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REVIEW

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Anticancer potential of quercetin: A comprehensive review

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Diet plays a key role to maintaining healthy life. Many natural products present in our diet, such as flavonoids, can prevent the progression of cancer. Quercetin, a distinctive bioactive flavonoid, is a dietary component that has attracted the attention of dietitians and medicinal chemists due to its numerous health-promoting effects. It is an outstanding antioxidant that has a well-documented role in reducing different human cancers. Quercetin exhibits direct proapoptotic effects on tumor cells and thus can inhibit the progress of numerous human cancers. The anticancer effect of quercetin has been documented in numerous in vitro and in vivo studies that involved several cell lines and animal models. On the other hand, the high toxic effect of quercetin against cancer cells is accompanied with little or no side effects or harm to normal cells. Accordingly, this review presents an overview of recent developments on the use of quercetin against different types of cancer along with mechanisms of action. In addition, the present review summarizes the literature pertaining to quercetin as an anticancer agent and provides an assessment of the potential utilization of this natural compound as a complimentary or alternative medicine for preventing and treating cancer.

KEYWORDS

cancer prevention, human cancers, mechanisms of action, quercetin

1 | INTRODUCTION

Flavonoids are abundantly present in nature in the form of benzo-γ-pyrone derivatives. Plants, vegetables, and flowers are the major sources of these compounds. Structurally, flavonoids have diverse frameworks with interesting biological properties and can play an important role in the body's defense system. The beneficial effects of flavonoid-rich foods have been demonstrated by various studies (Benavente-Garcia & Castillo, 2008). There are more than 4,000 types of various flavonoids in nature with diverse subcategories, such as flavones, isoflavones, flavanones, and chalcones. Amongst the various promising health benefits, flavonoids possess important biological activities, such as anti-inflammatory, antioxidant, hepato-protective, and antimicrobial properties (Kanadaswami et al., 2005).

Quercetin (Figure 1), chemically known as 3,3′,4′,5,7-pentahydroxyflavone ($C_{15}H_{10}O_7$), is a naturally occurring polyphenolic flavonoid that is commonly found in different fruits and vegetables such as capers, lovage, dill, cilantro, onions, apples, and berries as in chokeberries, cranberries, and lingonberries. Perhaps, the most important property of this flavonoid is its antioxidant effect. In addition, quercetin can be useful in cancer prevention (Iacopetta et al., 2017) and is known to have antiallergic, anti-inflammatory, and antiviral activities (Y. Liu et al., 2017). Most importantly, quercetin impedes the propagation of various types of cancers, such as lung, prostate, liver, breast, colon, and cervical (Y. Liu et al., 2017); these anticancer properties are exerted through various mechanisms that involve cellular signaling and the ability to inhibit enzymes responsible for the activation of carcinogens. Quercetin displays anticancer effects based on its binding to cellular receptors and proteins (Murakami, Ashida, & Terao, 2008; Shih, Pickwell, & Quattrochi, 2000). Furthermore, quercetin has been recently reported to have synergistic effects when combined with chemotherapeutic agents such as cisplatin, which may further improve the outcomes of the traditional chemotherapy (Brito et al., 2015).

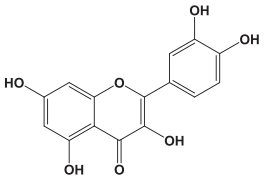

FIGURE 1 Quercetin

As soon as quercetin is absorbed in the gastrointestinal tract, it gets metabolized by phase II enzymes present in the epithelial cells of the stomach and intestines. The combined metabolites are then further processed in the liver and kidney (Abarikwu, Pant, & Farombi, 2012; Nabavi, Nabavi, Mirzaei, & Moghaddam, 2012). Mechanistically, the catechol structure (B-ring) is methylated at the 3′ or 4′ hydroxyl sites by catechol-O-methyl transferase to produce isorhamnetin and tamarixetin, respectively. Quercetin metabolites seem to accumulate in tissues shortly after quercetin-rich vegetables are consumed. In vitro studies indicated that quercetin metabolites, originating from enterocytes and the liver, serve as antioxidants by impeding oxidation of low-density lipoprotein cholesterol.

On the other hand, and even with the many technological and pharmaceutical advances over the past two decades, cancer continues to be a global concern (Seyed, Jantan, Bukhari, & Vijayaraghavan, 2016). Scientists attribute 90–95% of all cancers to lifestyle including obesity, outdoor pollution, alcohol consumption among others, whereas the remaining 5–10% are attributed to defective genes (de Martel et al., 2012). Cancer treatment methods include surgery, radiotherapy, and anticancer drugs (chemotherapy) in addition to other specialized techniques. For years, humans have used herbs as complementary therapy or dietary agents to treat different types of cancer and to influence cellular signaling (Martin, 2006). In this regard, natural compounds such as quercetin have been employed as alternative drugs in the treatment of cancer. Based on the above discussion, and owing to the wide range of therapeutic options of quercetin against various types of cancer, this review focusses on the current knowledge on the chemo-preventive and therapeutic ability of this natural flavonoid against different types of cancer, along with its mechanisms of action. For this purpose, recent relevant references have been obtained from different databases such as MEDLINE (PubMed), Google Scholar, ScienceDirect, Scopus, Cochrane, SID, and SciFinder. We hope this review will be a valuable addition to the field and will be a great help for researchers. Listed in Table 1 are the anticancer perspectives of quercetin along with the mechanisms in each type of cancer with a list of pertinent references, whereas shown in Figure 2 is the anticancer role of quercetin. Below are details about documented anticancer activities of quercetin.

2 | ANTICANCER PERSPECTIVES OF QUERCETIN

2.1 | Breast cancer

Recent research revealed that treatment of Michigan Cancer Foundation-7 (MCF-7) breast cancer cells with nano-quercetin enhances apoptosis and mRNA expression levels. In addition, quercetin was found to sensitize MCF-7 cells to doxorubicin (Dox) and reduce cellular NAD(P)H quinone oxidoreductase 1 and multidrug resistant protein 1 gene expression levels (Minaei et al., 2016; Suksiriworapong et al., 2016). Similarly, treatment of MCF-7 and MDA-MB-231 breast cancer cell lines with quercetin led to apoptosis along with G1 phase arrest and considerably suppressed the expression of Twist, CyclinD1, p21, and phospho p38 mitogen-activated protein kinases (p38MAPKs). It has also effectively controlled the expression of Twist, which induces apoptosis in MCF-7 cells due to p16 and p21. These findings suggest that quercetin induces apoptosis in cancer cells via suppression of Twist through p38MAPK (Liao et al., 2015; Ranganathan, Halagowder, & Sivasithambaram, 2015).

Research published by Dhumale and coworkers demonstrated that receptor for advanced glycation end-products (RAGE), which is a multi-ligand member of the immunoglobulin superfamily, plays an important role in maintaining cellular homeostasis. The elevated expression of RAGE and its ligand high-mobility group box proteins-1 (HMGB-1) was found in different types of cancer. In addition, aggregation of RAGE with its HMGB1 stimulates a complicated signaling network for cell viability and avoids apoptosis. Hence, quercetin augments apoptosis in MCF-7 cells by hindering the expression of RAGE and HMGB1; this also results in necrotic insult (Dhumale, Waghela, & Pathak, 2015). Furthermore, lack of estrogen, progesterone, and epidermal growth factor-2 receptors is the typical indicators of triple negative breast cancer (TNBC). Quercetin can induce the expression of E-cadherin and suppression of vimentin levels in TNBC. It has also shown the potential to regulate these epithelial mesenchymal transition (EMT) markers resulted in a mesenchymal-to-epithelial transition. In addition, quercetin stimulates antitumor activity of Dox by attenuating the migratory ability of TNBC cells (Srinivasan et al., 2016).

Recent studies indicated that quercetin can enhance the chemosensitivity of breast cancer cells to Dox via inhibiting cell proliferation and invasion, resulting improvement in cell apoptosis, and modulating expression of phosphatase and tensin homolog and p-Akt (S. Z. Li, Qiao, Zhang, & Li, 2015). Moreover, quercetin has exhibited the inhibitory effect on MCF-7 and MDA-MB-231 human breast cancer cell lines through multiple mechanisms such as up-regulation of miR-146a expression, induction of apoptosis, activation of caspase-3 and mitochondrial-dependent pathways, and down-regulation of the expression of epidermal growth factor receptor (EGFR; Tao, He, & Chen, 2015). It also lowers the tumor number (Metastasis), tumor volume, down-regulates 31 genes, and up-regulates 9 genes in human breast cancer (Steiner et al., 2014).

In breast malignancies, epidermal growth factor plays a critical role by propagating cell proliferation, angiogenesis, and metastasis. Silver nanoparticle-based quercetin caused a significant reduction in the expression of various proteins including vimentin, Snail, N-cadherin, Twist, Slug, matrix metalloproteinase-2 (MMP-2), MMP-9, vascular endothelial growth factor receptor 2 (VEGFR2), p-EGFR, protein kinase B (Akt), phosphoinositide 3-kinase (PI3K), and glycogen synthase kinase 3 beta (p-GSK3β) and enhanced E-cadherin protein expression in 7,12-dimethylbenz[a]anthracene-induced mammary carcinoma in Sprague–Dawley rats. It also reduced cell viability and capillary-like tube formation, suppressed tube and new blood vessel

TABLE 1 Anticancer perspectives of quercetin, along with mechanisms of action

Cancer types	Mechanisms	References
Breast cancer	Increases cell apoptosis and inhibits cell cycle progression Increases FasL mRNA expression and p51, p21, and GADD45 signaling activities. Induces protein level, transcriptional activity, and nuclear translocation of Foxo3a	Nguyen et al. (2017)
	Reduces downstream genes including NQO1 and MRP1	Minaei, Sabzichi, Ramezani, Hamishehkar, and Samadi (2016) and Suksiriworapong et al. (2016)
	Down-regulates the vimentin levels and modulates the epithelial mesenchymal transition (EMT) markers	Srinivasan et al. (2016)
	Reduces the expression of vimentin, Snail, N-cadherin, Twist, Slug, metalloproteinase-2 (MMP-2), MMP-9, VEGFR-2, p-EGFR, Akt, p-phosphoinositide 3-kinase (PI3K), and p-GSK3β Enhances E-cadherin protein expression	Balakrishnan et al. (2016) and Quagliariello et al. (2016)
	Causes cell cycle arrest and apoptosis in breast cancer cells via regulation of Akt and Bax signaling mechanistic pathways	Sarkar, Ghosh, Chowdhury, Pandey, and Sil (2016)
	Upregulates the levels of cleaved caspase-8 and caspase-3 Suppresses the expression of phospho-JAK1 and phospho-STAT3 Decreases STAT3-dependent luciferase reporter gene activity (BT-474 cells)	Seo et al. (2016)
	Inhibits the expression of P-glycoprotein	Lv et al. (2016)
Colon cancer	Inhibits the cell viability of CT26 and MC38 colon cancer cells Induces apoptosis through the mitogen-activated protein kinases (MAPKs) pathway Regulates the expression of EMT markers, such as E-, N-cadherin, β-catenin, and snail	Kee et al. (2016)
	Causes G_2 phase arrest Induces autophagic cell death through ERK activation	Y. Zhao, Fan, et al. (2017) and J. Zhao, Liu, et al. (2017)
	Enhances the expression of E-cadherin protein Decreases the expression of metastasis-related proteins of MMP-2 and MMP-9 Reduces the production of different inflammation factors including TNF-α, IL-6, and Cox-2	M. Han, Song, and Zhang (2016)
Pancreatic cancer	Reduces the expression levels of cellular FLICE-like inhibitory protein Activates c-Jun N-terminal kinase (JNK)	J. H. Kim, Kim, Choi, and Son (2016) and Nwaeburu et al. (2016)
	Reduces the tumor growth and drug resistance	Cao et al. (2015)
	Suppresses epidermal growth factor-induced movement action Inhibits the EGFR-mediated FAK, AKT, MEK1/2, and ERK1/2 signaling pathway	J. Lee, Han, et al. (2015), W. J. Lee, Hsiao, et al. (2015), Y. J. Lee, Lee, and Lee (2015), and S. H. Lee, Lee, Min, et al. (2015)
	Activates caspase-3, -8, and -9 and reduces the mitochondrial membrane potential Inhibits extracellular signal-regulated kinase (ERK) phosphorylation and promotes JNK phosphorylation	F. Y. Chen, Cao, et al. (2015), X. Chen, Dong, et al. (2015), and Q. Chen, Li, et al. (2015)
Liver cancer	Induces apoptosis	Guan, Gao, Xu, et al. (2016)
	Down-regulates the expression of PI3K, PKC, COX-2, and ROS Enhances the expression of p53 and BAX	Maurya and Vinayak (2015)
	Activates p53-ROS crosstalk and induces epigenetic modifications	Bishayee, Khuda-Bukhsh, and Huh (2015)
Lung cancer	Triggers BCL2/BAX-mediated apoptosis, as well as necrosis and mitotic catastrophe Inhibits the migratory potential of A549 cells	Klimaszewska-Wiśniewska et al. (2017)
	Inhibits aurora B activities Reduces the phosphorylation of histone 3	Xingyu et al. (2016)
	Enhances expressions of nm23-H1 and tissue inhibitor of metalloproteinase Inhibits the protein expression of MMP-2. GW9662, a PPAR-γ antagonist	Chuang et al. (2016) and Warnakulasuriya, Ziaullah, and Rupasinghe (2016)
	Increases miR-21 expression and causes inhibition of PDCD4 induced by [Cr(VI)]	Pratheeshkumar et al. (2017)
Prostate cancer	Decreases tumor improvement, down-regulates Ki67, and enhances caspase 7 Down-regulates growth factors such as VEGF and EGF	Sharma et al. (2016), P. Wang, Henning, et al. (2016), and Y. Wang, Zhang, et al. (2016)
	Prevents TGF-β-induced expression of vimentin and N-cadherin Decreases TGF-β-induced expression of Twist, Snail, and Slug in prostate cancer-3 cell line	Baruah, Khandwekar, and Sharma (2016)

(Continues)

TABLE 1 (Continued)

Cancer types	Mechanisms	References
Bladder cancer	Inhibits cell proliferation and colony formation of human bladder cancer cells by inducing DNA damage	Oršolić et al. (2016)
Gastric cancer	Inhibits EBV viral protein expressions, including EBNA-1 and LMP-2 proteins Prompts p53-subordinate apoptosis Induces the expression of p53, Bax, and Puma Cleaves caspase-3 and -9 and Parp	J. Lee, Lee, Kim, et al. (2016) and H. H. Lee, Lee, Shin, et al. (2016)
	Causes mitochondrial apoptotic-dependent growth inhibition via the blockade of PI3K-Akt signaling Activates caspase-3 and -9 Down-regulates the Bcl-2 and up-regulates the Bax and cytochrome c Causes mitochondrial apoptotic-dependent growth inhibition via the blockade of PI3K-Akt signaling	Shen et al. (2016)
Bone cancer	Decreases cyclin D1 expression in SKOV3 and U2OSPt cells	Catanzaro, Ragazzi, Vianello, Caparrotta, and Montopoli (2015)
	Inhibits 143B proliferation and up-regulates the expression of miR-217	X. Zhang, Guo, et al. (2015), J. Y. Zhang, Lin, et al. (2015), and X. A. Zhang, Zhang, et al. (2015)
Blood cancer	Activates caspase-3, -8, and -9 and promotes leukemic cell apoptosis Reduced expression of the antiapoptotic proteins B-cell, lymphoma (Bcl)-2. Enhances expression of the proapoptotic proteins Bcl-2-interacting mediator of cell death	F. Y. Chen, Cao, et al. (2015), X. Chen, Dong, et al. (2015), and Q. Chen, Li, et al. (2015)
Brain cancer	Suppresses COX-2 expression by Hsp27 inhibition and acts as both COX-2 and Hsp27 inhibitor Reduces MMP-2 expression	Q. C. Li, Liang, Hu, and Tian (2016) and J. Li, Tang, Li, Li, and Fan (2016) Santos et al. (2015)
	Decreases mitochondria and rough endoplasmic reticulum injury Reduces filopodia-like structures on the cell surface	
	Induces necrotic cell death and down-regulates the Bcl-2 mRNAs expression. Enhances mitochondrial mRNAs expression Modulates the mitochondrial pathway and the JAK2/STAT3 signaling	Wang et al. (2013)
Head and neck cancer	Retards colony growth of HSC-3 cells Suppresses the MMP-2 and MMP-9	Chan, Lien, Lee, and Huang (2016)
	Causes cells arrest at the G1 phase Induces apoptosis, suppresses the expression of Bax, and activates the expression of Caspase-3 and Bcl-2 Reverses gene-encoded Pglycoprotein-mediated MDR	Z. Yuan et al. (2015)
Cervical cancer	Inhibits antiapoptotic AKT and Bcl-2 expression Increases mitochondrial cytochrome-c level Causes cell cycle arrest at G2/M	Bishayee et al. (2013)
	Induces apoptosis via PI3k/Akt pathways	Xiang, Fang, and Wang (2014)
	Significantly inhibits UBE2S expression	Lin et al. (2017)
Skin cancer	Blocks UVB irradiation-induced COX-2 up-expression and NF-kB activation in Hacat cell line	Caddeo et al. (2016)
	Reduces the tumor size and the cumulative number of papillomas. Decreases the serum levels of glutamate oxalate transaminase, glutamate pyruvate transaminase, alkaline phosphatase, and bilirubin	Ali and Dixit (2015)
	Inhibits PI3K and MAPK signaling Attenuates MEK–ERK signaling and influences PI3K/Akt pathway	Rafiq et al. (2015)
Eye cancer	Decreases dose-dependently the RPE cell proliferation, migration, and secretion of VEGF Inhibits the secretion of VEGF evoked by CoCl2-induced hypoxia	R. Chen et al. (2014)
Thyroid cancer	Lowers the cell proliferation and increases rate of apoptosis by caspase activation Downregulates the levels of Hsp90 Decreases chymotrypsin-like proteasome activity	Mutlu Altundağ et al. (2016) and Quagliariello et al. (2016)
Ovarian cancer	Suppresses ROS-induced injury and increases the expression of endogenous antioxidant enzymes	W. Li, Liu, et al. (2014), N. Li, Sun, et al. (2014), X. Li, Wang, et al. (2014), and W. Li, Zhao, et al. (2014)

(Continues)

TABLE 1 (Continued)

Cancer types	Mechanisms	References
	Induces apoptosis of A2780S cells and activates caspase-3 and caspase-9. Down-regulates MCL-1 and Bcl-2. Up-regulates Bax and changes mitochondrial transmembrane potential	Gao et al. (2012)
Kidney cancer	Protects against DOX-induced nephrotoxicity and enhances the cytotoxic effects of DOX. Decreases renal expressions of TNF-α, IL-1B, iNOS, and caspase-3	Heeba and Mahmoud (2016)
Mesothelioma cancer	Modulates gene expression of cyclins and cyclin-dependent kinases Up-regulates JNK, p38, and MAPK/ERK pathways and enhances ERK phosphorylation	Demiroglu-Zergeroglu, Ergene, Ayvali, Kuete, and Sivas (2016)

Note. BT: breast tumor; EGF: epidermal growth factor; NQO1: NAD(P)H quinone oxidoreductase 1; MRP1: multidrug resistant protein 1; GADD45: growth arrest and DNA damage-inducible 45; JAK1: Janus kinase 1; FAK: focal adhesion kinase; PKC: protein kinase C; iNOS: inducible nitric oxide synthase; UBE2S: ubiquitin E2S ligase; RPE: retinal pigment epithelial; STAT3: signal transducer and activator of transcription 3.

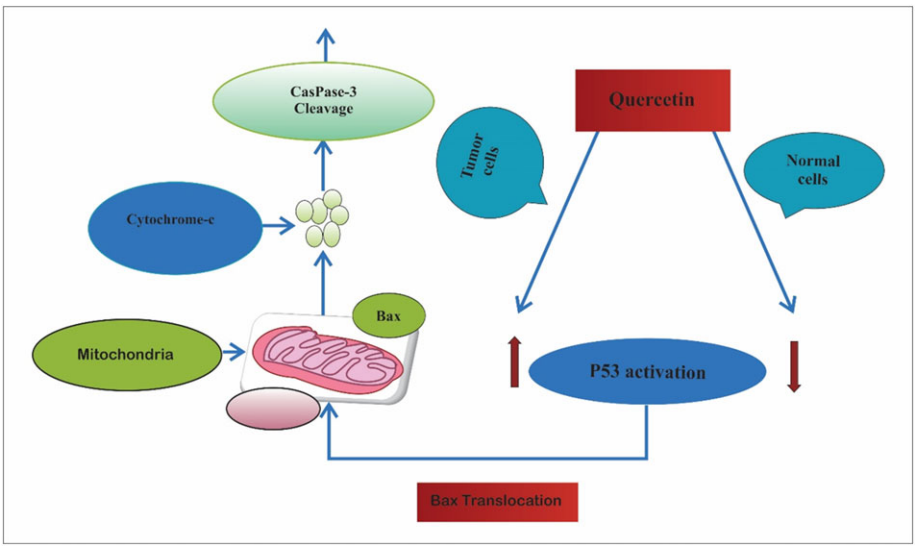

FIGURE 2 Anticancer role of quercetin. Bax: Bcl-2-associated X protein [Colour figure can be viewed at wileyonlinelibrary.com]

formation, and impeded tumor growth and metastasis of the breast cancer cells through the EGFR/VEGFR-2 signaling pathway (Balakrishnan et al., 2016; Quagliariello et al., 2016). Quercetin also causes cell cycle arrest and apoptosis in breast cancer cells via modulating Akt and Bcl-2-associated X protein (Bax) signaling mechanistic pathways (Sarkar et al., 2016). The administration of quercetin at 15 μM suppressed the breast cancer cell proliferation by inducing apoptosis, assuring cell cycle arrest, and attenuating the tumor growth (Rivera, Castillo-Pichardo, Gerena, & Dharmawardhane, 2016). Balakrishnan and colleagues have recently evaluated the effects of gold nanoparticles–conjugated quercetin (AuNPs-Qu-5) in MCF-7 and MDA-MB-231 breast cancer cell lines. These researchers showed that the administration of AuNPs-Qu-5 inhibits cell proliferation in breast cancer cell lines through induction of apoptosis and suppresses EGFR signaling. In addition, treatment with these nanoparticles up-regulated the proapoptotic proteins (Bax, Caspase-3) and down-regulated antiapoptotic protein (Bcl-2). Collectively, these AuNPs-Qu-5 particles could be a potential drug delivery system in breast cancer therapy (Balakrishnan et al., 2017).

In a recent investigation, Seo and colleagues have evaluated the effect of quercetin on the proliferation and apoptosis in breast cancer cells. These researchers found that quercetin reserves the proliferation and clonogenic survival of breast tumor-474 cells as a function of dose and time. This might be accompanied by an increase in sub-G0/G1 apoptotic populations. Quercetin could also induce up-regulation of the levels of cleaved caspase-8 and cleaved caspase-3 (caspase-dependent extrinsic apoptosis) and causing the cleavage of poly(ADP-ribose)polymerase (PARP). However, it did not induce apoptosis via intrinsic mitochondrial apoptosis pathway and did not affect the levels of Bcl-2 and Bax. Quercetin was also found to suppress the expression of phospho-Janus kinase 1 (JAK1) and phospho-signal transducer and activator of transcription 3 (STAT3) and attenuates STAT3-dependent luciferase reporter gene activity (breast tumor-474 cells; Seo et al., 2016). In a similar fashion, quercetin inhibits the activity and expression of P-glycoprotein and causes a significant reduction in Dox resistance in MCF-7/ADR breast cancer cells (Lv et al., 2016). In female BALB/c nude mice, it has attenuated tumor growth, oncocyte proliferation, and tumor necrosis. It has also modulated serum VEGF and markedly reserved tumor calcineurin activities. Additionally, it has down-regulated gene expression of VEGF and reduced protein levels of VEGF (X. Zhao et al., 2016). Adrenaline and noradrenaline (endogenous catecholamines) are secreted by adrenal gland and sympathetic nervous system on exposure to stress. The adrenergic system plays an important role in stress signaling, where

excessive stress can be linked to increased production of reactive oxygen species (ROS). Overproduction of ROS induces oxidative damage and causes the development of diseases such as cancer. Research findings revealed that quercetin suppresses (a) generation of ROS, (b) activation of cyclic adenosine monophosphate and reticular activating system (RAS), and (c) phosphorylation of extracellular signal-regulated kinases 1/2 (ERK1/2) and the expression of HMOX1, MMP-2, and MMP-9 genes. It also suppresses invasion of breast cancer cells by controlling β2-adrenergic signaling (Yamazaki, Miyoshi, Kawabata, Yasuda, & Shimoi, 2014). The (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay has recently been used to investigate the anticancer effect of quercetin and its underlying mechanisms in triple-negative breast cancer cells. Results indicated that quercetin increases cell apoptosis, inhibits cell cycle progression, and increases FasL mRNA expression and p51, p21, and growth arrest and DNA damage-inducible 45 (GADD45) signaling activities. These results suggest that quercetin induces apoptosis and cell cycle arrest via modification of Foxo3a signaling in triple-negative breast cancer cells (Nguyen et al., 2017).

2.2 | Colon cancer

Diet is an important factor associated with colon cancer. Diets that are low in fiber and high in fat, calories, and red meat and processed meats increase the risk of developing colon cancer. Cancer treatment depends on the type of cancer, the stage of the cancer (how much it has spread), age, health status, and additional personal characteristics (NCI, 2014).

Numerous studies have dealt with the effect of quercetin on colon cancer. Kee and coworkers used the water-soluble tetrazolium salts assay, annexin V assay, real-time polymerase chain reaction, western blot analysis, and gelatin zymography to study the inhibitory effect of quercetin on colorectal lung metastasis. These researchers found that quercetin can (a) inhibit the cell viability of colon 26 (CT26) and colon 38 (MC38) cells, (b) induce apoptosis through the MAPKs pathway in CT26 cells, (c) regulate the expression of EMT markers, such as E-, N-cadherin, β-catenin, and snail, by nontoxic concentrations of quercetin, and (d) inhibit the migration and invasion abilities of CT26 cells through expression of MMPs and tissue inhibitor of metalloproteinases (TIMPs) regulation. They concluded from this investigation that quercetin can inhibit the survival and metastatic ability of CT26 cells, and can suppress colorectal lung metastasis in the mouse model, and may be a potent therapeutic agent for the treatment of metastatic colorectal cancer (Kee et al., 2016). Similarly, an investigation by Zhao et al. concluded that 8-C-(E-phenylethenyl) quercetin, a novel quercetin derivative, triggers G_2 phase arrest in colon cancer cells and suppresses propagation. It also induces autophagic cell death through ERK stimulation (Y. Zhao, Fan, et al., 2017; J. Zhao, Liu, et al., 2017). Similarly, quercetin at a concentration of 5 μM could markedly suppress the migratory and invasive capacity of Caco-2 cells. In addition, results from this investigation revealed that the expression of E-cadherin protein was increased by quercetin, whereas metastasis-related proteins of MMP-2, MMP-9 expression got decreased by it in a dose-dependent manner.

The anti-toll-like receptor 4 (TLR4) antibody of pyrrolidine dithiocarbamate might influence the inhibition of quercetin on cell migration and invasion and the expression of various proteins such as E-cadherin, MMP-2, MMP-9, NF-κB p65, and TLR4. Moreover, quercetin could lessen the production of different inflammation factors including TNF-α, Cox-2, and interleukin 6 (IL-6). Hence, quercetin might exert its anti-colon cancer activity via the TLR4- and/or NF-κB-mediated signaling pathway (M. Han et al., 2016). The 1,2-dimethyl hydrazine-induced colon cancer causes nephrotoxicity and further increases the blood urea nitrogen, urea, creatinine, and eventually result in a number of aberrant crypts and foci formation. The potential protective effect of quercetin on cisplatin-induced nephrotoxicity was assessed through lowing the blood urea nitrogen, urea, and creatine and also reduced the aberrant crypt foci number (Q. C. Li, Liang, et al., 2016; J. Li, Tang, et al., 2016). Similar results were obtained by Saleem et al. (2015) who found that treatment of mice either with quercetin, sodium gluconate, or with the combination has a positive effect against 1,2-dimethyl hydrazine-induced colon cancer.

In human colon adenocarcinoma cells, quercetin significantly enhanced the expression of the endocannabinoids receptor (CB1-R) and further suppressed PI3K/Akt/mTOR. It also induced JNK/JUN pathways and modified the metabolism of β-catenin, either directly or via activation of CB1-R (Refolo et al., 2015). These findings were confirmed by other researchers (Xu et al., 2015). The research work conducted by Zhang et al. indicated that quercetin significantly prevents the proliferation of human colon cancer in CACO-2 and SW-620 cells by suppressing the NF-κB pathway, down-regulation of B-cell lymphoma 2, and up-regulation of Bax (X. Zhang, Guo, Chen, & Chen, 2015; J. Y. Zhang, Lin, et al., 2015; X. A. Zhang, Zhang, Yin, & Zhang, 2015). In addition, quercetin was found to have an inhibitory effect on Wnt/β-catenin in colon cancer cells SW480, DLD-1, and HCT116 cancer cells (Amado et al., 2014). Similarly, a study by Kim et al. demonstrated that the inhibitory role of quercetin in colon cancer cell lines through enhancing the apoptotic cell death via generating intracellular ROS and through enhancing sestrin 2 expression is accompanied by activated protein kinase (AMPK) activation. Moreover, these researchers found that the quercetin-induced apoptosis involves sestrin 2/AMPK/mTOR pathway by regulating increases intracellular ROS (Kim, Lee, & Kim, 2013; Kim, Moon, Ahn, & Cho, 2013).

For HT-29 colon cancer cells, Kim and coworkers found that quercetin induces apoptosis by attenuating membrane potential of the mitochondria producing intracellular ROS and elevating the expression of sestrin 2 via the AMPK/p38 mechanistic pathway (G. T. Kim, Lee, Kim, & Kim, 2014; M. C. Kim, Lee, Lim, et al., 2014). Similarly, several research groups independently showed that quercetin increases the antioxidant activity, increases PARP cleavage, and induces caspase-3-cleavage (twofold) in HT-29 colon cancer cells. It also lowers the expressions of specificity proteins (Sp) such as Sp1, Sp3, and Sp4 mRNA; this expression was accompanied by a decreased protein expression. In addition, the Sp-dependent antiapoptotic survival gene was also significantly decreased, both at mRNA and protein levels. It also attenuates microRNA-27a and induces a Sp-repressor, zinc finger protein ZBTB10 (Atashpour et al., 2015; Cho, Kim, Park, Choo, &

Chong, 2013; Del Follo-Martinez, Banerjee, Li, Safe, & Mertens-Talcott, 2013).

2.3 | Pancreatic cancer

Research revealed that quercetin induces apoptosis in tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in resistant pancreatic cancer cells. It was also found that a BH3-only protein BID considerably reduces attenuated TRAIL/quercetin-induced apoptosis. Quercetin has also the ability to reduce the expression levels of cellular FLICE-like inhibitory protein and to strongly save pancreatic cancer cells from TRAIL/quercetin-induced apoptosis, in a dose-dependent manner. Additionally, quercetin stimulates JNK, which influences the proteasomal degradation of cellular FLICE-like inhibitory protein, followed by sensitized pancreatic cancer cells to TRAIL-induced apoptosis (J. H. Kim et al., 2016; Nwaeburu et al., 2016). In human pancreatic cancer cell lines CFPAC-1 and SNU-213, quercetin-3-O-glucoside suppresses the migratory activity induced by transforming growth factor-beta (TGF-β) and vascular endothelial growth factor A even at relatively low dosages in CFPAC-1, but not in bFGF-activated SNU-213 cells. In addition, co-treatment with low dose of gemcitabine and quercetin-3-O-glucoside exhibited synergistic inhibition effects on the infiltrate activity induced by bFGF in CFPAC-1 and SNU-213 cells (J. Lee, Lee, Kim, & Kim, 2016; H. H. Lee, Lee, Shin, et al., 2016).

Cao et al. demonstrated that quercetin in combination with gemcitabine suppresses proliferation, invasion and self-renewal capacity, and cancer stem cells surface markers expression, with alterations of β-catenin in pancreatic cancer stem-like cells. In addition, it reduces tumor growth and drug resistance in pancreatic cancer (Cao et al., 2015). In a similar fashion, Lee et al. found that quercetin suppresses epidermal growth factor-induced migration activity and inhibits the infiltration activity of pancreatic cancer cells in a dose-dependent manner in human pancreatic cancer cell lines. Furthermore, these researchers found that antitumor effects of quercetin are mediated by selectively inhibiting the EGFR-mediated focal adhesion kinase, protein kinase B (AKT), MEK1/2, and ERK1/2 signaling pathway (J. Lee, Han, Yun, & Kim, 2015; W. J. Lee, Hsiao, et al., 2015; Y. J. Lee, Lee, & Lee, 2015; S. H. Lee, Lee, Min, et al., 2015). Similarly, quercetin significantly inhibits proliferation, promotes apoptosis, and induces cell cycle arrest within the G1 phase in pancreatic cancer cells. It can also activate caspase-3, -8, and -9 and reduces the mitochondrial membrane potential and can inhibit the expression level of the δ opioid receptor, whereas isoquercitrin was found to have no effect on the κ and μ opioid receptors. Furthermore, quercetin can inhibit ERK phosphorylation, promote JNK phosphorylation, and significantly inhibit xenograft growth in nude mice (F. Y. Chen, Cao, et al., 2015; X. Chen, Dong, et al., 2015; Q. Chen, Li, et al., 2015).

On the other hand, research conducted by Appari and coworkers revealed that quercetin significantly inhibits viability, migration, expression of MMP-2 and -9, aldehyde dehydrogenase 1 activity, colony, and spheroid formation and triggers apoptosis in pancreatic ductal adenocarcinoma. It also induces the expression of miR-let7-a and causes inhibition of K-ras in cancer cells (Appari, Babu, Kaczorowski, Gross, & Herr, 2014). Similarly, it induces apoptosis of PANC-1, characterized as nucleic acid and genomic DNA fragmentation, chromatin condensation, and sub-G0/G1 fraction of cell cycle increase. It also increases the buildup of intracellular Ca^{2+} ions and Grp78/Bip and GADD153/CCAAT enhancer-binding protein homologous protein (CHOP) protein expression and triggers mitochondrial dysfunction. Quercetin exerts this cytotoxicity against human pancreatic cancer cells trough endoplasmic reticulum stress-mediated apoptotic signaling including pathway, as well as ROS production and mitochondrial dysfunction (J. H. Lee et al., 2013). Other researchers found that quercetin exerts its antiproliferative effects in pancreatic cancer cells by inducing apoptosis and attenuating the growth of orthotopically transplanted pancreatic xenografts (Angst et al., 2013). In MIA PaCa-2 pancreatic adenocarcinoma cells, quercetin at 100 μM inhibits tracer glucose-derived glycogen labeling (Σm), slows down glycogen synthesis, and manages tumor cell proliferation (Harris et al., 2012).

2.4 | Liver cancer

The leading cause of liver cancer is cirrhosis due to either hepatitis B, hepatitis C, or excess alcohol intake (Naghavi, Wang, Lozano, et al., 2015). Other causes include aflatoxin, nonalcoholic fatty liver disease, and liver flukes. The most common types are hepatocellular carcinoma, which makes up to 80% of cases, and cholangiocarcinoma (NCI, 2016).

Previous studies demonstrated that treatment with nano-capsulated quercetin restricts all changes in diethyl nitrosamine-mediated development of hepatocarcinogenesis, suggesting that this nano-capsulated natural product may be accepted as a potent therapeutic agent in preventing diethyl nitrosamine-mediated hepatocarcinogenesis (Mandal et al., 2014). In addition, fatty acid esters of quercetin-3-O-glucoside were found to exhibit significant inhibition of HepG2 cell proliferation. Effect of this novel compound was associated with cell cycle arrest in S-phase and apoptosis. Furthermore, quercetin-3-O-glucoside esters showed significant low toxicity to normal liver cells than sorafenib, a chemotherapy drug used in the treatment of hepatocellular carcinoma (Sudan & Rupasinghe, 2015). Treatment with quercetin at a dose of 50 mg/kg in mice showed a protective effect on cisplatin-induced DNA damage in normal cells, without interfering with the antitumor efficacy of the combined treatment. These results suggest that quercetin can protect the blood, liver, and kidney cells of mice against HIPEC-induced injury and can increase survival of mice by improving the antitumor adaptive immunity with hyperthermia (Oršolić & Car, 2014).

Quercetin inhibits the growth of cancer cells, which can be attributed to various mechanisms, such as the induction of cell cycle arrest and/or apoptosis, as well as its antioxidant functions. In this respect, Zhao and coworkers evaluated the activity of quercetin in human liver cancer HepG2 cells. These workers found that quercetin can induce apoptosis in human liver cancer HepG2 cells with overexpression of fatty acid synthase. These results suggest that apoptosis is induced by quercetin via the inhibition of fatty acid synthase. Additionally, findings by these researchers suggest that quercetin may be useful for preventing human liver cancer (P. Zhao et al., 2014). Furthermore, it was demonstrated by a number of researchers that intake of quercetin seems to play a minor regulatory role, whereas supplement doses may have great effects on gene expression in hepatocytes. Further

work is certainly required in handling of quercetin supplements (Waizenegger et al., 2015a).

Controlled release of medications remains the most convenient way to deliver drugs. Bishayee and coworkers examined the effect of gold-quercetin loaded into poly(DL-lactide-co-glycolide) nanoparticles (NQ) on HepG2 hepatocarcinoma cells. Results revealed that quercetin loaded on the nanoparticles preferentially kill cancer cells, compared with normal cells. In addition, NQ interacted with HepG2 cell DNA and reduces histone deacetylases to manage cell proliferation and arrest the cell cycle at the sub-G stage. These nanoparticles induce apoptosis in HepG2 cells by activating p53-ROS crosstalk and by enhancing epigenetic modifications leading to inhibited proliferation and cell cycle arrest (Bishayee et al., 2015). Protein kinase C is a key regulator of cell growth in mammalian cells and is linked with tumor succession. Quercetin, on the other hand, exhibits antitumor activity both in vitro and in vivo in HepG2 cells. It down-regulates the expression of PI3K, protein kinase C, COX-2, and ROS. Additionally, it enhances the expression of p53 and BAX in HepG2 cells (Maurya & Vinayak, 2015). One of the shortcomings of quercetin in clinics is its poor solubility. To overcome these disadvantages, Guan and coworkers prepared quercetin (QT) as QT-loaded PLGA-TPGS nanoparticles (QPTN) and evaluated its therapeutic efficacy for liver cancer. Results indicated that QPTN could induce HepG2 cell apoptosis in a dose-dependent manner and that QPTN could suppress tumor growth by 59.07%. These researchers concluded that QPTN could be used as a potential intravenous dosage form for the treatment of liver cancer owing to the enhanced pharmacological effects of quercetin with increased liver targeting (Guan et al., 2016).

2.5 | Lung cancer

Several research papers have dealt with quercetin as a chemotherapeutic agent against lung cancer. An investigation by W. Chen, Wang, Zhuang, Zhang, and Lin (2007) revealed that quercetin significantly enhances TRAIL-induced cytotoxicity in non-small cell lung cancer cells. It also increases expression of death receptor (DR) 5 and has no effect on other components of the death-inducing signaling complex. In addition, these researchers demonstrated that quercetin can sensitize TRAIL-induced cytotoxicity in lung cancer cells via two mechanisms: (a) by induction of DR5 and (b) by suppression of survivin expression; these mechanisms may explain the lung cancer preventive activity of quercetin. Furthermore, researchers found that treatment of human lung cancer H-520 cells with quercetin increases the cisplatin-induced apoptosis by 30.2%, down-regulates Bcl-XL and Bcl-2, and up-regulates Bax (Kuhar, Sen, & Singh, 2006).

For JB6 Cl41 cells and A549 lung cancer cells, researchers showed that quercetin inhibits aurora B activities and reduces the phosphorylation of histone 3 (Xingyu et al., 2016). Quercetin also reduces ROS production induced by exposure to hexavalent chromium [Cr(VI)] in BEAS-2B cells. It also suppresses the malignant cell transformation, improves miR-21 expression, and causes inhibition of PDCD4 induced by [Cr(VI)] in a dose-dependent manner. Furthermore, quercetin reduces the tumor occurrence and suppresses the Cr(VI)-induced malignant transformation and tumorigenesis in nude mice injected with BEAS-2B cells (Pratheeshkumar et al., 2017). In human lung carcinoma A549 cells, researchers demonstrated that quercetin appreciably suppresses cell invasion and migration. It inhibits the activity and expression of MMPs-2 in a dose-dependent manner. It also increases the expressions of nm23-H1 and TIMP-2 and inhibits the protein expression of MMP-2. GW9662, a PPAR-γ antagonist (Chuang et al., 2016; Warnakulasuriya et al., 2016).

In their work on lung carcinogenesis, Chen and colleagues demonstrated that benzo[a]pyrene-induced human bronchial epithelial cell (HBEC) transformation is improved by IL-6 in vitro. The carcinogen/IL-6-transformed cells exhibit higher expression of signal transducer and activator of STAT3 when compared with cells transformed by BPDE alone. Furthermore, these researchers showed that treatment with quercetin (a) considerably decreases BPDE-stimulated IL-6 secretion from human lung fibroblasts via inhibition of the NF-κB and ERK pathways, (b) blocks IL-6-induced STAT3 activation in HBECs, and (c) abolishes IL-6 enhancement of HBEC transformation by BPDE (W. Chen et al., 2016). On the other hand, Zhao and coworkers examined the inhibitory effect of quercetin on the growth of A549 lung cancer cells and found that it induces apoptosis, decreases the levels of MMP-9 (mRNA and protein) and TGF-β1 protein, and reduces the number of tumor cells. These researchers also found that the combination of quercetin (at low concentrations) with TIMP-1 shows synergistic inhibitory effect on the growth of A549 cells (X. Zhao & Zhang, 2015). Quercetin also decreases claudin-2 expression in lung adenocarcinoma A549 cells in a time- and concentration-dependent manner, lowers the stability of claudin-2 mRNA, and increases the expression of miR-16. Categorically, quercetin reduces claudin-2 level through up-regulation of miR-16 expression (Sonoki et al., 2015). In lung cancer cells (A549 and H460 cells), quercetin reduced cell viability and inhibited heat shock protein 70 (HSP70) expression in both cell lines in a dose-dependent manner. Addition of a fixed quercetin dose improved gemcitabine-induced cell death, which was linked to increased caspase-3 and caspase-9 activities (J. Lee, Han, et al., 2015; W. J. Lee, Hsiao, et al., 2015; Y. J. Lee, Lee, & Lee, 2015; S. H. Lee, Lee, Min, et al., 2015; Y. Liu, Wu, & Zhang, 2015).

Similarly, quercetin prevented tumor proliferation by (a) initiating cell cycle arrest, (b) improving TRAIL-induced tumor cell death, (c) lowering the p62 protein expression, and (d) increasing GFP-LC3B in human lung cancer cells in a dose-dependent fashion (Moon, Eo, Lee, & Park, 2015; J. Wang, Zhang, Cheng, Zhang, & Li, 2015). It also induces apoptosis in A549 cells via mitochondrial depolarization by triggering an imbalance in B-cell lymphoma 2/Bcl2 antagonist X (Bcl2/Bax) ratio and by down-regulating the IL-6/STAT3 signaling pathway. Additionally, quercetin could block nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) action at early hours, which might cause a down-regulation of the IL-6 titer, and the IL-6 expression, in turn, could inhibit p-STAT3 expression. Down-regulation of both the STAT3 and NF-κB expressions might, consequently, causes down-regulation of Bcl2 because both are upstream effectors of Bc12. In A549 cells, modification in Bcl2 reactions may result in an imbalance in the Bcl2/Bax ratio, which could eventually lead mitochondria mediated apoptosis (Mukherjee & Khuda-Bukhsh, 2015).

Nair and colleagues examined the cumulative effects of curcumin and quercetin in inducing apoptosis in benzo(a)pyrene (100 mg/kg body weight)-induced lung carcinogenesis in mice. In benzo(a)

pyrene-treated animals, supplementation of curcumin (60 mg/kg body weight) and quercetin (40 mg/kg body weight), separate as well as combined, considerably reduced the protein expression of Bcl-2 and amplified the protein expression of Bax. Supplementation also improved the enzyme activities of caspase 9 and caspase 3 (Nair, Malhotra, & Dhawan, 2015). In addition, a peer group of investigators (Lam et al., 2012; Youn, Jeong, Jeong, Kim, & Um, 2013) determined that quercetin strongly inhibits cell production and enhanced sub-G1 and apoptosis despite of p53 status in H460 cells. It also improved the expression of genes linked with DR signaling TRAIL receptor, caspase-10, IL 1R DNA fragmentation factor 45, tumor necrosis factor receptor 1, FAS, inhibitor of kappa-B-alpha (IκBα), and cell cycle inhibition GADD45, p21 (Cip1). However, it reduced the expression of genes involved in activation of NF-κB and IKKα. It also suppressed the NF-κB and additionally improved the expression of DRs and cell cycle inhibitors (Lam et al., 2012; Youn et al., 2013). In A549 non-small cell lung cancer cells, Klimaszewska-Wiśniewska and colleagues have recently employed the methyl-thiazol-diphenyl-tetrazolium (MTT) assay, annexin V/propidium iodide test, electron microscopic examination, cell cycle analysis based on DNA content, real-time polymerase chain reaction assays, in vitro scratch wound-healing assay, fluorescence staining of F-actin, β-tubulin, and vimentin to examine the effect of quercetin on microfilaments, microtubules, and vimentin intermediate filaments. Results revealed that quercetin triggers BCL2/BAX-mediated apoptosis, necrosis, and mitotic catastrophe and suppresses the migratory potential of A549 cells. These findings suggest that quercetin-induced mitotic catastrophe involves the perturbation of mitotic microtubules, which results in monopolar spindle formation and to failure of cytokinesis (Klimaszewska-Wiśniewska et al., 2017)

2.6 | Prostate cancer

Numerous researchers have investigated the effect of quercetin, alone or in combination with other drugs, on colon cancer. Standard treatment for metastatic and castration-resistant prostate cancer includes chemotherapy with docetaxel (Doc). However, chemoresistance and side effects of Doc limit its clinical success. In this respect, different research groups investigated the effect of natural products such as quercetin on the efficacy of androgen-independent prostate cancer cells. These researchers found that quercetin (a) improves the healing practicality of Doc, (b) considerably lessens tumor progression, (c) cut down the Ki67, (d) increases cleavage of caspase 7, (e) lowers blood concentrations of growth factors, such as VEGF and epidermal growth factor, and (f) substantially lifts the levels of tumor silencer mir15a and mir330 (P. Wang, Henning, et al., 2016; Y. Wang, Zhang, Lv, Zhang, & Zhu, 2016). In castration-resistant prostate cancer cells, quercetin improves the therapeutic effect of Doc in through multiple mechanisms including down-regulation of chemoresistance-related proteins (P. Wang, Henning, et al., 2016; Y. Wang, Zhang, et al., 2016). Additionally, in PC3 and DU145 prostate cancer cell lines, a combined treatment with quercetin and curcumin, two known dietary phytocompounds with described DNMT-inhibitory activity, was much more effective than either of them in both inhibition of DNMT and in triggering apoptosis via mitochondrial depolarization. These two natural compounds have the potential for use as chemopreventive agents of androgen resistance in prostate cancer (Sharma et al., 2016).

The therapeutic potential of novel quercetin-loaded nanomicelles (to enhance the solubility of quercetin in water) for prostate cancer treatment was recently evaluated. Results indicated that quercetin can be efficiently encapsulated into micelles up to 1 mg per ml, which corresponds to a 450-fold increase of its water solubility. Additionally, a nanomicelle-based drug delivery system could be a promising and effective therapeutic strategy for clinical treatment of prostate cancer (X. Zhao et al., 2016). In LNCaP and PC-3 cells, Song et al. examined the effects of quercetin combined with 2-methoxyestradiol on the proliferation of androgen-dependent LNCaP and androgen-independent PC-3 human prostate cancer cells lines. Both quercetin and 2-methoxyestradiol could inhibit the growth of prostate cancer cells in a dose-dependent manner. In addition, different concentrations of quercetin ranging from 0 to 200 μmol/L suppress the growth rates of LNCaP and PC-3 cells by inducing apoptosis and triggering cell cycle arrest (Song, Wang, Wang, & Xing, 2016). Unmistakably, quercetin induces apoptosis, which leads to cytochrome c release, cleavage of caspase 3, and PARP. Quercetin also impedes generation of ROS and Akt/mTOR cell survival pathways in PC-3 cells (Hamidullah et al., 2015; Paller et al., 2015). The hyperoside and quercetin in blend inhibited the development of prostate cancer cells. It induced apoptosis, cell cycle arrest, and reduced invasive capacity, through inhibition of the miR-21 signaling pathway (F. Q. Yang, Liu, Li, et al., 2015; Z. Yang, Liu, Liao, et al., 2015; F. Yang, Song, et al., 2015).

In LAPC-4-AI and PC-3 prostate cancer cells, quercetin at a concentration of 5 μM significantly enhanced cell cycle arrest at G2/M phase and increased apoptosis. Quercetin also increased the inhibition of PI3K/Akt and the STAT3 signaling pathways compared with Doc alone and decreased the protein expression of multidrug resistance-related protein (Y. Wang, Han, et al., 2015; P. Wang, Henning, Heber, & Vadgama, 2015; P. Wang, Phan, et al., 2015; J. Wang, Zhang, Cheng, Zhang, & Li, 2015). Y. Wang, Han, et al. (2015), P. Wang, Henning, et al. (2015), P. Wang, Phan, et al. (2015) and J. Wang, Zhang, et al. (2015) evaluated the effect of a combination of arctigenin and quercetin, two promising natural chemo-preventive agents, on Androgen-dependent LAPC-4 and LNCaP prostate cancer cells. Results from this investigation revealed that the combination of the aforementioned compounds inhibits both androgen receptor and PI3K/Akt pathways. In addition, results showed that the mixture inhibitions cell migration in both cell lines compared with individual compounds tested (Y. Wang, Han, et al., 2015; P. Wang, Henning, et al., 2015; P. Wang, Phan, et al., 2015; J. Wang, Zhang, et al., 2015). In androgen-dependent LNCaP and androgen-independent PC-3 human prostate cancer cell lines of male BALB/c nude, the inhibitory effect of a combination of quercetin and 2-methoxyestradiol was investigated. Results showed that the combination appreciably inhibits prostate cancer xenograft tumor growth for both cell lines as compared with control, which suggests that the combination can serve as a novel clinical treatment regimen for prostate cancer (F. Q. Yang, Liu, Li, et al., 2015; Z. Yang, Liu, Liao, et al., 2015; F. Yang, Song, et al., 2015). Finally, a review by Baruah et al. (2016) concluded that quercetin can prevent TGF-β-induced expression of vimentin and N-cadherin and expand the outflow of E-cadherin in PC-3 cells, along these lines

forestalling TGF-β-initiated EMT. Besides, the relative expression of Twist, Snail, and Slug demonstrates that quercetin essentially diminishes TGF-β-induced expression of Twist, Snail, and Slug in PC-3 cell line (Baruah et al., 2016).

2.7 | Bladder cancer

Bladder cancer is one of the most common cancers of the urinary tract and a major cause of cancer-related mortality. Risk factors include smoking, occupational exposure to polycyclic aromatic hydrocarbons and aromatic amines, and, possibly, environmental pollution. On the other hand, fruits and vegetables intake may exert a protective effect (Di Lorenzo et al., 2016 and references therein). The cytotoxic and genotoxic effects of quercetin on human bladder cancer T24 cells have recently been investigated by Oršolić and colleagues by means of MTT test, clonogenic assay, and DNA damaging effect by comet assay. These researchers showed that quercetin at doses of 1 and 50 μM for introduction times (24, 48, and 72 hr) has cytotoxic and genotoxic impacts on human bladder T24 cells. These results suggest that quercetin may be an effective chemopreventive and chemotherapeutic agent and could prevent cell propagation and colony formation of human bladder cancer cells by expansion of DNA damage of T24 cells (Oršolić et al., 2016).

Similarly, the role of autophagy in quercetin-induced apoptosis in human bladder carcinoma BIU-87 cells in vitro was examined. Quercetin considerably inhibited proliferation of BIU-87 cells in a time- and dose-dependent fashion and that autophagy is induced earlier than apoptosis. Hence, autophagy may play a protective role at the initiation phase by delaying apoptosis and reducing the quercetin-induced death of BIU-87 cells (Wei et al., 2012). Additionally, in bladder cancer 253J cells, Y. Kim, Kim, and Cha (2011) found that large conductance Ca^{2+}-activated K^{+} (BK(Ca)) or MaxiK channels are expressed and that quercetin increases BK(Ca) current in a concentration-dependent and reversible manner. On the other hand, Su and coworkers have recently examined the mechanisms of quercetin on inhibition of bladder cancer. They employed MTT and cologenic assays to test the inhibitory sensitivity in vitro against two human and one murine bladder cancer cell lines and used western blot to examine AMPK pathway including 4E-BP1 and S6K. These researchers found that quercetin induces apoptosis and inhibits migration via activation of AMPK (Su et al., 2016).

2.8 | Gastric or stomach cancer

A group of researchers have recently examined the anticancer effects of quercetin and isoliquiritigenin in xenograft animals implanted with Epstein–Barr virus (EBV)(+) or EBV(−) human gastric carcinoma. These researchers found that quercetin exhibits anticancer effect in these cells by means of hindered EBV viral protein expressions, including EBNA-1 and LMP-2 proteins in tumor tissues from mice infused with EBV(+) human gastric carcinoma. Quercetin viably prompted p53-dependent apoptosis than isoliquiritigenin in EBV(+) human gastric carcinoma, and this enlistment was related with expanded expressions of the separated types of caspase-3, -9, and Parp. In EBV(−) human gastric carcinoma (MKN74), quercetin instigated the expressions of p53, Bax, and Puma and the separated types of caspase-3 and -9 and Parp at comparative levels (J. Lee, Lee, Kim, et al., 2016; H. H. Lee, Lee, Shin, et al., 2016). In gastric cancer stem cells, quercetin induced cell apoptosis in a mitochondrial-dependent approach through (a) lessening in mitochondrial membrane potential, (b) enhancement of caspase-3 and -9, (c) down-regulation of Bcl-2, and (d) up-regulation of Bax and cytochrome c. It, likewise, caused mitochondrial apoptotic-dependent growth inhibition by diminishing the PI3K-Akt signaling and suppressed the overexpression of Bcl-2 and kept the reduction in mitochondrial film potential. It similarly augmented the levels of caspases, Bax, and cytochrome c (Shen et al., 2016). In human gastric cancer MGC-803 cells, X. Zhang, Guo, et al. (2015), J. Y. Zhang, Lin, et al. (2015), and X. A. Zhang, Zhang, et al. (2015) demonstrated that a combined treatment with curcumin and quercetin essentially suppresses cell multiplication, accompanied by loss of mitochondrial membrane potential (ΔΨm), release of cytochrome c and diminished phosphorylation of AKT and ERK. On the other hand, Kim and colleagues employed western blot analysis and MTT assay to investigate the signaling pathway of quercetin-induced apoptosis in the AGS cells, a commonly used human gastric adenocarcinoma cell line. They found that quercetin exerts its effect against AGS cells through inducing apoptosis and suppressing the transient receptor potential melastatin (TRPM7) streams. Additionally, treatment with quercetin extended the apoptosis of HEK293 cells, which overexpress TRPM7. These researchers then concluded that quercetin might play an important pathophysiological role in AGS cells through MAPK signaling pathways and TRPM7 channels (G. T. Kim, Lee, Kim, et al., 2014; M. C. Kim, Lee, Lim, et al., 2014).

In human gastric carcinoma, the EPG85-257P cell line and its daunorubicin-resistant variation EPG85-257RDB, quercetin exerted antiproliferative impact (with an IC_{50} value of 12 μM after 72 hr), predominantly through induction of apoptosis, abatement of P-glycoprotein expression, hindrance of medication transport, and down-regulation of ABCB1 gene expression (Borska et al., 2012). Similarly, quercetin could inhibit the proliferation of human gastric cancer by down-regulation of the expressions of leptin and leptin receptor protein, leptin mRNA, and leptin receptor mRNA through the JAK–STAT pathway in MGC-803 cells (Qin et al., 2012).

In an effort to identify an effective drug as a potential candidate for gastric cancer, Wang and colleagues investigated the effect of quercetin on the apoptosis and morphology of gastric carcinoma BGC-823 cells, as well as a plausible mechanism of action. Results indicated that quercetin can induce apoptosis of the BGC-823 cells, accompanied by a decrease in Bcl-2/Bax ratio with increased expression of caspase-3. This implies that quercetin-induced apoptosis may be mediated through the mitochondrial pathway (K. Wang et al., 2011). Additionally, treatment of human gastric cancer cells MGC-803 with quercetin at 40 μmol/L considerably decreased the expression of VEGF-C and VEGFR-3 compared with the control group after 48 hr. This indicates that quercetin can down-regulate the expression of VEGF-C and VEGFR-3 in human gastric cancer cells MGC-803 (Yu et al., 2009).

2.9 | Bone cancer

Osteosarcoma is becoming the most common malignant bone tumor in children and young adults. The main difficulties in osteosarcoma

treatment are the occurrence of metastases, severe side effects, and chemoresistance. Treatment of human osteosarcoma cell line 143B with quercetin substantially caused growth inhibition, G2/M phase arrest, and prompted apoptosis (Berndt et al., 2013). Quercetin blocked the extension of human methotrexate safe osteosarcoma cell U-2OS/MTX300 in a dose and time-dependent route through inciting cell apoptosis, cutting down mitochondrial layer potential, releasing of mitochondrial cytochrome c to cytosol, and dephosphorylating of Akt (Yin et al., 2012). Similarly, the examination disclosures of Sekeroğlu and Sekeroğlu (2012) demonstrated that treatment with quercetin at a dose of 50 mg/kg bw/day for 10 days brought in an immense MTX-induced chromosomal aberrations from the norm in mouse bone-marrow cells of mice. It basically cut down the chromosomal aberrations and variation cells (Sekeroğlu & Sekeroğlu, 2012). Quercetin (50 or 100 mg/kg for 2 days) was neither clastogenic nor apoptogenic in mice inside and out reduced cisplatin-induced clastogenesis and apoptosis in the bone marrow cells in dose- and time-dependent manner. These researchers concluded that quercetin has a protective role in the abatement of cisplatin-induced clastogenesis and apoptosis in the bone marrow cells of mice and that quercetin can be a good choice to decrease the deleterious effects of cisplatin in the bone marrow cells of cancer patients treated with this drug (Attia, 2010).

In a similar fashion, treatment with quercetin at 10–50 μM doses for 48 achieved clear changes in the scattering of cell cycle phases in the CDDP-resistant SKOV3/CDDP ovarian cell line. The cyclin D1 expression decreased after quercetin treatment in SKOV3 and U2OSPt cells. (Catanzaro et al., 2015). Similarly, administration of quercetin (10 μM) inhibited 143B proliferation and up-regulated the expression of miR-217, whereas the target KRAS was down-regulated both at mRNA and protein levels. Quercetin also regulated cisplatin sensitivity by modulating the miR-217-KRAS axis (X. Zhang, Guo, et al., 2015; J. Y. Zhang, Lin, et al., 2015; X. A. Zhang, Zhang, et al., 2015). In human osteosarcoma cell line (MG-63), quercetin (a) induced the loss of mitochondrial membrane potential, (b) down-regulated the expression of antiapoptotic protein, Bcl-2, (c) up-regulated the expression of the proapoptotic proteins, Bax, and cytochrome C, and (d) activated caspase-3 and caspase-9 (Liang et al., 2011). It further induced apoptosis and significantly reduced mitochondrial membrane potential, caused the release of mitochondrial cytochrome c to the cytosol and activation of caspase-3, down-regulated the Bcl-2, p-Bad, up-regulated the Bax, and caused dephosphorylating of Akt (Xie et al., 2011).

2.10 | Blood cancer

HSP27 enhances the growth of leukemia by shielding cancer cells of apoptosis. In U937 human leukemia cells, quercetin synergistically inhibits cell propagation and induces apoptosis via lessening the Bcl2-to-Bax ratio. It considerably suppresses the penetration of tumor cells and the expression of angiogenesis-associated proteins HIF1α and VEGF. It additionally reduces the protein expression of cyclin D1 and therefore blocks the cell cycle at G 1 phase. Quercetin considerably reduced 2Notch 1 expression and the phosphorylation stages of the downstream signaling proteins AKT and mTOR. These results suggest that inhibition of HSP27 expression improves the anticancer effects of quercetin in U937 human leukemia cells (W. Chen et al., 2016). In BALB/c nude mice of P388 leukemic cells, quercetin and the antileukemic drug Adriamycin could significantly extend the survival of mice. Quercetin additionally might decrease the ratio of G0/G1 phase and increase the cell proportion in S phase and G2/M phase in mice. It additionally activates caspase-3 and promotes leukemic cell apoptosis, down-regulates the expression of BCL-2 and NF-κB gene, and up-regulates the expression of Bax gene. These findings suggest that quercetin can inhibit leukemia cell proliferation, promote apoptosis, and enhance the chemotherapeutic effects of adriamycin through controlling the expression of apoptosis-related genes (Y. Q. Han, Hong, Su, & Wang, 2014).

Similarly, treatment of human leukemic multidrug resistance K562/adriamycin cells with quercetin promoted cell apoptosis in a dose-dependent fashion, whereas treatment with a combination of quercetin and adriamycin resulted in synergistic enhancement of the apoptotic effect. In addition, treatment of K562/adriamycin cells with quercetin alone or in combination with adriamycin led to (a) loss of mitochondrial membrane potential, (b) activation of caspase-8, -9, and -3, (c) reduction in the antiapoptotic proteins Bcl-2 and Bcl-extra-large expression, and (d) improved expression of the proapoptotic proteins Bcl-2-interacting mediator of cell death, Bcl-2-associated death promoter, and Bax in the cells. These findings demonstrate that quercetin is important in multidrug resistance and might be developed into a new reversal agent for cancer chemotherapy (F. Y. Chen, Cao, et al., 2015; X. Chen, Dong, et al., 2015; Q. Chen, Li, et al., 2015). Similar results were obtained by Han and coworkers who explored the potential antileukemia effects of quercetin along with its mechanism of action. These researchers demonstrated that the combination of adriamycin, an anthracycline antibiotic widely applied in the chemotherapy for leukemia, and quercetin shows prolonged survival time and less peripheral white blood cells. Quercetin could improve the antileukemic effect of adriamycin through inhibiting the proliferation of white blood cells by trapping the cells at the S phase and activating caspase-3 via the expressional regulation of Bcl-2, Bax, and NF-κB (Y. Han et al., 2015).

In vitro and in vivo studies on P39 leukemia cells revealed that quercetin exhibits marked apoptosis, down-regulation of Bcl-2, Bcl-xL, and myeloid cell leukemia (Mcl)-1, up-regulation of Bax, and mitochondrial translocation, and activating cytochrome c discharge and caspases activation. Additionally, it moreover induced the expression of FasL protein and amplified cell arrest in G1 phase of the cell cycle, with noticeable reduction in cyclin-dependent kinase 2 (CDK2), CDK6, cyclin D, cyclin E, and cyclin A proteins (Maso et al., 2014). In acute HL-60 myeloid leukemia (AML) cells, quercetin considerably activated caspase-8, caspase-9, and caspase-3, initiated PARP cleavage, and caused mitochondrial membrane depolarization. Initiation of PARP cleavage by quercetin was additionally observed in THP-1, MV4-11, and U937 cell lines. Moreover, treatment with quercetin prompted continued activation of ERK and inhibition of ERK in HL-60 cells (J. Lee, Han, et al., 2015; W. J. Lee, Hsiao, et al., 2015; Y. J. Lee, Lee, & Lee, 2015; S. H. Lee, Lee, Min, et al., 2015).

In human K562 chronic myeloid leukemia cells, treatment with quercetin considerably reduced both the proportion of apoptotic cells and caspase-3 activity. It also altered the cell cycle profile, particularly

after 48 hr of exposure. In addition, it increased the Bcl-2 protein expression and stopped quercetin-induced down-regulation of Mcl-1 and Bcl-xL (Brisdelli et al., 2014). Interestingly, the combination quercetin and menadione (vitamin K3) can improve the outcome of conventional leukemia therapies mediated by opening of the mitochondrial permeability transition pore (Baran et al., 2014). In EBV-negative Burkitt's lymphoma cells, quercetin reduced c-Myc expression and inhibited the PI3K/AKT/mTOR activity. It additionally induced absolute autophagy flux in Burkitt's lymphoma cells that contributes to c-Myc reduction in some of these cells (Granato et al., 2016).

The effects of quercetin on Hedgehog signaling in chronic myeloid leukemia KBM7 cells were recently examined by Li and coworkers. These workers showed that quercetin significantly inhibits KBM7 cell proliferation, induces cell apoptosis, and blocks cell cycle at G1 phase, in dose-dependent manners. It can also increase p53 and Caspase-3 expression (W. Li, Liu, et al., 2014; N. Li, Sun, et al., 2014; X. Li, Wang, et al., 2014; W. Li, Zhao, et al., 2014). In a diffuse large B-cell lymphoma cell line, quercetin synergistically improved rituximab-induced growth inhibition and apoptosis. It additionally, exerted inhibitory activity against STAT3 pathway and down-regulated the expression of survival genes (W. Li, Liu, et al., 2014; N. Li, Sun, et al., 2014; X. Li, Wang, et al., 2014; W. Li, Zhao, et al., 2014). In human myeloma cell lines U266, KM3 and RPMI8226, and malignant mesothelioma (MM) derived cells, Ma and colleagues found that quercetin inhibits the propagation of MM cells in a dose- and time-dependent manner, accompanied by reduction of IQGAP1 expression at mRNA and protein levels and reduction in ERK1/2 activation. Furthermore, it inhibits the interaction between IQGAP1 and ERK1/2 in RPMI8226 cells (Ma et al., 2014).

Quercetin restores TRAIL-induced cell death in resistant transformed follicular lymphoma B-cell lines, despite the high Bcl-2 expression levels owing to the chromosomal translocation. It rescues mitochondrial activity by inducing the proteasomal degradation of Mcl-1 and by hindering survivin expression at the mRNA level, regardless of p53 (Jacquemin et al., 2012). Chang and coworkers have recently investigated the molecular mechanisms by which quercetin exerts its anticancer effects against HL-60 AML cells. Quercetin suppresses cell proliferation in the HL-60 cell line in vitro and in vivo, and quercetin-induced G_0/G_1-phase arrest occurs when expressions of CDK2/4 are inhibited and the CDK inhibitors, p16 and p21, are induced. These researchers concluded that quercetin induces cytoprotective autophagy in HL-60 cells, besides promoting apoptosis. This inhibition of autophagy can be an effective strategy to enhance the anticancer activity of quercetin in AML (J.-L. Chang et al., 2017).

2.11 | Brain cancer

Chae and coworkers evaluated the apoptotic effect of quercetin on human malignant pleural mesothelioma. Quercetin at 20–80 μM concentrations considerably reduced the mesothelioma cell viability and induced apoptotic cell death in human malignant pleural mesothelioma (MSTO-211H). It additionally enhanced the sub-G_1 cell population, and was found to interact with Sp1, and considerably inhibited its expression at the protein and mRNA levels. Quercetin also reduced the levels of Sp1 regulatory genes, such as cyclin D1, Mcl-1, and survivin. Interestingly, apoptotic signaling cascades are activated via the cleavage of Bid, caspase-3, and PARP, and by the down-regulation of Bcl-xL and the up-regulation of Bax. These results strongly suggest that Sp1 might be a novel molecular target of quercetin in human malignant pleural mesothelioma (Chae et al., 2012). In U87 glioma cells in a time- and dose-dependent approach, quercetin significantly suppressed the expression of PLD1 at the transcriptional level and additionally reduced the NFκB-induced PLD1 expression via inhibition of NFkB transactivation. It also suppressed stimulation of MMP-2 (Park & Min do, 2011). Q. C. Li, Liang, et al. (2016) and J. Li, Tang, et al. (2016) have recently studied the effects and interactions of Hsp27 inhibitor, quercetin, and *trans*-4-[4-(3-adamantan-1-yl-ureido)-cyclohexyloxy]-benzoic acid on glioblastoma cells and showed that a combination of quercetin and *trans*-4-[4-(3-adamantan-1-yl-ureido)-cyclohexyloxy]-benzoic acid synergistically impedes glioblastoma growth in vitro and in vivo. Quercetin additionally suppressed COX-2 expression by inhibiting Hsp27; hence, it acts as both COX-2 and Hsp27 inhibitor (Q. C. Li, Liang, et al., 2016; J. Li, Tang, et al., 2016).

Within human GL-15 glioblastoma cells, quercetin, and other flavonoids, reduced the number of feasible cells and the mitochondrial metabolism. Additionally, it damaged mitochondria and rough endoplasmic reticulum and induced apoptosis. These polyphenols also initiated delay cell migration, which is linked to a lessening in filopodia-like structures on the cell surface, decrease in MMP-2 expression and action, and an enhancement in intracellular and extracellular expression of fibronectin, and intracellular expression of laminin (Santos et al., 2015). In multiform glioblastoma U87 cells, diverse concentrations of quercetin (50, 100, and 150 μmol/L) induced apoptosis in a concentration-dependent fashion by considerably enhancing the expression of MDM2 mRNA and active caspase-3 protein but decreasing the expression of p53 in the cells (H. Wang et al., 2014). In human anaplastic astrocytoma (MOGGCCM) and glioblastoma multiform (T98G) cell lines, Jakubowicz-Gil, Langner, Bądziul, Wertel, and Rzeski (2013, 2014) have recently investigated the effect of sorafenib and quercetin on the induction of apoptosis and autophagy. Sorafenib and quercetin were effective cell death inducers especially in those cells where the expression of heat shock proteins was blocked.

Similarly, Pozsgai and coworkers employed techniques such as cell viability assay, flow cytometry analysis, colony formation assay, and western blot analysis to investigate the efficacy of treatment with irradiation, temozolomide, and quercetin, alone, or in combinations, on two glioblastoma cell lines, DBTRG-05 and U-251. A combination of the agents, including quercetin, greatly reduced cell viability and colony formation. Quercetin alone, or in combination with irradiation, increased the breakdown of caspase-3 and PARP-1, considerably reduced the level of phospho-Akt, and raised the levels of phospho-ERK, phospho-JNK, phospho-p38, and phospho-RAF1. These findings suggest that supplementation of standard therapy with quercetin enhances the efficiency of treatment of experimental glioblastoma by prompting apoptosis via the cleavage of caspase-3 and PARP-1 and by suppressing the activation of Akt pathway (Pozsgai et al., 2013). In a similar fashion, in C6 glioma cells, quercetin nanoliposomes initiated necrotic cell death and down-regulated the expression of Bcl-2 mRNAs, and enhance the expression of mitochondrial mRNAs through STAT3-mediated signaling pathways in C6 glioma cells. These

nanoliposomes additionally modulated the mitochondrial and the JAK2/STAT3 signaling pathway (Wang et al., 2013).

On the other hand, quercetin in several cells, including U87-MG glioblastoma, U251, and SHG44 glioma cell lines, suppressed cell viability in a dose-dependent approach. It considerably reduced glioma cell migration and enhanced cell senescence and apoptosis. Furthermore, treatment with quercetin significantly lowered the protein intensities of p-AKT, p-ERK, MMP-9, Bcl-2, and fibronectin. It additionally suppressed the Ras/MAPK/ERK and PI3K/AKT signaling pathways (Pan et al., 2015). Similarly, in U251 and U87 human glioblastoma cells, administration of 200 or 400 μmol/L of TMZ alone efficiently inhibited cell viability, whereas the combination of quercetin (30 μmol/L) with TMZ (100 μmol/L) considerably suppressed the cell viability and enhanced the inhibition rate of TMZ. Additionally, the combined effect significantly increased caspase-3 activity and prompted cell apoptosis. Taken all together, treatment with a combination of TMZ and quercetin can competently suppress human glioblastoma cell survival in vitro (Sang, Li, & Lan, 2014).

In a similar fashion, quercetin significantly inhibited propagation of U373MG cells in a concentration-dependent approach after 48 and 72 hr of incubation. It additionally induced cell death through apoptosis and further (a) enlarged number of cells in the sub-G1 phase, (b) reduced mitochondrial membrane potential, (c) activated caspase-3 and caspase-7, (d) increased caspase-3 and 9 activities, and (f) triggered degradation of PARP. Quercetin also activates JNK, enhances p53 expression, and initiates autophagy (G. T. Kim, Lee, et al., 2013; H. Kim, Moon, et al., 2013). Moreover, in peripheral T-cells, quercetin (50 mg/kg) exhibited a small decrease in lymphocytic permeation, a marker of good quality diagnosis in gliomas, and a small reduction in cell feasibility, in a time-dependent fashion (Zamin et al., 2014). In human glioblastoma multiform T98G cells, quercetin induces apoptosis accompanied with activation of caspase 3 and 9 activation, cytochrome c release from the mitochondrion, and a drop in the mitochondrial membrane potential. Increased expression of caspase 12 and the presence of several granules in the cytoplasm after temozolomide treatment with or without quercetin may propose that apoptosis is initiated by endoplasmic reticulum stress (Jakubowicz-Gil et al., 2013).

2.12 | Head and neck cancer

These cancers are more common among men than they are among women and are diagnosed more often among people over age 50 than they are among younger people. Treatment for head and neck cancer can include surgery, radiation therapy, chemotherapy, targeted therapy, or a combination of treatments (American Cancer Society, 2017a, 2017b). Quercetin in SAS human oral cancer cells has an anticancer role by inhibiting the expression and activity of MMP-2 and MMP-9 and reducing the protein levels of MMP-2, -7, -9, and -10, VEGF, and NF-κB p65. It can also reduce inducible nitric oxide synthase, COX-2, urokinase-type plasminogen activator, PI3K, IKBα, IKB-α/β, phosphorylated nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor kinase, alpha/beta (p-IKKα/β), focal adhesion kinase, son of sevenless homolog-1, growth factor receptor-bound protein-2, mitogen-activated protein kinase kinase kinase-3, mitogen-activated protein kinase kinase kinase-7, ERK1/2, p-ERK1/2, JNK1/2, p38, p-p38, Jun proto-oncogene (c-JUN), and p-c-JUN (Lai et al., 2013). In EGFR-overexpressing HSC-3 and TW206 oral cancer cells, quercetin treatment suppressed cell growth by inducing G2 arrest and apoptosis. It additionally suppresses the EGFR/Akt activation with associated initiation of FOXO1 activation. FOXO1 knockdown reduced quercetin-induced p21 and FasL expression, and subsequent G2 arrest and apoptosis, respectively (C. Y. Huang et al., 2013).

Furthermore, in oral squamous cell carcinoma (SCC), quercetin reduced the cell feasibility and colony-forming potential in a dose-dependent fashion. It also inhibited the production of SCC-25 cells by means of both G1 phase cell cycle arrest and mitochondria-mediated apoptosis and decreased the abilities of movement and invasion of SCC-25 cells in a dose-dependent approach (S. F. Chen et al., 2012; S. F. Chen et al., 2013). Quercetin significantly down-regulated the aldehyde dehydrogenase 1 activity and productions of Twist, N-cadherin, and vimentin in head and neck cancer-derived sphere cells in a dose-dependent fashion (W. W. Chang et al., 2013). In DMBA-induced hamster buccal pouch (HBP) carcinogenesis, quercetin has chemopreventive and chemotherapeutic special effects on cytochrome P450 (CYP)-mediated ROS production, ROS-induced cellular damage, and activation of the NFκB-signaling circuit. Administration of quercetin suppressed the growth of DMBA-induced HBP carcinomas by down-regulation of CYP-mediated ROS production via down-regulation of the expression of CYP1A1 and CYP1B1 and up-regulation of antioxidant defenses. It also mitigates ROS generation and abolishes NFκB signaling by stopping the phosphorylation and breaking down of IκB, nuclear translocation of NFκB, and transactivation of its target genes related to cell propagation and apoptosis evasion (Priyadarsini & Nagini, 2012). Similarly, in DMBA-induced HBP carcinomas, quercetin (a) lessens tumor occurrence and tumor liability, (b) considerably defers tumor growth, and (c) triggers cell cycle arrest and apoptosis and blocks invasion and angiogenesis (Priyadarsini, Vinothini, Murugan, Manikandan, & Nagini, 2011).

In numerous oral cancer cell lines (SCC-1483, SCC-25, and SCC-QLL1), administration of quercetin at a concentration of 40 μM significantly induced apoptosis and exhibited cleavage of PARP. Furthermore, Caspase-3 activity assay revealed that induction of apoptosis by quercetin was caspase-3-dependent (Kang et al., 2010). Similarly, in EGFR-overexpressing HSC-3 and FaDu head and neck squamous cell carcinoma (HNSCC) cells in HNSCC, quercetin at 10 μM suppressed cell migration and invasion. It also inhibits the colony growth of HSC-3 cells implanted in a Matrigel matrix and suppresses the expression and proteolytic activity of MMP-2 and MMP-9 in EGFR-overexpressing HNSCC. These results indicate that quercetin is an effective anticancer agent against MMP-2 and MMP-9-mediated metastasis in EGFR-overexpressing HNSCC (Chan et al., 2016). Yuan and colleagues have recently shown that treatment of KB/VCR oral cancer cells with quercetin at 25 to 100 μmol/L effectively inhibits the migration and invasion of cells and causes cells arrest at the G1 phase and decreases the amount of cells in the S and G2 phase. These researchers found that quercetin induces apoptosis, suppresses the expression of Bax, activates the expression of Caspase-3 and Bcl-2, and reverses gene-encoded Pglycoprotein-mediated MDR in KB/VCR cells by inhibiting the expression of Pglycoprotein (Z. Yuan et al., 2015).

2.13 | Cervical cancer

Cervical cancers are some of the principal causes of cancer-related death among women in developing countries (Ojesina et al., 2014). Surgery is still the first choice of cervical cancer treatments; however, chemotherapy has been widely suggested to avoid recurrence in post-operative management of cervical cancers (S. Y. Liu & Zheng, 2013). Due to drug resistance and sever toxicities, there is a need to explore more reliable and less toxic therapeutic approaches to treat cervical cancers. Quercetin proved to be a multipurpose anticancer molecule. In a recent publication, Zhang et al. examined the effect of quercetin on the expression of heparanase in HeLa and Caski cervical cancer cells in addition to the molecular mechanism of action. Quercetin lessened mRNA expression level of HPA, thus causing its reticence in a dose- and time-dependent (W. T. Zhang, Zhang, Zhong, Lü, & Cheng, 2013). Quercetin intercalated with calf thymus cell DNA and HeLa cell DNA and suppressed antiapoptotic AKT and Bcl-2 expression. It has also been reported for the increase of mitochondrial cytochrome-c level and depolarization of mitochondrial membrane potential with rise of ROS. In the same way, it was found to control the p53 and caspase-3 actions. These variations in signaling proteins and externalization of phosphotidyl serine residues are involved with initiation of apoptosis. Decreased AKT expression proposed in cell production and metastasis potential are accompanied with arrest of the cell cycle at G2/M (Bishayee et al., 2013).

A group of researchers showed that in HeLa cells, quercetin appreciably retards the growth and induces apoptosis in vitro in a time- and dose-dependent fashion. It causes cell cycle arrest at G0/G1 phase and further down-regulates the expression of the PI3K and p-Akt. It could additionally down-regulate the expression of bcl-2 and up-regulate Bax. These findings suggest that quercetin induces apoptosis in HeLa cells through PI3k/Akt pathways (Xiang et al., 2014). In a similar fashion, Wang and coworkers employed MTT, flow cytometry, and MDC staining to evaluate proliferation, apoptosis, and autophagy, respectively, after treatment with quercetin in HeLa cells. In addition, they used western blot assay to detect LC3-I/II, Beclin 1, active caspase-3, and S6K1 phosphorylation. Results revealed that quercetin can inhibit HeLa cell production and initiate protective autophagy at low concentrations (P. Wang, Henning, et al., 2016; Y. Wang, Zhang, et al., 2016). In human cervical carcinoma HeLa cells, quercetin caused introduction of apoptosis and remained efficient for extended period of time (48 hr), decreased Hsp27 and Hsp72 expression, and raised caspases actions (Bądziul, Jakubowicz-Gil, Paduch, Głowniak, & Gawron, 2014; Luo et al., 2016).

In human cervical cancer (HeLa) cells, quercetin suppressed cell viability in a dose-dependent fashion by initiation of G2/M phase cell cycle arrest and mitochondrial apoptosis via a p53-dependent mechanism (Vidya Priyadarsini et al., 2010). Additionally, in transplanted carcinoma in BALB/C nude mice, quercetin at different concentrations (6.25, 12.5, 25, and 50 μmol/L) for 24 hr (a) increased the suppression rate of the cells, (b) induced apoptosis, (c) considerably lessened mitochondrial membrane potential, (d) effectively enhanced the $[Ca^{2+}]i$, and (e) activated the caspase-3 in a dose-dependent manner (L. Q. Huang, Zhang, Yang, & Tao, 2009). Furthermore, in Hela cells, quercetin at concentrations of 20 to 80 μM increased the cell inhibition rate from 37% to 83% and increased rate of cell apoptosis from 18.71% ± 2.61% to 70.00% ± 4.05% (W. Zhang & Zhang, 2009). Finally, recent research by Lin et al. (2017) revealed that luteolin and quercetin considerably prevent ubiquitin E2S ligase expression in cervical cancer and that high ubiquitin E2S ligase in malignant cancers contributes to cell motility through EMT signaling.

2.14 | Skin cancer

Skin cancer is by far the most common type of cancer. It includes melanoma, basal and squamous cell, Merkel cell carcinoma, and lymphoma of the skin. Treatment normally includes surgery, radiotherapy, and chemotherapy, in addition to other specialized techniques. On the other hand, ultraviolet (UV) radiation has harmful effects and acts as a tumor maker and promoter. In Hacat cell line, quercetin-loaded nanoparticles can significantly protect against UVB irradiation and blocks UVB-induced COX-2 up-expression and NF-kB activation in Hacat. In addition, poly(d,l-lactide-co-glycolide)-d-α-tocopheryl polyethylene glycol 1000 succinate (PLGA-TPGS) nanoparticles could penetrate epidermis and reach dermis. Treatment of mice with quercetin-loaded NPs diminishes UVB irradiation-related macroscopic and histopathological variations in mice skin. These results demonstrate that copolymer PLGA-TPGS could be employed as drug nanocarriers against skin damage and disease and provide an external use of PLGA-TPGS in the treatment of skin diseases (Caddeo et al., 2016; Zhu et al., 2016).

Quercetin is a well-known inhibitor of PI3K and MAP kinase signaling. In UV-B-irradiated B16F10 melanoma cells, treatment with quercetin caused a decrease in cell viability and amplified apoptosis in a dose-dependent fashion. The proapoptotic effects of quercetin in UVB-irradiated B16F10 cells are mediated through (a) promotion of intracellular ROS formation, (b) calcium homeostasis disparity, (c) variation of antioxidant defense response, and (d) depolarization of mitochondrial membrane potential (ΔΨM). Additionally, enhancement of UVB-induced cell death by quercetin was revealed by breaking down of chromosomal DNA, caspase activation, PARP cleavage, and a rise in sub-G1 cells. Furthermore, quercetin significantly reduces MEK–ERK signaling, effects PI3K/Akt pathway, and improves the UVB-induced NF-κB nuclear translocation. Similarly, a combined treatment with UVB and quercetin decreased the ratio of Bcl-2 to that of Bax and up-regulated the expression of Bim and apoptosis-inducing factor. These results suggest the possibility of using quercetin in combination with UVB as a promising treatment alternative for melanoma in the future (Rafiq et al., 2015).

In a skin carcinogenesis mouse model, skin tumor was induced by DMBA and croton oil in Swiss albino mouse. Oral administration of quercetin, at a concentration of 200 and 400 mg/kg body weight daily for 16 weeks, reduced the tumor size and the number of papillomas. In addition, quercetin significantly reduced the serum levels of glutamate oxalate transaminase, glutamate pyruvate transaminase, and alkaline phosphatase and bilirubin and considerably elevated the levels of glutathione, superoxide dismutase, and catalase. It additionally prevented lipid peroxides production and reduced DNA damage as compared with DMBA and croton oil-treated mice (Ali & Dixit, 2015). On the other hand, in a DMBA-tetradecanoyl phorbol-13-acetate two stage

mouse skin carcinogenesis protocol, the quercetin diet (0.02% wt/wt) for 20 weeks extraordinarily deferred the occurrence of skin tumor by 2 weeks and reduced tumor growth by 35%. Additionally, quercetin supplementation substantially inhibited skin hyperplasia in Tg mice and suppressed (a) IGF-1 induced phosphorylation of the IGF-1 receptor, (b) insulin receptor substrate-1, (c) Akt and S6K, and (d) IGF-1 stimulated cell production, in a dose-dependent approach. These results suggest that quercetin exerts its anticancer activity through the inhibition of IGF-1 signaling (Jung, Bu, Tak, Park, & Kim, 2013).

2.15 | Eye cancer

In human retinal pigment epithelial cells, quercetin, and other flavonoids, reduced, in a dose-dependent fashion, the retinal pigment epithelial cell propagation, migration, and secretion of VEGF. It additionally inhibited the secretion of VEGF prompted by $CoCl_2$-induced hypoxia and substantially decreased cell viability by triggering cellular necrosis (R. Chen et al., 2014).

2.16 | Thyroid cancer

Radioactive iodine (best known as ^{131}I) is commonly employed in treating patients with thyroid diseases, including thyroid cancer and Graves' disease. Side effects of this treatment include DNA damage and chromosomal breakdowns, which could lead to cell death (Robbins & Schlumberger, 2005). Moreover, ^{131}I treatment is linked with increased genetic damage, and the occurrence of secondary malignancies and leukemia might increase with higher doses of radioiodine (Chow, 2005). Accordingly, there is a pressing need for protection of normal cells, which may mitigate side effects induced by ^{131}I. In human papillary thyroid cancer cells, quercetin has been shown to significantly lower cell proliferation and improves the rate of apoptosis by caspase activation. It, additionally, induces cell apoptosis by down-regulation of Hsp90 expression. The decrease of chymotrypsin-like proteasome activity suppresses growth and causes cell death in thyroid cancer cells (Mutlu Altundağ et al., 2016). In human medullary and papillary thyroid cancer cells, Quagliariello et al. showed that quercetin delivered from hydrogel displays a time- and CD44-dependent interaction with both cell lines with significant anti-inflammatory effects. On the other hand, a combination of quercetin and SNS-314 results in a synergistic cytotoxic effect on medullary TT and papillary BCPAP cell lines with a significant decrease of the IC_{50} value (Quagliariello et al., 2016). Similarly, treatment of thyroid papillary cancer cell lines with different concentrations of quercetin (between 10 and 75 μM) for 24 hr induces apoptosis by inhibiting HSP production on various cancer cell lines (Mutlu Altundag et al., 2014).

2.17 | Ovarian cancer

Ovarian cancer, one of the most common female malignancies, accounts for the leading death rate among the gynecologic cancers. Risk factors include age, null parity, early menarche, late menopause, and family history, whereas pregnancy and breastfeeding decrease this risk (Gao et al., 2012).

In the quest to develop drugs for cancer chemotherapy, Nessa and colleagues examined the use of combination of drugs acting synergistically to overcome drug resistance. In their study, two known anticancer phytochemicals, quercetin and thymoquinone, were combined with two platinum drugs, cisplatin and oxaliplatin, which are commonly used to treat different types of cancer, including ovarian cancer. This combination was tried against two human epithelial ovarian cancer cell lines, A2780 and its cisplatin-resistant form A2780. Results revealed that the greatest synergism is achieved when the phytochemical is added first followed by platinum drug 2 hr later, and the least synergism is observed when the two compounds were administered as a bolus. It was then suggested that addition of the phytochemical 2 hr before platinum drug may sensitize cancer cells to platinum action, thus offering a means to overcome drug resistance (Nessa, Beale, Chan, Yu, & Huq, 2011). Similarly, researchers encapsulated quercetin into biodegradable monomethoxy poly(ethylene glycol)-poly (ε-caprolactone) micelles for treating ovarian cancer, in an effort to increase its solubility in water. This nano-formulation of quercetin dose-dependently prevented the growth of A2780S ovarian cancer cells. In addition, treatment with quercetin induced apoptosis of A2780S cells and stimulated caspase-3 and caspase-9, down-regulated MCL-1 and Bcl-2, and up-regulated Bax and changed mitochondrial transmembrane potential. These events suggest that quercetin may induce apoptosis of A2780S cells via the mitochondrial apoptotic pathway (Gao et al., 2012).

Maciejczyk and Surowiak explored the effect of low doses of quercetin on the sensitivity of human ovarian cancer cell lines, SKOV-3, EFO27, OVCAR-3, and A278OP, and the effect on the sensitivity of these cell lines to cisplatin and paclitaxel. These researchers demonstrated that low doses of quercetin increase sensitivity of ovarian cancer cells to cisplatin and paclitaxel (Maciejczyk & Surowiak, 2013). In cisplatin-sensitive and cisplatin-resistant A2780s and A2780cp human ovarian cancer cell lines, the mixture liposomal-quercetin considerably suppressed tumor progression in both cell lines compared with free liposomes or quercetin. Furthermore, it induced apoptosis, decreased microvessel density, and inhibited proliferation of tumors in both cell lines (Long et al., 2013). Additionally, quercetin could sensitize human ovarian cancer cells to TRAIL and induced expression of DR5. Stimulation of DR5 was mediated via activation of JNK and up-regulation of a transcription factor CHOP. Up-regulation of DR5 was also mediated by production of ROS. These results suggest that quercetin enhancement of TRAIL-mediated inhibition of tumor growth of human SKOV-3 xenograft is associated with apoptosis and activation of caspase-3, CHOP, and DR5 (Yi et al., 2014).

In human ovarian cancer C13* and SKOV3 cells, quercetin at concentrations of 40–100 μM displayed proapoptotic effect. In addition, it suppressed ROS-induced injury, reduced intracellular ROS level, and improved the expression of endogenous antioxidant enzymes. These results suggest an ROS-mediated mechanism of reducing antineoplastic drugs. Furthermore, quercetin triggered a considerable reduction of therapeutic efficiency of cisplatin and ROS-induced damage in xenograft tumor tissue (W. Li, Liu, et al., 2014; N. Li, Sun, et al., 2014; X. Li, Wang, et al., 2014; W. Li, Zhao, et al., 2014). Similarly, quercetin repressed the proliferation of SKOV-3 cells in a time- and dose-dependent approach, prompted cell apoptosis, and initiated ovarian cancer SKOV-3 cell cycle arrest in the G_0/G_1 phase and a substantial reduction in the percentage of cells at the G_2/M phase

(Arzuman, Beale, Yu, & Huq, 2015; Ren, Deng, Ai, Yuan, & Song, 2015). Additionally, treatment of SKOV-3 and OVCAR-8 ovarian cancer cells with quercetin induced apoptosis, activated caspase-3 and increased sensitivity to cisplatin, and reduced expression and activation of EGFR.

In addition, quercetin deactivated MAPK–ERK pathway; induced down-regulation of cyclin D1, DNA-PK, phospho-histone H3, and up-regulation of p21; and arrested cell cycle development (Y. Wang, Han, et al., 2015; P. Wang, Henning, et al., 2015; P. Wang, Phan, et al., 2015; J. Wang, Zhang, et al., 2015). Similarly, quercetin significantly improved the expression levels of cleaved caspase-3 and prompted overexpression of miR-145 in SKOV-3 and A2780 ovarian cancer cells (Zhou, Gong, Ding, & Chen, 2015). Furthermore, in ovarian cancer, pretreatment with quercetin considerably increased cisplatin cytotoxicity and activated the three branches of endoplasmic reticulum stress. It additionally suppressed STAT3 phosphorylation, leading to down-regulation of the BCL-2 gene downstream of STAT3, and improved the antitumor effect of cisplatin in a xenograft mouse model of ovarian cancer (Arzuman, Beale, Chan, Yu, & Huq, 2014; F. Q. Yang, Liu, Li, et al., 2015; Z. Yang, Liu, Liao, et al., 2015; F. Yang, Song, et al., 2015). Finally, a review pertaining to quercetin and ovarian cancer has been recently published (Parvaresh et al., 2016).

2.18 | Kidney cancer

Kidney cancer, also known as renal cancer, is a type of cancer that starts in the cells in the kidney. Factors that increase the risk of kidney cancer include smoking, which can double the risk of the disease, regular use of nonsteroidal anti-inflammatory drugs such as ibuprofen and naproxen, obesity, faulty genes, a family history of kidney cancer, having kidney disease that needs dialysis, being infected with hepatitis C, and previous treatment for testicular cancer or cervical cancer (Lipworth, Tarone, & McLaughlin, 2006).

Protective effect of quercetin against cisplatin nephrotoxicity in a rat tumor model was evaluated by a number of scientists. Co-treatment with quercetin can partially prevent all renal effects of cisplatin without affecting its antitumor activity (Sanchez-Gonzalez, Lopez-Hernandez, Perez-Barriocanal, Morales, & Lopez-Novoa, 2011). On the other hand, the antitumor effect of quercetin, combined with antisense oligo gene therapy (inhibiting Snail gene), was recently investigated by Meng et al. (2015). Results revealed that in a Caki-2 clear cell renal cell carcinoma (ccRCC) cell line, each of the investigated therapeutic agents considerably suppressed cell proliferation and migration and triggered cell cycle arrest and apoptosis. However, the combination of both agents provided even strong inhibitory effects toward these cancer cells. This study clearly highlights the use of a combination of natural products and gene therapy for the treatment of renal cancer (Meng et al., 2015). Heeba and Mahmoud have probed the effects of different doses of quercetin on Dox-induced nephrotoxicity in rats. Results showed that oral administration of quercetin to adult male Albino rats for 14 days preserved renal function by reducing blood urea nitrogen, serum creatinine, renal malondialdehyde, nitric oxide, reduced glutathione, catalase activity, and renal expressions of TNF-a, IL-1B, inducible nitric oxide synthase, and caspase-3 (Heeba & Mahmoud, 2016). In a similar fashion, Li and colleagues investigated the anticancer activity of a 1:1 combination of quercetin and hyperoside on 786-O renal cancer cells. The combination decreased the production of ROS by up to 2.25-fold and increased the antioxidant ability by up to threefold in these cells. In addition, it induced caspase-3 cleavage (twofold), increased PARP cleavage, and reduced the expression of specificity protein Sp1, Sp3, and Sp4 mRNA (W. Li, Liu, et al., 2014; N. Li, Sun, et al., 2014; X. Li, Wang, et al., 2014; W. Li, Zhao, et al., 2014).

2.19 | Mesothelioma cancer

In MM SPC212 and SPC111 cell lines, quercetin substantially suppressed the propagation of cancer, modified the cell cycle distribution, and increased the level of caspase 9 and caspase 3 in a concentration and time-dependent fashion (Demiroglu-Zergeroglu, Basara-Cigerim, Kilic, & Yanikkaya-Demirel, 2010). Quercetin and quercetin in combination with cisplatin also moderated gene expression of cyclins, cyclin-dependent kinases, and cyclin-dependent kinases inhibitors and up-regulated genes involved in JNK, p38, and MAPK/ERK pathways. Moreover, quercetin + cisplatin increased phosphorylations of p38 and JNK and decreased and that of ERK (Demiroglu-Zergeroglu et al., 2016).

In MM MSTO-211H and H2452 cells, Lee and coworkers found that quercetin treatment suppresses cell growth by up-regulating Nrf2 at both the mRNA and protein levels. Reduction of Nrf2 expression with siRNA improved cytotoxicity, as demonstrated by (a) an increase in the level of proapoptotic Bax, (b) a decline in the extent of antiapoptotic Bcl-2 with improved cleavage of caspase-3 and PARP proteins, and (c) the appearance of a sub-G0/G1 peak in the flow cytometric assay. These findings highlight the importance of Nrf2 in cytoprotection, survival, and drug resistance, in addition to the potential significance of targeting Nrf2 as a promising strategy for overcoming resistance to chemotherapeutics in MM (J. Lee, Han, et al., 2015; W. J. Lee, Hsiao, et al., 2015; Y. J. Lee, Lee, & Lee, 2015; S. H. Lee, Lee, Min, et al., 2015).

3 | CONCLUSIONS

Diet in combination with chemotherapeutics agents has been gaining popularity in the fight against diseases such as cardiovascular disorders, cancer insurgence, and immune dysfunction. In addition, utilization of conventional therapies such as natural products, particularly in treating cancer, has attracted the attention of the scientific and medical communities due to their lesser side effects and cost. Quercetin, a flavonoid antioxidant found in plant foods, such as leafy greens, tomatoes, berries, broccoli, onions, and apples, is considered as one of the most abundant antioxidants in the human diet and plays an important role in fighting free radical damage, the effects of aging, and inflammation. Its wide accessibility, efficacy, and a broad range of activity, and low toxicity as compared with other examined compounds, make it an attractive chemical in the fight against diseases including cancer. It has been recognized and employed as an alternative drug in treating different cancers alone or in combination with other chemotherapeutic drugs. Certainly, a variety of evidences have

been presented in its favor in combatting cancer; however, some reports demand that further scientific research is needed. In this review, we have shown that quercetin provides a wide range of preventive and therapeutic options against different types of cancer, along with a description of the various mechanisms by which this compound exerts its action. In summary, this review reveals that quercetin can be an important complementary medicine for the prevention and treatment of different types of cancers, owing to its natural origin, safety, and low cost relative to synthetic cancer drugs. However, further studies are needed on this natural compound. Furthermore, because most of the findings cited in the current review are based on in vitro and in vivo studies, which do not necessarily represent the effect of quercetin in human, more investigations that involve different pharmacokinetic parameter are recommended in the future before this substance hits the market as a prescribed drug. Moreover, development of standardized extract or dosage could also be pursued in clinical trials.

CONFLICTS OF INTEREST

Authors declare no conflict of interest.

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