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POTENTIAL ACTIVITY OF QUERCETIN ON DIFFERENT TYPES OF CANCERS – A REVIEW

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Abstract

Diet assumes a critical part to keeping up solid life. Numerous normal items present in our eating regimen, like flavonoids, can forestall the movement of disease. Quercetin, an unmistakable bioactive flavonoid, is a dietary part that has pulled in the consideration of dietitians and therapeutic scientific experts because of its various health-promoting impacts. It is a remarkable cell reinforcement that has a well-documented job in decreasing diverse human diseases. Quercetin shows direct proapoptotic impacts on tumor cells and hence can repress the advancement of various human diseases. The anticancer impact of quercetin has been reported in various in vitro and in vivo examines that elaborate a few cell lines and creature models. Then again, the high poisonous impact of quercetin against disease cells is went with next to zero results or damage to typical cells. As needs be, this survey presents an outline of late advancements on the utilization of quercetin against various sorts of malignancy alongside components of activity. Moreover, the current survey sums up the writing relating to quercetin as an anticancer specialist and gives an appraisal of the expected usage of this regular compound as a free or elective medication for forestalling and treating cancers.

Introduction

Flavonoids are abundantly present in nature and the major sources of these compounds are plants, vegetables and flowers. Flavonoids have an interesting biological properties and diverse framework. In the body's defence system these flavonoids play a vital role. More than 4,000 flavonoids are present in nature and these flavonoids possess important biological activities such as antioxidant, hepato-protective, anti-inflammatory, and antimicrobial properties. (Kanadaswami *et al.*, 2005) Quercetin is a naturally occurring polyphenolic flavonoid, chemically known as 3, 3',4',5,7- pentahydroxyflavone (C₁₅H₁₀O₇), that is commonly found in different vegetables and fruits such as cilantro, onions capers, apples, cranberries, berries, and lingonberries. The foods which are high in quercetin are onions, kale, cherry tomatoes, broccoli, blueberries, and apples. The antioxidant effect is the most important property of this flavonoid. Phenyl benzoyl ketone is the basic parent nucleus of quercetin and is composed of 2 benzene rings and connected by an oxygen-containing pyrene ring, the three rings are planer and molecule is relatively polarized. The basic structure is C6-C3-C6.

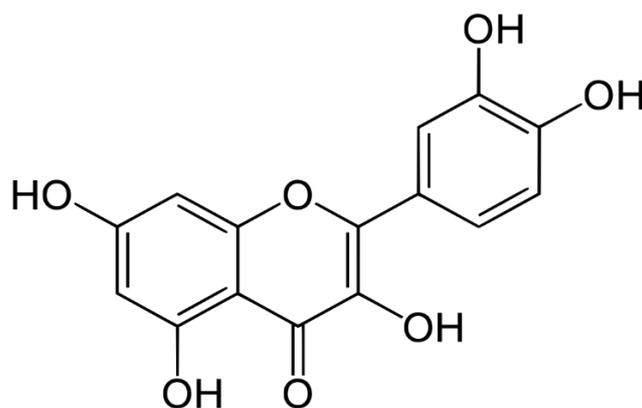


FIG 1: Structure of Quercetin

The sugars quercetin combines is mainly xylose, glucose, rhamnose, mannose and some oligosaccharides. Hypericum and rutin are disaccharide and are also the monoglycoside derivatives of quercetin. Quercetin is stable in human plasma, human urine and acetonitrile. It is unstable under alkaline conditions probably due to the unstability of its central ring structure. Quercetin is an active compound for antibacterial, antiviral, anticancer, anti-allergic and analgesic (Y. Liu et al 2017).

Role of quercetin in different types of cancers

Quercetin is an extraordinary cell reinforcement having an all around recorded job in diminishing diverse human diseases. Quercetin causes the apoptosis of tumor cells and thus inhibits the progress of numerous human cancers. The anticancer effect of quercetin has been documented in various in vivo and in vitro studies that elaborated various cell lines and animal models. On the other hand, the toxic effect of quercetin on cancer cells has less or no side effect to normal cells. Most importantly, quercetin hinder the spreading of different types of cancers, such as lung cancer, prostate cancer, liver cancer, breast cancer, colon cancer, and cervical cancer, through cellular signaling mechanisms and inhibition of enzymes responsible for activation of carcinogens these anticancer properties are exerted (Y. Liu et al., 2017). Anticancer effects are shown by quercetin based on its binding to proteins and cellular receptors (Murakama, Ashida, & Terao, 2008; Shih, Pickwell, & Quattrochi, 2000) Recently it has been found that quercetin has synergistic effects when combined with Cisplatin a chemotherapeutic agent, which further may improve the outcomes of the traditional chemotherapy (Brito et al., 2015). In the gastrointestinal tract the quercetin gets absorbed and is metabolized in the epithelial cells of intestines and stomach by the phase II enzymes. In kidney and liver the combined metabolites are then further processed (Abarikwu, Pant, & Faraombi, 2012; Nabavi, Mirzael, & Moghaddam, 2012). Shortly after the quercetin-rich vegetables are consumed quercetin metabolites seem to accumulate in tissues. In vitro studies specified that quercetin metabolites emerging from enterocytes and liver, serve as antioxidants by restraining oxidation of low-density lipoprotein cholesterol. Over the past few decades cancer continues to be a global concern, and even with many pharmaceutical and technological advances (Seyed, Jantan, Bukhari, & Vijayaraghavan, 2016). Cancer treatments include radiotherapy, surgery, and anticancer drugs (chemotherapy) methods. For over years, humans have used many herbs as complementary therapy for the treatment of different types of cancers (Martin et al., 2006). In this regard, for the treatment of cancer the natural compound such as quercetin have been employed as an alternative drug.

Different types of fruits and vegetables	Quercetin content (mg/100g)
Cranberries	14.00
Broccoli	3.21
Apples	4.70
Onions	22.00
Cherries	2.64
Cilantro	53.00
Tomatoes	4.56

The therapeutic and chemo-preventive ability of this natural compound (flavonoid) against different types of cancers along its mechanism of action.

Breast cancer

Breast cancer is the most common cancer after lung cancer and second leading cause of deaths in women around the world (Chow, 2003; Wang, 2016). For the treatment of breast cancer the common therapeutic strategies include surgery, chemotherapy, radiotherapy, endocrine therapy, and biological therapy (Normanno et al., 2009). Over the past thirty years, more than 100 clinical trials have proved the efficaciousness of the chemotherapy in the prevention of breast micro-metastases. The major obstacle in cancer treatment is the toxicity and side effects of chemotherapy. Quercetin is one of the anti-cancer agents which is widely found in foods and vegetables, and is easily accessible upon the isolation and extraction. Quercetin function through several mechanisms, such as cell cycle arrest at the G1and/ or G2/M phase, inhibition of the signal transduction pathways in cancer cells MAPKs (Mitogen activated protein kinase) and Akt (protein kinase B), prevention of cell proliferation by the regulation of synthesis of growth factor, and induction of apoptosis (Ackland, Van Erk, 2005; Ong CS, 2004; Quagliariello, 2016).

Proliferation

Quercetin has anti-proliferative activity and obstructs many significant molecules like tyrosine kinase (Cunningham, 1992; Ferriola, 1989; Kantengwa, 1991) protein kinase-C (Hofmann, 1988; Kang, 1997) and phosphatidylinositol-3 kinase (Srivastava, 1985; Weber, 1997) which are involved in few signaling pathways. Although the exact mechanism of quercetin in suppression and prevention of cancer is not fully explained, it is likely that quercetin influences several signaling cascades, such as inducing apoptosis (Wei et al., 1994), inhibition of tyrosine kinase (Ferry et al., 1996), reducing the level of p53 (Tumor protein p53) (Avila et al., 1994), and interfering with the pathways important for cell survival (Matter et al., 1992). Unregulated expression of tyrosine kinase leads to the excess proliferation of cancer cells, as it is having regulatory effect on the cell growth pathway (Bishop, 1987; Ullrich, 1990). Current studies have shown that the significance of tyrosine kinase pathways in the development of breast cancer (Biscardi, 2008; Burstein, 2008; Pietres, 1995; Scambia, 1993). In the first phase of some clinical trials the inhibitory effect of quercetin on tyrosine kinase has been addressed. Few scientists recruited 51 patients with cancer and injected 945mg/m² of quercetin. They showed that this dosage of quercetin injected intravenous was safe, and can obstruct the activity of the tyrosine kinase pathways in lymphocytes, resulted in the induction of programmed cell death in lymphocytes (Ferry et al., 1996).

Signal transduction

In many types of tumors, including breast cancer, ovarian cancer, and hepatocarcinoma in rats, the activity of signal transduction pathways is increased. Therefore tumor progression can be prevented by targeting these pathways (Singhal, 1995; Rizzo, 1994). Quercetin obstructs 1-phosphatidylinositol 4-kinase and 1- phosphatidylinositol 4-phosphate 5-kinase by a reduction in the concertation of inositol 1, 4, 5-trisphosphate (IP₃). The reduction of inositol triphosphate actually declines the release of calcium from its internal sources (Prajda, Yen Ya, 1995; Yamazaki, 2014). Since the assembly of ROS (Reactive oxygen species) induces oxidative damages, it can lead to some disorders like cancers. Studies have shown that quercetin delay the immoderate generation of ROS and restrains the activation of cyclic adenosine monophosphate (cAMP), reticular activating system (RAS), as well as phosphorylation of extracellular signal-regulated kinases 1/2 (ERK1/2) (Hartwell et al., 1994).

Cell cycle

Quercetin restricts the breast cells proliferation through the inhibition of cell cycle.it can also change the regulation of some proteins that participate in the process of cell cycle, leading the cell cycle delay at the S phase. In the process of cell cycle there are two checkpoints, G1/S and G2/M phases, in which cells needs to get assent to replicate. These checkpoints make sure that the downstream steps would not begin until the upstream stages would be correctly accomplished. Upon the damaging of the cells the process of apoptosis begins, and continuation of the cell cycle would be obstructed (Hartwell et al., 1986). Quercetin prevents the continuation of cells from the S phase to G2/M phase, as it was indicated by Cho et al. that the number of cells at S phase remarkably increased compared with those treated with quercetin at the G0/G1phase (Kang, 1997; Richter, 1999). The expression of CDK2 (Cyclin-dependent Kinase 2), cyclin A&E, and p57 proteins are reduced by the quercetin. The action of CDK2/cyclin E complex is necessary for the continuation of the cell cycle from G2 to M phase. The p53 protein plays important and main role in the inhibition of cell growth and apoptosis, through influencing the downstream molecules, such as p21, which is a primary downstream effector. This phenomenon blocks the activity of Cdk's by increasing the expression of p21, leading to growth inhibition and apoptosis (Choi, 2001; Kim, 2013).

Apoptosis

In breast cancer cells the quercetin induces apoptosis. For understanding the mechanisms involved in this process, the apoptosis related proteins such as Bcl-2 (b-cell lymphoma 2), caspase-6, -8, and -9, their expression as well as their changes in mitochondrial membrane potential ($\Delta\Psi_m$), was evaluated in the Michigan Cancer Foundatio-7 (MCF-7). The ratio of Bax (BCL2 Associated X) to BCL-2 settles whether arise or not. Bcl-2 obstructs the beginning of apoptosis by controlling the transition of calcium ion from the membrane of endoplasmic reticulum and its antioxidant activity. The Bax aggravates the activity of Bcl-2 and induces programmed cell death (Korsmeyer. Et al., 1993). The expression of Bax protein is considerably decreased in many malignant tumors (Cvejic, 2008; Nehls, 2007). The increment in the proportion of Bax to Bcl-2 can cause the release of cytochrome c from mitochondria into cytoplasm, thus encouraging the process of apoptosis. Many lines of evidence showed that when MCF-7 cells are treated with quercetin the expression of Bcl-2 is decreased while the level of Bax is increased. By changing the expression of Bax and Bcl-2 quercetin also reduces the amount of $\Delta\Psi_m$ (Yang et al., 1997). Quercetin can split pro-caspase 8 and 9, which play an important role in initiating apoptosis. By the activation of these caspases a downstream mediator called caspase-6 is stimulated which in turn leads to the induction of programmed cell death. To decide if the presence of caspases is significant for the enlistment of apoptosis by quercetin, Cho et al, brooded MCF-7 cells with caspase inhibitors and saw that in presence of inhibitors the apoptosis is essentially diminished (Chou et al., 2010).

Prostate cancer

Prostate cancer is a typical male threatening illness and its rate is expanding around the world, with an expected 233,000 new cases and 29,480 passings in 2014 in the United States. The frequency pace of new cases is 27% possessing the primary spot and the death rate is 10% involving the second spot simply mediocre compared to cellular breakdown in the lungs among body locales where tumorigenesis may happen (Siegel et al., 2014). At the point when prostate malignant growth is kept and doesn't attack the container or metastasize, it tends to be restored by revolutionary prostatectomy and radiation (Fleshner et al., 2005). All things being equal, most patients later experience the ill effects of neighborhood repeat and bone or other organ metastasis. Concerning these patients, androgen hardship treatment (ADT) is typically compelling toward the start. However, after a middle season of 18 two years, it advances to a more forceful stage, in particular CRPC described by movement during ADT, ceaseless expansion in serum prostate-explicit antigen (PSA), and rise of new metastatic injuries. Presently, first-line foundational chemotherapy for CRPC is the joined utilization of docetaxel and prednisone (Hotte SJ et al., 2010). Be that as it may, this helpful routine isn't therapeutic, and can't delay generally speaking endurance generally as contrasted and past blend or single-drug treatment, and it gives extreme results to patients (Tannock et al., 2004). Quercetin is a bioactive plant-determined flavonoid, bountiful in products of the soil especially in onions, apples, red wine and tea. In vivo concentrates in people exhibited that subsequent to being consumed by the small digestive tract, quercetin glycosides are hydrolyzed prompting an expanded assimilation pace of quercetin aglycone as high as 65-81% and it is microscopic organisms chemical autonomous (Walle et al., 2000). At that point quercetin is first processed including glucoronidation, methylation or sulphation to frame its principle forms: 3-O-methyl-quercetin (isorhamnetin), quercetin 3 O-glucuronide (Q3GlcA) and isorhamnetin 3-O-glucuronide. The entire metabolic interaction is ended in the liver where it has every one of the essential enzymatic frameworks for quercetin digestion (Mckeage, 2012; Russo, 2014). Quercetin can successfully hinder the development of numerous kinds of tumors and is non-poisonous. In addition, it is bountiful in leafy foods and can be adequately acquired through the everyday diet. In this manner, there exist expansive application possibilities for quercetin in malignant growth therapy including prostate cancer.

Anti-prostate cancer effects of quercetin

Considering the troubling circumstance in therapy for prostate malignant growth and the motivating consequences of the anticancer impacts of quercetin, it has been utilized in a progression of studies on human prostate disease and has displayed ideal impacts. At the point when utilized in vitro, regardless of whether alone or in blend, quercetin significantly captures the cell cycle, diminishes cell suitability, represses multiplication and prompts cell apoptosis.

Molecular mechanisms of the anti-prostate cancer effects

Inhibition of proliferation.

Cell mitosis and multiplication assume a significant part in the movement of tumors. Consequently, cell cycle capture and multiplication hindrance are successful measures for malignant growth treatment. Quercetin can assume this part in prostate disease. Researchers investigated the impact of quercetin on the expansion of human prostate malignancy PC-3 and LNCaP cells treated with fluctuating portions and tracked down that the hindrance rate showed a portion subordinate increment. IC50 estimations of quercetin were discovered to be 22.12 μM for PC-3 and 23.29 μM for LNCaP cells. Quercetin treatment not just brought about an expansion in the G2/M stage populace in both PC-3 and LNCaP cells, yet additionally expanded the S stage populace in PC-3 cells. Liu et al treated human prostate malignancy PC-3 cells with quercetin at different dosages (50-200 μM) for 24 and 48 h and found that cell reasonability was fundamentally diminished in a period and portion subordinate way. It was credited to acceptance of G0/G1 (31.4-49.7%) and sub-G1 (19.77%) cell cycle capture which was brought about by downregulation of cyclin D and E, CDK2, cdc25c and upregulation of p21, p53, p18 and p27 (Liu et al., 2014). In PPC1 prostate carcinoma cells, quercetin at a high portion captured the cell cycle and repressed multiplication. Notwithstanding, the p53 status ought to be contemplated (Samuel et al., 2012). Quercetin likewise showed expansion restraint in a portion subordinate way in PC-3 cells at a non-cytotoxic focus, during which endoplasmic reticulum (ER)-intervened and ER-autonomous pathways just as cell cycle hindrance incited by cyclin D1 and E downregulation might be the fundamental elements (Kumar et al., 2011).

Induction of apoptosis

Apoptosis is characterized as customized cell passing and assumes a significant part in keeping up adjustment of cell homeostasis. It is isolated into death receptor (DR)-intervened outward and mitochondrial-interceded characteristic pathways, and the two of them enact the normal 'executor' caspase-3 prompting cell apoptosis. As inadequate apoptosis is a basic reason for tumorigenesis, numerous medications treat cancers by actuating apoptosis (Vermeulen et al., 2005). Researchers led exploration to examine the impact of quercetin on PC-3 and LNCaP cells and found that quercetin initiated apoptosis by expanding favorable to apoptotic Bax and by diminishing enemy of apoptotic Bcl-2 protein bringing about a huge reduction in the Bcl-2/Bax proportion (Wang et al., 2012). After PC-3 cells were treated with quercetin, notwithstanding a diminishing in enemy of apoptotic Bcl-2 and an expansion in professional apoptotic Bax, ER stress-related proteins, for example, GRP78, ATF-4 α and IRE-1 α were likewise expanded, trailed by direct enactment of the caspase course prompting resulting apoptosis through the mitochondrial pathway and ER stress (Liu et al., 2014). From the recently distributed investigations, it very well may be reasoned that quercetin instigates apoptosis of prostate malignant growth principally by directing Bax, Bcl-2 and the Bcl-2/Bax proportion, in particular through mitochondrial-interceded inherent pathway, and it can likewise intervene the outward pathway (Kumar, 2011; Lee, 2008; Senthikumar, 2010). Acceptance of apoptosis in different sorts of prostate malignant growth cells by quercetin which might be the fundamental property of its enemy of prostate disease impacts has been broadly considered and is acquiring and more acknowledgment.

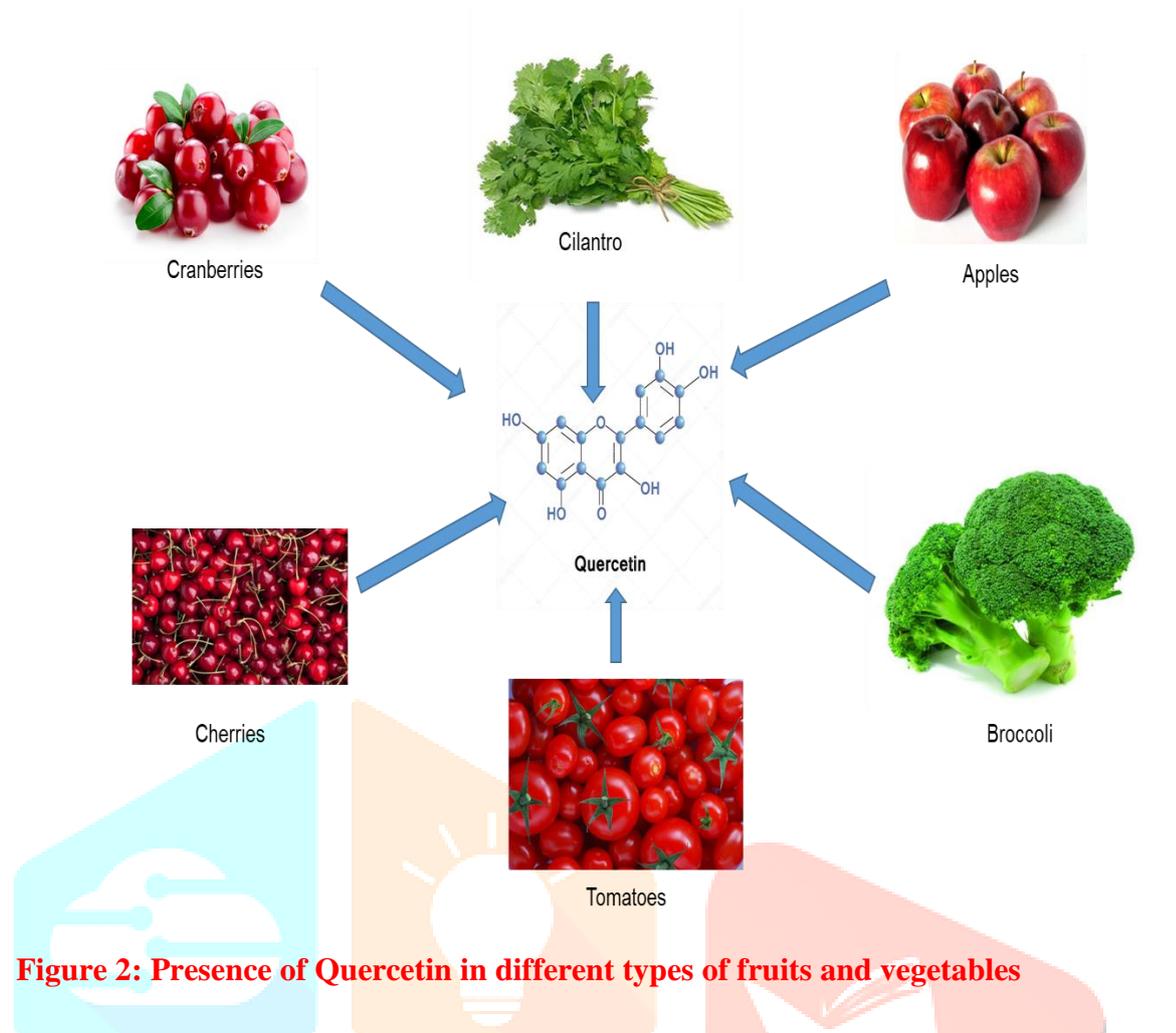


Figure 2: Presence of Quercetin in different types of fruits and vegetables

Lung cancer

A few examination papers have managed quercetin as a chemotherapeutic specialist against cellular breakdown in the lungs. An examination by W. Chen, Wang, Zhuang, Zhang, and Lin, 2007, uncovered that quercetin essentially improves TRAIL-induced cytotoxicity in non-small cell cellular breakdown in the lungs cells. It additionally builds articulation of death receptor (DR) 5 and has no impact on different parts of the death-inducing flagging complex. What's more, these specialists showed that quercetin can sharpen TRAIL-induced cytotoxicity in cellular breakdown in the lungs cells by means of two systems: (a) by acceptance of DR5 and (b) by concealment of survivin articulation; these instruments may clarify the cellular breakdown in the lungs preventive movement of quercetin. Besides, specialists found that therapy of human cellular breakdown in the lungs H-520 cells with quercetin builds 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 cellular breakdown in the lungs cells, specialists showed that quercetin represses aurora B exercises and decreases the phosphorylation of histone 3 (Xingyu et al., 2016). Quercetin additionally diminishes ROS creation instigated by openness to hexavalent chromium [Cr (VI)] in BEAS-2B cells. It additionally smothers the dangerous cell change, improves miR-21 articulation, and causes restraint of PDCD4 instigated by [Cr (VI)] in a dose-dependent way. Besides, quercetin decreases the tumor event and stifles the Cr (VI)-induced harmful change and tumorigenesis in naked mice infused with BEAS-2B cells. In human lung carcinoma A549 cells, analysts showed that quercetin considerably smothers cell attack and relocation. It restrains the action and articulation of MMPs-2 in a dose-dependent way. It additionally expands the declarations of nm23-H1 and TIMP-2 and represses the protein articulation of MMP-2. GW9662, a PPAR- γ foe (Chuang et al., 2016; Warnakulasuriya et al., 2016). In their work on lung carcinogenesis, Chen and partners exhibited that benzo[a] pyrene-induced human bronchial epithelial cell (HBEC) change is improved by IL-6 in vitro. The cancer-causing agent/IL-6-transformed cells display higher articulation of sign transducer and activator of STAT3 when contrasted and cells changed by BPDE alone. Besides, these specialists showed that treatment with quercetin (a) significantly diminishes BPDE-stimulated IL-6 discharge from human lung fibroblasts through hindrance of the NF- κ B and ERK pathways, (b) blocks IL-6-induced STAT3 actuation in HBECs, and (c) abrogates IL-6 upgrade of HBEC change by BPDE (W. Chen et al., 2016). Then again, Zhao and colleagues inspected the inhibitory impact of quercetin on the development of A549 cellular breakdown in the lungs cells and found that it initiates apoptosis, diminishes the degrees of

MMP-9 (mRNA and protein) and TGF- β 1 protein, and decreases the quantity of tumor cells. These scientists likewise tracked down that the mix of quercetin (at low fixations) with TIMP-1 shows synergistic inhibitory impact on the development of A549 cells (X. Zhao & Zhang, 2015). Quercetin additionally diminishes claudin-2 articulation in lung adenocarcinoma A549 cells in a time- and concentration-dependent way, brings down the steadiness of claudin-2 mRNA, and expands the outflow of miR-16. Completely, quercetin diminishes claudin-2 level through up-regulation of miR-16 articulation (Sonoki et al., 2015). In cellular breakdown in the lungs cells (A549 and H460 cells), quercetin diminished cell suitability and restrained warmth stun protein 70 (HSP70) articulation in both cell lines in a dose-dependent way. Expansion of a fixed quercetin portion improved gemcitabine-induced cell demise, which was connected to expanded caspase-3 and caspase-9 exercises (J. Lee, Han et al., 2015; W. j lee, Hsiao, et al., 2015; Y.J. Lee et al 2015). Essentially, quercetin forestalled tumor expansion by (a) starting cell cycle capture, (b) improving TRAIL-induced tumor cell demise, (c) bringing down the p62 protein articulation, and (d) expanding GFP-LC3B in human cellular breakdown in the lungs cells in a dose-dependent design. It likewise prompts apoptosis in A549 cells by means of mitochondrial depolarization by setting off an awkwardness in B-cell lymphoma 2/Bcl2 rival X (Bcl2/Bax) proportion and by down-regulating the IL-6/STAT3 flagging pathway. Furthermore, quercetin could impede atomic factor kappa- light-chain-enhancer of actuated B cells (NF- κ B) activity at early hours, which may cause a down-regulation of the IL-6 titer, and the IL-6 articulation, thusly, could restrain p-STAT3 articulation. Down-regulation of both the STAT3 and NF- κ B articulations may, therefore, causes down-regulation of Bcl2 on the grounds that both are upstream effectors of Bcl2. In A549 cells, change in Bcl2 responses may bring about an unevenness in the Bcl2/Bax proportion, which could ultimately lead mitochondria intervened apoptosis (Mukherjee & Khuda-Bukhsh, 2015).

Cervical cancer

Cervical cancer growths are a portion of the chief reasons for cancer-related passing among ladies in agricultural nations (Ojesina et al., 2014). Medical procedure is as yet the best option of cervical malignant growth therapies; be that as it may, chemotherapy has been broadly proposed to evade repeat in postoperative administration of cervical cancers (S. Y. Liu & Zheng, 2014). Because of medication obstruction and cut off poison levels, there is a need to investigate more solid and less poisonous helpful ways to deal with treat cervical tumors. Quercetin end up being a multipurpose anticancer particle. In a new distribution, Zhang et al. inspected the impact of quercetin on the outflow of heparanase in HeLa and Caski cervical malignancy cells notwithstanding the sub-atomic component of activity. Quercetin reduced mRNA articulation level of HPA, consequently causing its hesitance in a dose- and time-dependent (W. T. Zhang, Zhong, Lu, 2013). Quercetin intercalated with calf thymus cell DNA and HeLa cell DNA and stifled antiapoptotic AKT and Bcl-2 articulation. It has additionally been accounted for the increment of mitochondrial cytochrome-c level and depolarization of mitochondrial layer potential with ascent of ROS. Similarly, it was found to control the p53 and caspase-3 activities. These varieties in flagging proteins and externalization of phosphatidyl serine buildups are engaged with inception of apoptosis. Diminished AKT articulation proposed in cell creation and metastasis potential are went with capture of the cell cycle at G2/M (Bishayee et al., 2013).

A gathering of analysts showed that in HeLa cells, quercetin apparently hinders the development and instigates apoptosis in vitro in a time- and dose-dependent style. It causes cell cycle capture at G0/G1 stage and further down-regulates the outflow of the PI3K and p-Akt. It could also down-regulate the statement of bcl- 2 and up-regulate Bax. These discoveries recommend that quercetin incites apoptosis in HeLa cells through PI3k/Akt pathways. Likewise, Wang and collaborators utilized MTT, stream cytometry, and MDC staining to assess multiplication, apoptosis, and autophagy, individually, after treatment with quercetin in HeLa cells. Also, they utilized western blotch examine to recognize LC3-I/II, Beclin 1, dynamic caspase-3, and S6K1 phosphorylation. Results uncovered that quercetin can restrain HeLa cell creation and start defensive autophagy at low fixations (P. Wang, Henning, et al., 2016). In human cervical carcinoma HeLa cells, quercetin caused presentation of apoptosis and stayed productive for expanded timeframe (48 hr), diminished Hsp27 and Hsp72 articulation, and raised caspases activities. In human cervical malignancy (HeLa) cells, quercetin stifled cell feasibility in a dose-dependent design by inception of G2/M stage cell cycle capture and mitochondrial apoptosis by means of a p53-dependent component. Furthermore, in relocated vehicle cinoma in BALB/C bare mice, quercetin at various focuses (6.25, 12.5, 25, and 50 μ mol/L) for 24 hr (a) expanded the concealment pace of the cells, (b) incited apoptosis, (c) extensively reduced mitochondrial layer potential, (d) adequately upgraded the $[Ca^{2+}]_i$, and (e) initiated the caspase-3 in a dose-dependent way (L. Q. Huang, Zhang, Yang, & Tao, 2009).

Colon cancer

Diet is a significant factor related with colon cancer. Diets that are low in fiber and high in fat, calories, and red meat and prepared meats increment the danger of creating colon malignant growth. Malignancy therapy relies upon the kind of disease, the phase of the disease (the amount it has spread), age, wellbeing status, and extra close to home attributes (NCI, 2014). Various investigations have managed the impact of quercetin on colon malignant growth. Kee and colleagues utilized the water-soluble tetrazolium salts test, annexin V measure, real-time polymerase chain response, western smudge examination, and gelatin zymography to consider the inhibitory impact of quercetin on colorectal lung metastasis. These scientists found that quercetin can (a) hinder the cell feasibility of colon 26 (CT26) and colon 38 (MC38) cells, (b) initiate apoptosis through the MAPKs pathway in CT26 cells, (c) direct the declaration of EMT markers, like E-, N-cadherin, β -catenin, and snail, by nontoxic convergences of quercetin, and (d) restrain the movement and attack capacities of CT26 cells through articulation of MMPs and tissue inhibitor of metalloproteinases (TIMPs) guideline. They closed from this examination that quercetin can hinder the endurance and metastatic capacity of CT26 cells, and can stifle colorectal lung metastasis in the mouse model, and might be an intense restorative specialist for the therapy of metastatic colorectal malignant growth (Kee et al., 2016). Likewise, an examination by Zhao et al. presumed that 8-C-(E-phenylethenyl) quercetin, a novel quercetin subordinate, triggers G2 stage capture in colon disease cells and smothers proliferation. It likewise prompts autophagic cell passing through ERK incitement (Y. Zhao, Fan, et al., 2017; J. Zhao, Liu, et al., 2017). Also, quercetin at a convergence of 5 μ M could particularly stifle the transitory and intrusive limit of Caco-2 cells. Furthermore, results from this examination uncovered that the declaration of E-cadherin protein was expanded by quercetin, while metastasis-related proteins of MMP-2, MMP-9 articulation got diminished by it in a dose-dependent way. The anti-toll-like receptor 4 (TLR4) immune response of pyrrolidine dithiocarbamate may impact the hindrance of quercetin on cell relocation and attack and the outflow of different proteins, for example, E-cadherin, MMP-2, MMP-9, NF- κ B p65, and TLR4. In addition, quercetin could diminish the creation of various aggravation factors including TNF- α , Cox-2, and interleukin 6 (IL-6). Subsequently, quercetin may apply its anti-colon malignant growth action by means of the TLR4- or potentially NF- κ B-mediated flagging pathway (M. Han et al., 2016). The 1,2-dimethyl hydrazine-induced colon disease causes nephrotoxicity and further expands the blood urea nitrogen, urea, creatinine, and in the end bring about various unusual tombs and foci development. The likely defensive impact of quercetin on cisplatin-induced nephrotoxicity was evaluated through lowering the blood urea nitrogen, urea, and creatine and furthermore decreased the abnormal tomb foci number (Q. C. Li, Liang, et al., 2016; J. Li, Tang, et al., 2016). Comparative outcomes were gotten by Saleem et al. (2015) who found that therapy of mice either with quercetin, sodium gluconate, or with the mix has a beneficial outcome against 1, 2-dimethyl hydrazine-prompted colon malignancy.

In human colon adenocarcinoma cells, quercetin altogether upgraded the outflow of the endocannabinoids receptor (CB1-R) and further stifled PI3K/Akt/mTOR. It likewise initiated JNK/JUN pathways and altered the digestion of β -catenin, either straightforwardly or by means of enactment of CB1-R (Refolo et al., 2015). These discoveries were affirmed by different scientists (Xu et al., 2015). The exploration work led by Zhang et al. demonstrated that quercetin altogether forestalls the multiplication of human colon disease in CACO-2 and SW-620 cells by stifling the NF- κ B pathway, down-regulation of B-cell lymphoma 2, and up-regulation of Bax (X. Zhang, Guo, Chen, and Chen, 2015; J. Y. Zhang, Lin, et al., 2015; X. A. Zhang, Zhang, Yin, and Zhang, 2015). Furthermore, quercetin was found to inhibitorily affect Wnt/ β -catenin in colon disease cells SW480, DLD-1, and HCT116 malignant growth cells (Amado et al., 2014). Likewise, an examination by Kim et al. exhibited that the inhibitory part of quercetin in colon malignant growth cell lines through improving the apoptotic cell demise by means of producing intracellular ROS and through upgrading sestrin 2 articulation is joined by enacted protein kinase (AMPK) actuation. In addition, these specialists tracked down that the quercetin-induced apoptosis includes sestrin 2/AMPK/mTOR pathway by directing increments intracellular ROS (Kim, Lee, and Kim, 2013; Kim, Moon, Ahn, and Cho, 2013). For HT-29 colon malignancy cells, Kim and colleagues found that quercetin instigates apoptosis by weakening film capability of the mitochondria creating intracellular ROS and hoisting the statement of sestrin 2 through the AMPK/p38 unthinking pathway (G. T. Kim, Lee, Kim, and Kim, 2014; M. C. Kim, Lee, Lim, et al., 2014). Essentially, a few examination bunches freely showed that quercetin builds the cancer prevention agent action, expands PARP cleavage, and prompts caspase-3 cleavage (twofold) in HT-29 colon malignancy cells. It likewise brings down the declarations of particularity proteins (Sp) like Sp1, Sp3, and Sp4 mRNA; this articulation was joined by a diminished protein articulation. Moreover, the Sp-dependent antiapoptotic endurance quality was additionally altogether diminished, both at mRNA and protein levels. It additionally lessens microRNA-27a and actuates a Sp-repressor, zinc finger protein ZBTB10 (Atashpour et al., 2015; Cho, Kim, Park, Choo, and Chong, 2013; Del Follo-Martinez, Banerjee, Li, Safe, and Mertens-Talcott, 2013).

Liver cancer

The main source of liver cancer is cirrhosis due to either hepatitis B, hepatitis C, or overabundance liquor admission (Naghavi, Wang, Lozano, et al., 2015). Different causes incorporate aflatoxin, nonalcoholic greasy liver sickness, and liver accidents. The most widely recognized sorts 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 arrival of prescriptions stays the most helpful approach to convey drugs. Bishayee and collaborators inspected the impact of gold-quercetin stacked into poly (DL-lactide-co-glycolide) nanoparticles (NQ) on HepG2 hepatocarcinoma cells. Results uncovered that quercetin stacked on the nanoparticles specially murder malignancy cells, contrasted and ordinary cells. Also, NQ communicated with HepG2 cell DNA and lessens histone deacetylases to oversee cell expansion and capture the cell cycle at the sub-G stage. These nanoparticles instigate apoptosis in HepG2 cells by enacting p53-ROS crosstalk and by improving epigenetic alterations prompting repressed expansion and cell cycle capture (Bishayee et al., 2015). Protein kinase C is a vital controller of cell development in mammalian cells and is connected with tumor progression. Quercetin, then again, shows antitumor movement both in vitro and in vivo in HepG2 cells. It down-regulates the statement of PI3K, protein kinase C, COX-2, and ROS. Furthermore, it upgrades the statement of p53 and BAX in HepG2 cells (Maurya and Vinayak, 2015). One of the inadequacies of quercetin in centers is its helpless dissolvability. To conquer these hindrances, Guan and associates arranged quercetin (QT) as QT-loaded PLGA-TPGS nanoparticles (QPTN) and assessed its restorative adequacy for liver malignant growth. Results showed that QPTN could instigate HepG2 cell apoptosis in a dose-dependent way and that QPTN could smother tumor development by 59.07%. These analysts inferred that QPTN could be utilized as a potential intravenous measurement structure for the therapy of liver malignancy attributable to the upgraded pharmacological impacts of quercetin with expanded liver focusing on (Guan et al., 2016).

Conclusion

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.

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