Quercetin in Age-Related Diseases

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Polyphenols are the known group of phytochemicals that essentially consists of phenolic rings. These are the plant product present in varied fruits and vegetables. These secondary metabolites perform a protective function in plants from environmental and biological stress. When consumed as a human diet these are also known to prevent various age-associated diseases. Polyphenols are known to possess antioxidant properties and protect against oxidative stress. Quercetin is among the widely occurring polyphenol, found abundantly in nature. It is commonly present in different plant products. Onion is known to have the highest quantity of quercetin. This plant compound is possessed antioxidant properties and is considered to have a protective function against aging. It is known to be present in both free and conjugated forms. Quercetin has anti-oxidative, anti-inflammatory, anti-proliferative, anti-carcinogenic, anti-diabetic, and anti-viral properties.

Keywords: polyphenols ; antioxidant ; quercetin ; neurodegeneration ; diabetes ; cancer

1. Introduction

Polyphenols belong to a group of phytochemicals that consists of phenol rings. Polyphenols are known to be present in food obtained from plant products. These are largely present in different types of fruits and vegetables and the products which are derived from plants, which include tea, coffee, red wine, and chocolates [1]. Recent studies show that plant polyphenols play an important role and are known to protect from cancer, neurodegenerative, and cardiovascular disorders. These act as potent antioxidants and plays a defensive role against oxidative stress. These polyphenols are plant secondary metabolites and play an important role in plant defense mechanisms [2].

Polyphenols in general are compounds that are soluble in water and contain 12 to 16 phenolic groups. The molecular weight ranges from 500–5000 Da and has 5 to 7 aromatic rings in its structure. The antioxidant and anti-inflammatory properties of polyphenols act to interfere with the molecular signaling pathways and are held accountable for cascade reactions that lead to aging [3]. Polyphenols taken up in diet are mostly flavonoids and are effective against type 2 Diabetes mellitus, anti-inflammation, and have anti-tumor effects. Polyphenols are widely used in the treatment of Alzheimer's. Consumption of polyphenols reduces the risk of cardiovascular diseases [4]. Polyphenols also play an important role in the regulation of hormones and have antioxidant properties. Studies on polyphenols suggest their anti-proliferative, anti-microbial, and pro-apoptotic activities. Greater than 8000 polyphenols with different activities and bioavailability have been studied so far [5]. A negative correlation has been derived between dietary polyphenols and the occurrence of diseases such as cancer, diabetes, and cardiovascular disorders. Various phytochemicals have been studied with several health-promoting benefits. A detailed study on traditional medicinal plants of China shows the health benefits of different plant species. *Ziziphus jujuba*, a plant species is used for the nourishment of the heart and blood. Another plant species, *Cyclea insularis* finds its use to treat disorders of musculoskeletal. *Cyclobalanopsis delavayi* cures disorders related to the respiratory system [6].

The life expectancy of individuals has greatly increased over the years due to improved medical facilities and lifestyles. Aging is related to the progressive decline in functional activities, damaged cell accumulation, and increased risk of diseases. Aging is also related to the occurrence of various age-related diseases such as diabetes, cancer, and neurodegenerative and cardiovascular disorders [7].

"Quercetum", the Latin term for the flavonoid quercetin means oak forest. This belongs to the class flavonol and is not synthesized in the human body. Quercetin is known to use in the treatment of cancer, allergic reactions, inflammation, arthritis, and cardiovascular disorders. The flavonoid also plays an important role in platelet aggregation, and the peroxidation of lipids and enhances the biogenesis of mitochondria [8].

Quercetin is a potent molecule that can be used to cure various health-related issues. Quercetin manifests antioxidant properties both in vivo and in vitro. Free radical scavenging activity of quercetin protects from various age-associated

disorders [9]. A diet rich in quercetin has various health-promoting benefits. It acts as an agent to lower coagulation, hyperglycemia, inflammation, and hypertension. Various clinical studies show that supplementation of quercetin is used to prevent and treat various chronic diseases such as cardiovascular disorders [10].

2. Quercetin and Its Role in Age-Associated Diseases

2.1. Neurodegenerative Disorders

Flavonoids prove to be beneficial in preventing neurodegenerative diseases and might delay the neurodegeneration process. Studies prove the neuroprotective functions of quercetin. The neuroinflammatory process is suppressed by quercetin as it downregulates pro-inflammatory cytokines which include iNOS and NF-kB and thus stimulates the regeneration of neurons. Quercetin reduces the lipid peroxidation and hence prevents the oxidative damage of neurons. Neuronal cells when treated with lower concentrations as 5 μM and 10 μM quercetin functions as antioxidant and at higher concentration of 20 μM and 40 μM becomes toxic [11].

Even though quercetin has low bioavailability it can pass through the blood-brain barrier (BBB) due to its lipophilic nature and functions as neuroprotective. When the mouse model was treated with quercetin via intraperitoneal injection every 48 h for 3 months, extracellular β-amyloidosis was found to be decreased and astrogliosis and microgliosis were improved, and also in the hippocampus and amygdala region, tauopathy was reduced. Quercetin preserved the learning and emotional functions in old healthy triple transgenic AD mouse models [12].

The accumulation of β1–42 in the brain is presumed to be the main reason for the development of AD. It has been reported that quercetin lowers the β1–42 accumulation in the brain. Quercetin administration has been proved beneficial to improve learning and memory efficiency and it also reduces the activity of acetylcholinesterase (AChE) [13]. Quercetin is known to inactivate P13K/AKT/GSK3β and ERK1/2-JNK-P38 MAPK signaling pathways by downregulating the proteins which induce Alzheimer's disease in the okadaic acid-induced injury of hippocampal neurons of mice [14].

The oxidative damage of an individual is compromised as aging precedes. Increased oxidative damage is a major factor responsible for the occurrence of age-related neurodegenerative disorders. Oxidative damage, dysfunction of mitochondria, autophagy and defective neurotransmitters are some of the important factors which are responsible for the causation of neurodegenerative disorders [15]. Studies on quercetin possibly show that it exerts an effect on the central nervous system. Quercetin is known to exert a protective role against neurodegeneration. The compound is known to improve the activity of superoxide dismutase and catalase and thus prevent the depletion of glutathione [16].

2.2. Diabetes

Natural substances are inexpensive and can be easily obtained and therefore can be used as an alternative to treat diabetes and other pathologies. Quercetin due to its antioxidant, anti-inflammatory, hypoglycemic, and hypolipidemic activities is known to be involved in the treatment of type 2 diabetes mellitus. Quercetin reduces the concentration of blood glucose levels, preserves the function of islets cells, number of β cell numbers in model rats and mice with diabetes. Experiments show that quercetin intake has a positive impact to prevent and treat the occurrence of diabetes mellitus [17] [18].

Quercetin treatment of diabetic rats improved dyslipidemia, decreased the blood glucose level in serum, increased the level of insulin, and decreased oxidative stress. When quercetin was orally administered in rats, the sexual activity, sperm count and motility, and the testicular damage induced by diabetes were reduced. When administered intravenously, quercetin lowered the blood pressure in hypersensitive rats [19]. Quercetin reduces the effect of oxidative stress and also attenuates the β-cell injury of pancreatic cells. It has been reported that consumption of the compound reduces the injury of hepatic cells oxidative stress attenuation and elevates the antioxidant enzymes such as catalase and heme oxygenase. The administration of quercetin in diabetic mice for 10 days of 10 and 15 mg/kg shows a decrease in blood glucose level and triglycerides while it increased the activity of enzymes such as hexokinase and glucokinase [20].

Quercetin is regarded as a very important flavonoid with beneficiary metabolic functions. Studies performed by Mahabady et al. showed that the oral administration of 75 mg/kg of quercetin to diabetic rats reduced the number of placental glycogen cells as compared to the control group. The plant compound acts as an oxygen scavenger and is known to protect against lipid peroxidation when present in circulation. The antioxidant property of quercetin prevents the in vivo and in vitro oxidation of biomolecules. Quercetin is known to prevent embryonic malformations in pregnant diabetic mice [21]. Various in vivo studies suggest that quercetin within a range of 15 mg/kg to 100 mg/kg for 14–70 days is potential in the treatment of diabetes [22].

2.3. Cancer

Quercetin is a potent flavonoid known for its chemoprotective activities in various in vivo and in vitro models. The various anti-cancerous properties such as reduced proliferation, the ability for induction of apoptosis, inhibition of mitotic events, causing cell cycle arrest makes it a reliable molecule in the therapy for cancer [23]. Quercetin can be used as a potent therapeutic but it has poor solubility, poor permeability, and low bioavailability. One major drawback of quercetin is its instability which limits its usage as a therapy for cancer [24].

The molecule is insoluble in water and very less soluble in alcohol. The studies on quercetin were performed by dissolving it into an organic solvent. To increase the clinical usage of quercetin in cancer treatment the molecule was used in higher concentrations and was frequently administered. Therefore, other alternatives were developed to use quercetin clinically and hence nanoparticle formulations were made to overcome the above-mentioned drawbacks. The nanoparticle formulations of quercetin were more effectively used in biological systems in the treatment of cancer. Quercetin when encapsulated with a PGLA (poly lactic-co-glycolic acid) nanoparticle system improved it as an overall anti-cancer agent [25].

Treatment with appropriate dose makes quercetin non-toxic and shows inhibitory effects on the formation of tumors. Various in vivo and in vitro studies show that quercetin promotes apoptosis, inhibits metastasis, and regulates the cell cycle [26]. In colorectal cancer quercetin arrests the cell cycle, modulates receptors of estrogen, regulates signaling pathways, and hence exhibits its chemo-protective functions [27].

It has been studied that in leukemia in the case of human, quercetin arrests the cell cycle at G2. Quercetin is also known to regulate p53 related pathways in cancerous cells. It regulates the release of p53 and hence inhibits the activities of cyclin A, cyclin B, CDK2 and therefore stagnates the MCF-7 cells of breast cancer in the S phase of the cell cycle. Quercetin affects the apoptotic pathways of the cancerous cells and therefore induces the death of cancer cells. Treatment with appropriate dose of quercetin increases the proapoptotic protein expression and reduces the expression of the antiapoptotic protein. Studies on human metastatic ovarian cancer PA-1 cell lines show that quercetin induces the apoptotic pathway that is mitochondrial-mediated and thus inhibits the growth of metastatic ovarian cancer cells [28].

Anti-apoptotic molecules such as Bcl-2 and Bcl-xl increase as a result of quercetin treatment and pro-apoptotic molecules such as cytochrome c, Bid, Bax, Bad, caspase-3, and caspase-9 increase [29]. Quercetin is also known to inhibit the formation of poly-unsaturated fatty acid metabolites which are associated with the progression of cancer. It inhibits ‘lipoxygenase’, which is the enzyme responsible for metabolizing Poly unsaturated fatty acid (PUFA). The consequence of quercetin was observed in the treatment of chronic prostate cancer. Therefore, quercetin in combination or alone can be used as a therapeutic for the treatment of cancer [26][30].

As observed in hypertensive rats, quercetin plays an important role in the production of nitric oxide and decreases oxidative stress, activates AMPK signaling pathway, and is hence considered to have important anti-hypertensive properties. Activation of AMPK signaling impairs the contraction of vascular smooth muscle cells [31]. Quercetin is responsible for the activation of cell death domain which further activates FAS and FADD and causes the death of cancer cell lines by activating caspase 8. The apoptosis-inducing properties of quercetin are assessed by the Annexin V/PI method [32].

In cancer cells quercetin is known to mediate intrinsic as well as extrinsic cell death by apoptosis. It has been documented that the apoptosis induced by quercetin is in association with the reduced activity of heat shock proteins such HSP-70 and HSP-90 in the case of prostate cancer and leukemic cells. In chronic myeloid leukemia and acute lymphoid leukemia, quercetin suppresses telomerase activity [33].

2.4. Anti-Inflammation

Various studies in cells of human and animal models suggest that quercetin exhibits anti-inflammatory activities. In vitro studies in the epithelial cells of guinea pig shows that quercetin inhibits the activity of cyclooxygenase and lipoxygenase [34]. Quercetin is known to suppress the activity of NF-κB translocation, I-κB-phosphorylation, AP-1, and reporter gene transcription and hence fights against inflammation. It also modulates the activity of NF-κB, JNK, and AP-1 signaling pathways. The activity of TNF-α was also reduced when treated with quercetin [35].

Work carried out by Güran M et al. shows that the combined effect of quercetin and curcumin enhanced the anti-inflammatory activities by reducing the expression of COX-2 protein, inhibiting the production of nitric oxide and inhibiting the activation of NFκβ [36]. Quercetin as an immunostimulatory agent exhibits a strong affinity for basophils and mast cells.

Quercetin stabilizes the cell membrane of basophils and mast cells and prevents them from spilling its pro-inflammatory and allergy-causing mediators [37]. The anti-inflammatory activities of quercetin mainly owe to its function to inhibit the effects of pro-inflammatory cytokines such as IL-6, TNF-α, IL-1β, and inflammatory mediators as catalase and nitric oxide [30]. Various properties of quercetin have been depicted in **Figure 1**.

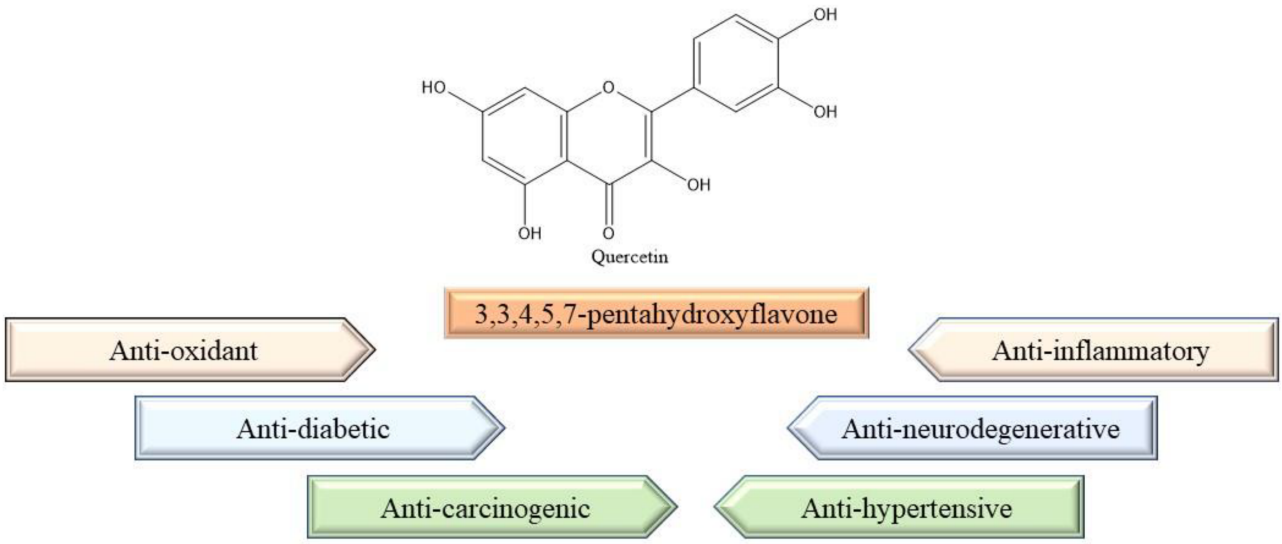

Figure 1. Structure and properties of quercetin.

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