Herbal drug-based nanotherapy for hepatocellular carcinoma: Quercetin-contained nanocarrier as a multipurpose therapeutic agent against hepatocellular carcinoma (Review)

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Abstract. Cancer remains one of the leading causes of morbidity and mortality worldwide, with hepatocellular carcinoma (HCC) accounting for ~75% of all primary liver cancers and exhibiting a high incidence rate. Unfortunately, the response rate to chemotherapeutic agents for liver cancer is relatively low, primarily due to the development of drug resistance and the lack of targeted therapeutic agents. The present study focused on the anticancer mechanisms of quercetin and the development of innovative nanocarriers designed to enhance its efficacy against HCC while mitigating drug resistance. Quercetin demonstrates a diverse array of biological activities, making it a promising candidate for therapeutic applications. Its mechanisms include inhibition of tumor cell cycle, induction of apoptosis, modulation of reactive oxygen species and inhibition of chemotherapeutic resistance. Given these properties, extensive research has been conducted in pharmaceutical engineering to develop well-designed nanocarriers that incorporate quercetin. These nanocarriers aim to improve the bioavailability and targeting of quercetin, thereby enhancing its therapeutic efficacy against HCC and overcoming the challenges associated with anticancer drug resistance. Through this approach, quercetin could potentially play a pivotal role in the future of HCC treatment, providing a synergistic effect when combined with traditional chemotherapy leading to improved patient outcomes.

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1. Introduction

Cancer remains a leading cause of morbidity and mortality globally, with liver cancer, particularly hepatocellular carcinoma (HCC), accounting for significant incidence and mortality rates. The Global Cancer Observatory (GLOBOCAN) reported 19.96 million new cancer cases and 9.74 million cancer-related mortalities in 2022, highlighting the urgent need for improved early diagnosis, treatment and prevention strategies (1,2).

HCC is the most prevalent form of primary liver cancer, representing ~75% of cases. Current chemotherapeutic agents, such as gemcitabine and cisplatin, show limited efficacy due to the chemoresistance from the cancer, often linked to overexpression of ATP-binding cassette transporter proteins and detoxification enzymes in liver cells. This resistance contributes to low response rates and severe adverse effects from traditional chemotherapy, including hair loss, nausea and fatigue (3-6). These are mainly being explained with non-targeted chemotherapeutics. Hence, reducing the chemotherapeutics-related adverse side effects has emerged as a crucial issue to improve the anti-cancer therapeutic efficacy.

At present, pharmaceutical engineering in the field of medicine has emerged to develop new tumor-targeted drug delivery systems and multi-purpose drug delivery systems to enhance the therapeutic efficacy of chemotherapy against cancer (7,8). As regards the tumor-specific drug delivery systems, a number of attempts have been tried to create near perfect nanocarriers

against cancer, which may have some specific capabilities such as tumor targeted without nonspecific cellular invasion, tumor sensitive without adverse side effects and ability to moderate multidrug resistance mechanisms (9,10).

Traditional herbal medicine has been recognized as one of important treatments against liver cancer for years. So far, a number of herbal plants such as *Cinnamomum* species (11), *Curcuma* species (12), *Artemisia* species (13), *Glycyrrhiza uralensis* (14), *Equisetum arvense* (15), *Rheum undulatum* (16) and *Scutellaria baicalensis* (17) have been shown to have anti-proliferative effects on HCC. However, traditional herbal medicine has some drawbacks, including direct anti-proliferative effects on normal and cancer cells and producing herbal medicine-related adverse side effects such as allergic reactions, asthmas, rashes, vomiting and diarrhea. In recent years, traditional herbal medicine has been intensively studied to investigate its anticancer activity in the field of cancer pharmacology. It has been considered to develop new drug delivery systems to improve traditional herbal medicine anticancer efficacy. A number of biologically active substances such as quercetin (18) and sesquiterpene lactone (19) from traditional herbal medicine have been extensively researched.

The present study aimed to describe the anticancer mechanisms and inhibition capacity against multidrug resistance mechanism of quercetin-containing multipurpose nanocarriers and their targeting potential for HCC.

2. Quercetin

A number of medicinal plants, vegetables and fruits, including *Moringa oleifera*, *Ficus religuisa*, *Styphnolobium japonicum* (20), *Polygonum hydropiper* (21), *Polygonum aviculare* (22), citrus, apple, broccoli, onions and chili pepper, produce abundant amount of quercetin as a metabolite in their life cycle, and it plays important roles in some physiological processes, growth and developmental stages such as photosynthesis, antioxidant system and seed germination (23). Quercetin is a flavonoid compound with a chemical structure of 3, 3', 4', 5, 7-pentahydroxyflavone (24). In recent years, quercetin has repeatedly been declared as an effective agent against cancer, an effective inhibitor of P-glycoprotein (P-gp) and well-known protector of chemotherapy-exposed cells (25). The quercetin effects on numerous types of cancers are associated with several mechanisms such as anti-proliferative effect, inhibition of angiogenesis, reactive oxygen species (ROS) induction in cancerous cells and apoptosis induction.

3. Quercetin-related mechanisms against HCC

Effects on cell growth and proliferation. A number of studies have attempted to explain the anticancer mechanism of quercetin against HCC. Anticancer chemotherapeutics have mainly been designed to inhibit the cancer cell cycle in their various stages (26). Cell growth and proliferation are biologically explained by cell cycle staged with growth 1 (G_1), synthesis (S), growth 2 (G_2) and mitosis (M), which are regulated via cyclin-dependent kinases (CDK/cyclin) and signal transduction pathways. The quercetin mechanism is related to the downregulation of cyclin B1, D, CDK1 and CDK2 by activating protein 27 (p27) and protein 21, which triggers cell cycle arrest in M, G_1, S and G_2 phases (Fig. 1A) (27,28).

Quercetin-related mechanisms against HCC have been reported to be primarily associated with downregulation of Wnt/β-catenin signaling pathway (Fig. 1B), enhancing Bcl-2-associated X protein (BAX), caspase family, extracellular signal-regulated kinase (ERK) and AMP-activated protein kinase/mammalian target of rapamycin pathway, suppressing B-cell lymphoma-2 (Bcl-2), epidermal growth factor receptor, dihydrotestosterone and phosphatidylinositol 3-kinase/protein kinase B pathway (Fig. 1C) (29-31). Moreover, it is reported that mitogen-activated protein kinase pathway and ataxia telangiectasia mutated kinase-mediated signaling pathway are induced due to quercetin exposure (Fig. 1D) (32,33).

Effects on apoptosis induction. A potential role of quercetin has been reported in the regulation and induction of apoptosis in cancer cells. It is known that quercetin has the proapoptotic effect which contributes to the upregulation of tumor protein 53 gene (34,35) and suppression of Bcl-2 protein (Fig. 2A). Moreover, quercetin has a potential to increase the expression of proapoptotic proteins such as Bax and cleaved caspase-3 and 9, which regulate negatively antiapoptotic proteins such as Bcl-2 and myeloid leukemia 1 (36-38). This apoptotic pathway highlights the potential of quercetin as a therapeutic agent in cancer treatment by promoting the elimination of malignant cells through the activation of intrinsic apoptotic mechanisms.

Effects on oxidative stress. Another mechanism of action of quercetin against HCC is inhibition of oxidative stress which plays a significant role in fighting cancer cells (Fig. 2B). The mechanism of the quercetin is mainly attributed to the upregulated expression of the antioxidant response element pathway, nuclear factor (erythroid-derived 2) gene and thioredoxin system. The upregulation of these mechanisms is triggered by quercetin radicals-mediated pro-oxidative state due to peroxidase-catalyzed oxidation in the cytoplasm (39-41).

Quercetin can reduce the ROS level in the cytoplasm by inhibiting the p66hc-mediated Ras-related C3 botulinum toxin substrate 1 activation to decrease the cell migration and proliferation (42).

Quercetin can undergo oxidation, leading to formation of reactive intermediates, specifically quercetin-semiquinone and quercetin-quinone. These radicals can interact with cellular components, contributing to an increase in overall ROS levels within cancer cells (43).

Notably, it has been reported that quercetin generates ROS in HepG2 by overexpressing the p53-indcible gene 3 and its product of oxidoreductase. The oxidoreductase enzyme catalyzes the quercetin and generate ROS with HepG2 cell lines (44).

4. Angiogenesis-related inhibition

The progression stage of HCC is also associated with the angiogenesis and metastasis. Thus, the angiogenesis inhibition may be a targeting option for HCC treatment. The mechanism of quercetin against angiogenesis is related to the vascular endothelial growth factor receptor (VEGF-R) 2 targeting, which regulates AKT/mTOR/P70S6K signaling pathway

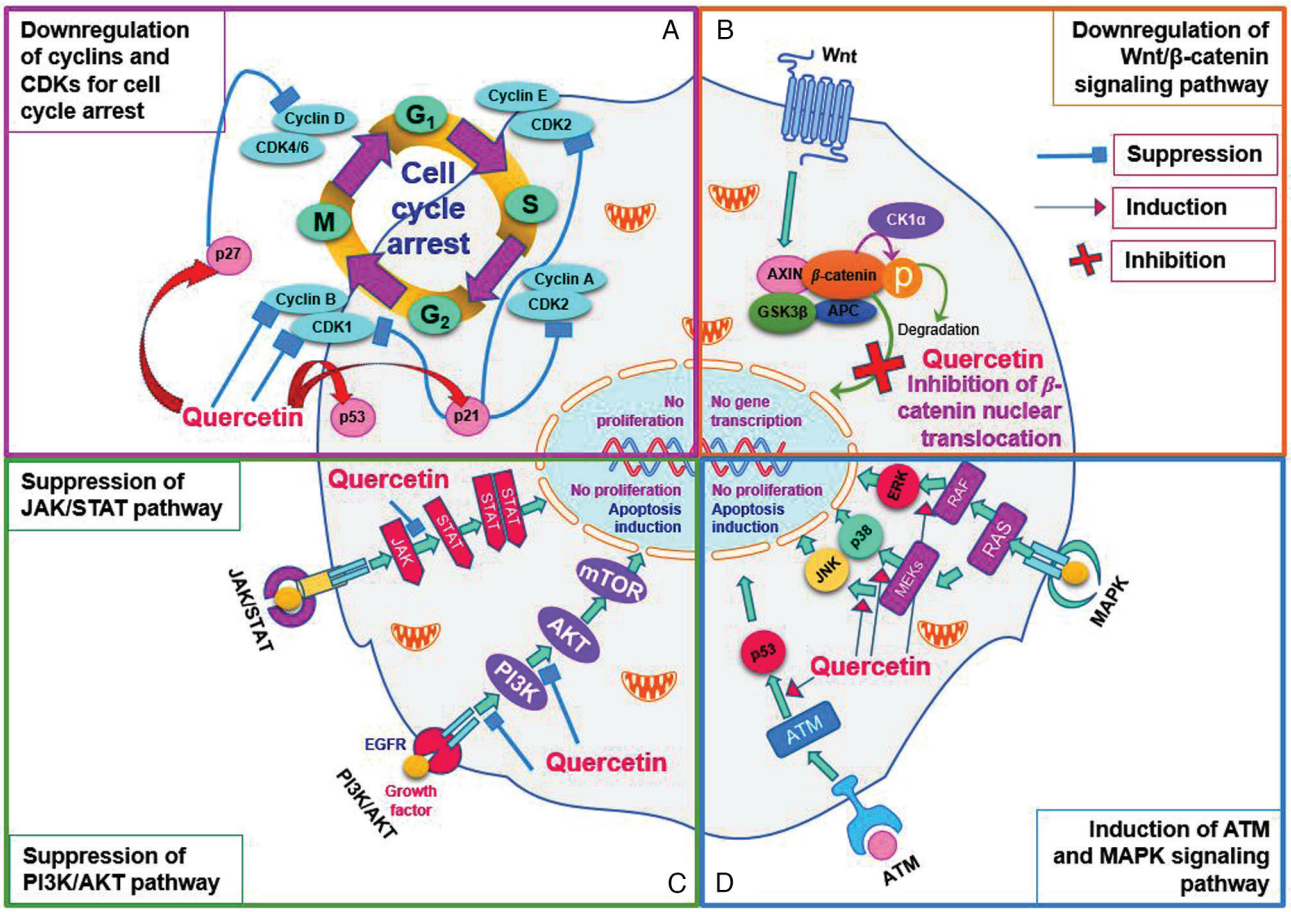

Figure 1. Effects of quercetin on cancer cell growth and proliferation. (A) Quercetin-triggered cell cycle arrest. Cell cycle is downregulated by quercetin-related mechanisms at the all stages. Cyclin B, a mitotic cyclin, is complexed with CDK1 to regulate the cell growth and mitosis progression (transition stage of G_2 to M). In the cell cycle, cyclin D is also known as a key regulator in transition stage of M to G_1 phase and is complexed with CDK4/6 to regulate the cell cycle. CDK2, a serine/threonine protein kinase, plays a crucial role in the initiation of DNA synthesis in the transition stage of G_1/S. CDK2 also has a role in the transition stage of S/G_2 in which it forms a complex of cyclin A/CDK2 to phosphorylate CDC6 and E2F1 and then triggers the S/G_2 phase transition. These functional proteins, including CDK1, CDK2, cyclin B and cyclin D, are suppressed in quercetin-exposed tumor cells. (B) Quercetin-triggered downregulation of Wnt/β-catenin signaling pathway. Wnt protein binds Fz family receptor in the signaling pathway and then it disrupts the function of destruction complex to inactivate the GSK3. This mechanism allows the β-catenin to localize in nucleus for activation of TCF/LEF transcription factors. In the Wnt/β-catenin signaling pathway, quercetin inhibits the nuclear translocation of the β-catenin. (C) Quercetin-triggered suppression of JAK/STAT and PI3K/AKT pathway. In the signaling pathway of JAK/STAT, a cytokine activates its receptor to trigger the cascade phosphorylation of its proteins (JAK and STAT proteins), which plays a crucial role for activating the transcription process-related genes. In the signaling pathway, the quercetin may suppress the phosphorylation of STAT by JAKs. As for PI3K/AKT pathway, it is triggered by EGF and the catalytic domain of EGFR kinases and then all protein kinases such as PI3K, AKT and mTOR are phosphorylated to regulate the cell growth and proliferation. This signaling pathway is also suppressed through quercetin-exposed mechanisms. (D) Quercetin-triggered induction of ATM and MAPK pathway. ATM signaling pathway can be induced by EGFR and Mre11 complex and it activates p53 protein for DNA reparation and cell apoptosis. As for the MAPK pathway, MEK and RAF are induced by quercetin to activate the JNK, p38 and ERK in the signaling pathway for apoptosis induction and proliferation suppression. CDK, cyclin-dependent kinase; CDC6, phosphorylate cell division cycle 6; E2F1, early region 2 binding factor 1; Fz, frizzled; GSK3, glycogen synthase kinase 3; TCF/LEF, T cell factor/lymphoid enhancing factor; JAK/STAT, Janus kinases/signal transducer and activator of transcription; EGF, epidermal growth factor; ATM, ataxia telangiectasia mutated kinase; Mre11, mitotic recombination 11; MEK, mitogen-activated protein kinase kinase; RAF, rapidly accelerated fibrosarcoma; p38, protein 38; CK1α, casein kinase 1α; APC, adenomatous polyposis coli.

(Fig. 2C) (45). Igura *et al* (46) first reported in 2001 that quercetin inhibited angiogenesis and then could be used as an efficient antitumor drug (47).

5. Quercetin nanocarriers for HCC

In recent years, several nanocarriers for quercetin have been designed to use its benefits for HCC treatment (Table SI).

Ren *et al* (48) synthesized quercetin nanoparticles by using gold nanoparticles, quercetin solution and poly (DL-lactide-co-glycolide) PLGA to treat liver cancer. As a result, the quercetin nanoparticles efficiently suppressed liver cancer cell growth and colony formation by upregulating p27 and downregulating c-Myc, cyclin-D1, CDK1, matrix metallopeptidase 7 and β-catenin within the cancer cells. Another possible mechanism was also revealed in that the quercetin nanoparticle markedly induced the apoptosis of liver cancer cells via activating cytochrome *c*/caspase signaling. The Akt/ERK1/2 signaling pathway was also inactivated by the quercetin nanoparticles, which suppressed liver cancer cell growth. It was also reported that the quercetin nanoparticles suppressed the transcriptional factor AP-2 alpha/human telomerase reverse transcriptase signaling pathway within the liver cancer cells. These results showed that the quercetin

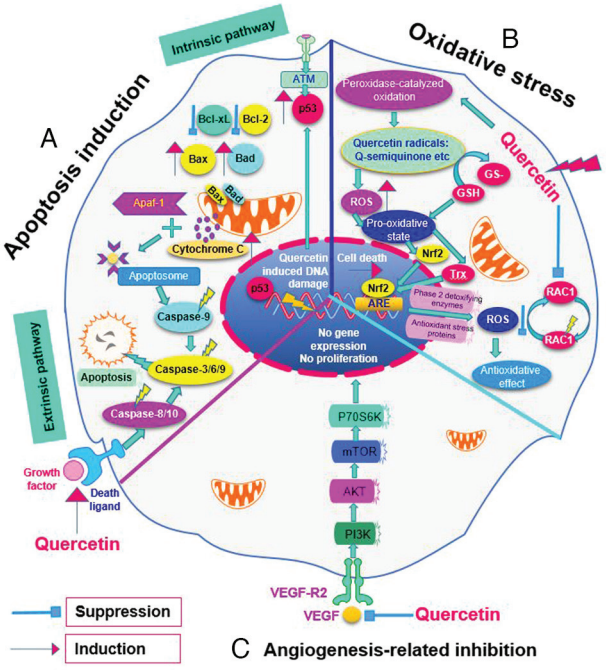

Figure 2. Effects of quercetin on cancer cellular biomolecules and functions. (A) Apoptosis induction. Quercetin promotes the upregulation of pro-survival proteins such as p53, Bcl-2 and Bcl-xl while simultaneously downregulating pro-apoptotic proteins such as Bax and Bad. This regulatory shift creates a favorable environment for apoptosis. When quercetin induces this expression pattern, it leads to the release of cytochrome *c* from the mitochondria into the cytoplasm, which is crucial for apoptosome formation. The formation of an apoptosome activates a cascade of caspase enzymes, including caspase-3, -6 and -9. The activation of these caspases is the final step that initiates the execution phase of apoptosis, leading to programmed cell death. (B) Oxidative stress. Internalized quercetin can be converted into quercetin radicals such as quercetin-semiquinone and quercetin-quinone due to peroxidase-catalyzed oxidation in the cytoplasm, which produces the pro-oxidative state in the cell. Then, it activates the Nrf2 and Trx in the cytoplasm and the activation of the ARE pathway to trigger antioxidant enzyme and protein synthesis. (C) Angiogenesis-related inhibition. VEGF and VEGF-R2 are activated to upregulate the PI3K/Akt signaling pathways, which promotes the endothelial cell proliferation and migration during cancer cell development. Quercetin reduces the availability of these potent angiogenetic factors. Nrf2, nuclear factor (erythroid-derived 2)-like 2; Trx, thioredoxin; ARE, antioxidant response element; ROS, reactive oxygen species; GSH, glutathione.

nanoparticles can be a multipurpose nanocarrier against liver cancer cells (48).

Guan *et al* (49) designed a quercetin-loaded nanoparticle by using poly (lactic-*co*-glycolic acid)-d-α-tocopheryl polyethylene glycol 1000 succinate (PLGA and TPGS1000) for the targeted treatment of liver cancer. Their research results proved that the quercetin by liver cancer cell uptake can be increased by using PLGA and TPGS1000 polymers and the cytotoxicity of liver cancer was efficiently increased by the designed nanoparticles. Also, they observed that quercetin nanoparticles markedly promoted cell apoptosis. The study suggested that quercetin nanoparticles had a higher suppressive effect on tumor growth by inducing the cell apoptosis and can be a potential tool to treat liver cancer.

Quercetin-loaded superparamagnetic polymeric micelles were prepared by a film hydration method to enhance the treatment efficacy against HCC and improve the disease monitoring. The designed quercetin-loaded micelles increased the cytotoxicity and apoptosis for the liver cancer cells. The main mechanism of action of the quercetin-loaded superparamagnetic polymeric micelles was explained by the higher accumulation of the quercetin nanoparticles within the targeted liver cancer cells due to the extrinsic magnetic field. Hence, Srisa-nga *et al* (50) suggested that co-delivery of quercetin and superparamagnetic iron oxide nanoparticles may increase the therapeutic efficacy against HCC and decrease the side effects-related to the chemotherapeutics.

A targeted lipid coated nanoparticle for hepatocellular carcinoma treatment was designed by using RGD peptide to conduct a co-delivery of sorafenib and quercetin (51). The RGD peptide has extensively applied as a targeting agent for cancer treatment due to its capability of targeting the tumor-associated blood vessels. As a result of the study, the liver cancer cell uptake of nanoparticles was increased up to 71.5% and the cytotoxicity was detected higher than control groups. Thus, it was suggested that RGD peptide modification may be more significant for liver cancer targeting and the combination of quercetin and sorafenib was more effective against HCC. Sorafenib is recognized as an effective multikinase inhibitor which effectively suppresses tumor cell proliferation and growth by downregulating VEGFR and platelet-derived growth factor receptor signaling pathways (52). It has now been reported that HCC cells are becoming resistant for sorafenib (53). Therefore, the sorafenib combination therapy with quercetin and an active targeting agent might be a more powerful therapeutic tool against HCC.

Quercetin encapsulated biodegradable plasmonic nanoparticles were obtained by preparing liposomes and loading quercetin into the liposomes. Gold coating was conducted to obtain the gold-coated liposomes. As a consequence of the photothermal therapy, the obtained quercetin-loaded and gold-coated liposomes had an efficient effect in inducing the apoptotic death of cancer cells by suppressing heat shock protein 70 (Hsp70) expression and also had a marked effect to trigger the disorganization of the microtubules network and DNA damage. A combination therapy of quercetin and photothermal therapy was a significant against cancer (54).

Varshosaz *et al* (55) fabricated a solid lipid nanoparticle with loaded quercetin and checked the cellular uptake of the nanoparticles. HepG2 cells markedly internalized the quercetin-loaded solid lipid nanoparticles compared with control cells. The viability of HepG2 cells was also significantly decreased. The research team suggested that all sterol-contained solid lipid nanoparticles had good inhibitory effects for cancer cells.

6. Quercetin effect on reversing multidrug resistance for anticancer treatment

Although anticancer drugs have efficient therapeutic effects by suppressing the growth or killing the cancer cells, a number of drawbacks or adverse effects triggered by the anticancer drugs have been reported and cause treatment failure.

Anticancer drug resistance in HCC is one of critical issues in clinical medicine for several reasons, such as limited treatment options and mechanisms of anticancer drug resistance. HCC has historically had limited treatment options, including surgery, locoregional and systemic therapies (56).

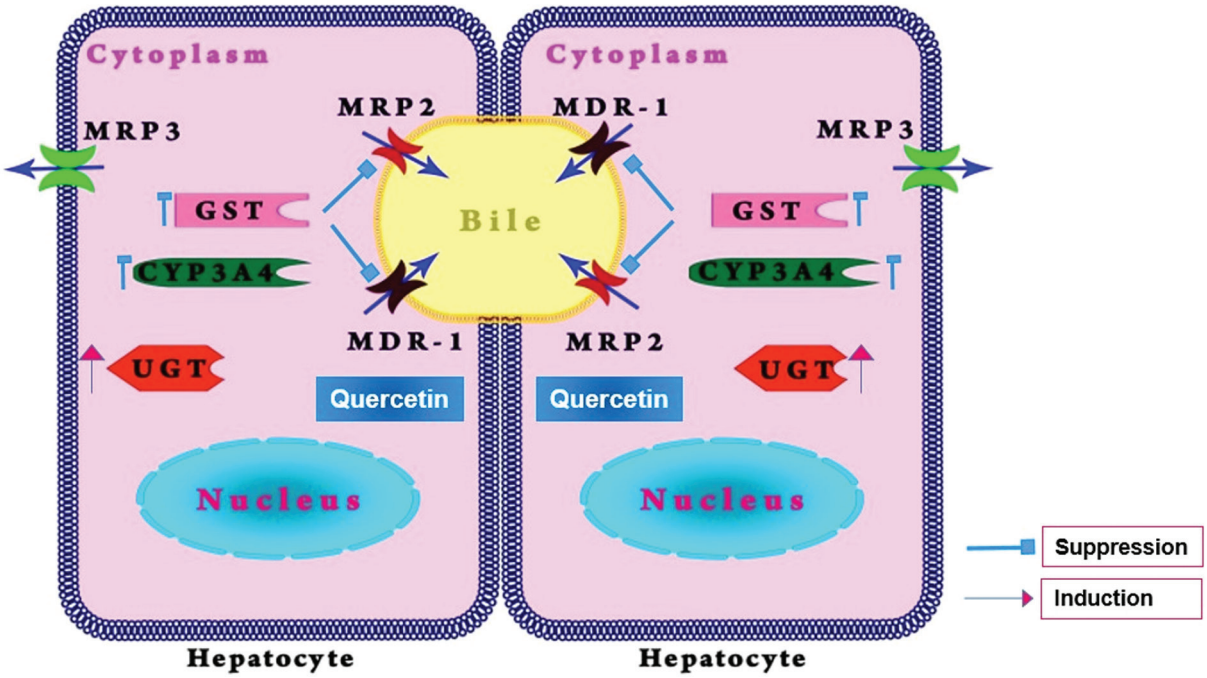

Figure 3. Effects of quercetin on cancer cell growth and proliferation. In the cells of HCC, quercetin can inhibit the metabolic enzymes such as GST and CYP3A4 for anticancer drug detoxification and metabolism and induce the function of UGT which is responsible for glucuronidation. Moreover, quercetin suppressed the efflux function of MDR1 (P-gp) and MRP2 which are responsible for transport of numerous anticancer drugs. HCC, hepatocellular carcinoma; GST, glutathione S-transferase; CYP3A4, cytochrome P450 3A4; UGT, uridine 5'-diphospho-glucuronosyltransferase; MRP, multidrug resistance-associated protein; MDR, multidrug resistance.

Main chemotherapeutics against liver cancer are gemcitabine, cisplatin, doxorubicin, etoposide and methotrexate and their treatment response rate is comparably low due to drug resistance mechanisms (5,57,58). Anticancer drug resistance leads to treatment failure and therefore is becoming imperative to discuss and address. HCC can exhibit various mechanisms of resistance to anticancer drugs, including alterations in drug metabolism, changes in tumor microenvironment and genetic mutations in genes which encodes the transporter proteins and detoxification enzymes (59).

During chemotherapy, the cancer cells may gain the capability to reduce the efficacy of chemotherapeutics by overexpressing P-gp and other proteins on the membrane of the cancer cells (Fig. 3) (60-62).

One of frequent causes to trigger the multidrug resistance of the anticancer drugs is P-gp (MDR1) which is encoded by the ATP-binding cassette sub family B member 1 (ABCB1) gene (63) and has the ability to efflux the anticancer drugs from the tumor cells. To reverse the P-gp-associated multidrug resistance of the cancer cells, a number of attempts have been conducted in last two decades and several inhibitors of the P-gp efflux pump discovered, such as amiodarone, verapamil, diosmin sesquiterpene, quercetin, naringin, biochanin and silymarin (64-68).

Multidrug resistance-associated protein 2 (MRP2) is another efflux transporter, primarily in the removal of organic anions and drug conjugates from cells. It is responsible for anticancer drug resistance (69). Quercetin has been shown to modulate MRP2 activity, especially suppressing the efflux mechanism of the transporter in cancer cells. Therefore, it leads to an increased accumulation of anticancer drugs inside cancer cells, which could enhance their anticancer effects (69).

Glutathione S-transferase (GST) is a family of enzymes involved in the detoxification process of chemical compounds. The enzyme binds to drugs and xenobiotics via glutathione and facilitates drug excretion. Quercetin may suppress the expression and activity of the enzyme, which can decrease the detoxification processes of chemotherapeutics and their efficacy (70). The mechanism of quercetin on GST enzyme may be attributed to suppressing GST activation through competitive or non-competitive inhibition (71).

Cytochrome P450 3A4 (CYP3A4) is a major enzyme in the liver which metabolizes numerous drugs, including a number of chemotherapeutics. It has been reported that quercetin can suppress its anticancer drug efficacy (72).

Among the inhibitors of P-gp, quercetin has attracted more attention from researchers to suppress the growth of cancer cells by blocking the cellular signaling pathway and reverse the multidrug resistance during the chemotherapy (73). The mechanism of the action of quercetin to inhibit P-gp is related to blocking the function of P-gp efflux pump by binding the interfaces of intracellular helices and nucleotide-binding domains (74).

7. Quercetin nanocarriers for P-gp inhibition

So far, quercetin has been used as a promising inhibitor for the design of nanocarriers with the ability to reduce anticancer drug resistance in HCC treatment (Table SII).

In a study, quercetin-chitosan micelles were prepared by the ultrasound method and doxorubicin was entrapped into the micelles. Then, *in vitro* cytotoxicity, cellular uptake and

inhibition of P-gp efflux were tested for the DOX-entrapped quercetin-chitosan micelles. Quercetin and quercetin-chitosan micelles had comparably effective inhibition of the P-gp efflux pump and produced a marked long-lasting cytotoxicity on cancer cells. These results suggested that the quercetin-chitosan micelles were a promising multipurpose nanocarrier for oral delivery of anticancer drugs (75).

Guo *et al* (76) designed a polymeric nanoparticle to attenuate the drug resistance mechanisms during cancer therapy by co-delivering paclitaxel and quercetin. The polymeric nanoparticle was prepared by a sonication method and characterized by checking its cellular uptake, *in vivo* biodistribution and antitumor efficacy. P-gp inhibition assay for the nanoparticle was conducted to evaluate its effect on drug resistance mechanism of anticancer drugs. As a result of the polymeric nanoparticle, an enhanced tumor-suppressing effect was observed due to decrease of P-gp expression in the cancer cells.

In another study, a polyethylene glycolated liposome was developed to conduct a codelivery of adriamycin and quercetin to reverse cancer therapy-related drug resistance. Adriamycin is known to be a substrate of P-gp and effluxes from the tumor cells during anticancer therapy. In the study, film-ultrasound technique with ammonium sulfate transmembrane gradient method was used to prepare the adriamycin and quercetin co-loaded liposome and pharmacokinetic study, cell toxicity study and pharmacodynamic study were also conducted. The relative tumor volume was decreased and P-gp was effectively suppressed (77).

An amphiphilic carboxymethyl chitosan-quercetin conjugate has been obtained by using a self-assembly technique to improve the oral delivery of paclitaxel. Paclitaxel is known as a substrate of P-gp and therefore leads to therapeutic failure due to chemotherapeutic efflux mechanism in the tumor cells. For this purpose, quercetin was applied as an inhibitor of P-gp to increase the capability of therapeutic efficacy of the drug. In this study, the antitumor efficacy of the nanocarrier was investigated in *in vivo* xenograft model and the inhibition of P-gp was evaluated by western blot analysis. As a result, paclitaxel-loaded carboxymethyl chitosan-quercetin polymeric micelles displayed an improved downregulation effect on P-gp (78).

Another team developed quercetin-loaded benzoylated methoxy-poly (ethylene glycol)-b-oligo (ε-caprolactone) polymeric micelles to overcome the drug resistance issues for cancer therapy. They used P-gp overexpressed leukemia cells (K562/ADR) and checked the effect of quercetin on P-gp function to reverse the multidrug resistance. According to the results, quercetin-loaded micelles were effective in reducing the overexpression of P-gp on K562/ADR cells (79).

Another nanomicelle was reported in 2018. Chitosan, quercetin and citraconic anhydride was used to design a pH-responsive nanomicelle to enhance the intracellular bioavailability of doxorubicin for cancer treatment. In the study, a self-assembly technique was used to obtain the nanomicelle and P-gp inhibition assay was performed for quercetin function on the efflux pump. The nanomicelle had an improved inhibitory effect on the P-gp efflux pump and obvious enhancement of suppressing effect on MCF-7/ADR cells (80).

Multiwalled carbon nanotubes-based nanoconstructs have been designed to enhance the therapeutic efficacy of drugs against multidrug resistant cancers. Using this nanocarrier, a combination of N-desmethyl tamoxifen and quercetin was delivered into MDA-MB-231 cells and indirectly checked the inhibition of P-gp. In this study, an increased biodistribution, biocompatibility and marked cellular uptake of the drug-loaded nanocarriers was observed. These results were explained by quercetin-related P-gp inhibition (81).

Qian *et al* (82) designed a core-shell micelle to deliver paclitaxel for treatment of multi drug resistant breast cancer. In this study, quercetin was also chosen as an inhibitor of P-gp. The characteristics and antitumor efficacy of the micelles were checked and the effect of quercetin on P-gp efflux pump was evaluated in MDA-MB-231/MDR1 cells. According to the results, the micelles enhanced the cellular uptake of antitumor drug by downregulating P-gp expression in MDA-MB-231/MDR1 cells.

8. Challenges and considerations

Major drawbacks of the anticancer therapeutics such as adverse effects and multidrug resistance cause failure in cancer treatment (83). A number of different strategies have been employed to overcome the drawbacks for effective cancer treatment. Herbal drug-based nanomedicine has recently gained attention for cancer treatment due to its biosafety, biodegradability, promising therapeutic efficacy and ability of combating anticancer drug resistance (84).

The field of pharmaceutical engineering has produced more data to develop a favorable therapeutic tool for cancer therapy (85).

Targeted drug delivery systems, which are methods of delivering drugs to specific parts of a diseased body, have been extensively researched in cancer nanotechnology. They have several benefits as drug delivery systems. They not only significantly improve the specificity of nanocarriers to tumor cells or diseased organs but also reduce the side effects of anticancer drugs in comparison with traditional chemotherapy (86). As for liver targeted delivery, receptor-mediated drug delivery systems such as asialoglycoprotein receptor (ASGPR), folate receptor and retinol binding protein receptor-mediated targeted delivery systems have been widely recognized as the most effective tools in treating HCC (87,88). Hepatic carcinoma cells are able to recognize galactose and N-acetylgalactosamine-terminated glycoproteins through ASGPR located on their surfaces. In recent years, a number of researches have been confirming that galactosylated nanoparticles (NPs) exhibit high hepatocyte specificity *in vitro* as well as *in vivo* for anticancer drug delivery (89).

At present, nanomedicines provide a great contribution to delivering high concentrations of chemotherapeutic drugs and MDR inhibitors to tumor cells, in which biodegradable, biocompatible nanomaterials and target-specific ligands play more important roles.

Quercetin is now a well-known anticancer agent with many purposes but it needs further improvement on its pharmacology and clinical applications (90). There are a number of drawbacks of quercetin-related chemotherapy including less absorption in gastrointestinal tract, easy metabolization by

enzymes, instability, poor solubility, low hydrophobicity and lack of specificity to the target site (91).

To overcome these challenges, researchers have been developing quercetin-loaded nanocarriers, which can enhance the therapeutic potential of quercetin, especially against drug-resistant HCC. Quercetin-loaded nanocarriers have enhanced bioavailability, targeted delivery and the possibility of overcoming drug resistance. Quercetin-loaded nanocarriers can improve the solubility and stability of quercetin, increasing its bioavailability in the bloodstream and allowing for more effective concentrations to reach tumor sites. Quercetin-loaded nanocarriers can be designed to target cancer cells specifically, minimizing damage to healthy tissues and enhancing the therapeutic effect on HCC cells. This targeting can reduce the overall side effects of treatment. Quercetin has been shown to modulate various pathways involved in drug resistance, such as inhibition of drug efflux pumps, induction of apoptosis and modulation of signaling pathways. As for the synergistic effect of quercetin, it can be used in combination with other anticancer drugs and quercetin can enhance their effectiveness and help overcome resistance mechanisms.

Hence, quercetin-supported nanocarriers with good therapeutic efficacy and cancer-targeting ability, as well as capacity of attenuating multidrug resistance have emerged as a promising approach to enhance the bioavailability and therapeutic efficacy of quercetin for cancer therapy. In further studies, addressing these aforementioned weaknesses of quercetin is now a major challenge to develop an effective nanocarrier with quercetin against HCC.

9. Conclusion

Based on these well-studied considerations, the present review demonstrated that quercetin has multiple antitumor properties. There are some limitations, but advances in pharmaceutical engineering may mitigate these. Consequently, comprehensive research is essential to develop effective nanocarriers for quercetin targeting HCC.

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Authors' contributions

AT performed the conception and design of the review article and provided administrative support. TB collected the information and performed the interpretation. The two authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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