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REVIEW

Quercetin: A Natural Ally in Combating Breast Cancer

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Abstract: Breast cancer is one of the most common cancers among women worldwide, exhibiting notably high incidence and mortality rates. Despite its high fatality, a comprehensive study that mechanism and treatment of herbal medicines has not yet been conducted. Quercetin, a natural flavonoid, exhibits multi-targeted therapeutic potential against breast cancer. The aim of this study is to investigate and assess the mechanism and treatment of quercetin in breast cancer. We collected articles published within five years using PubMed, Google Scholar, and Web of Science with "breast cancer" and "quercetin" as keywords. Correspondingly, a total of 272 relevant articles were retrieved. Quercetin exhibits multi-modal therapeutic potential in breast cancer through its ability to orchestrate diverse molecular mechanisms, particularly in TNBC, such as targeting IGF1/IGF1R pathway, PI3K/Akt/mTOR, Wnt/β-catenin, MAPK/ERK cascades, and PTEN promoter demethylation. Critically, quercetin demonstrates synergistic activity with chemotherapy by overcoming drug resistance and reducing toxicity. Its therapeutic efficacy arises from concurrently inducing apoptosis and inhibiting proliferation, migration, invasion and metastasis. This profile positions quercetin as a strategic agent against breast cancer's complex pathophysiology, effectively disrupting breast cancer malignant progression.

Keywords: quercetin, breast cancer, apoptosis, drug carrier, combination therapy

Introduction

Breast cancer, as one of the most common malignant tumors in women, accounts for approximately 2.3 million new cases globally each year, ranking at the forefront of the incidence and mortality spectrum of female cancers.[1] Its development is influenced by a combination of multiple factors, including age, reproductive risks, exposure to exogenous hormones, lifestyle, and histological abnormalities of the breast tissue.[2] Based on the expression patterns of hormone receptors (ER/PR/HER2), breast cancer can be classified into molecular subtypes such as luminal type, HER2 over-expression type, and basal-like type.[3] The basal-like type mainly includes Triple-Negative Breast Cancer (TNBC), which is characterized by strong invasiveness, high rates of metastasis and recurrence, and a significantly worse prognosis compared to other subtypes.[4] TNBC exhibits no responsiveness to HER2-directed therapies, which further restricts the range of treatment options available.[5]

Traditional Chinese medicine (TCM) has demonstrated potential for multitarget regulation in the treatment of breast cancer. Its active components can exert antitumor effects by inhibiting tumor proliferation, inducing apoptosis, and modulating pathways related to metastasis, such as epithelial-mesenchymal transition and angiogenesis.[6] For example, studies have shown that TCM can inhibit the epithelial-mesenchymal transition of renal tubular cells through the NF-κB/Snail signaling pathway.[7] Additionally, TCM has been found to modulate the immune microenvironment and inhibit key oncogenic signaling pathways such as PI3K/Akt and Wnt/β-catenin, which are crucial for tumor progression.[8] Furthermore, TCM can enhance the sensitivity of chemotherapeutic drugs, thereby improving treatment efficacy.[9] This multitarget and synergistic mechanism provides a novel therapeutic strategy for the intervention of breast cancer, especially for hormone receptor-negative or drug-resistant subtypes.[10]

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Quercetin, a representative flavonoid belonging to the class of natural polyphenolic compounds, is well-documented for its broad-spectrum health benefits, including anticancer, anti-inflammatory, antidiabetic, and antiviral effects.[11] Notably, quercetin—a prominent flavonoid—has garnered significant attention for its potential role in inhibiting breast cancer progression through diverse mechanisms,[12] including inducing cancer cell apoptosis, blocking metastasis by suppressing EMT processes and stem-like properties, overcoming drug resistance, targeting critical pathways like EGFR, IGF1R, and HuR protein, and synergizing with therapies through oxidative stress modulation and immune response enhancement.

Quercetin—History and Medicinal Use

Recently, research on plant-derived flavonoid compounds, particularly quercetin, has surged. Quercetin, a representative flavonoid, is abundantly found in common vegetables and fruits (Figure 1). Owing to its diverse biological activities, such as antioxidant, anti-inflammatory, immunoprotective, anti-hypertensive, anti-diabetic, antiviral, antibacterial and neuroprotective properties (Figure 2), quercetin has been widely used as a dietary supplement to treat or prevent a variety of diseases.[13] For antioxidant activity, Xu et al (2019) demonstrated that quercetin and its complexes exhibit significant antioxidant potential suitable for medicinal applications.[14] Regarding anti-inflammatory effects, Lesjak et al (2018) highlighted the antioxidant and anti-inflammatory activities of quercetin and its derivatives.[15] For immunoprotective activity, Saeedi-Boroujeni et al (2021) emphasized the anti-inflammatory potential of quercetin in COVID-19 treatment.[16] For anti-diabetic activity, Hassanien et al (2020) reported the antidiabetic activity of a cobalt–quercetin complex.[17] Regarding antiviral activity, Luo et al (2025) discussed the role of quercetin in reducing neuroinflammation by inhibiting central inflammatory pathways.[18]

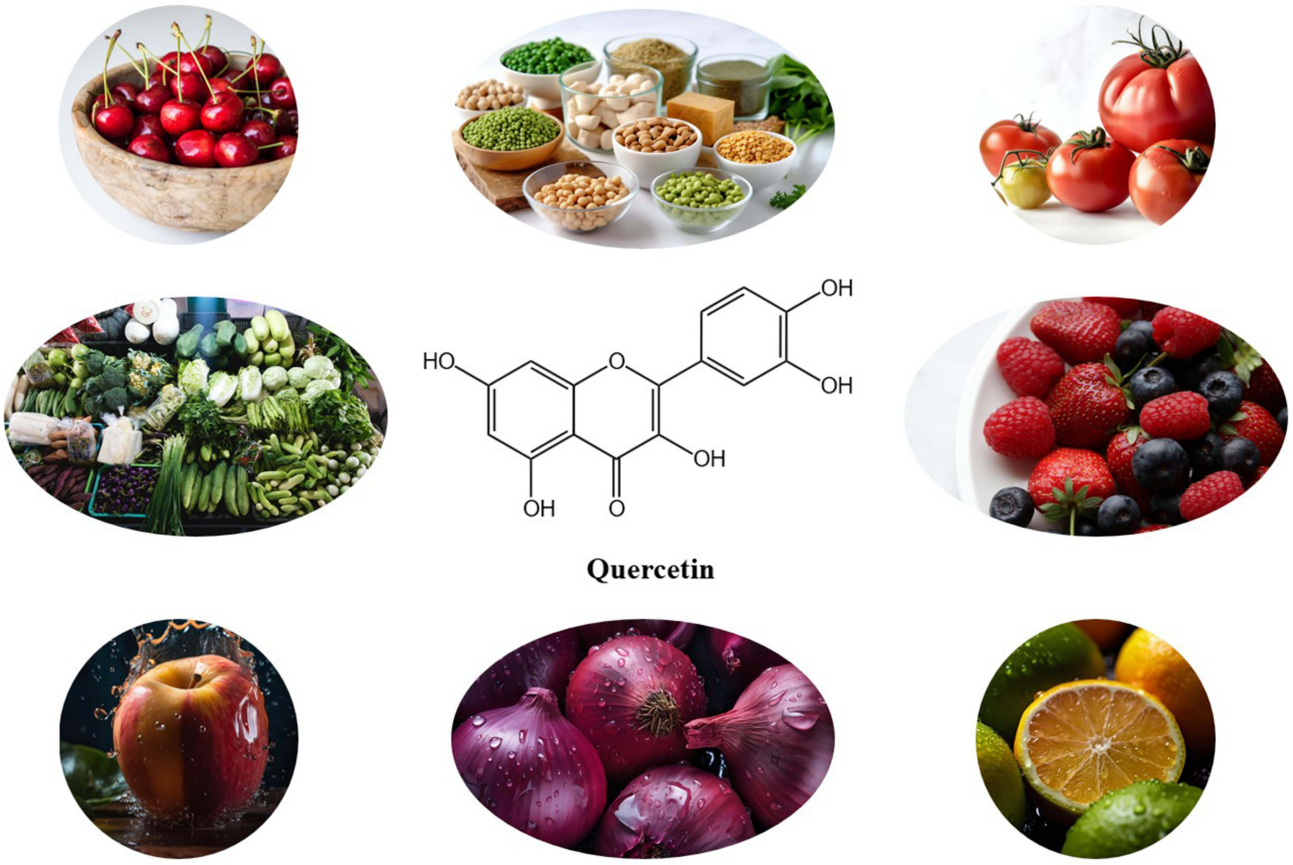

Figure 1 The sources of quercetin, including apples, onions (specifically red onions), citrus fruits (such as oranges, grapefruits, lemons), berries (such as strawberries, blueberries, raspberries), leafy green vegetables (such as spinach, kale, collard greens), legumes (such as lentils, green beans), cherries (especially dark-colored cherries), tomatoes, etc. Image created with BioRender.com,with permission.

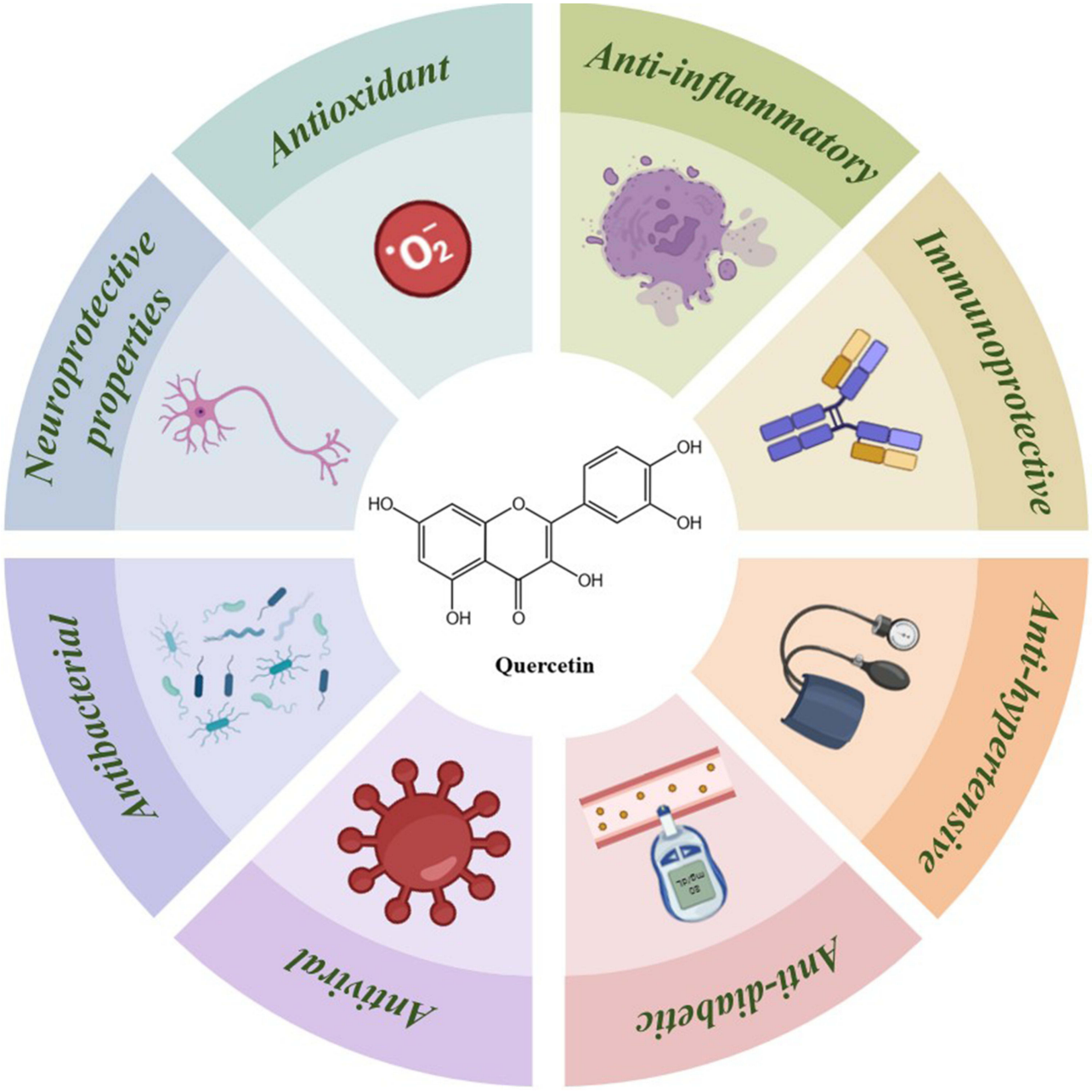

Figure 2 The biological function of quercetin, including antioxidant, anti-inflammatory, immunoprotective, anti-hypertensive, anti-diabetic, antiviral, antibacterial and neuroprotective properties. Image created with BioRender.com,with permission.

Quercetin has demonstrated potential in preventing chronic metabolic disorders like diabetes and non-alcoholic fatty liver disease by regulating glucose homeostasis, reducing oxidative stress, and mitigating insulin resistance.[19] Recent studies also highlight its role in cancer therapy, where quercetin suppresses tumor progression by modulating pathways linked to cell proliferation and apoptosis. Notably, quercetin inhibits CYP3A4 activity, a key enzyme involved in breast cancer advancement, thereby slowing disease progression.[20] Quercetin is capable of upregulating the expression of genes such as AKT1, MAPK1, PGR, SGK1 and PTEN, while downregulating the expression of ESR1 and MAPK3. These genes are expressed in various tissues, with AKT1 and MAPK1 being widely expressed in both normal and cancerous tissues, including breast, prostate, and colorectal tissues. PGR (progesterone receptor) is predominantly found in reproductive tissues such as the uterus and breast. ESR1 (estrogen receptor) is highly expressed in breast and ovarian tissues. SGK1 is expressed in a variety of tissues, including the kidney, lung, and heart. The selective action of quercetin

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against cancer cells, with minimal effects on normal cells, has been documented in several studies. For instance, quercetin has been shown to selectively induce apoptosis in prostate cancer cells by downregulating the expression of heat shock protein 90 (HSP90), a protein that is often overexpressed in cancer cells and is crucial for their survival. Additionally, quercetin's ability to modulate key signaling pathways contributes to its selective anticancer effects. This selective action is further supported by studies demonstrating that quercetin can arrest the cell cycle and induce apoptosis in cancer cells through the mitochondrial pathway, without significantly affecting normal cells.[21] This suggests that quercetin may modulate multiple signaling pathways by targeting key molecules, thereby playing a role in the prevention and treatment of spontaneous abortion (SA). This regulatory effect highlights the potential significance of quercetin in influencing hormonal responses and anti-inflammatory reactions. Several studies have demonstrated that consuming vegetables, fruits, and black tea rich in quercetin can reduce the risk of developing ovarian cancer.[22–28] These studies highlight the potential of quercetin as a therapeutic agent by demonstrating its ability to inhibit these pathways and induce apoptosis in cancer cells. Furthermore, research has indicated that quercetin possesses the ability to curb the progression and spread of cancer by targeting various signaling pathways, as referenced in.[29] This insight holds significant promise for the therapeutic management of a range of cancers, with particular relevance to the treatment of breast cancer.

Despite its bioactive properties, quercetin's clinical use is limited by several factors. Its poor bioavailability, due to low water solubility and extensive metabolism, results in low systemic availability and rapid clearance from the body.[30] Standardized dosing guidelines are lacking, complicating its clinical application.[31] Quercetin can also interact with medications, potentially altering their efficacy and safety.[32] Long-term safety concerns and complex pharmacological actions further limit its use.[33] Future research should focus on improving bioavailability and establishing standardized dosing and safety profiles.

Quercetin's poor water solubility restricts its direct application, leading to the development of solubility-enhanced formulations and derivatives. For example, Quercitrin 2"-O-arabinoside (Yunnan Xili Biotechnology Co., Ltd., product code 7484288) and quercetin-3-β-D-glucoside (Shanghai Aladdin Biochemical Technology, CAS: 482–35-9) are glycosylated derivatives with improved solubility and stability, suitable for pharmaceutical and nutraceutical research. Advanced delivery systems, such as quercetin-loaded glycerohyalurosome hydrogel (QUT-GHE-GEL) and cyclodextrin-based complexes (eg, quercetin/6-O-α-D-maltosyl-β-cyclodextrin inclusion complexes from Xi'an Qiyue Bio), enhance solubility and enable controlled release.[34] Natural extracts, like the Melia azedarach L. leaf extract containing quercetin-3-O-D-glucopyranoside and quercetin-3-O-(2″,6″-digalloyl)-β-D-galactopyranoside, are also utilized for their immunomodulatory effects.[35] These examples demonstrate how structural modifications (eg, glycosylation, esterification) and advanced delivery systems address quercetin's solubility limitations.

Quercetin's intrinsic fluorescence and chromogenic properties can significantly interfere with spectroscopic assays, potentially leading to false-positive signals in anticancer screening due to its nonspecific interactions with proteins. Alva-Ensastegui et al classify quercetin as a PAIN (pan-assay interference compound), characterized by its propensity to disrupt membrane dipole potential and generate assay artifacts through protein binding.[36] Structural modifications such as C-glucosylation have demonstrated efficacy in mitigating these PAIN-related behaviors by reducing membrane interference.[37] These findings underscore the necessity for implementing countermeasures, such as compound derivatization coupled with orthogonal assay validation, during pharmacological evaluations involving quercetin.

The Role of Quercetin in Tumor Chemotherapy

Quercetin, a natural product with multiple biological functions such as anti-inflammation, antioxidation, and anti-cancer, has shown anti-cancer activity against various systemic tumors. Current research indicates that quercetin has demonstrated anti-cancer potential in both in vitro and in vivo studies of various animal models and cell lines, and it selectively targets cancer cells with toxic effects, while sparing normal cells from significant toxicity (Table 1).[38]

Quercetin has been recognized for its potent anticancer capabilities in a spectrum of cancers. It exhibits its tumor-inhibiting effects in breast, colorectal, and liver cancers by modulating the intricate protein networks that are pivotal to the onset and progression of these diseases.[39] In the realm of oncology, quercetin has demonstrated significant therapeutic promise, particularly in the treatment of cancers of the blood, lung, and prostate. This is underscored by its capacity to

Table 1 Characteristics of Studies About the Anticancer Effect of Quercetin

Type of Treatment	Cell (or Animal) Model	Treatment Dose	Target	Effects Observed	Reference
Quercetin	MCF-10A, MCF-10AT, MCF-7 and MDA-MB-231 breast cancer cell lines	5 μM, 20 μM, 80 μM, 120 μM	JAK/STAT1[A] signaling pathway	Que increased the protein levels of IFNγ-R, p-JAK2 and p-STAT1 while decreasing the protein levels of PD-L1[B]	[33]
Quercetin	SPF grade ICR mice	2.5 mg/mL; 1.25mg/mL; 0.25 mg/mL	PI3K-Akt[C], VEGF[D], MAPK and core targets such as AKT1, albumin, caspase-3	Up-regulate AKT1[E], MAPK1[F], PGR[G], SGK1[H] and down-regulate ESR1[I], MAPK3	[34]
Quercetin	Human metastatic ovarian cancer PA-1 cell	50 μM 75 μM	PI3k/Akt, Ras/Raf pathways, EGFR[J] expression	Inhibit PI3k/Akt, Ras/Raf pathways and EGFR expression	[35]
Quercetin	MDA-MB-231 and MCF-7 cell lines	6 doses of 1 mg/kg orally, every third day	PI3K/Akt pathway	Inhibit PI3K/Akt and mitogen-activated protein kinase (MAPK) molecular pathways	[36]
Quercetin	MCF-7 cell lines	_	PTEN[K], PI3K/AKT and JNK pathways	Up-regulating the expression of PTEN, down-regulating the PI3K/AKT and JNK pathways	[37]
Quercetin	MDA-MB-231 and MCF-7 cell lines	_	PTEN, PI3K/Akt, mTOR	Up-regulates PTEN down-regulates PI3K, Akt, and mTOR promoting apoptosis and inhibiting proliferation	[38]
Quercetin	_	3mg/kg (human); 5mg/100g (rat)	Wnt[L], P13K/AKT, MAPK, NF-κB[M]	Inhibiting Wnt/β-catenin, PI3K/AKT/mTOR[N], p-STAT3[O], NF-κB	[39]
Quercetin	_	_	Wnt/β-catenin, PI3K/AKT, MAPK/Erk, JNK,[33] p38, p53, and NF-κB	Regulating signaling transduction pathways like Wnt/β-catenin, PI3K/AKT, MAPK/Erk, JNK and p38, p53, and NF-κB	[40]
Quercetin	MCF-7, HER2-positive SK-BR-3, TNBC MDA-MB-231, MDA-MB-468, BT-20, and Hs 578T	1μM	AMPK[P]	AMPK activation-based energetic stress was associated with the alkalization of intracellular milieu and increased levels of NSUN4.	[41]
Quercetin	_	10 mg/kg, 30 mg/kg, 40 mg/kg, 50 mg/kg	Bax[Q],caspase-3, p21, Akt, PLK-1, cyclin-B1, cyclin-A, CDC-2, CDK-2, Bcl-2	Upregulating Bax, caspase-3, and p21, downregulating Akt, PLK-1[R], cyclin-B1, cyclin-A, CDC-2, CDK-2[S], and Bcl-2	[42]
Quercetin	MCF-7 and MDA-MB-231 cell lines	0 mg/kg; 20 mg/kg; 50 mg/kg	IGF1/IGF1R, EMT[T] transcription (Snail, Slug)	Inhibiting the IGF1/IGF1R signaling pathway, and inhibits the expression of EMT transcription factors Snail and Slug	[43]
Quercetin	The normal human breast epithelial cell line (MCF-10A), human BC cell lines (MDA-MB231 and MCF-7)	0 μM, 10 μM, 20 μM, 40 μM, 80 μM, 160 μM	CDK4/6, circHIAT1/miR19a3[U]p/CADM2 axis[V]	Reverses resistance to CDK4/6 inhibitors by modulating the circHIAT1/miR19a3p/CADM2 axis	[44]
Quercetin	_	80 mg/kg; 40 mg/kg; 2mg/kg;	VEGF, MMPs[W], caspases, and KRAS	Influencing VEGF, MMPs, caspases, and KRAS[X]	[45]
Quercetin	MCF-7 and MDA-231 cell lines	0.1μM, 1μM, 10 μM	TFEB[Y]	Promote the expression of lysosome related gene LAMP1 by up-regulating the expression of TFEB	[46]
Quercetin	ZR-7,5–1MCF-7, T47D, MDA-MB-231 cell lines, MCF10A, MDA-kb2 cell lines	20 mg/kg; 40 mg/kg	CYP3A4[Z], Arachidonic acid	Inhibit CYP3A4 to diminish AA's generation of EETs[AA], preventing the nuclear translocation of p-Stat3[AB]	[47]
Quercetin	EAC (Ehrlich ascites carcinoma cells), MDA-MB-231 and BT-474 BC cell lines	50 mg/kg	VDR	Quercetin can improve hepatitis and fibrosis caused by breast cancer by activating vitamin D receptor (VDR)	[48]
Quercetin	_	_	AR, PSA[AC], Bcl-xL, caspase	Inhibiting AR, PSA; Inhibiting Bax from Bcl-xL and the stimulation of caspase families.	[49]

(*Continued*)

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Table 1 (Continued).

Type of Treatment	Cell (or Animal) Model	Treatment Dose	Target	Effects Observed	Reference
Quercetin	_	10μM, 25μM, 50μM, 80μM, 100μM, 200μM, 500μM, 1000μM	c-Jun, ERK1/2[19], P38, P90RSK,[20] S6, P70S6K[21]	Quercetin increased the phosphorylation of c-Jun N-terminal kinase, ERK1/2, P38, P90RSK proteins Inhibits S6, P70S6K	[50]
Quercetin	MCF-7 cell line	7 μg/mL	Caspases; Bcl-2;	Inhibit apoptosis by inhibiting the action of caspases and Bcl-2	[51]
Quercetin	MDA-MB-231 and MCF-7 cell lines	100 μM	GPR30[AD]	Quercetin interacts with GPR30 to activate EGFR, MAPK and triggers ELK1[AE] leading to c-Fos[AF]	
Quercetin	BALB/c mice (BCRD mice model); 4T1 cell lines, CORT	_	PTGS2[38]	Inhibits neuronal iron death by targeting a lipid metabolisation-related gene, PTGS2	[38]
Quercetin	MCF-7 cell lines	_	MD simulation; MM-GBSA[AG]	Downregulate in Nucleolin	[52]
Quercetin	_	_	PTX[AH]	Inhibit PTX-resistant BC cell proliferation and promote cell apoptosis, and restore the activity of drug-resistant cells against PTX	[53]
Quercetin	MDA-MB-231, MDA-MB-468, and 4T1 TNBC cell lines	_	(β2AR) /ERK1/2	Block the β2 adrenergic receptor (β2AR) /ERK1/2 signaling pathway, inhibit the progression of chronic stress-induced TNBC	[54]
Quercetin	4T1 cell lines	_	ASC, NLRP3[AI], caspase-1	Inhibiting pyroptosis and promoting the immune response	[55]
Quercetin	Breast cancer cell lines MCF-7, T47D, HCC1937, HCC1806, MDA-MB-231, and SKB-R3, BV-2 microglia cells	_	CNS[AJ]	Regulating the CNS and reverse the regulatory relationship between neuroinflammation in the CNS and breast cancer development	[56]
Quercetin	The MDA-MB-468 and MDA-MB-231 cell lines	_	HuR[AK]	Quercetin can inhibit the aggressive phenotype of TNBC by inhibiting HuR	[57]
Quercetin	MCF-7 cell lines	_	CDK2	Quercetin being antioxidant and antiproliferative agent acts by inhibiting CDK2	[58]
Quercetin; Chloroquine	MDA-MB-231 cell lines	10M, 20M, 30M,	Caspase-3, Akt, mTOR, ERK[AL]	Activation of caspase-3, inhibition of Akt, mTOR and ERK phosphorylation	[59]
Quercetin etoposide	MDA-MB-231 BC cell lines and human mammary epithelial cells (HMEC, A10565)	1μM	SASP[AM]	A novel senolytic agent QD3[AN] was described as acting against etoposide-induced senescent breast cancer cells in vitro	[59]
Quercetin microbiome	4T1 mouse model	50/mg/kg/BW 75/mg/kg/BW	PD-1[AO]	Quercetin and cyclophosphamide increased the whole-body frequency of T and NK cells to a greater extent	[60]
Quercetin; Docetaxel	The MDA-MB-231 cell lines	Docetaxel 7 nM + quercetin 95 μM	PI3K/AKT, MAPK/ERK, JAK/STAT3	The combination enhances the anti-cancer effect of MDAMB231 breast cancer cells by inducing apoptosis and regulating the PI3K/AKT, MAPK/ERK, and JAK/STAT3 signaling pathways	[61]
Quercetin; Naringenin	MCF-7 cell lines and MDA-MB-231 cell lines	44.3 μg/mL	Bcl-2 gene; caspase 3/7	CoQN[AP] treatment produced significant cytotoxicity, reduced Bcl-2 gene expression and increased caspase 3/7 activity	[62]
Acetylated quercetin; Methylated quercetin	MCF-7 cell MDA-MB-231 cell lines	60 μM	Caspase-3, cIAP-2[AQ], XIAP[AR]	4AcQ showed significant proliferation inhibition and apoptosis induction, while 4MeQ lost its activity	[62]
Quercetin; Chalcone	MCF-7 and MDA-MB-231, MCF-10A cell lines	10 μM 25 μM 50 μM 75 μM 100 μM 150 μM 300 μM	Caspases-3, caspase-8	The combined action induces cell cycle stagnation in the subG0/G1 phase in MDAMB231 cells and alters the expression of caspases 3, 8	[63]

Quercetin; Doxorubicin	A wild-type MCF-7 cell line	0.1 μM 0.01 μM 0.001 μM 10 μM	SNAI2, PLAU, CSF1[AS]	Quercetin could lead to a reversal of doxorubicin resistance via downregulation of the expression of important genes, such as SNAI2, PLAU and CSF1	[64]
Quercetin; 5-FU	MCF 7 cell lines	_	Bcl2, Bax, p53, caspase-9	Improved apoptosis by increasing the gene expression of Bax and p53 and caspase-9 activity and decreasing the Bcl2 gene expression	[65]
Quercetin; 5-FU	_	_	AKT	Blockade of AKT pathway activity to inhibit a variety of CRC cell lines	[66]
Quercetin; Quercetin derivatives	_	_	EGFR	Quercetin inhibits the ATP-binding site of EGFR	[67]
Quercetin; NaBu	MCF-7 breast cancer cell lines	_	ANXA5, ROS[AT]	The combination of QUE and NaBu inhibited cell proliferation, and reduced levels protein ANXA5, ROS and mRNA protein expression	[68]
Quercetin; SV	The human tumor cell line MCF-7	_	Caspase-9, Bax, Bcl-2, p53, TNF-α, NF-κB	Increased caspase-9, Bax, Bcl-2, and p53 mRNA expression; reduced the activity of TNF-α and NF-κB	[69]
Quercetin;Fisetin	MCF7 and MDA-MB-231 cell lines	_	miR-1275, miR-27a-3p	Combination therapies upregulate of miR-1275 and downregulate miR-27a-3p	[70]
Quercetin; Fisetin	MCF7, MDA-MB-231, BT549, T47D, and 4T1 breast cancer cell lines	_	Matrix metalloproteinase signaling and apoptotic pathways	Inhibit cancer cell proliferation, migration, colony formation, matrix metalloproteinase signaling and apoptotic pathways	[71]
Quercetin; ETO	MDA-MB-231 cell lines	_	Bax/Bcl2 gene	Combination enhances the apoptotic pathway by increasing the Bax/Bcl2 gene ratio, increasing p53 and p21 protein levels, and activating the caspase 3 and 9 enzymes	[72]
Quercetin; Letrozole	MCF-7 breast cancer cell lines	_	ROS	Co-loaded Spanlastics with quercetin and Letrozole showed enhanced cytotoxicity in MCF7 cells	[73]
Quercetin; eEF2K-siRNA	MDA-MB-231, BT-549, 4T1	_	_	Inhibited colony formation, and suppressed cell migration	[74]
Quercetin; Doxorubicin	MCF-7/DOX cells	_	ABCG2 efflux pump[AU], SRC[AV]	Suppressed SRC kinase signaling, leading to decreased PI3K/Akt expression and reduced ABCG2 overexpression in MCF-7/DOX cells	[75]
Quercetin; Taxol; Doxorubicin	MDA-MB 231 MDA-MB 468	12.90, 15.52, 6.9 μM;16.67, 19.16, 5.2 μM	ROS, ER[AW]	Induced ROS generation and ER stress; reduced mammosphere formation and cell migration. Additionally, induced cell cycle arrest, reduced cell proliferation, and induced apoptosis in TNBC cells	[76]
Quercetin	MCF-7	_	p38 /JNK, ERK[AX]	Promote the apoptosis of tumor cells by activating p38 and JNK signal pathways and suppressing ERK signal pathway	[77]
Quercetin-conjugated G4/G3 dendrimer	MCF-7	12.69 mM,4.13 mM; 18.80 mM,5.30 mM	MMP-2/9, VEGF[AY]	Induced apoptosis in more than 74% of MCF-7 cells and 55% of HepG-2 cells, downregulated VEGF gene expression levels	[78]

Notes: All annotations in tables are marked with alphabetical superscripts following this sequence: Begin with single letters A through Z (26 markers). Continue with two-letter combinations in lexicographical order: AA, AB, AC, AY (25 markers). Total markers shown: 51 (A to AY). Corresponding to these markers are listed at the table bottom in exact sequence order. [A]Janus Kinase/Signal Transducer and Activator of Transcription 1. [B]Programmed Death-Ligand 1. [C]Phosphoinositide 3-Kinase (PI3K) and Akt (Protein Kinase B). [D]Vascular Endothelial Growth Factor. [E]v-akt murine thymoma viral oncogene homolog 1. [F]Mitogen-Activated Protein Kinase 1. [G]Progesterone Receptor. [H]Serum and Glucocorticoid-Regulated Kinase 1. [I]Estrogen Receptor 1. [G]Epidermal Growth Factor Receptor. [K]Phosphatase and tensin homolog. [L]Wingless/Integration site. [M]Nuclear Factor kappa-light-chain-enhancer of activated B cells. [N]Mechanistic Target of Rapamycin. [O]Phosphorylated Signal Transducer and Activator of Transcription 3. [P]AMP-activated protein kinase. [Q]BCL2-associated X protein. [R]Polo-like kinase 1. [S]Cell Division Cycle 2, Cyclin-dependent kinase 2. [T]Insulin-like Growth Factor 1/Insulin-like Growth Factor 1 Receptor, Epithelial-Mesenchymal Transition. [U]Circular RNA hippocampus abundant transcript 1 / microRNA-19a-3p. [V]Phosphorylated Cell Adhesion Molecule 2 axis. [W]Matrix Metalloproteinases. [X]Kirsten rat sarcoma viral oncogene homolog. [Y]Transcription Factor EB. [Z]Cytochrome P450 Family 3 Subfamily A Member 4. [AA]Epoxyeicosatrienoic acids. [AB]Phosphorylated Signal Transducer and Activator of Transcription 3. [AC]Androgen Receptor, Prostate-Specific Antigen. [AD]G protein-coupled receptor 30. [AE]Ets-like protein 1. [AF]FBJ murine osteosarcoma viral oncogene homolog. [AG]Molecular Mechanics Poisson-Boltzmann Surface Area. [AH]Paclitaxel. [AI]Apoptosis-associated speck-like protein containing a caspase recruitment domain, NLR family pyrin domain-containing 3. [AJ]Central Nervous System. [AK]Human antigen R. [AL]Extracellular signal-Regulated Kinase. [AM]Senescence-Associated Secretory Phenotype. [AN]Quincy D. Jones III. [AO]Programmed Death-1. [AP]Coenzyme Qn. [AQ]Cellular Inhibitor of Apoptosis Protein 2. [AR]X-linked inhibitor of apoptosis protein. [AS]Snail family transcription factor 2, plasminogen activator, urokinase, and colony stimulating factor 1. [AT]Annexin A5, Reactive Oxygen Species. [AU]A membrane transporter protein that belongs to the ATP-binding cassette (ABC) family and is involved in the efflux of various substrates, including drugs, xenobiotics, and endogenous compounds. [AV]A proto - oncogene encoding a non - receptor tyrosine kinase, involved in cell signaling pathways regulating growth, adhesion, and survival. [AW]Reactive Oxygen Species, Endoplasmic Reticulum. [AX]p38 mitogen - activated protein kinase, c - Jun N - terminal kinase,Extracellular signal - regulated kinase. [AY]Matrix metalloproteinase - 2/9,Vascular endothelial growth factor.

manipulate various molecular factors that regulate key signaling pathways, as demonstrated in both experimental models in vitro and in vivo. Specifically, quercetin has been shown to impact the PI3K/Akt/mTOR, Wnt/β-catenin, and MAPK/ERK1 pathways, which are central to the progression of these malignancies.[40]

In vitro models and in vivo models, quercetin has shown antitumor activity against breast cancer cells, including inhibiting the cell cycle, promoting apoptosis, and reducing tumor volume.[41] In the context of cellular apoptosis mechanisms, quercetin displays its influence by reducing the expression of the anti-apoptotic protein Bcl-2 and simultaneously increasing that of the pro-apoptotic protein Bax. Furthermore, in vitro studies have illustrated quercetin's capacity to inhibit the activity of stem cells associated with breast cancer. Additionally, in vivo research has confirmed quercetin's potential to limit both the spread and growth of tumors, thereby underscoring its therapeutic relevance in oncology. In terms of inhibiting proliferation, quercetin achieves dose-dependent apoptosis by increasing DNA apoptotic subsets in the G0/G1 phase and decreasing the S-phase subsets.[42] Moreover, the compound quercetin has proven effective in managing breast cancer cell proliferation and in triggering apoptosis by modulating critical signaling cascades, including NF-κB, PI3K-AKT, MAPK, and mTOR, which are pivotal in the disease's progression.[35] In the TNBC cell line MDA-MB-231, quercetin exerts a suppressive effect on cell proliferation by increasing the number of cells in the S and G2/M phases while simultaneously reducing the number in the G0/G1 phase.[43]

For osteosarcoma, quercetin impacts the proliferation, apoptosis, invasion, and chemoresistance of osteosarcoma cells by modulating protein expression and signaling pathways.[44] In the setting of liver cancer, quercetin induces apoptosis in liver cancer cells through the upregulation of apoptotic markers like Bax, caspase-3, and p21, while concurrently downregulating the expression of anti-apoptotic and cell cycle-progression proteins such as Akt, PLK-1, cyclin B1, cyclin A, CDC2, CDK2, and Bcl-2.[45] In the treatment of ovarian cancer, quercetin exerts its potential therapeutic effects by targeting various molecular and cellular signaling pathways, including VEGF, MMPs, caspases, AKT, and KRAS.[39] For prostate cancer, quercetin can inhibit cell cycle transition and induce apoptosis in tumor cells. It affects prostate cancer cells by dissociating Bcl-xL and activating the caspase family, showing a specific cytotoxic effect on cancer cells.[46]

For colorectal cancer (CRC), quercetin shows positive effects on CRC cells in in vitro studies, including inducing cell apoptosis and reducing tumor size.[47] Moreover, research has demonstrated that quercetin exerts its anti-tumor effects by targeting and modulating key signaling transduction pathways, including Wnt/β-catenin, PI3K/AKT, MAPK/Erk, JNK, as well as p38, p53, and NF-κB, thereby showcasing its potential as an anti-neoplastic agent.[48] Among the various pathways influenced by quercetin, this flavonoid has been demonstrated to downregulate the Wnt/β-catenin signaling pathway, representing a pivotal alteration in the development of colorectal cancer.[47] Quercetin can also enhance the sensitivity of chemotherapy drugs and reduce the side effects of chemotherapy, showing an auxiliary effect in chemotherapy for colorectal cancer. Specifically, quercetin can enhance the chemotherapy effect of 5-fluorouracil (5-FU) and reduce its side effects.[48] Additionally, when quercetin is used in combination with 5-FU, it can significantly inhibit the growth of the colorectal cancer cell line COLO 320DM.[49]

In the scenario of nicotine-induced non-small cell lung cancer (NSCLC), quercetin demonstrates inhibitory actions on tumor cell migration and invasion, while simultaneously enhancing apoptosis and inducing cell cycle arrest. These salutary effects are postulated to originate from quercetin's capacity to repress the JNK/NF-κB/Akt signaling cascade and regulate the expression profiles of pivotal proteins: it increases the expression levels of Bcl-2-associated X protein (Bax), cleaved caspase-3, cyclin B1, and p21/WAF1 proteins, while decreasing the expression of B-cell lymphoma-2 (Bcl-2).[50] Within the context of NSCLC therapy, quercetin manifests its therapeutic impact through its capabilities to combat tumorigenesis, curb inflammation, hinder cell proliferation, impede angiogenesis, and encourage apoptosis.[50]

Mechanisms of Quercetin in Breast Cancer

In recent years, the mechanisms by which quercetin treats breast cancer have been progressively elucidated, including but not limited to promoting apoptosis within cancer cells and curbing their proliferation to effectively suppress tumor growth; additionally, impeding the migration, invasion, and metastasis of cancer cells to prevent the advancement and dissemination of tumors; the role of certain quercetin derivatives; and the prediction of quercetin's targets and pathways of action, etc (Figure 3 and Table 2). Quercetin exhibits both conserved and context-dependent anticancer mechanisms.

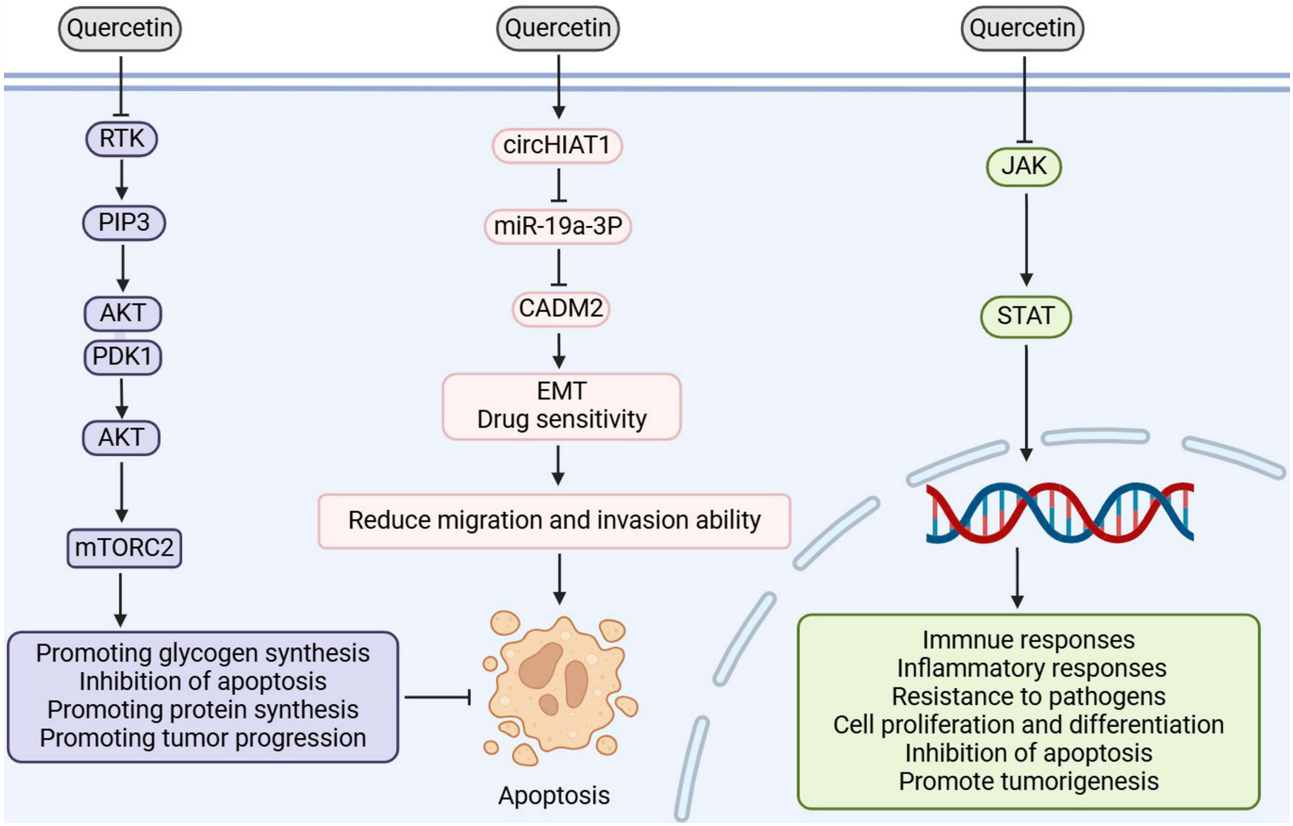

Figure 3 The mechanism of action of quercetin in breast cancer includes the regulation of PI3K/Akt/mTOR signaling pathway, JAK/STAT1 signaling pathway and the modulation of circHIAT1/miR19a3p/CADM2 axis. Image created with BioRender.com,with permission.

Although its core activities—such as antioxidant effects, apoptosis induction—are consistent with its effects on other cancer types (eg, breast, liver, colon), the specific molecular targets and pathways may vary depending on the tissue context. Further research is needed to fully understand the unique aspects of quercetin's action in breast cancer and to

Table 2 Quercetin Impact Upon Breast Cancer Models

Cell	Model	Effect	Mechanism	Reference
MCF-7	In vitro	Inhibition of cancer cell proliferation	Regulate the expression of nuclear protein	[79]
	In vitro	Promote apoptosis and inhibit cell proliferation	↑ PTEN[A], ↓PI3K, Akt, mTOR[B]	[80,81]
	In vitro	Promotes iron death in cancer cells	↑TFEB[C], LAMP1[D]	[79]
	In vitro	Induced apoptosis of MCF7 cells	P53-dependent pathway	[82]
	In vitro	Induction of apoptosis in breast cancer cells	The mitochondria-quercetin reaction	[83]
MDA-MB-231	In vitro, Xenograft	Block TNBC invasion phenotype and EMT[E]	Inhibit the IGF1/IGF1R[F] signaling pathway	[84]
	In vitro	Promoting gamma delta T cells to kill breast cancer cells	Modulating the JAK/STAT1[G] signaling pathway	[85]
	In vitro	The invasive phenotype of TNBC was inhibited	↓HuR[H]	[86]
	In vitro	Promoting chemotherapy-induced apoptosis to eliminate senescent breast cancer cells	↓ p27, IL-1β, IL-8, HSP70[I]	[87]
	In vitro	Inhibit the progression of chronic stress TNBC	Block the β2 adrenergic receptor (β2AR) / ERK1/2[J] signaling pathway	[88]

(*Continued*)

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Table 2 (Continued).

Cell	Model	Effect	Mechanism	Reference
4T1	Xenograft	Mitigating the progression of breast cancer-related depression	Inhibits pyroptosis and promotes immune responses	[89]
	Xenograft	To enhance the anti-tumor effect of cyclophosphamide in TNBC model	Complementarity between the microbiome and immune-mediated mechanisms	[90]
MDA-MB-231 BT-474	Xenograft	Improve hepatitis and fibrosis caused by breast cancer.	Activate the vitamin D receptor (VDR)	[91]

Notes: All annotations in tables are marked with alphabetical superscripts following this sequence: Begin with single letters A through J (10 markers). Notes corresponding to these markers are listed at the table bottom in exact sequence order. [A]Phosphatase and Tensin Homolog. [B]Mechanistic Target of Rapamycin. [C]Transcription Factor EB. [D]Lysosome-Associated Membrane Protein 1. [E]Insulin-like Growth Factor 1/Insulin-like Growth Factor 1 Receptor. [F]Epithelial-Mesenchymal Transition. [G]Janus Kinase/Signal Transducer / Activator of Transcription 1. [H]Human antigen R. [I]Cyclin-dependent kinase inhibitor 1B (CDKN1B), Interleukin 1 beta, Interleukin 8, Heat shock protein 70. [J]Extracellular signal-Regulated Kinase 1/2.

optimize its therapeutic potential. By demystifying the complex molecular mechanisms of quercetin's action, we can further explore its potential in the prevention and treatment of breast cancer.[51]

Mechanisms of Inducing Apoptosis and Inhibiting Proliferation

Several mechanisms by which quercetin may prevent and treat cancer have been discovered. Quercetin enhances cancer cell apoptosis and autophagy while decreasing cell viability through modulation of signaling pathways.[39] By interacting with its adenosine 5'-triphosphate (ATP) binding site, quercetin can effectively inhibit the epidermal growth factor receptor (EGFR), exerting its inhibitory effects through a process that includes the formation of hydrogen bonds, π-π stacking, and hydrophobic interactions.[50] Quercetin exerts regulatory effects on a variety of tumor-associated activities, such as oxidative stress, angiogenesis, cell cycle regulation, tumor necrosis factor activity, proliferation, apoptosis, and metastasis.[38] Quercetin exerts an anti-inflammatory effect and protects cells against oxidative stress by efficiently scavenging reactive oxygen species (ROS), thus playing a crucial role in both cancer prevention and therapeutic management.[47]

Studies have shown that in MCF7 cells containing quercetin, the expression of nuclear protein is significantly down-regulated 15.18 and 2.51 times (IC50= 160 μM) at 48 h and 72 h, respectively, which could potentially exert control over associated signaling pathways by adjusting the levels of nuclear protein expression in cancer cells, consequently impeding their proliferative capacity.[52] Quercetin induces selective apoptosis in breast cancer cells through a dual-pathway mechanism involving epigenetic modulation and kinase network regulation. Firstly, it reactivates the tumor suppressor PTEN by reducing promoter DNA methylation, enabling its lipid phosphatase function to attenuate critical oncogenic signaling cascades which decreases AKT Ser473 phosphorylation and subsequently inhibits downstream anti-apoptotic effectors. Additionally, it coordinately disrupts mTOR complex functionality, simultaneously blocking mTORC1-mediated survival signals to activate pro-apoptotic protein translation while impairing mTORC2-dependent AKT activation. This orchestrated interference with both upstream epigenetic regulation and downstream kinase cascades establishes a synergistic therapeutic framework that concurrently targets proliferative signaling and apoptotic resistance in breast cancer pathogenesis.[53,54] Furthermore, quercetin has the ability to suppress the IGF1/IGF1R signaling pathway. This chemical agent not only curbs the aggressive characteristics and the EMT linked to TNBC, but it also reduces the expression of EMT transcription factors Snail and Slug, preventing cancer cells from attaining stem-like characteristics.[55]

Quercetin can also promote apoptosis. On one hand, quercetin boosts the expression levels of the transcription factor TFEB, which subsequently enhances the expression of the lysosome-associated gene LAMP1, and this cascade of events results in the degradation of ferritin and the liberation of iron ions, ultimately triggering ferroptosis.[56] On the other hand, 4AcQ may induce apoptosis in MCF7 cells through a p53-dependent pathway.[57]

Quercetin can also enhance the synergistic effects of immune cells. For instance, MDA-MB-231 cells treated with quercetin are capable of enhancing the cytotoxic effects of γδ T cells against breast cancer cells through the modulation

of the JAK/STAT1 signaling pathway.[58] In clinical scenarios, quercetin exhibits the capability to address drug resistance in cancer cells, thereby augmenting the treatment of breast cancer. When combined with paclitaxel (PTX), quercetin can effectively and stably engage with vital targets within the EGFR/ERK signaling cascade. Furthermore, quercetin can suppress the proliferation of PTX-resistant breast cancer cells, induce cell apoptosis, and rejuvenate the responsiveness of PTX-resistant cells.[59] Studies have also shown that quercetin reverses resistance to CDK4/6 inhibitors by modulating the circHIAT1/miR19a3p/CADM2 axis.[60]

Mechanisms That Inhibit Migration, Invasion and Metastasis

Quercetin exerts a dual action on breast cancer cells by not only curbing their proliferation but also markedly inhibiting their invasiveness, playing a pivotal role in impeding the advancement of tumor metastasis.

EMT is a key process for TNBC breast cancer cells to acquire aggressiveness, and studies have shown that quercetin can inhibit this process by regulating some signaling pathways. On the one hand, quercetin can target the circHIAT1/miR-19a-3p/CADM2 axis, and on the other hand, quercetin can inhibit the IGF1/IGF1R signaling pathway.[55] Through these signaling pathways, quercetin inhibits breast cancer cells from acquiring stem-like properties and inhibits their migration.[60] The invasive phenotype and EMT of TNBC are blocked, thereby inhibiting cancer cell migration.[58]

In addition to modulating signaling pathways, quercetin also exerts its anti-cancer effects by targeting key proteins and environmental factors that influence cancer cell migration and metastasis. For instance, studies have shown that overexpression of the HuR protein is associated with decreased overall survival in TNBC patients. Quercetin has been demonstrated to inhibit the invasive phenotype of TNBC cells by downregulating HuR expression.[61] Furthermore, quercetin may inhibit breast cancer metastasis by affecting heat shock proteins and lipid peroxidation pathways.[11] These findings highlight quercetin's multifaceted mechanism of action in targeting various factors that contribute to the aggressiveness and metastatic potential of TNBC cells.

In summary, quercetin's anti-cancer effects are mediated through the inhibition of EMT-related signaling pathways, regulation of key proteins such as HuR, and modulation of environmental factors like lipid peroxidation. By targeting multiple pathways and factors associated with the aggressiveness and metastasis of TNBC cells, quercetin emerges as a promising therapeutic agent for the treatment of TNBC.

Mechanism of Action of Some Quercetin Derivatives

Quercetin, a widely studied flavonoid, has demonstrated significant potential in various therapeutic applications, including anticancer activity. However, its clinical use is often limited by its poor solubility and bioavailability. To address these limitations, researchers have developed various quercetin derivatives, which have shown improved pharmacokinetic properties and enhanced biological activities.

A mitochondrial targeted derivative of quercetin (mitQ7) induces apoptosis in breast cancer cells at a concentration as low as 1 μM, particularly in the context of glucose depletion.[62] This highlights the potential of quercetin derivatives to target cancer cells more effectively under specific metabolic conditions. The maximum 50 values of cytotoxic effects of derivatives 2q, 4q, 8q and 9q on IC were 39.7 ± 0.7, 36.65 ± 0.25, 35.49 ± 0.21 and 36.99 ± 0.45, respectively. Molecular docking also confirmed these results: 8q has the highest binding potential of 9.165 KJ/mole, making it a potent inhibitor of CDK2.[63] This suggests that quercetin derivatives can be optimized for specific targets, potentially enhancing their therapeutic efficacy. Quercetin derivatives, such as Quercetin derivatives (QD3) are able to eliminate senescent breast cancer cells by promoting their chemotherapy-induced apoptosis.[64] This indicates that quercetin derivatives may have a role in overcoming resistance mechanisms in cancer therapy.

In terms of safety, quercetin is generally recognized as safe for human consumption at dietary levels. However, higher doses may require careful consideration due to potential side effects. The ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profile of quercetin indicates that while it is well-tolerated at low doses, its poor bioavailability limits its therapeutic potential. Derivatization strategies aim to improve these properties, making quercetin derivatives more suitable for clinical applications.

Overall, the development of quercetin derivatives represents a promising approach to enhance the therapeutic potential of this natural compound, addressing its limitations in solubility, bioavailability, and target specificity.

Other Mechanisms

In addition to these mechanisms, quercetin has several other mechanisms to improve breast cancer symptoms. Quercetin's therapeutic potential extends beyond its direct anticancer effects, as it also influences multiple pathways and systems related to breast cancer development and progression. One intriguing aspect of quercetin's mechanism involves its interaction with the nervous system. Emerging evidence suggests that quercetin can modulate the CNS to influence breast cancer development. Specifically, studies have found that quercetin may reverse the regulatory relationship between neuroinflammation of the CNS and breast cancer progression.[65] This relationship is particularly relevant given the growing understanding of the bidirectional communication between the nervous system and cancer cells.

Further research has elucidated some specific mechanisms underlying quercetin's effects on the nervous system. For instance, the β2AR/ERK1/2 signaling pathway has been identified as a key pathway through which quercetin exerts its anticancer effects. Chronic stress is known to promote the progression of TNBC via this pathway, but quercetin has been shown to inhibit these effects by specifically targeting the β2AR/ERK1/2 signaling pathway.[66] This highlights quercetin's potential as a therapeutic agent for stress-related cancer progression.

Beyond its direct effects on breast cancer cells, quercetin also plays a role in managing additional complications associated with breast cancer. For example, quercetin has been identified as a crucial element in mitigating breast cancer-related depression (BCRD). By preventing the abrupt deterioration of BCRD and enhancing the immune system's response, quercetin can improve the overall quality of life for patient.[67] Additionally, quercetin's therapeutic potential extends to the management of other complications, such as hepatitis and fibrosis caused by breast cancer. Research has shown that quercetin can activate the vitamin D receptor (VDR), which may help in improving these conditions.[68]

Quercetin's ability to enhance the efficacy of other anticancer therapies is another important aspect of its therapeutic potential. For instance, studies have demonstrated that quercetin can significantly enhance the antitumor effects of cyclophosphamide, particularly in a TNBC model.[69] This synergistic effect is attributed to quercetin's ability to inhibit the activity of the enzyme CYP3A4 and the subsequent metabolism of arachidonic acid, thereby impeding the progression of breast cancer.[70] While these studies highlight quercetin's potential as an adjuvant therapy, further research is needed to fully elucidate the specific molecular mechanisms underlying these effects.

Quercetin, a natural flavonoid compound, demonstrates its anti-breast cancer potential through multi-target, multi-level synergistic mechanisms (Figure 4). Its core molecular structure induces apoptosis and ferroptosis by regulating signaling pathways and epigenetically activating PTEN, inhibiting AKT phosphorylation, suppressing downstream anti-apoptotic proteins, and blocking FAK-mediated survival signals. By targeting the IGF1/IGF1R pathway and the circHIAT1/miR-19a-3p/CADM2 axis, it inhibits EMT and reduces HuR protein expression, thereby attenuating the invasiveness and stem-like properties of TNBC. Derivatives such as mitQ7 and 8qPTEN enhance targeting specificity and efficacy through structural optimization. Systemic regulation involves suppressing the β2AR/ERK neuro-stress pathway, reversing resistance to paclitaxel and CDK4/6 inhibitors, and potentiating cyclophosphamide efficacy via CYP3A4/AA metabolic intervention, while alleviating complications such as neuroinflammation and fibrosis.

In summary, quercetin's therapeutic potential in breast cancer management is multifaceted, encompassing direct anticancer effects, modulation of the nervous system, enhancement of immune response, and improvement of treatment-related complications. Although the mechanisms underlying these effects are not yet fully understood, the existing evidence underscores quercetin's promise as a valuable therapeutic agent in the fight against breast cancer.

Study on Quercetin Related Drug Carrier

As previously mentioned, a multitude of studies and literature reports have confirmed that quercetin possesses significant anti-cancer potential. This natural compound has illuminated extensive therapeutic prospects in oncology and has positioned itself as a compelling contender for the advancement of novel anticancer pharmaceuticals. Many studies have begun to study quercetin drug carriers, and the relatively mature ones are nanocarriers and drug-carrying micelles.

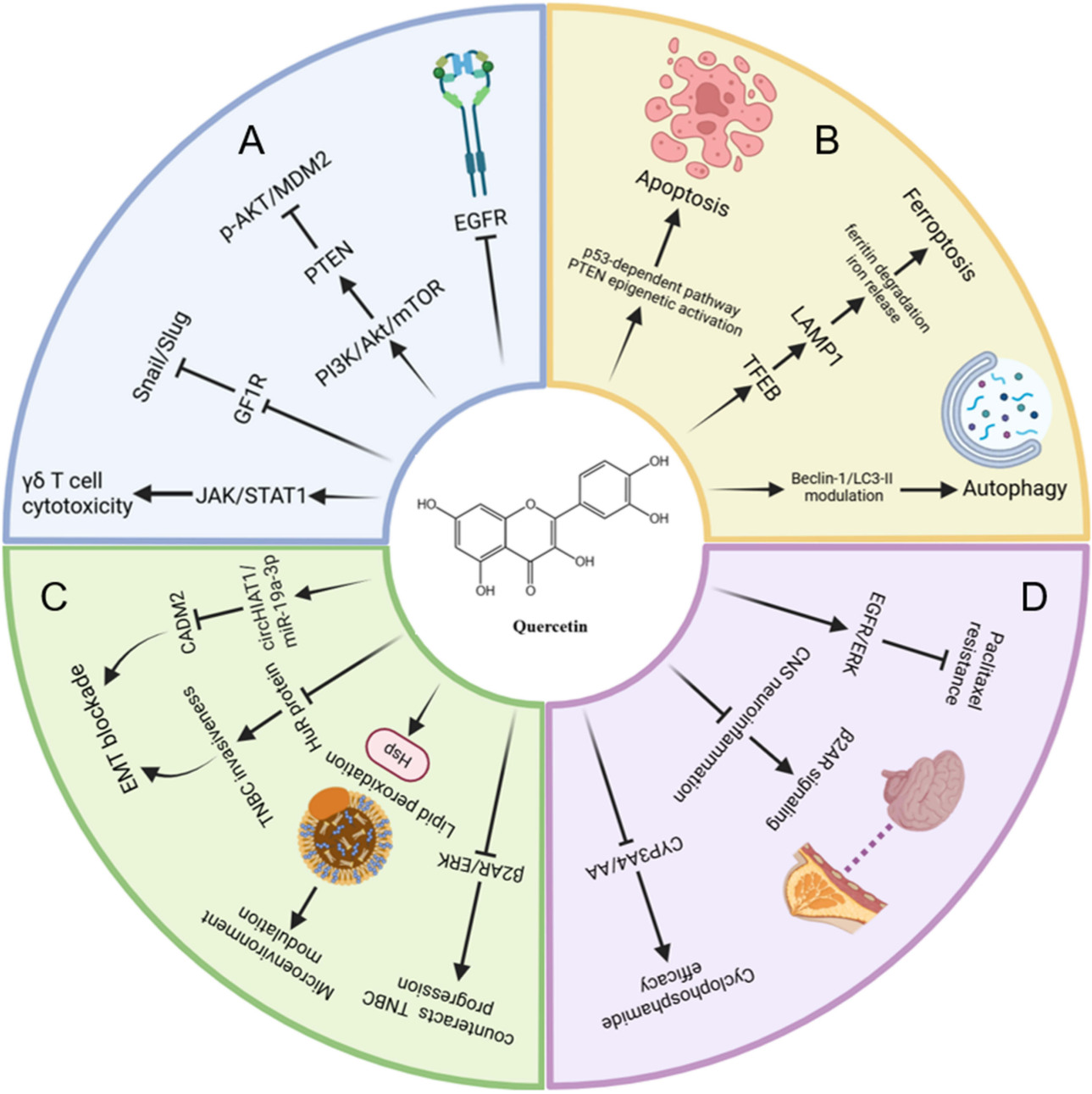

Figure 4 Quercetin's multimodal mechanisms in breast cancer intervention. This schematic integrates quercetin's core actions across four functional modules: (**A**) Signaling Pathway Regulation (**B**) Cell Death Induction (**C**) Metastasis Suppression (**D**) Systemic Coordination. Image created with BioRender.com,with permission.

Nanocarrier

The bioavailability and chemical stability of quercetin can be greatly improved in the form of nanomaterials.[71] Within the domain of nano-core drug delivery systems, the polymer-grafted magnetic graphene oxide (GOPVPFe3O4) serves as a nano-core carrier for quercetin, facilitating pH-triggered drug release specifically to breast cancer cells,[72] while magnetic core-shell metal-organic framework (MOF) nanocomposites Fe3O4COOH@UiO66NH2 are used for the targeted delivery of quercetin.[73] In the application of nano-liposomes, quercetin is prepared into nano-liposomes (QTNLs) to enhance its efficacy in the treatment of breast cancer,[74] notably, the QC-SLN possesses a particle diameter of 154 nm, exhibits a zeta potential of −27.7 mV, and achieves an encapsulation efficiency of 99.6%, which shows the best performance and can sustain the release of quercetin for up to 72 hours.[75]

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For TNBC, a novel hybrid nanoparticle (HNP) has been developed, consisting of a silver nanoparticle (AgNP) core and separately loaded with eEF2K-siRNA and the chemotherapeutic agent quercetin (QU). In vitro experiments on TNBC cell lines (MDA-MB-231, BT-549, 4T1) demonstrated reduced cell viability, inhibited colony formation, and suppressed cell migration. At a high siRNA concentration of 120 nM, 3D spheroid disintegration, activation of apoptotic pathways, and eventual necrotic cell death were observed. The results suggest that the developed HNP is non-toxic, effective, and has the potential to serve as a theranostic platform for TNBC treatment.[76]

The combination of nanocarriers and quercetin also offers a novel approach to addressing multidrug resistance (MDR) in breast cancer. A study based on β-cyclodextrin formulations prepared an inclusion complex encapsulating quercetin (QUE) and doxorubicin (DOX) (β-CD@QD IC). In vitro assays indicated that the inclusion complex significantly increased cellular cytotoxicity, induced nuclear condensation, disrupted mitochondrial membrane potential (ΔΨm), increased reactive oxygen species (ROS) production, and triggered apoptosis-related morphological changes. Hoechst efflux studies showed that QUE effectively inhibited the ABCG2 efflux pump, leading to increased accumulation of Hoechst dye in MCF-7/DOX cancer cells. QUE inhibited SRC kinase signaling, resulting in decreased PI3K/Akt expression and reduced ABCG2 overexpression in MCF-7/DOX cells. This study demonstrated that the β-CD@QD IC loaded with QUE effectively overcame DOX resistance in MCF-7/DOX cells.[77]

Furthermore, a novel pH and REDOX dual-stimuli-responsive polymethacrylate/ mesoporous silica nanoparticle core-shell structure has been formulated through the integration of precipitation polymerization with advanced sol-gel modifications, and modified with hyaluronic acid.[78] In terms of drug co-loading and synergistic therapy, quercetin is co-loaded with other drugs in nano-carriers to optimize drug delivery; for example, quercetin and curcumin administered intravenously via nano-emulsions have shown enhanced efficacy in breast cancer cells,[92] quercetin is co-loaded with Etoposide (ETO) in solid lipid nanoparticles (SLNs), and quercetin bound to magnetite nanoparticles (QMNPs) shows a synergistic therapeutic effect on breast cancer.[93]

In summary, the utilization of quercetin in nanotechnology not only enhances its bioavailability and stability for breast cancer treatment, but also amplifies therapeutic outcomes through co-delivery with additional medications and targeted administration. This highlights its considerable promise as an efficacious therapeutic option in the management of breast cancer.

Drug Micelles

Firstly, as a mature drug carrier, micelles have demonstrated their application potential in various fields. In the treatment of breast cancer, quercetin and curcumin are loaded into nano-micellar gels for local therapy, showcasing the advantages of drug micelles in local drug delivery.[94] In addition, to achieve targeted co-delivery of drugs, amphiphilic biomaterials PEITOS and HAQU self-assemble into core-shell micelles, which can carry both paclitaxel (PTX) and quercetin (QU), enhancing therapeutic effects and reducing side effects.[95] Meanwhile, for paclitaxel and quercetin, BSA hydrogel is also an excellent drug carrier. QUE, TAX encapsulated in BSA hydrogel (QUE@BSA hydrogel, TAX@BSA hydrogel and DOX@BSA hydrogel) reduced the formation of mammospheres and cell migration, caused cell cycle arrest in TNBC cells, decreased cell proliferation and induced apoptosis. They also induced ROS generation and ER stress, highlighting their potential to inhibit the progression of TNBC. The BSA hydrogel carrier demonstrated controllable drug release and enhanced therapeutic effects.[96] The combination of amphiphilic hyaluronic acid polymers (dHAD) with quercetin (QT) results in the formation of drug-laden micelles, designated as dHADQT, which also exhibit good stability and biocompatibility in drug delivery systems.[97]

In addition, a relatively mature micellar carrier, R-D-Q micelles, was developed by grafting quercetin and the peptide cRGDfk (Arg-Gly-Asp-(D-Phe)-Lys) onto dextran to synthesize the polymer-drug conjugates dextran-quercetin (D-Q) and cRGD-dextran (R-D). Subsequently, cRGD-modified dextran-quercetin polymer micelles (R-D-Q) were constructed through the self-assembly of D-Q and R-D. R-D-Q micelles possess an appropriate particle size (133.4 nm), a nearly neutral potential (8.14 mV), and an excellent drug loading efficiency (13.1%). Moreover, they exhibit higher cytotoxicity, apoptosis induction, and permeability to human breast cancer MCF-7 cells compared to unmodified micelles. R-D-Q micelles effectively inhibit tumor growth in tumor-bearing mice by delivering more quercetin throughout the tumor tissue. R-D-Q micelles promote tumor cell apoptosis by activating the p38 and JNK signaling pathways and

inhibiting the ERK signaling pathway. Additionally, R-D-Q micelles do not cause damage to normal tissues in mice at therapeutic doses. These results suggest that R-D-Q micelles have promising prospects as an effective drug delivery system for tumors.[98]

Through these studies, we can see the significant role of drug micelles in improving drug efficacy, achieving targeted delivery, and reducing side effects.

Quercetin Modifications and Cancer

Tree-like polymer carriers are also a promising direction for drug delivery. Compared with free quercetin (QUR), targeting MCF-7 and HepG-2 cancer cells, respectively, at its safe dose (EC100= 134.35–78.44 μM), MTT assay showed that all quercetin-conjugated tree-like polymers exhibited better anticancer potential (IC50= 12.690–29.316,4.137–29.090 μM). The combination of lassa and PEG increased the anticancer potency, ameliorated apoptosis and downregulated MMP-9 and VEGF gene expression levels in both treated cancer cells. In general, the more branched G4 dendrimers conjugates exhibit excellent overall anticancer properties compared to their respective G3 analogues, except for their MMP-9 inhibition, where the G3 conjugates appear to be more potent and selective than their G4 analogues.[99]

Recent advancements in the field of flavonoid chemistry have focused on modifying quercetin to enhance its biological activity and therapeutic potential. One such modification involves the acetylation and methylation of quercetin, which significantly impact its anti-cancer properties. Existing studies have demonstrated that acetylated quercetin (4AcQ) exhibits potent anti-cancer effects by significantly inhibiting cell proliferation and inducing apoptosis in various cancer cell lines.[60] This enhancement in biological activity is attributed to the increased stability and bioavailability of the acetylated form. Acetylation appears to modify the molecular structure of quercetin in a way that enhances its interaction with cellular targets, thereby amplifying its therapeutic efficacy. In contrast, methylated quercetin (4MeQ) has been shown to lose its anti-cancer activity.[60] Methylation, which involves the addition of a methyl group to the quercetin molecule, appears to alter its biological properties in a manner that neutralizes its ability to inhibit cell proliferation and induce apoptosis. This suggests that the specific chemical modifications of quercetin can have a profound impact on its therapeutic potential, highlighting the importance of careful structural design in drug development.

Additionally, beyond simple acetylation and methylation, other innovative approaches have been explored to enhance quercetin's efficacy. For instance, the phytosomes of quercetin bound to scorpiotoxin have demonstrated a significant anti-proliferation effect on the breast cancer cell line MCF7 in vitro.[42] This indicates that the acetylation of quercetin enhances its anti-cancer properties, while methylation appears to neutralize its biological activity.

The differential effects of acetylated and methylated quercetin, as well as the enhanced efficacy observed with quercetin-phytosomes, underscore the importance of chemical modifications and delivery systems in optimizing the therapeutic potential of natural compounds. Future research should focus on exploring additional modifications and delivery strategies to further enhance quercetin's anti-cancer properties and translate these findings into clinical applications.

Potential Limitations of Nanocarrier and Micellar Systems

Despite nanocarriers and micellar systems improving therapeutic delivery, their clinical translation faces significant challenges.[100] One of the primary challenges is scalability and cost issues arise from complex synthesis processes requiring specialized materials and equipment, compounded by stringent quality control needs, which hinder large-scale production and affordability, especially in resource-limited settings.[101] Another critical consideration is biocompatibility concerns persist due to risks of immune activation, inflammatory responses, and long-term tissue accumulation of nanoparticles, necessitating extensive safety evaluations.[102] Moreover, environmental sensitivity (pH, temperature, light) compromises stability, leading to premature drug release and reduced shelf life during storage/transport.[102] Finally, evolving regulatory frameworks struggle to address nanocarriers' structural complexity and unpredictable biological interactions, prolonging approval timelines.[103]

In conclusion, to advance clinical adoption, research must prioritize cost-effective manufacturing methods, enhanced material stability, rigorous biosafety profiling, and harmonized regulatory standards. Addressing these limitations is critical to balancing therapeutic efficacy with practical applicability in the actual healthcare systems.

Quercetin in Breast Cancer Therapy: Synergy, Integration, and Challenges

The Combination of Quercetin and Other Drugs and the Synergistic Mechanism

Quercetin (QUE), as a versatile natural compound, has exhibited notable promise in the management of breast cancer therapy, especially when integrated with other pharmaceuticals. By combining quercetin with chemotherapeutic agents, the efficacy of these drugs in combating tumors is heightened, while also diminishing the likelihood of tumor resistance to the treatment.[49] Quercetin can also enhance the anti-cancer activity of commonly used antitumor drugs, thereby reducing their dosage in the treatment process and making drug-resistant tumor cells sensitive again.[53]

For instance, the combined use of quercetin with NaBu has produced a significant synergistic inhibitory effect, which is stronger than the effect of using QUE or NaBu alone.[104] Moreover, the combined action of quercetin and chalcone can induce cell cycle arrest at the subG0/G1 phase in MDA-MB-231 cells and alter the expression of caspases 3 and 8.[79] The synergistic effects of quercetin/urushetin and naringin have also been observed in two cell lines, with combination therapy being more effective than monotherapy in reducing cell growth, inhibiting migration, and inducing apoptosis.[80] The use of quercetin with doxorubicin enhances the toxicity of doxorubicin against both sensitive and resistant MCF7 breast cancer cells,[81] and the use of quercetin with etoposide (ETO) enhances the apoptotic pathway by increasing the Bax/Bcl2 gene ratio, elevating p53 and p21 protein levels, and activating caspase 3 and 9 enzymes.[82]

Furthermore, the combined administration of quercetin with 5-fluorouracil (5-FU), in contrast to 5-FU monotherapy, exhibits a more potent apoptotic effect by augmenting the expression of Bax and p53, enhancing caspase-9 activity, and suppressing Bcl-2 gene expression.[83] In addition, this combined therapy also augments the anti-metastatic effects on MDA-MB-231 breast cancer cells.[84] The combined application of quercetin with docetaxel amplifies the anticancer efficacy against MDA-MB-231 breast cancer cells by inducing apoptosis and modulating the PI3K/AKT, MAPK/ERK, and JAK/STAT3 signaling cascades.[85] The combination of quercetin with Naringin (Nar) has synergistic antioxidant and anti-proliferative effects in MCF7 breast cancer cells.[86] Co-loaded Spanlastics with quercetin and letrozole show enhanced cytotoxicity in MCF7 breast cancer cells,[87] and the synergistic use of fisetin demonstrates markedly enhanced efficacy in assays pertaining to colony formation and wound healing.[88]

These studies indicate that combination therapies with quercetin have significant potential in improving therapeutic outcomes, inhibiting cancer cell metastasis, and enhancing anti-cancer activity.

Clinical Integration and Application of Quercetin in Cancer Therapy

The integration of quercetin into existing cancer treatment regimens holds significant potential as an adjunct therapy, enhancing the efficacy of existing chemotherapy drugs while potentially reducing their side effects. For instance, quercetin has been shown to sensitize cancer cells to chemotherapy agents such as cisplatin and doxorubicin, leading to more effective tumor regression. In a recent study, quercetin was found to enhance the antitumor effects of cisplatin in a TNBC model by modulating the tumor microenvironment and promoting apoptosis.[89] Additionally, quercetin has been shown to mitigate some of the adverse effects associated with chemotherapy, such as oxidative stress and inflammation, thereby improving patient outcomes.[90]

Quercetin exhibits multifaceted therapeutic potential in cancer management through its pro-apoptotic and antiproliferative effects mediated by modulation of critical signaling pathways. Notably, pre-treatment with quercetin in murine models of chemical-induced lung tumorigenesis significantly attenuated neoplastic progression, concomitant with elevated antioxidant enzymatic activity and suppression of lipid peroxidation. This dual regulatory mechanism suggests quercetin's capacity to counteract carcinogen-induced oxidative damage while suppressing tumorigenic signaling networks. 500 Moreover, quercetin has demonstrated chemopreventive effects by enhancing antioxidant enzyme activity and reducing lipid peroxidation. These properties make quercetin a valuable candidate for integrative cancer care.[91]

When considering the clinical application of quercetin, several factors should be taken into account. First, quercetin is available in various forms, including capsules, tablets, and liquid extracts. The optimal dosing for adjunct therapy is still under investigation, but current studies suggest that doses ranging from 500 mg to 1000 mg per day may be effective.[30] Additionally, clinicians should monitor patients for potential interactions with other medications, as quercetin can inhibit cytochrome P450 enzymes, which may affect the metabolism of certain drugs.[32] Lastly, patient education is crucial. Educating patients about the importance of adhering to prescribed dosages and the potential for interactions with other medications can help ensure safe and effective use.

Potential Challenges and Risks of Quercetin Combination Therapy

The synergistic effects of quercetin with therapeutic agents should be cautiously evaluated due to risks of unforeseen toxicity and drug-drug interactions, which may reduce therapeutic efficacy or amplify adverse effects.

Quercetin exhibits context-dependent bioactivity, which may lead to unforeseen toxicity when used in combination with other drugs. For example, in estrogen receptor-positive (ER+) breast cancer, quercetin demonstrates dose-dependent antagonistic effects when combined with tamoxifen. At low concentrations (eg, 5 μM), quercetin counteracts tamoxifen's anti-proliferative effects and potentially promotes tumor progression. Conversely, at high doses (eg, 50 μM), quercetin synergizes with tamoxifen to induce apoptosis but may exacerbate oxidative stress in normal tissues, raising concerns about toxicity.[105] Additionally, although quercetin can suppress hepatocellular carcinoma (HCC) progression by down-regulating P4HA2 and inhibiting the PI3K/Akt/mTOR pathway, its combination with PI3K inhibitors (eg, LY294002) may result in excessive pathway suppression, impairing normal hepatocyte survival and liver regeneration. When co-administration with PI3K activators (eg, 740Y-P) could antagonize quercetin's pro-apoptotic effects, inadvertently promoting tumor cell survival. These findings highlight the context-dependent risks associated with targeting overlapping signaling pathways.[106]

Quercetin regulates drug metabolism and pharmacokinetics through various mechanisms, and its effects may be influenced by potential drug-drug interactions. In cholangiocarcinoma, quercetin pretreatment reduced the IC50 of sorafenib and oxaliplatin, raising concerns about overdosing in patients with impaired hepatic metabolism.[107] Quercetin inhibits platelet aggregation and synergizes with anticoagulants (eg, warfarin), increasing bleeding risks in preclinical models.[108]

In conclusion, the dual role of quercetin in enhancing therapeutic efficacy while posing interaction risks demands systematic pharmacokinetic monitoring, patient stratification, and clinical validation of dose thresholds. Future studies should prioritize combinatorial regimens with real-time therapeutic drug monitoring and mechanistic validation to balance efficacy and safety.

Comparison of Quercetin with Prescription Breast Cancer Medicines

Mechanisms of Action and Efficacy

Traditional prescription medicines for breast cancer treatments, such as cisplatin, paclitaxel, and doxorubicin, primarily exert their antitumor effects through mechanisms like DNA damage induction or synthesis inhibition. For example, cisplatin forms intrastrand and interstrand DNA cross-links, disrupting DNA replication and transcription. Paclitaxel stabilizes microtubules, preventing cell division and inducing apoptosis. These drugs are often used in combination regimens to enhance therapeutic efficacy and mitigate resistance.[109]

Quercetin enhances the effectiveness of traditional prescription medicines like cisplatin by targeting different molecular pathways. It modulates signaling pathways involved in cell proliferation and apoptosis, making it a promising adjuvant for cancer therapy. Quercetin's selective action against malignant cells allows it to complement traditional chemotherapy agents, potentially improving overall treatment outcomes.[110]

In summary, traditional prescription medicines such as cisplatin, paclitaxel, and doxorubicin primarily target tumor cells through mechanisms like DNA damage and inhibition of cell division. These drugs often require combination therapies to enhance efficacy and overcome resistance. Unlike traditional prescription medicines, quercetin demonstrates selective action against cancer cells by targeting molecular pathways involved in cell proliferation and apoptosis. The selective targeting allows quercetin to potentially improve treatment outcomes through complementary mechanisms.

Safety and Toxicity

Traditional prescription medicines for breast cancer treatments, such as cisplatin, paclitaxel, and doxorubicin, are effective in tumor regression and improving survival rates. However, they often result in significant systemic toxicity. Common side effects include immunosuppression, gastrointestinal disturbances, and alopecia, which can severely impact patient quality of life.[111]

Quercetin demonstrates selective cytotoxicity against cancer cells with reduced toxicity at therapeutic doses. However, its clinical application is limited by pharmacokinetic challenges such as low oral bioavailability and poor aqueous solubility, but recent advancements in nanoparticle-based delivery systems offer promising solutions to enhance quercetin's bioavailability and efficacy.[91]

Traditional prescription medicines, despite their efficacy in tumor regression, are associated with significant systemic toxicity that can severely impact patient quality of life. In contrast, quercetin offers a safer alternative with selective cytotoxicity against cancer cells and reduced toxicity at therapeutic doses. Currently, nanoparticle-based delivery systems are addressing the limitations of quercetin's clinical application due to pharmacokinetic challenges, with the potential to enhance its bioavailability and efficacy while maintaining its safety profile.

Quercetin in Cancer Research: In Vivo and Clinical Studies

In Vivo Studies with Quercetin in Animal Models

Numerous in vivo studies have demonstrated the anticancer potential of quercetin in animal models of breast cancer. For example, quercetin has been shown to inhibit tumor growth and metastasis in breast cancer xenograft mouse models. Treatment with quercetin (50 mg/kg) significantly reduced tumor volume and decreased the expression of key proteins involved in tumor progression, such as VEGF and PKM2.[112] Furthermore, quercetin has been shown to enhance the antitumor effects of cisplatin in EMT6 tumor xenograft mouse models, leading to a more significant reduction in tumor size compared to cisplatin alone.[53]

Quercetin also modulates the tumor microenvironment by regulating the gut microbiota. In a TNBC mouse model, dietary supplementation with quercetin significantly increased the abundance of beneficial bacteria like *Akkermansia* and enhanced the activation of effector T cells and NK cells, thereby promoting anti-tumor immunity.[112] Additionally, quercetin has demonstrated significant metabolic and anti-inflammatory benefits in obese mice models, reducing liver fat and blood glucose levels while promoting beneficial gut bacteria.[112]

Clinical Trials of Quercetin in Different Types of Cancer

Currently, there are no clinical trials evaluating the effects of quercetin in breast cancer patients. This may be due to the numerous targets of quercetin's immunomodulatory action, its low oral bioavailability, and uncertainties surrounding effective dosages and potential toxic side effects.[112] However, preclinical studies have demonstrated the potential of quercetin as an anti-cancer agent in breast cancer.

Although clinical trials in breast cancer patients are lacking, several studies have been conducted on quercetin in patients with other types of cancer, providing insights into its potential therapeutic effects in breast cancer. For instance: In a Phase II clinical trial, quercetin in combination with gemcitabine was well-tolerated in patients with advanced pancreatic cancer and showed promising clinical benefits, with a median overall survival of 6.5 months and a median progression-free survival of 3.5 months.[69] Quercetin was found to enhance the efficacy of cisplatin in patients with non-small cell lung cancer. The combination treatment resulted in a higher response rate and longer progression-free survival compared to cisplatin alone.[69] Additionally, a Phase II clinical trial investigated the efficacy of quercetin in reducing buccal squamous cell carcinoma in patients with Fanconi anemia. Reyes-Farias et al found that quercetin reduced buccal micronuclei and the need for potentially lethal treatment with chemotherapy and/or radiation therapy.[21]

In summary, while there is currently no clinical evidence to support the use of quercetin in the treatment of breast cancer patients, the results of preclinical studies and clinical trials in other cancer types suggest that quercetin may have potential therapeutic effects in breast cancer. However, further research is needed to determine the optimal dosage, safety, and efficacy of quercetin in breast cancer patients. In future research, it is crucial to conduct well-designed clinical trials

to investigate the effects of quercetin in breast cancer patients, which will help lay the foundation for the clinical application of quercetin as a potential adjuvant in breast cancer treatment.

Discussion

Future research on quercetin in cancer therapy should prioritize rigorously designed clinical trials to validate its preclinical efficacy and translate findings into clinical practice. Key foci include optimizing quercetin's dosing and timing in combination therapies (eg, enhancing docetaxel efficacy in prostate cancer[113] and sensitizing ovarian cancer to cisplatin[114]), identifying predictive biomarkers (eg, genetic or metabolic profiles) for personalized treatment, and exploring its preventive potential via antioxidant/anti- inflammatory mechanisms in high-risk populations.[33] These efforts will bridge translational gaps, balancing therapeutic innovation with mechanistic validation to advance quercetin's role in oncology.

In comparison with the existing review articles, our review makes three key innovations. Primarily, it delivers unprecedented mechanistic granularity by delineating breast cancer specific molecular pathways, resolving subtype specific inconsistencies overlooked in prior reviews. Furthermore, it critically evaluates nanocarriers and micellar systems to address pharmacokinetic limitations of quercetin while interrogating biocompatibility and scalability challenges, providing a balanced analysis of delivery innovations lacking in prior analyses. Critically, it redefines quercetin as a multimodal agent synergizing apoptosis induction, metastasis suppression, and microenvironment modulation, while positioning flavonoid based strategies at the heart of precision breast cancer therapeutics through comparative efficacy and toxicity profiling against standard chemotherapies. Collectively, these advances establish quercetin as a multitargeted agent in breast oncology, integrating mechanistic specificity, delivery optimization, and clinical translation to pioneer a phytochemical driven paradigm for targeted cancer therapy.

Conclusion

In conclusion, quercetin, a natural flavonoid, holds the potential to inhibit cancer cell proliferation, induce apoptosis, and prevent metastasis. It has demonstrated significant therapeutic value, especially in TNBC, a subtype that lacks effective therapeutic targets. By modulating key signaling pathways and enhancing immune responses, quercetin effectively curbs tumor progression. Moreover, its synergistic effects with traditional chemotherapeutic agents not only significantly enhance the efficacy of chemotherapy but also help overcome drug resistance. The potential of this combination therapy may lead to the development of more effective treatment regimens.

Although the preclinical findings are encouraging, the necessity and urgency of conducting clinical trials and translational research to translate quercetin into clinical applications cannot be overstated. These studies are crucial for validating the safety and efficacy of quercetin in real-world treatments and ensuring that it can provide precise and effective therapeutic options for breast cancer patients.

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Disclosure

The authors report no conflicts of interest in this work.

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