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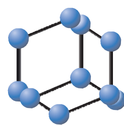

Application of Nanoparticles for Efficient Delivery of Quercetin in Cancer Cells

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Abstract: Quercetin (Qu, 3,5,7,3', 4'-pentahydroxyflavanone) is a natural polyphenol compound abundantly found in health food or plant-based products. In recent decades, Qu has gained significant attention in the food, cosmetic, and pharmaceutic industries owning to its wide beneficial therapeutic properties such as antioxidant, anti-inflammatory and anticancer activities. Despite the favorable roles of Qu in cancer therapy due to its numerous impacts on the cell signaling axis, its poor chemical stability and bioavailability, low aqueous solubility as well as short biological half-life have limited its clinical application. Recently, drug delivery systems based on nanotechnology have been developed to overcome such limitations and enhance the Qu biodistribution following administration. Several investigations have indicated that the nano-formulation of Qu enjoys more remarkable anticancer effects than its free form. Furthermore, incorporating Qu in various nano-delivery systems improved its sustained release and stability, extended its circulation time, enhanced its accumulation at target sites, and increased its therapeutic efficiency. The purpose of this study was to provide a comprehensive review of the anticancer properties of various Qu nano-formulation to augment their effects on different malignancies. Various targeting strategies for improving Qu delivery, including nanoliposomes, lipids, polymeric, micelle, and inorganic nanoparticle NPs, have been discussed in this review. The results of the current study illustrated that a combination of appropriate nano encapsulation approaches with tumor-oriented targeting delivery might lead to establishing QU nanoparticles that can be a promising technique for cancer treatment.

Keywords : Quercetin, cancer, nanoparticle, targeting delivery, flavonoid, apoptosis.

1. INTRODUCTION

Cancer is a general term referring to a set of diseases characterized by uncontrollable division and spread of abnormal cells that might result in metastasis-prone malignant tumors [1]. Nowadays, cancer is one of the leading causes of death, and it is estimated that the worldwide burden of cancer will increase by about 47% by 2040 [2-4]. So far, different approaches, such as biological therapy, chemotherapy, immunotherapy, radiotherapy, surgery, *etc.*, have been employed for cancer treatment. Despite their effectiveness and considerable medical advances in recent decades, such strategies have not shown adequate capabilities for treating malignant tumors. Since all cancer therapeutic methods have the risk of damaging normal cells and tissues, selectivity and targeting of cancerous cells are the major challenges in this way [5, 6].

Over recent decades, dietary and non-dietary phytochemical compounds, known as plant secondary metabolites, have attracted a great deal of attention in cancer studies and have shown the capability of being employed as promising anti-cancer agents due to their various functionalities and desirable safety features [7]. Phytochemicals own antioxidant activities and chemo-preventive roles leading to the inhibition of DNA damage prompted by oxidative stress in different types

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of cancer. Furthermore, phytochemicals modulate various cellular processes: angiogenesis, apoptosis, cell cycle, cell proliferation, DNA repair, inactivation of oncogenes, or activation of tumor suppressor genes [8]. Alkaloids, organosulfur, polyphenol, and terpenoid compounds are natural products displaying cancer chemotherapeutic and chemo-preventive potentials [9]. The most abundant natural polyphenols are flavonoids, phenolic acids, and stilbenes, while two-thirds of all polyphenols belong to the flavonoid group. These natural chemicals are found in plant-derived food materials such as fruits and vegetables. Flavonoid compounds such as curcumin, resveratrol, and quercetin have been remarkably studied in cancer treatment due to their biological activities and medical properties, namely anti-inflammation, cardio protection, antioxidant, antineoplastic and phytoalexin effects. Quercetin (Qu) is one of the flavonoids in various plant-based products, and its anti-cancer attributes have been investigated in several studies.

Numerous investigations have demonstrated that the co-application of Qu and conventional anti-cancer drugs has synergic effects on cancer treatment and improves efficiency. However, the clinical application of phytochemicals such as curcumin, resveratrol, and quercetin is restricted due to their low bioavailability and high hydrophobicity and, high therapeutic doses, low retention time in biological systems [10]. Recently, innovation in nanotechnology and its nanomedicine products, such as dendrimers, inorganic nanoparticles, liposomes, micelles, and polymers, has enhanced the efficiency of cancer treatment strategies. The application of Nanoparticles, particulate substances with a diameter between 1-100 nm, as medicine agents has improved advanced targeting and has a remarkable role in modern cancer therapies [11, 12]. The benefits of such nanomaterials compared with classic cancer treatment methods are their nanoscale and high surface-to-volume ratios. Therefore, they are adequately small to pass through the biological membrane, particularly those permeable vasculatures of malignant tumors. These properties resulted in the accumulation and increased levels of NPs around cancerous tissues. However, they are not only limited to passive delivery. Their surfaces can also be modified with various ligands, which may improve the targeting characteristics of NPs and reduce systemic toxicity [13-15]. Moreover, delivery systems based on nanotechnology are regarded as a promising approach to overcoming various challenges associated with the bioavailability, distribution, permeation, solubility, targeting, and toxicity of conventional chemotherapeutic drugs and natural antitumor materials such as curcumin, resveratrol, and quercetin [16, 17]. The main purpose of this review was to provide a comprehensive study on recent development in the encapsulation of Qu in NPs owning different formulations and compositions, as well as investigate the anticancer potentials of Qu-NPs in different types of cancer and their roles in the improvement of cancer therapeutic strategies.

2. QUERCETIN: A POTENT ANTICANCER AGENT

Quercetin (3,5,7,3', 4'-pentahydroxyflavanone) is one of the most abundant flavonoid compounds found in various fruits and vegetables such as acai berries, apples, broccoli, olive oil, onion, and red wine [18]. Following absorption in the small intestine, Qu is instantly metabolized *via* enzymes of the epithelial cells and then more metabolized in the liver. In its natural structure as a glycoside, Qu has the classic structure of flavonoids and is composed of two aromatic rings, A and B, attached through a heterocyclic ring comprising oxygen. Qu is an antioxidant compound that prevents other molecules from oxidation [19, 20]. When reacting with free radicals, Qu itself is converted to a free radical by donating a proton. The energy of radical forms of Qu is too low to be reactive because resonance delocalizes electrons. As Qu reacts with free radical species, its stability and antioxidant activities are provided by o-dihydroxyl groups in the B ring, 4-oxo, 2,3-alkene, 3-hydroxy, and 5-hydroxy groups [21, 22]. Although Qu has been known for its antioxidant activity, it exerts pro-oxidant properties at high concentrations. Additionally, Qu exhibits other bio-functions such as anti- or pro-apoptotic, anti-tumor, anti-inflammatory, as well as anti-proliferative effects and cell cycle arrest in the cell-scale studies [23]. Qu indicates its role in the suppressing cancer cell growth and proliferation by induction of apoptosis and autophagy, a decrease of metastasis *via* downregulation of epithelial-to-mesenchymal transition and reduction of multidrug or radiotherapy resistance which all related mechanisms are described in the following section.

3. MECHANISMS OF ANTICANCER EFFECTS OF QUERCETIN

3.1. Cell Cycle

The intervention of Qu with the cell cycle process is one of the prominent mechanisms by which tumor growth is suppressed. Qu can block the cell cycle at various phases by targeting different signaling molecules such as cyclins, cyclin-dependent kinase (CDK), cyclin-dependent kinase inhibitors (CDKI), and INK4 family (p15, p16, p18, p19). Lee *et al.* [24]

revealed that treatment of human leukemia cell lines (U937) with Qu (20 μM, 24 h) downregulated the expression of cyclin D, Cyclin E, and E2F while overexpressed cyclin B leading to cell cycle arrest at the G2/M phase. Administration of breast cancer cells with clinical doses of Qu (0-10 μM, 0-96 h) prevented the cell cycle at the G0/G1 phase *via* phosphorylation of pRb (protein retinoblastoma) followed by promotion of p21 which is an inhibitor of CDKs. Additionally, Qu reduced the regulation of cyclin B1 and CDK, illustrating the cell cycle arrest at the G2/M stage [25]. In human esophageal squamous cell carcinoma cell lines (KYSE-510) Qu (0-8 μM, 0-72 h) mediated cell cycle arrest at G2/M *via* overexpression of p21 and downregulation of cyclin B1 [26]. Similarly, administration of both ovarian carcinoma (SKOV3 cells) and cisplatin-resistant osteosarcoma (U2OSPt) human cell lines with Qu arrested the cell cycle *via* declining the regulation of cyclin D1 [27]. Furthermore, various investigations have disclosed that by affecting p53-associated pathways, Qu suppresses cell cycle development. In a study on human MCF-7 breast cancer cells, Qu (10-175 μM, 6-48 h) time and dose-dependently blocked the cell cycle at S and sub-G1 phases through decreased expression of CDK2, cyclin A and cyclin B and overexpressed p53 and p57 [28]. Priyadarsini *et al.* [29] indicated that Qu (80 μM, 24 h) inhibited cell cycle progression at the G2/M level by overexpression of p53, p21, and IκB along with downregulation of cyclin D1, IKKβ, NF-κB (p50 and p65), p-IκB-α, PCNA and Ub in HeLa cells. Hisaka *et al.* [30] studied the effect of Qu (0-100 μM, 0-72 h) on 13 different types of liver cancer cell lines and observed Qu may stimulate the cell cycle arrest at different G0/G1, G2/M, and S phases depending on cancer cell types. In a study on triple-negative breast cancer (MDA-MB-231 cells), it was reported Qu (0-80 μM, 0-72 h) arrested cell cycle at the S and G2/M phases *via* regulating the Foxo3a activity. Treatment of human colon cancer cells (HTC-116) with epigallocatechin Gallate (EGCC) and Qu (0-150 μg/mL, 0-24 h) significantly inhibited cell cycle progression at the G1 phase [31]. In an investigation into the $CD44^{+}/CD24^{-}$ phenotype of breast cancer stem cells, it was disclosed that Qu (0-50 μM, 48-72 h) considerably intensified the cytotoxicity of Doxorubicin (50-100 μM) in both normal and stem cells but their combination triggered cell cycle arrest at G2/M phase in the T47D cells and in a lower degree in $CD44^{+}/CD24^{-}$ cells [32].

3.2. Apoptosis

The programmed cell death process, known as apoptosis, is critical in the development, hemostasis, and integrity of multi-cellular organisms. Apoptosis is a set of biological processes, including bubbling, cell detachment, cytoplasm shrinkage, DNA breaking, and caspase activation *via* the extrinsic and/or intrinsic axis. Conclusive evidence shows that Qu suppresses cancer cell development by affecting intrinsic and extrinsic apoptosis pathways. In the intrinsic or mitochondrial process, Qu reduces the mitochondrial membrane potential and increases cytosolic calcium concentration resulting in the activation of caspase-3, -8, and -9, accompanied by releasing cytochrome C and cleaving poly-ADP-ribose polymerase (PARP). Moreover, Qu reduces the regulation of anti-apoptotic Bcl-2 proteins and increases the expression of the pro-apoptotic Bax protein and its translocation to the mitochondrial membrane. In extrinsic or the cell death receptor pathway, Qu induces apoptosis by affecting the modulation of FAS, TNFR1, TRAIL, *etc.* [33-35]. It was reported that Qu (0-100 μM, 6 h) stimulated apoptosis in Caco-2 and SW480 cell lines through overexpression of Bax and cleaved caspase-3, -9, and downregulation of Bcl-2 [36]. Teekaraman, Elayapillai *et al.* [37] revealed Qu (0-200 μM, 24 h) activated the intrinsic apoptosis pathway in human metastatic ovarian cancer PA-1 cell lines. In this way, Qu declined the levels of Bcl-2 and Bcl-xL and raised the expression of Bad, Bax, Bid, caspase-3, -9, and Cyt-c. Furthermore, in an investigation conducted by Shang *et al.* [38], Qu (0-200 μM, 24 h) by targeting both apoptotic pathways, *i.e.*, altering the regulation of Bad, Bax, Bid (pro-apoptotic molecules), Mcl-1, Bcl-2, Bcl-x (anti-apoptotic proteins) as wells TNFRSF10D and TRAIL as death receptors, decreased the viability of human gastric AGS cancer cells. Also, similar studies on colorectal, ovarian, and prostate cancer cells disclosed that Qu mediated both intrinsic and extrinsic apoptosis axis and decreased cell cancer proliferation [39-42].

3.3. Suppress Tumor Angiogenesis

Angiogenesis is the process of developing new capillaries mainly controlled by various proteins such as endostatin, adhesion molecules, growth factors, *etc.* In normal physiological conditions, angiogenesis is related to the development of the reproductive system and recovery of wounds. In contrast, dysregulation of angiogenesis is typically associated with neoplastic disorders and tumor invasion and metastasis. In the tumor angiogenesis, malignant cells interact with endothelial cells [43, 44]. Angiogenesis is a pivotal phase in cancer progression since providing nutrients and oxygen and escapes the environment for growing cancer cells. Additionally, tumor cells undertake a variety of circu-

lating pathways to establish and generate secondary tumors [45, 46]. Epidermal growth factor (EGF), basic fibroblast growth factor (b-FGF), vascular endothelial growth factor (VEGF), and matrix metalloproteinase (MMP) are protein agents mediating angiogenesis [47]. Several studies illustrated that Qu inhibits tumor growth and development by targeting angiogenesis. Applying human glioblastoma U251 cell lines, Liu *et al.* [48] demonstrated that targeting cancer cells with Qu (10 μg/mL, 24 h) suppressed cell migration and formation of the tube in human umbilical vein endothelial cells (HUVECs) mediated by downregulation of VEGFA, MMP2, and MMP9. Zhao *et al.* [49] investigated the effect of Qu (34 mg/kg/day, 21 days) on the MCF-7 cells xenografted into female BALB/c nude mice. It was exhibited that Qu reduced the level of VEGF, VEGFR2, NFATc3, sparse microvessel density, and calcineurin activity of injected tumors. In an *in-vitro* and *in-vivo* study on prostate cancer using PC-3 cell lines, it was revealed that Qu (0-50 μM, 24 h or 20 mg/kg/day, 16 days) reduced the expression VEGFR2 mediated Akt/mTOR/P70S6K signaling axis suggesting the potential of Qu in suppressing tumor growth and angiogenesis in PC-3 tumors [50]. Treatment of Eca109 of human esophageal cancer cell lines with Qu (0-10 μg/mL) led to a significance decrease in the level of invasion cells and migration distance. Also, Qu downregulated proteins mediating angiogenesis, including MMP-2, MMP-9, and VEGFA [51].

Endothelial-to-mesenchymal transition (EMT) is another crucial step in cancer metastasis. In this way, epithelial markers (E-cadherin, MUC1, *etc.*) downregulate while mesenchymal proteins (N-cadherin, Snail, Vimentin, *etc.*) overexpress. Studies have indicated that Qu, by targeting EMT-related proteins, inhibits tumor angiogenesis and invasion. Kee *et al.* [52] showed that Qu (10 or 50 mg/kg/2 days, 14 days) reduced the lung metastasis of colon cancer CT26 cell lines in xenograft BALB/c mice by targeting the EMT process, *i.e.*, downregulation of N-cadherin, β-catenin, and snail as well as increased expression of E-cadherin. Administration of Qu (50 μM, 24 h) into non-small cell A549 lung cancer cell lines injected into Female SCID mice suppressed A549 cell invasion and migration as well as bone metastasis. Further mechanistic studies illustrated that Qu inhibited the regulation of Snail-associated Akt *via* overexpression of maspin and a disintegrin and metalloprotease-9 (ADAM9) [53].

3.4. Regulate Autophagy

Autophagy is a fundamental catabolic process to provide integrity and viability to mammalian cells. In this process, aged and damaged cellular components and organelles are degraded by lysosomes leading to supporting self-stability and the energy cycle of cells [54, 55]. Under normal conditions, the rate of autophagy function is at a lower value with decreased cellular content degradation as well as nutrient recycling. However, under cellular stress conditions, autophagy is upregulated to preserve the integrity of cells by increasing cell substance degradation and recycling energy. Thus, dysregulation of autophagy may be associated with different pathological disorders such as cancer. In cancer, autophagy plays a double-edged sword. In the initial stages, autophagy functions as a tumor-inhibitor agent *via* the degradation of all harmful proteins and cellular materials. At the advanced stages, it plays a tumor-inducer agent by supporting the viability of cancer cells under a stressed environment or chemotherapeutic agents [56-58]. Wang *et al.* [59] represented that exposure of AGS and MKN28 gastric cancer cells with Qu (0-400 μM, 48 h) promoted the formation of autophagic vacuoles and acidic vesicular organelles, increased ratios of LC3-II to LC3-I and autophagy-related genes. Further studies indicated that Qu-induced autophagy *via* regulation of Akt/mTOR and hypoxia-induced factor-1α (HIF-1α) signaling cascades. In *in-vitro* and *in-vivo* studies on human leukemia HL-60 cells (0-100 μM, 24 h), it was disclosed that Qu inhibited the cell cycle, promoted apoptosis by PARP cleavage and caspase activation, and induced autophagy by augmented expression of light chain 3 (LC-3)-II, reduced expression of p62 and generation of acidic vesicular organelles [60]. Luo *et al.* [61] reported that treatment of human lung cancer cell lines (A549) with Qu (0-80 μM, 12 h) dose-dependently developed TRAIL-promoted A549 cell death by activation of autophagy flux *via* reducing the expression of p62 and upregulating GFP-LC3B. In a study on HeLa cervical cancer cells, Qu (0-100 μM, 24 h) increased the level of activated caspase-3, Beclin 1, and LC3-I/II ratio in a dose-dependent manner while the decreased the phosphorylation level of S6K1 suggesting suppressed cell proliferation due to autophagy and apoptosis induction [62]. In an investigation into human breast cancer cell lines (MCF-7 and MDA-MB-231) conducted by Jia, Huang [63], Qu (0-100 μM, 0-48 h) reduced glycolysis to suppress tumor migration *via* declining tumor microenvironment acidity. Additionally, Qu activated autophagy *via* blocking p-Akt/mTOR signaling leading to inhibiting tumor growth and metastasis.

4. DRUG DELIVERY STRATEGIES

Modern drug delivery approaches have been initiated since 1950 and being consistently developed over this period. Before 1950, drugs were formulated as a pill or capsule releasing their effective ingredients ins-

tantly upon exposure to water without any capability to regulate the release rate of drugs. However, the first drug formulation with sustained release enjoying 12 h efficacy was introduced in 1952 [64]. Yun *et al.* [65] represented three distinct generations in the development of drug delivery systems. Over the first generation between 1950 and 1980, the fundamental mechanisms of drug release particularly associated with oral and transdermal dosage forms were achieved in which dissolution- or diffusion controlled, ion-exchange and osmosis-based delivery mechanisms were of paramount importance. The second generation (1980-2010) of drug delivery technology was less prosperous than the first due to dealing with the complicated formulation. The most difficult part of this period was controlled-release time since drugs were incorporated in bio-degradable polymers to release for a month or more, while 50% of the drug was released in the first day or two, owning to initial burst release [66]. During 2nd generation time, smart polymers and hydrogels, as well as nanoparticles, were applied for peptide and protein, gene, and tumor-targeted delivery. Although such therapeutic strategies were promising based on animal models, they have limited success in clinical trials because of the inability to control the responses of the body following the delivery of parenterally administrated drugs [67]. The advantage of the third generation of drug delivery systems over previous ones is dominating both biological and physiological obstacles [68]. The most remarkable delivery strategies related to the last generation will be introduced in the following sections.

4.1. Nanoparticle Drug Delivery Systems

The effectiveness of anticancer drugs is associated with, firstly, the ability of drugs to penetrate through the body's biological barriers to reach the tumor tissues with minimum reduction in their activity or size in the blood circulation. Secondly, drugs should potentially selectively remove tumor cells without any adverse effects on normal ones. These fundamental objects may improve the survival rate of patients and their quality of life. Producing drugs with incremented intracellular concentration and declined dose-limiting toxicities concurrently may result in such purposes [69]. Cumulative investigations have indicated that nanoparticles (NPs) can meet both requirements for efficient drug delivery systems. Furthermore, most NPs -related studies have concentrated on targeted drug delivery, particularly tumor-targeted drug delivery [65, 68, 70].

Nanoparticles are nano-sized substances whose diameter is varied between 10-1000 nm. The advantages of applying NPs as delivery systems are improving drug half-life, increasing the solubility of hydrophobic drugs, and modulating drug release in a controlled or sustained way. Several studies have revealed that different types of NPs (Fig. **1**), including organic nanocarries such as lipids (liposomes and solid lipid nanoparticles), polymers (dendrimers, micelles, and polymeric nanoparticles), virus-based nanoparticles as well as inorganic nano-carriers such as carbon nanotube and mesoporous silica nanoparticles can be regarded as a promising strategy for targeted delivery systems [71].

5. QUERCETIN NANOPARTICLES

Regardless of the extensive antitumor activities of Qu mentioned in section 3, its *in-vivo* application its restricted due to poor water solubility, low bioavailability, weak oxidant stability, and huge limitation of biotransformation resulting in inadequate therapeutic effects. Despite various investigations that have been carried out in humans and animals, the pharmacokinetics of Qu has not been completely distinguished [72, 73]. Furthermore, immediately after entering the body, Qu is easily metabolized and exerted *via* urine, leading to its very low accumulation in the target site. Fast absorption, rapid elimination, trace accumulation, and short peaks are the significant features of the pharmacokinetics of Qu following oral administration in the human body. Low water solubility and insufficient absorbtion absorption and dissolution lead to reduced Qu bioavailability [74-76]. Due to the low bioavailability of Qu, novel NPs-Qu formulations have been developed to overcome such deficiency and enhance the pharmacological effects of Qu. In a rat model, the main absorption sites of Qu were the stomach and small intestine. Absorption of Qu from the small intestine to blood is predominantly conducted *via* passive diffusion of peptides as well as organic anion transporters (OAT). According to various studies, Qu and its metabolites are highly distributed and accumulated in the lungs (rats), liver, and kidney (pigs). The Biotransformation of Qu directs by the xenobiotic metabolism pathway, generally containing modification, conjugation, and elimination. Half-lif of Qu in plasma is low, and its metabolites are exerted as a prodrug by kidneys, feces, bile, and respiratory tract.

Hence, the challenge has been the effective delivery of Qu to the tumor with the minimum level of off-target elimination. One of the proposed strategies for overcoming such obstacles is the incorporation of Qu in NPs. It has been depicted that NPs enjoy massive advantages of delivering hydrophobic compounds such as Qu, namely high entrapment rate, increased circulation time, enhanced therapeutic effects, as well as targeted and controlled delivery. Different studies have

evaluated the pharmacokinetics of free and NPs forms of Qu. Sharma *et al.* [77] reported about 40% of Qu was released from MPEG-PLA-Qu NPs in 12 h after peritumoral injection due to the initial burst release followed by slow release of reminded Qu (about 60%) until 3 days owning to slow release of Qu from NPs. At the same time, rapid ablation of Qu was observed in mice treated with free Qu. In another study into LMPM-Qu NPs, it was observed intravenous administration of free-Qu or LMPM-Qu NPs (10 mg/kg) in rats led to a greater half-life of LMPM-Qu NPs [78]. Additionally, Qu-incorporated exosomes had higher stability, solubility, antioxidant, and anti-inflammatory properties and enhanced oral efficiency and drug loading [79]. Accordingly, different types of designed NPs systems have been advanced to the effective delivery of Qu to the tumor-specific site (Table **1**), and the most significant platforms will be presented in the following sections.

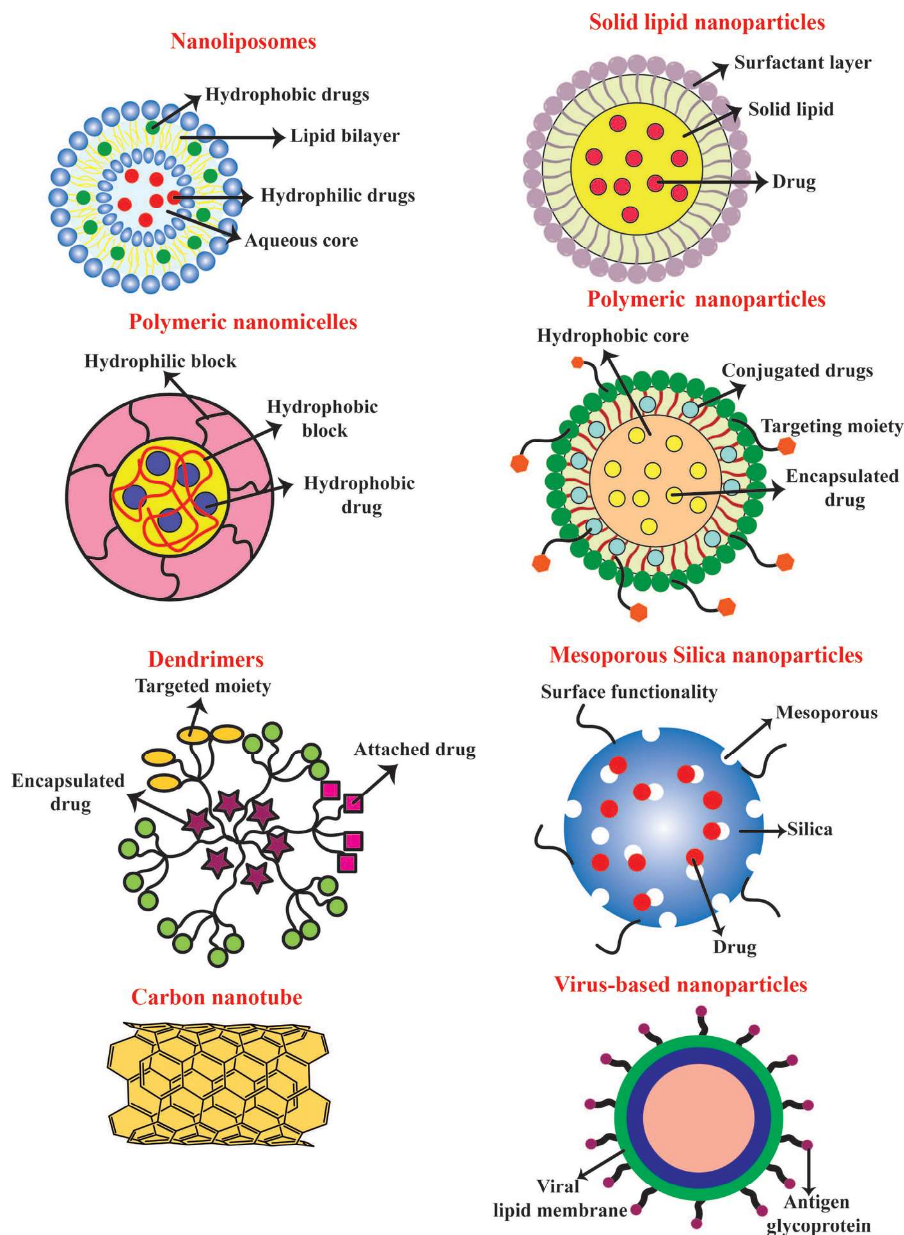

Fig. (1). Various NP systems applied in the development of Qu nanoformulation for cancer treatment. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 1. A brief of various studies related to application of Qu-NPs in cancer treatment.

NPs Type	Cancer Type	NPs Formulation	NPs Dose	Study Model	Effects	Mechanisms	References
Nanoliposomes	Breast	Qu-NLP	*In vitro*: 0-50 µM *In vivo*: -	*In vitro*: MCF-7 cell lines *In vivo*: -	Reduced cell viability and proliferation.	-	[166]
-	Breast	DSPE-PEG2000-Bi-Dox-Qu	*In vitro*: (Dox: 10 µg/mL) *In vivo*: (Dox: 5 mg/kg), tail vein injection	*In vitro*: MCF-7 and MCF-7/ADR cell lines *In vivo*: xenograft mice	Reduced cell survival, tumor size and overcome multi-drug resistance.	↑- ↓P-gp	[167]
-	Liver	Qu-CS-NL	*In vitro*: 0-10 µg/mL *In vivo*: -	*In vitro*: HepG2 cell lines *In vivo*: -	Decreased cell viability.	-	[85]
-	Cervix	Qu-NLP	*In vitro*: 0.1-100 µM *In vivo*:20 mg/kg, tail intravenous injection	*In vitro*: HeLa cell lines *In vivo*: Xenograft mice	Decreased survival rate and proliferation, declined tumor weight and size.	-	[86]
-	Lung	CDO14-GQu-siIGF-1R	*In vitro*: (GO: 0.25 µg, siRNA 0.1 µg, and CDO14: 25 µg per well) *In vivo*: (GO: 25 µg/20g, siRNA 10 µg/20 g, and CDO14: 250 µg/20g), tail vein injection	*In vitro*: A549 and NCI-H460 cell lines *In vivo*: Xenograft mice	Reduced cell viability, increased apoptosis rate, decreased tumor volume.	↑Bax ↓Bcl-2, IGF-1R	[87]
-	Breast and leukemia	AMD-Qu-NL	*In vitro*: 0.01-3.5 µg/mL *In vivo*: 15 mg/kg, tail vein injection	*In vitro*: HL-60, HL-60/-DAR, MCF-7 and MCF-7/ADR cell lines *In vivo*: xenograft mice	Reduced cell growth and tumor, size, decreased the resistance of cells to AMD.	-	[88]
-	Breast	MPA-LPN and Qu-LPN	*In vitro*: (MPA-LPN: 10-60 µg/mL, MPA-Qu: 10-60 µg/mL) *In vivo*: (MPA-LPN: 25 mg/kg, MPA-Qu: 25 mg/kg)	*In vitro*: MCF-7 cell lines *In vivo*: SD rats	Decreased cell proliferation, tumor burden, and size, induced apoptosis.	-	[168]
-	Breast	MPA-LPN and Qu-LPN	*In vitro*: (MPA-LPN: 10-60 µg/mL, MPA-Qu: 10-60 µg/mL) *In vivo*: (MPA-LPN: 25 mg/kg, MPA-Qu: 25 mg/kg)	*In vitro*: MCF-7 cell lines *In vivo*: SD rats	Reduced cell viability and tumor size.	-	[89]
Lipid nanoparticle	Liver	FA-Qu-PL-GA-LNP	*In vitro*: 10-100 µg/mL *In vivo*: -	*In vitro*: HepG-2 cell lines *In vivo*: -	Decreased cell growth rate, tumor size, and volume.	-	[100]
-	Bladder	LCP-QP	*In vitro*: - *In vivo*: 5.5-30 mg/kg, intravenous injection	*In vitro*: - *In vivo*: Xenograft mice (U-MUC3 cell lines)	Reduced tumor volume.	↑- ↓Wnt 16	[99]
Nanostructured lipid carriers	Melanoma	Qu-LNC	*In vitro*: - *In vivo*: 50 mg/kg, intravenous injection	*In vitro*: - *In vivo*: Xenograft mice (B16F10 cell lines)	Reduced tumor volume and lung metastasis.	↑- ↓-	[169]
-	Lymphoma	VCR-Qu-LNC	*In vitro*: 0-20 µg/mL *In vivo*: 20 mg/kg, intravenous injection	*In vitro*: Raji and Raji/VCR cell lines *In vivo*: Xenograft mice	Decreased cell growth and tumor volume.	↑- ↓-	[105]
-	Breast	BSA-Qu-LNC	*In vitro*: 0.5-10 µg/mL *In vivo*: -	*In vitro*: MCF-7 cell lines *In vivo*: -	Reduced cell viability and proliferation.	-	[106]

(Table 1) contd....

NPs Type	Cancer Type	NPs Formulation	NPs Dose	Study Model	Effects	Mechanisms	References
Nanoemulsions	Breast	Qu nanoemulsion	*In vitro*: 20-80 µg/mL *In vivo*: 50 mg/kg, oral administration	*In vitro*: MCF-7 cell lines *In vivo*: SD rats	Declined cell viability, angiogenesis, and tumor burden as well as size, promoted apoptosis.	↑- ↓IL-6, MMP2, MMP9, TNF-α	[170]
-	Breast	AG-PVP-Hap-Qu nanoemulsion	*In vitro*: 60 µg/mL *In vivo*: -	*In vitro*: MCF-7 cell lines *In vivo*: -	Decreased cell viability and induced apoptosis.	-	[171]
Nanopolymers	Ovarian	MPEG-PCL-Qu	*In vitro*: 0-30 µg/mL *In vivo*: 60 mg/kg, intravenous administration	*In vitro*: A2780 cell lines *In vivo*: xenograft mice	Reduced cell viability and proliferation, decreased tumor volume, induced apoptosis, collapsed mitochondrial membrane potential.	↑Bax, cleaved caspase-3, -9 ↓Bcl-2, Mcl-1, p-Akt, p-MAPK	[114]
-	Glioblastoma	PEG2000-DPSE-Qu	*In vitro*: 50-200 µM *In vivo*: -	*In vitro*: C6 cell lines *In vivo*: -	Decreased cell viability and tumor volume.	↑Caspase-3, Cytochrome-c, p53, ROS ↓-	[172]
-	Cervix, glioblastoma, and colon	PLGA-PEG--FA-Qu	*In vitro*: 10 or 100 µg/mL *In vivo*: 50 mg/mL, 250 µL, intravenous administration	*In vitro*: HeLa, CT-26, and C6 cell lines *In vivo*: xenograft mice (HeLa cells)	Decreased cell viability and tumor volume.	-	[173]
-	Breast	HA-Qu	*In vitro*: - *In vivo*: 8 mg/kg, intravenous injection *via* tail vein	*In vitro*: MCF-7 cell lines *In vivo*: Rats	Reduced cell viability and tumor weight.	-	[174]
-	Breast and ovarian	HA-NP-M-TO-Qu	*In vitro*: 0.01 or 10 µM *In vivo*: 1 mL, intravenous administration	*In vitro*: A2780(p), A2780(adr), and MCF-7 cell lines *In vivo*: Wistar rats	Decreased cell viability.	↑- ↓P-gp	[175]
-	Pancreatic	5-FU-Qu-Cs	*In vitro*: (Qu: 2.7-53 µM and 5-Fu: 5-100 µM) *In vivo*: -	*In vitro*: MiaPaCa2 cell lines *In vivo*: -	Reclined cell growth and viability.	-	[176]
-	Breast	mPEG-PLGA-Qu	*In vitro*: (Qu: 3.375-13.5 µg/mL) *In vivo*: 30 mg/kg (Qu: 0.5 and 4 mg/kg), peritumoral injection	*In vitro*: 4T1 and MDA-MB-231 cell lines *In vivo*: xenograft mice	Decreased cell survival rate and tumor volume.	-	[77]
-	Breast	mPEG-PLGA-Qu-Dox	*In vitro*: (Qu: 15 µg/mL, Dox: 2.5 µg/mL) *In vivo*: (Qu:30 mg/kg, Dox: 5 mg/kg)	*In vitro*: MDA-MB-231 cell lines *In vivo*: xenograft mice	Decreased cell viability and tumor volume and cardio-toxicity.	-	[116]
-	Breast	P(-CL)-TPGS-Qu	*In vitro*: 125-500 µg/mL *In vivo*: -	*In vitro*: SKBR3 cell lines *In vivo*: -	Reduced survival rate.	-	[177]
-	Glioblastoma and colon	Qu-FD-NM	*In vitro*: 50-400 nM *In vivo*: 25 mg/kg, intragastrical administration	*In vitro*: Caco-2 and C6 cell lines *In vivo*: Xenograft mice	Reduced C6 cell viability.	-	[19]
-	Colon and liver	PLGA-CS-PEG-Qu	*In vitro*: 0-100 µM *In vivo*: -	*In vitro*: HCT116 and HepG2 cell lines *In vivo*: -	Reduced cell viability.	↑- ↓-	[178]

(Table 1) contd....

NPs Type	Cancer Type	NPs Formulation	NPs Dose	Study Model	Effects	Mechanisms	References
-	Breast and skin	Dox-Qu-p-Phe-b-pHis-b-PEG	*In vitro*: 0.01-1 µg/mL *In vivo*: 5 mg/kg, Oral administration	*In vitro*: MCF-7, MDA-MB-231 and SCC-7 cell lines *In vivo*: xenograft mice	Reduced cell proliferation and tumor volume, induced apoptosis, increased oxidative stress, decreased migratory capacity, and arrested cell cycle at the G2/M phase.	↑Bax, Caspase-3, PARP ↓CD31, Ki67	[117]
-	Breast and lung	Qu-Cs NP	*In vitro*: 0.1-10 µg/mL *In vivo*: 5 mg/kg, intravenous administration	*In vitro*: A549 and MDA-MB-468 cell lines *In vivo*: SD rats	decreased cell growth and tumor weight.	↑- ↓-	[179]
-	Breast	BSA-Dox-Qu	*In vitro*: 12.5-200 µM *In vivo*: Dox: 2 mg/kg, intravenously tail vein administration	*In vitro*: MCF-7 and MDA-MB-231 cell lines *In vivo*: xenograft mice	Reduced cell proliferation and tumor weight.	↑- ↓P-gp	[180]
-	Breast and laryngeal	TF-Qu--PLGA	*In vitro*: 0-20 µg/mL *In vivo*: 5 mg/kg, intravenously tail vein administration	*In vitro*: HEp-2 and MDA-MB-468 cell lines *In vivo*: xenograft mice	Decreased cell survival and arrested the cell cycle at the Sub--G1 phase.	↑- ↓-	[181]
-	Breast	HPG-GO-Qu	*In vitro*: 3-48 µg/mL *In vivo*: -	*In vitro*: MCF-7 cell lines *In vivo*: -	decreased cell viability	↑- ↓-	[182]
-	Neuroblastoma	Dex-Ald-Qu	*In vitro*: 0-400 µg/mL *In vivo*: -	*In vitro*: BE [2]-C and SH-SY5Y cell lines *In vivo*: -	Decreased cell viability and triggered apoptosis.	↑cleaved caspase-3 ↓-	[183]
-	Breast	PCL-Cs--FA-Qu	*In vitro*: 50-400 nM *In vivo*: -	*In vitro*: MCF-7 and T-47D cell lines *In vivo*: -	Reduced cell viability.	-	[127]
-	Lung	PEG-Qu	*In vitro*: 0-150 µg/mL *In vivo*: -	*In vitro*: A549 cell lines *In vivo*: -	Reduced cell proliferation and induced apoptosis.	↑- ↓-	[184]
-	Papilloma	mPEG5K-NH2-Qu-Dox	*In vitro*: 1-1000 µg/mL *In vivo*: -	*In vitro*: KB cell lines *In vivo*: -	Decreased cell proliferation and increased Dox sensitivity.	↑- ↓-	[185]
-	Breast	LyP-1-LMWH-Qu-GA	*In vitro*: 3-48 µg/mL *In vivo*: 12 mg/kg, subcutaneous injection	*In vitro*: 4T1, HL-60, and MCF-7 cell lines *In vivo*: xenograft mice	Declined cell viability and angiogenesis.	↑- ↓P-gP	[123]
-	Ovarian	ADR-R-Qu	*In vitro*: 0.01-1000 nM *In vivo*: (ADR: 5 mg/kg, R: 19.68 mg/kg, Qu: 26.06 mg/kg), tail vein injection	*In vitro*: A2780ADR and ES2-Luc cell lines *In vivo*: Xenograft mice	Reduced cell viability and tumor volume, decreased the level of ADR-induced cardiotoxicity, promoted apoptosis.	↑- ↓CKM, cTnI	[115]
-	Breast	TQ-PEG--mAb	*In vitro*: TQ: 0.625-60 µM *In vivo*: TQ: 4.6 mg/kg, tail vein injection	*In vitro*: MCF-7, MCF-7/ADR and MDA-MB-231 cell lines *In vivo*: xenograft mice	Reduced cell viability and tumor size, depolarization of mitochondrial membrane potential.	↑ROS ↓-	[121]
-	Colon	Qu-Cs-Dox	*In vitro*: 6.25-100 µg/mL *In vivo*: -	*In vitro*: Caco-2 cell lines *In vivo*: -	Decreased cell viability and increased mucosal permeability for Dox.	↓P-gp	[124]
-	Breast	Qu-CA-Cs--Dox	*In vitro*: 3.125-50 µg/mL *In vivo*: -	*In vitro*: MCF-7/DAR cell lines *In vivo*: -	Reduced cell proliferation, improved drug intracellular accumulation, and efflux mitigation.	↓P-gp	[125]
-	Colon	Qu-Eudragit® S100	*In vitro*: 0.1-1000 µM *In vivo*: 12 mg/kg µL, subcutaneous injection	*In vitro*: CT26 cell lines *In vivo*: -	Reduced cell proliferation.	↑- ↓-	[186]
-	Lung	QHM-F@Cur-Bai	*In vitro*: 1-500 µg/mL *In vivo*: 1µg/g, tail vain injection	*In vitro*: A549 cell lines *In vivo*: -	Decreased cell viability and tumor volume.	↑- ↓-	[187]

(Table 1) contd....

NPs Type	Cancer Type	NPs Formulation	NPs Dose	Study Model	Effects	Mechanisms	References
-	Breast	FA-L-PEG-P-CL-Qu-TMX	*In vitro*: 4.1-20.7 µg/mL *In vivo*: 10 mg/kg, Oral administration	*In vitro*: 4T1 cell lines *In vivo*: xenograft mice	Reduced cell proliferation and tumor volume.	-	[128]
-	Colon	QA-M	*In vitro*: 0.04-200 µM *In vivo*: Qu: 3 mg/kg, A: 9 mg/kg, intravenous injection	*In vitro*: CT26-FL3 cell lines *In vivo*: Xenograft mice	Reduced cell proliferation, improved drug intracellular accumulation, and efflux mitigation.	↑CRT, p-AMPKα ↓Bcl-2, Bcl-xL mTOR, p-mTOR	[126]
-	Glioblastoma	PLGA-Qu	*In vitro*: 1-100 µg/mL *In vivo*: 12 mg/kg, subcutaneous injection	*In vitro*: C6 cell lines *In vivo*: xenograft mice	Decreased cell growth and viability.	↑- ↓-	[122]
-	Breast	HoS-Apo-Qu-Cur	*In vitro*: 0-80 µM *In vivo*: -	*In vitro*: MCF-7 cell lines *In vivo*: -	Reduced cell proliferation and stimulated apoptosis.	↑ROS ↓-	[188]
-	Breast	Qu NP	*In vitro*: 25-250 µg/mL *In vivo*: 20 mg/kg, injection *via* tail vein	*In vitro*: MCF-7 cell lines *In vivo*: SPF-SD rats	Reduced cell viability and tumor volume, repaired immune damage.	↑- ↓-	[189]
-	Lung	Lf-Ch-S-Res-Qu	*In vitro*: 6.25-200 µg/mL *In vivo*: -- mg/kg, injection *via* tail vein	*In vitro*: MCF-7 cell lines *In vivo*: SPF-SD rats	Reduced cell viability and tumor volume, repaired immune damage.	↑Caspase-3 ↓Ki-67, VGE-F-1	[190]
-	Lung	PL-GA-PEG-Qu-Gef	*In vitro*: 0.5-20 µg/mL *In vivo*: 20 mg/kg, tail vein injection	*In vitro*: PC-9 cell lines *In vivo*: xenograft mice	Reduced cell viability and tumor volume.	-	[191]
-	Prostate	PL-GA-PEG-LHRH-Qu-DTX	*In vitro*: 0-20 µg/mL *In vivo*: (Qu: 15 mg/kg, DTX: 5 mg/kg), tail vein injection	*In vitro*: LNCaP and PC-3 cell lines *In vivo*: xenograft mice	Reduced cell survival and tumor volume, induced apoptosis.	↑Caspase-3 ↓-	[192]
-	Breast	B780-Qu	*In vitro*: 1-20 µM *In vivo*: 2 mg/kg, tail vein injection	*In vitro*: 4T1 cell lines *In vivo*: xenograft mice	Decreased cell viability and tumor weight.	↑- ↓HSP-70	[193]
-	Breast	QDAF-Cur	*In vitro*: 0.5-20 µg/mL *In vivo*: -, tail vein injection	*In vitro*: MCF-7 cell lines *In vivo*: xenograft mice	Reduced cell proliferation, migration, and invasion, induced apoptosis, and necrosis, decreased tumor size.	↑- ↓-	[194]
-	Breast, colon, gastric, liver, and lung	F-127-Qu NP and Starch-Qu NP	*In vitro*: 0.5-20 µg/mL *In vivo*: 20 mg/kg, tail vein injection	*In vitro*: MCF-7, HC-T-116, BGC-823, HepG-2 and A549 cell lines *In vivo*: xenograft mice	Declined cell growth and proliferation.	-	[195]
-	Breast and liver	HA-Qu	*In vitro*: 0-80 µg/mL *In vivo*: 10 mg/kg, tail vein injection	*In vitro*: 4T1 and HepG2 cell lines *In vivo*: xenograft mice (4T1 cells)	Declined cell viability, induced apoptosis, and reduced tumor size.	Blocking CD44 receptors	[120]
-	Breast	Lyp-1-Qu-SF	*In vitro*: 0.1-32 µM *In vivo*: 5 mg/kg, intravenous injection	*In vitro*: 4T1 cell lines *In vivo*: xenograft mice	Reduced cell viability, metastasis, and invasion, declined tumor volume, induced apoptosis, and autophagy, Arrested cell cycle at G2/M.	↑LC3II ↓MMP2, MM-P9, PKM2	[118]
-	Breast	γ-Alumina-C-S-PVP-Qu	*In vitro*: 7 µg/mL *In vivo*: -	*In vitro*: MCF-7 cell lines *In vivo*: -	Decreased cell proliferation and induced apoptosis.	-	[196]
-	Breast, cervix, intestine, and gastric	PDA-Qu	*In vitro*: 0-30 µg/mL *In vivo*:	*In vitro*: HeLa, HIC, MCF-7, and SGC-7901 cell lines *In vivo*: -	Reduced cell proliferation.	-	[197]

(Table 1) contd....

NPs Type	**Cancer Type**	**NPs Formulation**	**NPs Dose**	**Study Model**	**Effects**	**Mechanisms**	**References**
-	Lung	Cet-CT-Qu and Cet-C-T-PTX	*In vitro*: Cet-CT-Qu: 0-32 µg/mL Cet-CT-PTX: 2 µg/mL *In vivo*: Cet-CT-Qu: 80 µg/kg Cet-CT-PTX: 10 µg/g intraperitoneal injection	*In vitro*: A549 and A549/-Taxol cell lines *In vivo*: xenograft mice	Decreased cell viability, tumor weight, and increased sensitivity of cells to paclitaxel.	↑- ↓p-Akt, p-ERK	[119]
Dendrimers	Glioblastoma	Telodendrimer-PEG-PLGA-Qu	*In vitro*: 01-100 µg/mL *In vivo*: 12 mg/kg, subcutaneous injection	*In vitro*: U251 cell lines *In vivo*: xenograft mice	Decreased cell growth and viability.	↑- ↓-	[132]
Carbon nanotube	Breast and pancreatic	N--TAM-TEG-MWCNT-Qu	*In vitro*: 0-500 µg/mL *In vivo*: -, tail vein injection	*In vitro*: MDA-MB-231 cell lines *In vivo*: xenograft mice	Decreased cell viability.	↑- ↓-	[137]
-	Breast and pancreatic	MWCNT-P-m-Qu	*In vitro*: 5.875-94 µg/mL *In vivo*: -	*In vitro*: MDA-MB-231 and PANC-1 cell lines *In vivo*: -	Reduced cell viability.	↑ROS ↓-	[138]
Graphene	Lung	Qu-GO	*In vitro*: 0.1-150 µg/mL *In vivo*: -	*In vitro*: A549 cell lines *In vivo*: -	Declined cell growth and induced apoptosis.	-	[198]
-	Ovarian	GO-PVP-Qu-Gef	*In vitro*: 0-10 µg/mL *In vivo*: -	*In vitro*: PA-1 cell lines *In vivo*: -	Reduced cell viability.	-	[140]
-	Lung	rGO-Fe_3O_4-GL-PF-Qu	*In vitro*: 0-120 µg/mL *In vivo*: -	*In vitro*: A549 cell lines *In vivo*: -	Declined cell survival.	-	[199]
Silica NPs	Breast	PAA-CS-MS-N-cRGD-Qu	*In vitro*: 0-2.1 µg/mL *In vivo*: 5 mg/kg intravenous injection	*In vitro*: MCF-7 and MDA-MB-231cell lines *In vivo*: xenograft mice	Decreased cell proliferation and tumor volume, induced apoptosis, and disturbed mitochondrial membrane potential.	↑ATF4, Bax, caspase-3 and -9, Chop, Cyt-C, JNK p53, p-ERK ↓Bcl-2	[144]
-	Breast	MSN-FA-Qu	*In vitro*: 0-100 µg/mL *In vivo*: 5 mg/kg intravenous injection	*In vitro*: MCF-7 and MDA-MB-231cell lines *In vivo*: xenograft mice	Reduced cell viability and migration, arrested cell cycle at the G1 phase, induced apoptosis, and reduced tumor volume.	↑Bax, cleaved caspase-3 ↓Akt,	[145]
-	Breast	Si-Qu	*In vitro*: 0-200 µg/mL *In vivo*: 5 mg/kg intraperitoneal injection	*In vitro*: 4T1 cell lines *In vivo*: xenograft mice	Reduced cell viability and tumor volume.	-	[200]
-	Breast	MSNs-Ch-S@PQ	*In vitro*: Qu: 1.5-45 µg/mL *In vivo*: 100 µg/kg, vein tail injection	*In vitro*: MCF-7/DAR cell lines *In vivo*: xenograft mice	Declined cell viability, induced apoptosis, arrested cell cycle at the G2/M phase, intensified microtubule destruction, enhanced sensitivity of cells to paclitaxel, decreased tumor volume.	↑- ↓P-gp	[201]
-	Colon	FA-Fe-S-BA-15-Qu	*In vitro*: Qu: 5-30 µg/mL *In vivo*: 15 µg/kg, intraperitoneal injection	*In vitro*: HCT-116 cell lines *In vivo*: xenograft mice (C-T-26 cells)	Decreased cell viability and tumor weight, induced apoptosis, depolarized mitochondrial membrane potential.	↑Apaf-1, Bax, Caspase-3 and -9, Cyt-C, ROS, p-JNK, p-p53, ↓Bcl-2, HSP27	[146]
Metallic Nanoparticle	Lymphoma	Qu-GA-Ag-Se NPs	*In vitro*: 0-500 µg/mL *In vivo*: -	*In vitro*: Dalton's lymphoma cell lines *In vivo*: -	Decreased cell viability.	↑- ↓-	[202]

(Table 1) contd....

NPs Type	Cancer Type	NPs Formulation	NPs Dose	Study Model	Effects	Mechanisms	References
-	Cervix, liver, and skin	Au-Qu-PLGA	*In vitro*: 10-60 µg/mL *In vivo*: -	*In vitro*: HeLa, HepG-2 and A375 cell lines *In vivo*: -	Reduced cell proliferation, arrested the cell cycle at the sub--G1 phase, induced apoptosis, depolarized mitochondrial membrane potential.	↑Apaf-1, Caspase-3 and -9, cleaved PARP, p21, p53, ROS ↓Bcl-2, Bcl-xL, Mcl-1, CDK1, Cyclin D1, HDAC, p-Akt, Rac	[150]
-	Breast and Cervix	SPION@APTES@FA-PEG@Qu	*In vitro*: 5-100 µg/mL *In vivo*: -	*In vitro*: Caski, HeLa and MCF-7 cell lines *In vivo*: -	Decreased cell viability and enhanced apoptosis.	↑Caspase-3, 7 ↓-	[155]
-	Breast	Au-Qu	*In vitro*: 0-125 µM *In vivo*: 25 mg/kg, intratumoral injection	*In vitro*: MCF-7 and MDA-MB-231 cell lines *In vivo*: SD rats	Reduced cell viability, invasion, and migration, inhibited the EMT process.	↑E-cadherin ↓Akt, N-Cadherin, MMP-2, MMP-9, p-EGFR, GSK3β, p-PI3K, Slug, Snail, Twist, VEGFR-2, Vimentin,	[152]
-	Glioblastoma	Au-Qu-PLGA	*In vitro*: 40 and 50 µg/mL *In vivo*: 40 and 80 µg/mL, intraperitoneal injection	*In vitro*: U87 cell lines *In vivo*: xenograft mice	Reduced cell viability and tumor size, induced apoptosis and autophagy.	↑Atg1, Beclin1, LC3I, LC3II, Apaf-1, Bad, Bax, Cleaved-caspase-3, Cleavead PARP, ERK, GAIP, p53 ↓Akt, Bcl-2, Bcl-xL mTOR, p62, PI3k	[203]
-	Cervix	Au-Qu-PLGA	*In vitro*: 10 and 20 µg/mL *In vivo*: 10-20 mg/kg, subcutaneous injection	*In vitro*: HeLa and Siha cell lines *In vivo*: xenograft mice	Decreased cell proliferation, triggered apoptosis and autophagy, inhibited the cell cycle at the G0/G1 phase, and reduced tumor size and weight.	↑Apaf-1, Bad, Bax, Caspase-3, p-GSK ↓Bcl-2, Cyclin D1, p-Akt, PI3K, p-JAK2, p-mTOR, p-STAT	[61]
-	Breast	Au-Qu	*In vitro*: 0-125 µM *In vivo*: -	*In vitro*: MCF-7 and MDA-MB-231 cell lines *In vivo*: -	Declined cell viability, invasion, and proliferation, induced apoptosis.	↑Bax, Caspase-3, GSK3β ↓Bcl-2, Cyclin D1, EGFR, Akt, p-PI3K, p-mTOR, p-PTEN	[151]

(Table 1) contd....

NPs Type	Cancer Type	NPs Formulation	NPs Dose	Study Model	Effects	Mechanisms	References
-	Lung	Fe3O4@-SiO2(-FITC)-BT-N/Qu/DOX	*In vitro*: 1-200 µg/mL *In vivo*: -	*In vitro*: A549 cell lines *In vivo*: -	Reduced cell viability and proliferation, triggered apoptosis, sensitize cancer cells to Dox, and suppressed the cell cycle at the G2/M phase.	↑- ↓-	[153]
-	Breast and Cervix	Fe_3O_4-P-CA-PEG-FA-Qu	*In vitro*: 25-100 µg/mL *In vivo*: -	*In vitro*: MDA-MB-231 and HeLa cell lines *In vivo*: -	Decreased cell viability and improved contrasts of MRI images.	-	[154]
-	Neuroblastoma	CP-Qu-NC	*In vitro*: 10-100 µg/mL *In vivo*: -	*In vitro*: Neuro-2A cell lines *In vivo*: -	Decreased cell growth and proliferation.	↑- ↓-	[204]
-	Liver	Au-Qu--PLGA	*In vitro*: 30-50 µg/mL *In vivo*: 30-50 mg/kg, subcutaneous injection	*In vitro*: Bel-7402, HC-CLM3, Hep3-Band MHC-C97H cell lines *In vivo*: xenograft mice	Decreased cell viability and migration, induced apoptosis, and declined tumor size.	↑P-27, cleaved caspase-3 and 9, cyt-C ↓AP-2β, β--catenin, CD-K1, COX-2, Cyclin-D1, hTERT, MM-P-7, p-Akt, p-ERK1/2, p-IKKα, p-IκBα, p-NF-κB, Raf	[205]
-	Breast	PVPylated-TiO_2-Qu	*In vitro*: 25-100 µg/mL *In vivo*: -	*In vitro*: MCF-7/DAR cell lines *In vivo*: -	Declined cell proliferation, induced apoptosis, increased ROS, and decreased cell membrane potential.	↑Caspase-3 ↓Bcl-2	[160]
-	Breast	BPQD-AuNC	*In vitro*: 0-100 µg/mL *In vivo*: -, tail vein injection	*In vitro*: MCF-7 and MCF-10A cell lines *In vivo*: -	Decreased cell viability and ATP activity, induced apoptosis, increased ROS, arrested the cell cycle at the G2/M phase.	↑- ↓P-gp	[206]
-	Skin	CHGZ-Qu	*In vitro*: 7.8-1000 µg/mL *In vivo*: -	*In vitro*: A431 cell lines *In vivo*: -	Reduced cell survival.	↑- ↓-	[207]
-	Lung	Qu-GNCs	*In vitro*: 0-150 µg/mL *In vivo*: -	*In vitro*: A549 cell lines *In vivo*: -	Declined cell viability.	↑ROS ↓-	[208]
-	Breast	PBA-ZnO-Qu	*In vitro*: 5-50 µg/mL *In vivo*: 33 mg/kg, intravenous treatment	*In vitro*: MCF-7 cell lines *In vivo*: xenograft mice	Decreased cell viability and tumor size, reduced mitochondrial membrane potential.	↑ROS ↓-	[158]
-	Breast and lung	Zr-MOF-Qu	*In vitro*: 50 µg/mL *In vivo*: 150 mg/kg, intravenous treatment	*In vitro*: A549, HCC-827 and MDA-MB-231 cell lines *In vivo*: xenograft mice (A549 cells)	The decreased survival rate, increased cell radiosensitive, induced apoptosis, reduced tumor volume.	↑Bax, Caspase-3, TUNEL ↓Bcl-2, CAIX, HIF-1α, Ki67	[164]
-	Breast	Qu-FA-Ag NP	*In vitro*: 0-300 µM *In vivo*: 20 mg/kg, intravenous injection	*In vitro*: MDA-MB-231 cell lines *In vivo*: xenograft SD rats	Diminished cell survival and tumor volume, stimulated apoptosis, enhanced effects of photo-thermal therapy.	↑ROS ↓-	[163]
-	Lung	IQuC-S@Zr-PEG	*In vitro*: 0-200 µg/mL *In vivo*: 50 mg/kg, tail vein injection	*In vitro*: A549 cell lines *In vivo*: xenograft mice	Reduced cell viability and tumor size, induced apoptosis, increased sensitivity of cancer cells to radiation.	↑- ↓-	[165]
-	Skin (epidermoid)	CS-CH-L-H-ZnO-Qu	*In vitro*: 7.8-1000 µg/mL *In vivo*: -	*In vitro*: A431 cell lines *In vivo*: -	Decreased survival rate.	↑- ↓-	[157]

(Table 1) contd....

NPs Type	Cancer Type	NPs Formulation	NPs Dose	Study Model	Effects	Mechanisms	References
-	Breast	Al_2O_3/TiO_2-(-PAC_{16})@guest G1/G2@shell 1: Aluminum Oxide or Titanium oxide -PAC_{16}- @ guest Quercetin or 7-a-mono-4-methylcoumarin @ sodium dodecyl benzene sulfonate	*In vitro*: 25 μg/mL *In vivo*: -	*In vitro*: MCF-7 cell lines *In vivo*: -	Reduced cell proliferation, enhanced radiation efficiency, declined mitochondrial membrane potential.	↑ROS ↓-	[161]
-	Liver	Qu-AG-NP	*In vitro*: 12.5-75 μg/mL *In vivo*: -	*In vitro*: HepG2 cell lines *In vivo*:	Decreased cell viability.	↑- ↓-	[209]
-	Breast	AG-FeO_2-Qu	*In vitro*: 13.3-67.5 μg/mL *In vivo*: -	*In vitro*: MCF-7 cell lines *In vivo*: -	Reduced cell proliferation.	↑- ↓-	[210]
-	Breast	H-MOF-Dox-Qu	*In vitro*: 0.1-10 μg/mL *In vivo*: 20 mg/kg, tail vein injection	*In vitro*: A549/Dox cell lines *In vivo*: Xenograft mice	Reduced cell viability and tumor size, stimulated apoptosis, inhibited the cell cycle at the G0/G1 phase, reversed multidrug resistance in A549/-Dox cells.	↑Cleaved caspase-3, Cyt-C ↓Bcl-2, P-gp	[211]
-	Breast	Cu-Qu- DA-IO@HA	*In vitro*: 250-2000 μM *In vivo*: 5.5 mg/kg, intravenous injection	*In vitro*: MDA-MB-231 and HCC1395 cell lines *In vivo*: xenograft mice	Decreased cell growth and tumor volume, induced apoptosis.	↑- ↓-	[159]
-	Breast	Au-PG9-Qu	*In vitro*: 25-800 μg/mL *In vivo*: -	*In vitro*: MCF-7 cell lines *In vivo*: -	Decreased cell viability.	↑- ↓-	[212]
-	Breast	ZnO-Qu	*In vitro*: 0.01-1 μg/mL *In vivo*: -	*In vitro*: MCF-7 cell lines *In vivo*: -	Decreased cell viability.	↑- ↓-	[156]
-	Breast	Zn-Pc-Qu-LPNs	*In vitro*: 5-50 μg/mL *In vivo*: 2 mg/kg, tail vein injection	*In vitro*: MCF-7 cell lines *In vivo*: SD rats	Increased cell growth inhibition, decreased tumor burden, and weight.	↑- ↓-	[213]
Nanodiamonds	Cervix	ND-Qu	*In vitro*: 5-200 μg/mL *In vivo*: -	*In vitro*: HeLa and B16F10 cell lines *In vivo*: -	Decreased cell proliferation and induced apoptosis.	↑caspase-3 ↓-	[139]
Nanodots	Liver	Qu-PEG-Ag_2S-ND	*In vitro*: 0-300 μg/mL *In vivo*: 2.5 mg/mL, intravenous tail vein injection	*In vitro*: HepG-2 cell lines *In vivo*: xenograft mice	Decreased cell viability, tumor volume, and weight, improved the efficiency of photothermal therapy.	↑- ↓-	[162]
Nanophytosomes	Breast	Qu-NPYT	*In vitro*: 0-75 μM *In vivo*: -	*In vitro*: MCF-7 lines *In vivo*: -	Decreased cell viability.	↓MRP, NQO1	[214]
Nanoribbons	Breast	Qu nanoribbons	*In vitro*: 100 μg/mL *In vivo*: -	*In vitro*: 4T1 cell lines *In vivo*: xenograft mice	Decreased cell viability.	-	[215]
Nanosponges	Breast	P(AVL-VL)-Qu-TMX	*In vitro*: 0-10 μg/mL *In vivo*: -	*In vitro*: 4T1 cell lines *In vivo*: -	Decreased cell viability.	↓CYP 3A4 and UGT 1A9	[216]

5.1. Nanoliposomes (NLs)

Nanoliposomes (NLs) are closed, self-assembled colloid vesicles composed of one or more phospholipid bilayers. The structure of liposomes consists of an aqueous core surrounded by external lipid bilayers being able to entrap both hydrophobic and hydrophilic compounds [80]. These characteristics, along with their high biocompatibility, biodegradability, and bio-

stability, cause liposomes to be cited as versatile therapeutic delivery systems [81]. Various fabrication methods have been suggested for liposomes, including thin-film hydration-sonication or Bangham, ethanol injection, Reverse phase evaporation supercritical fluids, heating, and Mozaffari techniques [82]. The stability of liposomes can be improved by coating them with various types of polymers, such as chitosan or polyethylene glycol (PEG) [83]. Despite being effective carrier systems, liposomes are lacking in a sufficiently on-demand release rate. Accordingly, various approaches, such as X-ray-triggered or thermosensitive liposomes, have been fabricated to enhance their efficiency [83, 84]. A study conducted by Hao*et al.* [85] declared that encapsulation of Qu in NLs coated with chitosan NPs significantly reduced the viability of liver cancer cell lines (HepG2) in a dose-dependent manner. Li *et al.* [86] reported Qu- NLs could suppress the growth of cervical cancer cells (HeLa). Furthermore, *in-vivo* studies indicated that treatment of xenograft mice bearing U14 cervical cancer with Qu- NLs have stronger inhibitory effects than free Qu with no apparent hepatic or kidney cytotoxicity. In another study, the impact of co-delivery of 7-O-geranyl Qu (GQu) and IGF-1R siRNA (siIGF-1R) entrapped in CDO14 NLs on human non-small cell lung cancer (A549 and NCI-H460 cell lines) was evaluated. The result indicated the anti-tumor activity of CDO14-GQu-siIGF-1R in xenograft mice inoculated by A549 or NCI-H460 cells was much stronger compared to CDO14-GQu or CDO14-siIGF-1R. Further mechanistic studies demonstrated that CDO14-GQu-siIGF-1R *via* downregulation of siIGF-1R and Bcl-2, as well as increased expression of Bax, suppressed cancer cell viability [87]. One of the distinct properties of multidrug resistance (MDR) membrane cells is over-expressed P-gp. In a study in 2019 on breast cancer, Qu was employed in NLs structure as a P-gp inhibitor agent to reverse MDR, and it was expressed that NLs incorporated Qu and Dox could significantly improve the cell toxicity in Dox-resistant breast and leukemia cell types (MCF-7ADR and HL-6/ADR). Additionally, the co-delivery of Qu and Dox with NLs reduced tumor growth and volume in xenograft mice models [88]. Patel *et al.* [89] prepared Qu NLs and mycophenolic acid (MPA) individually and reported the combination therapy, including Qu-NLs and MPA-NLs, alleviated cell viability in both *in-vitro* (MCF-7 cells) and *in-vivo* (xenograft SD rats) models in comparison with individual ones. Some studies have indicated that the efficiency of cutting-edge NP improves *via* sensitizing them to specific stimuli such as pH, light, or temperature [90-92]. Hemati *et al.* [93] fabricated cationic PEGylated noisome for encapsulation of Dox, Qu and siRNa and evaluated the drug release behavior of niosomes in different temperature (37 and 42°C) and pH (6.5 and 7.4) in four different cell lines including HFF, MCF-7, AGS, and PC3. The results indicated HFF cells had the lowest death rate (50%) while the viability rate of other cancer cells reduced to 25%. Moreover, the thermo- and pH-sensitive Qu-niosomes had the fastest Qu release at 42°C and pH of 6.5 (77.6% in 72 h). Although such Qu-NPs were sensitive to an appropriate pH for cancer treatment, temperature 42°C is an unfavorable temperature for the human body. Thus, usage of such Qu-NPs in *in-vivo* may be limited to their simultaneous application with NPs with magnetic hyperthermia or photothermal specifications.

5.2. Lipid Nanoparticles

Generally, lipid NPs are colloidal dispersion comprising lipids, water, emulsifiers, and co-emulsifiers. They are classified into two main groups: solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) [94]. High-Pressure Homogenization (HPH), Hot HPH, microemulsion, solvent emulsification evaporation, solvent emulsification diffusion, solvent injection/solvent displacement, phase inversion, coacervation, micro emulsion cooling, super critical fluid, gas-assisted melting atomization, ultrasonication strategies are the most important approaches for lipid NPs production [95].

5.2.1. Solid Lipid Nanoparticles

As the first generation of lipid NPs, solid lipid nanoparticles (SLNs) are delivery platforms consisting of non-polar or neutral solid lipids such as saturated fatty acids or triglycerides and remaining solid at room and body temperature [96, 97]. Thus, SLNs bear extremely ordered crystalline structures stabilized *via* an external layer of emulsifier. The main advantage of SLNs is their solid structure leading to decreased mobility of encapsulated drugs in the lipid matrix. It is required that SLNs should enjoy high thermal resistance, more than body temperature (37°C), to keep their physical structures following oral administration and successful transport of incorporated drugs to their target size [98]. Hu, Miao [99] synthesized a targeted lipid-calcium-phosphate NPs including Qu and represented Qu-LNPs significantly reduced the expression of Wnt16, collagen, and α-SMA+ fibroblast resulting in remodeling the tumor microenvironment to enhance the penetration of second-wave NPs (cisplatin) to the tumor area. Furthermore, the administration of HepG2 cells with FA-Qu-PLGA-LNP decreased cancer cell growth and tumor volume and size in mice bearing HepG2 tumors [100].

5.2.2. Nanostructured Lipid Carriers

The manufacture of SLNs by highly purified lipids results in the formation of regularly ordered lipid crystals and, consequently expulsion of embedded drugs during the polymorphic transition [101]. Such limitations of SLNs promoted the development of the second generation of lipid NPs presented as nanostructured lipid carriers (NLCs). Nanostructured lipid carriers (NLCs) are composed of a mixture of both solid and liquid (unsaturated fatty acids) lipids. NLCs are solid at room and physiological temperatures, but they have an imperfect crystalline structure [102]. Due to using both saturated and unsaturated fatty acids in NLCs formulation, they have less crystalline packing and rigidness as well as more space between fatty acid chains resulting in a higher rate of drug loading and lower drug release during storage time [103]. However, it has been reported that the controlled release of NLCs may be deteriorated due to reduced diffusion length of lipid structure. Changing the ratios of solid and liquid lipids may lead to overcoming this drawback [104]. In an investigation into Raji/VCR lymphoma cell lines, Qu-NLCs attenuated cell viability and proliferation. Additionally, *in-vivo* studies in Raji/VCR lymphoma tumor-bearing mice revealed Qu-NLCs decreased tumor weight and volume [105]. Kumar *et al.* [106] proved conjugation of Qu-NLCs with BSA reduced MCF-7 cell viability and proliferation.

5.3. Polymer-Based Drug Delivery Systems

Recently, polymer-based nanocarriers have gained significant attention in cancer treatment. These systems' morphology is configured so that they can be tailored to passive or surface-characterized delivery to active targeting to desired sites [107]. Polymeric delivery systems are categorized into three classes: polymeric nanoparticles (polymer-drug conjugates), polymeric micelles (amphiphilic core/shell), and dendrimers (hyperbranched macromolecules)

5.3.1. Polymeric Nanoparticles (Polymer-drug Conjugates And Polymeric Micelles)

Polymer-drug conjugates (PDCs) are described as the covalent conjugation of polymer backbones and molecules with pharmacological activities such as aptamers, peptides, proteins, and other small bioactive compounds. Polymeric nanoparticles are colloidal structures consisting of biodegradable polymers which can form both nanocapsules and nanospheres. Dissolution or dispersion of the drug in the liquid core results in nanocapsule formation, while nanospheres are constructed by incorporating the drug in the polymer network [108]. Various studies have depicted that PDCs enjoy appropriate potential in modulating drug features to achieve proper in-transient and on-site delivery outlines [109]. In the design of PDCs, both natural polymers such as albumin, chitosan, and heparin, as well as synthetic polymers, namely N-(2-hydroxypropyl)-metacrylamide copolymer (HPMA), polyethylene glycol (PEG), poly-L-glutamic acid (PGA), and polystyrene-maleic anhydride copolymer, are implemented. Coupling reactions, ring-opening polymerization, and reversible addition-fragmentation chain transfer (RAFT) polymerization are the most well-known strategies for PDCs fabrication. PDCs have presented various benefits, including improving therapeutic efficacy, decreasing drug side effects, increasing flexibility in drug administration, and enhancing patient compliance [110].

Amphiphilic di-or tri-block copolymers may self-assemble into numerous types of mesoscopic platforms, such as micelles depending on the ratio of hydrophilic to hydrophobic parts. The self-assembly of Amphiphilic block copolymers in an aqueous phase leads to the fabrication of nanoscale micelles presenting versatile functions in drug delivery applications [111]. Polymeric micelles have a lipophilic core and a hydrophilic shell that can entrap hydrophobic and hydrophilic drugs, respectively [112]. Co-solvent evaporation, dialysis, direct dissolution, freeze-drying, oil-in-water emulsification, poly-ion complexation, solvent evaporation, and thin-film hydration are various methods of polymeric micelles synthesis [113]. Nowadays, several applications of polymeric micelles, including imaging, targeting ligands, and delivering drugs, are progressing and will be more conventional.

Gao *et al.* [114] fabricated mPEG-PCL nanomicelles to enhance the water solubility and delivery of Qu for the treatment of ovarian cancer. *In vitro* studies displayed that Qu suppressed the viability of A2780S cell lines in a dose and time-dependent fashion. Intravenous injection of mPEG-PCL-Qu to xenograft mice suppressed tumor growth by exerting apoptosis and antiangiogenetic activities. Further investigation illustrated mPEG-PCL-Qu NPs through depolarization of mitochondrial membrane potential, activating Bax, caspase-3, and caspase-9, as well as downregulation of Mcl-1 and Bcl-2, p-Akt, and p-MAPK reduced cancer cell proliferation. In another study on the ovarian cancer xenograft model, two different nanomicelles Qu and resveratrol (R), as well as Qu and curcumin (C), were synthesized to enhance the efficiency of Adriamycin (ADR) with alleviating its cardiotoxicity. The result of this study showed Qu-R-ADR significantly decreased tumor growth and volume along with cardio-

vascular damage [115]. In a study, co-delivery of hydrophobic Qu and hydrophilic doxorubicin (Dox) by a nanocarrier composed of methoxy poly(ethylene glycol)or mPEG and poly(D, L-lactide-*co*-glycolide) or PLGA was investigated [116]. The results of this study indicated that Qu-Dox nanoparticles reduced the viability of breast cancer cells in both *in-vitro* and *in-vivo* conditions.

Additionally, the co-delivery of Qu-Dox protected normal vascular endothelial cells from toxicity potentials of both free and nanoparticulated Dox, suggesting a promising approach for improving anticancer properties and alleviating Dox-induced histopathological heart damage. Ramasamy *et al.* [117] applied a polypeptide-based nano-vehicles (poly(phenylalanin)-b-poly(L-histidine)-b-PEG (pPhe-b-pHis-b-PEG)) for co-delivery of Qu-Dox. They found that the presence of Qu in nanoparticles increased the cytotoxicity effects of Dox against breast and skin cancer cells along with stimulated apoptosis, altering cell cycle patterns and suppressing the migration capability of both sensitive and resistant cancer cells. Precisely, Qu in the nanoparticle significantly declined the GSH/GSSG ratio, augmented ROS, and damaged cellular components. Moreover, the injection of nanomedicine into the SCC-7 xenograft mice disclosed the tumor shrinkage intensified by Qu compared to only Dox-incorporated formulations. Qu-Dox increased the expression of Caspase-3 and PARP and reduced the level of ki67 and CD31, as well as inhibited cancer cell growth. Delivery of Qu by nanoparticle consisting of Lyp-1 functionalized *via* regenerated silk fibroins (Lyp-1-Qu-NP) led to increased drug absorption to the 4T1 cell and their accumulation in mitochondria. Furthermore, Lyp-1-Qu-NP illustrated pro-apoptotic effects as well as inhibited cell migration and invasion by inducing autophagy by increasing regulation of LC3II and reducing expression of MMP-2, MMP-9, and PKM2. Also, administration of Lyp-1-Qu-NP to 4T1 xenograft mice suppressed breast tumor growth. It inhibits lung metastasis and may lead to an efficient strategy for the treatment of breast cancer and associated lung metastasis [118]. In another investigation, Wang *et al.* [119] studied whether Qu could decline the resistance of NSCLC, A549, cells to paclitaxel (PTX)-based chemotherapy. Accordingly, the incorporation of Qu-PTX to cetuximab-chitosan (Cet-Cs) NPs restricted the growth and viability of PTX-resistant A540/Taxol cells. Also, the co-delivery of Qu-PTX reduced tumor growth and volume in xenograft mice through apoptosis induction and reduced phosphorylation of Akt and ERK with no adverse effect on the heart, liver, lung, kidney, and spleen. In a study on murine breast and human hepatoma cancer cells, it was exhibited that hyaluronic acid (HA)-Qu NPs significantly decreased the viability of 4T1 and HepG2 cell by stimulating apoptosis and blocking CD44 receptors. Injection of HA-Qu NPs to xenograft mice bearing 4T1 cells demonstrated the novel nano-delivery system inhibited tumor growth compared with Qu alone [120].

One of the leading causes of multi-Drug resistance (MDR) effects in tumor cells is the upregulation of ATP-binding cassettes (ABC) receptors in the cell membrane, suppressing the entrance of chemotherapeutic agents to the cancer cells. Gu *et al.* [121] fabricated a self-assembled TPP-Qu/Dox-PEG-mAB to hinder MDR. In this process, TPP-Qu conjugate remarkably triggered mitochondrial destruction *via* ROS generation and depolarization of mitochondrial membrane potential, which dramatically reduced the required ATP for ABC transporters. In these conditions, the accumulation of intracellular Dox increased while efflux reduced in MCF-7/ADR cells administrated with TPP-Qu/Dox-PEG-mAB NPs. Additionally, *in-vivo* observations disclosed that administration of such NPs into mice bearing Dox-resistant breast cancer decreased tumor growth rate without any toxic effects on other organs. Treatment of C6 glioma cell lines with Qu-PLGA NPs significantly decreased cell proliferation and increased cellular uptake compared to free Qu. In addition, Qu-PLGA NPs reduced the levels of MDA associated with declined ROS in cancer cells [122]. Tian *et al.* [123] designed novel NPs based on LyP-1-LMWH-Qu-GA conjugates to target the co-delivery of anti-cancer agents to cancer cells with over-expressed p32 as well as peritumoral lymphatic vessels. The results showed that the cellular uptake of LyP-1-LMWH-Qu-GA NPs was significantly higher than non-functionalized NPs. Also, applied NPs suppressed angiogenesis by reducing bFGF-triggered neovascularization, disrupted the formation of lymphatic, and downregulated the expression of P-gp in MCF-7 xenograft mice. Thus, such NPs are suitable candidates for the delivery of chemotherapeutic and antiangiogenetic compounds to inhibit MDR and metastasis in breast cancer. In a study on colon Caco-2 cancer cell lines, it was conducted a chitosan-quercetin (Cs-Qu) conjugate was developed for improving the oral delivery of Dox.

The self-assembled Cs-Qu nanomicelles appropriately encapsulated Dox and increased the cellular uptake of Dox than free Dox. Furthermore, the level of trans epithelial electrical resistance (TEFR) of Caco-2 cells effectively declined *via* Cs-Qu-Dox treatment, indicating a high permeability coefficient of Dox [124]. The same author, in another work synthesis Qu-Cs-

CA-Dox nanomicelles, reported that these NPs enhanced the cellular uptake of Dox in MCF-7/ADR drug-resistant cell lines, suggesting the potential of Such NPs for overcoming MDR-associated tumor therapy [125]. Synthesis of Qu-A (alantolactone) nanomicelle decreased CT26-FL3 cell viability and tumor growth at both *in-vitro* and *in-vivo* levels. In this process, Qu-A, by increasing the expression of CRT, p-AMPKα and downregulating Bcl-2, Bcl-xL mTOR, and p-mTOR inhibited cancer development [126]. Rezvani *et al.* [127] employed chitosan-polycaprolactam (Cs-PCL) nano complex for delivery of Qu as a chemotherapeutic agent and functionalized NPs with folic acid (FA) for targeting them to cancer cells. The result of cell viability indicated the proper potential of Cs-PCL-FA-Qu in reducing the survival rate of breast cancer cells, MCF-7 and T-47D. In another investigation, FA-L (lysin)-PEG-PCL nanomicelle was fabricated to co-delivery of Qu and tamoxifen (TMX). *In-vitro* (4T1 cell lines) and *in-vivo* (xenograft mice) depicted that FA-L-PEG-PCL-Qu-TMX could inhibit cell viability as well as tumor growth and volume. Therefore, this formulation had accepted potential for oral delivery of both Qu and TMX [128]. Since polymeric nanoparticles bear a large particle size (more than 100 nm), threatening their colloidal stability, their surface charge should be regulated to prevent such NPs from agglomeration. Modifying the surface of polymeric nanoparticles with different ligands or developing stimuli-responsive is a promising approach to improve the efficient delivery of Qu and significantly alleviate its side effects.

5.3.2. Dendrimers

Dendrimers are the latest nano-delivery systems for a wide range of bioactive compounds. Dendrimers are artificial macromolecules with a tree-like or hyperbranched structure to accommodate and deliver drugs [129]. With their 3D structures, Dendrimers contain a multipurpose internal core, branching groups, surface or external moieties. The core part has cavities forming cages and channels to simply build branching groups to integrate bioactive molecules. Branches cause dendrimers to have great miscibility, reactivity, and solubility. Moreover, the surface structure of dendrimers can be modified by complexation with different types of active compounds [130]. Since the surface units of dendrimers are easily modifiable, they have the potential to conjugate with different agents, such as targeting ligands and therapeutic molecules. Divergent, convergent, double stage convergent, branched monomer, double exponential, orthogonal coupling, lego chemistry, and click chemistry methods are different approaches of dendrimer NPs manufacture [131]. Choi *et al.* [132] developed telodendrimer PEG-PLGA nanomicelles and reported treatment of U251 glioblastoma spheroids with Qu-dendrimers reduced the viability of cancer cell lines. Various studies have indicated that although dendrimers, particularly cationic ones, are toxic for cancer cells, they are sometimes toxic for normal cells at high doses. Hence, it is suggested some modifications in their synthesis should be considered to overcome such disadvantages and apply as nanocarrier in cancer therapy.

5.4. Carbon-based Nanoparticles

Carbon nanotubes, carbon-based quantum dots, fullerenes, graphene, and nanodiamonds are the main carbon-based nanotubes, among which carbon nanotubes (CNTs) have recently achieved particular interest. CNTs are formed by folding graphene sheets into a cylinder-like configuration. Their diameters are nanoscale, and their lengths are a thousand times their diameters [133, 134]. Carbonization, chemical oxidation/exfoliation, liquid phase exfoliation, chemical vapor deposition, direct current arc-discharge, direct exfoliation, Hummers' method, near-infrared radiation, polymerization/blending, solvothermal reduction, spin coating, thick film technology, vacuum filtration are some practical method for CNTs synthesis [135]. These nanoparticles are completely insoluble in all solvents; however, chemical modification of their structure makes them water-soluble compounds. CNTs have been employed in biology as DNA and protein detecting sensors, diagnostic tools for differentiation of the various proteins in serum samples, and vaccine or protein delivery systems. These structures are superior nanocarriers in the targeted delivery due to their ability to enter cells *via* a specific strategy known as needle--like penetration [136]. Kumar *et al.* [137] synthesized multiwall carbon nanotubes (MWCNTs) for co-delivery of Qu as a P-gp efflux suppressor, and N-TAM (N-desmethyl tamoxifen (N-TAM) to the treatment of MDR breast cancer cells, MDA-MB-231. It was observed that synthesized N-TAM-TEG (tetra ethylene glycol)-MWCNTs-Qu targeted MDR cancer and increased cell cytotoxicity and death. In another study, fabricated MWCNT-Qu-Pm (pemetrexed) fabricated remarkably affected the morphology of pancreatic cancer cells, and fabricated declined cell viability by augmenting the number of lysosomes and ROS level [138]. Gismondi *et al.* [139] conjugated nanodiamonds (ND) with Qu and indicated that these NPs decreased the proliferation and viability of human (HeLa) and murine (B16F10) cancer cells. Additionally, Qu's pro-oxidant, cytotoxicity, and pro-apoptosis potential de-

creased in the ND association case. Another study evaluated the co-delivery of Qu and gefitinib (GEF) to cancer cells by GO-PVP nano vehicles. It was disclosed that the antitumor effects of GO-PVP-Qu-Gefinitib were significantly more than free Qu-GEF and effectively reduced the number of PA-1 ovarian cancer cells [140]. Despite owning extensive capacity of CNTs in drug delivery systems, there are still serious considerations associated with their toxicity because of their small size and high aspect ratio. Some histopathological studies have claimed CNTs may lead to occupational health concerns, including inflammation, epithelial granulomas, and progressive fibrosis. Thus, extensive investigations should be conducted to evaluate the preclinical effectiveness of CNTs and successful intracellular delivery [141].

5.5. Silicon-based Nanoparticles

Silica nanoparticles (SiNPs) are fabricated from silicon dioxide (SiO2), the most abundant compound on the earth, and widely applied in various industries, including drug delivery owning to their versatile particle size, favorable surface area, and considerable biocompatibility, simple synthesis, and suitable endocytic manner [142]. SiNPs are manufactured *via* numerous methods, including dissolving reconstruction, fast self--assembly, hydrothermal, modified aerogel, soft or hard templating, and Stober techniques [143].

Murugan and Rayappan [144] investigated the effect of the co-delivery of topotecan (TPT) and Qu on triple-negative breast cancer (MDA-MB-231) and MDR-type breast cancer cell lines (MCF-7) *via* the incorporation of therapeutic agents to mesoporous silica NPs (MSN) decorated by poly(acrylic acid) (PAA) and chitosan (Cs). In the next step, arginine-glycine-aspartic acid peptide (AGA) was grafted on the surface of NPs to enhance their cellular uptake in tumor tissues. *In-vitro* and *in-vivo* studies revealed that MSN-PAA-C-s-AGA through downregulation of Bcl-2 and overexpression of ATF4, Bax, caspase-3 and -9, Chop, Cyt-C, JNK p53, p-ERK altered various molecular pathways in the nucleus, mitochondria, and endoplasmic reticulum resulting in inducing cell death in both breast cancer types. In another study on breast cancer, it was reported the synthesis of Qu NPs *via* MSN conjugated with folic acid (Qu-MSN-FA) led to greater cellular uptake and higher drug bioavailability to the cancer types, including upregulated folate receptors. Further mechanistic studies represented decreased cancer cell viability due to apoptosis induction and cell cycle arrest triggered by modulation of the Akt and Bax signaling axis [145]. Mishra *et al.* [146] developed a pH-sensitive MSN-Qu NPs functionalized with folic acid (FA) and Fe_3O_4 magnetic NPs. Evaluation of anticancer efficiencies of FA-Fe-MSN-Qu NPs in both *in-vitro* and *in-vivo* human colorectal cancer models indicated that considered NPs activated the mitochondrial apoptosis system *via* a redox-modulated cellular signaling pathway. Moreover, FA-Fe-MSN-Qu NPs increased the level of c-JNK mediated the phosphorylation of H2AX and p53 leading to augmented apoptotic death of cancer cells.

Therefore, one of the practical approaches for enhancing the therapeutic activities of silica NPs is chemically modifying their structures with targeting agents such as FA, HA, AGA, *etc.* Furthermore, such NPs can be functionalized with various molecules to generate several target distinctions. Despite low encapsulation efficiency and drug loading of silica NPs in most investigations, a few studies only reported their pH sensitivity characteristics and sustained release behavior, which may lead to reducing adverse effects of Qu. Thus, these criteria should be considered in future studies.

5.6. Metallic Nanoparticles (MNPs)

Since their discovery in 1971, various types of metallic nanoparticles (MNPs) have been applied in clinical trials. MNPs such as gold substantially benefit cancer treatment because their charge, shape, size, and surface properties can be modified and controlled precisely. Furthermore, these compounds can simply absorb cancer cells compared to other NPs of similar size. Thus MNPs can be more effective in cancer therapy [147]. Extensive usage of MNPs in biomedicine is related to their physicochemical specification, such as high surface area-to-volume ratio, incremented surface energy, high-energy atoms on the particle surface, the potential of electron storage, as well as owning edges and corners [148]. Gold, silver, copper, Iron/iron oxide, and Zinc/zinc oxide are examples of MNPs in drug delivery systems. Bulk metal grinding/mechanical milling, laser ablation, lithography, Sputtering, thermal decomposition, Turkevich, Brust, and green methods are the most useful strategies for MNPs fabrication [149].

In a study conducted by Bishayee *et al.* [150], it was reported that Au-PLGA-Qu NPs reduced the viability of cervical (HeLa), liver (HepG-2), and skin (A375) cancer cell lines. More studies on HepG2 cells showed that Au-PLGA-Qu NPs arrested the cell cycle at the sub-G1 phase *via* a change in the regulation of p21, p-Akt, and CDK1, induced apoptosis *via* affecting p53-ROS crosstalk, and depolarization of mitochondrial membrane potential resulting in inhibited cancer

cell proliferation. Administration of Au-Qu NPs in MCF-7 and MDA-MB-231 breast cancer cells led to inducing apoptosis *via* upregulation of Bax and Caspase-3 and reduced expression of anti-apoptotic Bcl-2. Furthermore, Au-Qu NPs suppressed the expression of EGFR and its downstream signaling pathway PI3K/Akt/mTOR/GSK-3. Thus Au-Qu NPs, *via* apoptosis induction and EGFR suppression, exerted their anti-proliferative effects [151]. Same authors in a similar study demonstrated that Au-Qu NPs significantly downregulated Akt, MMP-2, MMP-9, N-cadherin, p-EGFR, p-GSK3β, Slung, Snail, Twist, VEGFR-2, as well as vimentin and promoted expression of E-cadherin causing to reduce angiogenesis, migration and invasion of breast cancer cells. Additionally, *in-vivo* studies expressed that Au-Qu NPs inhibited the formation of new blood vessels, angiogenesis, and tumor growth in SD rats bearing mammary carcinoma [152]. Treatment of cervical cancer cells with Au-PLGA-Qu NPs suppressed the expression of JAK-2, decreasing cervical cancer cell viability *via* induction of apoptosis and autophagy and preventing cell proliferation. Molecular studies disclosed that Au-PLGA-Qu NPs inhibited the development of cervical cancer *via* STAT/Bcl-2/Caspase-3 and PI3K/Akt/GSK/mTOR pathways [61].

Daglioglu [153] synthesized multifunctional pH-responsive NPs consisting of Fe_3O_4-FTIC-SiO_2-BTN-Dox-Qu NPs to co-delivery of Dox and Qu to MDR A549/Dox lung carcinoma cell lines. In this nanostructure, Fe_3O_4, FTIC, and BTN were utilized as magnetic contrast probes, optical contrast probes, and the particular ligand targeting tumors. The results of this study represented improved intracellular delivery and cytoplasmic retention of Fe_3O_4-FTIC-SiO_2-BTN-Dox-Qu NPs in cancer cells leading to induced apoptosis, inhibited the cell cycle at the G2/M phase, reduced cell viability and enhanced the cytotoxicity of Dox against MDR lung cell carcinoma indicating synergic effects between Qu and Dox to suppress MDR cancer. In an investigation carried out by Malek zadeh *et al.* [154], it was observed that Fe_3O_4-PCA-PEG-FA-Qu NPs effectively entered the HeLa cells containing over-expressed folate receptors resulting in enhanced NPs cytotoxicity. Additionally, T2-weighted MRI images of these NPs revealed the improved magnetic resonance signals in water with augmenting NPs concentration, and also Fe_3O_4-PCA-PEG-FA-Qu NPs were employed as MRI contrast probes with r_1 and r_2 as 3.4 $mM^{-1}s^{-1}$ and 99.8 $mM^{-1}s^{-1}$, respectively. In another study, carboxylated Qu was incorporated into superparamagnetic iron oxide NPs (SPION) functionalized with 3-aminopropyl triethoxysilane (APTES), folic acid, and carboxylated polyethylene glycol. SPION@APTES@FA-PEG@Qu had more cytotoxic effects on HeLa and MCF-7 cell lines with overexpressed folate receptors compared with A549 cell lines with no folate receptors. Furthermore, these NPs caused higher apoptotic and necrotic death in HeLa and MCF-7 cells than in A549 lung cancer cells [155].

It also has been indicated that ZnO-Qu nanocomposites have the capability of declining the growth and viability of MCF-7 cancer cell lines [156]. George *et al.* [157] stated incorporation of Qu into ZnO NPSs conjugated with chitosan (Cs), L-histidine (HIS), and dialdehyde cellulose (DAC) reduced the growth and proliferation of A431 (skin) cancer cell lines. In another study, the antiproliferative effects of ZnO-Qu NPs conjugated with phenylboronic acid (PBA) on human breast cancer cells were evaluated. It was displayed that ZnO-Qu-PBA NPs stimulated apoptosis in MCF-7 cells *via* increased oxidative stress and promoted mitochondria damage. Moreover, *in-vivo* studies in mice bearing EAC tumors indicated these NPs reduced tumor size and growth along with declined tumor-related toxicity in the kidney, liver, and spleen [158]. Cheng *et al.* [159] synthesized CuQDA/IO@HA NPs and investigated their effect in combination with magnetic navigation on TNBC. It was reported that this therapeutic approach damaged DNA and inhibited PARP through CD44 targeting. Additionally, these NPs increased the median survival of xenograft mice from 43 to 61 days compared to Qu treatment alone mainly associated with augmenting levels of H2AX and inducing apoptosis.

Ponraj *et al.* [160] reported incubation of MCF-7/ADR cell lines with PVPylated-TiO_2-Qu NPs increased the level of ROS, depolarized mitochondrial membrane potential, released cytochrome-c to the cytosol, dysregulated Bcl-2, and activated caspase-3 leading to induction of apoptosis in cancer cells. In another investigation on breast cancer, NPs based on TiO_2 and Al_2O_3 for delivery of Qu and 7-amino-4methylcoumarin were developed. It was illustrated that X-ray irradiation facilitated the release of therapeutic agents into the cytoplasm and subsequently elevated the rate of ROS generation. Additionally, Qu and 7-amino-4methylcoumarin induced apoptosis through the mitochondrial-dependent pathway and reduced mitochondrial membrane potential following x-ray irradiation [161]. Zhong *et al.* [162] fabricated PEG-Qu-Ag_2S nanodots and illustrated these NPs could effectively inhibit the proliferation of HepG2 cell lines in both *in-vitro* and *in-vivo* models. Moreover, PEG-Qu-Ag_2S nanodots improved the efficiency of photo-thermal therapy

due to the role of Qu in the downregulation of heat shock proteins (HSP-70). Detailed *in-vitro* and *in-vivo* investigations on novel synthesized Qu-FA-Ag NPs disclosed that NPs effectively delivered Qu to the tumor site, triggering hyperthermia under NIR laser irradiation and leading to selective removal of cancer cells. Following cellular uptake, Qu-FA-Ag NPs emerged their photothermal effects that, in combination with chemotherapeutic properties caused apoptosis induction in breast cancer cells and inhibited tumor growth [163]. In another research work, Qu was encapsulated into the Zr-MOF nanocomposite to obtain duplicate synergic sensitization effects: Zr-MOF as the inhibitor of carbonic anhydrase IX (CA IX) and Qu as a radiosensitizer agent. Treatment of both lung and breast cancer cells with Zr-MOF-Qu NPs dramatically decreased cell viability and improved the effect of radiotherapy. Studying cellular and animal models displayed that Zr-MOF-Qu NPs decreased the level of Bcl-2, CA IX, HIF-1α, Ki67 and upregulated Bax, Caspase-3, TUNEL leading to inducing apoptosis and cancer cell death [164]. In another study, Chen *et al.* [165] evaluated the effect of microwave (MW) induced IQuCS@Zr-PEG NPs on lung cancer in both *in-vitro* and *in-vivo* models and reported that NPs released oxygen following irradiation leading to increasing tumor reoxygenation and downregulating HIF-1α and eventually improved the efficiency of radiation and microwave cancer therapy. Also, the administration of IQuCS@Zr-PEG NPs to xenograft mice reduced tumor size and volume [166-216].

MNPs are promising approaches for adequate targeted delivery of Qu with satisfactory results. Most of the MNPs enjoy the capability of being functionalized and are safe. However, more studies are required to enhance the loading efficiency of these nanocarriers, which is almost insufficient in comparison with other nano-delivery systems. Additionally, their stimuli-responsive behaviors in various conditions, such as temperature and pH, should be regarded as affecting variables on their anticancer efficacy.

CONCLUSION

In recent years, a marked tendency has emerged to use natural polyphenol compounds such as Qu in the treatment of various disorders, including cancer. Qu is a polyphenolic flavonol found in various food materials and is regarded as an anticancer substance due to its potential to arrest the cell cycle, inducing apoptosis, autophagy, and reverse MDR, as well as inhibit cancer invasion and metastasis. However, poor water solubility, oxidative stability, low bioavailability, specificity, and selectivity of Qu have reduced its efficiency in cancer treatment. The advent of nanotechnology in cancer treatment has led to dominating the various limitations of conventional therapeutic strategies. The introduction of Qu in NP platforms resulted in improved Qu anticancer activities *via* exerting its modulatory effects on various mechanisms and signaling pathways involved in tumor initiation and development, such as apoptosis, angiogenesis, cell cycle, DNA damage, invasion, migration, metastasis, and proliferation. Additionally, the combination of Qu with traditional anti-cancer or diagnostic agents in the formulation of NPs would be more beneficial in tumor treatment. Along with the complexity of different chemo-preventive processes, pharmacokinetic barriers associated with Qu should be considered. Qu has been investigated in a variety of approaches, including different formulations and combinations with other chemotherapic agents, whether natural or synthetic. Although this field of cancer treatment studies is new, the potential for more significant success in this field has been recognized. Since the results of such formulations are contradictory, it is not reasonable to offer them for high-scale formulation and clinical applications. Hence extensive trials should be conducted to obtain the best formulation based on Qu without any chance of antiproliferative effects. Despite all formulations enjoying the capability of enhancing chemotherapeutic efficacies and pharmacokinetics attributes of Qu, it seems formulations of Qu based on nano-drug delivery systems have the best capacity in advancing Qu. Nano-based strategies protect bioactive compounds such as Qu against physicochemical environmental conditions and deliver with other drugs or bioactive compounds to enhance their chemo-preventive effects. This approach can be regarded as a new direction for further studies.

In conclusion, numerous studies have depicted that various Qu nano-platforms are promising techniques for achieving efficient cancer treatment. However, employing Qu NPs in tumor-targeting drug delivery systems requires further investigations, particularly in the context of reproducibility, scale-up, physicochemical stability, composition (conjugating with different ligands, stimuli-responsive agents, or conventional anticancer drugs) to minimize its side-effect, increase its accumulation in targeted sites and finally obtain more anti-tumor responses. Moreover, clinical trials should be considered to increase the application of Qu NPs in cancer treatment.

AUTHORS' CONTRIBUTIONS

MH, AA, ZA, and BY take part in creating the idea, design, and composing of the manuscript.

LIST OF ABBREVIATIONS

ABC = ATP-binding cassette
AMPK = Adenosine monophosphate-activated protein kinase
BAX = Bcl-2 associated X protein
Bcl-2 = B-cell lymphoma-2
CKM = Creatin kinase M
cTnI = cardic TroponicI
COX-2 = Cyclooxygenase-2
DNA = Deoxyribonucleic acid
EGFR = Epithelial growth factor receptor
EMT = Endothelial to mesenchymal transition
ERK = Extracellular signal-regulated kinase
Foxo3a = Forkhead box O3
GAIP = Gα interacting protein
H2AX = H2A histone family member X
HCC = Hepatocellular carcinoma
HDAC = Histone deacetylase
HIF-1α = Hypoxia-inducible factor-1α
IGF-R1 = Insulin-like growth factor type 1 receptor
IL = Interleukin
JAK = Janus kinase
JNK = C-Jun N-terminal kinase
MAPK = Mitogen-activated protein kinase
MMP = Matrix metalloproteinase
mTOR = Mammalian target of rapamycin
ncRNA = Non-coding RNA
NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells
PCNA = Proliferating cell nuclear antigen
PI3K = Phosphoinositide 3-kinases
Akt = Protein kinase B
PTEN = Phosphatase and tensin homolog
ROS = Reactive oxygen species
STAT = Signal transducer and activator of transcription
TNF = Tumor necrosis factor
VEGF = Vascular endothelial growth factor
Wnt/β-catenin = Wingless-type MMTV integration site family
5-FU-Qu-Cs = 5-fluorouracil-Quercetin-Chitosan
ADR-R-Qu = Adriamycin-Resveratrol-Quercetin
AG-FeO2-Qu = Silver-Iron oxide-Quercetin
AG-PVP-Hap-Qu = Agarose-polyvinylpyrrolidine-hydroxyapatite
AMD-Qu-NL = Adriamycin-Quercetin-Nanpliposome
Au-PG9-Qu = Gold nanoparticle-polyethylene glycol 9000-quercetin
Au-Qu-PLGA = Gold-Quercetin-poly(d=L-lactide-co-glycolide)
B780-Qu = Biotin-tailored IR780-Quercetin
BPQD-AuNC = Biotin-polyethylene glycol-SH-Quercetin-Doxorubicin-Gold nanocage
BSA-Dox-Qu = Bovin serum albumin-Doxorubicin-Quercetin
BSA-Qu-LNP = Bovin Serum albumin-quercetin-liposome nanoparticle
CDO14-GQu-siIGF-1R = CDO14-7-O-geranyl quercetin-IGF-1R siRNA
Cet-CTS = cetuximab-chitosan
CHGZ-Qu = Chitosan-Dialdehyde Cellulose-Zinc oxide-Quercetin
CS-CH-LH-ZnO-Qu = Chitosan-Cellulose hydrogel-L-histidine -Quercetin

Cu-Qu-DA-IO@HA = Copper-Quercetin-dextran aldehyde-superparamagnetic iron oxide nanoparticle-hyaluronic acid

Dex-Ald-Qu = Dextran aldehyde-Quercetin

Dox-Qu-pPhe-b-pHis-b-PEG = doxorubicin-Quercetin -poly(phenylalanin)-b-poly(L-histidine)-b-poly(ethylene glycol)

DSPE-PEG-2000-Bi-Dox-Qu = poly(ethylene glycol)-2000-Bioton-Doxorubicin-Quercetin

FA-Fe-SBA-15-Qu = Folic acid-iron oxide- SBA-15-Quercetin

FA-L-PEG-PCL-Qu-TMX = Folic acid-lysin-polyethylene glycole-polycaprolactone-quercetin-tamoxifen

FA-Qu-PLGA-LNP = Folic acid-Quercetin-poly(d= L-lactide-co-glycolide)-lipid nanoparticle

Fe3O4@SiO2 (FITC)-BTN/Qu/DOX = Iron Oxide-Silica-Fluorescein isothiocyanate-Biotin-Quercetin-Doxorubicin

Fe3O4-PCA-PEG-FA-Qu = Iron oxide-poly citric acid-polyethylene glycole-folic acid-Quercetin

GO-PVP-Qu-Gef = Graphene oxide-polyvinylpyrrolidone-Quercetin-Gefitinib

HA-NP-MTO-Qu = hyaluronic acid-Nanoparticle- Mitoxantrone dihydrochloride-Quercetin

HA-Qu = Hyaluronic acid-Quercetin

H-MOF-Dox-Qu = Heparin-meta-organic framework-Doxorubicin-Quercetin

HoS-Apo-Qu-Cur = Horse spleen Apoferritin-Quercetin-Curcumin

HPG-GO-Qu = Hyperbranched polyglycerol-geraphene oxide-Quercetin

IQuCS@Zr-PEG = Interleukin-Quercetin-Cupric oxide-Silica@Zinc oxide-poly(ethylene glycole)

LCP-QP = lipid calcium phosphate-Quercetin phosphate

LyP-1-LMWH-Qu-GA = LyP-1 peptide-modified low molecular -weight heparin-Quercetin-gambogic acid

Lyp-1-Qu-SF = Lyp-1(CGNKRTRGC= cyclic nanopeptid)-Quercetin-Silk fibroin

MPA-LPN = Mycophenolic acid-lipid polymer hybrid nanoparticle

mPEG5K-NH2-Qu-Dox = methoxy poly(ethylene glycol) 5000 amine-Quercetin-Doxorubicin

MPEG-PCL-Qu = monomethoxy poly(ethylene glycol)-poly(ε-caprolactone) -Quercetin

mPEG-PLGA-Qu-Dox = methoxy poly(ethylene glycol)-poly(d= L-lactide-co-glycolide)-Quercetin-Doxorubicin

MSN-FA-Qu = Mesoporous silica nanoparticle-Folic acid-Quercetin

MSNs-ChS@PQ = Mesoporous silica nanoparticle-Chondroitin sulfate-Paclitaxel-Quercetin

MWCNT-Pm-Qu = Multiwalled carbon nanotube-Pemetrexed-Quercetin

ND-Qu	=	Nanodiamond-quercetin
N-TAM-TEG-MWCNT-Qu	=	N-desmethyl tamoxifen-tetraethylene glycole-Multiwalled carbon nanotube-Quercetin
P(AVL-VL)-Qu-TMX	=	Poly(α-allyl-δ-valerolacton- δ-valerolacton) -quercetin- tamoxifen
P(CL)-TPGS-Qu	=	poly(ε-caprolactone)-co-d-α-tocopheryl poly(ethylene glycol-1000) Succinate
PAA-CS-MSN-cRGD-Qu	=	Poly(acrylic acid)-Chitosan-Mesoporous silica nanoparticle-Arginine-glycine-aspartic acid-Quercetin
PBA-ZnO-Qu	=	phenylboronic acid-Zinc oxide-Quercetin
PCL-Cs-FA-Qu	=	polycaprolactam-Chitosan-Folic acid-Quercetin
PDA-Qu	=	polydopamine-quercetin
PEG-Qu	=	poly(ethylene glycol)- Quercetin
PLGA-CS-PEG-Qu	=	poly(d= L-lactide-co-glycolide)-Chitosan-poly (ethylene glycol)-Quercetin
PLGA-PEG-LHRH-Qu-DTX	=	poly(d= L-lactide-co-glycolide)-poly(ethylene glycol)-Luteinizing-hormone-releasing hormone-Quercetin-Docetaxel
PLGA-PEG-Qu-Gef	=	poly(d= L-lactide-co-glycolide)-poly(ethylene glycol)-Quercetin-Gefitinib
PVPylated-TiO2-Qu	=	Polyvinylpyrrolidone-titanium oxide-quercetin
QA-M	=	Quercetin-alantolactone-micelle
QDAF-CUR	=	Quercetin-3’3-dithiodipropionic acid-Astragalus polysaccharides-Folic acid Curcumin
QHMF@Cur-Bai	=	Quercetin-dithiodipropionic acid-oligomeric hyaluronic acid-Mannose-Ferulic acid
Qu-AG-NP	=	Quercetin-Silver nanoparticle
Qu-CA-Cs-Dox	=	Quercetin-Citraconic anhydride-Chitosan-doxorubicib nanomiclles
Qu-Cs-CA-Dox	=	Quercetin-Chitosan-citraconic anhydride-doxorubicin
Qu-Cs-Dox	=	Quercetin-Chitosan-doxorubicin
Qu-CS-NL	=	Quercetin-Chitosan-nanoliposome
Qu-FA-AgNP	=	Quercetin- folate receptor-targeted-plasmonic silver nanoparticle;
Qu-FD-NM	=	Quercetin-Freeze dried-Nanomicelle
Qu-GA-Ag-Se NP	=	Quercetin-Gallic acid-silver-selenium nanoparticle
Qu-GNCs	=	Quercetin-Gold nanocluster
Qu-GO	=	Quercetin-Graphene oxide
Qu-LPN	=	Quercetin-lipid polymer hybrid nanoparticle
Qu-NLC	=	Quercetin-Nanostructured lipid carrier
Qu-NLP	=	Quercetin-nanoliposome
Qu-NPYT	=	Quercetin-nanophytosome
Qu-PEG-Ag2S-ND	=	Quercetin- poly(ethylene glycol)- Ag2S nanodots
rGO-Fe3O4-GL-PF-Qu	=	superparamagnetic graphene oxide-iron oxide-Ganoderma lucidum extract-Pluronic F-127-Quercetin
SPION@AP-TES@FA-PEG@Qu	=	superparamagnetic iron oxide nanoparticle-3-aminopropyle triethoxysilane-Folic acid-carboxylated polyethylene glycole-Quercetin

TF-Qu-PLGA	=	Transferrin-Quercetin-poly(d= L-lactide-co-glycolide)
TQ-PEG-mAb	=	triphenylphosphine-Quercetin-poly(ethylene glycol)-monoclonal antibody
VCR-Qu-LPNs	=	Vincristine-Quercetin-Lipid-Polymeric nanoparticles
ZnO-Qu	=	Zinc oxide-quercetin
ZnPc-Qu-LPNs	=	Zinc phthalocyanine-Quercetin-lipid polymer hybrid nanoparticle
Zr-MOF-Qu	=	Zirconium-Metal organic frame work-Quercetin
Γ-Alumina-CS-PVP-Qu	=	γ-Alumina-Chitosan-polyvinylpyrrolidone-Quercetin

CONSENT FOR PUBLICATION

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