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An Update of Various Pharmacological Actions of Quercetin

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Abstract: Quercetin is a potential dietary flavonoid which is generally found in leafy vegetables, apple, onion, tea and wine etc. It is present in much concentration in capers. It lacks aqueous solubility and also having very poor oral bioavailability. It is very challenging aspect to enhance the solubility and oral bioavailability by using many kinds of delivery systems such as nanosuspension, nanoparticles, microparticles, liposomes and emulsions etc. Absorption and metabolism of quercetin is held in the body with the help of specific enzymes and various molecular mechanisms. Quercetin also having many therapeutic applications such as antioxidant activity, aging, allergy, anti-inflammatory, mood disorders, asthma, exercise performance, anti-obesity, arthritis and prevention of cardiovascular disease. The current review focuses on the various pharmacological actions of quercetin.

Keywords: Quercetin, Bioavailability, Nanosuspension, liposomes, Antioxidant, Anti-inflammatory and Anti-obesity.

Introduction:

Quercetin is an essential dietary flavonoid which widely obtained from onion, leafy vegetables, tomato, lettuce, caper and black chokeberry. Quercetin is found in the bound form with ethers, phenolic acids and etc. [1]Quercetin has interested enhancing the attention due to its anti-oxidant, anti-obesity, anti-inflammatory and anti-carcinogenic effects. Now, Quercetin and its derivatives have been recorded to have solid potential in the medication of

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

cancer. Moreover, Quercetin and its derivatives have come into target of application as nutraceutical component in pharmaceutical and food companies.[2]

Quercetin lacks aqueous solubility, oral bioavailability, and chemical instability, which may decreased its adequacy when utilized in pharmaceutical and nourishment industries. [3] It is lipophilic in nature and it is soluble in acetonitrile and moderately soluble on ethanol and better soluble in dimethyl sulfoxide but it is poorly soluble in water. [4] Many kind of delivery system like nanoparticles, microparticles, liposomes and emulsion have been appeared to fundamentally improve the medicinal potency of many pharmaceutical and nutraceuticals by enhancing their oral bioavailability. Furthermore, thermal and light degradation of bioactive compound and stability is enhanced by these types of delivery system. [5]

Chemical structure of Quercetin:

Quercetin has distinctive flavonoid structures which contain five hydroxyl groups and it is generally obtained in glycoside form, different kinds of sugar moieties take place in the structure by replacing hydroxyl group. Quercetin-O-glycoside is the major group and others are common derivatives of Quercetin. Quercetin and all derivatives lack aqueous solubility; also all derivatives are yellow in color in the form of powder and crystal.[2]

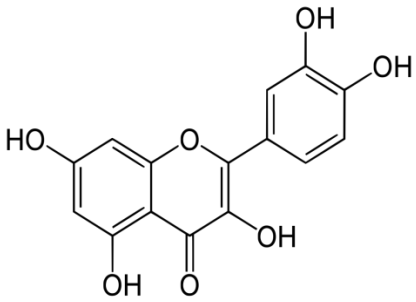


Figure 1: Structure of Quercetin

Properties of Quercetin: [6]

Physical description	Yellow colour powder and crystal
Molecular weight	302.2357g/mol
Molecular formula	$C_{15}H_{10}O_7$
Density	1.799g/cm^2

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

Colour	Yellow
Melting point	316.5℃
Boiling point	Sublimes
Solubility	Less soluble in aqueous , generally dissolve in acetonitrile, ethanol, methanol, ether, acetic acid
Vapour pressure	2.82×10^{-14}
Decomposition	It radiates irritating fumes and acrid smoke by decomposition through heat.
Spectral properties	Maximum absorption: 373nm

Table 1: General properties of Quercetin

Dietary Sources of Quercetin:

Many food plants and their consumable portions like various fruits, leafy vegetables, spices and herbs, bulbs and tubers also tea and wine consumes quercetin in the form of favonols. Generally, quercetin type favonols contain quercetin glycosides which linked with sugar moieties and these are present in more quantity in dietary products.[7]

Dietary source	**Quercetin content (mg/g) edible part**
Capers	233.84
Peppers	50.73
Blueberries	7.67
Onions	39.21
Lettuce	7.62
Apples	3.85
Tea	2.46
Cherries	2.23
Broccoli	3.24
Asparagus	15.13
Tomato	4.09
Wine	1.02

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

Table 2: Quercetin amount in selected dietary sources

Quercetin absorption and biotransformation:

The in-vivo absorption, biodistribution, biotransformation and oral bioavailability have been reported in animal and human models. In mouth, soluble quercetin-protein binary aggregates are formed during the interaction of salivary protein with quercetin which is released from the food. [8]

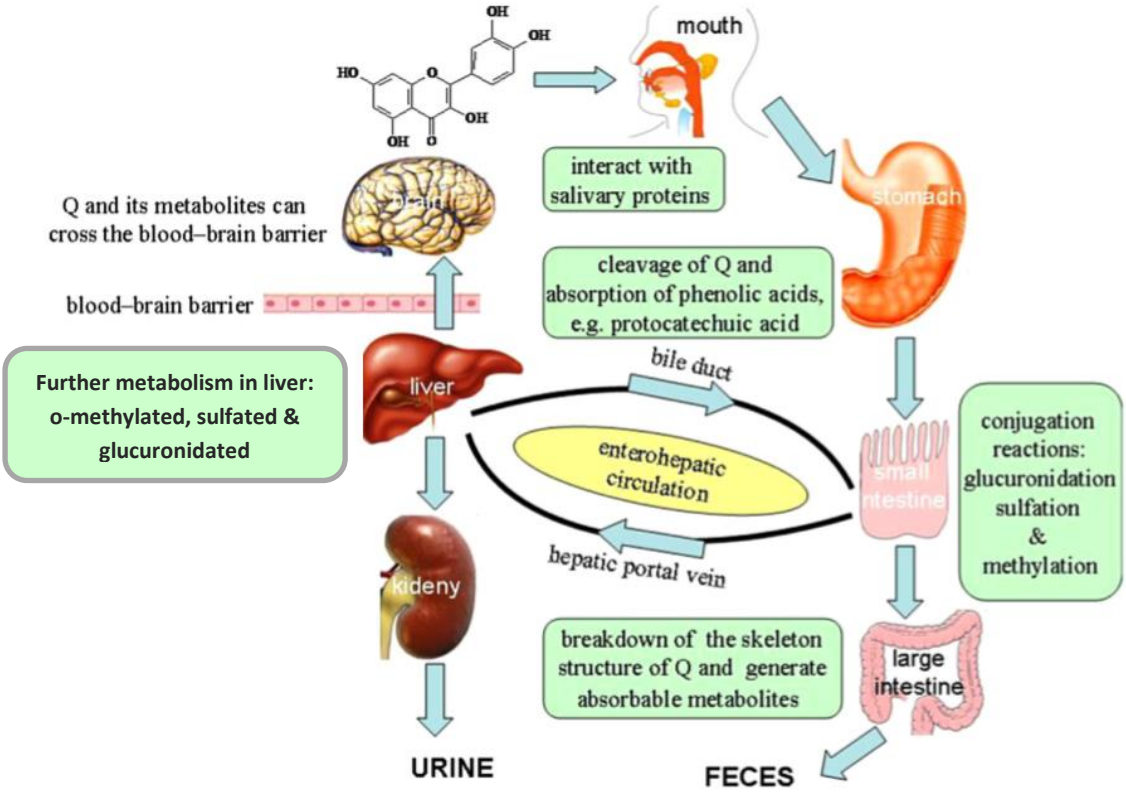


Figure 2: Absorption and metabolism of quercetin, Q represents quercetin.[2]

In stomach, quercetin is exposed into the lower pH conditions of stomach; phenolic acids are produced by binary ring fission which means skeletal structure of quercetin is breakdown. [9]

In small intestine, there is an extensive glucuronidation and O-methylation of Quercetin by the activity of uridine diphosphate glucuronosyl-transferases and catechol-O-methyltransferase respectively.[10] Furthermore, Quercetin and its derivatives are delivered to liver through hepatic portal vein and again metabolized in liver by O-methylation, glucuronidation and sulfation. The derivatives of quercetin and active quercetin transported to liver through portal vein of liver.[11]

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

In large intestine, when colonic bacteria disassimilate the quercetin and its derivatives; then absorption is take place in large intestine. *Clostridium orbiscindens* performs essential role in the braking of quercetin C-ring. [12]

Quercetin bioavailability:

Bioavailability is defined as that the amount and extent of drug is circulate in systemic circulation in unbound form after the oral route of administration.[6] In pharmacokinetic, it is founded. Absolute bioavailability is progressively defined, whereas relative bioavailability is modest, but not much accurate. [13]In the earliest research, after the administration of single dose of quercetin, it showed very lesser oral bioavailability; [14]successively, in humans, absolute bioavailability of free quercetin was estimated as 44.8% , estimated the radioactivity of plasma before administered the radiolabeled quercetin aglycone dissolved in ethanol. [15] Additionally, , if intake of quercetin in food is less than 6-18 mg/ day and sufficient plasma response can be create by administered more than 50 mg quercetin aglycone and its derivatives.[16-18] however, to determine the potential therapeutic use of the quercetin molecule, quercetin organ distribution and half-life gives useful information.[19, 20] Nowadays, researches conducted on humans and animals have progressive broad understanding about quercetin bioavailability.

Quercetin biodistribution:

Biodistribution study is defined as that in which determines the drug content in vital organs. After the oral administration of Quercetin, remove the major organ like liver, kidney, brain heart and spleen at distinct time points and after all process of homogenization, find the concentration of quercetin in these organs with the help of RP-HPLC. The major content of QT in the kidney, brain, liver, spleen and heart were determined 43.67±2.28, 22.91±3.35, 21.44±3.97, 19.44±1.35 and 18.88±2.09 μg/mL respectively. But, with the help of different delivery systems like nanoparticles, nanosuspension, solid-lipid nanoparticles, nanocrystals etc; concentration in different organ can be increased. [21]

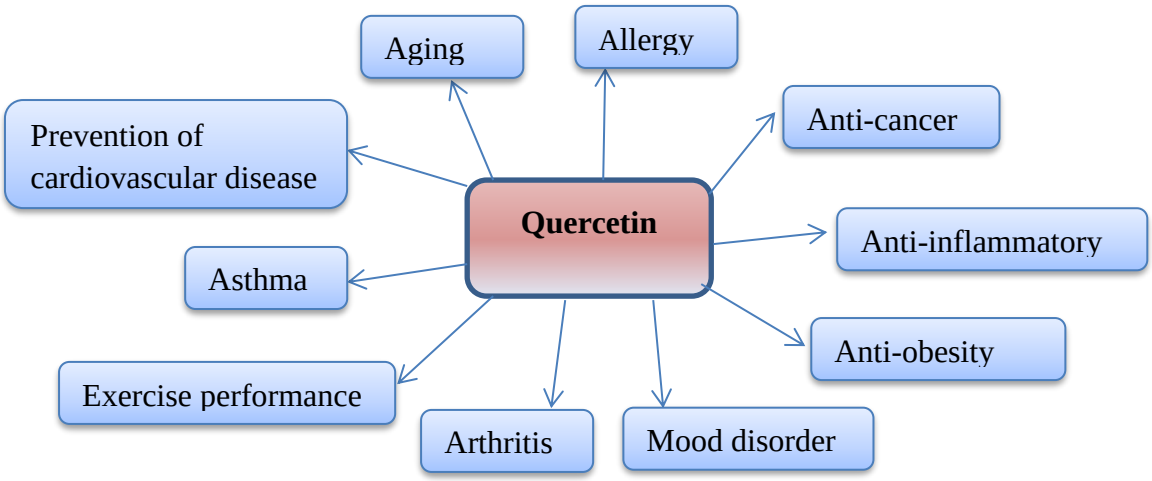
Tissue	C_{max} (μg/mL)	AUC_{total}(μg.h/mL)
Kidney	43.67±2.28	603.66±35.26
Brain	22.91±3.35	201.76±43.63
Liver	21.44±3.97	248.91±11.36

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

Spleen	19.44±1.35	284.09±27.66
Heart	18.88±2.09	124.91±60.40

Table 3: Pharmacokinetic parameters of organ distribution of Quercetin[21]

Therapeutic applications of quercetin:



A. Aging: Natural antioxidants prevent the natural activities which are responsible for ageing. In this context vitamin E[22], kinetin[23], carnosine[24] and garlic[25] are only few examples of natural sources that have been shown a noticeable pro-longevity effect on human primary cultures. Due to the antioxidant property of quercetin and relationship among oxidative stress and maturing examine the quercetin role and also established the effect of quercetin on viability, survival and life cycle of primary human fibroblast; moreover, when senescent fibroblasts were grown in the presence of quercetin, a recovering effect was observed.[26]

B. Allergy: Quercetin acts same as histamine to inhibits the in-vitro growth of certain tumor cells and also shows unique anti-cancer properties, moreover quercetin is a natural component that blocks elements involved in allergical reactions and is also able to act as an inhibitor of mast cell secretion, causing a reduce in the discharge of tryptase, MCP-1 and IL-6 and the down-regulation of histidine decarboxylase (HDC) mRNA from few mast cell lines.[27] As other flavonoids polyphenolic compounds that exert many anti-inflammatory and anti-microbial affects, and exhibit an anti-allergic action, quercetin has been recently shown as a potential drug against allergy.[28]

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

C. **Anti-cancer:** Many flavonoids which show anti-cancer activity and quercetin also have been reported to have the pro-apoptotic activity in tumor cells. However, although mitochondria seem to be focused by quercetin inducing apoptosis and the cancer cell death in vitro until nowadays a reliable quercetin intracellular target has not yet been found; of course, the challenge is to identify an eligible target in order to better define possible natural compounds to be added in food extracts or pharmaceuticals.[29] Positively, the antioxidant activity as well as the kinase and cell cycle inhibition, and the induced apoptosis are all essential for the anti-cancer properties shown by quercetin.[30] Thus, to partly explain the molecular effect of quercetin on malignancy cells, among the different substrates suspected to be activated by quercetin a study reports the ability of quercetin to inhibit some protein kinases involved in releasing the cell growth in cancer cells.[31] It has been proven that the most effective quercetin action is on brain, blood, uterine, lung and salivary gland cancer as good as upon melanoma with a cytotoxic activity much higher in the more destructive cells than in the slow growing cells suggesting that the most harmful cells are the ones mainly focused.[32]

D. **Anti-inflammatory:** Quercetin exhibits a shows anti-inflammatory activity. Some researchers suggest that quercetin could suppress lipopolysaccharide (LPS)-induced cytokine production in different cells. For example, quercetin can inhibit LPS induced tumor necrosis factor production in macrophages [33] and LPS-induced interleukin (IL)-8 productions in lung cells.[34] Furthermore, reported that quercetin can inhibit LPS-induced mRNA levels of cytokines in colloid cells, such as tumor necrosis factor (TNF)- α and IL-1α. They also found that the apoptosis of neuronal cell was decreased in a microglial-neuronal coculture by the addition of quercetin. The anti-inflammatory effect of quercetin is associated with its antioxidative and free radical scavenging properties in some reports.[35] Reactive oxygen species not only exist in the oxidation process, but a real so involved in inflammatory response by activation of transfer factors such as nuclear factor-k-gene binding.[36] Moreover, NF-kB could induce the production of TNF-α cytokines. Therefore, eliminating reactive oxygen species could prevent oxidation and inhibit inflammation simultaneously. Furthermore, interpreted that quercetin could inhibit the gene expression of TNF-α by adjustment of NF-kB in peripheral blood mononuclear cells.[37]

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

E. Anti-obesity: Lipid metabolism related to hepatic gene expression which is regulated by quercetin.[38] In specific, supplementation of quercetin in mice expressively reduced the high-fat diet (HFD) which induced obesity and also reduce the body weight. The enhancement in triglyceride, thiobarbituric acid-relative substance (TBRAS) including serum lipids and cholesterol by high-fat diet can be reduced by quercetin. Consistent with the reduced liver weight and white adipose tissue weight, hepatic lipid accumulation and the size of lipid droplets, pads in the epididymal fat were also reduced by quercetin supplementation.[6]

F. Mood disorder: Quercetin helps to protect against changes in behavior caused by alcohol withdrawal.[39] Several possible mechanisms might explain the ability of quercetin to improve mood. Thus, in vitro and in vivo evidences indicate that quercetin can inhibit monoamine oxidase A, [40]whereas in vivo experiments indicate that quercetin can decrease the levels of the stress-induced brain corticotrophin releasing factor (CRF) which is associated to anxiety and depression.[41] In addition, quercetin-treatment also reduces the stress-induced increases of both the plasma corticosterone and the adrenocorticotropic hormone.[42]

G. Arthritis: When quercetin combined with other nutrients then it might reduce symptoms of osteoarthritis (OA), but at the same time it does not appear to be beneficial in rheumatoid arthritis (RA). In fact, as a study report,[43] twenty patients with rheumatoid arthritis daily received three capsules of quercetin (166 mg/capsule) plus vitamin C (133 mg/capsule), α-lipoic acid (300 mg/capsule), or placebo for four weeks allowing a two-week washout period before the next supplementation. After this period the serum concentrations of pro-inflammatory cytokines or C-reactive protein (CRP) did not show considerable differences and disease scores severity did not differ among treatment periods. When glucosamine, chondroitin, and quercetin glucoside were given for three months to 46 persons with OA and 22 persons with RA, appreciable ameliorations in daily activities (walking and climbing up and down stairs), pain symptoms, visual analogue scale, and synovial fluid properties were observed in OA subjects; conversely, no beneficial effects were noticed in RA subjects.[44]

H. Exercise performance: Besides studies that have investigated whether quercetin supplementation can prevent post-exercise immune system changes and sensitivity to infections, other studies have sought to determine whether quercetin shows some

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

ergogenic potential. Existing evidence seems to support some ergogenic effect of quercetin in untrained people, but not in trained athletes.[6]

I. **Asthma:** There is an opposite relationship among the administration of quercetin and asthma incidence according to researches of human epidemiological .[45] However, anti-asthmatic activity and activity in other atopic diseases of quercetin in currently missing, but quercetin glycoside (isoquercetrin) have some effect on allergic symptoms and also two researches have been reported in the same .[46] In this case, starting four weeks prior to the onset of pollen release, subjects took 100-200 mg/day of isoquercitrin or a placebo for eight weeks. Results proved that ocular symptoms can be treated with this specific quercetin glycoside, but nasal symptoms which are caused by pollen that cannot be treated.[6]

J. **Prevention of cardiovascular disease:** The risk of coronary artery disorders can be reduced by eating of nutraceuticals in food. The consumption of Quercetin (730mg/day, 4weeks) was recorded to reduce systolic pressure (by 7mm Hg), diastolic pressure (by 5 mm Hg).[47] In a same research, after the administration of quercetin/day (40 days), lower in the atherogenic LDL level and systolic pressure in some obese patients.

   In the animal (rat) model, quercetin was orally administered to wistar rats for one week. Quercetin treated the myocardial infarction by lowering the lipid peroxidation components for conjugated dienes and lipid hydroperoxides in heart and plasma.[48]

Conclusion: Quercetin, a dietary flavonoid which have various effects in the treatment of diseases such as anti-inflammatory, anti-cancer, anti-asthmatic, anti-obesity and in the prevention of cardiovascular disorders. But one of major challenge is to enhance the solubility and relative bioavailability. The current review discusses various properties of quercetin as well as various pharmacological actions of quercetin.

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

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