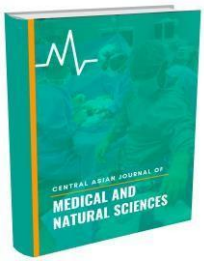

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Article

Quercetin as a PI3K/Akt Pathway Inhibitor in Hepatocellular Carcinoma: Therapeutic Potential and Drug Delivery Challenges

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Abstract: Hepatocellular carcinoma (HCC) is one of the major causes of cancer death globally with most of them being diagnosed late, resistant to treatment and recurring. The phosphoinositide 3-kinase/protein kinase B (PI3K/ Akt) signaling pathway is among the essential molecular mediators of HCC progression and its regulation of the processes of tumor cell proliferation, cell survival, angiogenesis, and metabolic reprogramming. Supernormal induction of PI3K/Akt signaling also leads to an increase in tumor proliferation and response to traditional chemoproteomics. Quercetin, which is a common flavonoid present abundantly in fruits and vegetables, has been discovered as an effective anticancer agent with multi-targeted molecular properties. The review illustrates the therapeutic value of quercetin as a PI3K/Akt inhibitor in HCC. It has been proven by experimental means that quercetin inhibits PI3K/Akt activation, apoptosis by the regulation of Bcl-2/Bax ratio, mTOR signaling, angiogenesis, as well as, epithelial-mesenchymal transition (EMT). Also, quercetin increases oxidative stress mediated tumor cell death and could sensitize HCC cells to conventional therapies, including sorafenib. Even with these encouraging anticancer effects, their clinical application in practice is still deficient because of low water solubility, bioavailability, and metabolism of the molecules and reduced tumor-targeting ability. In recent times, the development of drug delivery systems, such as nanoparticles, liposomes, polymeric micelles and nanoemulsions, has demonstrated a potential of enhancing quercetin stability, pharmacokinetics and targeted delivery to hepatic tumors. Altogether, quercetin is a strong natural PI3K/Akt-modulator with high therapeutic potential in HCC, but the pharmacokinetic and formulation issues need to be overcome to implement the compound in the clinical setting.

Keywords: Hepatocellular Carcinoma, Quercetin, PI3K/Akt Pathway, Targeted Therapy, Nanoparticle Drug Delivery

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1. Introduction

Hepatocellular carcinoma (HCC) poses a significant menace to the health of people around the world as it is the sixth most common type of cancer and the third leading cancer mortality [1],[2]. A broad variety of oncogenic factors promote HCC initiation and progression, and the Phosphoinositide 3-kinase (PI3K) / Protein Kinase B (Akt) signaling pathway is widely recognized as a key driver of HCC tumorigenesis. Growing evidence gathering since the 1990s demonstrates the capability of the natural flavonoid quercetin to modulate the PI3K/Akt pathway and to exert anti-HCC activity in both preclinical studies and actual clinical practice. Nonetheless, fundamental questions remain concerning the

specific molecular mechanisms through which quercetin influences the PI3K/Akt cascade and the nature of pharmacological activity exerted via additional signaling pathways. The therapeutic relevance of quercetin as a potential HCC-intervention agent continues to attract the interest of the scientific community [3],[4]. Quercetin has also been recognized as a prominent candidate for chemoprevention and pharmacological intervention against HCC due to its liver-protective and anti-cancer activity. As quercetin is also a widely recognized food component, the high interest in it as an anti-HCC agent has stimulated research specifically focused on the underlying mechanisms of action, delivery strategies, and metabolic changes during its preclinical and clinical use [5],[6].

The PI3K/Akt Pathway in Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC), a leading cause of cancer mortality worldwide, is characterized by extensive aberrations of the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway [7],[8]. This pathway plays a crucial role in regulating cellular growth, survival, and function and is hijacked by HCC oncogenes such as hepatitis B virus large surface protein, Ras, and mutant p53, leading to abnormal activity. Recent studies indicate that HCC growth and progression can occur independently of Akt activation; however, persistent signaling through the pathway remains an early event in carcinogenesis and contributes to chemoresistance and aggressive tumor behavior as shown in figure 1. The signaling network also interacts with the (mammalian target of rapamycin) mTOR pathway to coordinate oncogenic functions. Various anti-HCC compounds can potently suppress enzyme activity, execute diverse cellular functions, or diminish therapeutic efficacy [9],[10].

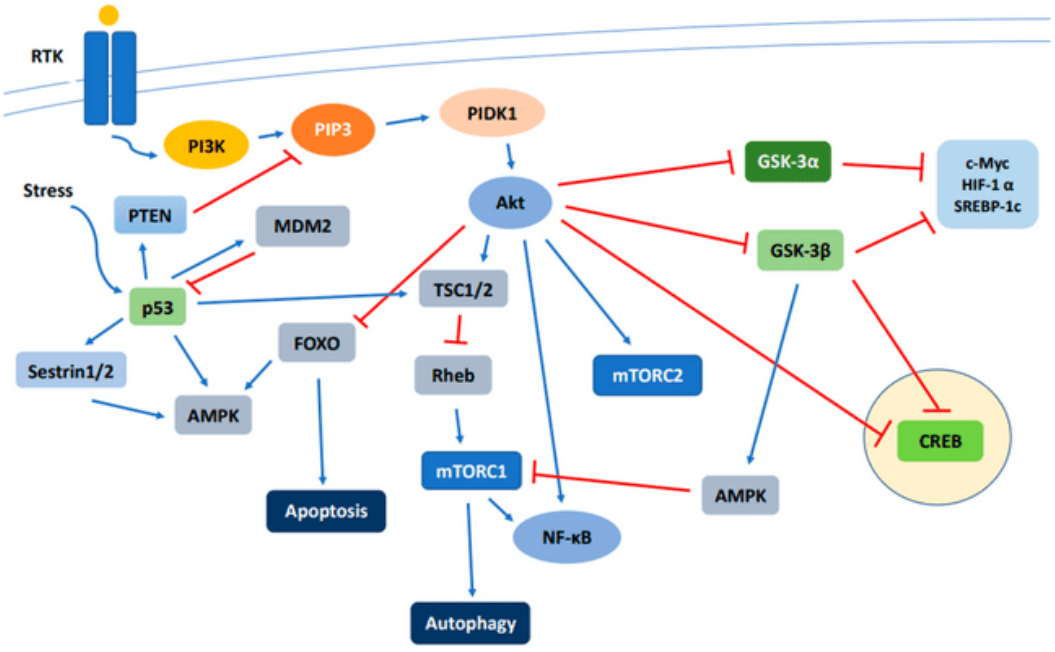

Figure 1. Dysregulated PI3K/Akt/mTOR Signaling Cascade in Hepatocellular Carcinoma

2. Materials and Methods

Design methodology: This review was designed with a structured narrative approach and was conducted to critically examine the therapeutic property of quercetin as a PI3K/Akt pathway inhibitor in hepatocellular carcinoma (HCC) however no synthesis or meta-analysis. Major scientific databases were used for an extensive literature search for relevant peer-reviewed articles with a particular focus on experimental studies, preclinical studies, and recent reviews on quercetin, PI3K/Akt signaling and HCC development. Table 1: Selected characteristics of the included articles Inclusion criteria Molecular mechanisms, pharmacological effects, drug delivery strategies Exclusion criteria Studies with no clear

experimental or clinical significance as described Summary of new aspects We performed a conventional narrative review of the literature on treatment for COVID-19, searching PubMed, Embase and Chinese National Knowledge Infrastructure (CNKI) from December 2019 to November 2020, using relevant key words including COVID-19, treatment, enduring and online but coupled a formal narrative synthesis of the available in vitro, animal and clinical data with a systematic qualitative appraisal of articles to provide a more comprehensive overview of the available literature. Syntheses of extracted data were addressed with a qualitative focus on the functionality of quercetin in the specific modulation of key signaling pathways including PI3K/Akt/mTOR, apoptosis regulation, oxidative stress, and epithelial–mesenchymal transition. We focus on experimental evidence relevant to the effects of quercetin on tumor growth, inhibition of angiogenesis, and effects on chemosensitivity. The methodology also included pharmacokinetic barriers such as poor solubility, rapid metabolism, and low bioavailability, and novel nanotechnology-based delivery systems (i.e., nanoparticles, liposomes and polymeric micelles) to improve the therapeutic effects. Additionally, comparative evaluation for detection of quercetin synergy with standard therapies including sorafenib were performed. In addition, the safety, toxicity, and translational aspect were reviewed to assess the potential for clinical usage. However, the lack of clinical evidence and heterogeneity of experimental models were critically discussed as the major limitations. Thus, this integrative methodological framework facilitated a holistic characterization of the molecular and translational aspects of the activity of quercetin in the management of HCC.

3. Results and Discussion

Quercetin: Pharmacological Profile and Mechanisms of Action

The polyphenol quercetin [3,3′,4′,5,7-pentahydroxyflavone] is a flavonoid widely distributed in nature, and its occurrence is documented in more than 300 vegetable species [11]. Quercetin is present in vegetables, fruits, nuts, seeds, and flowers such as onions, apples, tea, and grapes [12]. The flavonoid is further reported to exhibit a broad range of biological activities. Evidently, quercetin has a role as an anticancer agent against various cancer types and is non-toxic to normal human cells. The anticancer activity of quercetin involves dysregulation of multiple signaling pathways such as phosphoinositide 3-kinase [PI3K], protein kinase B [Akt], mammalian target of rapamycin [mTOR], extracellular signal-regulated kinases [ERKs], mitogen-activated protein kinases [MAPKs], p53, phosphatase and tensin homolog deleted on chromosome ten [PTEN], and others. Therefore, quercetin possesses the capability to act as an inhibitor of the PI3K/Akt pathway since the pharmacological agent effectively modulates PI3K and Akt on other cancer types [13],[14]. This modulation leads to quercetin-mediated effects on other downstream effectors involving the GSK-3β, mTOR, and BAD proteins, and to significant anticancer effects such as apoptosis, cell cycle disarray, and growth inhibition. Quercetin itself and a number of derivatives are reported to inhibit the PI3K/Akt oncogenic pathway, demonstrating an extensive structure–activity relationship. Further advancement in potentially enhancing the pharmacological profile of quercetin can thus be developed based on the polyphenol as a Probe 2 PA intra-cellular modulator of PI3K–Akt signaling [15],[16].

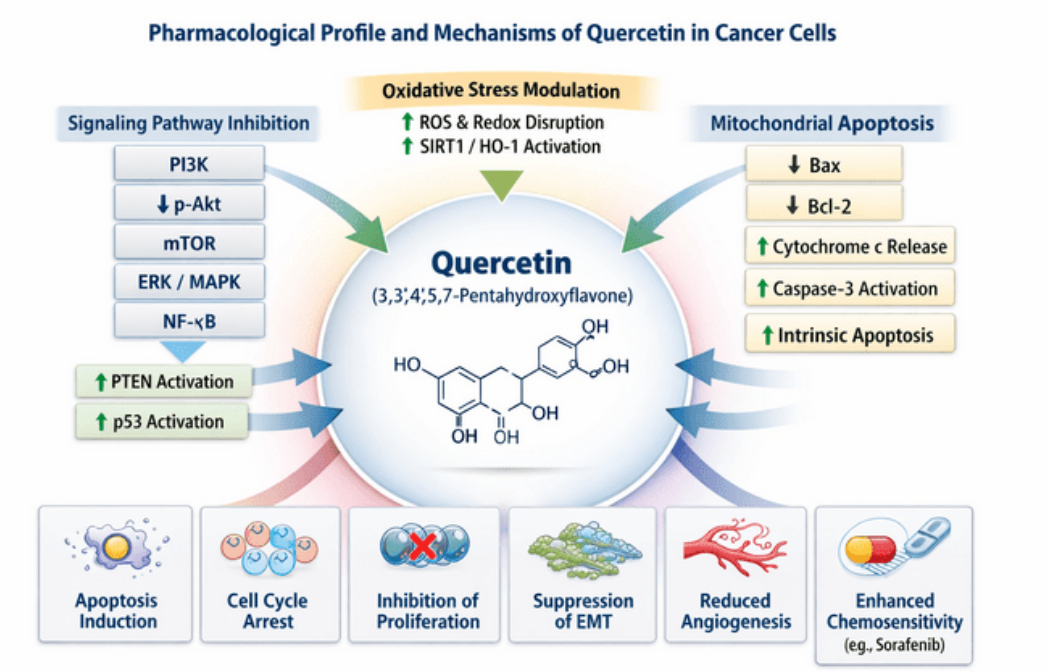

Figure 2. Multi-Target Pharmacological Mechanisms of Quercetin in Cancer Cells: Inhibition of PI3K/Akt/mTOR Signaling and Induction of Mitochondrial Apoptosis

Therapeutic Potential of Quercetin in Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) ranks as the sixth most common cancer and is the third leading cause of cancer-related mortality worldwide [17]. In 2020, the global incidence of liver cancer approached one million new cases, with approximately 700,000 deaths attributable to the disease. The phosphoinositide 3-kinase (PI3K)/Akt signaling pathway plays a crucial role in the pathogenesis of HCC. Activation of PI3K/Akt signaling results from a variety of genetic mutations and epigenetic modifications. Amplification of PI3KCA, mutations in PIK3CA, loss-of-function mutations in the tumor suppressors PTEN and FBXW7, and increased levels of the activating miRNA miR-19 have been identified as driver mutations in human HCC [18]. Beyond HCC, aberrations in the PI3K/Akt/mTOR pathway can also be found in cancers of the pancreas, prostate, and brain. The disruptive influence of the PI3K/Akt pathway extends to diverse cellular processes, including protein translation and epigenetic regulation, by modulating the activity of a wide range of downstream signaling partners. Multiple preclinical studies have highlighted the significance of PI3K/Akt signaling as an attractive therapeutic target in HCC. Extensive research has focused on the development of small-molecule inhibitors targeting the PI3K/Akt/mTOR signaling pathway, yet no pharmacological agents have secured approval for clinical use [19]. Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is a polyphenolic flavonoid naturally occurring in various fruits and vegetables. Quercetin offers potent antioxidant effects and delivers positive outcomes in various conditions ailing humans, including metabolic syndrome, cardiovascular diseases, neurodegenerative illnesses, as well as various types of cancer [20]. Quercetin is an anticancer agent with a wide spectrum of response to breast, prostate, lung, colon, pancreatic, liver, and ovarian cancer. The food additive has also direct modulatory action on PI3K/Akt/mTOR pathway. Thorough analysis of DTP, MeSH, and PubMed databases has revealed more than 35 direct pathways by which quercetin alters PI3K/Akt signalling pathway. In a wide variety of malignancies, quercetin has been described as a normal perturbor of the PI3K/Akt pathway. Quercetin as a potential drug candidate has a good future due to its status as a natural compound, which has a well-known safety profile. The preclinical trials have shown the capability to counter drug resistance of the existing frontline therapies. Taking into consideration the

high level of cancer burden and considering the absence of approved small-molecule inhibitors of PI3K/Akt in HCC, it is possible to investigate the potential of quercetin in HCC [20].

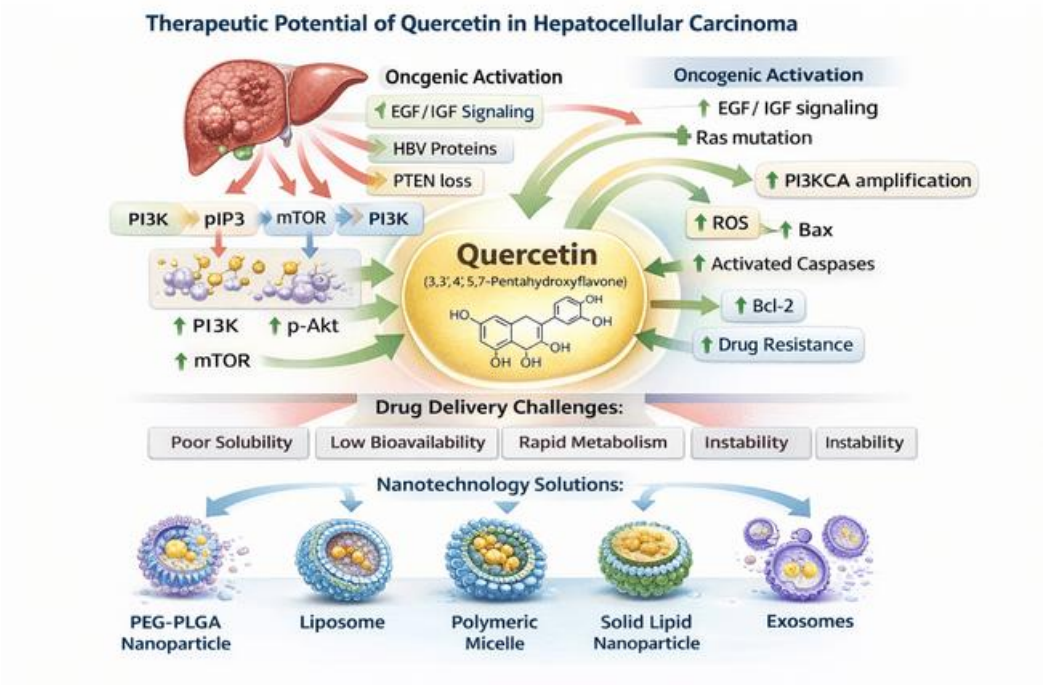

Figure 3. Therapeutic Potential of Quercetin in Hepatocellular Carcinoma: Targeting PI3K/Akt Signaling and Overcoming Drug Delivery Challenges

Drug Delivery Challenges and Strategies for Quercetin

Hepatocellular carcinoma (HCC) is the leading cause of cancer mortality worldwide, and continues to rise despite the introduction of new drugs. Targeting the frequently activated phosphoinositide-3-kinase (PI3K)/Akt pathway is therefore a pertinent challenge for HCC. The natural product quercetin (3,3′,4′,5′,7-pentahydroxyflavone) is a potent PI3K/Akt modulator that shows clear therapeutic potential in this indication. Despite promising preclinical and early clinical evidence, quercetin remains under-explored due to unresolved drug-delivery challenges. HCC is regularly associated with chronic liver diseases, including hepatitis B (HBV) and C (HCV) viral infection, aflatoxins, alcohol, dichloroethane and nonalcoholic fatty liver disease (NAFLD). These factors cause liver inflammation and fibrosis, resulting in cirrhosis, the major risk factor for HCC [21],[22].

Quercetin is a polyphenolic compound and mainly exists in nature as flavonol with 3-hydroxyl, 3′-hydroxyl, 4-carbonyl and 5-hydroxyl groups [23],[24]. These groups play an important role in its pharmacological effect. However, its pharmacokinetic properties are unfavourable, including low solubility and bioavailability, rapid metabolism and elimination from the body, and instability in storage. Nanoparticles and a range of various nanocarriers (liposomes, polymeric carriers, conjugates and stimuli-responsive formulations) have been developed to enhance solubility, stability and bioavailability; quercetin-loaded lipid-core nanocapsules, polymeric micelles, solid lipid nanoparticles and PEG-PLGA-PE micelles have shown good performance in preclinical studies of different disease models [25],[26].

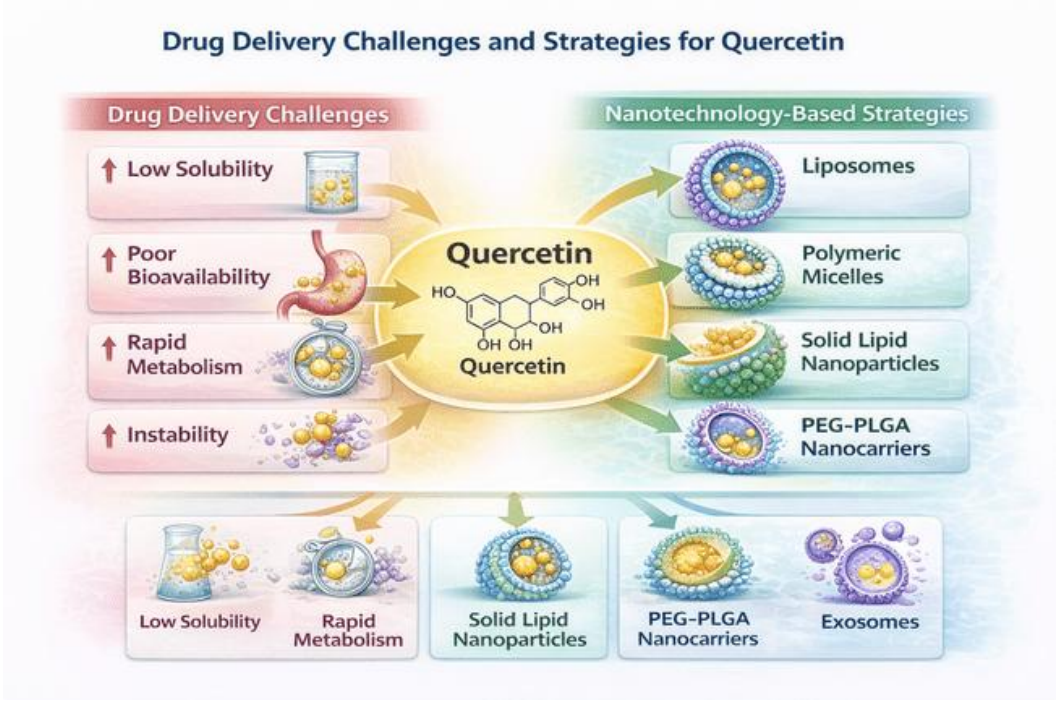

Figure 4. Drug Delivery Challenges and Nanotechnology-Based Strategies to Enhance Quercetin Bioavailability and Therapeutic Efficacy

Preclinical Evidence and Translational Considerations

Quercetin has been reported to have strong anticancer effects against several human cancers, including hepatocellular carcinoma (HCC). Upon treatment it was observed to suppress the expression of p-PI3K, p-Akt, and p-mTOR and induce apoptosis through a PI3K/Akt-dependent mechanism. It has also been demonstrated that quercetin can simultaneously target multiple pathways, thereby exerting the anticancer effect in a more efficient manner. While quercetin has become an attractive agent to treat HCC, a key limitation is its bioavailability profile. In order to increase the anticancer efficacy of quercetin, advanced delivery systems comprised of various materials, such as polymeric, liposome, lipid nanoparticles, nanogold, metal-organic framework, microneedle patches, and exosomes have been developed [27],[28].

Safety, Toxicity, and Pharmacokinetics

The safety, toxicity, and pharmacokinetics of quercetin are summarized here. Its hepatoprotective, neuroprotective, and antioxidative activities have been well documented in preclinical studies, the effects being attributed primarily to modulation of oxidative stress pathways 29. Nanoparticle delivery enhances antioxidant activity and cellular protection. Involvement of quercetin in the sirtuin 1 and heme oxygenase 1 pathways has been implicated in protection against liver injury caused by a variety of toxins. The compound also exhibits potential in tumor imaging and targeted gene delivery and induces programmed cell death in tumor cells. Overall, extensive pharmacological investigation supports the safety and reasonable use of quercetin even in the case of liver problems [29],[30].

Quercetin has been shown to attenuate PI3K–AKT signaling in T-cell lymphoma exposed to hydrogen peroxide [31],[32]. Agents capable of maintaining reactive-oxygen-species homeostasis are predicted to improve cancer-care options. Reactive-oxygen-species homeostasis is controlled by a variety of stimulators and inhibitors, and alterations in this balance affect cancer-cell survival and responses to treatment. Natural agents such as curcumin and quercetin have been shown to modulate reactive-oxygen-species levels as well as downstream signaling through the PI3K–AKT, mTOR, and Ras/Raf/MAPK

pathways, thereby inducing apoptosis, preventing tumor growth, and enhancing the antitumor efficacy of drugs such as cisplatin. Conversely, starving agents, including glucose and glutamine, diminish the antiproliferative effects of doxorubicin under relevant conditions [33],[34].

Clinical Perspectives and Future Directions

Among various cancer therapeutic approaches, targeting specific cellular signal transduction pathways has received particular attention. The phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) signaling pathway is among the most frequently dysregulated pathways in human cancers. In hepatocellular carcinoma (HCC), the PI3K/Akt pathway is involved in the control of apoptosis and therefore in the regulation of tumor growth. Quercetin is a naturally occurring flavonoid that has demonstrated anticancer activity by inhibiting the PI3K/Akt/mTOR signaling pathway [35],[36]. A few experimental studies indicate that quercetin is effective against HCC and can act synergistically with the cancer therapeutic sorafenib to inhibit HCC cell proliferation and induce apoptosis 37. However, no clinical trials have been conducted to investigate the antitumor effects of quercetin in HCC. The available literature on the therapeutic potential of quercetin against HCC and the challenge posed by low bioavailability and other drug-delivery issues necessitates the present consideration of quercetin as a promising candidate for further investigation in this regard [37].

HCC has been among the major causes of cancer-related deaths in the world. Existing therapeutic options against advanced HCC are only partially beneficial to the patient and thus there is an acute need to come up with active treatment modalities. Interactions of drugs with varied mechanisms of action, e.g. the standard sorafenib and quercetin, may be beneficial approaches to this unmet need [38,39]. Considering the above, quercetin can be nominated as a promising option to consider in future experimental procedures and pre-clinical trials against advanced HCC. The questions to be clarified are the reason to target the PI3K/Akt pathway in HCC and the exact roles of structural features of quercetin in its selectivity among the components of the PI3K/Akt/mTOR signaling cascade as compared to those of structural analogues [40].

4. Conclusion

Hepatocellular carcinoma is number six most common cancer and third leading cause of cancer related death in the world with worrysome increase in incidences in some parts of the world. The phosphatidylinositol-3-kinase (PI3K)/AKT pathway propagates oncogenic signals that are initiated at surface receptors and is of critical importance in the etiology of hepatocellular carcinoma. Quercetin is an ideal example of a natural flavonoid that is abundantly found in fruits and vegetables and capable of suppressing the PI3K/AKT pathway and exhibits anti-cancer effects across most malignancies. The description of the PI3K/AKT signaling network in hepatocellular carcinoma along with an in-depth account of the pharmacological nature of quercetin, its working mechanisms, and its pharmacodevelopment issues shows its therapeutic potential and grounds future research. Quercetin is an antiviral, anticancer agent against many different forms of malignant neoplasma, hepatocellular carcinoma. In addition to quercetin delivery, other research priorities include bioavailability improvement, PI3K/AKT asymmetrical targeting, testing in suitable in vivo models, response biomarker characterization to direct patient selection, determination of quercetin dosing-regimen in clinical-body models, combination analysis agent, and combination approach to other malignancies.

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Declaration of Competing Interest

The authors indicate that they have no known personal or financial relationships or financial interest that may have appeared to have influenced the work in this study.

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