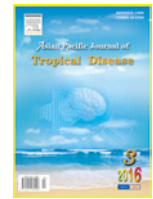




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Quercetin: A wonder bioflavonoid with therapeutic potential in disease management

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ABSTRACT

In the last decade, considerable efforts have been made to develop health promising nutritional supplements. Quercetin is a plant-derived bioflavonoid which is recently gaining scientific interest for its antioxidant free radical scavenging effects and anti-inflammatory properties. This wonder flavanol exhibits therapeutic potential in various ailments like cancer, coronary artery, asthma and alzheimer (neurodegeneration) diseases. Additional clinical uses include treatment of inflammatory conditions like gout, pancreatitis and prostatitis. It has been extensively studied for its gastroprotective effects, anti-obesity action, immune booster, reducing risk of cataract and reduction of diabetic complications. The present review briefly discusses about biological activity, mechanism of action and therapeutic potential of quercetin in prevention and mitigation of diseases.

1. Introduction

With the recent advances in the field of herbal technology products, there has been an increased interest in search of phytochemicals that have health promoting potential. Quercetin is a promising plant based flavonol on which a lot of research-based studies are under investigation by researchers, scientists and nutritionists for its pharmacodynamic and pharmacokinetic properties. Quercetin - the name comes from the Latin - *quercetum*, meaning oak forest, *Quercus* oak. In the words of the German nutrition expert Prof. Stephan C. Bischoff, "Quercetin is a most promising compound for disease prevention and therapy". Quercetin is the aglycone form of a number of flavonoid glycosides, such as rutin and quercitrin, and is found in plants like citrus fruits, onions and buckwheat tea. It forms two glycosides *i.e.* quercitrin and rutin in combination with sugars called as rhamnose and rutinose, respectively. Foods rich in quercetin include cocoa powder, cranberries, lingonberries, kale, celery, broccoli, lettuce, tomatoes (red ripe), ginkgo biloba and carrots[1].

Other names of quercetin are sophoretin, meletin, quercetine, xanthaurine, and quercetol.

2. Chemistry and biosynthesis

Its chemical structure is 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one (Figure 1).

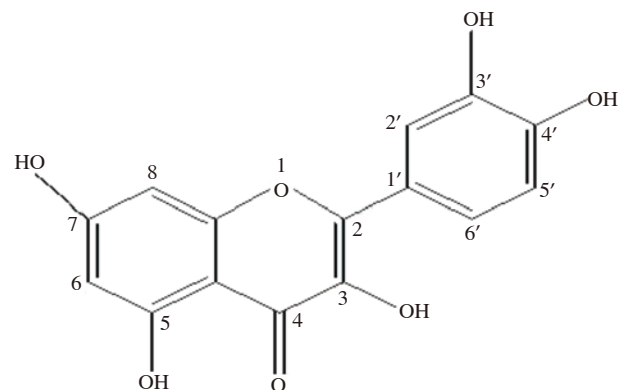


Figure 1. Chemical structure of quercetin.

The steps involved in biosynthesis of quercetin can be summarized in Figure 2. Here, phenylalanine (1) is converted to 4-coumaroyl-CoA (2) in a series of steps known as the general phenylpropanoid pathway by using enzymes phenylalanine

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ammonia lyase, cinnamate-4-hydroxylase, and 4-coumaroyl-CoA ligase. Then 4-coumaroyl-CoA is combined with three molecules of malonyl-CoA (3) by using 7,2'-dihydroxy-4'-methoxyisoflavanol synthase which leads to the formation of tetrahydroxychalcone (4). Now, tetrahydroxychalcone is then converted into naringenin (5) by using chalcone isomerase. Then, by the help of enzyme flavanoid 3'-hydroxylase, naringenin is converted into eriodictyol (6). The formed eriodictyol is then converted into dihydroquercetin (7) with flavanone 3-hydroxylase which is ultimately converted into quercetin by using enzyme, flavanol synthase[2].

absorbed after an oral dose[3]. The main determinant responsible for absorption of quercetin glycoside/conjugates is the nature of the sugar moiety present in it. For example, absorption of quercetin glucoside takes place from the small intestine, while quercetin rutinoside gets absorbed from the colon after removal of the carbohydrate moiety through bacterial enzyme action over it. Flavonoids are poorly absorbed because the sugar moieties present in these naturally occurring glycosides elevate the molecules' hydrophilicity, and no enzyme is able to split the glycosidic bond. However, aglycones (sugar-free flavonoids) can pass very efficiently through the gut wall, but flavonoids are not found in plants in aglycones form or found rarely.

3. Pharmacokinetics

3.1. Absorption

According to a study by Murota *et al.*, only 2% of quercetin gets

3.2. Distribution

After absorption in small intestine, quercetin is transported to the

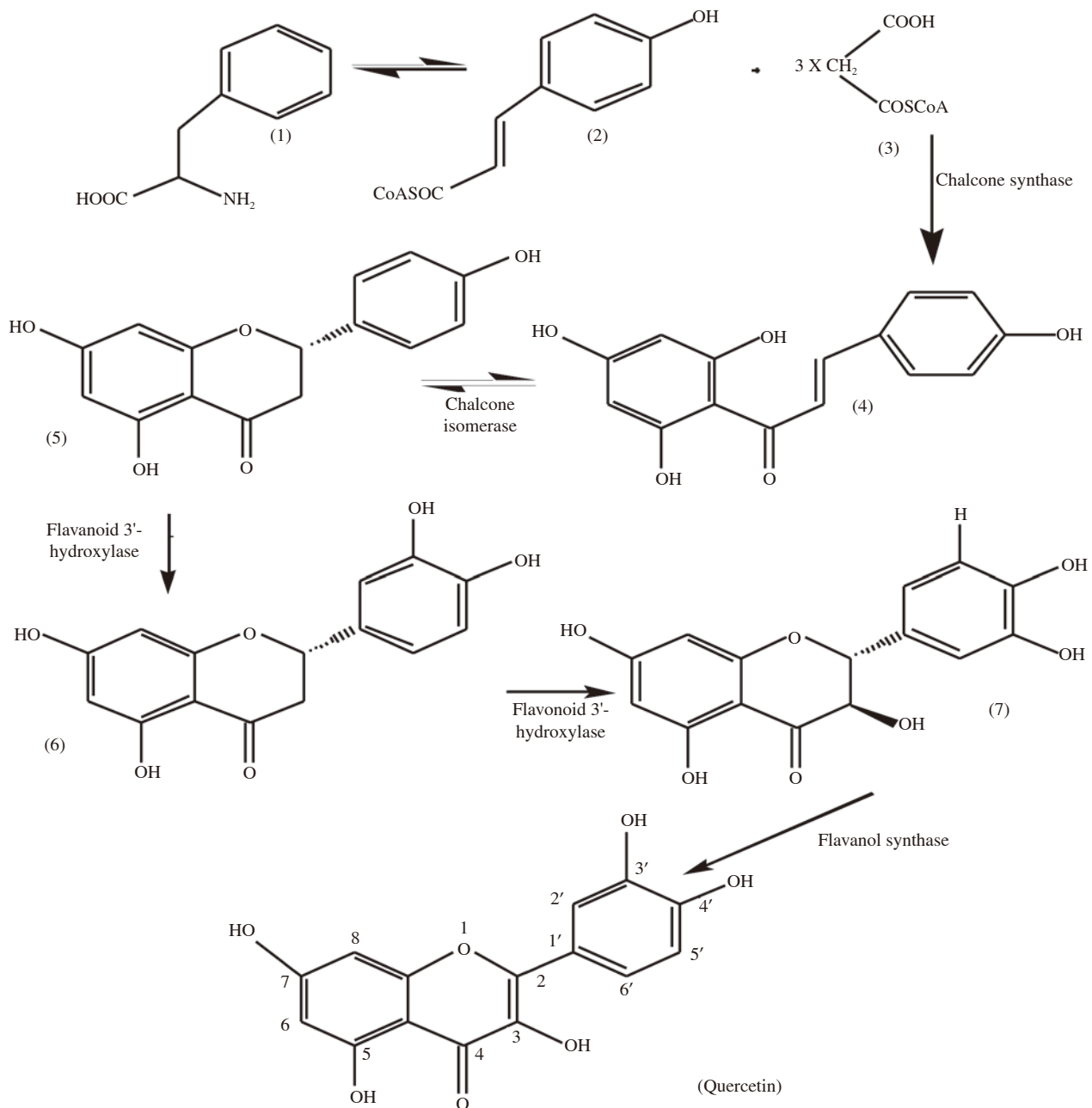


Figure 2. Biosynthesis of quercetin.

(1): Phenylalanine; (2): 4-Coumaroyl-CoA; (3): Malonyl-CoA; (4): Tetrahydroxychalcone; (5): Naringenin; (6): Eriodictyol; (7): Dihydroquercetin.

liver via portal circulation, where it undergoes first pass metabolism. It gets strongly bound to the albumin in plasma. Following ingestion of quercetin, peak plasma level reaches in 0.7–7.0 h.

3.3. Metabolism

Quercetin is reported to be metabolized in the liver and the intestine. Metabolism of absorbed quercetin mainly takes place in liver, while the unabsorbed part of quercetin is metabolized by intestinal micro-organisms in the gut. In intestine, the ring structure of quercetin is cleaved into 3,4-dihydroxyphenylacetic acid by eubacterium ramulus (anaerobic bacterium). Primary metabolism of quercetin occurs in the liver. Biotransformation of ingested quercetin occurs by glucuronidation, hydroxylation, methylation, and sulfonylation. Here, glucuronidation occurs usually during passage across the epithelium as well as in the liver. The enzymes responsible for this metabolic reaction involve uridine diphosphate-glucuronosyltransferases (UGT) such as UGT1A9 (in human liver), and UGT1A1 and UGT1A8 (in intestinal epithelium). In intestinal epithelial cells, quercetin is found to be metabolized into two glucuronides, namely, quercetin-3- and quercetin-7-glucuronides. Quercetin glucuronides are also found to be metabolized further through 2 pathways: first pathway involves methylation of the catechol functional group of both quercetin glucuronides by methyltransferases; second one involves initial hydrolysis of the glucuronide by endogenous beta-glucuronidase enzyme, and then sulfation to quercetin-3-sulfate. Metabolism of quercetin also takes place by process of methylation, sulfonylation, and hydroxylation in the liver. After its metabolism, it is often found as unconjugated quercetin aglycone in blood plasma, even if quercetin glucuronides are thought as the main circulating metabolites in humans[4].

3.4. Excretion

After oral administration, the absorbed [¹⁴C]-quercetin is rapidly excreted into the bile and urine within 48 h as the glucuronide and sulphate conjugates of [¹⁴C]-quercetin, 3'-O-monomethyl quercetin and 4'-O-monomethyl quercetin[5]. The elimination half life of quercetin is approximately 25 h. The elimination of quercetin is significantly delayed after its ingestion with fat-enriched diets.

4. Mechanism of action

A number of quercetin's effects appear by reason of its antioxidant activity which is due to its ability to scavenge free radicals and bind transition metal ions[6]. These properties of quercetin allow it to inhibit lipid peroxidation[7]. Lipid peroxidation is the process by which unsaturated fatty acids are converted to free radicals via the abstraction of hydrogen[8]. The subsequently formed free radicals are oxidized by molecular oxygen and lead to the formation of lipid peroxy radicals. This process is further propagated by the resulting lipid peroxy radicals and hydrogen ions from other unsaturated fatty acid molecules and results in more free radicals formation. Lipid peroxidation can be catalyzed by the presence of transition metal ions present in trace amounts. By scavenging oxygen radicals,

quercetin inhibits xanthine oxidase, and inhibits lipid peroxidation *in vitro*. When the flavonol quercetin (3,5,7,3',4'-pentahydroxyflavone) reacts with a free radical, it donates a proton and becomes a radical itself, but the resulting unpaired electron is delocalized by resonance, making the quercetin radical too low in energy to be reactive. Generally, 3 criteria considered to assess the antioxidant activity of flavonoids *in vitro* include ring (A) with 5,7-dihydroxyl groups, ring (B) with 2 hydroxyl groups (adjacent), and ring (C) with 2,3-double bond, 4-oxo, and 3-hydroxyl group. As quercetin meets all 3 criteria, it indicates stronger antioxidant activity[4].

5. Therapeutic uses

5.1. Anticancer property

In various studies, it has been found that quercetin inhibits the growth of cancer cells including those from colon, breast, prostate, brain, liver, lung, gastric and other tissues[9,10]. The anticancer cellular mechanisms invoked by quercetin include antioxidant property resulting in decreased reactive oxygen species induced DNA damage, suppressed cellular proliferation, and enhanced programmed cell death, inhibition of angiogenic process and cell cycle arrest[11]. Major molecular mechanism of action found to be involved is antiproliferation[12]. Quercetin inhibits melanoma cell growth due to deactivation of STAT3 signaling and shows antitumour activity[13].

5.2. Anti-inflammatory activity

Quercetin has been found to have antioxidant and inhibitory effects on inflammation producing enzymes cyclooxygenase and lipoxygenase and subsequent inhibition of inflammatory mediators including leucotrienes and prostaglandins[14]. Quercetin leads to inhibition of cytokine tumor necrosis factor- α (TNF- α) which is one of the major proinflammatory cytokine involved in the pathogenesis of chronic inflammatory disease[15]. TNF- α regulates the growth, proliferation, differentiation and viability of activated leucocytes. Therefore, quercetin can be widely used as an anti-TNF- α therapy and possess potential anti-inflammatory activity.

5.3. Anti-obesity effect

Quercetin inhibits fat accumulation in maturing human fat cells by blocking the uptake of glucose from the blood. Quercetin is also found to exert anti-adipogenesis activity by activating the adenosine monophosphate-activated protein kinase signal pathway in 3T3-L1 preadipocytes. Also, it triggers apoptosis (programmed destruction) in existing fat cells via modulation of the extracellular signal regulated kinase and c-Jun N-terminal kinase pathways[16,17].

5.4. Coronary heart disease

Intake of anti-oxidant quercetin protects against coronary heart disease caused by oxidized low density lipoprotein. It has also shown antiplatelet aggregating effect via inhibition of thromboxane

A2. Antihypertensive effect produced by quercetin is via reduction of oxidative stress markers either by a direct superoxide anion scavenger effect or inhibition of superoxide generating enzymes[18,19]. Quercetin glucuronide conjugate shows protective effects on smooth muscle vascular disorders leading to progression in arteriosclerosis disease[20].

5.5. Asthma and lung disease

It is used in the treatment of asthma due to its antioxidant property and thereby, scavenges free radicals and other oxidizing agents which are responsible for stimulation of bronchial constriction. Quercetin inhibits release of allergic mediator (immunoglobulin E-mediated) from mast cells and basophils and also inhibits release of immunoglobulin G-mediated histamine and slow-reacting substance of anaphylaxis (peptido-leukotriene) during *in vitro* studies[21]. Besides, it has effect on peptido-leukotriene biosynthesis by acting as 5-lipoxygenase inhibitor.

5.6. Neuroprotective

It has found to possess capability to improve cholinergic function and antioxidant activity, thereby acting as potential candidate for neuroprotective agent against Alzheimer's disease[22]. However, this action is restricted by its poor absorption and difficult to pass blood-brain-barrier[23]. But nasal administration of quercetin liposomes protects against neurodegeneration in hippocampus via increasing the survival neurons and cholinergic neurons density in hippocampus[24].

5.7. Dermatological disorders - photodamaging and psoriasis

Quercetin has shown innovative possibilities in preventing photodamaging effects on skin. In a study conducted on hairless mice, quercetin inhibits UVB irradiation-induced oxidative damage. The UV photodamage leads to increase in myeloperoxidase activity, decrease of endogenous antioxidant glutathione and increase of metalloproteinase activity[25,26]. Quercetin by virtue of its multiple antioxidant mechanisms leads to topical beneficial effects as it significantly inhibits myeloperoxidase activity and increases endogenous antioxidant glutathione depletion. The isolated flavonoid quercetin from the rhizome of *Smilax china* has shown significant antipsoriatic activity[27]. Quercetin shows orthokeratosis, anti-inflammatory and antiproliferative activities and inhibits leucocytes migration. To prove anti-psoriatic potential of flavonoid quercetin, confirmation by human intervention trial is needed.

5.8. Antiaging effects

Proteasome activities are decreased upon replicative senescence, whereas activation of proteasome provides enhanced survival against oxidative stress, lifespan extension and maintenance of the young morphology for a longer period of time in primary fibroblasts of human beings. Quercetin and its derivative, namely, quercetin caprylate have shown proteasome activator properties that influence

cellular lifespan, survival and viability of human fibroblasts[28].

5.9. Diabetic complications

Quercetin has been found to be an inhibitor of the enzyme aldose reductase, which plays a role in converting glucose (sugar) to sorbitol (a sugar alcohol) in the body. People with diabetes develop secondary problems, such as neuropathy, retinopathy, diabetic cataracts, and nephropathy because of sorbitol buildup in the body. Therefore, quercetin may be beneficial in the nutritional management of diabetes[29].

5.10. Other actions

Quercetin also shows anti-gout properties due to its inhibitory action on xanthine oxidase enzyme, which leads to decreased formation of uric acid. Besides this, it has also shown effectiveness in prostatitis, interstitial cystitis, age-related macular degeneration and neuroleptic-induced extrapyramidal side-effects[30,31].

6. Dosing and precautions

Very few clinically proven reports are available regarding quercetin usage in children. However, general dosage recommended for adults is 100–250 mg three times per day[32]. Its usage should be avoided in pregnant, breast feeding women and people with kidney disease.

7. Drug interactions

Quercetin has a pro-oxidant effect and will increase the iron-dependent DNA damage induced by bleomycin. It acts by reducing iron to the ferrous state, which allows bleomycin to complex more readily with oxygen and produce more efficient DNA damage. *In vitro* studies suggest that quercetin may interact with quinolone antibiotics like ciprofloxacin or levofloxacin via binding to the DNA gyrase site in bacteria. Therefore, due to same site of action it can act as a competitive inhibitor to the quinolone antibiotics and thereby may decrease their effectiveness[33,34].

8. Conclusions

In past decade, quercetin has presented opportunities to manage various forms of cancer, lung disease, chronic heart disease, prostate disease *etc.* that may even exceed those afforded by today's pharmaceuticals. Its usage as an adjunct therapy has been corroborated by various *in vitro* and *in vivo* performances. Quercetin has tremendous potential and its beneficial actions are documented in various ailments studied so far. Hence, there is an urgent need of more research based attention and clinical studies to harness complete potential of this flavonoid.

Conflict of interest statement

We declare that we have no conflict of interest.

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