A Review of Quercetin: Anticancer Activity

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HIGHLIGHTS
> Quercetin has powerful antioxidant and free radical scavenging properties.
> Quercetin has important roles in the inhibition of tumor, cancer cells on the breast, colon, prostate, ovary, endometrium and lungs.
> Quercetin also exhibits various pharmacological effects, including antiviral, antioxidant, anticancer, antimicrobial, anti-inflammatory, neurological effects, cardiovascular and hepatoprotective.
> The chemoprotective effect of quercetin against tumor cell lines through apoptosis and metastasis makes it a strong candidate as a potential anticancer agent.

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ABSTRACT
Quercetin is the principal flavonoid compound commonly extracted from cranberries, blueberries, apples and onions. It possesses a wide spectrum of bio-pharmacological properties and may offer promising new options for the development of more effective chemo-preventive and chemo-therapeutic strategies owing to its powerful antioxidant and free-radical scavenging properties. Several studies demonstrated that quercetin has a significant role in inhibition of tumor and cancer cells on breast, colon, prostate, ovary, endometrium, and lung. Quercetin treatment has been associated with selective anti-proliferative effects and induction of cell death, probably through an apoptotic mechanism, in breast or other cancer cell lines but not in normal cells. Quercetin is universally known for its low toxicity as a natural product despite the limited information on dosing regimens. The major problem associated with the use of quercetin, is the very low bioavailability. Beside cancer chemotherapy, it also exhibits various pharmacological actions including: antiviral, antioxidant, anticancer, antimicrobial, anti-inflammatory, neurological effects, cardiovascular, and hepatoprotective. Quercetin has been reported as a potent anticancer agent during in vitro studies on various cancer cell lines and in vivo studies on rodents especially mice. Quercetin has radical scavenging potential, therefore, it is capable of preventing cancer induced by oxidative stress. The chemo-protective action of quercetin through apoptosis and metastasis against tumor cell lines makes it a strong candidate as a potential anticancer agent.

Contents
1. Introduction .............................................................................................................................................. 2
2. Chemistry of Quercetin and Its Derivatives ............................................................................................... 2
3. Bioavailability and Metabolism of Quercetin ............................................................................................. 3
4. Safety of Quercetin...................................................................................................................................... 3

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1. Introduction

The medicinal properties of various phytochemicals, such as anti-oxidative, anti-inflammatory, antimicrobial and anticancer activities, have been known to mankind since ancient times. Flavonoids are well known phytochemicals possessing medicinal properties and are found in fruits and vegetables as secondary metabolites. To date, around 9000 types of flavonoids are classified in natural foods [1, 2]. Flavonoids seems to be strong among in vitro anti-proliferative agents against colorectal, ovarian, lymphoid and breast cancer cells [3, 4]. Furthermore, they have been shown to induce chromatin condensation and apoptosis in some cancer cells [5]. Although the exact mechanisms of flavonoid induced cytotoxicity are not very clear, the impact of disruption of signaling events was an important factor in the occurrence of apoptosis. Abnormal cell signal transduction arising from protein tyrosine kinases has been implicated in the initiation and progression of a variety of human cancers. Over the past two decades, efforts were focused to develop compounds that can selectively modulate the abnormal signaling pathways. In the past five years, enormous progress has been made in developing tyrosine kinase inhibiting compounds [6]. Among compounds of known structure, quercetin (QCN) deserves special attention as a protein tyrosine kinase inhibitor [7].

QCN is among these dietary flavonoids and has been attracting increasing interest as a novel medicinal biomolecule with diverse therapeutic properties [8]. Among identified flavonoids, QCN is well known for possessing potent antioxidant activity; due to its ability to eliminate highly reactive oxygen species (O₂ and ONOO⁻) [9, 10]. Henceforth, the augmentation of mutated cell apoptosis by modulating cell signaling pathways is reported, which may result in the inhibition of cancer growth [11, 12]. QCN is a plant pigment, abundantly present in many ethnic plants, especially onion and tea, therefore, a sufficient amount may be consumed daily [13]. It has importance in terms of ethnopharmacology such as its use as antioxidant, anticancer and neuroprotective [14]. It has been reported as an efficient free radical scavenger (antioxidant) [15]. In clinical trials (phase-I), QCN has been reported to exhibit inhibitory effect on tyrosine kinase which suggests that it has antitumor therapeutic potentials [16]. QCN treatment has been shown to have caused cell cycle arrests such as G2/M arrest or G1 arrest in different cell types. Moreover, QCN-mediated apoptosis may result from the induction of stress proteins, disruption of microtubules and mitochondrial, release of cytochrome c and activation of caspases [17]. QCN is the principal flavonoid compound (3, 3’, 4’, 5, 7-pentahydroxyl flavanone) commonly extracted from cranberries, blueberries, apple and onions. It possesses a wide spectrum of biopharmacological properties and may offer promising new options for the development of more effective chemopreventive and chemotherapeutic strategies because of its powerful antioxidant and free-radical scavenging properties. QCN treatment has been associated with selective antiproliferative effects and induction of cell death, probably through an apoptotic mechanism, in breast or other cancer cell lines but not in normal cells [18].

2. Chemistry of Quercetin and Its Derivatives

QCN (3, 3’, 4’, 5,7-pentahydroxyflavone), is a naturally occurring flavonoid which contains five hydroxyl groups that are responsible for its biological activities and derivative diversification. Flavonoid generally consists of two benzene rings linked by pyran or pyrone rings [19]. Additionally, the conformational analysis of QCN exhibited the presence of 12 conformations of this molecule having Gibbs energies in the range of 0 to 5.33 kcal/mole. Furthermore, QCN reveals strong intramolecular H-bonding, illustrating its diverse biological activities and renders it the potentiality to form strong complex interactions, even with metals, affecting its bioavailability and transport [20]. Among these H-bonds, two bonds are with carbonyl groups and third one is between hydroxyl groups [21].
from study done by Murota K et al. showed that an enormous quantity of QCN found in foods is likely to be absorbed from the intestine and subsequently converted to its respective metabolites [30]. In the transportation of the metabolites of QCN, the body’s lymphatic system is also involved [31]. The frequent consumption of onion resulted in deposition of QCN metabolites in various tissues and blood, which reached a total plasma concentration of 0.6 µM after 1 week. Therefore, it is pivotal to maintain the plasma concentration of QCN metabolite at an acceptable and significant level [32]. It is perceptible from recent studies the metabolites of QCN were promptly distributed among different organs at low levels after intake of dietary quercetin for a long time [33]. Furthermore, it is also noticeable that the frequent consumption of dietary QCN introduces accumulation of metabolites throughout the body [34]. Generally, the transformation of QCN to their metabolic constituents diminishes its antioxidant activity, but there are few breakdown products of QCN which are able to remove the reactive species from the body. Moreover, during the process of inflammation, quercetin-3-glucuronide is metabolized, consequences as a storage of QCN aglycone [35]. The research by Shimoi K et al. revealed that glucuronide, a more active form of aglycone metabolite of QCN, was used for the incorporation into macrophages [33]. The investigation exhibited those actions of QCN metabolites which are mostly site specific in nature and are recommended for inflammatory conditions. "A new configuration of QCN" are found in human blood and stored in inactive forms, which are further transformed into active residues and ultimately turned into the active derivatives to exert their roles at targeted sites.

4. Safety of Quercetin

In case of humans, the side effects of QCN was not associated from a single oral dose of up to four grams. Single intravenous (i.v) bolus doses of 100 mg of QCN were evidently well accepted as well. Meanwhile, i.v bolus of 1400 mg/ m2 (approximately 2.5 grams in a 70-kg adult) once weekly for three weeks was linked with renal toxicity in two out of ten patients. The two patients observed a decline rate of glomerular flow approximately 20 percent in the first 24 hours. The reduction frequency is determined within one week, and this outcome was not cumulative over subsequent doses in the phase-I trial in a population of advanced cancer patients. In one patient, nephrotoxicity was averted on subsequent doses by administration of intravenous saline (0.9% w/v of Sodium Chloride) before delivery of QCN and by administration of 5% dextrose after QCN delivery. Transient flushing and pain at the injection site were noted in a dose-dependent manner. The 1400 mg/m2/ week dose was suggested for a phase II trial. QCN has long been known to be among the most mutagenic of the flavonoids. This property has been demonstrated in the Ames test, in cell culture, and in human DNA. The urine and feces of rats having administration of QCN via oral or intraperitoneal doses have been observed to have mutagenic activity, advising this property might be quite considerable in vivo. Mutagenicity does not always imply carcinogenicity. However, most research exhibited that QCN to have no carcinogenic activity in vivo. An early study constituted that rats consuming diets containing up to 1-percent QCN.

3. Bioavailability and Metabolism of Quercetin

In order to examine the QCN efficacy regarding its anticarcinogenic effect, it is crucial to understand the bioavailability of QCN, intestinal absorption as well as its conversion rate of metabolism. When QCN was administered intravenously to rodents, it immediately disappeared from the plasma. Meanwhile, it is documented from the experiment that QCN was promptly metabolized and eliminated from the body through urine and no evidence was perceived with regard to storage condition of QCN inside the tissues and body fluids. Formerly, there was a usual percept regarding the excretion of QCN into feces without being absorbed by the intestine, but it is apparent

Naturally occurring QCN acts by inhibiting auxin transport and hinders the bilateral growth of plant embryos [23]. The commonly available derivatives of QCN are glycosides and ethers [24, 25]. QCN O-glycoside consists O-glycosidic bonds at the C-3 carbon hydroxyl group. Moreover, a rare QCN derivative form, a C-glycoside whose glycosylation site is the C-6 carbon, was also found in Ageratina calophylla [26]. In addition, a rarer derivative of QCN, identified in the red alga Acanthophora spicifera and grapes (Vitis vinifera), is QCN 3-O-α-L-fucopyranoside where quercetin is linked to α-L-fucopyranosyl moiety via glycosidic linkage at the C-3 position [27, 28]. Moreover, QCN derivatives may also encompass acyl and sulfur substituents in addition to sugar moieties. Similarly, in case of ether derivatives the hydroxyl groups of QCN are joined with alcohols through ether bonds. Despite the fact that QCN is lipophilic, the glycosylation of QCN derivatives can enhance the hydrophilicity as well as facilitate the molecules to transfer through all parts of the plant [29].

Figure 1 Quercetin and some of its derivatives [22]
(roughly 400 mg/kg) over 410 days had no increase in gross pathology. Importantly, the total body weight, as well as organ weights was found to be similar to control animals. No susceptibility of cancer was noticed in QCN-treated animals as compared to controls [36].

5. Molecular Mechanisms of Quercetin

QCN is used for wide range of therapeutic applications in various disorders mainly because of its antioxidant properties. The reactive oxygen species (ROS) scavenging activity is attributed to a change in OH ions, which has a relation to electron exchange [37]. The in vitro study estimated that, due to this particular characteristic, QCN has a protective role in the nervous system. In the current scenario, the neuroprotective activity of QCN cannot be ignored and additional in vivo studies should be investigated with different humanized animal models to translate the efficacy. QCN demonstrates its antioxidant potentiality by competitively impeding the xanthine oxidase enzyme and noncompetitively blocking the xanthine dehydrogenase enzyme. The inhibitory capabilities are due to its flavonoid structure rather than to its antioxidant potential [38].

5.1. HMGB1 Signaling Pathway

High-mobility group box protein 1 (HMGB1) is a nuclear protein which is highly preserved. This protein is produced by the functions of macrophages previously activated and it works as a crucial “late” facilitator of fatal endotoxemia and sepsis formation [39]. The HMGB1 protein, which is present outside the cell, can motivate the release of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and other inflammatory mediators from monocytes [37, 40]. QCN activates the inhibition of HMGB1-induced TNF-α and IL-1β mRNA expression, which recommends that QCN regulates cell signaling that in turn controls the action of pro-inflammatory cytokines. The activation of mitogen-activated protein kinase (MAPK) signaling pathway is a determining step in the HMGB1-induced gene expression process, which promotes the release of inflammatory cytokines—such as TNF-α, and IL-1β—inside macrophages, neutrophils, and endothelial cells. HMGB1-induced cytokine release partially interferes with MAPK pathways. HMGB1 or lipopolysaccharides (LPS) time-dependently induce phosphorylation of p38, c-Jun N-terminal kinase, and extracellular signal-regulated kinase in macrophages. The QCN importantly inhibits HMGB1- or LPS-induced phosphorylation of each kinase [41]. Beside the activation of MAPK, the nuclear factor-κB (NF-κB) signal transduction pathway is also involved in HMGB1-induced cellular activation, and NF-κB-dependent transcriptional activity is very important for cytokine expression [42, 43]. In cells, NF-κB subunits (p50 and p65) exist as inactive trimers in the cytosol through the interaction with IκBα, which is the most important member of the IκB family [44]. QCN significantly inhibits IκBα degradation and nuclear translocation of NF-κB p65. Therefore, after stimulation with HMGB1 or LPS, p65, the key activator of NF-κB regulated transcription, becomes available to NF-κB-regulated genes in the nucleus and nuclear localization is most effectively inhibited by QCN.

5.2. Thymic Stromal Lymphopoietin (TSLP) Activation

The level of TSLP, which is an epithelial-derived cytokine with a role in T helper (Th) cells Type-2 immunity, is considerably increased in human skin as well as blood. The signal transduction of TSLP is initiated through proteins, namely IL-7 chain of receptor, which has potential to enhance the triggering of B lymphocyte and dendritic cells [45]. Primary skin keratinocytes are vitally responsible for revealing the TSLP in smooth muscle and lung connective tissues. Additionally, TSLP demonstrates their crucial physiological activities by affecting various cells [46]. It is documented that TSLP has the ability to stimulate both CD4+ T and CD8+ cells along with other B lymphocytes differentiation. Consequently, the promotion of release and activation of chemokines occurs. Furthermore, it can elevate the secretory mechanism of the Th2 cytokines from mast cells. While binding of TSLP with respective receptors the various signaling pathways are accelerated [47]. In a current research it has been reported that due to the activation of these receptors, there is a remarkable promotion in the phosphorylation process of Janus kinase-signal transducers and activators of transcription (JAK-STAT) signaling, which further stimulate skin inflammation [48]. Therefore, targeting the above signaling pathway is a recommended approach to develop a treatment plan for several inflammatory diseases, including cancer.

5.3. JAK-STAT Signaling Pathway

JAK-STAT signaling pathway is a typical signal transduction pathway for various types of inflammatory cytokines and growth regulatory factors. The binding of ligands to their respective receptors corresponds to the activation of JAK, which further intensifies the phosphorylation process and hence leads to the activation of STAT. The STATs, which are already activated, enter the nucleus, where they start the regulation of gene expression [49]. Studies have indicated that the activated mast cells promote the formation of the Th2 cytokines and decrease the synthetic mechanism of Th1 cytokines. JAK-STAT signaling is activated by mast cells, which ultimately increase the production of IL-13 in the Th2 cell line [50]. The QCN has the capability to strongly inhibit the JAK-STAT signaling pathway in numerous inflammatory disorders. Furthermore, treatment of activated T cells with QCN in vitro hampered the interleukin-12 (IL-12)-induced phosphorylation of JAK2, tyrosine kinase-2 (TYK2), STAT3, and STAT4, which in turn results in reduced levels of T cell propagation and Th1 variation [51]. Therefore, these anti-inflammatory and anti-apoptotic properties of QCN have a key role in the reduction of cancer by controlling the toll-like receptor-2 (TLR2) and JAK2/STAT3 pathway and causing the inhibition of STAT3 tyrosine phosphorylation within inflammatory cells [52]. Pre-treatment of cholangiocarcinoma cells with QCN hindered the cytokine-mediated up regulation of inducible nitric oxide synthase (iNOS) and expression of intercellular adhesion molecule-1 (ICAM-1) in the JAK/STAT cascade pathway. Meanwhile, QCN obstructed the activation of inflammatory cytokine interleukin-6 and interferon-γ [53]. It was authenticated that LPS-induced STAT1 activation was
inhibited by QCN in combination with its profound inhibitory effects on iNOS and NF-κB expression, which are persistently involved in activation of (IL-2) interleukin-2 [54].

6. Anticancer Activity of Quercetin

Cancer has been examined in sixty different parts of the human body and currently requires new therapeutics for its treatment. In case of in vitro studies, QCN has been observed as a potent anticancer agent in many cancer cell lines and in vivo studies in rodents especially mice [14]. QCN has strong anti-oxidant properties; therefore, it is able to prevent cancer induced by oxidative stress [55]. The chemo-protective action of QCN through apoptosis and metastasis against tumor cell lines makes it a strong candidate as a potential anticancer agent [56]. Moreover, it has been reported that QCN in combination with intratumoral doxorubicin injection revealed that the enhancement of immune responses against enlargement of breast tumors [57]. However, during in vitro study using human MCF-7 cells (Michigan Cancer Foundation-7), QCN formulations such as QCN-loaded nanoparticles and nanoemulsions has been proclaimed to inhibit angiogenesis in tamoxifen-resistant cancer in breast cells [58]. Furthermore, Oxidative DNA damage is a predisposing factor of cancer development. In fact, QCN having antioxidant properties thought to elicit a pivotal role in protecting cells from oxidative stress induced by reactive oxygen species (ROS). It is progressively suggested that ROS and reactive nitrogen species (RNS) play a crucial role in human cancer development, especially as evidence is growing that antioxidants may resist or hinder the onset of some types of cancer. ROS is a collective term often used interchangeably by biologists to include oxygen radicals, superoxide, hydroxyl, peroxy and alkoxyl and certain non-radicals that are either oxidizing agents [55].

The cancer preventing effects of QCN have been broadly demonstrated in various cancer cells, the effect of QCN in renal cancer cells remain uncertain though. Meanwhile, QCN assessed remarkable inhibition of cell proliferation and enhanced apoptosis in human renal cell adenocarcinoma cells and it exerted an apoptotic effect through inhibiting survivin mRNA and protein expression and activating caspase 3. The caspase 3 is a one of the major determining components of apoptosis activity. In addition, QCN induced apoptosis of renal cancer cell possibly through inhibiting survivin expression and caspase-3 activation [59]. The various in vitro findings have documented that QCN plays a key role in cancer prevention and tumor suppression in different cell lines [60]. The doses of QCN that showed anticancer effects in vitro were ranging from 3 to 50 µM [36]. The cancer prevention properties of QCN in vivo studies have been confirmed in colon cancer, melanoma. Additionally, QCN is reported to be active against prostate cancer [61, 62]. However, the results of testing against PC-3 cell lines indicate that neither QCN nor the synthesized analogues are able to inhibit the growth in PC-3 cell lines significantly. PC-3 cell lines are androgen independent, p53 null prostate cancer cell lines. Minimal activity of QCN, Q-OCl, Q-OCBH3 against this cell line may indicate that alteration of signaling pathway by QCN in prostate cancer involves p53 in a major way [63, 64]. According to research data, QCN demonstrates multifactorial anti-tumor activity reducing both the risk of cancer as well as growth and spread of cancerous cells. One of the anti-cancer mechanisms of QCN can relate to its antioxidant properties and protection of cells from oxidative stress, inflammation, and DNA damage which all lead to carcinogenesis. In addition, a direct interaction of QCN with cellular components such as enzymes or transcription factors could provide beneficial biochemical responses keeping the cells in a “healthy” state. Interestingly, there is a growing body of evidence suggesting that quercetin may contribute to remodeling of chromatin (genetic material organization in the cell nucleus/complex of DNA, RNA and proteins) and thus interfere with unwanted epigenetic alternations (non-genetic influences on gene expression) [56]. The action of QCN on cancer stem cells is still unknown; however, various research studies have demonstrated promise with proposed potential mechanisms of action regarding the effect of QCN on cancer stem cells when co-administered with other chemotherapies. Cancer stem cells are unlike normal cells in that they undergo abnormal differentiation as well as a deregulated self-renewal. It is generally considered that QCN may elicit its response as efflux pump inhibitor and enhances the drug’s bioavailability through inhibition of BCRP, MRPI, and P-gp (P-glycoprotein). Thus, QCN thought to induce chemotherapeutic effects of chemotherapy at their non-toxic concentrations. Leukemic progenitor cellular growth can also be influenced by QCN by a mechanism associated with the transforming growth factor β1 (TGF-β1) in vitro. The TGF-β1 has powerful hematopoietic regulatory properties, and depending on their stage progenitor differentiators, acts to either stimulate or inhibit the growth of noncancerous myeloid progenitors. Moreover, QCN similarly inhibits the growth of ovarian cancer cells by a mechanism associated with TGF-β1 [65].

6.1. Inhibition of Cell Growth

QCN reveals its anti-proliferative effects on various types of cancer, both in vitro and in vivo. For example, several in vitro studies exhibited growth inhibitory effects of QCN in different cancer cell lines including leukemia cell lines L1210 and P-388, breast cancer cells, colon cancer cells COLO 20DM, ovarian cancer cells OVCA 433, liver cancer cells HepG2, epidermoidal cancer cells A431 and gastric cancer cells. The possible interaction of QCN with signaling pathways which are responsible for cancer growth may lead to growth inhibition. Some of the signaling pathways explored are PI3K/Akt, Her-2/Neu, Wnt/β-catenin and EGFR. This flavonoid was found to hinder the rapamycin (mTOR) activity of mammalian target which gets hyper activated during cancer and controls essential cell growth pathways, autophagy and biosynthesis of proteins, and interfere with the activation of PI3K/Akt signaling pathway. Suppression of PI3K/Akt pathway was also demonstrated in other cell lines like breast cancer cell HCC1937, SkBr3 cells, liver cancer cell HepG2, and HL-60 leukemia, upon QCN treatment.

6.2. Inhibition of Metastasis

The metastasis is one of the important phenomenon through which the mechanism regarding transmission of cancer from one organ or part to other within a body takes place and it is considered as one of the utmost danger factor for cancer.
spread. Metastasis is related to the production of matrix metalloproteinases (MMPs) enzymes which are responsible for degrading extracellular matrix proteins in a variety of cells or tissues they encounter. They are classified into four types: stromelysins, gelatinases, collagenases and membrane type MMPs. Earlier studies reported that MMPs are required for the invasion/metastasis of cancer cells, such as MMP-9 and MMP-2. Therefore, suppression of MMPs synthesis in cancer cells can diminish the chances of metastasis and can be a useful tool in cancer treatment. The potential of QCN in inhibiting MMPs secretion was reported in various studies. The investigation identified that quercetin can prevent metastasis of breast cancer cells by suppressing the activation and migration of MMP-9 in 12-O-tetradecanoyl phorbol-13-acetate (TPA)-treated MCF-7 cells [52]. Additionally, QCN also inhibited up-regulation of MMP-9 by tumor necrosis factor (TNF)-α in JB6 P+-mouse epidermal cells. Along with MMP-9, QCN also decreased the secretion of MMP-2 in A431 epidermoid cancer cells, MiaPaCa-2 pancreatic cancer cells [63].

7. Conclusion

The QCN and its components are multifunctional comprising diverse range of pharmacological properties including antiviral, antioxidant, anticancer, antimicrobial, anti-inflammatory, neurological effects, cardiovascular, and hepatoprotective. Some of the most well-studied and available QCN delivery systems are based on liposomes, Poly-lactic-co-glycolic acid (PLGA) Poly-lactic acid (PLA), chitosan and silica. Both in vivo and in vitro studies have highlighted the anti-proliferative effect of QCN-loaded nanoparticles on various types of cancer cells. However, the application of such nanoparticles at a clinical level still needs extension of process optimization to increase their specificity and efficacy for their efficient clinical translation. In vitro experiments assess that QCN may be effective in treatment of various types of cancer and it may be combined with other anticancer drugs to reduce their doses and subsequently their side effects. However, the degree to which QCN is absorbed, and thus its bioavailability, leaves some doubt as to whether QCN can exert an antioxidant effect in vivo. Similarly, there is still no conclusive evidence regarding its exact mode of action in order to enhance its clinical application in the treatment of human cancer.

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