedicines further paves the way for their potential clinical application.

Discussion

The rising incidence of cancer worldwide underscores a pressing need for effective therapeutic strategies. Cancer remains one of the leading causes of morbidity and mortality, with complex pathophysiological mechanisms that necessitate innovative approaches for treatment. Among various therapeutic modalities, chemotherapy and radiotherapy have been cornerstones in cancer management; however, they are often associated with significant adverse effects and resistance mechanisms that limit their efficacy. As a result, there is a growing interest in adjunctive therapies that can enhance the effectiveness of these traditional treatments while minimizing their harmful side effects, particularly in solid tumors such as breast and lung cancer, which are prevalent and challenging to treat.

Recent studies have highlighted quercetin, a natural flavonoid, as a promising candidate for enhancing cancer therapy. Quercetin has demonstrated multifaceted mechanisms of action, including modulation of various signaling pathways that can sensitize cancer cells to chemotherapeutic agents and radiotherapy.[16,138,139] Furthermore, it exhibits protective properties for normal tissues, thereby reducing the toxicity associated with conventional treatments. This review encapsulates the latest advancements in understanding the mechanisms underlying quercetin's anticancer effects, its structural optimization through nano-derivatives, and its potential clinical applications as an adjunct therapy in cancer treatment. In recent years, the structural modifications and nanoparticle formulations of QUE have garnered significant attention in the realm of cancer therapy due to their potential to enhance the bioavailability and therapeutic efficacy of this flavonoid. Structural modifications, such as glycosylation, methylation, sulfation, and glucuronidation, play critical roles in altering the pharmacokinetics and pharmacodynamics of QUE. For instance, QUE glycosides, such as quercetin-3-glucoside, exhibit improved solubility and stability, which translates to enhanced bioavailability. Studies suggest that glycosylation increases the absorption of QUE in the intestines, with quercetin-3-glucoside being absorbed more effectively than its aglycone counterpart, thereby promoting its therapeutic efficacy in vivo. Moreover, methylated derivatives of QUE have been shown to inhibit cancer cell migration and invasion, indicating that these modifications can confer enhanced anticancer properties. However, the metabolic processes involved in the conjugation of QUE may reduce its inherent anticancer effects, as seen with sulfated and glucuronidated forms. Therefore, understanding the implications of these structural modifications is essential for optimizing QUE's therapeutic potential in clinical settings.

Nanocarriers have emerged as a transformative approach in improving the delivery and efficacy of QUE in cancer therapy. By encapsulating QUE within various nanoparticle structures, such as metal-QUE complexes, polymer nanoparticles, liposomes, and nano-micelles, researchers have successfully enhanced the solubility, stability, and targeted delivery of QUE to tumor sites. For instance, the combination of QUE with metal nanoparticles, like Zn, has been shown to potentiate its anticancer effects while concurrently reducing the viability of cancer cells. Additionally, polymeric nanoparticles facilitate the passive accumulation of QUE at tumor sites through the enhanced permeability and retention (EPR) effect, thus maximizing therapeutic outcomes while minimizing side effects. The encapsulation of QUE in liposomes has also demonstrated promising results in inducing apoptosis in various cancer cell lines, indicating the potential of this delivery system in overcoming the limitations associated with conventional QUE formulations. Collectively, these advancements underscore the necessity for continued research and development of QUE-based nanocarrier systems, as they hold great promise in addressing the challenges of cancer therapy and enhancing the clinical applicability of QUE.

Despite the promising potential of QUE in cancer therapy, additional research and clinical trials are needed to validate its efficacy and safety in clinical practice. There are various challenges that need to be addressed, such as the stability and targeted delivery of QUE, as well as the evaluation of its long-term effects and safety profile. In addition to enhancing the efficacy of cancer treatment, QUE exhibits protective effects on normal tissues.[140,141] Chemotherapy drugs and radiotherapy can induce cardiotoxicity, pulmonary fibrosis, hepatotoxicity, nephrotoxicity, and bone marrow suppression. QUE has been shown to ameliorate these toxicities through various mechanisms. For example, QUE attenuates chemotherapy-induced cardiotoxicity by inhibiting NF-κB and NLRP3 inflammasome activation, and it improves cardiac energy metabolism through the modulation of the AMPK signaling pathway. Furthermore, QUE can interfere with DNA repair mechanisms, leading to increased sensitivity of tumor cells to radiotherapy.[142] Therefore, QUE nanomedicine assisted cancer radiotherapy and chemotherapy is also the focus of our next research. Continued research and optimization of nanocarrier systems for QUE delivery will contribute to the development of clinically applicable formulations.

Conclusions

QUE and its nano-derivatives represent a promising avenue for enhancing cancer therapy through their multifaceted mechanisms of action. The growing body of literature reflects an increasing recognition of QUE's potential to synergize with conventional treatments while mitigating their toxicity. However, to translate these findings into clinical practice, comprehensive studies are essential to assess the safety, efficacy, and optimal formulations of QUE-based therapies. At present, clinical studies have shown that the maximum dose for the human body is 93.5mg, which is in line with the daily dietary intake range of 2.6–3.83mg and demonstrates good safety Future research directions should prioritize larger, well-controlled clinical trials, alongside investigations into the metabolic pathways and biological activities of QUE nanomedicines under diverse physiological contexts. By addressing these critical gaps, we can better harness the therapeutic benefits of QUE nanomedicines and improve patient outcomes in cancer treatment.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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