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Quercetin Nanoparticles- A Promising Approach to Cancer Treatment: A Review

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Abstract: Quercetin, a naturally occurring polyphenolic element, has rapidly received attention as an anticancer agent. Although quercetin has demonstrated potent medical value, its application as an antitumor drug is limited because of poor solubility, low absorption, and fat metabolism. Nanoparticles are effective and versatile drug delivery devices because they can improve the solubility, pharmacokinetics, bio distribution, and in vivo stability of the free drug. The utilization of Nano-carrier scanning increases the bioavailability of the drug. Quercetin nanoparticles have shown high encapsulation efficiency, stability, sustained release, extended circulation time, improved accumulation at tumor sites, and therapeutic efficacy. This review article aims to estimate the anticancer efficiency of polymeric nanoparticles of quercetin. The majority of research is based on the preclinical anticancer activities of quercetin nanoparticles. MCF cells of breast cancer (BC), A 549 cells of lung cancer, cells of HepG2 liver malignancy, and cells of malignance are the primary targets for possible anticancer activity. Furthermore, combining quercetin with other diagnostic or therapeutic agents in a single Nano carrier has resulted in improvements in tumor detection or treatment. The antitumor outcome of drugs that are used in cancer therapy can also be supported by quercetin nanoparticles by increasing the anti-tumor development or decreasing the systemic toxicity level of the drug.

Keywords: Quercetin, nanoparticle, cancer, cancer treatments and anticancer activity.

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1. INTRODUCTION

Quercetin (QCT) is utmost common naturally occurring polyphenolic flavonoid in our foods[1]. In the plant kingdom quercetin is commonly a secondary plant metabolite, in which it was mostly found in the form of Quercetin glycosides (molecules of quercetin conjugated with sugar residue)[2]. These are renowned flavonoids in various vegetables, fruits, and nuts, e.g. apples, onions[3], *Ginkgo Biloba,* and red wine[4].It has antioxidant, antitumor, and hepatoprotective properties[5]. Previous studies show that certain flavonoids can reduce invasion, dedifferentiation of the neoplastic cell, and cell proliferation [6]. As a result, flavonoids are thought to be helpful in the treatment of thyroid, lung, and stomach cancer[7,8]. Quercetin, a major bioactive flavonol, inhibits various cell signaling pathways and induces cytotoxicity in cancer[9]. Insilico studies stated that quercetin has potential as an anticancer agent[10]. Cancer is the world's most dangerous disease[11]. Chemotherapy, immunotherapy, radiation, and Surgery are various approaches to treating cancer worldwide[12]. The main drawbacks of standard cancer treatments include their high toxicity, bio-distribution, poor bioavailability, non-specific, and administration of an anticancer drug for normal and malignant cells[13]. As a result, novel, efficient therapies are rapidly required to reduce the significant mortality and morbidity rates[13]. Recent studies state that a diet enriched with vegetables and fruits decreases the chances of different types of cancer[14]. So the research for novel therapeutic drugs, multiple researchers has to investigate the anticancer potential of natural components (phytochemicals) found in fruits and vegetables [15]. Quercetin has been shown apoptotic action against many cancer lines including, SW-480 colon cancer[16]A431 epidermoid tumor cell[17], 4T1 murine mammary cancer[18], and leukemia HL-60[19]. In several biomedical fields, i.e., disease prevention, diagnosis, and controlled drug delivery, nanotechnology, and nanoparticulate carriers have special potential. Nano-scale components have novel physicochemical characteristics which were invented for a wide range of uses, specifically in pharmacy and cosmeceutical productions. Polymeric nanoparticles (PNPs) are colloidal particles that are submicron size drug-loaded PNPs that are based on a targeted drug delivery system and are utilized for anticancer treatments to the site-specific targets[20]. A drug delivery system based on nanotechnology can regenerative bioavailability and absorption capacity, loaded with phytochemicals, and just gathered curiosity in the pharmaceutical field[21]. Additionally, nano-delivery structures also prevent the therapeutic molecule metabolized by the enzyme and can improve the stability and circulation time[22]. Cancer cell-specific targeting moieties with nano-drugs help in efficient selective drug uptake by cancer cells in comparison with healthy cells[23]. Many nanoparticle-based drugs have been established in recent years, and some of these have been tried in clinical trials or used for sickness detection and treatment therapy[24]. These nanoparticles, which include liposomes, polymeric micelles, and inorganic nanoparticles can bring a variety of loads to target areas, which include small molecule medicines, peptides, proteins, nucleic acids, and analytic agents[25]. The stability of the drug can be increased, circulation time is extended, and tumor accumulation is enhanced, all of which lead to greater therapeutic results when a drug is entrapped into nanoparticles[26]. The use of nanoparticles for tumor diagnosis and treatment has increased significantly. In this study, we want to review the anti-cancer activities of QCT in different malignancies and any nanoformulation of QCT that can potentially inhibit which type of cancer. The effectiveness of quercetin's systemic uses and anticancer activity is further hampered by its poor solubility, dispersion, and short rotation time, which will be addressed through a review of a nanoparticle-based QCT delivery system.

2. SOURCE, ABSORPTION, AND METABOLISM OF QUERCETIN

Quercetin (QCT) was discovered as glycoside (Quercetin glucosides or, quercetin retinoid) within the edible portions of different plants[14]. QCT can be seen in a wide range of plants, including berries[27], broccoli, tea leaves, onions, and other leafy vegetables[28], although it is primarily derivative from *Sophro japonical*[29]. These fruits and vegetables are among the most important flavonoid-containing foods in the western diet (350 ppm, expressed as aglycones)[30]. Furthermore, black tea, red wine, and other fruit liquids are abundant in dietary quercetin[31]. In the USA, the typical day-to-day consumption of flavonoids such as flavones, flavanones, flavanols, anthocyanins, catechins, and biflavans, is an around 1 g/day (as expressed in the quercetin equivalents), with flavones, flavanones, as well as flavanols accounting for 160-175 mg/day depending on season[32]. Individuals who consume QCT-rich fruits and vegetables, such as onions, and tomatoes, should expect to consume 200-500 mg of quercetin per day[33]. In other various countries such as Japan and Australia, an average dietary intake minimum of 5 mg to 40 mg per day has been observed[34,35]. The bioavailability of quercetin or the quantity of pharmacological active medication captivated after oral administration can be used to assess its therapeutic effectiveness[36]. Following quercetin consumption, bacteria in the intestine can produce glycosidase and enzymatically digest glycosidase derivatives' sugar unit QCT, releasing QCT in its aglycone form[37]. QCT aglycone is absorbed additionally in the stomach[38] or small intestine[39], either through passive diffusion or through absorption mediated by the organic anion transporting polypeptide (OATP)[40]. In human plasma QCT aglycone is converted into various pharmacological active O-methyl, glucuronide, or sulfated derivatives, i.e., 31-methyl ether, QCT 3-O-D-glucuronide (Q3GA), and QCT-31-sulfate[41,42]. Foods high in QCT i.e. onions, apples, and berries, can boost plasma levels of quercetin derivatives to micromolar levels, where each is subsequently digested by the liver and other organs[43]. The major percentage of quercetin present in the blood are digested in the lungs and eradicated as CO_2 (23%-81.1%). A study found that just 3.3%-5.7% of quercetin may be found in urine and only 1.6%-4.6% in feces[44]. According to studies, colonic microflora transform quercetin in glucuronide and sulfate in derivatives into phenolic acids before excretion[45]. A study found that after eating onions, the urine contained around 21 various forms of quercetin metabolites[46]. In addition, in a recent study, less than 8% intragastric injected quercetin was identified in the kidney and liver of rats[47]. As a result, the energetic QCT molecule's circulation duration and bioavailability are restricted due to the quick metabolism of quercetin within the body. In addition, quercetin has a limited water solubility (about 1 G/mL), which limits its therapeutic efficacy. Besides, quercetin solubility in the stomach and form intestine was conveyed at 5.5 g/mL and 28.9 g/mL correspondingly. To sustain the quercetin level in blood and other tissues for an extended period of time, the water solubility must be increased and its metabolism must be delayed. QCT has been studied for its possible harmful properties, such as genotoxicity, mutagenicity, and pro-oxidant activity, the hormonal metabolism enzymes inhibition and mitochondrial toxicity, in addition to its therapeutic

characteristics[48]. Another study found that plasma models assembled from rats after administration orally of QCT were not mutagenesis, but feces and urine samples were, implying that QCT is converted into non-mutagenic derivatives after absorption[49].

2.1 Biological Functions of Quercetin

A typical flavonoid which exists in an extensive variation of foods and plants is Quercetin. It is known as 3,3′ ,4′ ,5,7-pentahydroxyfavone by the International Union of Pure and Applied Chemistry (IUPAC). (Fig. 1).

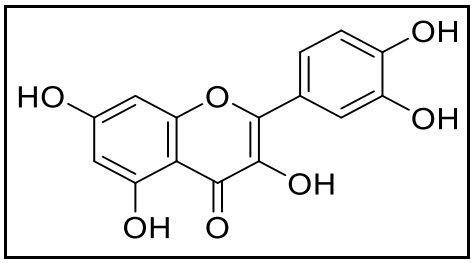

Fig. 1. Chemical structure of Quercetin

The compound is also known as 3,3′ ,4′ ,5,7-pentahydroxy-2-phenylchromen-4-one, and its distinguishing feature is the presence of five hydroxyl groups at the positions 3, 5, 7, and 3′ of the flavonoid[50]. There are numerous positive effects of quercetin on social well-being, including anti-inflammatory efficacy, cardiac safety, and antitumor activities[51]. In a study, the pharmacokinetic effects of quercetin intravenously given at dosages of 60–2000 mg/m^2 in cancer patients were examined. The researchers determined that 945 mg/m^2 was the safe level[52]. Vomiting, elevated blood pressure, nephrotoxicity, as well as a reduction in blood serum potassium, could be seen at increased levels of doses which can be detected as toxic[53]. One of the crucial cancer-related processes is angiogenesis[54]. It has been demonstrated that quercetin has antiangiogenic effects in a variety of malignancies. Additionally, smoking and other free radicals can be defended against by Quercetin[55]. Erythrocyte membranes are susceptible to irreversible damage from free radicals produced by cigarette smoke[55]. Moreover, QCT and its couple metabolites have been described to have the potency to guard erythrocytes against harm to the membrane resulting from smoking. In the event that the human body is uncovered to destructive or problematic inducements, inflammation is a form of biological reaction via which self-protective measures are implemented. Infections and inflammatory diseases are not fundamentally the same[56]. Infection typically results from a bacterial, virus-related, or fungus-related cause, but inflammatory processes also involve the body's response to self-healing[57]. One of its crucial and important properties is its potential to reduce inflammation. The efficacy of dietetic flavonoid, such as QCT, as systemic anti-inflammation agents were examined by nutritionists at Michigan State University[58]. Increased levels of C-reactive protein (CRP) have been linked to lupus, obesity, and heart disease among other medical conditions. The researchers came to the conclusion that eating certain foods reduced the amounts of variables that increase the risk of infection (CRP). QCT can drastically lower the stages of inflammation modifiers such as NO synthesis, COX-2, and CRP in human hepatocyte-derivative cell lines, according to preclinical research[59]. QCT (80 mg comparable dosing) repressed both critical and enduring inflammatory conditions in rat studies, and it also exposed important anti-arthritis capabilities against adjuvant-induced arthritis[60,61]. In a study, the effects of a two-month supplementation with the flavonoid quercetin (500 mg) were investigated in healthy amateur athletes who regularly exercised. The findings of this research led to a significant drop in CRP levels[62]. However, in pathologic settings, this drug did not significantly alter CRP levels in female rheumatoid arthritis patients (RA). The RA patients were given 500 mg/day of QCT as part of the study's ongoing 8-week period[63]. Quercetin has the ability to fight off nearly all types of bacteria, and it particularly affects the gastrointestinal, respiratory, urinary, and cutaneous systems. Its antiviral characteristics most likely account for its anti-infection and anti-replication qualities. Adenovirus, Japanese encephalitis virus, respiratory syncytial virus, and herpes simplex virus are among the viruses that typically react to flavonoids[64,65]. Due to their consistent performance, strong therapeutic potency, and minimal toxicity, a natural compound like Quercetin are now acknowledged as a significant agent for both cancer prevention and treatment[66]. Various researchers examined the efficacy of the QCT molecule on several cell lines of cancer[53].

Table.1 Therapeutic efficacy of Quercetin on different cancer[53]

Categories of cancer	Mechanism	Model	References
Gastric cancer(GC)	Interrupting uPA/uPAR function via modulation of NF-b, PKC-, ERK1/2, and AMPK has antimetastatic effects on GC cells.	In vitro	67
Breast cancer (BC)	miR-146a overexpression inhibits proliferation and invasion while increasing the levels of Bax and cleaved caspase-3.	In vitro, In vivo	68
Colorectal carcinoma (CRC)	p53 regulation is used to encourage 5-fluorouracil-induced programmed cell death in MSI CRC cells.	In-vitro	69
Oral carcinoma	inhibits cell movement, invasion, and viability via modifying the miR-16/HOXA10 axis.	In vitro	70
Liver cancer	Has hepatoprotective action vs bile duct ligation resulted in liver injury through a decrease in Rac1 and NADPH oxidase1 appearance	In-vivo	71
Prostate cancer (PCa)	Reduces cell survival and inhibits anti-apoptotic mechanisms to repress PCa.	In vivo	72

Thyroid carcinoma	Reduces cell proliferation and helped apoptosis by caspase initiation and downregulating Hsp90 appearance	In vitro	[73]
Hematological cancer	Increased the efficacy of TRAIL-inducing apoptosis in KG-1 cells and increases the appearance of DR genes, particularly DR4 and DR5, while decreasing the appearance of p65 and the IAPs c-IAP1, c-IAP2, and XIAP.	In-vitro	[74]
Lung carcinoma	A549 non-small cell lung tumor cells' cytoskeleton is affected, which has an antiproliferative and antimetastatic effect.	In vitro	[75]
Pancreatic cancer	promoted TRAIL-induced apoptosis via cFLIP turnover mediated by JNK activation.	In-vitro	[76]

2.2 Pharmacological Effects Quercetin

Numerous cancer types have benefited from quercetin, which has no negative efficacy on healthy cells (Fig. 2). QCT showed in several studies to conquer tumor cells both in vitro and in vivo by various mechanisms, such as cell cycle arrest, cell death, and inhibits angiogenesis and metastasis. In addition, quercetin inhibits P-glycoprotein (P-gp) and multidrug resistance-related proteins (MRPs), lowering intracellular GSH levels, and reducing tumor multidrug resistance (MDR). Additionally, it can alter the expression of TGF- and IL-10, CD8+T and monitoring T cells (Tregs), and other immune cells and cytokines in a tumor microenvironment, enhancing anticancer immune responses[24].

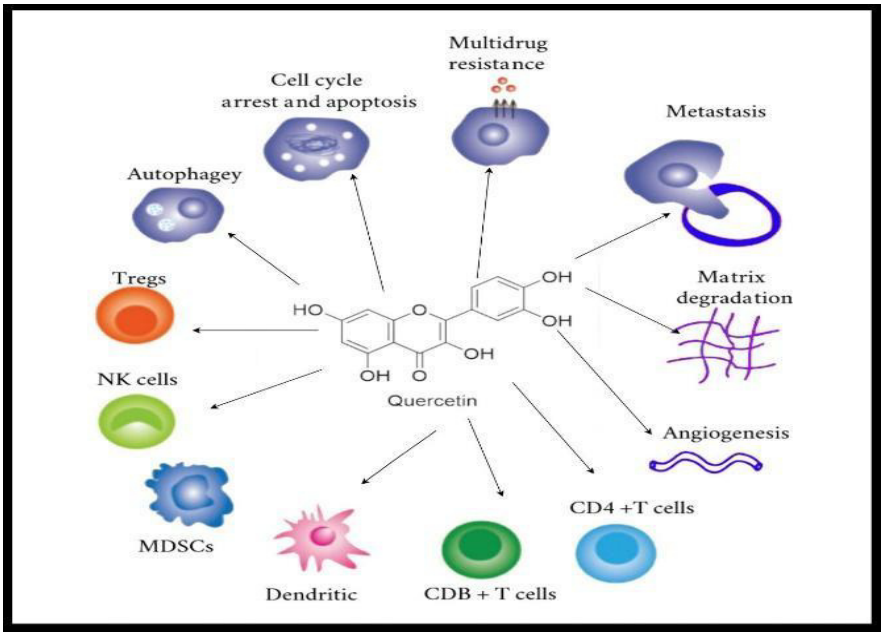

Fig. 2 Pharmacological events of Quercetin in a tumor microenvironment[24]

2.3 Causing Cell-Cycle Arrest and Apoptosis in Tumor Cell

Various research showed, Quercetin can end the progression of lung, breast, pancreatic, colorectal, ovarian, and prostate cancer. G2/M cell cycle arrest and downregulation of cycle-related proteins (cyclinB1) were both seen after Quercetin administration. MiR-34a silencing reduced the sensitivity to quercetin and SIRT1 overexpression, and the microRNA test revealed that miR-34a and p53 upregulating were seen in HepG2 cells (p53 wild) somewhat than Huh7 cells (p53 mutant). This revealed that the p53/miR-34a/signal feedback loop is a possible pathway via which quercetin can influence the cancer cell cycle. The majority of cancer types have elevated levels of cyclin-dependent kinase 6 (CDk6), which is important for the G1-to-S phase and metabolic changes. In MCF-7 and A549 cells, quercetin demonstrated a significant binding empathy for CDK6 and downregulated its appearance, which decreased cell survival and colony formation. In tumor cells, quercetin can operate as a GLUT-1 inhibition to decrease glucose metabolism and pause the cell cycle at various stages. In Nalm6, KB, and MCF-7 cells, quercetin also resulted in the depolarizing efficacy of mitochondrial membrane potency and induced S phase arrest without altering intracellular ROS levels. Additionally, systemic treatment of quercetin controlled a notable reduction in tumor volume and a rise in a lifetime in mice with tumors. By inhibiting proliferative and survival signals such c-Fos, c-Jun, Raf-1, N-Ras, and p-EGFR, quercetin reduced the number of prostate PC-3 cells that proliferated. Quercetin reduced PA-1 cells and caused their programmed cell death, which was demonstrated by AO/EtBr and DAPI labeling and DNA disintegration assay in the context of metastatic ovarian cancer. The intrinsic apoptosis-related molecules were also changed by quercetin therapy, with pro-apoptotic caspase 3&9, Bid, Bad, Bax, and cytochrome C increasing and anti-apoptotic Bcl-2 and Bal-xL decreasing[24].

2.4 Encouragement of Autophagy

Lysosomes have a complex role in tumor development and therapeutic response, and autophagy is a procedure that breaks down cytoplasmic components in these organelles. QCT is a well-known persuader of autophagy in addition to inhibiting tumorous cell production by causing cell cycle arrest and apoptosis. It is not identified whether the inhibition efficacy of QCT on a tumor cell is functionally attributed to autophagy. Therefore, it was examined to check if quercetin

could prevent hepatocellular carcinoma (HCC) via promoting autophagy. Quercetin boosted autophagosomes and autolysosomes in HCC by activating the MAPK path while decreasing the AKT/mTOR pathway, according to in-vitro studies. According to in-vivo findings, QCT inhibited tumor growth via increasing apoptosis and autophagy, whereas HCQ, an inhibitor of autophagosomes, greatly reduced the anticancer effects of quercetin. Additionally, the autophagy inhibitor chloroquine prevented quercetin from enhancing TRAIL-inducing cell death. Nevertheless, autophagy is a double-edged sword that has opposing positive and negative consequences in malignancies. By blocking the PI3K/AKT/mTOR and STAT3 pathways, quercetin enlarged autophagic flux and contributed to the endurance of primary expression lymphoma cells. Therefore, quercetin-induced cell death in primary effusion lymphoma may be further improved by autophagy suppression with pharmacological or genetic inhibitors[24].

2.5 Contrary Multidrug and Radio Therapeutic Resistance

The primary factor in the failure of tumor therapy is multidrug resistance (MDR), which is brought on by cancer's defense mechanisms. MDR may result from the variability of mechanisms, which include an increase in the restoration of drug-inducing DNA impairment, a decrease in drug uptake, ATP-binding cassette transporters like ABCB1 (also known as P-glycoprotein or P-gp), which deliver chemo-therapeutics, the activity of detoxifying systems (like glutathione/Glutathione-S transferases), carcinoma stem cells that resist predictable therapy, and modifications to aspects that control cell cycle regulation. Several medicines which can reverse MDR have been discovered, however, the majority of them have been unsuccessful because they have severe side effects or quickly induce MDR. To inverse MDR without noticeable systemic harm, QCT has been shown to prevent resistant tumor cells or to desensitize them to standard chemotherapeutics. More significantly, it has been shown that QCT increases the sensitivity of tumor cells to chemotherapeutic agents in a non-toxic dose. Gemcitabine, for instance, can block ribonucleotide reductase, the cell cycle at the G1/S phase conversion, and directly interfere with DNA synthesis. The ineffectiveness of gemcitabine as a treatment, however, may be caused by inadequate drug absorption and the initiation of an alternate DNA restoration path. Through the PI3K/AKT/mTOR path, quercetin might successfully reduce the appearance of the receptor for progressive glycation end products. In GEM resilient pancreatic PACA-2 cells, this promoted cell cycle arrest and chemosensitivity. Researchers discovered that quercetin significantly inhibited the metabolism of D-glutamine and D-glutamate. It also down-regulated the glutamine transporter SLC1A5, which in turn inhibited the ATP-driven transport activity of P-glycoprotein (P-gp) and increased the cytotoxicity of doxorubicin to P-gp SW620/Ad300 cells. QCT has the ability to alter intracellular ROS levels, cause a significant drop in GSH, raise the sub-G1 population, and trigger death in HL60/VINC cells that have P-gp overexpression as well as HL60/MX2 cells with mutant and missing isoforms of topoisomerase II. Quercetin strongly suppressed the nuclear translocation of YB-1 and destroyed carcinoma stem cells in addition to downregulating P-gps to convert MDR in BC when combined with doxorubicin, paclitaxel, or vincristine. According to these findings, quercetin may be a possible MDR reverse modulator to enhance therapeutic effectiveness. By ionizing radiation reacting with oxygen during radiation therapy, peroxide-free radicals are produced. These radicals have the ability to kill tumor cells by destroying the intracellular DNA macromolecules. Although radiation has made progress against many tumor forms, radio-resistance still poses a significant challenge in cases of pancreatic cancer and glioblastoma. Regardless of initial sensitivity of the tumor to radiation therapy, tumor relapse worsens radio-resistance in the majority of tumor types. Therefore, the creation of radiosensitizers is urgently required to increase the effectiveness of radiotherapy. The crucial component in DNA damage response, ATM kinase, can be inhibited by quercetin, which increases tumor photosensitivity both in-vitro and in-vivo[24].

2.6 Angiogenesis Inhibition

When tumors are larger than a particular size, the development of vascularization is crucial for waste removal, oxygenation, and nutrition delivery. Matrix metalloproteinase (MMP) and vascular endothelial growth factor (VEGF) are significant pro-angiogenic mediators in this process. By reducing the appearance of VEGFA, MMP2 and MMP9, quercetin was able to prevent HUVEC tube development in-vitro that was caused by the glioblastoma cell line U251. 38 An endogenous antiangiogenic substance called thrombospondin-1 (TSP-1) can stop tumor growth and angiogenesis. Researchers studied the functions of TSP-1 and QCT in the prostate in vitro and in vivo to confirm the link between QCT-induced anti-angiogenesis and TSP-1 overexpression. The findings showed that QCT boosted TSP-1 appearance antagonizing angiogenesis in a dose-dependent way in both vitro and vivo, postponing the development of human prostate melanoma growth of a PC-3 cell xenograft tumor[24].

2.7 Minimizing Invasion and Metastasis

More than 90% of all cancer-related morbidity and mortality result from metastasis, which involves primary tumor development, angiogenesis, invasion, and spread. An epithelial-to-mesenchymal transition (EMT) causes the primary cancer cells to lose their adhesion and motility throughout the metastasis process, while extracellular matrix deprivation by matrix metalloproteinase enables the primary tumor cells to move into the lymph and blood. In oral squamous carcinoma cell lines, quercetin enlarged the appearance of the epithelial proteins E-cadherin and caludin-1 while reducing the appearance of mesenchymal proteins like fibronectin, vimentin, and -SMA. This suggests that quercetin has the ability to inhibit metastasis by inhibiting EMT and matrix metalloproteinases. Regarding colon cancer, quercetin also controlled MMP and its tissue inhibitor, as well as EMT indicators like E-, N-cadherin, -catenin, and Snail, which reduced the lung metastasis of CT26 cells in-vivo. Researchers discovered that quercetin reduced the amounts of the proteins E-cadherin and Twist by downregulating S100A7, p-Src, and p-STAT3, consequently inhibiting metastasis via the Src/Stat3/S100A7 pathway. Gelatinases like MMP-2 and 9 can dissolve the extracellular matrix and allow migratory tumor cells to proliferate[24].

2.8 Intonation of Immune Responses

In addition to connecting the cytoplasmic domains of E-cadherin and -catenin, -catenin participates in the Wnt signaling track, which can accelerate cancer growth by controlling the tumor-immune cycle in the majority of nodes,

includes dendritic cells, T cells, and tumor cells. By increasing the ratio of CD8+ T cells to Tregs and the effector capabilities of CD8+ T and CD4+ T cells, blocking Wnt/-catenin may improve clinical results. In 4T1, SW480, or HEK293 cells transfected with the -catenin gene, -catenin and its downstream components were found to be transcriptionally inactive by quercetin. Additionally, second-wave nanoparticle transport into tumor nests was improved by systemic treatment of quercetin phosphate, which resulted in a considerable downregulation of Wnt16 expression, -SMA+ fibroblast, and collagen. According to research, QCT may alter CD4+T and CD8+T cell permeation and activity in a tumor micro-environment to enhance anticancer immunotherapy. An earlier study showed that inhibiting HSPs could make tumor cells more vulnerable to NK cell-mediated cytotoxicity. In K562, SNU1, and SNU-C4 cells, quercetin dramatically increased the induction of several NKG2D ligands and the inhibition of HSPs via the NF-B and PI3K pathway, increasing their vulnerability to NK-92 cells. This may offer a tempting method to enhance NK cell-based tumor immunotherapy through quercetin-mediated induction of NKG2D and reduction of HSP70 expression. Nevertheless, research revealed that quercetin might lessen production of MHC II and costimulatory molecules as well as decrease LPS-induced DC activation and release of proinflammatory components. 58 Therefore, while using quercetin for tumor therapy, the immunosuppression that it causes in a tumor microenvironment should be taken into account[24].

Table.2 Pharmacological activities of quercetin in tumors[24]

Pharmacological activities	Mechanism of action	Tumor type	References
Cell cycle arrest	Upregulation of MiR-34a and p53	HepG2 cells	77
	Unites and down-regulating CDK6	MCF-7 and A549 cell	78
	Block GLUT1	Hepatic cancer	79
Inducing apoptosis	Depolarizing mitochondrial membrane	Nalm6, KB cells	80,81
	Suppress survival signaling and proliferative signaling	Prostate PC-3 cells	82
Promotion of autophagy	AKT/mTOR pathway inhibition and MAPK pathway activation	Hepatocellular cancer	83
Resisting reverse multidrug	Drug sensitivity and MDR cells are inhibited	HL60/VCR, K562/ADR	84
	Stem cell carcinoma elimination and nuclear translocation inhibition	Breast carcinoma	85
Increasing radiosensitivity	ATM kinase inhibition	MCF-7 cells	86
	CSC-makers reduction	Colon carcinoma in human	87
Angiogenesis inhibition	T cell pathway activation of the factor of VEGFR2 and its medication	Mice	88
	TSP-1 expression increases by antagonized angiogenesis	Human prostate carcinoma PC-3 cell	89
Metastasis reduction	Downregulating Matrix and EMT metalloproteinase	Oral squamous cancer cell	90
Immune response modulation	Enhancing survival and T-cell suppressing factors	K562 cells	91

2.9 Benefits and Drawbacks of Quercetin

Poor water solubility and instability in the physiological medium are the main drawbacks of employing quercetin therapeutically, which limits the usage of this flavonoid to oral delivery. Additionally, these two chemicals cannot be dissolved in a single benign solvent. The number of newly created medicinal compounds with poor water solubility and poor availability has increased during the past ten years. The most difficult tasks in drug development are to increase these innovative medicines' oral bioavailability and solubility. Giving pigs 0.4 to 5 mg of quercetin at various intervals and using HPLC to evaluate blood samples for quercetin allowed researchers to study the bio-availability of the flavonol following arterial and oral application. The findings suggested that flavonol QCT is mostly riveted in the form of glucuronides from the small intestine. The solid dispersal of QCT with polyvinylpyrrolidone kollidon® 25 (PVP K25) advises an intriguing way to boost QCT solubility, antioxidant activity, and subsequently bioavailability by a variety of methods. This was made possible by the rise in quercetin solubility brought on by the formation of the solid dispersion. It was tested whether the instability of quercetin in cell culture will affect in vitro studies[92].

3. EFFECT OF QUERCETIN ON CANCERS

Although various significant advancements in cancer treatment, cancer is still considered a life-threatening fatal disease in humans[93]. Though chemotherapy is the standard cancer treatment, it is proven that its use is limited across most cancers due to various grounds including resistance to chemotherapy and adversative effects. Natural compounds i.e, QCT is recognized as an effective agent for the prevention as well as heal cancer due to their expected presentation, increased therapeutic potency, and less toxic effect. It seems that QCT is a significant anti-proliferative and anti-cancer agent and a stimulator for apoptosis[94]. QCT showed it can inhibit the spread of different cancers i.e, gastric cancer (GC)[95], BC[96], colorectal cancer (CRC)[97], oral cancer[98], liver cancer[99], prostate cancer[100], thyroid cancer[101], leukemia[102], pancreatic cancer[103], and lung cancer[104]. The two leading major causes of cancer-related death worldwide are quercetin and gastrointestinal malignancies. By lowering the urokinase production of the activator of the plasminogen (uPA) and the receptor of plasminogen activator (uPAR), two proteins that

are intimately linked to GC metastasis, QCT significantly reduced GC cell movement, viability, and invasion. By interfering with the regulation of the uPA/uPAR arrangements, AMPK, NF, ERK/2, and PKC- modulation, quercetin may be useful as an anti-metastatic medication for GC metastases cells. Quercetin has been recently combined with novel phenylboronic acid (PBA) loaded ZnO nanoparticles (PBA-ZnO-Q) design. It has been observed that PBAZnO-Q can be effective in inhibiting cancer development. The incorporation of gold nanoparticles (AuNPs) and poly lactide-co-glycolide nanoparticles into quercetin effectively reduced cell propagation, formation of colony, movement, and migration of cells of live cancer. Research studies showed the concept contained QCT enhanced caspase-mediated cell death by increasing caspase-3, and caspase-9, and causing further release of Cytochrome-C release (cyto-c). QCT nanoparticles also inhibit the signaling pathway of Akt/ERK1/2, reverse telomerase transcriptase (hTERT) through imminent AP-2β h TERT, and cyclo-oxygenase 2 (COX-2) via inactivating the K B/cox-2. The treatment of HSC-6and SSC-9 cell lines, which are derived from oral cancer, with 50μM of QCT, showed condensed viability of cell, migration, and incursion by attenuating the excessive MMP-9 and MMP-2 in the cells. Moreover, QCT therapy reduced the appearance of miR-16, which improved in cell lines and tissues of oral cancer [105].

4. QUERCETIN IN GASTROINTESTINAL CANCERS

One-fourth and 9% of all carcinoma fatalities globally are caused by gastrointestinal malignancies, which are also the most common types of cancer, have an increasing prevalence and place a significant impact on society's health. Quercetin severely condensed the endurance, relocation, and incursion of GC cells by down-regulation of the expression of the proteins urokinase plasminogen activator (uPA) and urokinase plasminogen activator receptor (uPAR), which are closely linked to GC metastasis. By interfering with the control of the uPA/uPAR systems, AMPK, NF-, ERK1/2, and PKC-, Quercetin may be employed as an anti-metastatic drug against GC metastases cells. Recently, a brand-new PBA-ZnO-Q construct was used to deliver Quercetin. It was found that PBAZnO-Q can effectively slow down tumor growth in vivo. Up to 40% of CRC patients have a confirmed mutation in the carcinogenic gene KRAS, which makes chemotherapy less effective and worsens the prognosis for CRC patients. On the basis of MTT assay and colony formation methodologies, the efficacy of QCT on CRC cells expressing the KRAS mutant gene showed that quercetin might reduce cell capability and enhance programmed cell death in tumor cells. In KRAS-mutant cells, the c-Jun N-terminal kinase (JNK) pathway is activated and the AKT pathway is suppressed, which can be the underlying mechanisms. The growth, cluster formation, development, and relocation of liver tumor cells were all considerably inhibited by the combination of gold nanoparticles (AuNPs) and QCT in polylactide-co-glycolide nanoparticles. Statistics show that the construct comprising QCT improved apoptosis by increasing caspase-3, and caspase-9, activating additional release of cytochrome c (cyto-c). The signaling pathway of Akt/ERK1/2, telomerase reverse transcriptase (hTERT) via imminent AP-2/hTERT, and cyclooxygenase 2 (COX-2) through inactivated NF-B/COX-2 were likewise suppressed by QCT nanoparticle. Treatment of oral cancer cell lines HSC-6 and SCC-9 with 50 M of quercetin resulted in decreased cell viability, migration, and invasion by reducing the overproduction of MMP-9 and MMP-2 in those cells. Additionally, miR-16 appearance was reduced by QCT therapy, which was elevated in oral cancer cell lines and tissues.

5. QUERCETIN IN HEMATOLOGICAL CANCERS

Hematological carcinoma is a disease of irregular precursor and stem cells that developed from epigenetic and genomic changes which disrupt cell variation, production, and self-renewal [106]. Mostly cancers having, the bone marrow, peripheral blood, lymphatic nodes, and the spleen, which is a tributary lymphoid organ, are the most frequent positions for cancer localization[107]. It is already proved that quercetin is having various positive effects on hematological cancer. In a study, it showed that the production of MM-1R, ARP-1, and RPMI8826 various melanoma cell lines including apoptosis along with cell cycle arrest are done by inhibition of quercetin in the G2 or M phase. Overall, the QCT combined with dexamethasone can inhibit tumor growth and enhance cystosis[108]. In another study, it was reported that several cancer cell productions by expression of down-regulation of IQGAP1 and ERK activation is inhibited by quercetin. It was observed that QCT inhibits STAT3 and pathways of PI3K/AKT/mTOR in primary effusion lymphoma (PEL) cells, results in low production of prosurvival cellular proteins expressions such as cMyc, cyclin D1, and c-FLIP[109]. Moreover, QCT reduced the IL-6 and IL-10 release, causing PEL cell death. Quercetin also improved prosurvival autophagy, which can enhance the toxic effects of bortezomib, which can inhibit protease[110]. Another study observed that QCT induces cytoprotective autophagy and intrinsic apoptosis and that can inhibit autophagy with chloroquine enhances the apoptotic capacity of QCT in T cell of human acute lymphocytic leukemia, Jurkat clones[111]. Previous studies have shown that apoptosis related to TNF can induce ligand (TRAIL) as a biological cytokine that plays a crucial part in initiating programmed cell death by binding to the antagonist receptors, but its application has been limited due to particular cancers[112,113]. Thus, a team of researchers looked into the interaction between QCT and TRAIL in KG-1 cells in myeloid leukemia in humans and discovered that QCT can operate as a sensitizing element when paired with TRAIL, boosting the TRAIL-induced apoptotic induction in KG-1 cells. Quantitative Real-time PCR findings show that quercetin treatment increased the death receptor (DR) expression genes which includes DR4 and DR5, while QCT can reduce the anti-apoptotic protein expression of p65 e.g., c-IA12 and XIAP[114].

6. QUERCETIN IN GYNECOLOGICAL CANCERS

Gynecological tumor is the fourth utmost popular kind of melanoma in women, which typically afflicts the reproductive organs and tissues such as the cervix, vulva-vagina, uterus, as well as ovaries[115,116,117]. Numerous researches have been executed to demonstrate the efficiency of QCT in treatment of gynecological cancers. For example, a study discovered that quercetin inhibits cervical cancer cell invasion by decreasing the appearance of UBE2S, which is significantly articulated in malignant tumors and leads to cell death by transition of epithelial-mesenchymal signaling[118].

7. QUERCETIN IN OVARIAN CANCER

Among gynecologic malignancies, ovarian melanoma is one of the most common forms in females and causes the most fatalities. Some of the risk factors for this malignancy include age, family history, late menopause, and null parity, while

pregnancy and breastfeeding lower the probability of incidence. Ovarian cancer cells primarily spread within the peritoneal cavity and are only mildly invasive, which distinguishes its biology from that of hematogenous metastasizing tumors. However, ovarian cancer is a fatal disease because the quickly growing tumors compress visceral organs and are only momentarily chemo-sensitive. There are two types of ovarian cancer: type I (low grade) and type II (high-grade serous and carcinosarcoma). Some researchers examined the efficacy of drug combinations that worked in synergy in the effort to create cancer chemotherapeutic medications. The impact of graphene oxide polyvinylpyrrolidone- quercetin-gefitinib (GO-PVP-QSR-GEF) on ovarian cancer cells has been investigated (PA-1). They demonstrated that quercetin may enhance the anticancer effects of gefitinib in PA-1 cells, an ovarian cancer-originating cell line. Furthermore, it showed that quercetin reduced the viability of PA-1 cells in a dose- and time-dependent manner. Doxorubicin is a chemotherapy drug used to treat cancers of the ovary, thyroid, breast, and lung, although its usage is restricted due to serious adverse effects such as cardiotoxicity. Scientists used doxorubicin and quercetin as a chemosensitizer to get around this restriction. A study in an ovarian cancer xenograft model found quercetin can lessen the cardiotoxicity caused by doxorubicin. In order to provide an experimental basis for the therapeutic application of quercetin in the treatment of ovarian cancer, its effects on the growth and apoptosis of the ovarian cancer cell line SKOV-3 were examined. The ability of ovarian cancer SKOV-3 cells to proliferate was time- and dose-dependently inhibited by quercetin. Quercetin could also increase apoptosis in SKOV-3 cells and reduce the expression of the surviving protein. According to a flow cytometry analysis, quercetin caused SKOV-3 cells to cycle arrest in the G0/G1 phase and significantly fewer cells to be in the G2/M phase; in addition, the percentage of apoptosis was found to increase as a result of quercetin therapy. The ER stress pathway, which is the cause of cell death and apoptosis, can be stimulated by quercetin. Quercetin directly promoted apoptosis by increasing levels of GRP78, CHOP, which are both indicators of ER stress, and cleaved caspase 4, which has been identified as a key player in ER-driven apoptosis in ovarian cancer cell lines and primary ovarian cancer cells. Some scientists have concentrated on the p-STAT3/Bcl-2 axis, which has been shown to be able to influence caspase-cleavage to inhibit apoptosis, in order to investigate the mechanism of quercetin-induced ER stress and apoptosis. The results showed that activation of the p-STAT3/Bcl-2 axis results in quercetin-induced ER stress, which is linked to the mitochondrial apoptosis pathway. Unexpectedly, quercetin-induced apoptosis could not be reversed by suppressing ER stress.

Potentially therapeutic compounds suffer from certain limitations in their effectiveness, which can be improved by delivery methods based on nanoformulations. Quercetin has been delivered using a variety of methods, including microemulsions, nanoparticles, liposomes, and solid lipid nanoparticles, for a variety of purposes, including the treatment of aging and neurodegenerative diseases. Drugs that are hydrophobic when not encapsulated into nanoparticles become totally water-soluble and injectable. Clinical practice presently makes use of anticancer medications that are given by biodegradable polymeric nanoparticles, which are excellent candidates for anticancer drug delivery systems. The simple production, amphiphilicity, and biodegradability of poly(3-caprolactone)/poly(ethylene glycol) (PCL/PEG) block copolymers point to potential applications in drug administration systems. Utilizing PCL/PEG nanoparticles to encapsulate medications and improve the hydrophobic medications' water solubility has gained attention recently. On ovarian cell proliferation and colony formation, the impact of quercetin nanoformulation was studied. Quercetin was placed in biodegradable monomethoxy poly (ethylene glycol)-poly(caprolactone) (MPEG-PCL) micelles in an effort to provide proof-of-concept results for the treatment of ovarian cancer[53].

8. QUERCETIN IN VARIOUS CANCERS

Quercetin decreased the expression of antagonizing androgen receptor signaling AR-V7 and hnRNPA1 and enhanced the sensitivity of the enzalutamide-resistant cells of prostate cancer to the drug enzalutamide therapy, according to a study.[119]. Recently, it was demonstrated that QCT can decrease the possibility of A375SM malignance cells by provoking apoptosis in the context of melanoma treatment.[120]. However, in another report, quercetin is a strong anti-cancer drug to treat brain malignancies, such as glioblastoma multiforme. Quercetin substantially reduced cell development and increased programmed cell death in the human cell line of papillary cancer (B-CPAP) via caspase activation[121]. It also triggered cell death by Hsp90 expression, which can be related to a decrease in activity of proteasomes like chymotrypsin. The gin thyroid cancer cells[122]. Another study, in non-small cells of A549 lung cancer, investigated the outcome of QCT on major cytoskeletal components for example microfilaments, microtubules, and processes driven by cytoskeleton. The researchers showed that QCT triggered apoptosis through the BCL2/BAX regulation, along with cell death and mitotic upheaval, and inhibited the migration of those cells[123]. The disassembly effect of QCT on filaments of vimentin, microtubules and microfilaments as well as its suppressing outcome on N-cadherin and expression of vimentin, can reflect the reason of cells of A549 migrate less in response to QCT therapy[124,125]. It similarly alleged that the probable mechanism under QCT-inducive mitotic failure comprises the disorder of mitotic microtubules which can cause monopolar spindle formation and therefore the breakdown of cytokinesis[126]. It was also described that QCT may cause actin filaments disintegration, which results in cytokinesis failure. Prostate cancer (Pca) cells got treatment for 72 h with 40 μ M QCT which lowered the cell viability and enhanced the apoptosis followed by cell death was observed with comparison to untreated cells. Additionally, quercetin has a positive outcome on mitochondrial integrity and dependent on the oxidative condition of the cells, which maybe occur as an antioxidant or a pro-oxidant to balance responsive oxygen species (ROS) generation in PCa cells. Based on research, QCT inhibited PCa by improving survival of cell, blocking the anti-apoptotic paths, and participating in signaling pathways of MAPK, Akt, and NF-B in various cell lines of PCa with or without p53 mutations. This study showed that quercetin, through the control of ROS, Akt, and NF-B paths, has an anti-cancer efficacy and might be used as a chemotherapeutic drug to improve medical outcomes in PCa patients [127]. In another survey, the expression of miRNA in AsPC1 (cell line of pancreatic cancer) cells pre and post-QCT therapy and showed that quercetin can increase the miR-200b-3p appearance. This miRNA regulates whether a Pancreatic Ductal Adenocarcinoma (PDA) cell divides symmetrically or asymmetrically by modulating Notch signaling[128]. Symmetric cell division produces two identical daughter cells and guide to exponential development of cancer but asymmetrical division

of cell made two diverse daughter cells and is offered by stem cells of cancer (CSCs) for hemostasis[129,130,131]. Moreover, miR-200b was shown to be strongly expressed in normal pancreatic cells while being down – regulated in PD cells. The illustration level of miR-200 was regulated after quercetin treatment in PDA cells[132], resulting in control to cell fate and suppression of initiation of cancer proliferation, and invasion[133].

Table.3-Effects of Quercetin on various cancer types[134]

Organ	Cancer cell line	Model system	Mechanism	References
Breast	MCF-7 cells of breast carcinoma	In-vitro	Antiproliferative efficacy induction and apoptosis by increasing Bcl-2	135
	4T1 BC cell	In-vitro	Antiproliferative efficacy induction by regulation signaling pathway Wnt/β -catenin.	136
	MCF-7 and MDA-MB-231 breast carcinoma cells	In vitro	Induction apoptosis by suppressing Twist by p38MAPK pathway	137
Pancreas	MIA PaCa-2 and BxPC-3 carcinoma cells of the pancreas	In vitro and in vivo	Tumor growth inhibition.	138
Colon	SW480 colon carcinoma cells	In vitro	Growth inhibition by cyclin D (1) inhibition	139
	HT-29 and HCT116 colon carcinoma cells	In vitro	Inducing apoptosis by AMPK signal pathway	140
Prostate	PC-3 prostate carcinoma cells	In vitro	Prevent metastasis via transcriptional repressor suppression.	141
Liver	HepG2 hepatic cancer cells	In vitro	Induction growth inhibition by cell cycle arrest at G1 phase	142
Ovary	SKOV3 ovarian carcinoma cells	In vitro	Cell growth inhibition by reducing cyclin D1 expression	143
Lung	Cancer cell of A549 lung	In vitro	QCT-3-glucuronide and QCT-3'-sulphate enriched plasma induced cell growth	144

9. QUERCETIN NANOPARTICLES IN VARIOUS CANCERS

Quercetin inhibits the development and genesis of various tumor cell lines[145]. Due to poor solubility in water and low absorption of quercetin, various *In vivo* and *In vitro* studies have been performed on nanoparticles to enhance physiochemical qualities[146]. PEG, PLA, polylactic co-glycolic acid (PLGA) are the most commonly used nanoparticles with quercetin. It has been shown that PEG nanoparticles can lengthen the rotational period of QCT in the blood-circulation and raise the stability and solubility[147]. A study showed that PEG-derived phosphatidylethanolamine Nano micelles increase the anticancer activity of quercetin and the nanoparticles show more effect than pure quercetin in A549 lung cancer[148]. In another study, it was found that de-PEGylate nanoparticles based on triphenylphosphine- QCT were more efficient therapeutic agents in A549, MCf-7, and HepG2 cancer cells than pure quercetin[149]. A study discovered that Quercetin-loaded PEG nanoparticles have anticancer activity and the result showed that orally administered quercetin-loaded nanosized emulsion of PEG showed cytotoxic efficacy against B16F10 melanoma cells[150]. Moreover, the angiogenesis of ovarian cancer was inhibited by QCT-loaded PEG-liposomal nanoparticles[151]. A study shows that for antitumor drug delivery 1,2-stearoyl-sn-glycerol-3-phosphoethanolamine-N-methoxy (polyethylene glycol) (DSPE-MPEG) is an effective nanocarrier[152]. Another study showed that quercetin-loaded PLGA nanoparticles fully protected the liver's mitochondrial membrane against cancers caused by diethyl nitrosamine[153]. Nanoparticles of PLGA loaded with QCT and tamoxifen (TMX) inhibit tumor growth in BC cells of MCF-7 in oral administration[154]. Quercetin-loaded monomethoxy poly (ethylene glycol)-poly-(ε -caprolactone) (MPEG-PCL) nanoparticles suppressed the development of tumors in the ovary by mitochondrial apoptotic mechanism[155]. Similarly, the antineoplastic activity of GeluPearl, Quercetin-loaded Precirol ATO 5 lipid (GPSLN) nanoparticles compared to B16F10 melanoma cells was observed[156]. PVP was used to study the anticancer effect of QCT on BC[157]. Gold- PLA nanoparticles were also employed to enhance the efficacy of quercetin[158]. The *in vivo* studies have explained the probable possibility of QCT nanoparticles to treat cancer[159].

9.1 Quercetin Nanoformulations for Tumor Treatment

The features of quercetin, such as limited water solubility, inadequate bioavailability, instability to oxidants, and intense biotransformation confinement, pose a challenge for its in vivo application despite a wide variety of anticancer actions. According to several research, quercetin is rapidly digested and eliminated through the urine, causing a relatively little buildup in sick areas. So, the subsequent difficulty has been to efficiently and selective deliver QCT to a tumor with minimal off-target consequences. To increase solubility and permeability of quercetin, one method is to chemically modify it in order to create semi-synthetic derivatives. In contrast, nanoparticles have shown powerful benefits in the delivery of hydrophobic medications like QCT, with high encapsulating efficacy, extended flow time, tumor-specific biodistribution, controlled release, and increased therapeutical effect. As a result, various tailored nanoparticle platforms were created, and quercetin delivery for anticancer therapy showed substantial advancements. Since then, several nanoparticles have been created to contain QCT and increase its anti-tumor effectiveness, including liposomes, polymeric micelles, PLGA nanoparticles, metal-organic frameworks, and inorganic nanoparticles[24].

9.2 Liposomes

Mycophenolic acid (MPA) may be an effective cancer treatment because it has the ability to specifically prevent the enzyme inosine monophosphate dehydrogenase (IMPDH), which is overexpressed in tumor cells. Due to MPA's poor

pharmacokinetic behavior and first pass metabolism into inactivation by P450 and UDP-glucuronosyltransferase, the application of MPA was completely halted. Therefore, in order to slow down the metabolism of mycophenolic acid (MPA) and increase its solubility in water, researchers mixed MPA with quercetin utilizing liposomal nanoparticles (LNPs). Due to reduced cellular absorption of free MPA and quercetin via saturable hNTs for MPA and OATP1B3 for a quercetin transporter and P-gp overexpression, these compounds showed a lower inhibitory impact[160]. In vivo studies demonstrated that the synergistic action of MPA and quercetin, which served as both a P450 inhibitor and an antitumor agent, reduced the tumor burden through the sustained pharmacokinetic patterns of the drugs, greater bioavailability, enhanced permeation and retention (EPR) effect, and higher tumor accumulation of LNPs. Emulsion-evaporation and a low-temperature curing technique were used to create PEG-DSPE coated liposomal quercetin. The findings revealed that PEG-DSPE-quercetin nanoparticles showed concentration-dependent cytotoxicity to C6 glioma cells and that p53 was upregulated by ROS buildup, which was consistent with elevated cytochrome C and caspase 3 levels. By combining biotin with liposomal quercetin (DOX/QUE BPL), which increased doxorubicin accumulation and displayed the best level of cytotoxicity in MCF-7/ADR cells by downregulating P-gp without affecting ATP synthesis, it was possible to improve the targeting ability[24].

9.3 Polymeric Micelles

Most promising nanocarriers for drug delivery are polymeric micelles, which are made up of hydrophilic and hydrophobic building blocks. It has been suggested that trapping hydrophobic anticancer medications inside PEG-poly (lactide) micelles (PEG-PLA) may increase their absorption effectiveness and cytotoxicity in tumor cells while also extending their circulation time and accumulation in tumor areas. PEG-PLA micelles (PEG-PLA-Qu) were employed to encapsulate quercetin and boost its anticancer effectiveness in order to get around its therapeutic limitations. PEG-PLA-Qu, which contains more quercetin intracellularly than free quercetin, may trigger apoptosis in MDA-MB-231 cells. Significantly more inhibitory effects and apoptotic cells have been seen in a group treated with PEG-PLA-Qu than in a group given free quercetin at the same dosage in a xenograft model of BC. It's likely that the mixed micelles of acryloyl-PEG-PCL and folate-PEG-polycarprolactone (PEG-PCL) were adjusted to include quercetin by a nanoprecipitation technique. With high entrapment efficiencies (83.7 percent for gefitinib and 82.3% for quercetin), researchers created a gefitinib and quercetin co-delivery system of PEG-PLGA nanoparticles that dramatically inhibited PC-9 tumor development. Against A549, HepG2, BGC-823, MCF-7, and HCT116 cells, starch and F127 nanoparticles loaded with quercetin demonstrated increased inhibitory activities compared to the free drug; specifically, for A549 cells, the inhibitory efficacies reached were 55.16 percent and 64.06 percent, respectively[161].

9.4 PLGA Nanoparticles

Due to regulated and sustained release, prolonged circulation time, and targeted distribution, Poly (lactic-co-glycolic acid), a synthetic pharmaceutical excipient accepted by the FDA, has received a lot of attention in the drug delivery industry. The ability of PLGA nanoparticles to transport a variety of therapeutic agents, including biomacromolecules and small molecule medicines, has been demonstrated. Using a single emulsion solvent evaporation technique, researchers created and examined quercetin-loaded PLGA nanoparticles (Qu1NPs, Qu2NPs, and Qu3NPs) with various sizes and encapsulating characteristics. Qu1NPs treatment also considerably reduced the level of MDA in C6 cells, reducing intracellular oxidative stress. According to these results, quercetin's internalization, anticancer effectiveness, and antioxidative capability in C6 cells may all be enhanced by smaller PLGA nanoparticles. In addition, PLGA can be applied as a shell to cover other nanoparticles to improve their mechanical stability, biocompatibility, and strength. The significance of quercetin-gold encapsulated in PLGA nanoparticles in controlling anticancer activity in neuroglioma, cervical, and liver cancers was investigated. Regarding liver cancers, treatment with quercetin-gold loaded PLGA nanoparticles reduced tumor cell proliferation, migration, and colony formation via activating Caspase 9 and 3 breakage and the release of cytochrome C. Additionally, telomerase reverse transcriptase (hTERT) and the Akt and ERK1/2 signaling pathway were inhibited by AuNPs-Qu PLGA nanoparticles. Through p53-ROS activation and epigenetic changes, the nanoparticles may interact with DNA and lower histone deacetylases to suppress HepG2 cell proliferation and halt the cell cycle at the sub-G stage[162].

9.5 Metal-Organic Framework Nanoparticles

Metal-organic frameworks (MOFs), which are three-dimensionally organized porous nanomaterials made of inorganic clusters and connected by organic ligands, offer a hitherto unheard-of prospect for tumor therapy as therapeutic agents or drug delivery systems. To combat MDR, quercetin and doxorubicin were enclosed within Zn-methylimidazole framework nanoparticles (HM/Dox/Que). Additionally, compared to mono-drug loaded nanoparticles, co-delivery of Dox and quercetin increased drug accumulation within tumor cells while concurrently decreasing the expression of P-gp protein. According to the in vitro assay, HM/Dox/Que showed a stronger anticancer impact than HM/Dox or free Dox while having no overtly harmful effects on mouse body weights[163].

9.6 Inorganic Nanoparticles

The development of inorganic materials as nanocarriers in recent decades has demonstrated considerable promise for medication delivery and disease diagnostics. Silica nanoparticles, metal oxides, graphene oxide, and gold nanoparticles are the inorganic nanoparticles that are most frequently studied[164]

9.7 Silica Nanoparticles

Due to their structure and advantageous surface chemistry, silica nanoparticles—which contain silicon (46.83 %) and oxygen (53.33 %)—make good drug carriers. due to its low in vivo toxicity, excellent stability, and versatility in ligand functionalization to provide targeted drug delivery. Additionally, mesoporous silica nanoparticles have a large surface area and ordered, controllable porosity, which results in superior release kinetics and excellent drug loading efficiency. Studies revealed a 154% improvement in oral bioavailability over a free, poorly water-soluble medication. Furthermore, silica nanoparticles have reportedly been found to offer important advantages such simple production,

controllable pore diameters, and favorable endocytic function. Mesoporous silica nanoparticles (MSNs) are promising porous materials with outstanding surface characteristics, including submicron-sized pores that may load a variety of molecules. For the treatment of colon cancer, quercetin was created to be delivered using pH-sensitive multifunctional envelope-type mesoporous silica nanoparticles (FA-FE-SBA15QN) conjugated with folate. In HCT 116 cells, FA-FE-SBA15QN therapy induced mitochondrial-dependent apoptosis, c-Jun N-terminal Kinase (JNK)-mediated H2AX phosphorylation, and p53 activation, which increased apoptotic destiny. In BC cells with overexpressed folate receptors, folate-armed mesoporous silica nanoparticles loaded with quercetin also enhanced cellular absorption and cell death. in vitro tests demonstrated quercetin-conjugated silica nanoparticles' potential to drastically decrease cell viability by preventing the cell cycle and causing apoptosis. Quercetin was functionalized with poly (acrylic acid)-chitosan and applied to the surface of silica nanoparticles (CPMSN) that had mesoporous pores and were topotecan-loaded[24]. After that, argininegylcine-aspartic acid was coupled on the nanoparticles to aid in cellular absorption by cancer cells and to cause drug release when it degraded in endosomes and lysosomes. In CD44-overexpressed tumor cells, such as BC, a hyaluronic acid (HA) coating on mesoporous silica nanoparticles has been shown to inhibit drug release and enhance biodistribution. To improve the effectiveness of gastric cancer chemotherapy, researchers created doxorubicin and quercetin co-delivery silica nanoparticles (HA-SiLN/QD) coated with hyaluronic acid (HA). Additionally, an in vivo anticancer experiment showed quercetin-mediated P-gp and Wnt16 downregulation in SGC7901/ADR carrying mice, which reversed MDR to allow DOX accumulation and changed the tumor microenvironment, displayed considerably increased efficacy in comparison to HA-SiLN/Q. Porous silicon nanoparticles, in contrast to mesoporous silica, have a higher surface area and pore volume (more than 10 nm), which gives them more flexibility when it comes to loading various cargoes, such as tiny molecule medicines, peptides, proteins, genes, and even quantum dots. However, because of the easily accessible big holes, the loaded cargos may be violently expelled into body fluids, inactivating any medications or side effects that may have been present. To address this issue, scientists added 3-aminopropoxy-linked quercetin (AmQu) to porous silicon nanoparticles (DOX@FAP), followed by "catechol-metal" synthesis through Fe3+ incubation, so that doxorubicin could chelate with metal ions to form complexes and be released in a pH-dependent way[165].

9.8 Carbon Based Nanoparticles

In terms of carbon-based nanomaterials, fullerenes, carbon nanotubes, graphene, nanodiamonds, and carbon-based quantum dots are the most common. These materials have drawn a great deal of interest in a variety of fields due to their distinctive structures and characteristics. Among these, carbon nanotubes have been widely used as drug carriers in tumor therapy due to their exceptional qualities, including large surface area and thermal durability. Multiwalled carbon nanotubes (MWCNT-Pm-Q) in interaction with pemetrexed and quercetin were used by Badea as a medication delivery system. Researchers discovered that, in comparison to its pure forms, quercetin's inhibitory effects on HeLa and B16F10 were amplified after treatment with nanodiamonds[166].

9.9 Gold Nanoparticles

Modifying quercetin to enhance its pharmacokinetics and therapeutic effectiveness is of great interest. In an important demonstration, quercetin was covalently linked to gold nanoparticles as a therapeutic payload for BC. The PI3K/Akt/mTOR and MAPK pathway has been demonstrated to play a role in controlling the proliferation and survival of breast carcinoma cells as well as their resistance to chemotherapeutic therapy when the epidermal growth factor and receptor (EGFR) is overexpressed[167].

9.10 Other Nanoparticles

Researchers created quercetin nano micelles using phosphatidyl ethanolamine (PE)-derivatized polyethylene glycol (PEG) as a block copolymer to increase the effectiveness of orally administered quercetin. They also examined how nanomicelles interacted with Caco-2 cells and investigated how they inhibited the proliferation of A549 lung cancer cells and a mouse xenograft model. With a margin of 1.5-fold greater than free quercetin, quercetin nanomicellar solution demonstrated suppressive tumor development while exhibiting no harm in relation to weight loss. It has also been successful to use a unique technique called physical vapor deposition (PVD) to create quercetin nanoribbons in order to increase the solubility of the antioxidant. Quercetin nanoribbons' enhanced water solubility and drug release profile were also shown by the higher growth-inhibitory effect they had on 4T1 BC cells. However, additional research is still necessary to comprehend the underlying mechanism of the anticancer action of quercetin nano formulations[24,168].

Table.4-ANTICANCER EFFICACY IN *IN VIVO* STUDIES OF QCT NANOPARTICLES

Forms of nanomaterial	Form of cancer	Result	Form of study	References
PEG (polyethylene glycol)	Melanoma	growth of tumor restraint	Animal model(mice)	169
PLA (poly dl-lactide-co-glycolide)	Hepatocellular carcinoma	Restriction in the growth of hepatocarcinogenic	Animal model(rat)	170
PVP (polyvinyl pyrrolidine)	Cancer in breast	Antioxidative action and effective photothermal eradicating outcome to cells of 4T1 cancer	Animal model(mice)	171
PEG (phosphatidylethanolamine)	Cancer in lung	Anticancer activity in cancer cells of the lung	Animal model(mice)	172
QCT-loaded PLGA-TPGS(QPTN) poly- (di-lactic-co-glycolic acid)-D-α -tocopherol polyethylene glycol succinate	Malignancy in liver	The cell of HepG2 and HCA-F tumor suppression	Animal model(mice)	173
PEG-liposomal polyethylene glycol-liposomal	Malignance in ovary	Initiation of apoptosis and inhibit angiogenesis	Animal model (mice)	174

PLGA-TMX (ploy lactic co- glycolic acid) tamoxifen	Malignancy in breast	Orally administered proficiently controlled the tumor angiogenesis	Animal model(rats)	[175]
TPP- PEG Triphenylphosphine QCT nanoparticles polyethylene glycol	Mitochondrial tumor therapy	MCF-7, a459, and HepG2 cells.	Animal model(mice)	[176]

10. NANOENCAPSULATION AND ITS ADVANTAGES

One "naturally produced" method for protecting biological organization is called as encapsulation. Encapsulation is used to shield critical constituents from oxidation, isomerization, and degradation, extend the shelf life of materials over time, and deliver controlled/sustained amounts of functional substances when swallowed into the body. It is a technique used in product development. The solubility and pharmacokinetics profiles of insoluble medicines are improved via nanoencapsulation. Targeted drug delivery is frequently much improved, bioavailability to the target tissues and cells is dramatically boosted, and toxicity is decreased. It can significantly improve the transport of such medications to tumor tissue and lessen their adverse effects on healthy cells. There are a variety of polymers from which to choose to encapsulate the medication, but it's crucial that the polymer has the ability to bind the drug without changing its activity. Bovine Serum Albumin (BSA) is a suitable medication carrier because the protein-based nanoparticles it produces are easily adaptable to the human body. Typically, the liver and spleen just eliminate the big particle. Decreasing the size of colloidal particle carriers and improving the stability of the nanoparticle carriers. The effect of the monomer/co-stabilizer ratio, various types of initiators, and the redox pair composed of hydrogen peroxide and ascorbic acid were studied and investigated in the nanoencapsulation of quercetin, a potent antioxidant and radical scavenger, via methyl methacrylate miniemulsion polymerization. Miglyol 812 served as the costabilizer and lecithin served as the surfactant. When compared to nanospheres, a higher quercetin recovery was attained with nanocapsules. Recently, attempts have been made to obtain imprinted nanoparticles for use in drug delivery. It was reported that quercetin, MAA, and ethylene glycol dimethacrylate (EGDMA) were used as the template, functional monomer, and cross-linking agent, respectively, in the synthesis and characterization of imprinted nanospheres with strong swelling properties. When the template is taken out, binding holes that preserve the size and shape of the template molecule are left in the polymer organization, which exhibits increased selectivity for the release of quercetin. The potential for using these monodispersed imprinted nanoparticles as tools for the regulated and sustained release of quercetin was explored. The imprinted polymers that will be used for drug delivery should be somewhat flexible in order to reduce potential irritation to surrounding tissues and achieve a quick equilibrium between the release and reuptake of the template in the cavity. They should also be able to maintain the conformation of the imprinted cavities even when the template is not present, in order to maintain their selectivity properties. It was stated that the cytotoxicity tests and in vitro release studies in plasma simulating fluids demonstrated the suitability of these materials as tools for the controlled/sustained delivery of quercetin in biological fluids and that quercetin's anti-proliferative activity was maintained after loading onto MIP materials. Scanning electron microscopy, atomic force microscopy, and a UV-Vis spectrophotometer have all been used to characterize the quercetin-loaded PLA nanoparticles. It has also been assessed how quercetin-loaded PLA nanoparticles affect BSA protein fluorescence quenching. To enhance its performance in the pharmaceuticals industry, the quantification of encapsulation effectiveness, antioxidant activity, and in vitro release was also done. Quercetin molecule in PLA encapsulation exhibits greater water solubility and consistent release. Quercetin has been used as a prototype medication. Three fabrication techniques, including high-pressure homogenization, bead milling, and cavi-precipitation, were studied in the synthesis of quercetin nanocrystals. The products' particle size, saturation solubility, and dissolution were all compared using these methods. A different study looked into the topical delivery of quercetin using lecithin-chitosan nanoparticles. The quercetin-loaded nanoparticles demonstrated greater skin penetration and markedly enhanced quercetin accumulation, particularly in the epidermis. Due to high skin permeability of quercetin, the contact between nanoparticles and the skin surface altered the stratum corneum's shape and disrupted the tight conjugation of the corneocyte layers. The formulation of chitosan lecithin nanoparticles that was developed offers potential as a topical delivery system for quercetin, it may be said. When the antioxidant properties of quercetin and -carotene were combined in nanoparticles for study, it was shown that quercetin-containing nanoparticles reacted more quickly than those containing -carotene. Researchers found that linoleic acid (LA) was encapsulated utilizing ultrasonic into a dual polymer system comprising whey protein and Kappa-carrageenan in the presence or absence of quercetin. 83% of the LA was successfully encapsulated, according to tests on the stability of encapsulated LA and the antioxidative activity of quercetin. Quercetin's bioactivity can be increased through nanotechnology encapsulation, and liposomes should be able to distribute Ag and quercetin securely and expertly for the Ag-specific suppression of inflammatory arthritis. In ischemia reperfusion-induced young and old rats, quercetin nano encapsulated orally plays a protective function against oxidative damage by reducing the loss of pyramidal neurons from the hippocampus CA1 and CA3 subfields. But shorter periods of reperfusion do significantly less harm. DMSA may offer a more effective therapeutic approach in the management of arsenic toxicity and also presents a novel method of combining hydrophilic and hydrophobic drugs into a single delivery system. Quercetin and DMSO were synthesized as nano encapsulated formulations to investigate their healing function in a rat model of chronic arsenic toxicity. A study claimed that in A2780S ovarian cancer cells, quercetin displayed anti-cancer action. Quercetin was encapsulated in MPEG-PCL micelles, which caused cancer cells to die and inhibited angiogenesis in vivo, hence slowing the growth of established xenograftA2780S ovarian tumors. Thus, quercetin's medicinal effects will be enhanced by polymer encapsulation[177].

11. LIMITATIONS AND FUTURE PROSPECTS

The medicines utilized and the Physico-chemical characteristics of the nano-particulate structure have a significant impact on the pharmacologic activity of QCT-loaded nanoparticles. These characteristics can raise quercetin's stability, bioavailability, and target selectivity.

Despite several in-vivo and in-vitro investigations demonstrating quercetin's anticancer effectiveness, there are still several challenges and restrictions for the clinical application, including cost, side effects, and safety[178]. Oral administration of quercetin nanoformulations became the preferred method of administration following extensive research on the anticancer potential of quercetin nanoparticles[179]. The necessity for additional stability and target-specific nanoparticles persists even though several quercetin nanoparticles can boost the bioavailability of quercetin in the body[180]. The adverse effect and toxicity of QCT-loaded nanoparticles should be tested before they are used for therapeutic purpose[181]. This can be achieved by combining nanoparticles with targeting molecules that are specific to cancer cells. By doing so, it will be possible to improve the delivery of nano formulations to their intended targets while reducing interactions with healthy cells and lowering the risk of adverse drug reactions. Furthermore, to meet the safety requirements set forth by the government, more controlled nano formulation production will be required. The cost usefulness of the nano formulations will also be a major barrier before they can enter the market as a medicinal agent. [182]

12. CONCLUSION

An increasingly important class of naturally occurring polyphenolic flavonoids is known as quercetin. However, because of its poor solubility, low absorption, and quick metabolism, anticancer potential of QCT is insufficient. Utilizing nanotechnology has improved quercetin's bioavailability and antitumor effectiveness. Both *In vivo* and *In vitro* studies on quercetin nanoparticles demonstrated its potential as a cancer treatment. Preclinical research accounts for the majority of studies on nanoparticles for anticancer properties. There is still a need to perform various research on the effect of various types of quercetin nanoparticles to reduce the spread of tumors.

13. AUTHORS CONTRIBUTION STATEMENTS

Every author in the present manuscript has equally participated and contributed to the preparation of the manuscript to take public responsibility for appropriate portions of the content. The author's contribution statement for the manuscript entitled "POLYMERIC NANOPARTICLES OF QUERCETIN FOR CANCER TREATMENT: A REVIEW" with their Applications is as given below:

Barsha Deb carried out the literature survey and design the manuscript, formatted and carried out a plagiarism check for the prepared manuscript. Dr. Nishant Thakur: This idea was conceptualized by Nishant Thakur.

14. CONFLICT OF INTEREST

Conflict of interest declared none.

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