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REVIEW ARTICLE

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# Quercetin: A functional dietary flavonoid with potential chemo-preventive properties in colorectal cancer

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Recently, an intense attention has been paid to the application of natural compounds as a novel therapeutic strategy for cancer treatment. Quercetin, a natural flavonol present in many commonly consumed food items, is widely demonstrated to exert inhibitory effects on cancer progression through various mechanisms. Since there is a strong association with diets containing abundant vegetables, fruits, and grains, and significant decline in the risk of colon cancer, accumulation studies have focused on the anticancer potential of quercetin in colorectal cancer. Cell cycle arrest, increase in apoptosis, antioxidant replication, modulation of estrogen receptors, regulation of signaling pathways, inhibition of and metastasis and angiogenesis are among various mechanisms underlying the chemo-preventive effects of quercetin in colorectal cancer. This review covers various therapeutic interactions of Quercetin as to how targets cellular involved in cancer treatment.

**KEYWORDS**
apoptosis, colorectal cancer, flavonoids, quercetin

## 1 | INTRODUCTION

Colorectal cancer, one of the most common types of cancer, is the third leading cause of cancer related deaths worldwide paralleling a significant enhancement in the estimated number of new individuals diagnosed every year (e Melo et al., 2017). During normal physiological conditions, colon stem cells, located at the base of colonic crypts, are continuously dividing and differentiating into epithelial cells. Following the movement to the topical part of crypts, these daughter cells undergo apoptosis (Fessler & Medema, 2016). These continuing operations of proliferation, differentiation, and apoptosis are strictly regulated, and easily predisposed to various genetic mutations (Fessler & Medema, 2016). The risk factors for genetic mutations, as well as development of colon cancer included, but not limited to diet, lack of physical activity, obesity, excessive alcohol consumption, smoking, stress, and ingestion of red meat (Pique, Ferrerira, & Esteller, 2017). In spite of promising advances in diagnostic techniques, as well as understanding the molecular pathogenesis of colon cancer, a considerable percentage of diagnosed patients are already at later stages of advanced carcinoma, with high degree of metastasis (Linnekamp, Wang, Medema, & Vermeulen, 2015), which could potentially lead to the usage of numerous chemotherapeutics for the treatment of this type of cancer (Sharma & Allison, 2015). Thus, researchers are focused on the searching novel and effective

  

substances with potent anticancer effects and minimal side effects (Majidinia & Yousefi, 2016; Majidinia & Yousefi, 2017; Sharma & Allison, 2015, Yousefi et al., 2015; Yousefi, Samadi, Baradaran, Shafiei-Irannejad, & Zarghami, 2016). Recently, high number of studies have been reported that diets containing abundant vegetables, fruits, and grains, containing fibers, vitamins, and micronutrients are strongly associated with significant decline in the risk of colon cancer (Aoyama et al., 2014; Turati, Rossi, Pelucchi, Levi, & La Vecchia, 2015). The flavonoids, as the largest class of polyphenolic compounds, have been numerously demonstrated to suppress in vitro and in vivo tumor cell growth (Turati et al., 2015). Quercetin is one of the most important and well-studied flavonoids abundant in various types of vegetables and fruits, including capers, lovage, dill, cilantro, broccoli, onions, various berries (e.g., chokeberries, cranberries, and lingonberries), and tea (Sak, 2014). In addition, quercetin has been shown to effectively inhibit cancer growth (Khan, Niaz et al., 2016). The specific and exact mechanisms responsible for the antitumoral effect of quercetin are not quite understood, but inhibition of tyrosine kinases of mitogenic signal transduction pathways, modification of important signaling pathways involved in the tumorigenesis, interplay with specific receptors and proteins, are among the most acceptable mechanisms for the anticancer effects of this flavonoid (Khan, Paul et al., 2016). In recent years, an intense attention has been paid to the chemo-preventive and antitumoral functions of quercetin on colorectal cancer and increasing number of studies have been investigated these effects in vivo and in vitro. In this review, we will first briefly discuss the anticancer properties of quercetin, and then summarize the promising aspects of quercetin, as a novel therapeutic agent in the treatment of colorectal cancer.

## 1.1 | Colon cancer: Histopathology and molecular pathology

Similar to most human cancer, four stages are defined for colorectal patients; stage I–II include patients with local tumors and restricted to the colon or rectum wall (Fessler & Medema, 2016). Approximately, 40% of colorectal cancer patients are classified in this group. Nearly, 36% of patients present regional disease, in which cancer cells invade to adjacent tissues or lymph nodes (stage III) (Fessler & Medema, 2016). Patients with stage IV colorectal cancer (nearly 20%) have metastatic invasion (Fessler & Medema, 2016). As origin point view of colorectal cancer, the majority of cases, approximately 70–80%, have sporadic component, while around 20–30% of colorectal cancers have a hereditary origin (Bogaert & Prenen, 2014). The inherited malignancies are commonly due to high-risk, susceptibility syndromes, including Lynch Syndrome (3–4%) and familial adenomatous polyposis (~1%), or low-risk alleles such as Shroom2 (Giardiello et al., 2014). A small percentage of colorectal cancer cases (1–2%) arise from inflammatory bowel diseases (Lutgens et al., 2013). Although surgical intervention is a gold standard treatment strategy for the colorectal cancer patients with local and regional diseases, development of novel and more effective therapeutic modalities is an urgent requirement for patients with late-stage colorectal cancer, particularly those showing aggressive phenotype. For patients with stage III tumors, as well as those with stage II tumors with high-risk phenotype, which are characterized by the presence of poor differentiation; obstruction or tumor perforation; invasion to vascular, lymphatic, or perineural regions; number of lymph nodes sampling less than 12; direct invasion of tumor into the surface of visceral peritoneum, adjuvant chemotherapy is recommended following radical resection (Van Cutsem, Nordlinger, Cervantes, & Group, 2010). While, for stage IV patients, administration of chemotherapeutic agents including fluoropyrimidine, oxaliplatin, and irinotecan is the first-line therapeutic modality instead of surgical intervention (Van Cutsem et al., 2010).

The classification of the colorectal cancer, as a heterogeneous malignancy, into different subtypes characterized by exclusive molecular and morphological properties is based on microsatellite instability (MSI), chromosomal instability (CIN), and CpG island methylator phenotype (CIMP) (Sideris & Papagrigoriadis, 2014). Microsatellite disorders are one of the most prevalent molecular events in colorectal cancer, and are detectable in about 22% of all malignant cases, as well as have a significant impact on colorectal cancer prognosis (Corso et al., 2013). MSI is a hypermutable phenotype susceptible to frame-shift mutations and base-pair substitutions, which caused by the loss of DNA mismatch repair (MMR) activity (Jass, 2007). CIMP status, which is characterized by the hypermethylation of CpG island promoter, is another basis for colorectal cancer classification. In addition to CIMP status, some studies use its correlation to CIN and MSI for classification (Jass, 2007; Ogino & Goel, 2008; Simons et al., 2013). An important causative reason for CIMP is the transcriptional silencing of specific DNA repair and tumor suppressor gene products, such as MLH1 (Simons et al., 2013). Tumors in CIN category have aneuploidy and polyploidy, which are defined as chromosomal gains and losses, with or without structural rearrangements, respectively, and are seen in about 60% of colorectal cancer cases (Church, Midgley, & Kerr, 2012; Domingo et al., 2013; Gerling et al., 2011; Migliore, Migheli, Spisni, & Coppedè, 2011). Distal location, poor prognosis and well- or moderately differentiation, higher incidence in male are specific features of CIN-positive tumors. Taking together, unifying independent gene expression-based colorectal cancer classification approaches, the CRC Subtyping Consortium classified a large number of colorectal cancer samples into one of four main consensus molecular subtypes (CMSs) including CMS1, CMS2, CMS3, and CMS4, the main characteristics of whom are expressed in Figure 1.

## 1.2 | Quercetin

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is a yellow crystalline solid, insoluble in water, and soluble in glacial acetic acid as well as aqueous alkaline solutions (Parvaresh et al., 2016). As mentioned before, quercetin is bioactive component belonged to the natural flavonoids group, which contain a flavone nucleus (Russo et al., 2014). A heterocyclic pyrone ring which linked two benzene rings forms this

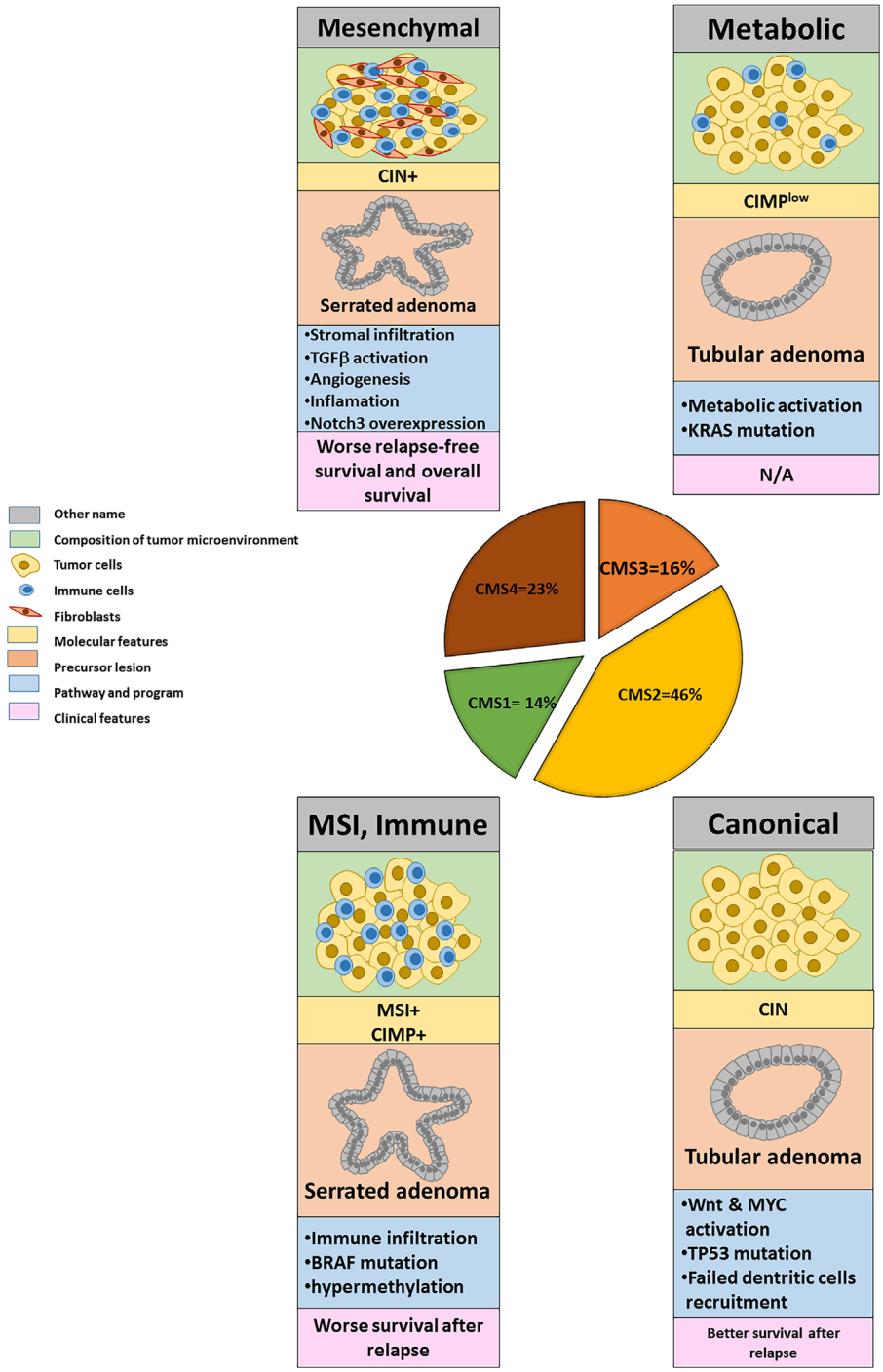


**FIGURE 1** Four main consensus molecular subtypes (CMSs) of colon cancer and their main characteristics

central nucleus (Russo et al., 2014). Daily human intake of quercetin is around 10–100 mg, and in the case of consuming highly purified extracts, it can reach 500–1000 mg. Hydrophilic glycosides (quercetin-glucose conjugated) is the major form of the quercetin in plants, which cannot be directly and easily absorbed in the enterocytes (Filipa Brito et al., 2015). Within enterocytes, quercetin glucosides undergo several important enzymatic reactions such as, hydrolysis, methylation, sulfonylation, glucuronidation by specific transferases (Filipa Brito et al., 2015). Following transportation into intestinal lumen and then liver, quercetin metabolites, the major quercetin-derived circulating compounds in plasma, quercetin-3-glucuronide, and quercetin-3′-sulfate, are formed via other conjugation reactions (Alrawaiq & Abdullah, 2014). Absorption rate of quercetin is more efficient in the conjugated form, and peak plasma concentration is 3.5–5.0 μmol $L^{-1}$, whereas unconjugated quercetin is absorbed inefficiently and the peak plasma concentration is less than <0.33 μmol $L^{-1}$(Alrawaiq & Abdullah, 2014). A broad spectrum of beneficial features are ascribe to quercetin including, anti-oxidative activity; anti-inflammatory effects; increase

the endurance exercise capacity; inhibitory effects against atherosclerosis, thrombosis, hypertension, and arrhythmia; as well as anticancer effects. The antioxidant activity of quercetin is one of the best studies biochemical features of quercetin, which is ascribed to its chemical structure. These structural features include; catechol functionality (ortho-dihydroxyl) on B ring, hydroxyl groups at C-3 and C-5 carbons in the benzopyrone AC ring, a Δ2 double bond adjacent to a 4-oxo group in pyrone C ring (Khan, Niaz et al., 2016). Therefore, the ability of quercetin in scavenging radical species is greatly influenced by the structural variables such as substitution, configuration, and a number of hydroxyl groups. Inhibition of lipid peroxidation, reduction of highly oxidizing free radicals due to its lower redox potential, inhibition of the free radicals production due to its ability to chelate metal ions, are other anticancer properties of quercetin (Khan, Paul et al., 2016).

## 1.3 | Anticancer effects of quercetin

Because of direct anticancer effects and chemo-preventive properties, the role of polyphenolic compounds in cancer biology and therapy has drawn more attention (Nourazarian, Nourazarian, Majidinia, & Roshaniasl, 2016, Russo, Tedesco, Spagnuolo, & Russo, 2017). It was reported that consumption of onions, which have among the highest concentration of quercetin reduced cancer risks in stomach, colon, and rectal cancers (Dorant, 1994). Additionally, various studies have been shown that diets rich in quercetin are positively correlated with lower rates of stomach, breast, and lung cancers and particularly, colon cancer (Caltagirone et al., 1997; Noori-Daloii et al., 2011; Ranelletti et al., 1992; Tan et al., 2003). Various molecular pathways are mentioned by previous studies to be the possible molecular targets of quercetin in inhibition of cancer. From the chemical point of view, quercetin is able to interact with phosphatidylinositol 3-kinase (PI3K)-Akt/PKB (protein kinase B), SAPK/ERK kinase 1 (SEK1), c-Jun N-terminal kinase 1/2 (JNK1/2), extracellular signal-regulated kinase (ERK) kinase (MEK1), ERK1/2, Raf, and mitogen-activated protein kinase (MAPK) (GULATI, LAUDET, ZOHRABIAN, Murali, & JHANWAR-UNIYAL, 2006; Kumamoto, Fujii, & Hou, 2009; Lee & Lee, 2008). This binding is reported to achieve by hydrogen bonding between amino acid residues of kinases and various hydroxyl groups of quercetin (Khan, Niaz et al., 2016; Raman, Chen, & Cobb, 2007). All mentioned kinases and their signaling pathways are involved in inducing reprogramming events related to gene expression through phosphorylation of multiple key intracellular molecular targets, and thus potentiate cellular growth, spreading, and antiapoptotic properties. Another possible mechanism proposed for the anticancer activity of quercetin is senescence induction, which is suggested to mediate by significant inhibition of Akt phosphorylation and targeting telomerase activity (Cosan et al., 2011; Zamin et al., 2009). The expression levels of telomerase are significantly high in excessively proliferating human cells (Hanahan & Weinberg, 2011). Investigations on the adenocarcinoma and breast carcinoma patients revealed the telomerase inhibitory effect of quercetin (Cosan et al., 2011). More importantly, another noteworthy effect of quercetin is the cell cycle control by regulating and targeting several molecules such as p21, cyclins, p27, cyclin-dependent kinases (CDKs), and topoisomerase II (Bandele, Clawson, & Osheroff, 2008; Jeong, An, Kwon, Rhee, & Lee, 2009; López-Lázaro, Willmore, & Austin, 2010; Mu et al., 2007; Nair et al., 2004; van Waalwijk van Doorn-Khosrovani et al., 2007; Yang et al., 2006; Zhang, Zhao, & Wang, 2009). It was demonstrated that quercetin is able to block the cell cycle at G2/M or at the G1/S transition, depending on the cell type, and tumor origin (Jeong et al., 2009; Mu et al., 2007; Zhang et al., 2009). The proapoptotic effect of quercetin is another alternative approach to chemoprevention, which may cause by numerous pathways: (i) increase in cytosolic Ca2+ concentration and reduction in the mitochondrial membrane potential, hence promotion the activation of caspase-3, -8, and -9 (Chien et al., 2009; Ferraresi et al., 2005; Lee et al., 2006; Lugli et al., 2005; Mouria et al., 2002); (ii) downregulation of the transcriptional activity of β-catenin/Tcf signaling pathway, with the consequent reduction in the expression levels of cyclin D1 and survivin (Kuo, Liu, & Chao, 2004; Ma, Nguyen, Lee, & Kahn, 2005; Siegelin, Reuss, Habel, Rami, & von Deimling, 2009; Shan, Wang, & Li, 2009); (iii) the production of reactive oxygen species (ROS), activation of AMPKα1, and ASK1, accompanied by p38 activation and recruitment of caspases (Lee, Hwang, Kwon, Surh, & Park, 2010); (iv) directly binding to tubulin, stimulating the depolymerization of cellular microtubules (Gupta & Panda, 2002); (v) induction of apoptosis through enhancement of TNF-related apoptosis-inducing ligand (TRAIL), and hence the increase in the expression of death receptor (DR)-5 (Jung, Heo, Lee, Kwon, & Kim, 2010). Furthermore, several studies have been reported that the anticancer effects of quercetin could be mediated through its ability in binding to various receptors, particularly, aryl hydrocarbon receptor (AhR). AhR is a ligand-gated transcription factor, which is involved in the controlling the expression levels of cytochrome P-450 (CYP) 1 family (Denison, Pandini, Nagy, Baldwin, & Bonati, 2002; Guengerich & Shimada, 1991). Quercetin is also involved in suppressing the transformation of AhR and consequently, protecting the cells from the dioxins-induced toxicity (Ashida, Fukuda, Yamashita, & Kanazawa, 2000). On the other hand, since quercetin is a strong antagonist for AhRm it was showed that it exerts potent effects against carcinogenicity developed by polycyclic aromatic hydrocarbons (PAHs) (Fukuda & Ashida, 2008; van der Woude et al., 2005). Quercetin is also able to modulate the androgenic receptors in prostate cancer (Xing, Chen, Mitchell, & Young, 2001).

## 1.4 | Inhibitory effects of quercetin against colorectal cancer

Considering the complexity of the cancer and the importance of the targeted therapy, as the most effective therapeutic intervention, as well as the inspiring results of the anticancer effects of quercetin, an increasing body of in vivo and in vitro studies has focused on the investigation of the chemo-preventive and chemotherapeutic potential of quercetin in colorectal cancer and underlying mechanisms (Figure 2). In vitro studies have revealed that quercetin, whether alone or in combination, could inhibit the progression of colon cancer cells through some possible mechanisms such as, cell cycle arrest, decrease

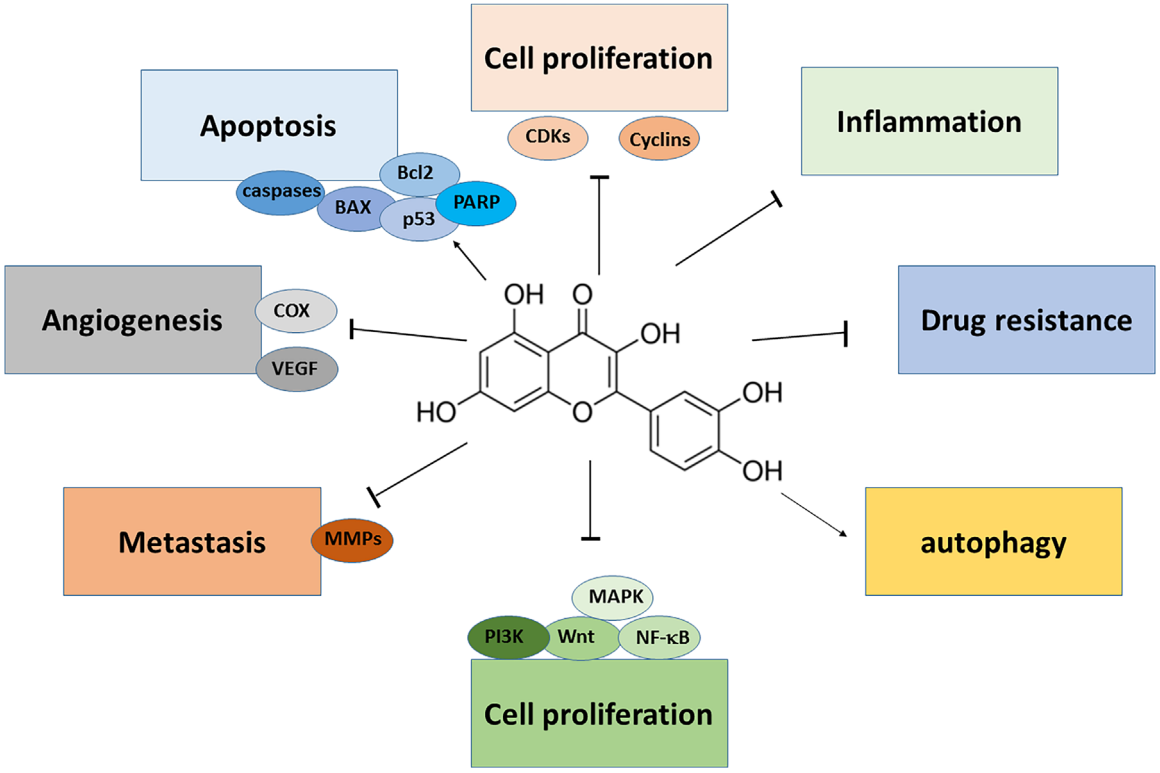


**FIGURE 2** Various mechanisms of anticancer effects of quercetin in colon cancer

in cell viability, modulation of some oncogenic signaling pathways, induction of apoptosis and autophagy, and inhibition of metastasis (Table 1). Similarly, it is demonstrated that quercetin effectively inhibits the colorectal cancer progression in vivo models of colon cancer such as, colorectal cancer cell xenograft, as well as azoxymethane- induced colorectal cancer in rats and mice (Table 2).

## 1.5 | In vitro molecular mechanisms of the anti-colon cancer effects

### 1.5.1 | Inhibition of proliferation

Cell mitosis and proliferation have a pivotal function in the initiation/progression of human malignancies, in particular colorectal cancer (Otto & Sicinski, 2017). Therefore, cell cycle arrest and modulation of key components of cell cycle such as cyclins, cyclin dependent kinases, and cyclin dependent kinases inhibitors, are effective measures for cancer treatment by quercetin. van Erk et al. (2005), demonstrated that treatment of Caco-2 cells by 5 μM quercetin for 48 hr resulted in the downregulation of the cell cycle genes such as CDC6, CDK4, and cyclin D1, suppression of cell proliferation and induction of cell cycle arrest in these cells. Additionally, exposure of cancer cells to 50 μM quercetin significantly reduced cell proliferation, and further arrested cell cycle at sub-G1 phase. In another study by Shan et al. (2009), it was demonstrated that quercetin reduced cell viability of SW480 and clone 26 cells. Cells treatment by 160 μM quercetin for 24 hr decreased the expression levels of cyclin D1 and the survivin. Hosokawa et al. (1990) showed that quercetin inhibited growth of COL0320 DM cells and its complete removal from the culture media partially reversible the inhibitory effect. In addition, it was also revealed that quercetin perturbed the cell cycle, induced a frozen cell cycle pattern and arrested cell cycle at the G1/S phase. Moreover, the addition of quercetin resulted in specific inhibition of the synthesis of a 17-kDa protein, which was recovered following the progression of the cells from G1/S boundary into S-phase after removal of quercetin. Since the expression of 17-kDa protein was low in G1, and high in S-phase of the cell cycle, it was suggested that it is cell-cycle-related protein. Quercetin combined with kaempferol exerts more powerful anti-proliferative effects in comparison with single treatment of each flavonol. The authors stated that the decrease in cell proliferation was related to reduction in the expression of nuclear proliferation antigen Ki67, as well as reduced total protein levels in treated cells relative to controls (ACKLAND, VAN DE WAARSENBURG, & Jones, 2005). Despite numerous studies reporting the beneficial effects of quercetin in suppressing the proliferation of colon cancer cell lines, two studies suggested that more attention must be paid to using this flavonoid as an anticancer agent. At physiological concentration, Dihal, de Boer et al. (2006) showed that the quercetin modulated Caco-2 cell proliferation in a biphasic way and suppressed cell differentiation. Biphasic modulation of cancer cell growth occurred at a later time point and was suggested to relate to the differentiation status of Caco-2 cells and/or the presence of quercetin metabolites. Cell

**TABLE 1** In vitro investigations of the quercetin anticancer potential

| Target cells | Quercetin con. | Major effects of quercetin | Ref. |
|---|---|---|---|
| Caco-2 cells | 5 or 50 μM | downregulation of the cell cycle genes such as CDC6, CDK4 and cyclin D1 Cell cycle arrest | van Erk et al. (2005) |
| SW-480 and clone 26 cells | 160 μM | G1/S phase arrest Inhibition of cyclin D1 and survivin expression through Wnt/β-Catenin signaling | Shan et al. (2009) |
| COL0320 DM cells | 17.5 μM | Downregulation of cell-cycle-related 17 kDa protein G1/S phase arrest | Hosokawa et al. (1990) |
| HuTu-80 and Caco-2 cells | 5 μM | Decrease in expression of nuclear proliferation antigen Ki67 Decrease in total protein levels | ACKLAND et al. (2005) |
| Caco-2 cells | 0–80 μM | Biphasic role for quercetin was reported | Dihal, de Boer et al. (2006) |
| HCT-116 and HT-29 cells | 30 or 80 μM | Biphasic role for quercetin was reported | van der Woude et al. (2003) |
| human colon cancer stem cells | Quercetin in amla extraction | Downregulation of c-Myc and cyclin D1 | Vadde et al. (2016) |
| HT-29 cells | 100 μM | Induction in apoptosis via phosphorylation of AMPK and p53 | Kim et al. (2010) |
| HT-29 cells | 100 or 200 μM | Induction in apoptosis via AMP kinase/cyclooxygenase-2 pathway | Lee et al. (2009) |
| HCT-116 cells | 100 μM | Induction in apoptosis via AMPK signaling pathway | Kim et al. (2012) |
| DLD-1 cells | 0.1–1 μM | Induction in apoptosis via ERβ-Dependent Signals | Bulzomi et al. (2012) |
| HCT-116 cells | 0–40 μM | NAG-1 up-regulation mediated by EGR-1 and p53 is critical for quercetin-induced apoptosis in HCT116 colon carcinoma cells | Lim et al. (2007) |
| HCT-116 cells | 50 μM | Induction of ER stress and mitochondria-mediated apoptosis Increase in ROS production | Khan, Niaz et al. (2016) |
| HT-29, SW-620, Caco-2 cells | 30 μM | Enhancement of TRAIL-mediated apoptosis by inducing the accumulation of death receptors in lipid rafts | Psahoulia et al. (2007) |
| HT-29 cells | 150 μM | Induction of apoptosis | Wenzel et al. (2004) |
| LoVo cells | 100 μM | Induction of apoptosis Increase in ROS production | Zhang et al. (2012) |
| HT-29, Caco-2 cells | 100 μM | Induction of apoptosis | Kuntz et al. (1999) |
| HT-29, Caco-2 cells | 30–40 μM | Induction of apoptosis | Kuo (1996) |
| CO-115 cells | 100 μM | Induction of apoptosis | Murtaza et al. (2006) |
| HT-29 and Caco-2 cells | 15–120 μM | inhibition of lactate release Decrease of total cellular ATP content | Agullo et al. (1994) |
| HT-29 cells | 7 μM | Inhibition of lactate release | Agullo et al. (1996) |
| DLD-1 cells | ≥50 μM | Decrease in ornithine decarboxylase activity, and polyamines biosynthesis | Linsalata et al. (2010) |
| Caco-2 and DLD-1 cells | 10, 20, and 50 μM | Induction of estrogen responsive receptor (CB1-R) | Refolo et al. (2015) |
| HT-29, WiDr, COLO 20 I, and LS- I74T cells | 10nM-10 μM | Binding interaction with type-II EBS | Ranelletti et al. (1992) |
| Caco-2 cells | 20 μM | Induction of autophagy | Psahoulia et al. (2006) |
| SW-620 and HCT-116 cells | 15 μM | Induction of autophagy through phosphorylation of ERK | Zhao et al. (2017) |
| SW-480 cells | 50 μM | Inhibition of Wnt/β-catenin/TCF signaling through suppression of the binding of the TCF complexes to its specific DNA-binding sites | Park et al. (2005) |
| Caco-2 and SW-620 cells | 200 μM | Induction of apoptosis Inhibition of NF-κB signaling pathway | Zhang et al. (2015) |
| HT-29 cells | 50 and 100 μM | Decrease in COX-2 production and suppression of IκBα degradation | Narayansingh and Hurta (2009) |
| HT-29 cells | 100 μM | Induction of apoptosis Decrease in the expression of ErbB2 and ErbB3 proteins Decrease in AKT activation | Kim et al. (2005) |
| HCT-15 and CO-115 cells | 20 and 15 μM | Induction of apoptosis Inhibition of MAPK/ERK and PI3 K/AKT signaling pathways | Xavier et al. (2009) |
| HT-29 cells | 25 μM or 50 μM | Induction of apoptosis by generating the production of ROS Increase in the expression of sestrin 2 Inhibition of MAPK signaling pathway | Kim et al. (2014) |

(Continues)

**TABLE 1** (Continued)

| Target cells | Quercetin con. | Major effects of quercetin | Ref. |
|---|---|---|---|
| HCT-116 cells | 25 μM or 50 μM | Regulation of Sestrin 2-AMPK-mTOR Signaling Induction of Apoptosis Increase in intracellular ROS | Kim et al. (2013) |
| HT-29 cells | 0–200 μM | Induction of Apoptosis inhibition of the Akt-CSN6-Myc signaling axis | Yang et al. (2016) |
| colorectal cancer stem cells (CSCs) and HT-29 cells | 75 μM | Increase in cytotoxicity and apoptosis induction of doxorubicin Induction of G2/M arrest | Atashpour et al. (2015) |
| HT-29 cells | 50 μM | Increase in cytotoxicity and apoptosis induction of doxorubicin Induction of apoptosis Inhibition of the activation of NF-κB expression | Jin et al. (2016) |
| CO-115 and HCT-15 cells | 12 μM | Increase in cytotoxicity and apoptosis induction of 5-FU Induction of apoptosis | Xavier et al. (2011) |
| COLO 320 DM | 100 μM | Increase in cytotoxicity of 5-FU Inhibition of cell proliferation | Boersma et al. (1994) |
| DLD-1 cells | 0–100 μM | Enhance tumor radiosensitivity by targeting the ATM | Lin et al. (2012) |
| Caco-2 | 5 μM | Suppresses the migration and invasion through regulating toll-like receptor 4/nuclear factor-kappa B pathway | Han et al. (2016) |

proliferation increased with quercetin concentrations up to 20 mM, decreased at higher concentrations. Similar results were reported for HCT-116 and HT-29 cell lines. van der Woude et al. (2003) reported that cells treatment with high concentrations of quercetin (30 μM for HCT-116 and 80 μM for HT-29 cells) significantly inhibited cell proliferation, which confirmed the anticancer potential of quercetin. However, quercetin at lower concentrations stimulated cell proliferation. In addition to these studies, which reported the therapeutic potential of quercetin in colon cancer, two studies reported the chemo-preventive role of this agent through inhibition of colorectal cancer proliferation. The effects of Indian gooseberry (Amla) extract, rich in flavonoids such as quercetin, were evaluated for on CD133+ human colon cancer stem cells (Vadde, Radhakrishnan, Kurundu, Reddivari, & Vanamala, 2016). It was demonstrated that Amla extracts suppressed proliferation and induced apoptosis independent of p53, a tumor suppressor gene, in stem cells. Further, Amla extracts suppressed cell proliferation by suppression the expression of c-Myc and cyclin D1, key proteins involved in cell proliferation (Vadde et al., 2016). Another study showed that there was a synergistic antiproliferative action of the quercetin in combination with kaempferol in HuTu-80 and Caco-2 colorectal cancer cell lines (ACKLAND et al., 2005). These finding suggested a dualistic impact of quercetin on cell proliferation which might influence the present views on the suggested anti-proliferative function.

## 1.6 | Induction of apoptosis

Another reason for increasing attention to quercetin as a potent anticancer agent could be the pro-apoptotic potential with specific and individual effects on cancer cells rather than normal, non-transformed cells. Several studies have investigated the underlying mechanism for pro-apoptotic effects of quercetin in colorectal cancer (Kuntz, Wenzel, & Daniel, 1999; Kuo, 1996; Murtaza et al., 2006; Wenzel, Herzog, Kuntz, & Daniel, 2004; Zhang et al., 2012). Zhang et al. (2015) showed that quercetin induced colon cancer Caco-2 and SW-620 cell lines apoptosis by inhibiting the NF-κB signaling pathway, as well as down-regulation of Bcl-2 and up-regulation of Bax. It was also reported that quercetin exerted chemoprerventive effects on HT-29 cell lines through cell cycle arrest and induction of apoptosis, as well as the phosphorylation of AMP-activated protein kinase (AMPK) (Kim et al., 2010). A significant increase in AMPK phosphorylation was resulted when cells treated with quercetin. Additionally, quercetin caused a change in the expression levels of p53 downstream effectors such as Bax and Bcl-2. Cleaved- poly (ADP-ribose) polymerase (PARP) and cleaved-caspase-3 was also increased in the quercetin-treated cells. Therefore, the authors suggested that quercetin induces apoptosis via phosphorylation of AMPK and p53 (Kim et al., 2010). Similar results was reported by Lee et al. (2009) showing the activation of AMPK in quercetin treated HT-29 colon cancer cells, in relation to a reduction in cyclooxygenase-2 (COX-2) expression. Inhibition of COX-2, either by pharmacological inhibitor or gene knockout confirmed that AMPK is an upstream signal of COX-2, and is also essential for the pro-apoptotic and anti-proliferatory effects of quercetin. Moreover, cells treatment with AMPK inhibitor Compound C completely abolished the suppressive effects of quercetin on COX-2 (Lee, Park, Kim, Lee, & Park, 2009). In HCT-116 colon cancer, quercetin was demonstrated to significantly attenuated tumor growth and induced apoptosis under hypoxic condition with a substantial reduction of AMPK activity (Kim et al., 2012). Bulzomi et al. (2012) demonstrated that quercetin induced apoptosis in similar to 17β-estradiol (E2) in DLD-1 colon cancer cell lines. This effect of quercetin was shown to be mediated through p38 activation, which potentially can stimulate the activation of the caspase-3 and the cleavage of PARP. On the other hand, similar to E2, quercetin enhanced the expression levels of the phosphatase and tensin homolog (PTEN), suppressed ERb-dependent cyclin D1 promoter activity, and subsequently increased transcription of the estrogen-responsive element (Bulzomi et al., 2012). In another study

**TABLE 2** In vivo investigations of the quercetin anticancer potential

| Target | Cancer inducing agen | Quercetin con. | Major effects of quercetin | Ref. |
|---|---|---|---|---|
| Fisher 344 rats | Azoxymethane | 2% diet | Decrease in ACF number | Matsukawa et al. (1997) |
| Fisher 344 rats | Azoxymethane | 10 g/kg | Decrease in ACF number Reduction in colorectal carcinogenesis | Dihal, Woutersen et al. (2006) |
| Fisher 344 rats | Azoxymethane | 100 mg/kg | Decrease in ACF number | Femia et al. (2003) |
| CF1 mice | Azoxymethane | 2% diet | Increase in apoptotic index Increase in the number of apoptotic cells Positive cyclin D1 expression in treated group | Yang et al. (2000) |
| Fisher 344 rats | Dimethylhydrazine | 50 g/kg | Decrease in ACF number | Gee et al. (2002) |
| balb-c mice | Human colon-25 tumor | 1.6 mg/mL | Reduction in tumor size | Hayashi, Gillen, and Lott (2000) |
| CF1 mice | Azoxymethane | 2% diet | Suppression in tumor multiplicity Reduction in tumor incidence | Deschner et al. (1991) |
| Sprague-Dawley rats | Azoxymethane | 4.5 g/kg | Suppression in expression of proinflammatory mediators such as COX-1, COX-2, and iNOS Decrease in ACF number Induction in apoptosis | Warren et al. (2009) |
| Fisher 344 rats | Azoxymethane | 30000 p.p.m. | Induction in apoptosis via the mitochondrial pathway | Volate et al. (2005) |
| Wistar rats | N-methylnitrosourea | 50 mg/kg | Reduction in serum TAG72 and GAL3 levels Suppression of colonic Wnt5a gene expression and amplification of colonic Axin-1 gene expression positive reaction for Bax in mucosal epithelium Induction in apoptosis | Ahmed et al. (2016) |
| Sprague-Dawley rats | Azoxymethane | 0.45% diet | down-regulation the expressions of COX-1 and COX-2 | Turner et al. (2007) |
| Sprague-Dawley rats | Azoxymethane | 0.5% diet | Decrease in ACF number down-regulation the expressions of iNOS and COX-2 | Choi et al. (2006) |

by Lim et al. (2007) quercetin was shown to exert chemo-preventive effects through increase the apoptotic rate of HCT116 colon cancer cells through induction in the expression of NAG-1 (Non-steroidal anti-inflammatory drug activated gene-1), which is a TGF-β superfamily protein (Eling, Baek, Shim, & Lee, 2006). Additionally, the activation of the NAG-1 promoter required the early growth response-1 (EGR-1) and p53. Overexpression of NAG-1 potentiated the pro-apoptotic effect of quercetin, and inhibition of quercetin-induced NAG-1 expression attenuated quercetin-induced apoptosis in these cells (Lim et al., 2007). Khan, Paul et al. (2016) evaluated the apoptotic effect of TEF (5, 30-dihydroxy-3, 7, 40-triethoxyflavone), a quercetin derivative on HCT-116 colon cancer cells. Increase in the cytoplasmic and mitochondrial ROS production was reported to be the underlying mechanism by which TEF inhibited the proliferation and induced apoptosis. Cancer cells treatment with TEF resulted in an increase in expression levels of IRE1 and activation of calcium ions (Ca2+) and subsequent enhancement in JNK levels. Elevated Ca2+ ion translocates from endoplasmic reticulum to mitochondria which leads to ROS release and oxidative stress. In addition, TEF treatment enhanced the expression of pro-apoptotic factors and decreased the level of Bcl2. TEF led to activation of mitochondrial JNK, which has a pivotal function in oxidative stress and caspase mediated apoptosis (Khan, Niaz et al., 2016). Another potential mechanism for pro-apoptotic effects of quercetin is the induction of the accumulation of death receptors in lipid rafts. Psahoulia et al. (2007) examined that quercetin redistributed DR4 and DR5 death receptors into lipid rafts and increased the TRAIL-induced apoptosis. This effect is impeded by nystatin, a cholesterol-sequestering drug. Nystatin also sensitized the cancer cells to TRAIL-induced apoptosis. In addition, it was showed combination of quercetin, as an chemo-preventive agent, with TRAIL stimulated the mitochondrial-dependent apoptotic pathway indicated by Bid cleavage and the release of cytochrome c to the cytosol (Psahoulia, Drosopoulos, Doubravska, Andera, & Pintzas, 2007).

## 1.7 | Alternation in cancer cell metabolism

Emerging evidence suggesting that quercetin might alter the typical cellular metabolism of actively proliferative cells (i.e., the glycolytic pathway and energetic metabolism) because of the preferential cytotoxic effect on actively proliferating cells compared with slowly growing cells. Agullo, Gamet, Besson, Demigné, & Rémésy, 1994 reported that treatment of HT-29 and Caco-2 cells by 15–120 μM quercetin exerted a preferential cytotoxic effect on active proliferating cells. This inhibitory effect was accompanied by a significant suppression of lactate release and a decline in total cellular ATP content. In another study on the HT-29 call lines, it was also demonstrated that the cytotoxic effect of quercetin was associated with an early decrease in lactate release in the culture medium (Agullo et al., 1996). However, the authors failed to report any correlation between the effect of quercetin on cellular cAMP levels as well as HT-29 cell growth or viability (Agullo et al., 1996). Moreover, Linsalata et al. (2010) demonstrated that DLD-1 colon cancer metabolism altered through significant decrease in ornithine decarboxylase activity and polyamines biosynthesis such as (putrescine and spermidine), and was more effective in ≥50 μM concentration compared to 0.1 μM concentration. Quercetin concentrations ≥70 μM resulted in a drastic

decrease in cancer cells proliferation and hence could be an effective preventive agent for colorectal cancer (Linsalata, Orlando, Messa, REFOLO, & Russo, 2010).

### 1.8 | Modulation of estrogen receptors

Quercetin has been also reported to modulate the expression levels of cellular receptors known as "estrogen responsive," such as cannabinoid CB1 receptor (CB1-R) with an inhibitory tone on cell proliferation (Refolo et al., 2015). CB1-R is a G-protein-coupled cannabinoid receptor, which is also involved in colorectal cancer cell proliferation. Quercetin has a structural similarity to estrogens, therefore can bind to CB1-R to regulate cell growth rate in colorectal cancer in Caco2 and DLD-1cells Refolo et al. (2015). In cancer cells treated with quercetin, there was a significant increase in the expression levels of CB1-R, and this induction was partially abrogated when a specific CB1-R antagonist was added to cell culture medium. This proposed that quercetin acted through the binding to the CB1-R. Quercetin also caused cell cycle arrest at S phase, which was partially resolved by the combination with SR141716 (Refolo et al., 2015). Ranelletti et al. (1992) studied the chemo-preventive function and inhibitory effect of quercetin on the growth rate of HT-29, WiDr, COLO 20 I, and LS- I74T colon cancer cell lines. They showed that quercetin reversely suppressed cancer cell proliferation through cell cycle arrest at G0/G1 phase. It was also demonstrated that all cells contain type-II estrogen-binding sites (type-II EBS). The growth-inhibitory potential of quercetin, as well as cancer cell sensitivity to this flavonoid was related to affinity for type-II EBS (Ranelletti et al., 1992).

### 1.9 | Regulation of signaling pathways

#### 1.9.1 | Wnt/β-catenin signaling pathway

The Wnt/β-catenin pathway is one of the important signal transduction pathways involved in colon carcinogenesis (7–10). In the absence of any stimuli, a cytoplasmic multiprotein complex named adenomatous polyposis coli (APC) destabilizes β-catenin for degradation in proteasomal system. Therefore, low intracellular levels of β-catenin repress Wnt signaling through transcription factors of the TCF/LEF family. Following to occupy of Wnt receptors, β-catenin phosphorylation and degradation is prevented. Accumulation of free β-catenin in the cytoplasm and subsequent translocation into the nucleus, TCF/LEF-driven gene transcription is stimulated, which can lead to cell proliferation resulting in induced or blocked apoptosis. Quercetin was reported to suppress cell proliferation of colorectal cancer cells through modulation of Wnt/β-catenin signaling pathway. To test whether quercetin modulates Wnt/β-catenin/TCF signaling, Shan et al. (2009) used SW480 colon cancer cells transfected with wild and mutant TCF-4 genes as well as reporter gene constructs containing two copies of either an optimized wild (TOPflash) or mutant (FOPflash) TCF-binding element. After cell transfection with gene constructs and following treatment with quercetin, it was observed that quercetin inhibited the TCF transcriptional activity cancer cells. Quercetin also reduced β-catenin/TCF transcriptional activity, while the FOP flash activity was not affected. Quercetin-induced decrease in TCF signaling proposed that the interaction between β-catenin/TCF may be essential for TOPflash and that is, quercetin appears to be a chemo-preventive polyphenol and a strong suppressor of β-catenin/TCF signaling (Shan et al., 2009). Another study reported the quercetin, as a potent inhibitor of β-catenin/TCF signaling in colorectal cancer, was done by Park et al. (2005). The authors showed that quercetin inhibited the transcriptional activity of β-catenin/TCF in SW480 cells containing mutant β-catenin gene. The authors concluded that the inhibitory mechanism of quercetin was related to β-catenin itself or downstream components. The precise underlying mechanism was suggested to be suppression of the binding of the TCF complexes to its specific DNA-binding sites by quercetin (Park et al., 2005). In another attempt, the effect of quercetin on expression of 4,000 human genes in Caco-2 cells was studied to elucidate possible mechanisms involved in quercetin mode of action in colon cancer (van Erk et al., 2005). It was reported that cells treatment by quercetin at both low (5 μM) and high (50 μM) concentration resulted in significant suppression of the α-catenin expression. Overexpression of α-catenin could be a substantial underlying mechanism for chemoprevention because α-catenin can act as an invasion inhibitor (van Erk et al., 2005). α-catenin expression in colon cancer cells is associated with an suppression of TCF-dependent transcription (van Erk et al., 2005).

#### 1.9.2 | NF-κB signaling pathways

The nuclear factor-kappa B (NF-κB) pathway plays an important role in various processes such as enhanced proliferation, apoptosis resistance, and genomic instability in colon cancer cells. Therefore, it is reported that NF-κB pathway is one of the most aberrant activated signaling pathways in colorectal cancer. Activation of this signaling through binding of various pro-inflammatory signals to receptors, inhibitor of κB kinase (IKK)-dependent phosphorylation and ubiquitin-mediated degradation of IκB proteins, the transcription of genes multiple downstream factors are activated. Zhang et al. (2015) demonstrated that quercetin presented a potent anticancer effect by inhibiting NF-κB signaling pathway. They showed that NF-κB DNA binding activity was drastically decreased after quercetin treatment. Moreover, quercetin induced the dephosphorylation and up-regulation of IκB-α (Zhang, Zhang, Yin, & Zhang, 2015). In another study, it was reported that quercetin, as an chemo-preventive compound, effectively inhibited IκBα degradation resulting in repression of NF-κB activation (Narayansingh & Hurta, 2009). Treatment of cancer cells with quercetin resulted in 100% increase in IκBα expression, as well as suppression of COX-2 expression levels. Therefore, it was suggested that there was an inverse relationship between COX-2 and IκBα expression in which quercetin decreased COX-2 production and suppressed degradation of IκBα (Narayansingh & Hurta, 2009). Taken together, these results suggested that quercetin displayed rapid and potent anti-tumor effects against colon cancer cell lines.

### 1.9.3 | PI3K and MAPK signaling pathways

The MAPK/ERK and the phosphatidylinositol 3-kinase (PI3K)/Akt are two signaling pathways with major function in oncogenic transformation in colorectal cancer. Aberrant expression of these pathways results in development of a proliferative phenotype and resistance to therapy. Various studies have suggested that key elements of MAPK/ERK and PI3K/Akt pathways can be targeted for successful inhibition tumor progression. Some recent studies investigated whether the anti-proliferative and pro-apoptotic roles of quercetin is mediated trough PI3K and MAPK signaling pathways. In another study, inhibition of the Akt-CSN6-Myc signaling was reported to be the main mechanism for quercetin-induced apoptosis of HT-29 colon cancer cells (Yang et al., 2016). The treatment of HT-29 cells by quercetin resulted in the cell cycle arrest at the S-phase. Quercetin also decreased the expression levels of p-Akt and increased CSN6 protein degradation; therefore, exerting a direct effect on the expression levels of Myc, p53, Bcl-2, and BAX. The increase in the expression levels of CSN6 decreased the impact of quercetin treatment on HT-29 cells, suggesting that quercetin-induced apoptosis may involve Akt-CSN6-Myc signaling axis in HT-29 cells (Yang et al., 2016). Some other studies also investigated the chemo-preventive effects of quercetin through modulation of these signaling pathways. For example, Xavier et al. (2009) examined the impacts of quercetin and other flavonoids on cell proliferation and apoptosis of HCT-15 and CO-115 cell lines, harboring KRAS and BRAF activating mutations. They observed that the test compounds inhibited proliferation and induced apoptosis in both cell lines. They also showed that quercetin only (20 μM) significantly suppressed the phosphorylation of ERK protein in HCT-15 cells, but not in CO-115 cells. Additionally, in CO-115 cells, the expression levels of phospho-Akt was significantly depressed in response to quercetin (15 μM) (Xavier et al., 2009). In another study by Kim et al. (2005) it was reported that quercetin inhibited colorectal cancer cells proliferation, as well as induced apoptosis through significant decrease in the expression levels of ErbB2, ErbB3, Akt, Bax, and Bcl-2. In addition, it was observed that the quercetin-induced apoptosis were associated to a significant decrease in the expression levels of p-Akt. In HT-29 cell treated with 25 μmol/L quercetin, the phosphorylated form of Akt was significantly lower, but it was undetectable at the 100 μmol/L concentration. It is well recognized that ErbB3 activation and subsequent PI3K activation lead to the activation of Akt. Quercetin at high concentrations results in a dose-dependent inhibition of ErbB2 and ErbB3 expression in HT-29 cells (Kim et al., 2005). Kim et al. (2014) reported that increase in the intracellular ROS production and the expression levels of sestrin 2, as a downstream effector of p53, could be another potential mechanism for quercetin-induced apoptosis. In other words, the quercetin induced apoptosis in cancer cell in a AMPK/p38 signaling pathway and sestrin 2-dependent manner. However, in the cells with silenced sestrin 2, quercetin did not regulate AMPK or p38 phosphorylation. It was also demonstrated greater expression levels of sestrin 2 and ROS production in response to quercetin was independent of p53 (Kim, Lee, Kim, & Kim, 2014). Similar results were found by another study conducted by the same author in HCT116 colorectal cancer cell line (Kim, Lee, & Kim, 2013). They showed that quercetin increased apoptotic cell death through ROS production and sestrin 2 expressions. Enhanced sestrin 2 expression was followed by AMPK activation. Interestingly, mTOR activity by sestirn 2 expression was dependent on AMPK phosphorylation (Kim et al., 2013).

## 1.10 | Inhibition of metastasis and angiogenesis

Angiogenesis, an essential process for magnification and metastasis of tumor cells is defined as the growth of incipient vessels from the existing microvascular network in order to supply nutrition oxygen for growing cancer cells. Angiogenesis requires a number of important angiogenic proteins including vascular endothelial cell growth factor (VEGF), epidermal growth factor (EGF), fundamental fibroblast growth factor (bFGF), and matrix metalloproteinases (MMPs). It is well documented that the suppression of angiogenesis can be a substantial strategy for cancer treatment. There are several lines of evidence demonstrating that quercetin can have antiangiogenic effects inhuman malignancies. A reduction in the expression and activity of MMP-2 and MMP-9 was observed in in primary (Caco-2) and metastatic (LoVo and LoVo/ADR) colon cancer cells after treatment with quercetin (Ademosun et al., 2016). Ademosun et al. (2016) examined the effects of phenolic extracts from orange peels (containing quercetin and other flavonoids) on glutathione reductase, glutathione peroxidase, and total MMP activities in the cells. It was revealed that the extracts enhanced the activities of glutathione reductase and glutathione peroxidase in the cells, as well as suppressed the total MMP activities, hence suggested to exert an antioxidant activity (Ademosun et al., 2016). In another study, it was demonstrated that quercetin significantly suppressed COX-2-mediated angiogenesis in human endothelial cells treated with the conditioned medium collected form DLD-1 colon cancer cells (Xiao et al., 2011). In addition, an inhibitory potential role of quercetin on cancer progression is suggested to be augmented by affecting tumor invasion and migration. Han et al (Han, Song, & Zhang, 2016). reported that quercetin inhibited the migration and invasion of Caco-2 cells via regulating toll-like receptor 4/NF-κB signaling pathway. Quercetin could remarkably suppress the migratory and invasive capacity of Caco-2 cells via decrease in the expressions of MMP-2, MMP-9, and increase in the expression of E-cadherin. Interestingly, the anti-TLR4 antibody or pyrrolidine dithiocarbamate could affect the inhibition of quercetin on cell migration and invasion, as well as the protein expressions of MMP-2, MMP-9, E-cadherin, tall like receptor (TLR4), and NF-κB p65. In addition, quercetin could reduce inflammatory markers such as, tumor necrosis factor (TNF)-α, COX-2, and interleukin (IL)-6 (Han et al., 2016).

## 1.11 | Induction of autophagy

Autophagy is considered a highly conserved cellular degradation process, in which the cell's own lysosomic system degraded long-lived proteins or entire organelles; however, it has recently been shown to

be an important mechanism for programmed cell death (type II). Autophagy os essentially associated with preservation of cellular homeostasis and cell viability, as well as involvement in certain conditions such as nutrient starvation, oxidative stress, irradiation, and misfolded protein accumulation. Autophagic capacity of cancer cells is much lower than normal cells, proposing that manipulation of autophagy could be a therapeutic tool for treating cancer. To examine effects of quercetin on cell survival and autophagic cell death of colorectal cancer cell, Psahoulia et al. (2006) designed a systems of human colorectal cancer development with conditional expression of RAS. Their findings showed that quercetin decreased the half-life of oncogenic Ras protein levels in which proteasome inhibitor MG132 was inhibited. In addition, they reported that oncogenic Ha-RAS sensitized cells to autophagy, and quercetin further promoted this process, which was accounted for the reduced cell viability of Caco-H2 (Ha-RASV12-transformed) cells, and chemoprevention. Quercetin also mainly affected the cell cycle of the Caco-K15 (Ki-RASV12-transformed) cells and promoted autophagy primed by the Ha-RASV12 oncogene in the Caco-H2 cells (Psahoulia et al., 2006). Zhao et al. (2017) reported that 8-C-(E-phenylethenyl) quercetin (8-CEPQ), a novel quercetin derivative induced autophagic cell death in colon cancer cells, which was confirmed by silencing of Atg7 or Beclin-1, as two key genes involved in autophagic cell death. Silencing of Atg7 or Beclin-1 by siRNA significantly inhibited autophagy with corresponding attenuation of LC3-II accumulation in SW-620 and HCT-116 cells. Furthermore, treatment with 8-CEPQ induced phosphorylation of extracellular signal-regulated kinase (ERK) and inhibition of ERK phosphorylation by the specific inhibitor attenuated 8-CEPQ-induced autophagy, which reversed 8-CEPQ-mediated cell growth inhibition (Zhao et al., 2017).

## 1.12 | Increase the cytotoxic effects of anticancer agents

It is well-studies that development of resistance against chemotherapeutic agents is a main burden in successful treatment of cancer (Yousefi, Zarghami, Samadi, & Majidinia, 2016). Previous studies have been reported that quercetin can act as an efflux pump inhibitor. It appears that quercetin can increase the bioavailability of drugs by competitively inhibiting key proteins involved in the development of the drug resistance including; P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), multidrug resistance-associated protein 1 (MRP1), and the metabolizing enzyme CYP3A4 (Chen, Zhou, & Ji, 2010; Du et al., 2010). Thus, it is suggested that co-administration of quercetin with conventional chemotherapeutic agents may exert better anticancer effects than nontoxic concentrations of quercetin. Quercetin was shown to increase cytotoxicity and apoptosis induction of doxorubicin at low concentration in colorectal cancer stem cells (CSCs) and HT-29 cells (Atashpour et al., 2015). Combination treatment of quercetin with doxorubicin induced G2/M arrest in the HT-29 cells and to a lesser extent in CSCs (Atashpour et al., 2015). In addition, quercetin enhanced cisplatin-induced apoptosis of colon cancer HT-29 cells (Jin, Han, Ma, Zhou, & Zhao, 2016). The combination of quercetin with cisplatin strongly inhibit cancer cell proliferation and induce apoptosis. The possible mechanism could be attributed to inhibitory role of quercetin on activation of NF-κB expression. These finding suggested that quercetin in combination with cisplatin might potentially provide an effective approach in treatment of patients with colon cancer (Jin et al., 2016). Xavier, Lima, Rohde, and Pereira-Wilson (2011) investigated the effect of quercetin on sensitivity of microsatellite instability (MSI) colorectal cancer cells (CO-115 and HCT-15 cells) to 5-flourouracil (5-FU). The combination treatment of 5-FU with quercetin increased apoptosis through the activation of mitochondrial pathway (Xavier et al., 2011). Boersma et al. (1994) demonstrated a synergism between the cytotoxic effects of 5-FU and quercetin in colorectal cancer cell lines. It was reported that combination of both agents resulted in significant suppression of proliferation COLO 320 DM cells. The authors concluded that the cytostatic action of combination of quercetin with 5-FU in COLO 320 DM cells is superior to when each was consumed alone (Boersma et al., 1994). In addition to chemo-sensitization, quercetin is involved in the increase in the radiosensitivity of colon cancer cells. Lin et al. (2012) showed that combination of quercetin with radiotherapy could increase tumor radiosensitivity by suppressing the ataxia–telangiectasia-mutated (ATM) mediated pathways. Quercetin enhanced irradiation-induced γ-H2AX and 53BP1 focus formation (Lin et al., 2012).

## 1.13 | In vivo molecular mechanisms of the anti-colon cancer effects

Despite high number of in vitro studies, there are a few in vivo studies investigated the roles of quercetin on colorectal cancer. In vivo studies in animal models are critical strategies as to investigate molecular mechanisms of colorectal carcinogenesis, and to translate hypotheses derived from cell models into the complex physiology of the colon (Johnson & Fleet, 2013). There are various animal model of colorectal cancer, as well as numerous chemical compounds with mutagenic potential to controllably induce this type of cancer. Studies on the effects of quercetin in animal models of colorectal cancer reveal the chemotherapeutic potential of this polyphenol, and in some case, its chemo-preventive function.

## 1.14 | Inhibition of proliferation

The compound 1,2-dimethylhydrazine (DMH) and its metabolite, azoxymethane (AOM), are the two most commonly used chemical carcinogens to induce and promote colorectal cancer in rats and mice (Bissahoyo et al., 2005). In animal models of colorectal cancer, various studies reported that quercetin is an effective chemo-preventive agent through inhibition of cell proliferation. The tumor preventive effects of quercetin was examined in DMH- and AOM- induced colorectal cancer in animals. Matsukawa et al. (1997) examined the effect of dietary quercetin on formation of aberrant crypt foci (ACF) induced by AOM in the colon of female F344 rats. ACF, as the earliest detectable abnormality in colorectal cancer and precursor of adenomas, is the collections of abnormal appearing colonic crypts and express mutations in the *apc* gene and the *ras* oncogene (Bird, 1995, Khare, Chaudhary, Bissonnette, & Carroll, 2009). Dietary quercetin

resulted in the decrease in the number of ACF in F344 rats with AOM- induced colorectal cancer. Femia et al. (2003) investigated the effect of diets supplemented with tomatoes or onions with variable quercetin-glycoside content on AOM-induced ACF in the colon of rats. The results showed a significant decrease in the ACF number after quercetin treatment. Similar results was also reported by Dihal, Woutersen, Van Ommen, Rietjens, and Stierum (2006) when 10 g/kg concentration quercetin was administered. Yang et al. (2000) showed that quercetin administration resulted in significant chemo-preventive effect through increase in the number of colonic epithelial cells per crypt column in normal and AOM-treated mouse. Additionally, quercetin resulted in greater number of apoptotic cells/column and apoptotic indices in cancer group. Apoptotic cells expanded throughout the colonic crypts after quercetin and AOM supplementation. Positive cyclin D expression was detected in mice in diets supplemented with quercetin. In addition, quercetin was shown to significantly suppress AOM-induced focal areas of dysplasia (FADs) (Deschner, Ruperto, Wong, & Newmark, 1991). Female CF1 mice fed with 2% quercetin had a significant reduction of tumor incidence and multiplicity, (i.e., fewer tumors/animal arose) in this groups than in the AOM-treated control mice. Moreover, quercetin significantly reduced activity of AOM-induced hyperproliferation in colonic epithelial cells as well as FAD incidence (Deschner et al., 1991). In another study, Gee, Hara, and Johnson (2002) showed that administration of quercetin resulted in a significant decrease in the frequency of crypt cell mitosis in proximal, mid, and distal small intestine and distal colon. In rats with DMH- induced colorectal cancer, quercetin (1 g/kg) suppressed crypt cell mitosis and significantly decreased number of ACF in the distal colon of treated animals. In a study by Howells et al. (2010) the chemo-preventive effects of quercetin analogue, 3′,4′,5′-Trimethoxyflavonol (TMF) was evaluated in $Apc^{Min}$ mice and human-derived HCT116 adenocarcinoma–bearing nude mice. Consumption of TMF reduced adenoma burden of small intestinal in $Apc^{Min}$ mice compared with control mice. The TMF early regimen approximately reduced HCT-116 tumor size by 50%, decreased tumor proliferation, and increased apoptosis, whereas the TMF late regimen had no significant effect when compared with controls. In tumor tissues from mice, in which TMF reduced tumor development, p53 expression was increased in $Apc^{Min}$ and HCT116 tumor–bearing mice. The results of all mentioned studies suggest that quercetin can be a good candidate with respect to safety and efficacy as a cancer chemo-preventive agent in colon cancer therapy.

## 1.15 | Induction of apoptosis

In addition to suppression of the proliferation and ACF generation, quercetin was also demonstrated to induce apoptosis in animal models of colon cancer. In AOM- induced colon cancer, Volate, Davenport, Muga, and Wargovich (2005) showed that chemo-preventive function of quercetin to modulate ACFs may be attributed to induce apoptosis via the mitochondrial pathway, which was seen form Western blot analysis of caspase 9, Bax (proapoptotic) and Bcl-2 (antiapoptotic) proteins. In a N-methylnitrosourea rat model of colon cancer, quercetin elicited significant reduction in serum tumor associated glycoprotein 72 (TAG72) and galectin-3 (GAL3) levels, as well as a significant suppression of colonic Wnt5a gene expression and amplification of colonic Axin-1 gene expression (Ahmed, Aglan, Zaazaa, & Shalby, 2016). Also, it caused moderate positive reaction for Bax in mucosal epithelium. Therefore, it was suggested that inhibitory effects of quercetin on colon cancer development might be related to regulatory action on Wnt signaling and induction of apoptosis (Ahmed et al., 2016). Quercetin also exerted chemo-preventive function and suppressed the formation of early preneoplastic lesions in AOM induced colorectal cancer in rats, which occurred in concert with reductions in proliferation and increases in apoptosis (Warren et al., 2009).

## 1.16 | Inhibition of inflammation

Quercetin has been suggested as chemo-preventive agents interfering adverse inflammatory signals, which it has been reported in animal models of colon cancer. For example, Warren et al. (2009) showed that quercetin influenced proliferation and apoptosis, as well as ACF formation through suppression of inflammation. In rats with AOM- induced colorectal cancer, quercetin significantly inhibited expression of pro-inflammatory mediators including COX-1 and COX-2. Turner et al. (2007) also reported the same impact of quercetin on COX-1 and −2 in AOM induce colorectal cancer. In another study by Choi, Park, Kim, Kim, and Sung (2006) the effects of quercetin supplementation on AOM-induced colon carcinogenesis and inflammatory responses in rats fed with high-fat diet rich in ω-6 fatty acids was evaluated. The authors showed that quercetin supplementation reduced the number of ACF only in animals fed high-fat diet; however, no significant difference in tumor incidence was found. The expression of inducible nitric oxide synthase (iNOS) was reduced by quercetin without a statistical significance. No change in prostaglandin E2 (PGE2) levels was observed.

## 1.17 | Quercetin application in clinic for colorectal cancer

As mentioned above, in vitro investigations have thus far established that quercetin could effectively suppress the proliferation of multiple colorectal cancer cell lines. In vivo studies have also demonstrated that administration of quercetin in animal models of colorectal cancer inhibit tumor growth. Although the substantial mechanisms evaluated vary and no preclinical trials exist, the results are still promising. Providing direct evidence is one of the most important advantages of clinical trials which can increase the applicability of quercetin. The pharmacokinetics impact of quercetin has been examined in the human body and clinical case control studies suggesting that quercetin is effective as a chemo-preventive agent by significantly reducing risk factors associated with colorectal cancer. For example, in a large case-control study, the associations between dietary intake of the six major flavonoid subgroups (flavonols, flavones, flavan-3-ols [catechins], procyanidins, flavanones, and phytoestrogens) and individual flavonoid compounds (quercetin, catechin, epicatechin, naringenin, and hesperitin) with colorectal cancer risk was examined on the 1,456 cases and 1,456 controls. Enhanced consumption of flavonols, quercetin, catechin, and

epicatechin was reported to significantly reduce colorectal cancer risk (Theodoratou et al., 2007). Another study showed that the protective effects of quercetin on risk of proximal colon cancer were significant only when either high fruit intake or low tea consumed. Interestingly, when total fruit intake was low, increased intake of quercetin resulted in significant increased risk of distal colon cancer (Djuric, Severson, & Kato, 2012). The authors concluded that quercetin exerts contrasting effects on colon cancer risk, which depends on the amount of dietary intakes of fruit or tea, and that quercetin had protective effects only on proximal, not distal, colon cancer (Djuric et al., 2012). Taking together, it is proposed that quercetin should be broadly investigated and used for clinical treatment for the time being because of increasing incidence rate of colorectal cancer and absence of any satisfactory comprehensive treatment for colorectal cancer.

## 2 | CONCLUSION

In this review, we discussed chemotherapeutic and chemo-preventive roles of this flavonoid compound on colorectal cancer, which has been demonstrated to be mediated through various mechanisms. Confirming the preferential anti-carcinogenetic function of quercetin on human colorectal cancer is proposed to be important for considering this compound as a potential anticancer agent. However, there is still some considerable limitations, which are noteworthy need more investigations. Some of these limitations include low aqueous solubility, low intrinsic activity, high metabolic rate, rapid clearance form body, poor absorption, inactive metabolic product. On the other hand, quercetin metabolic conversion strongly affects the bioavailability and efficacy of this polyphenol. In similar to other xenobiotics, conjugation may depress quercetin reactivity. Some conjugated metabolites of quercetin exerts biological activity and active aglycone, which various biological targets are introduced for it, may be produced by the site-specific activation of hydrolytic enzymes. Therefore, further in-detailed investigation are required for elucidating more comprehensive information about the targets and mechanisms of action of quercetin and its active metabolites. Therefore, to overbearing these restrictions, delivering them through nanostructure carriers such as polymers, liposomes, chitosan, and other ones, maybe an applicable strategy. These delivery carriers are reported to increase polyphenols solubility in water, absorption in body, circulation time, and target specificity. In the case of quercetin, this field is in its infancy, and also is good choice for increasing the applicative outcome of this polyphenols in various types of cancer, particularly in colorectal cancer. In addition, future research should certainly focus on the synergistic approaches of quercetin with other anticancer drugs. It is also worthwhile to design and conduct clinical trials regarding to the therapeutic and preventive effect of quercetin on colorectal cancer. The updating of dietary databases for flavonoids will provide important information for future epidemiological studies. In conclusion, despite a promising results of quercetin in improving risk factors associated with colon cancer, future studies are required to fully elucidate underlying mechanisms as well as any potential adverse impact.

## CONFLICTS OF INTEREST

None.

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