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Review on the Bioactivities of Quercetin

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Abstract : Quercetin, the most active bioflavonoid which is produced as a secondary metabolite by plants, is a polyphenol with a wide spectrum of bioactivities. This bioflavonoid is the ―nature‘s biological response modifier‖ as it interferes with the various allergens and other reactive compounds. Apple, oranges, tomatoes, onions, black tea and green tea are good sources of quercetin and it is also available commercially. After absorption in the small intestine and colon, quercetin conjugates with glucuronic acid and binds to albumin and passes to liver and benefits the body by its various bioactivities. Quercetin‘s antioxidant activity enhances the radical scavenging activity and metal chelation of the ions but the prooxidant activity depends on its high concentration. Further, quercetin interferes with the formation of leukotrienes from arachidonic acid showing its anti-inflammatory effect. A combined effect of quercetin and bromelain effectively suppresses the allergic reactions and the excessive inflammation resulting from bruising and tissue damage. The mutualistic effect of vitamin C and quercetin protects each other from getting oxidized. A direct relationship was also found to exist between quercetin's antiviral activity and enhancement of cyclic adenosine monophosphate (cAMP), which is a second messenger involved in many biological processes. Quercetin helps in down regulation of mutant gene p53 and inhibits the growth of cancerous cells by putting a check at G1 phase. This also controls the surpassing of the normal regulatory growth by the tumor cells and inhibits the production of heat shock proteins and thus showing its anticancer properties. Owing to the potential pharmaceutical properties of quercetin, the bioactivities, principle uses and mechanisms involved in the treatment of various diseases were reviewed in this paper. In addition, safety issues involved in the partake of quercetin by humans have also been discussed.
Keywords : Bioactivities of Quercetin.

Introduction

Quercetin, a naturally occurring polyphenolic secondary metabolite derived from plants is generally present in the form of pigments responsible for giving colors such as red, blue and yellow in onions, tea, apples, berries, etc. (1,2). In plants, they resist from diseases and UV light and prevent damage to seeds until its germination. The aglycone form of a number of other flavonoid glycosides is predominantly found in citrus fruit, buckwheat and onions. With rhamnose and rutinose, quercetin forms glycosides quercitrin and rutin respectively. Quercetin because of its wide range of bioactivities, has received considerable attention

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Quercetin is the 3,3′,4′,5,7, pentahydroxyflavone (Figure 1). Quercetin is the most active form of all other flavonoids, and the bioactivity of many medicinal plants depends upon the concentration of quercetin. This gives an emergency quick response unit‘ for any trouble caused by inflammation or allergic reactions to the body. Studies done among other flavonoids showed similar effects among bioflavonoids, but quercetin showed superior effect over them. Quercetin conjugates with glucuronic acid and binds to albumin and passes to liver and benefits the body by its various bioactivities after it gets absorbed in the small intestine and colon. Quercetin has given a significant amount of anti-inflammatory activity because it directly acts against several initial processes of inflammation. They inhibit both the production and release of histamine and other allergic/inflammatory mediators. It is a good antihistamine and also helps in diminution of the inflammation that results from hay fever, allergies, bursitis, gout, arthritis, and asthma. This also assists in the antioxidant activity by scavenging free radicals and allows vitamin C to work more efficaciously. Quercetin may have positive effects in the prevention of cancer, prostatitis, heart disease, cataracts, allergies/inflammations, and respiratory diseases such as bronchitis and asthma. This flavonoid inhibits reverse transcriptase, by which the retroviruses (such as HIV) spread throughout the body, and it can also be used in the treatment of piles, varicose veins and bruises. They also exhibit pro-oxidant, immunomodulatory, anticancer and gastro- protective activities.

The dynamic property of quercetin permits the body to sustain energy for a longer period of time. Intake of quercetin increases the sum total of mitochondria produced by the body, which allows the cells to produce more energy. Therefore, it relieves from fatigue and illness (3). This review will provide quercetin a good exposure of its multiple bioactivity and mechanisms involved in its different activities such as antioxidants, pro-oxidants, antiallergens, and antiviral, etc, and be useful for the future drug development from natural resources due to its active form in nature

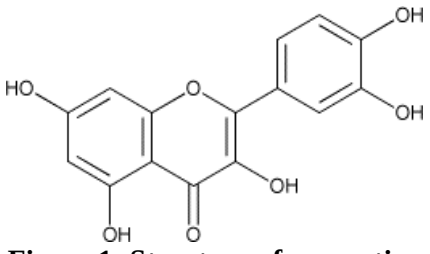

Figure 1: Structure of quercetin

Sources

The leaves and petioles of Rheum species, and asparagus, flowers of pagoda tree, fruits such as apples, orange, grapefruit, lemon, lime and berries such as mulberry, ash tree fruits and cranberries and vegetables such as onions, tomatoes, and broccoli are also good sources of quercetin. Additionally, green and black teas, as well as wine, are also significant sources of quercetin. A study revealed that organically grown tomatoes had about 80% more quercetin than ‒conventionally grown‖ (4).

Quercetin is being studied by many researchers for its bioactivities because of which it is used in the treatment of various allergic and disease conditions. Some of the bioactivity and the mechanism involved are discussed below. Fig 2 represents the amount of quercetin present in the food given (5). Fig. 3 represents quercetin derivatives in different sources (A–D) and concentration of quercetin derivatives in beans (E) and mango (F). The content of few common quercetin derivatives in different sources are shown in Fig. 3. High concentrations of quercetin 3-*O*-galactoside (Fig. 3A) and quercetin 3-*O*-glucoside (Fig. 3B) was significantly found in mango compared to other sources. Quercetin 3-*O*- rhamnoside, derivative of quercetin (Fig. 3C) is most predominantly found in pepper. Quercetin 3-*O*-glucoside (Fig. 3E) and quercetin 3-*O*-galactoside were found in beans and mango respectively (101).

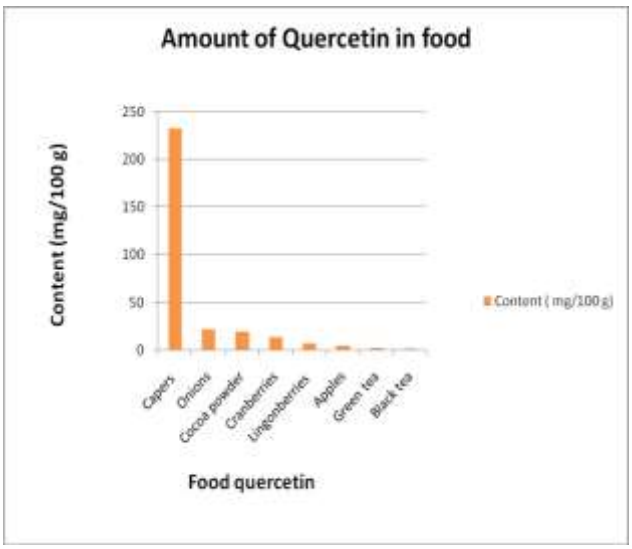

Figure 2 : Amount of quercetin present in the food given (5).

1. Antioxidant and prooxidant activities

Flavonoids show strong antioxidant properties. The activity rely upon the degree and position of hydroxylation: all flavonoids having the 3,4-dihydroxy conformation have shown antioxidant activity. This activity of flavonoids is only shown in the aromatic hydroxyl groups (21). Quercetin has five functional hydroxyl groups that undergo oxidation or reduction, and its activity not only rests in these groups but intensified by the presence of carbonyl group, although, generally, the introduction of a carbonyl group in phenol decreases the antioxidant activity. Flavonoids build complexes with metals ions and chelation at the keto and hydroxyl groups. This activity is referable to their radical-scavenging and metal-chelating properties, of which the prior one dominates.

Quercetin acts as a prooxidant at higher concentration. It is violently reactive and search cells to onrush in order to balance itself and in the process, quercetin destroys cells. So, by applying high doses of quercetin to cancer tumors, the cancer cells are damaged and destroyed. Testing for this effect has only happened in laboratories so far. Human studies are needed to assess quercetin's value in destroying tumors in humans.

Mechanism

Quercetin transfers an electron to free radicals, neutralizing the abnormal cells that scavenge healthy cells and DNA in search of balance. By giving an electron, this prevents the damage caused by free radicals which may lead to cancer and other serious diseases. Quercetin when reacts with the free radical, it transfers a proton becoming a radical itself, but the resulting unpaired electron is delocalized by resonance, making the quercetin radical too low in energy to be reactive (20). Three chemical groups helps quercetin to maintain its stability and when reacting with free radicals: the B ring o-dihydroxyl groups, the 4-oxo group in conjugation with the 2,3- alkene, and the 3- and 5-hydroxyl groups (19). These functional groups can transfer electrons to the rings, that increase the number of resonance forms present, in addition to those created by the benzene structure (20).

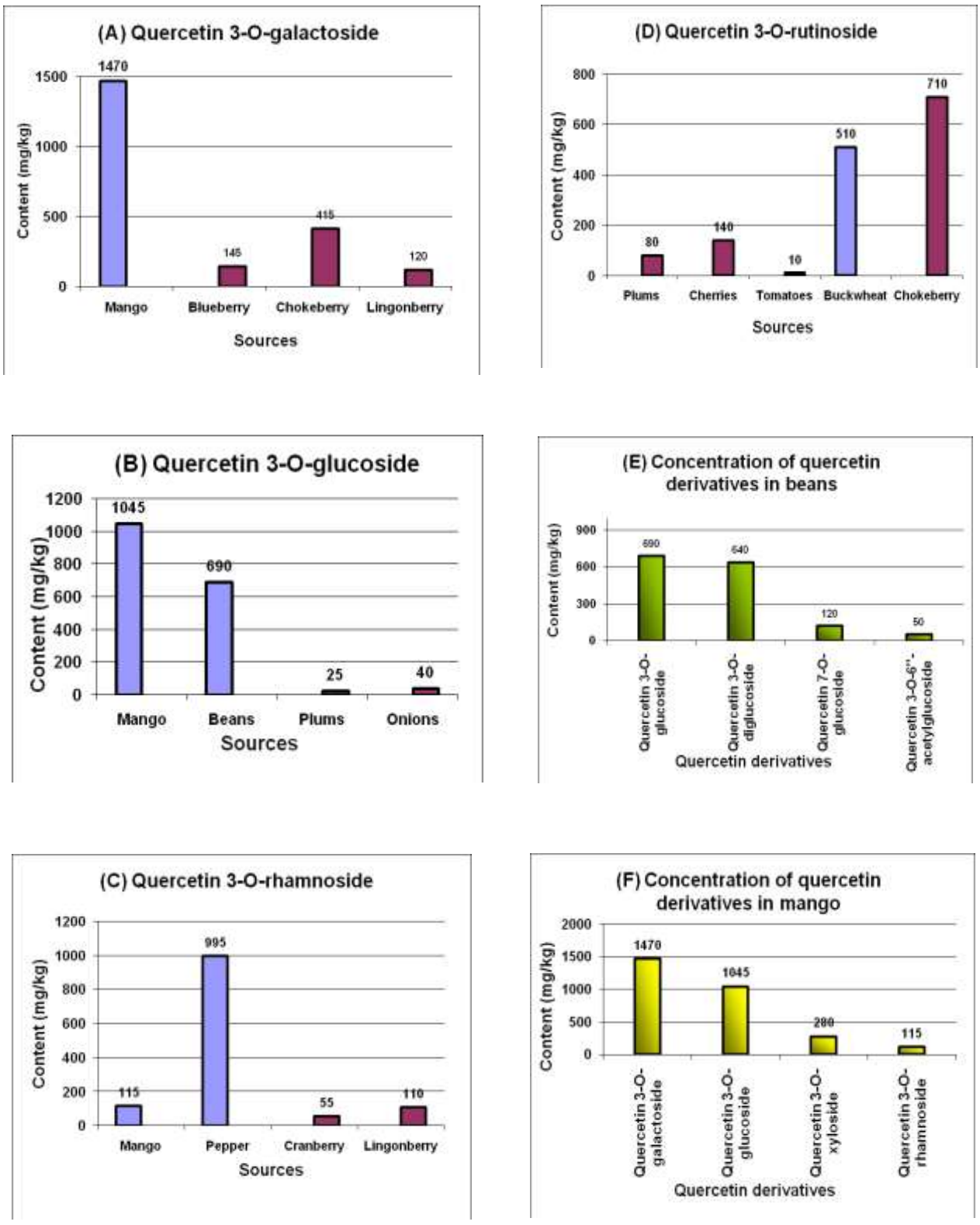

Figure 3: Quercetin derivatives in different sources

It has been studied that the hydroxyflavone has a pH-dependent effect on quercetin's antioxidant activity which is mainly due to an increased radical scavenging ability of the flavonoids upon their deprotonation. Since deprotonation mainly increases the antioxidant action of the hydroxyflavones, the ionization potential (IP) becomes significantly lower upon deprotonation. So this can be summarized that electron donation is the predominant mechanism of antioxidant action of hydroxyflavones afterwards deprotonation. Upon deprotonation, the radical scavenging capability increases because electron transfer becomes very much easier. This stated that not only the ease of radical scavenging but also the chemical mechanism of antioxidant activity may change upon deprotonation, and electron transfer is significant for flavonoid antioxidant action at physiological pH (22).

Another oxidative mechanism of flavonoid is transition metal chelation. This hinders with the transition of hydrogen peroxide into hydroxyl radical (Haber-Weiss reaction) (24). Hydroxyl radical is principally responsible for lipid peroxidation, which interferes the normal function of cell membranes: motility and permeability. It has been given that metal- chelation by flavonoids preclude lipid peroxidation by prohibiting the approach of the metal ions toward fatty acids in phospholipids either in natural or in synthetic membranes.

In vitro condition

Quercetin salvages oxygen radicals (13,14), inhibits xanthine oxidase (15), and avoids lipid peroxidation (16). It subdues oxidation of cholesterol low density lipoproteins (LDL), mainly by shielding vitamin E in LDL or by resynthesizing oxidized vitamin E (17). Quercetin hydroxyanisole (BHA) and butylated hydroxytoluene (BHT), to stabilize fish oils (6,7). Quercetin as such or in combination with others, at low concentration it shows stabilizing effect in pork patties (9), cook- chill chicken (11), beef patties (10), ground fish (23) and fish oil (9). Karastogiannidou (12) surveyed that the antioxidant effect of onion, was equal to that of its measured quercetin content.

In vivo condition

Quercetin by itself, and when paired with ascorbic acid, decreases the incidence of oxidative damage to neurovascular structures in skin, and subdues damage to neurons caused by experimental glutathione depletion (18). Quercetin appears to produce health benefits such as anti-inflammatory, antibacterial, antiviral and antihepatotoxic activity (8) mainly because of its antioxidant property. Fortification of food products with natural antioxidants (10–12) with co- occurrence of other flavonoids from fruit and vegetables in the diet, may contribute to the overall protective activity of such antioxidants in the body.

2. Anti-inflammatory activity

Quercetin not only acts as an antioxidant but also possesses anti- inflammatory action. The principle mechanism behind its anti-inflammatory action is that they inhibit enzymes, such as phospholipase A2 and lipoxygenase that produce arachidonic acid. Arachidonic acid, which is the main fatty acid found in many cell membranes form leukotrienes by the action of these enzymes. These leukotrienes are responsible for several allergic inflammations. Quercetin thus interferes with the formation of leukotrienes from arachidonic acid by inhibiting the action of these enzymes.

Quercetin possesses antihistamine property. The immune cells such as basophils and mast cells contain histamines and other allergic chemical mediators. When allergens encounter the blood, these immune cells bring forth a number of histamines that add up the reaction (31). Since quercetin has affinity to these immune cells, the release of IgE-mediated mediators (histamines) from these cells is inhibited (31,32). A recent research showed quercetin inhibited IgG- mediated histamine and SRS-A (peptido- leukotriene) release from the lung fragments of actively sensitized guinea pigs. The expression of pro-inflammatory genes induced by polychlorinated biphenyls (PCBs) is significantly reduced when the endothelial cells are treated with quercetin (25). These flavonoids also down regulated the inflammatory pathways through mechanisms associated with functional caveolae. Quercetin attenuating the release of late pro-inflammatory mediator HMGB1 in animals was established with endotoxemia (26). Quercetin inhibited the release and activities of cytokines of HMGB1 with macrophages *in vitro* (26). It also exerts its anti-inflammatory action in epithelial cells through mechanisms that inhibit cofactor recruitment at the chromatin of pro-inflammatory genes (28).

Quercetin shares a synergistic effect with bromelain which is a proteolytic enzyme that is active at a wide range of pH. This proteolytic enzyme enhances the absorption capacity of quercetin in gastro- intestinal (GI) tract (27,30). A combined effect of quercetin and bromelain effectively suppresses the allergic reactions and the excessive inflammation resulting from bruising and tissue damage. This attribute of quercetin has emphasised the researchers to focus in the intervention of allergic reactions (29).

3. Vitamin C-sparing action

Vitamin C known as ascorbic acid helps in maintaining bones, teeth, collagen and blood vessels (capillaries), enhancing the formation of iron absorption and red blood cells, utilization of carbohydrates and synthesis of fats and proteins, fighting bacterial infections, and interacts with other nutrients. Vitamin C is a natural antihistamine. Ascorbic acid detoxifies the histamines and thus prevents its release. A study has demonstrated that the antihistamine activity is exhibited only when there is a regular intake of ascorbic acid. A single dose of ascorbic acid did not show any antihistamine effect whereas regular intake of it showed a decrease in blood histamine to about 40% (33)

Both vitamin C and Quercetin have mutualistic effect on each other. The antioxidant property of quercetin protected the ascorbic acid from getting oxidized (34). Quercetin with thiol compounds such as glutathione enhances the reduction of dehydroascorbic acid to ascorbic acid (35,36). The promoting effect of ascorbate on quercetin-induced suppression of photohemolysis in human erythrocytes was studied (37) and has also been suggested that ascorbate regenerates quercetin from its oxidized state through the reduction reaction (38). An interesting interaction was observed between ascorbate and quercetin and quercetin was shown to exhibit antiviral activity only when oxidative degradation was inhibited by ascorbate (39).

4. Antiviral activity

Quercetin exerts antiviral activity against various types of viruses including herpes simplex virus type 1, polio virus type 1, reverse transcriptase of HIV and other retroviruses (40). A free hydroxyl group at 3-position plays an important role in the antiviral activity, so quercetin has to be protected from getting oxidized in the environment in which it is present. This protection is provided by ascorbate as it protects quercetin from oxidative degradation (42).

Quercetin interferes with the action of reverse transcriptase, an enzyme that plays an important role in the replication of virus. Quercetin causes a reduction in the infectivity of virus in a concentration- dependent manner, and also reduces the intracellular replication of viruses (40). Thus both antiinfective and antireplicative abilities are exhibited by quercetin. A direct relationship was found to exist between quercetin's antiviral activity and enhancement of cyclic adenosine monophosphate (cAMP), which is a second messenger involved in many biological processes (41). The antiviral activity against herpes virus is enhanced when quercetin is combined with acyclovir, an antiviral drug that is very selective and low in cytotoxicity (43).

Though many studies on the antiviral activity are performed *in vitro*, only few studies have been carried out *in vivo*. Attempts are being made in the synthetic modification of natural compound (quercetin) so as to improve the antiviral activity of quercetin to effectively act against the viruses.

5. Anticancer activity Mechanism

Inhibition of mutant p53 protein

Quercetin (248 µM) was seen to decrease the manifestation of mutant p53 protein to almost undetectable levels in human breast cancer cell lines. Low concentration of quercetin gave less decrement (45). The suppression of expression of p53 was studied and it puts an end to the cells undergoing G2-M phase of the cell cycle. This down regulation was seen to be much lesser extent in cells with an integral p53 gene (46). Mutations of p53 are amidst the most common genetic problems of human cancers (47).

G1 phase check

G1 check point is located at the end of the cell cycle just before the entry into the S phase making the decision of whether the cell should divide, delay division, or enter a resting stage. Quercetin showed that it inhibits human leukemic T-cells in the later stage of G1 phase of the cell cycle. When 70 µM of quercetin was supplied, 64% of cells were in G0/G1 phase when compared with 50% in control cultures (48). G1 check was seen in gastric cancer cells, when treated with quercetin. When 70 µM were administered it was found to lessen DNA replication to 14% of control values, steer to a time hold of cell division. This effect was being reversed upon dismissal of quercetin from the medium. At 70 µM concentration, it showed that quercetin reduced growth of cell cultures to 10% when compared to controls (49).

Inhibition of tyrosine kinase

A family of proteins i.e. tyrosine kinases are located in and around the cell membrane involved in the transduction of growth factor signals to the nucleus. The lymphocyte tyrosine kinase suppression was observed after 16 hours of quercetin administration (44). The same results have been confirmed in both non-malignant cells (50) and rat mammary tumor cells (51) when the experiments were done *in vitro*. Tyrosine kinase when expressed is viewed to be connected with oncogenesis which has the power to pass over the normal regulatory growth control (44,52). Drugs targeting against tyrosine kinase activity (tyrphostins) are visualized as possible antitumor agents without any cytotoxic side-effects seen with formal chemotherapy (53). The first compound used against tyrosine kinase was quercetin and was tested in human phase I trial (44).

Down regulation of heat shock proteins

Quercetin has also shown to inhibit production of heat shock proteins (Hsp) in different malignant cell lines, breast cancer (54), leukemia (55), and colon cancer (56). Heat shock proteins have a complex link with mutant p53, which grant the tumor cells to outflank normal mechanisms of cell cycle check. Hsp also permit for graded cancer cell endurance under various body stresses (low circulation, fever, etc.), and also depended on ‗shorter disease free survival'and drug resistance for chemotherapy mainly seen in breast cancer.

Inhibition of ras protein expression

Quercetin (10 µM) inhibits the expression of the p21-ras oncogene in cultured colon cancer cell lines (59). Alteration in this significant gene normally subverts cellular GTP-ase activity, which has the impression of continuous stimulation of the signal for DNA replication. Mutation of ras proto-oncogenes was found in more than 50% of colon cancers, also in many other tumor types.

6. Hypertension

Hypertension is mostly due to unsuitable humoral control (61) separated by increased oxidative stress, high output of endothelin-1 (ET-1), low nitric oxide (NO) yield and/or bioavailability, and/or over input of the rennin–angiotensin system (RAS). However, these modifications have been related to cardiovascular disease (CVD) (61–67) and there is a direct connectivity between hypertension and risk for cardiac arrhythmia, cardiac hypertrophy, myocardial infarction, and heart failure (60,68).

Mechanisms involved in blood pressure reduction

Various evidences are there to support mechanisms by which quercetin step-down blood pressure (BP) and reduces the severeness of hypertension in animals and humans. For example, quercetin decreases oxidative stress, intervenes with the RAS, and rectifies endothelial or vascular function.

Mechanism in oxidative stress

It has been seen that when quercetin is induced there is notable blood pressure (BP) decrease in hypertensive animals and humans which has assigned a diminution in oxidative stress. Animal studies have shown decrease in BP after quercetin supplementation and also showed betterment in oxidant status, such as decrease in plasma lipid peroxides (70–72) and urinary isoprostanes (70) when compared with controlled

animals. It was speculated that advancement in oxidant condition was the inherent mechanism after improved vascular function discovered in these studies (70–72).

Mechanism in rennin–angiotensin system

The rennin–angiotensin system (RAS) is tangled in regulating BP and fluid loss from the body. Long time overactivation of the RAS brings about hypertension and also negative cardiovascular effects (68). Treatment of the RAS by pharmacological acetyl choline esterase (ACE) inhibitors such as captopril and imidapril decreases circulating angiotensin II, a powerful vasoconstrictor, bringing about low blood pressure and little cardiovascular issues in very risk populations (60,69). Pharmacological inactivators, such as captopril and imidapril, inhibit the ACE molecule by binding a zinc molecule at the active site and bringing down the transition of angiotensin I to angiotensin II (64,76). Quercetin has the ability to bind metal ions, such as zinc (75) and there are grounds that quercetin has the ability to stop ACE activity through this mechanism (77). The possibility of quercetin to bring down BP through ACE attenuation has been tried in animal models. Hackle *et al.* (73) examined the intense outcomes of oral and intravenous (IV) quercetin and captopril by giving medication on the BP mechanism to bradykinin and angiotensin I extract in normotensive Wistar rats.

Mechanism involved in vascular function

Endothelial cell protecting the walls of the arterioles and performs a very significant role in the maintenance of vascular homeostasis, vascular tone, cardiovascular and microvascular health. Endothelial dysfunction is a vital case in the development of disease of CVD and an independent forecaster of cardiovascular consequences (78). It is a normal feature in all kinds of CVD, allowing hypertension (78,79). The endothelium liberates different varieties of vasoactive contents such as nitric oxide (NO) and endothelin-1 (ET-1), which functions, to modulate BP and blood flow (61,63,78,80,81). A mutual feature of endothelial dysfunction is weakened by the bioavailability of the vasodilator NO which affects to a lesser extent in endogenous opposition to circulating vasoconstrictors such as ET-1 (63). NO and ET-1 seem to have a reciprocal regulation; as NO bioavailability reduces, there is enhanced synthesis of ET-1 (63). Endothelial dysfunction can be reversible and can also decrease the risk for CVD, as such by exercise and pharmaceuticals, and can also amend endothelial function (63).

Studies done with animal models have shown that quercetin attenuation resulted in reductions in BP which were tended by grading in endothelial function and biomarkers of endothelial function (70– 72,75). For example, Duarte *et al.* (70) studied that quercetin decreased BP in spontaneously hypertensive rat (SHR), and cleared endothelium-dependent vasorelaxation of isolated aorta. In another study, Duarte *et al.* (72) gave the NO synthase (NOS) inhibitor, L-NAME, in the drinking water of rats making them to stimulate hypertension. When rats were treated with quercetin, they showed less intense L-NAME-induced hypertension and endothelium-relying dysfunction of arteries. Yamamoto *et al.* (71) used a dietary model of hypertension and gave report that systemic hypertension, decreased aortic NOS activity, and reduced urinary NO metabolites were ameliorated in rats which at the same time consumed quercetin. When assembled, the studies indicated that quercetin improved endothelial function by increasing NO bioavailability, and these results are responsible for the reduction of BP.

Mechanism involved in vascular smooth muscle

Positive evidences prove that quercetin can decrease BP through chemical reactions not dependent of the endothelium. For example, quercetin has shown to elicit vasorelaxation in endothelial balded vessels, proposed that quercetin can work on the vascular smooth muscle (VSM) directly (74,75,82). The other flavonoids, metabolites of quercetin can also act on VSM. Perez-Vizcaino *et al.* (74) reported that quercetin and isorhamnetin (quercetin metabolite) stimulate vasorelaxation of rat aortic rings regardless of whether the endothelial layer of vessels was intact or denuded.

7. Principle uses of quercetin

Quercetin due to its multiple bioactivities has been used in the treatment of various allergic and inflammatory reactions like asthma, hay fever, in the prevention of cancer, prostatitis, etc.

The antioxidant property of quercetin has contributed to treatment of gout. Gout is an acute anti-inflammatory arthritis characterized by red, tender, swollen joint (82). The most common site is the metatarsal-phalangeal joint (94). Gout is caused by the deposition of uric acid which crystallizes in bones and tendons. Xanthine oxidase, an enzyme is responsible for the gout formation. This enzyme oxidizes hypoxanthine to xanthine and further to uric acid. Quercetin has the ability to inhibit the action of xanthine oxidase thereby reducing the formation of gout. Thus quercetin plays a great role in the treatment of gout.

The antioxidant activity of quercetin also contributes to anticancer property. As they scavenge free radicals that can cause cancer in cells, quercetin is known to possess anticancer property. The anticancer activity helps in regulating cell cycle and inhibits tyrosine kinase enzyme. Early research study suggested that quercetin causes cancer in animals (86) but the recent study proved that they are safe and contribute anticancer property (87–90). Quercetin delayed tumor growth and inhibited the colonization of melanoma cells of lungs in an animal study (91).

An *in vitro* study demonstrated the protective effect of quercetin against ultraviolet A (UVA)-induced oxidative stress due to the production of glutathione and catalase enzymes by quercetin (92).

Quercetin due to its anti- inflammatory activity helps in the treatment of asthma, hay fever, etc. Asthma is caused by leukotrienes that cause the actual symptoms of shortness of breath, chest tightness, wheezing, coughing, etc. Quercetin interferes with the formation of these leukotrienes by inhibiting the action of two enzymes (phospholipase A2 and lipoxygenase), thereby helping in the prevention of asthma. Quercetin inhibits the inflammatory responses by hyaluronidase. Hyaluronidase is an enzyme that catalyses the hydrolysis of hyaluronic acid which leads to collagen destruction and increased permeability of tissues to fluids. The anti-inflammatory property of quercetin helps in clearance of nasal passages, relieves sinus pressure, reduces the symptoms of cold, etc.

With vitamin C, quercetin helps in strengthening immune system and blood vessels, prevents the ruptures of capillaries and connective tissues, provides relief for aches and pains. Quercetin also helps in chronic venous insufficiency (83). Intake of beverages such as coffee and tea by individuals has shown less risk of myocardial infarction, ischemic heart disease (84,85).

Other benefits of quercetin are in the treatment of prostatitis, diabetic cataracts, prevention of coronary heart diseases, etc. Prostatitis is the inflammation of the prostate gland occurring in men, where oxidative stress and inflammation occur in the prostrate gland. On oxidative stress, the immune cells produce beta-endorphins at the site of injury so as to modulate the pain. Quercetin helps in curing prostatitis by decreasing the inflammation and oxidative stress due to their anti-inflammatory and antioxidant activities and increasing the concentrations of these beta-endorphins.

Quercetin is a strong inhibitor of aldose reductase enzyme, which plays an important role in diabetic cataract. Aldose reductase is very important in the eyes as they convert glucose to sorbitol but in galactosemic and diabetic individuals, these enzymes initiate the process of cataract (93). Quercetin is converted to quercetrin by intestinal flora. These quercetrin significantly reduces the accumulation of sorbitol in the lens thereby potentially delaying the cataract development. Thus quercetin plays an important role in the treatment of various diseases due to its bioactivities.

8. Safety issues of Quercetin

It is considered that quercetin is antimutagenic *in vivo* and long-term studies have provided that quercetin is noncarcinogenic (100). Negative side effects have been studied for a short term (<3 months), with high intakes of quercetin. The following allergic reactions such as nausea, headache, and tingling of the extremities with chronic quercetin supplementation of 1,000 mg/day were studied (96–98,100). The studies done so far with humans, and the research in progress, have not given any unfavourable side effects with a continuous dose of 730 mg/day for 28 days, or with an acute dose of 1,095 mg quercetin aglycone in humans (97). Quercetin is a good inhibitor of CYP3A4, which is an enzyme that has the capability to suppress many normally prescribed drugs by the doctor; hence, quercetin should not be administered with drugs that elide on this enzyme for metabolism. Since many flavonoids have been studied to inhibit platelet aggregation (by

inhibiting thromboxane A2) (95,99), quercetin also has the potential that could increase the risk of bleeding when taken with anticoagulant drugs.

Conclusion

Eventhough quercetin has broad range of activity in different ailments, it has not been fully recommended by doctors for usage as drugs. It holds promise for the treatment of hypertension, cancer, viral diseases, allergic reactions such as hay fever, asthma, respiratory diseases prostatitis, atherosclerosis, cataracts, edema, gout, peptic ulcer, retinopathy, etc and also reduces CVDs such as, cardiac arrhythmia, myocardial infarction etc. With vitamin C, quercetin acts as antiviral and anticancer agents and strengthens the immune system. *In vitro* and *in vivo* research works in animal models have shown multiple activity of quercetin that lower the effect and also the severity in different medical grounds. Though it is known to possess various bioactivities, studies still are in progress with humans. Hence long-term studies examining the safety of quercetin supplementation need to be conducted before recommending this flavonoid as a treatment.

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