Quercetin: A Promising Flavonoid with a Dynamic Ability to Treat Various Diseases, Infections, and Cancers

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Abstract

Quercetin is a multifaceted dietary flavonoid with a multitude of biologic activities that can be used to treat various ailments. These include cancer, bacterial and viral infections, cardiovascular disease, and diabetes. A greater emphasis on cancer is discussed within this paper by highlighting some of the beneficial qualities of quercetin without including other related dietary flavonoids and quercetin analogs. In vitro and in vivo analysis are evaluated without making recommendations on dosage, dosing regimens, or administration since quercetin has not been subjected to rigorous clinical trials despite the significant amount of research that has been conducted with quercetin.

Keywords

Quercetin, Cancer, Infection, Biomarkers, Diabetes, Mast Cell, Cardiovascular

1. Introduction

Quercetin is a flavonol, a type of flavonoid which is commonly present in various foods including onions, fruits, and vegetables [1] [2]. Quercetin, at nontoxic concentrations, is known to have a multitude of recognized biologic effects in which many of its mechanisms remain a mystery [3] [4]. Despite most of the information known about quercetin being based on in vitro and murine models, there is significant evidence that quercetin is a molecule with several biologically beneficial properties. These properties support quercetin’s role as a treatment for oxidative damage, cancer, inflammation, bacterial and viral infections, cardiovascular disease, and diabetes. The evidence for each of these categories varies in the level that it has been investigated. Conclusive

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findings of quercetin’s benefits, to our knowledge, has not completed all the rigors of pharmaceutical clinical trials. Although there are many quercetin analogs and dietary flavonoids with varying evidence to support their claims, this paper will focus exclusively on quercetin and its known mechanism and properties itself.

Quercetin derives its name from quercetum which means oak forest. It is a flavonoid that derives its name from flavus which means yellow. Quercetin’s structure is derived from 2-phenylchromene-4-one which is also classified as flavone. There are many proposed qualities that quercetin could potentially have in plant biology. These include plant protection from UV light, in addition to an impact on bacterial, viral, and fungal infections, as well as an enzyme inhibitor, a potential pollinator attractor, and plant hormone controllers [5].

2. Bioavailability

Some of the earliest analyses of quercetin’s bioavailability after a single oral dose claimed the bioavailability to be approximately 2% [6]. By means of radiolabeled quercetin, the bioavailability was determined to be closer to 44.8% associated with mouse blood plasma analysis [7]. However, since the half-life of radiolabeled carbon ranges between 11 - 28 hours, the bioavailability of quercetin might actually be higher than initially reported, especially if quercetin is continuously supplemented [8][9]. Quercetin is universally known for its low toxicity as a natural product despite the limited information on dosing regiments.

3. Antioxidant Capabilities

Quercetin’s ability to scavenge free radicals and bind to transition metal ions makes it considered a strong antioxidant [10]. This is due largely to the pharmacophores found within quercetin including a catechol group found in ring B [11]. Quercetin is the most potent scavenger of $\cdot O_2^-$, and ONOO$^-$ [12][15] within the flavonoid family [16][17] and its qualities as an antioxidant makes quercetin a strong lipid peroxidation inhibitor [18][19]. In addition to its antioxidant properties, quercetin also increases glutathione concentrations [20] of which can inhibit free radical formation [21]. Quercetin itself is also a powerful free radical scavenging antioxidant [22]. The antioxidant properties of flavonoids like quercetin are often correlated with the reduction of rates of several chronic diseases including coronary heart disease, stroke, and diabetes [23][24].

4. Cancer

The effect of quercetin on cancer is two-fold since it has direct anticancer properties in addition to chemopreventive properties. These findings are not without controversy since the intake of various substances rich in dietary flavonoids have not been shown to reduce cancer risk. Some of these dietary sources include black and green tea consumption [25] and red wine consumption [26][27]. However, consumption of onions, which have among the highest concentration of quercetin and flavonols, were shown to reduce cancer risks in stomach, colon, and rectal cancers [28].

Diet high in quercetin are correlated with lower rates of stomach, colon, breast, and lung cancers [29][32]. Many of the studies associated with quercetin’s effect on cancer are based on the chemical induction of cancer with either coadministration of quercetin or administration of quercetin after cancer was induced. Experimentation regarding the blocking of cancer formation with quercetin using TPA/methylcholanthrene showed quercetin was able to block cancer formation in low doses but not at high doses [33]. In another experiment involving the chemopreventive properties of quercetin on skin cancer, mice were administered quercetin 30 mins before the carcinogenic primer 12-O-tetradecanoyl phrobol-13-acetate [34]. Such inhibition of skin cancer formation suggests quercetin might be considered an effective agent of skin cancer prevention [35].

Although the mechanism associated with quercetin’s chemopreventative and anticancer properties is unknown, there are interactions that could illuminate the mode of quercetin’s beneficial characteristics with regard to its role in cancer treatment and prevention. Quercetin is a known phytoestrogen and has the potential to interact with estrogen responsive receptors including cannabinoid CBI receptor (CBI-R) [36] which can influence an inhibitory tone on cell growth [37][38].

The mechanism for the chemopreventive properties of quercetin is unknown, but there are a few intercellular mechanisms that can advance the discussion. These models include the inhibition of nuclear factor-$\kappa$B (NF-$\kappa$B) in addition to potentially involving the PI3K/Akt/IKK/NF-$\kappa$B signaling axis. This mechanism is consistent with other flavonoids that have NF-$\kappa$B inhibitors [39][41]. NF-$\kappa$B, in particular, has been a target of interest in drug discovery using natural agents [42][43]. Quercetin may work either by direct or indirect effects on NF-$\kappa$B.
NF-κB is stimulated by IkB kinase which is associated with either pro or anti-apoptotic pathway through regulation of the p53 gene [44]. However, quercetin is known to promote apoptosis of cancer cells similarly to other flavonoids [45]-[47]. This is done by a mechanism that may not involve a p53 signaling pathway [48]. Quercetin and other flavonoids are also able to inhibit PI3K/AKT axis in addition to inhibition of various PI3K isoforms [49]-[51]. However, there is still a significant amount of information that remains unknown, and there is a possibility to quercetin inhibits other kinases and enzymes other than PI3K and NF-κB [52].

*In vitro* analysis of quercetin may have the ability to re-sensitize cancer cells to chemotherapy, in addition to reversing drug resistance associated with chemotherapeutic [53]-[57]. For example, quercetin can reserve tamoxifen resistance in breast cancer cells [58]. Other studies suggest that quercetin has the potential to potentiate other chemotherapies’ effectiveness including agents such as topotecan, doxorubicin, cisplatin, ribavirin, tamoxifen, adipomycin, genistein, and carboxyamidotriazole [59]-[73].

Quercetin has the capability of inhibiting the transcription of heat shock protein (HSP) and hypoxia inducible factor-1 (HIF-1), essentially reducing the influence of a hypoxic cellular condition has on oncogenesis [74]. Quercetin also had an effect on the translocation of protein kinase C δ (PKCδ) to the cellular membrane [74]. Hypoxia induced signaling involving heat shock factor (HSF) and HIF-1 are likely associated with PKCδ signaling [74]. Quercetin is also shown to inhibit tumor invasion and metastasis by suppression of the PKCδ/ERK/AP-1-dependent matrix metalloproteinase-9 activation in breast cancer cells [75].

The anticancer activity of quercetin may involve downregulation of reactive oxygenated species (ROS) and TNFR1 levels [76]. PKC is essentially a housekeeping enzyme, but under conditions of increased oxidative stress, it can promote tumorigenesis and malignancy [77] [78]. It is important to note that oxidation of the NH2 terminal activates PKC but oxidation of the COOH terminal can inactivate PKC [79]. PKC’s activity was shown to be down regulated after quercetin treatment in mice bearing Dalton’s lymphoma [76]. Quercetin is said to modulate conventional, novel, and atypical PKC pathways [76].

Quercetin was also shown to induce apoptosis in non-small-cell lung cancer cell line A549 via a mechanism likely related to the upregulation of caspase 3, a major gene associated with apoptosis [80]. Other evidence from the same study showed an increase in Bax, a major apoptotic protein in addition to a marked decrease in Bcl2, a major anti-apoptotic protein [80]. Quercetin also reduces titers of interaction interleukin 6 (IL-6), an inflammatory cytokine promotes cancer formation in a mechanism associated with downstream regulation of STAT-3 [80].

The effect of quercetin on cancer stem cells is still unknown, however, several studies have shown promise with proposed potential mechanisms of action regarding the effect of quercetin 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 dysregulated self-renewal. It is thought that quercetin acts as an efflux pump inhibitor and increases the bioavailability of drugs through inhibition of BCRP, MRP1, and P-gp [81]. Thus, at non-toxic concentrations of quercetin, quercetin is thought to enhance chemotherapeutic effects of chemotherapies [81]. Leukemic progenitor cellular growth can also be influenced by quercetin by a mechanism associated with the transforming growth factor β1 (TGF-β1) *in vitro* [82]. TGF-β1 has powerful hematopoietic regulatory properties [83]-[85], and depending on their stage progenitor differentiators, acts to either stimulate or inhibit the growth of noncancerous myeloid progenitors [83] [86]-[89]. Quercetin similarly inhibits the growth of ovarian cancer cells by a mechanism associated with TGF-β1 [90].

There are several identified biomarkers that quercetin can be effective with regard to treating cancer. Biomarkers associated with cancer stem cells (CSC) include ALDH-high, Oct4, Nestin, and Nanog [91]. Many of these biomarkers are transcription factors associated with the stemness of the cancer stem cells [91]. Biomarker HSP-27 was found to be inhibited in breast CSC by quercetin which correlates with observation that HSP-27 is involved in the suppression CSC population and the suppression stemness properties [92]. In head and neck cancer, quercetin was able to suppress ABCG2 and MDR1 inhibition of HSP-27 [93]. Pancreatic cancer can be affected by quercetin by cytotoxic action or by the inhibition of the biomarker associated with the Wnt/β-catenin signaling in addition to chemosensitzation to gemcitabine [94]. Pancreatic CSC biomarker ALDH can experience a decrease in activity by quercetin in addition to quercetin’s ability to potentially induce apoptosis in those cells [95]. Other known cancer biomarkers that can be targeted by quercetin include the potential biomarker of the egf-Pi3K-AKT pathway, the established biomarkers of Wnt/β-catenin and estrogen receptor (ER), and the putative biomarkers JAK-STAT, Notch 1, and Notch 2 [96]-[101]. The induction of death receptor 5 (DR-5) and survivin suppression mark an additional two biomarkers that are affected by quercetin [102].
list of biomarkers affected by quercetin is presented in Table 1.

Photodynamic therapy can be a complementary treatment modality that can be administered before or after chemotherapy, radiotherapy, or surgery without adversely affecting other treatments [107][108]. Photodynamic therapy involves the excitation of photosensitive molecules using visible light and a mechanism that also involves molecular oxygen [109][110]. The creation of reactive oxygen species, including singlet oxygen, inside the cell by photodynamic therapy results in photo-damage and leads to cell death [111][112]. HEp-2 cells showed significant sensitivity to photodynamic therapy and quercetin in concentrations of 50 μM and 100 μM independently [113]. However, the combination of photodynamic therapy and quercetin at a concentration of 50 μM and 100 μM showed a significant decrease in cellular density as compared to the photodynamic therapy alone [113].

5. Inhibition of Mast Cells

Mast cells are derived from hematopoietic progenitors that, depending on the microenvironmental conditions, mature in tissue [114][115]. Mast cells are known for their role as effector cells in allergic reaction [116][119] associated with their secretion of histamine, prostaglandin D2 (PGD2), leukotrienes (LT), a variety of multifunctional cytokines, and proteolytic enzymes [120][122]. Inflammation via activation and recruitment of immune cells in addition to late-phase reactions describe the primary function mast cell secretions [123][124]. Quercetin

<table>
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<th>Putative biomarkers</th>
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<tr>
<td>ALDH high</td>
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<tr>
<td>Oct4</td>
<td>[91]</td>
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<td>Nestin</td>
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<td>Nanog</td>
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<tr>
<td>HSP-27</td>
<td>[92][93]</td>
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<tr>
<td>Wnt/β-catenin</td>
<td>[94][100]</td>
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<tr>
<td>Egf-Pi3K-AKT pathway</td>
<td>[101]</td>
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<tr>
<td>ER</td>
<td>[96]</td>
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<tr>
<td>JAK-STAT</td>
<td>[98]</td>
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<td>Notch 1</td>
<td>[99]</td>
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<td>Notch 2</td>
<td>[99]</td>
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<tr>
<td>TNFR1</td>
<td>[76]</td>
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<td>PKC</td>
<td>[76]</td>
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<tr>
<td>HIF1</td>
<td>[74]</td>
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<tr>
<td>NF-κB</td>
<td>[97]</td>
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<tr>
<td>PI3K</td>
<td>[49][50][51]</td>
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<tr>
<td>Cannabinoid receptor</td>
<td>[36]</td>
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<tr>
<td>Death Receptor</td>
<td>[102]</td>
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<tr>
<td>Survivin</td>
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<td>EGF</td>
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<td>IGF</td>
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<td>[104]</td>
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<td>p21</td>
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has been shown to attenuate the activation of the transcription factor NF-κB which in turn inhibits the downstream expression of TNF-α, IL-1, IL-6, and IL-8 [41]. Activation of cytokines in mast cells via IgE-mediated mast cell activation was also inhibited by concentrated extract containing significant levels of quercetin [125].

6. Bacterial Infections

Quercetin alone or in combination with other supplements or antibiotics has been shown in vitro and in vivo to kill the bacterium. Quercetin alone has been shown to have antibacterial properties in vitro against Actinobacillus actinomycetemcomitans, Actinomyces nasefndii, Actinomyces viscosus, Fusobacterium nucleatum, and Porphyromonas gingivalis [126] [127]. Helicobacter pylori were shown to be sensitive to the antimicrobial effects of quercetin in both in vitro and in vivo studies [128]-[130]. Quercetin in combination of supplements morin and rutin and antibiotics including amoxicillin, ampicillin, cephradine, ceftriaxone, imipenem, and methicillin showed a synergistic effect against methicillin resistant Staphylococcus aureus (MRSA) in vitro [131]. A synergistic effect against MRSA was also seen when natural compounds quercetin and epigallocatechin gallate were administered together in vitro studies [132].

7. Viral Infections

There is mounting evidence that quercetin and its analogs have antiviral properties. Although there are many proposed mechanisms for how quercetin and its analogs accomplish their antiviral activity, a universal mechanism is unknown. This leads many to believe that the evidence suggests that quercetin might have multiple mechanisms of action depending on the type of virus and viral targets. Some of quercetin’s earliest viral studies show quercetin has antiviral activity against enveloped viruses including herpes virus simplex 1, parainfluenza type 3, pseudorabies, and Sindbis [133] [134]. The mechanism of action may involve interference with viral nucleic acid synthesis. However, the suppression of hepatitis C by quercetin is likely caused the inhibition of a multifunctional viral protease NS3 [135].

8. Cardiovascular

There are several cardiovascular benefits associated with quercetin. Much of the evidence remains in murine models and the mechanisms of action have not been resolved as of yet. The severity of ischemia-reperfusion had been reduced when mice were given 20 mg/kg of quercetin before clamping of the aorta and once again after reperfusion [136]. A 5 mg/kg single dose of quercetin was also able to reduce the effects of reperfusion damage in rats [137]. 50 mg/kg of quercetin has been shown to treat atherosclerosis in mice through a mechanism associated with the interference associated with foam cell formation and by reducing macrophage induced oxidant/proinflammatory response [138]. Quercetin has been determined to accumulate in human atherosclerosis lesions despite not being found in normal aorta [139]. Quercetin is potentially an effective drug for the treatment of pulmonary arterial hypertension in part by a mechanism associated with the TrkA/AKT signaling pathway [140].

9. Diabetes

Although there is significant evidence of the effects of quercetin on diabetes and diabetic related ailments, the mechanism of action remains unknown. This includes the lowering of glucose in blood plasma, preservation of β-cell activity in the pancreas, glucose tolerance test normalization, in addition to protection against diabetic effects on mood, cognition, and renal functions in rat models [141]-[147]. Quercetin also acts to protect against high glucose induced damage and may also aid in improvements associated with vascular repair in addition to the promotion of the biological functions in endothelial progenitor cells [148]. In a small clinical study involving 34 men and women with either type 1 or type 2 diabetes with diabetic neuropathy, patients were given a topical treatment containing quercetin ascorbyl palmitate, and vitamin D3 or placebo three times a day for a period of four weeks [149]. Patients who used the quercetin topical treatment experienced improved quality of life in addition to a reduction of pain, numbness, and irritation [149].

10. Discussion

There is still much left to be discovered about the beneficial qualities of quercetin in all of the topics listed. The
list of potential benefits of quercetin in this paper is not exhaustive, and there are likely more benefits to be discovered in the future. Although the intake of dietary flavonoids does little to exhibit the qualities listed in this paper, there is some evidence that quercetin supplements may induce the desired results. Since quercetin is poorly regulated, concentrations of quercetin from various kinds of extracts can lead to varying levels of other plant products which can lead to variability in the mass of pure quercetin in dosages. Some disreputable distributors of quercetin may not have quercetin in it at all. Nevertheless, a consistent dosage for each of the proposed benefits of quercetin remains contentious and should be left to the recommendation of physicians despite its remarkably low toxicity.

Quercetin is involved in a multitude of cellular functions and the human body likely evolved with consumption of dietary flavonoids like quercetin. The ubiquitous nature of quercetin in various biologic functions makes the resolution of the complete effects associated with the mechanisms of action of quercetin to be remarkably difficult. Quercetin’s ubiquitous nature in effecting a variety of biological functions combined with research from various independent research groups has diminished the focus, often effecting follow up work, and has lead to a significant amount of knowledge pertaining quercetin to not reaching the depth of knowledge that would satisfy all the rigors of clinical trials. More research should be done to follow up on what is known about quercetin and further the knowledge to create a clear, and if possible, universal biochemical pathway or pathways associated with quercetin.

It is important to note that quercetin can act on a variety of different cancers that express biomarkers and molecular pathways described in this paper. A significant amount of research has resolved cancer to be more of a disease related to cellular mutation rather than based solely as a disease of tissue. For this reason, quercetin’s mechanism or mechanisms of action can be utilized in various cancers that have similar genotypic or phenotypic expression of biomarkers and various molecular pathways.

11. Conclusion

It is clear that the research on quercetin may lead to potentially promising new treatment options for the various diseases discussed. More research is needed to develop a clear picture of how quercetin works from a biochemical standpoint. Extensive clinical research should follow up to determine whether or not quercetin can work in similar ways as described in various in vitro and murine models. This is particularly relevant with understanding the optimal dosage, frequency of dosages, and routes of administration. However, despite the low toxicity of quercetin and its ubiquitous nature as a dietary flavonoid, it is important to consult a physician to limit adverse events when used with other pharmacological substances.

References


