https://doi.org/10.48047/AFJBS.6.5.2024.10482-10501

AfricanJournalofBiological Sciences

OVERVIEW OF ANTICANCER EFFECTS OF QUERCETIN AND ITS SYNERGISM WITH OTHER CANCER THERAPEUTIC DRUGS

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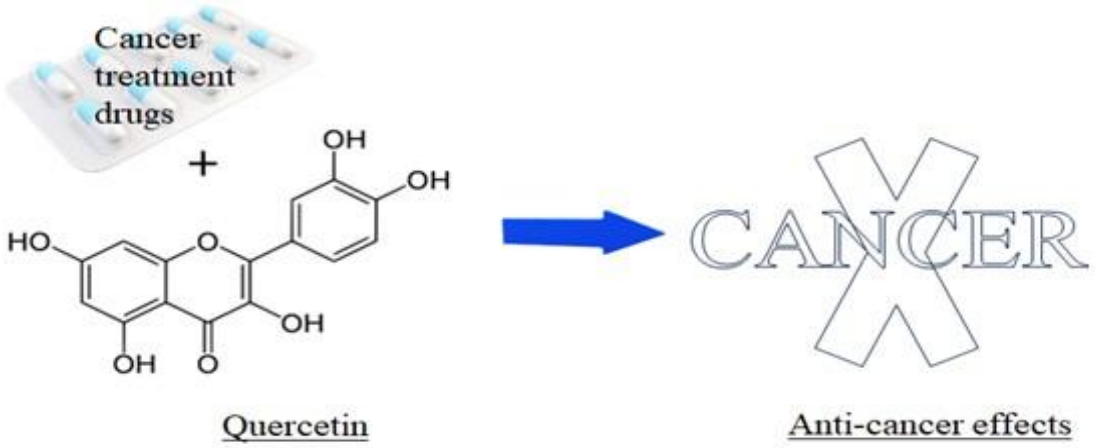
Article History
Volume 6, Issue 5, 2024
Received: 22 May 2024
Accepted: 03Jun 2024
doi:*10.48047/AFJBS.6.5.2024.10482-10501*

Abstract

Naturally occurring compounds are considered promising for testing in cancer therapy due to their expected multifaceted actions and low toxicity. These compounds are seen as potential anti-cancer agents in both standard and combination therapy. In this review, it is unveiled that quercetin can directly interact with DNA and initiate apoptosis in cancer cell lines and tumor tissues through the activation of different pathways. It was shown that quercetin exhibits synergism with anticancer drugs, making it an ideal flavonoid for consumption during cancer therapy. To address challenges such as slow response with small molecules, low solubility, and low bioavailability, various strategies are stated. Besides its anticancer properties, quercetin exhibits geno-protective, anti-inflammatory, and wound-healing activities. Quercetin has demonstrated satisfactory antitumor effectiveness by inducing apoptosis, halting the cell cycle, reducing metastasis and angiogenesis, reversing drug/radiotherapy resistance, and modulating tumor immunity.In this article, an overview of the anticancer properties of quercetin targeting different hallmarks of cancer and its synergistic activity with other natural compounds or chemotherapeutic agents to inhibit carcinogenesis by modulating various cellular pathways involved in cancer development was provided to enhance therapeutic efficacy in cancer treatment.

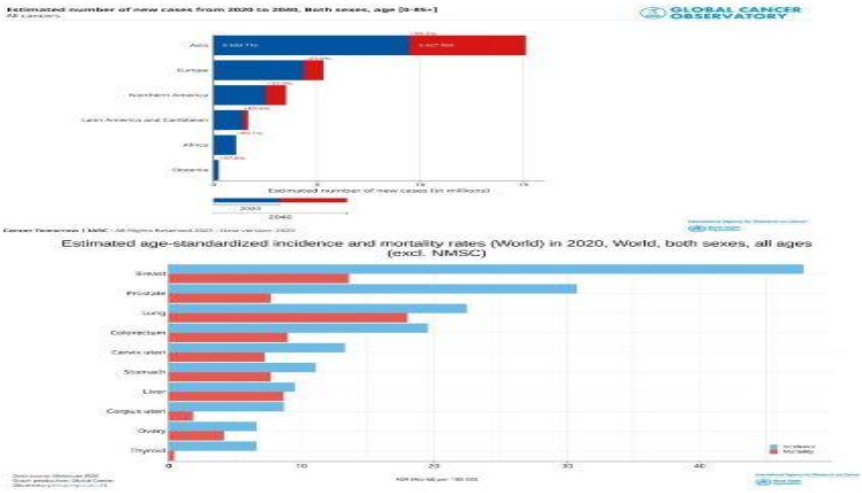
Keywords
Quercetin, anti-cancer activity, apoptosis,p53,small molecules.



Literature review

In 2020, there were an estimated 19.3 million new cases of cancer and nearly 10.0 million cancer-related deaths globally, excluding nonmelanoma skin cancer. Female breast cancer is rated higher than lung cancer as the most frequently diagnosed cancer, with an estimated 2.3 million new cases, accounting for 11.7% of all cases. Lung cancer remained the preceding cause of cancer, with an expected 1.8 million fatalities where the remainingare female breast cancerat around 6.9%, stomach cancer at 7.7%, liver cancer at 8.3%, colorectal cancer at9.4%. By 2040, the global cancer burden is projected to increase to 28.4 million cases, representing a 47% rise from 2020, with a more noticeable increase in transitioning countries (Global Cancer Statistics 2020). This rise will be higher in transitioning countries, ranging from 64% to 95% compared to transitioned countries, ranging from 32% to 56%. It is crucial to focus on cancer prevention and care in transitioning countries as a vital component of global cancer control efforts. The spectrum of treatment options includes surgical procedures, radiation therapy, immunotherapy, chemotherapy, and hormonal therapy. Around 40-50% of patients undergo radiation treatment during their illness making it a crucial approach in cancer treatment (3). Over 70% of anticancer compounds are natural products or natural product-derived substances and quercetin is one among them. Quercetin, a naturally occurring flavonoid, exhibits anticancer properties and has gained increasing interest from scientists worldwide. Quercetin's anticancer properties were proven to be efficient against many cancer cells like cervical cancer (14,29), lung cancer (13,26), prostate cancer cells (19), and colorectal cancer (1). Recent investigations reported the encapsulation of quercetin in chitosan nanoparticles to target the tumor microenvironment and enhance its efficacy in cancer therapy (3). It was shown that a diet supplemented with 2% quercetin significantly reduced the onset of colorectal cancer (8).

The estimated cancer incidence and mortality rates reported by WHO are shown in Figure1.



Source: https://gco.iarc.fr/today

Discussion

Quercetin is aneffectiveantioxidant, often found in fruits and vegetables such as onions, grapes, berries, cherries, and broccoli. Although it has been well reported for its anticancer activities and anti-inflammatory activity, the combinational activity of this flavonoid with other drugs is in progress. This review emphasizes thesynergistic anticancer activity (highlighting key cancer pathways) of quercetinand anticancer drugs including small molecules, which would drive further cancer research on quercetin.

Quercetin anticancer activity

In vitro

Quercetin showed strong antimutagenic effects against alkylating agents like Cyclophosphamide and Methyl methane sulfonate, pro-mutagens, and DNA adducts such as benzo(a)pyrene, as well as a direct damaging agent, sodium azide, in the Ames test. This protective role of quercetin was consistently seen in both prokaryotic and eukaryotic test systems using L5178Y TK+/- cells. In the chromosomal aberration test, there was a significant decrease in benzo(a)pyrene-induced mutagenicity (p value-0.03) and cyclophosphamide-induced mutagenicity (p-value: 0.04) in the presence ofa metabolic activation system. (21).

Cytotoxicity

When researchers tested quercetin's toxic effect on three leukemic cell lines (CEM, K562, and Nalm6), two breast cancer cell lines (T47D and EAC), and two normal cell lines (293T and MEF1), they found that quercetin induced cell death, dose-dependently in all the leukemic cell lines. (22). These results reveal that quercetin has a cytotoxic effect on cancer cells.

Quercetin effect on Apoptosis and other key factors

In vitro MTT assay was used to evaluate the anticancer effects of quercetin in nine different tumor cell lines, which included LNCaP, CT-26, PC3, PC12, MCF-7, U266B1, MOLT-4, Raji, and CHO cells. The results showed that quercetin triggered apoptosis in LNCaP, CT-26, MOLT-4, and Raji cell lines compared to the untreated group ($P<0.001$) (9).

A study found that quercetin triggers pro-apoptotic effects through various mechanisms, including antioxidant effects and downregulation of BCL-2 protein. The inhibition of BCL-2 gene transcription reduces the inhibitory effect on BAD protein in the mitochondria,the initiator of apoptosis for the intrinsic pathway.

About 50% of cancers are sustained due to alteration in the Tp53 gene. Quercetin's role in apoptosis mediated by p53 was studied in different cancer cell lines. When p53 is inhibited, cells become more vulnerable to quercetin-induced cytotoxicity. In addition to regulating the cell cycle and stimulating apoptosis, p53 acts as a modulator of intracellular levels of ROS (reactive oxygen species). In this context, p53 exerts antioxidant effects in cells with no or little stress by regulating genes involved in such activity, including aldehyde dehydrogenase 4 family member A1 (ALDH4A1), microsomal GSH transferase homolog PIG12, manganese superoxide dismutase (SOD2), Gpx1and catalase. Some studieshave shown that the effect of quercetin may be independent of p53. Although p53 often mediates apoptotic cell death caused by DNA damage, other proteins, such as p73 and p63, may be involved in this process. Chien et al. demonstrated that quercetin-induced apoptotic cell death was due tothe low levels of p53 expression in breast cancer cells. In addition, quercetin inhibited induced cell death and metabolic activity through apoptosis, leading to an increase in BAX expression and a simultaneous decrease in the expression of anti-apoptotic proteins. (8). These results reveal the key role of quercetin in regulating the p53 apoptotic pathway in cancer cells.

Heat shock proteins (HSPs) are commonly elevated in various types of cancer. Badziul et al demonstrated that quercetin reduced the transcription and translation of HSP27 and 72 in the T98G cell line. These proteins play a role in cell proliferation and inhibiting their production, can lead to cell apoptosis. HSP27 was found to support leukemia development by protecting tumor cells from apoptosis through multiple mechanisms. Another study examined the impact of the small hairpin (sh)RNA-mediated HSP27 knockdown on the anticancer effects of quercetin in U937 human leukemia cells. The findings revealed that shHSP27 and quercetin synergistically inhibited U937 cell proliferation and induced apoptosis by reducing the Bcl2/Bax ratio. Additionally, this combined treatment significantly suppressed tumor cell infiltration and the expression of angiogenesis-associated proteins, hypoxia-inducible factor 1α (HIF1α), and vascular endothelial growth factor (VEGF).

Apart from regulating heat shock proteins, quercetinis found to have anticancer effects through various other mechanisms, such as releasing cytochrome c, inhibiting DNA topoisomerase I/II, and activating caspase 3(8).

In a separate study, alterations in the mitochondrial membrane potential in Nalm6 cells resulted, in both early and late apoptotic cells with Annexin V/PI staining, the presence of TUNEL staining-positive cells in tumor tissues and DNA fragmentation through gel assays together indicate the activation of apoptosis after exposure to quercetin. This process entails a reduction in antiapoptotic proteins and a rise in proapoptotic proteins. Quercetin treatment resulted in improved expression of p53. Additionally, the downregulation of antiapoptotic proteins such as BCL-xL and BCL2, the upregulation of BAX and p-p53, the release of cytochrome C as well as the cleavage of caspase 3, caspase 9, MCL1and PARP1suggest the involvement of the intrinsic mitochondrial pathway. The intercalation of small molecules affects conformational changes in DNA, which can result in physiological processes such as transcription, replication, translation, and repair (22).

Quercetin was found to regulate heterogeneous nuclear ribonucleoprotein A1 (hnRNPA1) in a study using the prostate cancer cell line PC3. It prevented hnRNPA1 from moving between the nucleus and cytoplasm, causing it to be retained in the cytoplasm. Earlier studies have suggested that quercetin may also boost TRAIL-mediated apoptosis in colon adenocarcinoma cells. (22).

Quercetin also exhibited DNA damage protection by reducing proteasome 20S levels, involved in cell cycle regulation, transcription and proliferation (5), indicating the protective role of quercetin against DNA damage.

Its anticancer effects are also exerted through the cell death domain mechanism at the cell surface which is a key step in the extrinsic apoptotic pathway. Quercetin activates the cell death domain, resulting in FAS and FADD activation, and induces cell death in a cancer cell line through caspase 8 activation. These findings demonstrated the apoptotic-inducing properties of quercetin(8).

Quercetin may enhance the effectiveness of antitumor treatments and boost the immune system to improve outcomes for lung cancer patients when combined with other therapies. In the case of NSCLC, Quercetin can directly inhibit the growth of tumor cells by acting as an aurora B inhibitor, which is highly expressed in various cancer cells and contributes to the development and advancement of tumors.(13).

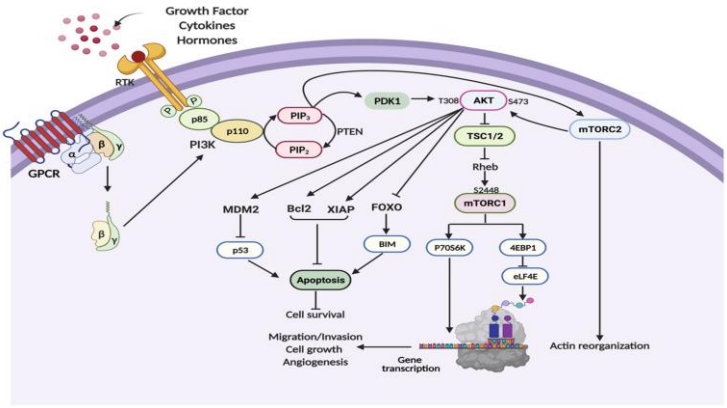
Quercetin effect on different pathways

The effect of quercetin on different cancer pathways (by regulating the signaling pathways MEK/ERK, VEGFR2, MEK/JNK, and PI3K/AKT was well demonstrated (43).

Quercetin was discovered to regulate the PI3K/Akt/mTOR pathway and shares structural similarities with the PI3K inhibitor, LY294002 (LY). This plant compound was observed to block the PI3K-Akt pathway in breast cancer cell lines and thus plays a key role in downregulatingangiogenesis. Also, quercetin inhibits breast cancer invasion by deactivation (e PKC/ERK/AP-1-dependent MMP-9 activation (8).

Additionally, the Notch/AKT/mTOR signaling pathway plays a role in tumor aggressiveness. The combination of shHSP27and quercetin has led to a notable reduction in phosphorylation levels of mTOR and AKT and Notch 1 expression which are downstream signaling proteins. (8).

Essential factors involved in Apoptosis are shown in Figure 2:



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Quercetin was found to block pathways that promote cell survival and reduce the expression of pro-inflammatory cytokines, which can lead to cancer. Specifically, it inhibits the production of tumor necrosis factor (TNF)-α, a key molecule in chronic inflammatory diseases that can lead to tumor development. (8).

Quercetin has shown an inhibitory effect on angiogenesis in human prostate tumors. When prostate cancer cells were treated with quercetin, protein expression analysis showed a reduction in the phosphorylation of VEGFR-2 caused by angiogenic factor VEGF(vascular endothelial growth factor), as well as its associated targets like,Akt, mTOR and ribosomal S6 kinase. (8).

Earlier research indicated that quercetin may impact the PI3K-Akt and Ras signaling pathways, which are key pathways in cancer. Also, quercetin was found to inhibit the hedgehog signaling pathway in prostate cancer.(22).

In vivo

Among flavonoids, quercetin is a notable bioactive flavonoid, that exhibits broad antioxidant activities and various therapeutic functions. However, low bioavailability resulting from poor water solubility, quick clearance, and enzymatic degradationrestricts its biological and clinical application.

Nano drug delivery might improve the bioavailability and solubility of this flavonoid resulting in enhanced availability.

Administering quercetin nanoparticles intravenously to tumor xenograft mice with A549 and MDA MB 468 cells led to a significant reduction in tumor volume compared to the control

groups ($p < 0.05$). Additionally, the levels of the serum antioxidant enzyme superoxide dismutase (SOD) which acts against oxidative stress were markedly increased in the quercetin nanoparticle-treated tumor-bearing mice compared to those treated with quercetin(3).

Another research studyinvestigated the impact of quercetin on mice with CT-26(colon carcinoma) tumors and found that it notably decreased tumor size and improved survival rates. Earlier studies have also demonstrated quercetin's anticancer properties on breast and prostate cancers in animal models. (8,9).

In a study, when mice were treated with quercetin in combination with the mutagens benzo(a)pyrene (G5) and cyclophosphamide monohydrate, a significant decrease in

MNPCE (micronucleated polychromatic erythrocytes) percentwas observed when compared to mice treated with the same mutagens in mouse bone marrow micronucleus test (21), indicating the synergistic effect of quercetin with anticancer drugs.

When 50 mg/kg quercetin was intraperitoneally injected into HCT116 tumor xenograft nude mice, the tumor volume was significantly reduced in quercetin-treated mice compared with the control group. Quercetin also significantly inhibited AMPK (activated protein kinase) in HCT116 human cancer xenografts, which can induce angiogenesis (11).

Cell cycle

Depending on the origin of the tumor, quercetin can disrupt the cell cycle at the G2/M stage or the G1/S stage. In breast cancer cells, low-dose quercetin causes mild DNA damage and activates Chk2, which is responsible for the expression of p21(the protein that acts as a cell cycle inhibitor). In the case of human hepatoma cell lines (hepG2), when quercetin was administered it upregulated p27, p27, and p53, resulting in cell cycle arrest at the G1 stage.

When compared with shHSP27(sh)RNA-mediated HSP27 knockdown)or quercetin alone, shHSP27 and quercetin combination remarkably decreased the expression of cyclin D1, resulting in cell cycle arrest at the G1 phase(8).

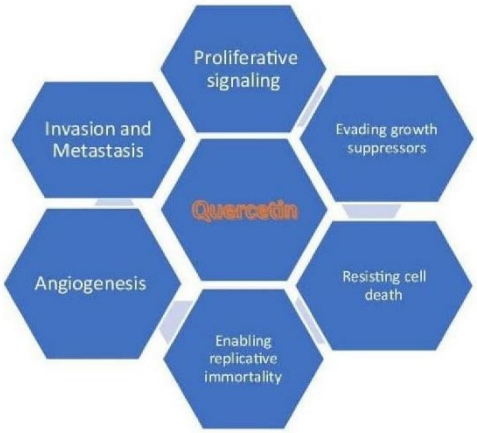
Angiogenesis

Angiogenesis is the growth of tumors mediated by chemical signals. The growth factors that accelerate angiogenesis include fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), transforming growth factor-beta (TGF-β), tumor necrosis factor-alpha (TNF-α),

and angiopoietins (Ang). Quercetin was shown to have a regulatory effect on these factors. MALAT1 and MIAT lncRNA are among those involved in angiogenesis. MALAT1 stimulates hypoxia-induced angiogenesis by overexpressing angiogenic genes. Downregulation of MIAT1 could result in the inhibition of endothelial cell proliferation, migration, and tube formation. In a study, quercetin-treated HUVEC cells showed a decrease in MALAT1 and MIAT lncRNA (7).

The above function of quercetin was provenin another study,stating that the flavonoid could inhibit angiogenesis by regulating the signaling pathways MEK/ERK, VEGFR2, MEK/JNK and PI3K/AKT (43).

From the above findings, anticancer activity of quercetin against hallmarks ofcancer wasrevealed including eluding growth inhibitors,regulating growth factors, boosting angiogenesis,activation ofinvasion and metastasis. Quercetin multimodal action is represented in Figure 3.



Small molecules and other anti-cancer therapeutic drugs

Small molecules are considered effective in targeted therapy. Many small molecules like nutlin-3, PRIMA, and RITA gained attention for their anticancer properties in cancer treatment. Some of these small molecules were tested for their synergism with natural compounds to reduce their side effects, for improved efficacy in cancer treatment. They were demonstrated to be more effective than individual drug treatment.

In a study, it was revealed that small molecules targeting p53 other than the MDM2-binding site are identified as essential for their interaction.

In a study, it was revealed that small molecules targeting p53 other than the MDM2-binding site are identified essential for their interaction. Additionally, the study found that the binding of small molecule RITA promotes a compact conformation of the partially unstructured N-terminus, inhibiting its interaction with MDM2 and MDMX. Certain small molecules were shown to prevent p53/MDM2 interaction, leading to p53 accumulation and increased transcriptional activity, ultimately inducing p53-dependent apoptosis in tumor cells of various origins, both *in vivo* and *in vitro*(20,30,31).

Furthermore, a study demonstrated that the combination of p53 activator and Temozolomide effectively inhibited cell proliferation and promoted apoptosis. The specific molecular mechanisms involved in the responses to small molecules remain unclear, although several groups reported the induction of a p53-dependent DNA damage response. A recent study also showed synergistic induction of apoptosis by a p53 activator in combination with small molecules like Nutlin-3(12,19,28).

Another study found that small molecule RITA induced DNA damage signaling enhanced the antiproliferative response to 5FU and Oxaliplatin when tested with CRC cells (27). Moreover, disruption of Mdm2-p53 binding was shown to induce apoptosis by activating p53 and sensitizing lung cancer cells to chemotherapy (23). MDM2 antagonists can induce both mitotic arrest and apoptosis in the same tumor-derived cells. The study also revealed that, along with p53 reactivation, the proapoptotic p53-activator HIPK2 is degraded by MDM2 in Nutlin-3-treated cells however stimulated by reduced MDM2 levels in cells treated with another MDM2 antagonist (18).

Certain small molecules triggered the activation of proapoptotic p53 targets NOXA, PUMA, and BAX while suppressing the expression of pro-proliferative factors CyclinB1, CDC2, and CDC25C. This led to p53-dependent apoptosis and cell cycle arrest. Significantly, cervical cancer xenografts were markedly suppressed in vivo (33).

Gain-and-loss-of-function experiments indicated that combining natural compounds with chemotherapeutic drugs is a more effective approach for combination therapy than using two

similar groups of drugs. Furthermore, certain small molecules were found to activate the transcription of proapoptotic p53 targets while repressing the expression of pro-proliferative factors, resulting in p53-dependent apoptosis and cell cycle arrest(33).

A study demonstrated that quercetin has the potential to reverse Paclitaxel resistance by inhibiting Akt and ERK phosphorylation and membrane potential (MMP) depolarization in A549/Taxol cells (26).

When combined with cisplatin, quercetin exhibited a synergistic effect in inhibiting cell proliferation and resulted in increased inhibition of cell migration and invasion compared to either compound alone in cervical cancer cells. Additionally, quercetin enhanced the apoptosis-inducing effects of cisplatin inthe cancer cells. These findings are significant as they pertain to proteins involved in cancer cell growth, migration, invasion, and drug resistance (29).

The resistance of tumor cells to chemotherapy is primarily attributed to the high expression of the human MDR1 gene and the P-glycoprotein (P-gp) transporter encoded by MDR1. Quercetin and aconitine were also found to synergistically induce human cervical carcinoma HeLa cell apoptosis by inhibiting the proliferation of the MDR1 gene and the P-glycoprotein transporter. Additionally, quercetin and aconitine were observed to synergistically induce ER stress by activating pathways (unfolded protein response) in HeLa cells (14).

In a study, the co-application of siRNA, doxorubicin, and quercetin on breast, gastric, and prostate cancer cells resulted in higher toxicity towards cancer cells (10).

Quercetin and curcumin combination has the potency to show anti-inflammatory and immunomodulatory properties by altering the activation of ERK, MAP kinase, and NF- kappa B transduction pathways (34,35,36).

Quercetin, when tested in combination with 5-fluorouracil (an anticancer drug used in the treatment of various cancers breast, colon, rectal, gastric, and head and neck cancers) showed a synergistic effect when tested on HT-29 cells and fibroblast cells in rats (37).

Much research is being carried out to overcome drug resistance for cancer treatment. In a study, it was demonstrated that pre-treatment for 24 h with quercetin sensitizes DU-145 and PC-3

(aggressive) CaP prostate cancer cells to lower doses of docetaxel and reported reversing drug resistance in both DU-145/R and PC-3/R CaPcells (prostate cancer cells) (38).

Breast cancer is one of the most common cancers in women in the world and by 2040, it is estimated that breast cancer cases are predicted to increase to over 3 million (39). The synergic effect of quercetin and raloxifene showed potent anticancer properties on the breast cancer cell lines MCF-7 and MDA-MB-231, inhibited cell migration and invasion, down-regulated Bcl2 gene, and upregulated p53, MMP2, and MMP9, inducing apoptosis (40).

Nanofibers produced by electrospinning have attained great attention and are namedelectro-spun complex nanostructures. In a recent study, it was verified that quercetin was released rapidly with slow and sustained release of tamoxifen citrate which is an anticancer drug used for breast cancer (41).

Erlotinib is a small molecule, is a reversible inhibitor of the wild-type EGFR autophosphorylation is under clinical trials and is used for oral squamous cell carcinoma (OSCC), often categorized as a head and neck squamous cell carcinoma (HNSCC). Quercetin is observed to induce apoptosis with the knockdown of PKM2 re-sensitized ERL-R cells to Erlotinib and blocked the development of erlotinib-mediated resistance (42).

Extensive research is going on to evaluate the efficacy of the combination of small molecules and natural compounds. In this context, we believe that this review will serve as the basis for further research to evaluate the efficacy of quercetin in combination with anticancer drugs.

Limitations

Quercetin is a widely existing plant flavonoid having a good range of pharmacological benefits like antioxidant, cardiovascular protection, anti-inflammatory,anti-anaphylaxis, anti-cancer, and anti-aging properties. Even yet the pharmaceutical application of quercetin is limiteddue toits low bioavailability, limited solubility, inherent instability, and poor permeability (Cai X 2013). To enhance the bioavailability of quercetin, various strategies can beapplied and are tabulated in Table 1.

Type of Quercetin Molecule	Function	Reference
Quercetin Phytosome	Quercetin phytosome is a complex made by combining phospholipids with quercetin. This combination can boost the solubility of quercetin in water, potentially enhancing its absorption in the gastrointestinal tract.	(2)
Quercetin Nanoparticles	Encapsulation of quercetin nanoparticles shields them from degrading in the digestive system and enhances their absorption.	(6)
Quercetin Glycosides	Quercetin glycosides are altered versions of quercetin with attached sugar molecules to the quercetin molecule. These glycosides are often more stable and may offer better bioavailability when compared to free quercetin.	(25)
Liposomal Quercetin	Liposomes are lipid-based vesicles that can be used to encapsulate quercetin, safeguarding it from degradation and improving its absorption.	(6)
Quercetin Prodrugs	Prodrugs areinactive compounds that are to be converted into active form in the body. Some quercetin prodrugs, such as Pentabenzensulfonate (QPBS) are developed to improve their absorption and bioavailability.	(17)
Quercetin Conjugates	Quercetin can be conjugated with amino acids or peptides to improve its absorption in the gut, as seen with the example of quercetin-chitosan conjugate (QT-CS) nano micelles.	(15)
Quercetin Complexes with Cyclodextrin	Cyclodextrins can form complexes with quercetin to increase its solubility and for improving its bioavailability. One such complex is β-cyclodextrin polymer which was proven to be effective in overcoming P-glycoprotein-mediated multidrug	(16)

	resistance.	

Conclusion

Phytochemicals are considerably used to estimate their cancer remedial properties. To target cancer cells which generally serve several pathways to get over chemotherapy, it's pivotal to target several important pathways associated with tumorigenesis by combinationtreatment.

In conclusion, Combination therapy with the herbal drug quercetin and chemotherapeutic agents enhances the effect of treatment due to the multimodal action and conquers the existing cancer drug resistance.

Acknowledgments

The authors express their gratitude for the financial support received from the research grant committees of both MAHE University, Mangalore, and Palamur Biosciences Pvt. Ltd. This support was provided in the form of an allowance dedicated to the modernization of academic research.

Disclosure statements

No potential conflict of interest was reported by the authors.

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