Various mechanisms of quercetin on inhibiting breast cancer growth: A review.

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Abstract

Breast cancer is the second leading cause of death among women after lung cancer. Although chemotherapy is the most common therapeutic strategy for the treatment of breast cancer, its side effects are always a major obstacle in cancer treatment. Quercetin is a flavonoid compound abundantly found in fruits and vegetables, and it has been proven to possess anti-cancer potential in breast cancer. Quercetin, through several mechanisms, exerts its anti-tumor properties, including the cell cycle arrest at G1 and/or G2/M inhibition of the signal transduction pathways in cancer cells, regulation of growth factors to prevent cell proliferation, and the induction of apoptosis. This article reviews the molecular mechanisms of quercetin in the elimination of breast cancer cell lines.

Keywords: Breast cancer, Flavonoid, Quercetin, Chemoprevention.

Introduction

Breast cancer is the most common cancer and the second leading cause of cancer deaths among women after lung cancer, with an annual growth rate of 1%-2% [1-4]. Common therapeutic strategies for the treatment of breast cancer include surgery, radiotherapy, chemotherapy, endocrine therapy, and biological therapy [5]. Although over the past three decades, more than 100 clinical trials have confirmed the effectiveness of chemotherapy in the prevention of breast micro-metastases, the toxicity and side effects of chemotherapy are always a major obstacle in cancer treatment [6].

Therefore, the discovery and development of new anti-tumor drugs with limited adverse effects would be an advantage. One of these anti-cancer agents is quercetin that is widely found in foods and vegetables, and it is easily accessible upon the extraction and isolation. Quercetin is a type of flavonoid compound that has many biological properties, including anti-inflammatory, antihypertensive, vasodilatory, anti-obesity, anti-hyper-cholesterolemic, anti-atherosclerotic, anti-viral, anti-allergic, and antioxidant activities [7-10]. Previous studies have shown that quercetin inhibits cell growth in various human cancer cell lines such as the breast, liver, and colon. Quercetin acts through several mechanisms, such as the cell cycle arrest at the G1and/or G2/M phase, suppression of the signal transduction pathways in cancer cells MAPKs (Mitogen-activated protein kinase) and Akt (Protein kinase B)), regulation of the synthesis of growth factor to prevent cell proliferation, and induction of apoptosis [11-14].

Literature Review

It has been reported that quercetin can hinder cell growth and induce apoptosis in the HT-29 human colon cancer cell line, thereby a reduction in the expression of ErbB2 (Erb-B2 Receptor Tyrosine Kinase 2) and ErbB3 (Erb-B2 Receptor Tyrosine Kinase 3) proteins [15]. Yang and colleagues investigated the impact of quercetin on the human lung cancer cell line NCI-H209 and observed that it could oppress the proliferation of these types of cells through the cell cycle arrest at the G2/M stage, as well as the activation of caspase-3, leading to the initiation of apoptosis [16]. Another study conducted by Cruz-Correa et al., they used quercetin for the treatment of adenomatous in patients with familial adenomatous polyposis. They showed that the number and size of ileal and rectal adenomas were decreased in these patients without causing any signs of toxicity [17]. A study performed by Choi et al. assessed the impact of quercetin on human breast cancer MCF-7 (Michigan Cancer Foundation-7) cells and observed that quercetin inhibited the proliferation of these cells by inducing apoptosis and arresting the cell cycle[18]. Therefore, a large number of studies have shown the anti-cancer properties of quercetin in various stages of cancer. In this paper, we will discuss the mechanisms by which quercetin exerts anti-tumor activity in breast cancer cells.

Proliferation

Quercetin has anti-proliferative activity and inhibits many significant molecules that are involved in some signaling pathways, contributing to the carcinogenesis process, namely tyrosine kinase [19-21], protein kinase-C [22,23], and phosphatidylinositol-3 kinase [24,25]. Although the precise mechanism of quercetin in the prevention and suppression of cancer is not fully elucidated, it is likely that quercetin influences several signaling cascades, such as the inhibition of tyrosine kinase [24,26], inducing apoptosis [27], reducing the level of p53 (Tumor protein p53) [28], and interfering with the pathways vital for cell survival [29].

Unregulated expression of tyrosine kinase, which has a regulatory effect on the cell growth pathway, leads to the excess proliferation of cancer cells [30,31]. Recent studies have shown the significance of tyrosine kinase pathways in the progression of breast cancer [32-35]. The inhibitory effect of quercetin on tyrosine kinase has been addressed inthe first phase of some clinical trials. In this context, Ferry and

colleagues recruited 51 patients with cancer and injected 945 mg/m2 of quercetin. They showed that the intravenous injection of quercetin was safe when administered at this dosage, and it can hinder the activity of the tyrosine kinase pathways in lymphocytes, resulting in the induction of programmed cell death in these cells [26]. Scambia et al. demonstrated that quercetin exhibited a growth inhibitory effect on the MCF-7 cell line, thereby the interaction with the type-II estrogen binding site (type-II EBS) [35].

Signal transduction

The activity of some signal transduction pathways is increased in many types of tumors, including breast cancer, ovarian cancer, and hepatocarcinoma in rats. Therefore, targeting these pathways can prevent tumor progression [36-38]. Quercetin inhibits l-phosphatidylinositol 4-kinase and 1-phosphatidylinositol 4-phosphate 5-kinase by a reduction in the concertation of inositol 1,4,5-trisphosphate (IP3). The decrease of inositol triphosphate actually diminishes the release of calcium from its internal sources [39-41].

Since the production of ROS (Reactive oxygen species) induces oxidative damages, it can lead to the development of some disorders such as cancer. Studies have shown that quercetin impedes the excessive generation of ROS and suppresses the activation of cyclic adenosine monophosphate (cAMP), reticular activating system (RAS), as well as phosphorylation of extracellular signal-regulated kinases 1/2 (ERK1/2) [42].

Cell cycle

Quercetin controls the proliferation of breast cells through the inhibition of the cell cycle. It can alter the regulation of some proteins that participate in the cell cycle process, leading to the cell cycle arrest at the S phase. There are two checkpoints in the process of the cell cycle, the G1/S and G2/M phases, in which the cell needs to get permission to replicate. These checkpoints ensure that the downstream steps would not be initiated until the upstream stages would be correctly performed. Upon damages to the cells, the apoptosis process begins, and the progression of the cell cycle would be prevented [42,43]. Cho et al. indicated that the number of cells at the S phase was significantly increased compared with those treated with quercetin at the G0/G1 phase, suggesting that quercetin prevents the cell progression from the S to G2/M phase [23,44]. Quercetin declines the expression of CDK2 (Cyclin-dependent kinase 2), cyclin A&E, and p57 proteins. The activity of the CDK2/cyclin E complex is essential for the progression of the cell cycle from the G2 to the M phase. The p53 protein plays a central role in the inhibition of cell growth and apoptosis, via affecting downstream molecules, such as p21, which isa major downstream effector. This phenomenon increases the expression ofp21 and blocks the activity of Cdks, leading to apoptosis and growth inhibition [18,45]. Notably, quercetin induces the cell cycle arrest at the S phase, thereby decreasing the expression levels of CDK2 along with cyclin A and B [18,46].

It has also been proven that even at low doses, quercetin can induce the cell cycle arrest through several mechanisms that include hypo-phosphorylation of pRb (retinoblastoma protein) [47] which, in turn, induces the expression of the P21 inhibitor protein, activation of Chk2 (Checkpoint kinase 2) kinase [48], and reduction of the transcription levels of the cyclin B1 gene [49].

The effects of quercetin on the cell distribution at thesub-G1 and S phasesof MCF-7 cell line

To understand whether the cell cycle arrest, thought to be induced by quercetin, is responsible for reducing the number of viable cells, or inducing apoptosis, the distribution of cells in different phases, i.e., G0/G1, S or G2/M phases, of the cell cycle were assessed by Chou and his associates. After treatment with quercetin, the number of cells in the S phase was significantly increased while the frequency of the cells at the G0/G1 phase was markedly decreased. Thus, it is inferred that quercetin can induce the cell cycle arrest at the S and sub-G1 phases of MCF-7 cells, indicating the induction of cell death after 48 hours of treatment with quercetin [46].

The impact of quercet in on the percentage of viable MCF-7 cells

In two distinct studies conducted by Chou et al. and Deng et al., using the flow cytometry analysis, the effect of quercetin on cell viability was evaluated by exposing the cells to different concentrations of quercetin for 24 and 48 hours. Depending on the duration of treatment and the dosage of quercetin, the cell viability was reduced to 12-90%. The IC50 (half maximal inhibitory concentration) value of quercetin was 92.4 μM when assayed at 48 hours [46,50].

The effect of quercetin on protein, DNA, and RNA synthesis, as well as the morphology of MCF7 human breast cancer cell

Quercetin acts as a potent inhibitor of the protein, DNA, and RNA synthesis in the MCF7 cell line. DNA synthesis is highly sensitive upon the exposure to quercetin; so that, even at the low concentrations, it is able to inhibit DNA synthesis. For instance, Rodgers & Grant demonstrated that 5 and 50 μM quercetin can lower the rate of DNA synthesis (via the oppression of DNA polymerase) to 76 ± 3% and 34 ± 3% of the control cells, respectively.

This study also reported that quercetin at the concentration of 10 μM>can diminish the RNA synthesis to 76 ± 4% of the control cells. The inhibition of protein synthesis occurs when the cells are treated with 25 μM>quercetin. It has been reported that when MCF7 cells were exposed to 25 μM quercetin for 24 hours, the morphology of the cells was altered, and they exhibited spherical-like shapes, and some holes were evident in their cell membrane. These phenomena are related to the induction of apoptosis in these cells [51].

Apoptosis

Quercetin induces apoptosis in breast cancer cells. To understand the mechanisms involved in this scenario, the expression of the apoptosis-related proteins such as Bcl-2 (B-cell lymphoma 2), caspase-6, -8, and -9, as well as the changes in mitochondrial membrane potential (ΔΨm), was evaluated in MCF-7 cells. The ratio of Bax (BCL2 Associated X) to Bcl-2 determines whether apoptosis occurs or not. Bcl-2 prevents the initiation of apoptosis by controlling the transition of calcium ion from the membrane of the endoplasmic reticulum and its antioxidant activity. The Bax antagonizes Bcl-2 activity and induces programmed cell death [52]. In many malignant tumors, the expression of the Bax protein is substantially decreased [53,54].

The increased proportion of Bax to Bcl-2 can result in the release of the cytochrome c from mitochondria into the cytoplasm, thus promoting the process of apoptosis. Several lines of evidence indicated that the expression of Bcl-2 is decreased while the level of Bax is increased when MCF-7 cells are treated with quercetin. Quercetin also reduces the amount of ΔΨm by changing the expression of Bax and Bcl-2 [55]. Quercetin can cleave the pro-caspase 8 and 9, which play an essential role in initiating apoptosis. The activation of these caspases, in turn, stimulates a downstream mediator called caspase-6, leading to the induction of programmed cell death. In order to determine whether the presence of caspases is necessary to induce apoptosis by quercetin, Cho et al. incubated MCF-7 cells with caspase inhibitors and observed that apoptosis is significantly decreased in the presence of inhibitors [46]. Also, some studies showed that the treatment of MDA-MB-231 and MCF-7 breast cancer cell lines with quercetin could induce the cell cycle arrest at the G1 phase and cause cell death, accompanied by a significant reduction in the expression of CyclinD1, p21, Twist and phospho-p38 mitogen-activated protein kinases (p38MAPKs). Of note, the reduced expression of Twist, as a result of p38MAPKs, can promote the apoptosis process [56-58].

Results

P53 is a tumor suppressor gene that its expression determines the cell fate, mediated by regulating the G1 and G2/M phases of the cell cycle [59]. Studies reported that DNA damage activates P53, which, in turn, induces the cell cycle arrest [60-62]. Accordingly, quercetin is a substance that incites the expression and activity of P53, leading to the inhibition of cell proliferation [63]. Also, quercetin is capable of suppressing the expression of the phospho-signal transducer and phospho-Janus kinase 1 (JAK1) and activator of transcription 3 (STAT3), as well as decreasing the activity ofSTAT3-dependent luciferase reporter gene in breast tumor-474 cell line [64]. It has been demonstrated that receptor for advanced glycation end-products (RAGE), a multi-ligand member of the immunoglobulin superfamily, has a prominent role in maintaining cellular homeostasis. High-mobility group box protein-1 (HMGB-1) and its receptor, RAGE, are increased in various types of cancer. The RAGE protein regulates several signaling cascades involved in apoptosis and cell proliferation. Several studies have shown that the binding of RAGE to its cognate receptor, HMGB-1, activates the NF-kB pathway, resulting in cancer cell growth and the suppression of apoptosis. On the other hand, quercetin decreases the expression of the two genes mentioned earlier, thus increasing the rate of apoptosis in cancer cells [65,66].

Studies	Type of treatment	Treatment dose	Duration	Cancer cell line	Effect observed
ACKLAND 1 et al. (2005)	Combination of quercetin and kaempferol	Quercetin or Kaempferol or combination therapy 1, 5 or 10 μM	72 h	PMC42	Synergistic effect of quercetin and kaempferol
Halide Akbas et al. (2005)	Combination of Quercetin and Topotecan	Quercetin 10 to 0.62 μM Topotecan 100, 160 mg/ml	24 h	MCF-7 MDA-MB 231	Enhancing the cytotoxicity of Topotecan by 1.4 folds in MCF-7 and 1.3 folds in the MDA-MB-231 cell line
Avila et al. (1994)	Quercetin	Quercetin 5, 10, 15 and 30 μg/ml	72 h	MDA-MB 231	Cell cycle arrest in G2/M
Balakrishnan et al. (2016)	Gold nanoparticle–conjugated quercetin	free AuNPs (0–125 μm), free Qu (0–125 μm) AuNPs-Qu-5 (0–125 μm)	24 h	MCF-7 MDA-MB 231	significant reduction in protein expression of vimentin, N-cadherin, Snail, Slug, Twist, MMP-2, MMP-9, p-EGFR, VEGFR-2, p-PI3K, Akt and pGSK3β, and enhanced E-cadherin protein expression
Chien et al. (2009)	Quercetin	Quercetin 0, 50, 100, 150, 200, 250 and 300 mM	48 h	MDA-MB-231	Inducing apoptosis through mitochondrial- and caspase3-dependent pathways
Choi et al. (2008)	Quercetin	Quercetin 1–100 μM	3–24 hrs	MDA-MB-453	Cell cycle arrest at sub-G1 phase
Chou et al. (2010)	Quercetin	Quercetin 10–175 μM	24 and 48 h	MCF-7	Increasing the number of S phase

					and sub-G1 phase cells
Deng et al. (2013)	Quercetin	Quercetin 0, 2.5, 5, 10, 20 and 40 mg/ml	24 or 48 h	MCF-7	inducing G0/ G1 phase arrest and promoting apoptosis
Dhumale et al. (2015)	Quercetin	Quercetin 10, 25, and 50 μM	6, 12, 24, and 48 h	MCF-7	Promoting apoptosis by attenuating the expression of RAGE and its ligand HMGB1
DUO et al. (2012)	Quercetin	Quercetin 12.5, 25, 50, 100, 200 μM	48 h	4T1	Inhibiting cell growth and inducing apoptosis via increasing the expression of Bax and decreasing of Bcl-2
Liao et al. (2015)	7-O-butylquercetin (BQ) 7-O-geranylquercetin (GQ)	Quercetin, BQ and GQ 10-100 μM	48 h	MCF-7	Greater inhibitory and apoptosis-inducing effects of BQ and GQ than quercetin
Li Lv et al. (2016)	Quercetin in combination with doxorubicin	10-100 μg/ml	48 h	MCF-7 MCF-7/ADR cells (doxorubicin-resistant MCF-7 breast cancer cells)	Enhancing the efficacy of DOX in a drug-resistant MCF-7/ADR by the inhibition of both activity and expression of P-gp
Nguyen et al. (2017)	Quercetin	2.5- 80 μM	24 h, 48 h, and 72 h	MDA-MB-231	Increasing cell apoptosis and inhibiting cell cycle progression via modification of Foxo3a signaling
Purba et al. (2013)	Quercetin in combination with doxorubicin	Ratio combination D:Q 1;00 1;34 1;17 1;90 1;20 1;0.8 1;0.4 1;0.2 0;1	24 h	MCF-7	Inhibiting the growth of MCF-7 cells increasing the sensitivity of human breast cancer cell line MCF-7 to doxorubicin through synergistic interactions synergistic interaction between quercetin and doxorubicin at all ratios (isobologram analysis)
Ranganathan et al. (2015)	Quercetin	Quercetin (10 μM to 100 μM)	24h and 48h	MCF-7 MDA-MB-231	Inducing cell death especially at the G1 phase in the MCF-7 cell line suppressing the expression of CyclinD1, p21, Twist and phosphor-p38MAPK in the MCF-7 cell line but not in the MDA-MB-231 cell line
Rodgers et al (1998)	Quercetin	Quercetin h 25, 50 or 100 μM	24 h	MCF-7	Inhibiting protein, DNA and RNA synthesis increasing intracellular reduced glutathione (GSH) content, and alteration of cell morphology after 24 h
SCAMUIA et al. (1993)	Quercetin	Quercetin	24 h	MCF-7 MDA-MB-231	Positively regulation of type-II estrogen binding site (type-II EBS) in MCF-7 (ER-positive) and in MDA-MB23 I (ER-negative) breast cancer cell lines increasing the sensitivity of cancer cells to the inhibitory properties of low

					quercetin concentrations
Seo et al. (2016)	Quercetin	Quercetin 20-60 μM	24, 48, or 72 h	BT-474	Inducing the extrinsic apoptosis pathway by upregulating the levels of cleaved caspase-8 and cleaved caspase-3, and inducing the cleavage of poly(ADPribose) polymerase (PARP) not affecting the reducing the expression of phospho-JAK1 and phospho-STAT3 and inhibiting the MMP-9 secretion levels of Bcl-2 and BAX
Srinivasan et al. (2016)	Quercetin	Quercetin 0–100 μM	24 h	Triple-negative breast cancer (TNBC)	inhibiting TNBC metastasis via inducing the expression of E-cadherin and also downregulating vimentin levels
Yamazaki et al. (2014)	Quercetin-3-O-glucuronide	0.1 μM	8 h and 12 h	MDA-MB-231	suppressing ROS generation, cAMP and RAS activation, phosphorylation of ERK1/2 and the expression of HMOX1, MMP2, and MMP9 genes and also suppressing the invasion of MDA-MB-231 breast cancer cells and
					MMP-9 induction

Table 1*: In vitro effects of quercetin on breast cancer cell lines.*

Discussion

Impact of quercetin on the levels of specific proteins associated with the apoptosis and cell cycle arrest

The levels of procaspase-3 and -12, thymidylate synthase, procaspase-8 and -9, cyclin A and E, PARP (Poly (ADP-ribose) polymerase), Bid (Bax-like BH3 protein) and X-linked inhibitor of apoptosis protein (XIAP) are decreased in MDA-MB-231 cell line when treated with quercetin. In contrast, the expression of proteins ATF6-a (Activating transcription factor 6), PERK (Protein kinase R-like endoplasmic reticulum kinase), p53, p57, GRP78 (78kDa glucose-regulated protein), caspase-3, cytochrome c, Fas, Bax and AIF (Apoptosis-Inducing Factor) are increased in quercetin-treated cells. The increased levels of ATF6-a, PERK, GRP7, along with the decreased expression of caspase-3 indicate that quercetin can induce the release of calcium from the inside of the endoplasmic reticulum. The reduced levels of cyclins A and E, as well as thymidylate synthase, denote the cell cycle arrest at the S phase. Changing the level of specific proteins indicates that cell scan undergo apoptosis in multiple ways; for example, the increased levels of caspase-8, and -3, Fas and Bax along with a decrease in the level of XIAP and PARP can drive cells to apoptosis [46,67]. Survivin is a member of the IAP (Inhibitor of Apoptosis) family that is capable of oppressing the process of apoptosis. In many types of tumors, its expression is increased, and the rate of its expression is in line with the progression of tumors [68-70]. Studies showed that quercetin could lower the expression of survivin in a dose-dependent manner; thus, the use of high amounts of quercetin can significantly decline the synthesis of survivin inside tumor cells as this fact has been shown when the expression of this protein was measured at gene and protein levels [71].

The mechanisms by which quercetin suppresses tumor cells without causing toxicity on normal cells

Hypoxia-inducible factor-1 alpha (HIF-1) is a transcription factor that is activated during hypoxia or oxygen depletion in the cell environment [72,73]. While quercetin has inhibitory effects on cancer cells, it can protect normal cells, possibly through the modulation of HIF-1, these two types of cells. As quercetin induces the breakdown of HIF-1 in tumor cells, the concentration of this protein is increased within normal cells, is it accumulated inside the cells. It is thought that the different response of normal and cancer cells to quercetin is potentially mediated by HIF-1 [74-76].

Effects of quercetin on mitochondrial membrane potential (ΔΨm) and reactive oxygen species (ROS) of MCF-7 cells

Many studies verified the antioxidant properties of quercetin. In a study performed by **Mahesh** and colleagues, they evaluated the impact of quercetin on oxidative stress in streptozotocin-induced diabetic rats and showed that the oral administration of quercetin to diabetic rats reduced the levels of plasma hydroperoxides, blood glucose, and thiobarbituric acid reactive substances. Also, quercetin diminished the increased activity of superoxide dismutase and catalase to baseline levels. Therefore, quercetin can reverse detrimental changes caused by oxidative stress in rats induced by diabetes [77]. In another study, the impact of quercetin on oxidative stress induced by tert-butyl hydroperoxide in HepG2 cells was assessed. The results showed that quercetin markedly reduced the generation of reactive oxygen species while the activity of glutathione peroxidase, superoxide dismutase, glutathione reductase, and catalase was not increased significantly. Consequently, quercetin protects HepG2 cells against oxidative stress [78]. Also, in the study of Chou et al., there was no significant increase in the concentration of ROS in quercetin-treated cells while quercetin induced the cell cycle arrest and apoptosis in human breast cancer MCF-7 cells through the activation of the caspase activation cascades [46]. It is now known that ΔΨm has a strong correlation with apoptosis, and it is decreased at the endpoint of apoptosis. For the determination of ΔΨm, DiOC6, a specific mitochondrial stain, was used. The results showed that ΔΨm is considerably reduced in quercetin-treated cells in a time-dependent manner [67,79].

Metastasis

Triple-Negative Breast Cancer (TNBC) cell shave some exclusive characteristics, such as lack of estrogen, progesterone, and the epidermal growth factor-2 receptor. Studies demonstrated that quercetin could elevate the expression of E-cadherin and reduce the level of vimentin. Also, quercetin regulates the epithelial-mesenchymal transition (EMT) markers, which facilitate the transition of the cells from mesenchymal to epithelial cell morphology. A large body of evidence shows that quercetin could have a synergistic anti-tumor activity when combined with doxorubicin, thereby lowering the migratory ability of TNBC cells. Other studies indicated that quercetin increases the chemosensitivity of breast cancer cell lines to doxorubicin by modulating the expression of p-Akt, Phosphatase and tensin homolog (PTEN) [80,81]. Lvet al. reported that quercetin is capable of suppressing the expression of P-glycoprotein, leading to a meaningful decrease in MCF-7/ADR breast cancer cells, which are doxorubicin-resistant [82]. Furthermore, quercetin stimulates the initiation of apoptosis, suppresses the cell cycle progression via the alteration of the Foxo3a signaling pathway, and increases the expression of FasL (Fas ligand), p51 and p21 genes in TNBC cells [83].

Epidermal growth factor has a significant role in breast malignancies, through increasing cell proliferation, angiogenesis, and metastasis. Recent experiments showed that silver nanoparticles containing quercetin caused a substantial reduction in the expression of different proteins including VEGF (Vascular endothelial growth factor), vascular endothelial growth factor receptor 2 (VEGFR2), matrix metalloproteinase-2 (MMP-2), MMP-9, Snail, p-EGFR (phosphorylated epidermal growth factor receptor), N-cadherin, vimentin, Slug, Akt, Twist, glycogen synthase kinase-3 beta (p-GSK3β) and phosphoinositide 3-kinase (PI3K)as well as a marked elevation in the expression of E-cadherin protein in 7,12-dimethylbenzanthracene-inducedbreast cancer in rats [13,84].

Quercetin and carcinogens

The protective effects of fruits and vegetables against cancer, in addition to the presence of some antioxidant agents, such as vitamin C and carotenoids, can also be attributed to the presence of phenolic compounds, including flavonoids, phenylpropanoids, and phenolic acids. Although the mechanism(s) underlying the efficacy of these molecules is still opaque, it may be due to interactions with the enzymes responsible for metabolizing xenobiotics, which inhibit the activation of carcinogens.

Many types of carcinogens require to be activated by the phase I metabolizing enzymes to be able to bind DNA and cause deleterious effects on cell survival. Cytochrome P450 enzymes area group of enzymes that convert inactive carcinogens to highly active metabolites. Some studies indicated that quercetin has an inhibitory effect on these groups of enzymes [85-87]. Moreover, quercetin has been shown to hinder the activity of the CYP3A4 (Cytochrome P450 3A4) enzyme, an enzyme abundantly found in the liver, which plays a crucial role in activating carcinogens [88,89]. Studies have also demonstrated that quercetin may have anti-inflammatory effects through the inhibition of thecycloxygenase-2 (COX2) enzyme [90,91].

Drug resistance

Multidrug Resistance (MDR) is a major barrier to cancer treatment, as some anti-MDR drugs, such as cyclosporine A and verapamil, failed to conquer this effect [92].

Various factors can be responsible for the development of MDR, such as angiogenesis, disruption of apoptosis, and activity of ATP binding cassette (ABC) transporters. In fact, in MDR, the cellular concentration of an anti-cancer agent is reduced by the drug efflux mediated by some proteins including P-glycoprotein (P-gp, ABCB1), breast cancer resistance protein (BCRP, ABCG2) and multidrug resistance-associated protein1 (MRP1, ABCC1). Consequently, the inhibition of ABC transporters increases the efficacy of chemotherapy [93,94].

For instance, doxorubicin (DOX), a common chemotherapeutic compound, is able to inhibit the topoisomerase-2 enzyme. It has been shown that the long-term use of DOX, a substrate of P-gp, leads to enhanced expression of P-gp, which in turn increases the resistance of cancer cells to DOX [95].

This obstacle motivates researchers to use polyphenolic compounds, such
as quercetin, which can inhibit the drug efflux system, which is mediated by BCRP, P-gp, and MRP1 through interacting with ABC transporters. Indeed quercetin increases the uptake of chemotherapeutic drugs via reducing the expression of P-gp and enhancing the cell membrane permeability in several types of cancer cells, including MCF-7 cells. It has been reported that the combination of quercetin and DOX is capable of reducing the side effects on normal cells and improving the inhibitory effects on the MCF-7 cell line [96-98].

Conclusion

Despite common therapeutic strategies used for the treatment of cancer, the rate of mortality has been increasing. In the recent decade, natural anti-tumor compounds, such as quercetin, have attracted much attention. This mini-review attempts to focus on the different molecular mechanisms of quercetin by which stops the progression of breast cancer cells. In this review article, the effect of quercetin on breast cancer cell proliferation, signal transduction pathways, cell cycle arrest, apoptosis induction, metastasis, and drug resistance are discussed. Although the existing data represent the efficacy of quercetin alone and in combination with chemotherapeutic agents on breast cancer cells, further studies would be required to clarify the precise mechanism of quercetin in the inhibition of tumorigenesis.

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Conflict of Interest

The authors have no competing interests.

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