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Beneficial effects of Quercetin on Age related Health Problems

Fauzia Khan[1]
[1]Assistant Professor (Zoology) Veerangana Rani Avantibai Lodhi Rajkiya Mahila Mahavidyalaya, Bareilly

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Abstract

Natural polyphenols from various plant sources have shown their beneficial effects since long and contribute in protection from cancer, neurodegenerative, and cardiovascular disorders and act as potential antioxidants which play defensive role against oxidative stress. Free radical and reactive oxygen species play important role in age associated health problems and antioxidant perform crucial role to restrain. Quercetin, a polyphenol antioxidant, is used for the prevention of many diseases like cancer, allergic reactions, inflammation, arthritis, and cardiovascular problems. In this review article role of quercetin has been discussed not only as preventive agent but also as supplementary food and medicine with special reference to age related health problems. quercetin has been observed to be effective polyphenolic antioxidant and can be used to implement cure for various age-associated disorders.

Keywords: Quercetin, Oxidative stress, antioxidant, Neurogenerative disorders

Introduction

Natural polyphenols, the phytochemicals containing phenol rings, are found in various fruits, vegetables and plant derived products[1]. These have been shown to play an important role in protection from cancer, neurodegenerative, and cardiovascular disorders and act as potential antioxidants which play defensive role against oxidative stress[2]. Till now about thousands of polyphenols with varied bioactions and bioavailability have been reviewed[3] and studies suggest their anti-proliferative, anti-microbial, and pro-apoptotic properties.

Polyphenols used in diet are commonly flavonoids and have shown to be effective in diabetes, anti-inflammation and have preventive effects against tumour, Alzheimer's and cardiovascular diseases[4]. The antioxidant and anti-inflammatory characteristics of polyphenols interfere with the molecular signalling pathways that are responsible to aging[5]. Aging is referred to the gradual regression in functional behaviour, damaged cell accumulation, high risk of disease incidence and is conferred as increase in incidence of diseases such as diabetes, cancer, and neurodegenerative and cardiovascular disorders[6].

One of the most used flavonoid Quercetin is known for its use in the treatment of cancer, allergic reactions, inflammation, arthritis, and cardiovascular disorders[7]. This plays an imperative role in platelet aggregation, peroxidation of lipids and enhances the biogenesis of mitochondria[7]. A diet enriched with quercetin shows several health-promoting advantages. Quercetin has been shown to display antioxidant properties both *in-vivo* and *in-vitro*. Free radical scavenging reaction of quercetin safeguards from various age-associated disorders[8]. It functions to lower coagulation, hyperglycemia, inflammation, and hypertension and numerous medical based research confirmed that quercetin supplementation in food is used to prevent and treat various chronic conditions[9].

Free radicals are molecules with unpaired electrons produced during cell metabolism and can be very reactive and short lived. Reactive oxygen species (ROS) are free radical produced by oxygen metabolism. ROS includes hydroxyl radicals (OH^-), superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and nitric oxide

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(NO) and are important for the homeostasis and maintenance of cellular activities[62]. When these are present in high concentration, can damage molecular components. Antioxidants are the compounds which can neutralize ROS. The difference between the reactive oxygen species (ROS) concentration and the antioxidant process to counterbalance them is described as oxidative stress.

Polyphenols interact with the reactive oxygen species and can terminate the chain reaction thus act as antioxidant[10], hence lowering the chance of incidence of diseases related to it[11]. These play role in the control of neurodegenerative diseases, cardiovascular diseases, cancer, and type 2 diabetes[12] Their antioxidant and other such properties are known to reduce the risk of age-related diseases such as cancer, neurodegenerative disorders, obesity, and cardiovascular diseases and studies have correlated the functions of various edible polyphenols in the diet with the process of aging[13]. In this review article beneficial effects of quercetin on various age-related problems have been discussed with help of available literature.

Quercetin

Quercetin (3,3,4,5,7-pentahydroxyflavone), is one of the commonly occurring secondary metabolites in fruits and vegetables and is commonly present as glycosides, i.e., it is found conjugated with residues of sugar[14]. It forms a routine ingredient of the daily human diet. It is yellow coloured compound, easy to dissolve in lipids and alcohol, and insoluble in cold water. Quercetin is most commonly found in large quantities in different fruits and vegetables which include onions, cherries, red leaf lettuce, berries, apple, asparagus, and in small quantities in tomatoes, broccoli, peas, and pepper[15]. It is reported to occur in citrus fruits, seeds and nuts, and red grapes[16]. Onion is known to have the highest amount of quercetin[17]. Quercetin is also shown to be present in herbs such as dill, few varieties of tea, and wine[18] and has also shown its presence in various medicinal plants such as Gingko, American elderberry, and Hypericum species[19].

It is used as a dietary supplement and is available in both free and conjugate forms like glycoside, sulfate, ethers, and prenylated quercetin[20]. Flavonoid quercetin has antioxidant, anti-inflammation, anti-diabetic, antimicrobial and anticarcinogenic, anti-proliferative[21]. Quercetin is a scavenges free radicals and therefore is a potent antioxidant[22]. it is lipophilic and passes through the plasma membrane easily[23]. Quercetin has antihypertensive and vasodilation[24] and its treatment regulates the blood glucose and lipid levels during fasting, decreases the amount of fat deposition in the liver, reduces the severity of renal fibrosis, and plays important role in autophagy process[25]. Quercetin constitutes about 75% of the flavonoid in our routine diet, Rutinose being its sugar conjugated form. Among all the flavonoids, glycosides of quercetin are known to have better absorption in humans and have metabolism[26]. The ingested quercetin diffuses to enterocytes for metabolism and then enter systemic circulation for tissue distribution.

Quercetin as Antioxidant

Quercetin is known to possess antioxidant properties and said to have a protective function against aging[27]. It is one of the most researched flavonoids and is derived from the amino acid, phenylalanine. Quercetin can donate its hydrogen atoms and cease the action of reactive oxygen species. It interacts with the intracellular signalling pathways, responsible for the antioxidant function[28]. Quercetin is a potent scavenger for free radicals in the flavonoid group and thus displays potential antioxidant activities[29]. Its hydroxyl group inactivates the free radicals by providing active hydrogen and thus oxidizes free radicals making them stable[30]. Quercetin scavenges several free radicals which include ROS and RNS[31], hydrogen peroxide, superoxide, and hydroxyl radicals[32]. At high concentration quercetin behaves as pro-oxidant and its pro-oxidant property is credited to the prevention of the growth of tumors[33].

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Quercetin ensures the oxidative equilibrium and so is said to be a strong antioxidant. Increased production of superoxide dismutase, catalase, and glutathione has been reported with the pre-treatment of quercetin[34]. Massive studies have shown that quercetin interacts directly with DNA and the antioxidant effect of quercetin-DNA was discovered to be more than that of quercetin alone[35]. Quercetin in circulation ameliorates vascular circulation and in its conjugated form reduces the incidence of cardiovascular disorders. Quercetin is known to affect the stability and flexibility and fluidity of the lipid bilayer and influences the activity of ATP-dependent protein transporter[36]. In the following section we have discussed effect of quercetin in different age-related disorders.

Neurodegenerative Disorders

Flavonoids have been evidenced to be beneficial in checking neurodegenerative diseases and tend to delay the neurodegeneration process. The neuroinflammatory process is suppressed by quercetin as it downregulates pro-inflammatory cytokines and thus stimulates the regeneration of neurons[37]. Quercetin reduces the lipid peroxidation and hence prevents the oxidative damage of neurons and showed antioxidant functions at lower concentration while becomes toxic at higher ones[38].

Quercetin can pass through the blood-brain barrier due to its lipophilic characteristics and can function as neuroprotective agent. Quercetin was observed to preserve the learning and emotional functions in old healthy triple transgenic Alzheimer mouse models[39]. The accumulation of β1–42 in the brain is presumed to be. Quercetin has been reported to lower the β1–42 accumulation in the brain, the main reason for the development of Alzheimer disease and its treatment has been shown to be beneficial to improve learning and memory power[40]. Quercetin is known to inactivate the related signalling pathways by downregulating the proteins which induce Alzheimer's disease in the induced injury of hippocampal neurons of mice[41].

Individual's compatibility to deal with oxidative damage is compromises as aging precedes and enhanced oxidative damage is a foremost factor accountable for the prevalence of age-related neurodegenerative disorders[42]. Quercetin is proven to employ a shielding mechanism against neurodegeneration and is known to enhance the activity of superoxide dismutase and catalase and thus prevent the depletion of glutathione[43].

Diabetes

Natural substances are extensively used and liked as an alternative treatment for diabetes. Quercetin due to its antioxidant, anti-inflammatory, hypoglycaemic, and hypolipidemic activities is known to be involved in the treatment of type 2 diabetes mellitus[44]. It reduces blood glucose levels, preserves the function of islets cells, number of β cell numbers in model rats and mice with diabetes and its intake has a positive effect to inhibit and treat the occurrence of diabetes mellitus[45]. Quercetin treatment of diabetic rats treated dyslipidemia, decreased the blood glucose level in serum, increased the level of insulin, and decreased oxidative stress and when given intravenously, quercetin lowered the blood pressure in hypersensitive rats[46].

Quercetin reduces the effect of oxidative stress and attenuates the β-cell injury of pancreatic cells[47]. The administration of quercetin in diabetic mice for 10 days of 10 and 15 mg/kg showed a decline in blood glucose level and triglycerides while it enhanced the action of enzymes such as hexokinase and glucokinase[48]. Studies executed by Mahabady et al. displayed that the oral administration quercetin to diabetic rats reduced the number of placental glycogen cells as compared to the control group and was observed to prevent embryonic defects in pregnant diabetic mice[49]. Various in vivo studies also suggest that regular use of quercetin within a range is potential in the treatment of diabetes[50].

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Cancer

Quercetin is a potent flavonoid known for its various chemoprotective abilities such as reduced proliferation, the ability for induction of apoptosis, inhibition of mitotic events, causing cell cycle arrest and thus can be said to be a reliable molecule in the therapy for cancer[21]. Different in vivo and in vitro research show that quercetin endorses apoptosis, inhibits metastasis, and regulates the cell cycle and handling with suitable concentration shows repressive effects on the tumour development[51]. In colorectal cancer quercetin has been observed to arrest the cell cycle, modulates receptors of estrogen, regulates signalling pathways, and hence exhibits its chemo-protective features[52].

Various research has shown data that support role of quercetin induced apoptosis. Research on human metastatic ovarian cancer PA-1 cell lines displayed that quercetin induces mitochondrial-mediated apoptotic pathway thus reduces the growth of metastatic ovarian cancer cells[29]. Anti-apoptotic molecules such as Bcl-2 and Bcl-xl were observed to decrease by quercetin treatment and pro-apoptotic molecules such as cytochrome c, Bid, Bax, Bad, caspase-3, and caspase-9 were observed to increase[20]. Quercetin inhibits lipoxygenase responsible for metabolizing Poly unsaturated fatty acid (PUFA) related with the development of cancer[51]. Quercetin alone or with other drugs can be used in therapy of chronic prostate cancer[53]. Quercetin has been observed to show anti-hypertensive properties and play crucial in controlling oxidative stress, activating AMPK signalling pathway in hypertensive rats[54]. It also displayed apoptosis inducing properties via activating cell death domain and causing death of cancer cell lines[55]. In another studies also apoptosis induction was observed by quercetin with reduced heat shock protein activities in chronic myeloid leukemia and acute lymphoid leukemia where it suppressed telomerase activity[56]. The nanoparticle formulations of quercetin have been used more effectively in biological systems in the treatment of cancer[57].

Anti-Inflammation

anti-inflammatory function of quercetin has been suggested by several studies of human cells and animal. Quercetin was found to inhibit activity of cyclooxygenase and lipoxygenase in the epithelial cells of guinea pig *in-vitro*[58]. Quercetin modulates the activity of NF-κB, JNK, AP-1 signalling pathways and TNF-α[59].Güran M et al. reported that quercetin with curcumin improved the anti-inflammatory activities by reducing the expression of COX-2 protein, restricting nitric oxide production and preventing the activation of NFκβ[60].

Quercetin also exhibit immunostimulatory properties as it shows affinity for basophils and mast cells stabilizes the their cell membrane to prevent from damage to its pro-inflammatory and allergy-triggering mediators[61]. The anti-inflammatory activities of quercetin are attributed to its ability to inhibit the impacts of pro-inflammatory cytokines such as IL-6, TNF-α, IL-1β and mediators as catalase and nitric oxide[53].

Conclusions

Quercetin, a secondary metabolite forms a basic element in the human diet. It is known to display antioxidant characteristics and has shown protective function against aging in various ways. Quercetin has shown antioxidant, anti-inflammation, and anti-proliferative, anti-diabetic, anti-carcinogenic, and anti-microbial properties. Because of rapid metabolism and it is not accumulated in the body. Being lipophilic, quercetin can cross the blood brain barrier easily and exhibits neuroprotective activity. The molecule is known to control the blood glucose levels. Various in vitro and in vivo studies have proven that quercetin to be anti-cancerous and a dependable drug in cancer therapy. It has also displayed crucial role as an anti-inflammatory molecule. To conclude, quercetin is effective molecule and can be used to implement cure for various age-associated disorders.

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