UDC 606.61:615.014:615.456.3 https://doi.org/10.15407/biotech19.02.005

EFFECTIVENESS OF LIPOSOMAL DRUG DELIVERY SYSTEMS FOR CREATING THERAPEUTIC FORMS OF QUERCETIN

D. M. PYLYPENKO[1] *(https://orcid.org/0000-0002-4727-0476)*
G. S. GRIGORYEVA[2] *(https://orcid.org/0009-0009-5079-4295)*
Yu. M. KRASNOPOLSKY[3] *(https://orcid.org/0000-0003-3469-5827)*

[1]State Biotechnological University, Ukraine
[2]State Institution "Institute of Pharmacology and Toxicology of the National Academy of Medical Sciences of Ukraine"
[3]National Technical University "Kharkiv Polytechnic Institute", Ukraine

E-mail: yuriykrasnopolsky@gmail.com

Quercetin is a well-known natural antioxidant with a wide spectrum of pharmacological activities, including in oncology, cardiology, ophthalmology, and other areas. Quercetin's lipophilic nature limits its clinical use and necessitates the development of effective delivery systems. Liposomal forms of quercetin are being actively studied and improved.

Aim. The article analyzes modern research on liposomal formulations of quercetin as a promising drug-delivery strategy.

Materials and methods. Analysis of modern national and foreign research on the creation of liposomal forms of quercetin and the evaluation of the efficacy of this drug delivery system in the treatment of oncological, cardiological, viral, and other diseases accompanied by oxidative stress. To search for sources of information for the study, open-access electronic resources of scientific periodicals were used.

Results. The development of liposomal quercetin formulations enabled increased bioavailability and expanded administration options, including injection. The use of liposomal quercetin in complex cancer therapy increased tumor growth inhibition while reducing side effects in healthy tissues. To improve the efficacy of quercetin delivery to tissues, it was proposed to modify liposome surfaces with hyaluronic acid, mycophenolic acid, polyethylene glycol, and magnetic particles. The possibility of using other carriers for quercetin delivery was demonstrated, including solid lipid nanoparticles, gold nanoparticles, and polymers.

Conclusions. Quercetin nanopreparations demonstrate high pharmacological efficacy and a significant increase in quercetin bioavailability, and their safety, biodegradability, and reduced toxicity are also important.

Key words: quercetin, antioxidant, anticancer therapy, dosage form, drug delivery system, nanoparticle, liposome, bioavailability.

Natural polyphenolic compounds have proven themselves in medicine. Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is one of the best-known natural polyphenols with diverse biological activities, including broad-spectrum antiviral, antioxidant, and immunomodulatory effects [1–3]. Quercetin inhibits tumor cell growth and reduces cardiotoxicity and nephrotoxicity when used with cytostatics such as docetaxel, gemcitabine, vincristine, and mycophenolic acid. The antitumor activity of quercetin has been demonstrated across

Citation: Pylypenko, D. M., Grigoryeva, G. S., Krasnopolsky, Yu. M. (2026). Effectiveness of liposomal drug delivery systems for creating therapeutic forms of quercetin. *Biotechnologia Acta*, 19(2), 5–15. https://doi.org/10.15407/biotech19.02.005

various cancer types (blood, prostate, lung, breast, etc.) [4, 5]. Quercetin exhibits pro-apoptotic activity against tumor cells and inhibits the growth of various carcinoma cell lines at different phases of the cell cycle. The antioxidant activity of quercetin is also well-known [6, 7]. Quercetin effectively reduces oxidative stress across a range of pathological processes by scavenging free radicals in vitro and in vivo across various human cell lines and animal models. Quercetin exhibits synergistic effects with other drugs, improving the efficacy of therapy [6, 7]. However, the use of lipophilic polyphenolic compounds is limited by their extremely low oral bioavailability due to poor water solubility. Thus, the main problems with the pharmacological application of quercetin are its low bioavailability and rapid metabolism. The aim of this review is to analyse the use of quercetin both in free form and as part of drug delivery systems, such as liposomal and other nanoparticles.

Materials and Methods

To search for sources of information for the study, open-access electronic resources of scientific periodicals were used: scientific databases Google Scholar, PubMed, Clarivate, Web of Science, Scopus, etc.; electronic repositories of higher education institutions and scientific institutions, where dissertation abstracts, scientific publications, and other scientific works are stored. Research methods used: information search, theoretical analysis, and systematization of data from scientific sources, and logical analysis.

The Use of Quercetin in Free Form

Although the use of free quercetin has a number of challenges and is limited primarily to oral administration, a number of research are focused on its pharmacological activity, in particular in the complex treatment of cancer. Docetaxel is a cytostatic widely used in a treatment of various types of cancer, including breast cancer and metastatic prostate cancer. However, the use of docetaxel is limited by side effects and tumor resistance. Moreover, docetaxel is a lipophilic compound, which in turn requires various auxiliary substances or encapsulation in nanoparticles for its administration [8].

The effect of the combination of quercetin and docetaxel on the human breast cancer cell line MDA-MB-231 was studied [5]. Cell viability and apoptosis induction were assessed using flow cytometry. The role of tumor protein p53 in apoptosis was assessed using qRT-PCR. The levels of BAX, BCL2, ERK1/2, AKT, and STAT3 proteins were measured using Western blotting. Monotherapies of docetaxel or quercetin decreased the viability of MDA-MB-231 cells after 48 hours, while the combination of docetaxel (7 nM) and quercetin (95 μM) resulted in the maximum synergistic effect, accompanied by upregulation of p53 and a significant increase in BAX levels, as well as a significant decrease in BCL2, pERK1/2, AKT, and STAT3 protein levels. The complex combination of docetaxel and quercetin inhibited cell growth, inducing apoptosis and inhibiting cell survival. In addition, a decrease in docetaxel toxicity was observed in combination with quercetin, which increased the possibility of its therapeutic efficacy [5]. The potential of docetaxel and quercetin complex was also demonstrated in the treatment of breast cancer [9]. LEF-1 overexpression is known to be associated with progression in a number of tumors, leading to drug resistance. The authors hypothesized that inhibiting LEF-1 (a potential target) may resensitize cells to docetaxel. Quercetin treatment reduced LEF-1 expression and resensitized cells to docetaxel. LEF-1 inhibition also suppressed the expression of ABCG2, VIM, and CFV-1 and similarly reduced activation of the SMAD-dependent TGF-β signaling pathway. The combination of docetaxel and quercetin showed synergistic activity, significantly reducing the viability of drug-resistant cells.

Docetaxel is a first-line treatment for metastatic prostate cancer, and the emergence of resistance reduces the efficacy of docetaxel therapy. Quercetin has multiple anticancer effects, including reducing chemoresistance in many cancer types. The mechanisms by which quercetin reduces docetaxel resistance in prostate cancer cells and xenograft models were studied [10]. The ability of quercetin to reverse the docetaxel resistance was demonstrated both *in vitro* and *in vivo* models [11]. In a model of docetaxel-resistant cells (LNCaP/R, PC-3/R) derived from docetaxel-sensitive cells (LNCaP, PC-3), quercetin reversed docetaxel resistance in prostate cancer cells during proliferation, colony formation, migration, invasion, and apoptosis. The use of docetaxel alone had no significant effect on cells resistant to the cytostatic agent. However, the combination of docetaxel with quercetin proved to be significantly more effective. The combined therapy could maximally inhibit the PI3K/Akt pathway and promote apoptosis. As

shown in an *in vivo* study, xenograft tumors treated with docetaxel and quercetin had poor growth. Docetaxel-resistant subclones showed stronger activation of the androgen receptor and the PI3K/Akt pathway, more pronounced mesenchymal and stem cell phenotypes, and higher P-gp expression than parental cells.

The protective effect of quercetin was demonstrated in a rat model of docetaxel-induced testicular damage [12]. Intraperitoneal administration of a docetaxel single dose caused a significant increase in the level of TBARS (thiobarbituric acid reactive compounds) and a significant decrease in the levels of SOD, GPX, CAT, and GSH in testicular tissues compared to the control group. In contrast, oral administration of quercetin resulted in a significant reduction in lipid peroxidation, as evidenced by decreased TBARS levels and increased SOD, CAT, GPX, and GSH levels. After docetaxel administration, sperm motility and concentration, testicular and epididymal weights were significantly reduced, while abnormal sperm velocity and histopathological changes were increased. However, these effects of docetaxel on sperm parameters, histological changes, and tissue weight were reversed by quercetin treatment. Thus, quercetin treatment prevented docetaxel-induced testicular damage (oxidative stress, testicular tissue damage, and sperm parameters) in rats [12].

The effect of quercetin in the combined treatment of castration-resistant prostate cancer with docetaxel was studied [13]. The individual and combined effects of quercetin and docetaxel at different doses and combinations on viability, proliferation, and apoptosis of two prostate cancer cell lines, DU-145 (moderately aggressive) and PC-3 (highly aggressive), were assessed. Monotherapy showed dose-dependent cytotoxicity, but only docetaxel monotherapy showed a statistically significant difference in maximum inhibition (IC_{50} of 4.05 ± 0.52 nM for PC-3 and 2.26 ± 0.22 nM for DU-145). The combined treatment of quercetin and docetaxel showed the most favorable effect when quercetin was pretreated for 24 h, followed by low doses of docetaxel for another 24 h. Authors observed synergism at low docetaxel concentrations (0.5 and 1.0 nM) and all quercetin concentrations (2.0–20.0 μM). An additive effect was established at moderate and high docetaxel concentrations (1.5, 2.0, and 2.5 nM) and all quercetin concentrations in both cell lines. Quercetin pretreatment also allowed overcoming docetaxel resistance in resistant prostate cancer cells and enhanced the therapeutic effect of docetaxel in the treatment of resistant prostate cancer.

The efficacy of quercetin combination with another perspective polyphenolic compound (curcumin) was demonstrated in inhibiting the acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [14]. The therapeutic benefits of the complex oral supplement of curcumin and quercetin in combination with standard treatment of the early stage of COVID-19 infection were studied. Patients were randomized in two equal groups: the curcumin/quercetin treatment group ($n = 25$) or the control group ($n = 25$). The curcumin/quercetin daily supplement consisted of 168 mg of curcumin and 260 mg of quercetin, administered as two softgels capsules twice daily for 14 days. A week after the start of treatment, the majority of patients in the curcumin/quercetin group demonstrated accelerated viral recovery (72 %, 18 patients). The results indicate the potential of curcumin/quercetin therapy in the early stages of COVID-19. The authors hypothesized that the combination of quercetin and curcumin synergistically inhibits SARS-CoV-2 replication and thus promote rapid recovery in the early stages of COVID-19.

The Use of Quercetin in a Form of Drug Delivery Systems

Harmless lipophilic plant-derived molecules such as quercetin, curcumin, isoflavones, catechins, hesperidin, etc. have demonstrated significant adjuvant effects in the therapy of cancer and cardiovascular diseases, as well as in reducing the side effects of chemotherapy [15]. These biologically active compounds exhibit anticancer effects by interfering with signaling pathways in cancer cells. Furthermore, these lipophilic compounds protect non-cancerous cells from the side effects of chemotherapy. However, their low bioavailability significantly limits their use in oncology, cardiology, ophthalmology, and other fields. To increase the bioavailability and efficacy of polyphenols, drug delivery systems that encapsulate quercetin in nanoparticles have been proposed.

Liposomal composition of quercetin and curcumin has been proposed [16, 17]. The authors used various lipid compositions and encapsulation methods to eliminate the low water solubility and instability of polyphenols in physiological environments.

Liposomal quercetin (trade name “Lipoflavon”) was developed in Ukraine [18–20] and licensed in 2006. Lipoflavon is

a lyophilisate for emulsion for injection. The vial contains 15 mg of quercetin, 550 mg of egg phosphatidylcholine (as membrane-forming lipid), and lactose (as cryoprotectant). The particle size was 130–160 nm [21]. Indications for the use of Lipoflavon include acute myocardial infarction, stable and unstable angina pectoris, and myocarditis. Lipoflavon is also used to prevent toxic myocardial damage during cycles of polychemotherapy for breast cancer, for example, in case of anthracycline antibiotics. Lipoflavon is recommended to be administered 24 hours before the cytostatic [22–25]. In ophthalmology, Lipoflavon is used to treat diabetic retinopathy, cataracts, uveitis, and other conditions [26].

The use of liposomal quercetin for the prevention of cardiovascular diseases and the reduction of cytostatic toxicity in the treatment of tumors is largely based on its antioxidative and anti-inflammatory actions [6, 7, 27, 29]. The first is achieved by increasing antioxidant mediators (SOD, GSH, and CAT), and the second by decreasing proinflammatory mediators (such as IL-6 and TNF-α) and increasing anti-inflammatory mediators (such as IL-10).

Liposomal quercetin was used to reduce the hepatotoxicity of gemcitabine, which is widely used in the treatment of many tumors (such as ovarian, bladder, and pancreatic cancer) [30]. The optimal composition of liposomal quercetin was determined by particle size distribution, polydispersity index, zeta potential, entrapment efficiency, and *in vitro* release. The resulting composition was used to treat rats with gemcitabine-induced hepatotoxicity. The severity of liver injury in rats was determined by measuring liver function tests, antioxidant capacity, anti-inflammatory markers, and nuclear factor erythroid 2-related gene (Nrf2) expression. Orally administered liposomal quercetin reduced the severity of gemcitabine-induced hepatotoxicity in rats by improving the liver function tests and total antioxidant capacity of the liver, as well as liver tissue histology.

Furthermore, liposomal quercetin increased Nrf2 mRNA expression. It decreased hepatic proinflammatory mediator expression, such as NF-κB and TNF-α, suggesting that liposomal quercetin may be an effective and safe hepatoprotector during chemotherapy [30]. A dose-dependent therapeutic effect of liposomally encapsulated quercetin was demonstrated in both liver function and histopathological studies [31]. Liposomal composition in different concentrations was significantly more effective compared with traditional quercetin treatment, and even low concentrations of liposomal quercetin demonstrated a protective effect against liver injury in rats.

A novel formulation of a quercetin-encapsulated liposomal gel stabilized with hydroxypropyl-β-cyclodextrin (HPCD) was developed for the treatment of chronic skin inflammation (psoriasis) [32]. HPCD interacts with phospholipids via hydrogen bonds, forming a coating layer on the liposome surface, thereby increasing stability. HPCD-modified liposomes interacted with matrix lipids and keratins in the stratum corneum, thereby increasing skin permeability and promoting drug penetration and retention. The developed liposomal gel with quercetin improves the efficacy of psoriasis treatment *in vivo* compared to free quercetin. The bilayer structure of phospholipids and the three-dimensional network of hydrogels delay the release of quercetin from liposomal nanoparticles. As a result, the thickening of the skin and a decrease in proinflammatory cytokines, including TNF-α, IL-17A, and IL-1β, were observed. The authors demonstrated that an HPCD-modified liposomal gel can serve as a stable carrier for local quercetin therapy in psoriasis.

Pancreatic cancer is characterized by a significant increase in tissue pressure in the tumor's extracellular matrix, which makes it resistant to most chemotherapeutic agents. An increased concentration of hyaluronic acid in tumor tissue protects it from drug exposure. To deliver quercetin to tumor tissue, a liposomal drug delivery system conjugated with hyaluronidase on its surface was proposed [33]. The proposed drug was mainly accumulated in the tumor due to increased permeability and retention. The use of quercetin in liposomes with hyaluronidase-conjugated surfaces suppressed tumor growth in mice without toxic effects. Developed composition exhibited strong inhibition of cell proliferation, leading to cell apoptosis and G2/M cell cycle arrest in cell lines, three-dimensional cultured spheroids, and organoids derived from pancreatic ductal adenocarcinoma. The authors hypothesized that a hyaluronidase-conjugated liposomal surface degrades hyaluronic acid in the tumor microenvironment, enhances the penetration of liposomal nanoparticles, inhibits tumor cell growth, thereby increasing the efficacy of antitumor therapy [33].

The antitumor activity of a liposomal quercetin formulation was studied in prostate

cancer stem cells overexpressing CD44 receptors [34]. Liposomes were modified with hyaluronic acid. The liposomal particles had an average size of 134 nm and a quercetin encapsulation efficiency of 96.9%. Human prostate cancer cells were treated with 10 μM of free quercetin or with liposomal quercetin at the same concentration for 72 hours. Free quercetin reduced the viability of androgen-resistant cells by 16%, while liposomal quercetin significantly reduced it by 60%. Induction of apoptosis accompanied by upregulation of cytochrome C, Bax, caspases 3 and 8, and downregulation of surviving and Bcl-2 was observed. Unlike free quercetin, hyaluronic acid-modified liposomal quercetin composition increased E-cadherin expression, inhibited cell migration, and decreased fibronectin, N-cadherin, and MMP9 expression. Treatment of PC3 cell tumor spheroids with liposomal quercetin decreased the number of CD44+ cells and inhibited the expression of CD44, Oct3/4, and Wnt. Moreover, the liposomal composition suppressed p-ERK expression while increasing p38/MAPK and NF- B protein expression. In androgen-sensitive LNCaP cells, the efficacy of liposomal composition was significantly improved compared to free quercetin, reducing cell viability from 10% to 52%. Using hyaluronic acid-modified liposomes as a drug delivery system for quercetin increased its efficacy at lower concentrations, reduced the CD44+ cell population, and effectively inhibited prostate cancer cell proliferation and migration [34].

Liposomal quercetin with encapsulation efficiency of 41%, zeta potential of 0.47 mV, and particle size of 100 nm was prepared, and its antiproliferative effect was studied on MCF-7 human carcinoma cells *in vitro* [35]. The effect of liposomal quercetin on MCF-7 cells was compared with the effect of empty liposomes and free quercetin. Empty liposomes showed a minimal effect on cell viability. Liposomal quercetin significantly improved the solubility and bioavailability of quercetin. The inhibitory activity of the liposomal form was equal to or greater than equimolar concentrations of free quercetin. Liposomal quercetin, like free quercetin, effectively inhibited cell proliferation *in vitro*, and the inhibitory effect was dose-dependent. Thus, when MCF-7 cells were treated with Ls-quercetin for 48 hours, the level of inhibition at concentrations of 1 μM/ml, 10 μM/ml, and 50 μM/ml was 21%, 73%, and 83%, respectively. Moreover, liposomal quercetin showed a more pronounced antioxidant effect in MCF-7 cells compared to free quercetin.

Mycophenolic acid is a natural antitumor agent derived from the metabolic products of *Penicillium stoloniferum* or *Penicillium echinulatum* that promotes cancer cell apoptosis by inhibiting purine nucleotide synthesis [36]. Combined therapy with liposomal mycophenolic acid (particle size of 183±13 nm) and liposomal quercetin (particle size of 157±9.8 nm) was studied on breast cancer cells *in vitro* in comparison with monotherapy [37]. Higher cellular uptake and cytotoxicity of the combined therapy were demonstrated. Pharmacokinetic studies in female rats showed a 1.94-fold longer T1/2 for the combination therapy compared with mycophenolic acid. Furthermore, the efficacy of breast cancer treatment *in vivo* with the combination of liposomal quercetin and mycophenolic acid was also significantly higher compared to other groups of rats.

Magnetic CoFe2O4 nanoparticles were conjugated to liposomes, and quercetin was encapsulated in these magneto-liposomes, forming an original drug delivery system that can be used under an alternating magnetic field for chemotherapy/hyperthermia tumor treatment [38]. Liposomes were characterized by an average particle size of 38 nm and a quercetin encapsulation level of 69%. The high cytotoxic and hypersensitivity effects of the proposed quercetin drug delivery system were demonstrated *in vitro* in MCF-7 breast cancer cells, inducing 35% early and 55% late apoptosis.

Polyethylene glycol (PEG) 4000 was used to surface-modify quercetin-encapsulated liposomes, thereby increasing quercetin solubility by 2.2-fold [39]. PEG4000-modified liposomes had a particle size of 254±69 nm, low polydispersity index of 0.236±0.018, zeta potential of −35.4±0.6 mV, quercetin encapsulation level of 87.6±5.6 %, and PEG loading level of 22.2 ± 6.9%. The antitumor effect of the liposomal composition was studied in HeLa cells; the IC50s of PEG-liposomal quercetin and free quercetin were 16.3 μg/mL and 88.3 μg/mL, respectively. PEG-liposomes significantly reduced the cell adhesion and colony-forming ability of HeLa cells according to crystal violet staining tests. Moreover, qPCR analysis of gene expression levels showed that PEG-liposomal quercetin had a greater effect on mitochondrial apoptosis in HeLa cells than free quercetin. Using the hemolysis assay, the applicability of PEG-liposome for parenteral use was confirmed.

Liposomal quercetin composition was developed based on its binding with copper [40]. Quercetin ratio of quercetin to lipid was 1:5, and quercetin concentration in the resulting emulsion was at least 5, which was added directly to copper-containing liposomes. Copper-quercetin complex A molar mg/mL, ensuring a more than 100-fold increase in solubility of the polyphenol (solubility of quercetin in aqueous solution is less than 10 μg/mL). When administered intravenously to mice, the proposed drug delivery system showed no toxicity at a dose of 50 mg/kg, and the AUC(0-24h) of the copper-quercetin composition at this dose was 8382.1 μg·h/mL. Furthermore, it was shown that quercetin, not the copper-quercetin complex, dissociates from liposomes. Given that the IC50 of quercetin on lung adenocarcinoma cell lines was at least 10 μM in the presence of irinotecan, the authors suggest liposomal quercetin as a prospective drug delivery system for tumor chemotherapy [40].

A pharmacologically active liposomal composition containing quercetin and zinc was proposed [20]. It exhibits anti-inflammatory activity and was recommended for use as a pharmacotherapeutic agent for acute respiratory distress syndrome by inhalation or injection.

Non-liposomal Drug Delivery Systems for Quercetin Therapy

A gel of nanocochelates loaded with quercetin and curcumin was proposed for the adjuvant therapy of breast cancer [41]. Previously prepared liposomal forms of quercetin and curcumin were treated with $CaCl_2$ as a binding agent and used as a reference. The liposomal quercetin had a particle size of 327 nm, a zeta potential of −16.8 mV, and quercetin encapsulation and release efficiencies of 85.28% and 80.23%, respectively. The liposomal curcumin had a particle size of 328.6 nm, a zeta potential of −15.0 mV, and curcumin encapsulation and release efficiencies of 82.30% and 77.19%, respectively. The nanocochleate gel containing quercetin and curcumin was also characterized for pH, spreadability, and viscosity. Using the MTT assay, it was shown that nanocochleates loaded with quercetin and curcumin exhibited the greatest *in vitro* inhibition compared to the control, quercetin monotherapy, liposomal quercetin, and nanocochleates loaded with only quercetin. Thus, a nanocochleate gel containing quercetin and curcumin may be a promising drug delivery system for local treatment of breast cancer.

Studies aimed at creating polymeric nanoparticles containing quercetin were conducted [42–44]. Gold-quercetin nanoparticles in a complex with poly(DL-lactide-co-glycolide) exhibited antitumor activity by inhibiting proliferation and inducing apoptosis in liver cancer cells [44]. Quercetin-containing nanocomplexes accelerated caspase-9 and -3 cleavage and induced cytochrome C release, promoting apoptosis in liver cancer cells. Nanoparticles with quercetin also promote the inhibition of telomerase reverse transcriptase (hTERT) by reducing AP-2β expression and its binding to the hTERT promoter. NPQUE also inhibits cyclooxygenase 2 (COX-2) by suppressing NF-κB nuclear translocation and its binding to the COX-2 promoter. The nanocomposition also inactivated the Akt and ERK1/2 signaling pathway. Thus, the authors suggest that quercetin nanoparticles exert antitumor effects by inactivating the caspase/cytochrome C pathway, suppressing AP-2β/hTERT, inhibiting NF-κB/COX-2, and interfering with the Akt/ERK1/2 signaling pathways, making quercetin nanoparticles a promising agent for potential therapeutic strategies and targets for the inhibition of liver cancer.

Polymers such as polyvinylpyrrolidone (PVP) can be used as carriers for quercetin, forming a water-soluble complex that allows intravenous injection. In Ukraine, the drug “Corvitin” was licensed 25 years ago and is successfully used in clinical cardiovascular pathologies. The vial contains quercetin, which is a complex of quercetin with PVP with a molecular weight of 7,100–11,000 (0.05 g of quercetin, 0.45 g of PVP). In this form, quercetin acts as a modulator of the activity of various enzymes (such as phospholipase, phosphogenase, cyclooxygenase) involved in phospholipid degradation, free radical processes, and the cellular biosynthesis of nitric oxide and proteinases. The inhibitory effect of quercetin on membrane-bound enzymes, particularly 5-lipoxygenase, leads to a decrease in leukotriene synthesis (such as LTC4 and LTB4).

Furthermore, quercetin dose-dependently increases nitric oxide levels in endothelial cells, which are critical for its cardioprotective effect against ischemic and reperfusion injury of the heart. The Quercetin-PVP complex has antioxidant and immunomodulatory properties, reduces the production of cytotoxic superoxide anion, normalizes the activation of lymphocyte subpopulations, and reduces their activation levels. “Corvitin” significantly

reduces the area of necrotic myocardium and enhances reparative processes by inhibiting the production of proinflammatory cytokines (such as IL-1β and IL-8) [45–47]. A dispersion of quercetin with PVP-10,000 was developed [48]. This complex enabled the creation of an injectable, water-soluble form of quercetin, increasing its solubility 20,000-fold. This formulation reduced blood pressure in normal and spontaneously hypertensive rats, both in the short- and long-term [48].

Drug delivery systems based on solid lipid nanoparticles (SLNs) are also being developed. These spherical particles contain solid lipids (such as stearic acid), stabilizing surfactants, and binding agents. SLNs containing quercetin, Span 60, and Poloxamer 407 were proposed as anthelmintic agents. In this formulation, the hydrophobic part of Poloxamer 407 is linked to a stearic acid lipid core containing quercetin, while the hydrophilic polyethylene glycol tails of Poloxamer 407 interact with an aqueous medium and dissolve quercetin [49]. The cytostatic activity of quercetin-loaded SLNs (particle size of 132.6 nm) based on stearic acid, tripalmitin, Tween 80, and Span 80 was demonstrated on colorectal adenocarcinoma cells [50]. The level of quercetin encapsulation into SLNs was 97.8%. Under the influence of the drug, apoptosis was a cause of cell death, while the necrosis rate was insignificant.

Conclusions

The possibility of using various drug delivery systems (liposomes, SLNs, and polymers of various structures) for quercetin encapsulation to increase its bioavailability and pharmacological efficacy was discussed. Quercetin-loaded nanoparticles demonstrated significantly improved antitumor, cardioprotective, hepatoprotective, ophthalmoprotective, and antioxidant effects. Most importantly, quercetin-loaded drug delivery systems demonstrate safety, biocompatibility, and biodegradability, and help reduce the toxicity of a range of drugs, including cytostatics. The mechanisms of quercetin action in targeted cancer therapy, heart disease, antioxidant action [6, 7, 51–55], skin diseases [32, 55], etc., were discussed.

Prospects for further research. Further research on the development of quercetin-loaded drug delivery systems will focus on complex formulations and the synergistic effects of quercetin and other active pharmaceutical ingredients to increase the efficiency and safety of the therapy.

Conflict of interest

The authors declare no conflict of interest.

Funding source

The work was performed within the research program of "Use of biotechnological methods in rational nature management, veterinary medicine and innovative production" (State Registration No. 0121U113717, 2022–2026).

Author's contributions

D. M. Pylypenko — relevant source collecting, original draft preparation, technical editing;

G. S. Grigoryeva — relevant source collecting, review and editing;

Yu. M. Krasnopolsky — concept development, relevant source collecting, review and editing.

REFERENCES

1. Huk, I., Brovkovych, V., Nanobash Vili, J., Weigel, G., Neumayer, C., Partyka, L., ..., Malinski, T. (1998). Bioflavonoid quercetin scavenges superoxide and increases nitric oxide concentration in ischaemia-reperfusion injury: an experimental study. *The British journal of surgery*, 85(8), 1080–1085. https://doi.org/10.1046/j.1365-2168.1998.00787.x
2. Kovalev, V. B., Kovgan, V. V., Tolchina, E. Yu. (1999). Mechanisms of therapeutic actions of the bioflavonoid quercetin (literature review). *Ukrainskyi medychnyi almanakh*, 2(4), 176–184. (In Ukraiiqan).
3. Stefanov, O. V., Tumanov, V. A., Garinova, N. O. (2002). Pouring Lipina onto aphids quercetin on lipid oxidation peroxide in the blood and organs of the vaginal squints during maximum physical attention. *Liki*, 3–4, 70–72. (In Ukrainian)
4. Lotfi, N., Yousefi, Z., Golabi, M., Khalilian, P., Ghezelbash, B., Montazeri, M., ..., Eskandari, N. (2023). The potential anti-cancer effects of quercetin on blood, prostate and lung cancers: An update. *Frontiers in immunology*, 14, 1077531. https://doi.org/10.3389/fimmu.2023.1077531
5. Safi, A., Heidarian, E., Ahmadi, R. (2021). Quercetin Synergistically Enhances the Anticancer Efficacy of Docetaxel through Induction of Apoptosis and Modulation of

PI3K/AKT, MAPK/ERK, and JAK/STAT3 Signaling Pathways in MDA-MB-231 Breast Cancer Cell Line. *International journal of molecular and cellular medicine*, 10(1), 11–22. https://doi.org/10.22088/IJMCM.BUMS.10.1.11

6. Pylypenko, D. M., Gorbach, T. V., Katsai, O. G., Grigoryeva, A. S., Krasnopolsky, Y. M. (2019). A study of oxidative stress markers when using the liposomal antioxidant complex. *Pharmakeftiki*, 31(1), 40–47.
7. Pylypenko, D., Gorbach, T., Krasnopolsky, Yu. (2020). Study of antioxidant activity of liposomal forms of quercetin and curcumin ischemic heart disease. *BioTechnologia*, 101(4), 273–282. https://doi.org/10.5114/bta.2020.100420
8. Krasnopolsky, Y. M., Dudnichenko, A. S. (2017). Experimental study of liposomal docetaxel analysis of docetaxel incorporation and stability. *Experimental oncology*, 39(2), 121–123.
9. Prieto-Vila, M., Shimomura, I., Kogure, A., Usuba, W., Takahashi, R. U., Ochiya, T., Yamamoto, Y. (2020). Quercetin Inhibits Lef1 and Resensitizes Docetaxel-Resistant Breast Cancer Cells. *Molecules (Basel, Switzerland)*, 25(11), 2576. https://doi.org/10.3390/molecules25112576
10. Lu, X., Yang, F., Chen, D., Zhao, Q., Chen, D., Ping, H., Xing, N. (2020). Quercetin reverses docetaxel resistance in prostate cancer via androgen receptor and PI3K/Akt signaling pathways. *International journal of biological sciences*, 16(7), 1121–1134. https://doi.org/10.7150/ijbs.41686
11. Hussain, Y., Mirzaei, S., Ashrafizadeh, M., Zarrabi, A., Hushmandi, K., Khan, H., Daglia, M. (2021). Quercetin and Its Nano-Scale Delivery Systems in Prostate Cancer Therapy: Paving the Way for Cancer Elimination and Reversing Chemoresistance. *Cancers*, 13(7), 1602. https://doi.org/10.3390/cancers13071602
12. Altintas, R., Ciftci, O., Aydin, M., Akpolat, N., Oguz, F., Beytur, A. (2015). Quercetin prevents docetaxel-induced testicular damage in rats. *Andrologia*, 47(3), 248–256. https://doi.org/10.1111/and.12253
13. Sharma, S., Cwiklinski, K., Mahajan, S. D., Schwartz, S. A., Aalinkeel, R. (2023). Combination Modality Using Quercetin to Enhance the Efficacy of Docetaxel in Prostate Cancer Cells. *Cancers*, 15(3), 902. https://doi.org/10.3390/cancers15030902
14. Ujjan, I. D., Khan, S., Nigar, R., Ahmed, H., Ahmad, S., Khan, A. (2023). The possible therapeutic role of curcumin and quercetin in the *early-stage* of COVID-19-Results from a pragmatic randomized clinical trial. *Frontiers in nutrition*, 9, 1023997. https://doi.org/10.3389/fnut.2022.1023997
15. Jain, A., Madu, C. O., Lu, Y. (2021). Phytochemicals in Chemoprevention: A Cost-Effective Complementary Approach. *Journal of Cancer*, 12(12), 3686–3700. https://doi.org/10.7150/jca.57776
16. Alexopoulou, E., Georgopoulos, A., Kagkadis, K. A., Demetzos, C. (2006). Preparation and characterization of lyophilized liposomes with incorporated quercetin. *Journal of liposome research*, 16(1), 17–25. https://doi.org/10.1080/08982100500528594
17. de Albuquerque, P. B. S., de Souza, M. P., Bourbon, A. I., Cerqueira, M. A., Pastrana, L., Jauregi, P., ..., das Graças Carneiro-da-Cunha, M. (2023). Production and Properties of Quercetin-Loaded Liposomes and Their Influence on the Properties of Galactomannan-Based Films. *Applied Nano*, 4(2), 159–177. https://doi.org/10.3390/applnano4020009
18. *Patent of Ukraine No. 76393*. Method for extracting liposomal extract, which take quercetin. 2007. Stefanov, O. V., Grigor'eva, G. WITH., Solovyov, A. I., Pasechnikova, N. V., Khromov, O. S., Konakhovich, N. F., Krasnopolsky, Yu. M.
19. *Patent of Ukraine No. 111762*. Method for removing pharmacologically active liposomal dose, which contains quercetin. Grigor'eva, G. S., Krasnopolsky, Yu. M., Konakhovich, N. F., Pasechnikova N. V.
20. *Patent US No 12168018 B1*. Grygorieva, G., Konakhovych, N., Krasnopolsky, Y., Pylypenko, O., Prokhorov, V., Suvorova, Z., Yadlovsky, O. Pharmacologically active liposomal composition comprising quercetin and zink. 2024. .
21. Pylypenko, D. M., Grigoryeva, G. S., Konakhovych, N. F., Krasnopolsky, Yu. M. (2022). Influence of the lipid composiotion of the properties, technology and quality indicators of liposomal drug. *Biotecnologia Acta*, 15(5), 23–30. https://doi.org/10.15407/biotech15.05.024
22. Belik, G. V., Grigor'eva, G. S., Derimedvid, L. V. (2004). Features of liposomal form of quercetin on the doxorubicin model cardiomyopathies. *Liki*, 5–6, 60–64. (In Ukrainian).
23. Antipova, S. V., Shepil, A. V., Ryabtseva, O. D. (2009). Experience with the use of lipoflavone to prevent the development of cardiac complications in patients with operable breast cancer receiving treatment with anthracyclines. *Problems of modern medical science and education*, 2, 44–45. (In Ukrainian).

24. Shchetinina, T. A., Shepil, A. V. (2008). Evaluation of the effectiveness of Lipoflavon for the prevention of cardiac complications in patients with operable breast cancer receiving anthracycline therapy. *Ukrainskyi medychnyi almanakh*, 11(5), 207–208. (In Ukrainian).
25. Suvorova, Z. S. (2024). Anti-fuse activity of the liposomal form quercetin. *Pharmacology and medicinal toxicology,* 18(3), 185–190. (In Ukrainian). https://doi.org/10.33250/18.03.185
26. Krasnopolsky, Yu. M., Pilipenko, D. M. (2023). Development of antigen delivery systems and paints based on artificial and natural lipid nanoparticles: liposomes and exosomes (monograph). Kharkiv: Drukarnya Madrid, 179. (In Ukrainian).
27. Uzlenkova, N., Grygoryeva, A., Skorobogatova, N., KryvkoA., Leonova, I., Konakhovich, N., ..., Yadlovsky, O. (2024). Radioprotective activity of the liposomal composition of quercetin in acute radiation syndrome (experimental study). *Ukrainian Journal of Radiology and Oncology*, 32(2), 231-243. https://doi.org/10.46879/ukroj.2.2024.231-243
28. Aguayo-Morales, H., Poblano, J., Berlanga, L., Castillo-Tobías, I., Silva-Belmares, S. Y., Cobos-Puc, L. E. (2024). Plant Antioxidants: Therapeutic Potential in Cardiovascular Diseases. *Compounds*, 4(3), 479–502. https://doi.org/10.3390/compounds4030029
29. Rezaei-Sadabady, R., Eidi, A., Zarghami, N., Barzegar, A. (2016). Intracellular ROS protection efficiency and free radical-scavenging activity of quercetin and quercetin-encapsulated liposomes. *Artificial cells, nanomedicine, and biotechnology*, 44(1), 128–134. https://doi.org/10.3109/21691401.2014.926456
30. El-Emam, M. M. A., Alobaida, A., El-Sayed, M. M., Qelliny, M. R., Ibrahim, M., Khamis, T., ..., Subaiea G. M. (2025). Development of quercetin-loaded liposomal nanocarriers for alleviation of gemcitabine-induced hepatotoxicity: Optimization, in-vitro, and in-vivo evaluation. *Journal of Drug Delivery Science and Technolog,* 105, 10665. https://doi.org/10.1016/j.jddst.2025.106659
31. Yin, N., Pang, J., Liu, X. (2025). Exploration of the optimal concentration of quercetin liposome nanoparticles for the treatment of liver damage. *BMC pharmacology & toxicology*, 26(1), 112. https://doi.org/10.1186/s40360-025-00951-x
32. Zhang, Y., Gong, S., Liu, L., Shen, H., Liu, E., Pan, L., ..., Huang, Y. (2023). Cyclodextrin-Coordinated Liposome-in-Gel for Transcutaneous Quercetin Delivery for Psoriasis Treatment. *ACS applied materials & interfaces*, 15(34), 40228–40240. https://doi.org/10.1021/acsami.3c07582
33. Sun, G., Wu, Y., Li, J., Yang, M., Xu, H., Li, Y., ..., Kong, X. (2025). Quercetin liposomes conjugated with hyaluronidase: An efficient drug delivery system to block pancreatic cancer. *Journal of controlled release : official journal of the Controlled Release Society*, 382, 113642. https://doi.org/10.1016/j.jconrel.2025.113642
34. Turkekul, K., Erdogan, S. (2023). Potent Suppression of Prostate Cancer Cell Growth and Eradication of Cancer Stem Cells by CD44-targeted Nanoliposome-quercetin Nanoparticles. *Journal of cancer prevention*, 28(4), 160–174. https://doi.org/10.15430/JCP.2023.28.4.160
35. Rezaei-Sadabady, R., Eidi, A., Zarghami, N., Barzegar, A. (2016). Intracellular ROS protection efficiency and free radical-scavenging activity of quercetin and quercetin-encapsulated liposomes. *Artificial cells, nanomedicine, and biotechnology*, 44(1), 128–134. https://doi.org/10.3109/21691401.2014.926456
36. Benjanuwattra, J., Chaiyawat, P., Pruksakorn, D., Koonrungsesomboon, N. (2020). Therapeutic potential and molecular mechanisms of mycophenolic acid as an anticancer agent. *European journal of pharmacology*, 887, 173580. https://doi.org/10.1016/j.ejphar.2020.173580
37. Patel, G., Thakur, N. S., Kushwah, V., Patil, M. D., Nile, S. H., Jain, S., ..., Kai, G. (2020). Liposomal Delivery of Mycophenolic Acid With Quercetin for Improved Breast Cancer Therapy in SD Rats. *Frontiers in bioengineering and biotechnology*, 8, 631. https://doi.org/10.3389/fbioe.2020.00631
38. Elbeltagi, S., Abdel Shakor, A. B., Alharbi, H., Tawfeek, H. M., Aldosari, B. N., Eldin, Z., ..., Abd El-Aal, M. (2024). Synergistic effects of quercetin-loaded $CoFe_2O_4$@Liposomes regulate DNA damage and apoptosis in MCF-7 cancer cells: based on biophysical magnetic hyperthermia. *Drug development and industrial pharmacy*, 50(6), 561–575. https://doi.org/10.1080/03639045.2024.2363231
39. Demirbolat, G. M., Erdoğan, Ö., Coşkun, G. P., Çevik, Ö. (2022). PEG4000 modified liposomes enhance the solubility of quercetin and improve the liposome functionality: *in vitro* characterization and the cellular efficacy. *Turkish journal of chemistry*, 46(4), 1011–1023. https://doi.org/10.55730/1300-0527.3411

40. Chen, K. T. J., Anantha, M., Leung, A. W. Y., Kulkarni, J. A., Militao, G. G. C., Wehbe, M., ..., Bally, M. B. (2020). Characterization of a liposomal copper(II)-quercetin formulation suitable for parenteral use. *Drug delivery and translational research*, 10(1), 202–215. https://doi.org/10.1007/s13346-019-00674-7
41. Tilawat, M., Bonde, S. (2023). Curcumin and quercetin loaded nanocochleates gel formulation for localized application in breast cancer therapy. *Heliyon*, 9(12), e22892. https://doi.org/10.1016/j.heliyon.2023.e22892
42. Sanoqrot, S., Abujamous L. (2019). pH-sensetive polymeric nanoparticles of quercetin as a potential colon cancer targeted nanomedicine. *Journal of Drug Delivery Science and Technology,* 52, 670-676. https://doi.org/10.1016/j.jddst.2019.05.035
43. Tefas, L. R., Tomuţă, I., Achim, M., Vlase, L. (2015). Development and optimization of quercetin-loaded PLGA nanoparticles by experimental design. *Clujul medical (1957)*, 88(2), 214–223. https://doi.org/10.15386/cjmed-418
44. Ren, K. W., Li, Y. H., Wu, G., Ren, J. Z., Lu, H. B., Li, Z. M., Han, X. W. (2017). Quercetin nanoparticles display antitumor activity via proliferation inhibition and apoptosis induction in liver cancer cells. *International journal of oncology*, 50(4), 1299–1311. https://doi.org/10.3892/ijo.2017.3886
45. Moibenko, O. O. (2002). New technologies cardioprotection. *Journal of Physiology*, 48(4), 85–87. (In Ukrainian).
46. Moibenko, O. O., Parkhomenko, A. N., Kozhukhov, S. N. (2003). Efficacy of a water-soluble form of quercetin (corvitin) in the treatment of acute coronary syndrome (with ST-segment activation). *Journal of the National Academy of Medical Sciences of Ukraine*, 9(2), 61–70. (In Ukrainian).
47. Parkhomenko, A. N., Kozhukhov, S. N. (2014). Results of an open-label, randomized study to evaluate the tolerability and efficacy of Corvitin in patients with congestive heart failure and left ventricular systolic dysfunction. *Ukrainian Medical Journal*, 4, 71–76. (In Ukrainian).
48. Porcu, E. P., Cossu, M., Rassu, G., Giunchedi, P., Cerri, G., Pourová, J., ..., Gavini, E. (2018). Aqueous injection of quercetin: An approach for confirmation of its direct *in vivo* cardiovascular effects. *International journal of pharmaceutics*, 541(1–2), 224–233. https://doi.org/10.1016/j.ijpharm.2018.02.036
49. Sharma, S., Thukral, R., Singla, L. D., Singla, N., Choudhury, D. (2025). Quercetin-loaded solid lipid nanoparticles for enhanced anti-helminthic activity *International Journal of Pharmaceutics,* 672, 125308. https://doi.org/10.1016/j.ijpharm.2025.125308
50. Mohamed, J. M. M., Ahmad, F., El-Sherbiny, M., Al Mohaini, M. A., Venkatesan, K., Alrashdi, Y. B. A., ..., El Deeb, S. (2024). Optimization and characterization of quercetin-loaded solid lipids nanoparticles for biomedical application in colorectal cancer. *Cancer Nano,* 15, 16. https://doi.org/10.1186/s12645-024-00249-3
51. Das, S. S., Hussain, A., Verma, P. R. P., Imam, S. S., Altamimi, M. A., Alshehri, S., Singh, S. K. (2020). Recent Advances in Liposomal Drug Delivery System of Quercetin for Cancer Targeting: A Mechanistic Approach. *Current drug delivery*, 17(10), 845–860. https://doi.org/10.2174/1567201817666200415112657
52. Chen, K., Rekep, M., Wei, W., Wu, Q., Xue, Q., Li, S., Tian, J., ..., Liu, Y. (2018). Quercetin Prevents In Vivo and In Vitro Myocardial Hypertrophy Through the Proteasome-GSK-3 Pathway. *Cardiovascular drugs and therapy*, 32(1), 5–21. https://doi.org/10.1007/s10557-018-6771-4
53. Lin, X., Lin, C. H., Zhao, T., Zuo, D., Ye, Z., Liu, L., Lin, M. T. (2017). Quercetin protects against heat stroke-induced myocardial injury in male rats: Antioxidative and antiinflammatory mechanisms. *Chemico-biological interactions*, 265, 47–54. https://doi.org/10.1016/j.cbi.2017.01.006
54. Liu, H., Guo, X., Chu, Y., Lu, S. (2014). Heart protective effects and mechanism of quercetin preconditioning on anti-myocardial ischemia reperfusion (IR) injuries in rats. *Gene*, 545(1), 149–155. https://doi.org/10.1016/j.gene.2014.04.043
55. Liu, C., Cheng, X., Wu, Y., Xu, W., Xia, H., Jia, R., ..., Cheng, Z. (2023). Antioxidant Activity of Quercetin-Containing Liposomes-in-Gel and Its Effect on Prevention and Treatment of Cutaneous Eczema. *Pharmaceuticals (Basel, Switzerland)*, 16(8), 1184. https://doi.org/10.3390/ph16081184

ЕФЕКТИВНІСТЬ ЛІПОСОМАЛЬНИХ СИСТЕМ ДОСТАВКИ ЛІКІВ ДЛЯ СТВОРЕННЯ ТЕРАПЕВТИЧНИХ ФОРМ КВЕРЦЕТИНУ

Д.М. Пилипенко[1] *(https://orcid.org/0000-0002-4727-0476)*
Г.С. Григор'єва[2] *(https://orcid.org/0009-0009-5079-4295)*
Ю.М. Краснопольський[3] *(https://orcid.org/0000-0003-3469-5827)*

[1]Державний біотехнологічний університет, Україна
[2]Державна установа «Інститут фармакології та токсикології Національної академії медичних наук України»
[3]Національний технічний університет «Харківський політехнічний інститут», Україна

E-mail: yuriykrasnopolsky@gmail.com

Кверцетин є відомим природним антиоксидантом із широким спектром фармакологічної активності, у тому числі в онкології, кардіології, офтальмології та ін. Ліпофільна природа кверцетину обмежує його використання у клініці і обумовлює потребу у створенні ефективних систем доставки. Ліпосомальні форми кверцетину активно вивчаються та вдосконалюються.

Мета. Стаття присвячена аналізу сучасних досліджень ліпосомальних форм кверцетину як перспективної стратегії доставки ліків.

Матеріали й методи. Аналіз сучасної вітчизняних та іноземних досліджень, присвячених створенню ліпосомальних форм кверцетину та оцінці ефективності даної системи доставки ліків у терапії онкологічних, кардіологічних, вірусних та інших захворювань, які супроводжуються оксидативним стресом. Для пошуку джерел інформації для дослідження було використано електронні ресурси відкритого доступу наукових періодичних видань.

Результати. Створення ліпосомальних форм кверцетину дало можливість використовувати підвищити його біодоступність та розширити способи введення, у тому числі ін'єкційно. Показано досвід використання ліпосомального кверцетину в комплексній терапії раку, що дозволяє підвищити ефективність інгібування росту пухлини та одночасно знизити побічні ефекти на здорові тканини. Для підвищення ефективності доставки кверцетину в тканини запропоновано модифікацію поверхні ліпосом гіалуроновою та мікофеноловою кислотами, поліетиленгліколем, магнітними частинками, тощо. Показано можливість використання інших носіїв для доставки кверцетину, серед них тверді ліпідні наночастинки, наночастинки золота, полімери.

Висновки. Нанопрепарати кверцетину демонструють високу фармакологічну ефективність та суттєве підвищення біодоступності кверцетину, а також важливими є їх безпечність, біорозкладність та знижена токсичність.

Ключові слова: кверцетин, антиоксидант, протипухлинна терапія, лікарська форма, система доставки ліків, наночастинка, ліпосома, біодоступність.

Received 2026/01/14
Revised 2026/01/23
Accepted 2026/04/30