Review Article

A Review on Quercetin: Assessment of the Pharmacological Potentials and Various Formulations Strategies

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ABSTRACT

Quercetin being a bioactive flavanol belonging to class II of BCS (Biopharmaceutical classification) occurs in different fruits and vegetables such as onions, red lettuce etc. It has been investigated by researchers to evaluate its potential to treat various diseases. It possesses anticancer, anti-prostate and anti-inflammatory activities and along with its valuable effects on viral infections, high cholesterol, asthma, kidney transplantation, diabetes, schizophrenia pulmonary and cardiovascular diseases. This article focuses on quercetin utility in treatment of these diseases along with mode of action. However, quercetin bioavailability is low due to its hydrophobicity and its extensive phase-II and phase III metabolism. To combat these issues various strategies have been proposed such as by fabrication of liposomes, microspheres, nanoparticles, micro beads, solid dispersions etc.

Keywords: Quercetin, Pharmacological activities, Formulation approaches, Bioavailability, Solubility.

INTRODUCTION

QUERCETIN

The flavonol quercetin is naturally occurring polyphenol which occurs as secondary plant metabolite in plant kingdom, it is present in form of quercetin glycoside[1]. The quercetin name originates from a Latin word called "Quercetum". It is a yellow colour substance which dissolves in lipids and alcohol but poorly soluble in hot water and insoluble in the hot water[2]. Other names of quercetin are quercetine, sophoretin, xanthaurine, quercetol and meletin[3]. Dietary intake of quercetin is approximately 15mg/day[4]. Quercetin is a kind of aglycone flavonoid glycosides, like quercitrin and rutin that founds in citrus fruit plants, buckwheat tea and onions. Two type of glycosides are formed in combination rutin and quercitrin with sugars called as rutinose and rhamnose respectively[5]. Quercetin is found in ample quantity in nature. It resides in fruits mainly in apples, cranberries, grapes, cherries and in vegetables also such as in peppers, onion, asparagus and in other food items like black or green tea, wine. Composition of quercetin in different food items shows variations. The concentration of quercetin in various food products is shown in figure 1. Onions are the most important source of quercetin contains mainly quercetin-3,4'-diglucoside andquercetin-4'-glucoside whereas apples contain quercetin-3-O-rhamnoside quercetin-3-O-glucoside, quercetin-3-O-rutinoside, quercetin-3-O-galactoside[1].

Quercetin glycosides are found in form of quercetin galactoside, quercetin glucoside and quercetin arabinoside. All these gylcosides are deglycosylated into aglycone quercetin before there absorption in the small intestine quercetin is present in highly hydrophilic glycosylated forms, mainly as β-glycosides.

Figure 1:

Figure 1: Quercetin Concentration in Different Food Sources

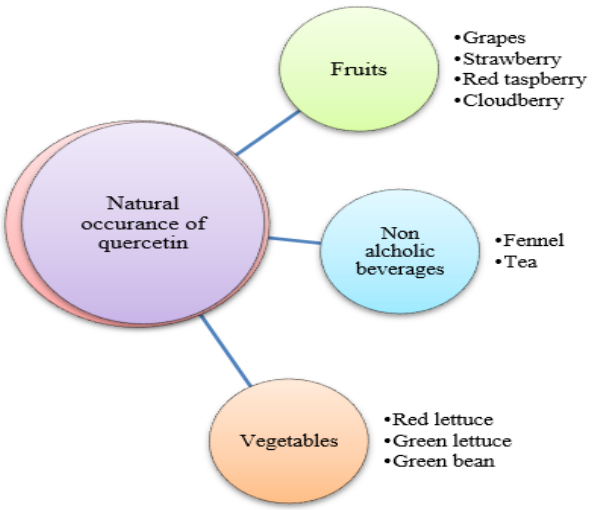

Figure 2: Natural Occurrence of Quercetin

Administration Distribution Metabolism Excretion

Before the absorption of quercetin in gut, all flavonoids are required to be separate from the plant tissues through proper chewing of it in mouth cavity then they are further processed by digestive juices and micro flora present in colon or intestine. In enterocytes, there exists two different routes of absorptions for quercetin as shown in figure 3. Initially, absorption occurs through transporter then by deglycosylation take place within enterocytes via cytosolic glycosidase enzyme. Secondly, deglycosylation is carried out by luminal hydrolase enzyme, followed by transportation of aglycone part in enterocyte through passive diffusion or by other transporters such as sulfation, methylation of OH part and glucuronidation, which occurs only in hepatocytes or enterocytes[4].

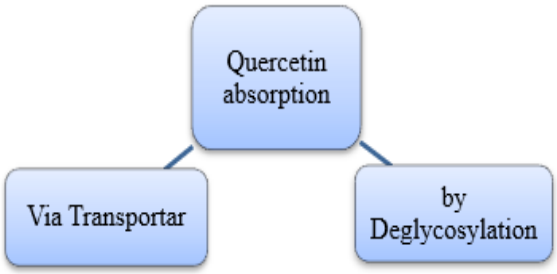

Figure 3: Quercetin Absorption Via Different Mechanisms

Inevitably, thereafter intake of quercetin-based glucosides and aglycones, methylated, sulphated, glucuronidated, and other quercetin derivatives like Quercetin glucuronide sulphate, isorhamnetin-3-glucuronide, methylquercetin diglucuronide and quercetin diglucuronides etc., founds in human plasma. This is supposed that all these derivatives are formed in small intestine and are then further transported through portal vein and is converted into many different metabolites in liver due to phase II and III metabolism. Compounds that doesn't absorbs in small intestine reaches large intestine; there colonic microflora destroys structure. After returning from blood streams they excrete in urine through kidneys. Some amount of quercetin is then converted into low molecular weight based phenolic acids, like 4-dihydroxyphenylpropionic acid, 3-methoxy-4-hydroxyphenylpropionic acid and 3-hydroxyphenylpropionic acid[4].

Structural aspects

The chemical structure of quercetin is 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one.

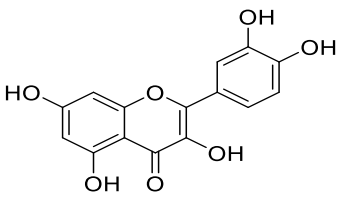

Figure 4: Structure of Quercetin

Activities of Quercetin

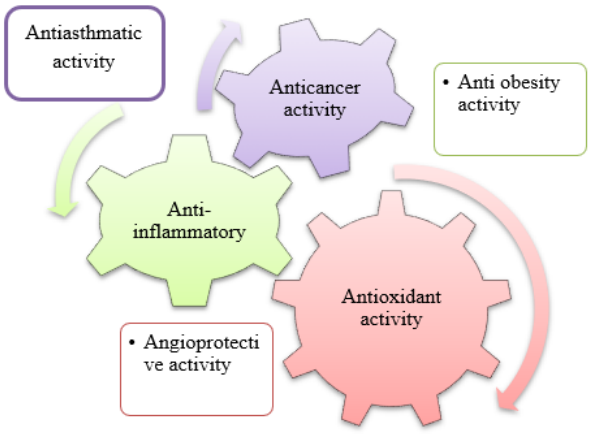

Figure 5: Pharmacological Activities of Quercetin

Utilization of Quercetin in Curing Diseases[3, 5]

Quercetin is used in curing various diseases such as

Cancer

The anticancer activity of quercetin comprises of its antioxidant activity that decreases reactive oxygen species that are responsible for DNA damage. It suppresses cancer cells proliferation, enhances carcinogenic cell death and inhibits angiogenic procedure and arrest cell cycle. Majorly antiproliferation activity of quercetin results in its anticancer activity. It restricts melanoma cell growth because of deactivation of STAT3 signaling. Various types of cancers are cured by quercetin such as liver, colon, breast, prostate, brain, lung, gastric cancers.

Inflammation

Antioxidant and inhibitory effects of quercetin are responsible for its anti- inflammation activity. It produces inhibitory action on cyclooxygenase and lipoxygenase enzyme and ultimately inhibits mediators of inflammation such as prostaglandins and leukotrienes. It also inhibits cytokine tumor necrosis factor-α which regulates growth, proliferation and differentiation of leucocytes.

Obesity

Quercetin restricts accumulation of fat in mature human adipose cells by blocking uptake of glucose from blood. Quercetin also activates the adenosine monophosphate-activated protein kinase signal pathway in the 3T3-L1 pre adipocytes and initiates apoptosis in preexisting fat cells through modulation of signal regulated kinase extracellularly and c-Jun N-terminal kinase pathways

Coronary Heart Disease (CHF)

Intake of small quantity of quercetin protects from coronary heart disease which is caused due to oxidized low-density lipoproteins. It also shows antiplatelet effect via inhibition of thromboxane A2. Antihypertensive effect is due to reduction of oxidative stress by inhibition of

superoxide generating enzymes or direct superoxide anion scavenger effect. A quercetin conjugate mainly glucuronide tends to show protective effect on smooth muscles.

Diabetes

Quercetin inhibits aldose reductase enzyme, which converts glucose to sorbitol. Diabetes patient develops secondary diseases also, such as diabetic cataracts, neuropathy, retinopathy and nephropathy as sorbitol develops in body.

Asthma and Lung Disease

It inhibits the release of all allergic mediators from basophils and mast cells, inhibits release histamine and peptido-leukotriene. Besides, it also has effects on biosynthesis of leukotriene by acting as inhibitor of 5-lipoxygenase.

Neuroprotective

It improves cholinergic functions and antioxidant activity. It acts as ultimate neuroprotective agent for Alzheimer's disease.

Dermatological Disorders - Photodamaging and Psoriasis

It prevents photodamaging effects on skin and inhibits myeloperoxidase activity and increases endogenous glutathione depletion. The flavonoid quercetin extracted from rhizome of Smilax china shows antipsoriatic activity.

Antiaging Effects

Decrease of proteasome activity occurs on 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.

Allergy

Quercetin inhibits cyclin-dependent kinases and histamine, certain malignant cells, inhibitors of mast cell secretions, causing decrease in IL-6, MCP-1 and tryptase and histidine decarboxylase down-regulation.

Angioprotective Activity

Quercetin angioprotective properties are mediated by its proteolysis effect on proteasomes.

Exercise Performance

Quercetin is found to be ergogenic substance. It has outstanding effects on oxidative stress, post exercise inflammation, reduction of illness rates immune function, endurance performance, after exercise. Still for athletes effects are not affirmed.

Gastroprotection

Quercetin possess gastro protective activity, still protective activity of quercetin injury against gastric ulcers remains unknown. When GES-1cells were treated with quercetin and then treated with H2O2 following changes were observed: a) there was decrease in cell viability due to H2O2.

b) Decrease in Ca2+ influx and intracellular reactive oxygen species.
c) Under oxidative stress there is upregulation of peroxisome proliferator-activated receptor-γ coactivator (PGC-1α) expression
d) Declined cell apoptosis
Following parameters shows that quercetin protects gastrointestinal cell from death.

Mood Disorders

It shows antidepressant and anxiolytic-like effects. The antidepressant effect is due to inhibitory action on receptor called NMDA and formation of nitric oxide. Quercetin also protects against behaviour changes caused due to withdrawal of alcohol.

Dietary Supplement

Quercetin is utilized as dietary supplement with recommended dose of 200–1200 mg, also used as nutraceutical in concentration range of 10–125 mg.

Potential Drug Interactions

1. Quercetin enhances bioavailability of various drugs such as tamoxifen[6], diltiazem[7], Paclitaxel[8]. irinotecan, etoposide, doxorubicin, digoxin, verapamil, valsartan, ranolazine, paracetamol[1].
2. Quercetin bioavailability decreases with intake of following drugs such as simvastatin and cyclosporine[1].
3. There is no significant changes of drug bioavailability were observed for nifedipine, rosiglitazone, saquinavir, digoxin, warfarin, cefprozil. Reduced bioavailability was reported for midazolam and talinolol[1].
4. An increased bioavailability was observed for cyclosporine, pravastatin and fexofenadine.
5. Quercetin shows pro-oxidant effect and it also increases iron dependent damage to DNA by induction with bleomycin.
6. Quercetin also interacts with quinolone based antibiotics like levofloxacin and ciprofloxacin by binding with site of DNA gyrase[3].

Solubility and Bioavailability Crises

Quercetin is a class IV-based compound in accordance to BCS (Biopharmaceutical Classification System). It exhibits poor aqueous solubility and poor oral absorption even when ingested in large amount. Poor bioavailability also curtails its benefit potential to health of human. This limitation is due to its crystallinity and poor solubility ranging from 2.15 to 7.7 g/mL at 25◦C in secretion of gut,

as well as due to luminal efflux by epithelial cells of gut, extensive phase II and phase III metabolism. Improved solubility increases bioavailability by enhancing amount of drug for absorption and saturates metabolic enzymes of Phase-III and Phase-II effect results in increased net influx in circulation.

Therefore, Improvement of pharmacokinetic profile of quercetin flavonoids is only a way to provide potential drugs to market. Various strategies are utilized to increase the solubility of quercetin have been challenged to be beneficial in enhancing solubility and bioavailability.

Recent Formulation Approaches

Array of methodologies have been developed in order to improve bioavailability of quercetin including complexation, solid dispersions, formation of nanoparticles and microparticles, self-emulsifying drug delivery systems, liposomes, micelles[9], polymeric nanocapsules[10], microparticulates[11], nanosponge[12], phytosomes complexation with phosphatidylcholine, phospholipids, nanoemulsion, proniosomes and niosomes etc

Table 1: Description of Various Formulation Approaches

S.no	Formulation approach	Objectives	Method of preparation (s)	Author(s)	Reference(s)
1.	Core-sheath nanofibers	Development for structural nanocomposite of multiple components	Coaxial electro-spinning	Li *et al* (2013)	13
2.	Solid dispersions	Enhancement of solubility of quercetin	Double casting	Otto *et al* (2013)	14
3.	Tablets	Enhancement of oral bioavailability and optimization	Direct compression	Caddeo *et al* (2014)	15
4.	Liposomes	Quercetin liposomal effect of microwave ablation on hepatic parenchyma destruction	Rotary evaporation	Xuhua *et al* (2017)	16
5.	Magneto-liposomes	Investigation of interaction between quercetin and asolectin-based magnetoliposomes	Modified reverse-phase evaporation	Cruz *et al* (2018)	17
6.	Nanoparticles	Protective effect of nanoparticles of quercetin against tartrazine	Ionic cross-linking	Eman *et al* (2018)	18
7	Casein nanoparticles	Preparation and optimization of nanoparticles loaded with quercetin and casein	Coacervation	Peñalva R *et al* (2019)	19
8.	Liposome-chitosan hydrogel bead delivery system	Development of linseed oil and quercetin co-loaded liposomes-chitosan hydrogel beads to enhance their stability and solubility	Ethanol injection method	Huang J *et al* (2019)	20
9.	Quercetin-loaded β-lactoglobulin	Investigating the preparation, characterization, and application of β-Lactoglobulin	Modified anti-solvent method	Chavoshpour-N Z *et al* (2019)	21
10.	Microparticles	Characterization and release kinetics	Solution casting method	Farrag Y *et al* (2019)	22
11	Nanoparticles	Self-assembly, functionality, and *in-vitro* properties of quercetin loaded nanoparticles based on shellac-almond gum biological macromolecules	Anti-solvent method	Sedaghat Doost A *et al* (2019)	23
12	Nanoparticles	Nanoparticles were fabricated through one pot synthesis strategy with Fe3+, quercetin and polyvinyl pyrrolidone	Freeze-drying	S H. Tang *et al* (2019)	24

CONCLUSION

The potential of quercetin in combating diverse disease states have been explained briefly along with mechanism of action concerned with it. The bioactive founds abundantly in nature, the various sources of quercetin extraction are also elaborated. The hydrophobicity and phase II and phase III metabolism of quercetin are major problems to be concerned. To overcome these issues various strategies are enrolled such as fabrication of prodrug technology, liposomes, phytosomes, nanoparticles, solid dispersions etc. these are the novel approaches utilized in improving the functioning of quercetin.

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