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QUERCETIN AND A REVIEW ON ITS IMPORTANCE

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ABSTRACT

Flavonoid quercetin is phytochemical compounds, phenolic in nature &is present in abundance as dietary flavonoid in certain vegetables, grains, fruits, flowers, bark roots, stem, wine and tea.It possess potent antioxidant & anti-inflammatory properties which can be coupled with hepatoprotective and cardioprotective action, in autoimmune disease like Diabetes Mellitus with varying doses. It also has anti-viral, anti-malarial property and therefore finds its application as immunomodulatory and thus, can be effective anti-cancer drug. Quercetin as herbal drug has less side effects, but should be used wisely as there are chances of drug-drug interactions or it may also interfere with the drugs that are metabolized in liver by Cytochrome P450 2C8, 2C9, 3A4, 2D6 substrates.

KEYWORDS: Quercetin, Cancer, Phytochemical, Phenolic, Anti-malarial.

INTRODUCTION[1,2]

Quercetin: The name quercetin (3,3',4',5,7-pentahydroxyflavone) comes from the Latin word "Quercetum" which means Oak Forest, belongs to the class called flavonols that cannot be produced in the human body. It is yellow colour and is poorly soluble in hot water, quite soluble in alcohol and lipids and is insoluble in cold water.

Top Natural Sources of Quercetin

Some of the top sources of quercetin diet include.

Vegetables	Fruits	Beverages	Others
Tomatoes	Apples	Red wine	Herbs
Cruciferous veggies	Dark cherries	Tomato canned juice	Beans
Green leafy veggies	Raw grapes	Black brewed tea	Olive oil
Sweet potato	Raw lemon	Green brewed tea	Peppers
Capers	Cranberries	Decaf brewed tea	Cocoa
Spring onion	Citrus fruits		

Pharmacokinetics[3,4,5,6]

Upon oral administration of quercetin, only 3.1% was metabolized in the liver & about 93.3% was metabolized in the gut. The absorption rates are influenced by quercetin conjugates. Intestinally, quercetin was found to have 52+/-15% uptake, where supplemental quercetin aglycone had a 24+/-9% uptake and quercetin rutinoside (tea) had 17+/-15% up-take. Supplementation of 50mg, 100mg, and 150mg quercetin dihydrate helps elevating blood concentrations of quercetin.

Consumption of 500mg quercetin reviewed the delivery of quercetin had C_{max} of 1051.9+/-393. 1ug/mL dose of 3.66 hours study showed T_{max} and C_{max} of Food bar format and juice suspension reaching 354.4+/-87.6µg/L (4.7h) and 698.1+/-189.5µg/L (in 2.3h) respectively.

After metabolism quercetin occurs solely in blood as quercetin glucuronides. Before being released in systemic circulation, all forms of quercetin get hydrolysis and glucuronidated in liver. Quercetin supplementation also exposed about intestinal permeability of quercetin.

Bioavailability of quercetin[7,8,9]

Studies reveal that depending on source, quercetin has moderate to low bioavailability**.** In contrast to most form of supplements, much of the quercetin in foods is attached to a sugar molecule and this conjugate is known as a glycoside. Apple trees and tea plants tend to attach rutinose to yield rutin while onion plant tends to attach glucose to form quercetin-3-glucoside (iso-quercetin). Differences in quercetin-conjugated glycosides affect its bioavailability. Difficulty in crossing membranes in the gut is observed due to the size and polarities of these compounds. Oppositely, this is not the case for iso-quercetin. Likewise, compared to quercetin and rutin animal studies showed superior bioavailability of iso-quercetin.

In another study, bioavailability of quercetin glucoside derived from onion is greater as compared to quercetin rhamnoside and quercetin galactoside which are derived from apple. In this study, C_{max} and AUC_{0-24h} of quercetin following the consumption of onions were 3and 4 times greater respectively, than those following the consumption of apples. Likewise, $t_{1/2}$ of onion-derived quercetin was more than 4 times greater than apple-derived quercetin. These findings support that due to greater absorption onion, onion-derived quercetin is more bioavailable.

Bioavailability of quercetin is related to its solubility in the vehicle used for its administration and thereby its bio-accessibility. Quercetin is relatively lipophilic with low water solubility. The poor solubility of quercetin and crystalline form at body temperatures limiting its bio-accessibility and its bioavailability. Absolute bioavailability of quercetin was observed as 16% in rats and its C_{max} was 2.01 µM following when suspended in aqueous solution. Administration of quercetin aglycone dissolved in an ethanol and PEG 200 solution increased its absolute bioavailability to 27.5% and C_{max} to 3.44µM.Octanol-water partition coefficient of quercetin-3-glucoside (0.76±0.01), is nearly half of that of quercetin (1.82±0.32) and it is lower than that of kaempferol (3.11±0.54). Quercetin is soluble in water at 1.53-12.5 mg/L at gastrointestinal pH levels (pH 2-7).

Pharmacological Actions of Quercetin

Anticancer activity of quercetin[10,11,12]

Flavonoid quercetin is one of the most powerful cancer killer. Quercetin is found in number of fruits and vegetables and is capable to fight disease on multiple fronts make it effective as cancer preventive and also curative compound. Research has shown that people with the highest intake of quercetin experience significantly lower risks of death from major types of cancer, including lung, colon, gastric and breast cancer.

Secondary to cardiovascular disease cancer is the leading cause of death in today's world. While conventional cancer care tends to leave patients weak and vulnerable to recurrence to cancerous growths and development of new malignancies. That's because these treatments make use of dangerous chemicals and deadly radiation which destroy the immune function and increase the risk of premature death. Researchers in china conducted the study of quercetin on breast cancer cells and the study revealed about its anti-tumor properties. One of the benefit of quercetin is that it works at the cellular level interfering with the process that transforms healthy cells into malignant cancer cell. Cancer inducing agents cause dangerous

mutations in cellular DNA which can be protected by anti-inflammatory & anti-oxidant properties of quercetin. Literature also reveal that regular and frequent intake of quercetin rich foods lowers the risk of lung cancer. Research has shown that people with the highest intake of quercetin experience significantly lower risks of death from of major types of cancer, including lung, colon, gastric and breast cancer.

Cardiovascular effects of quercetin[13,14]

Studies show that quercetin supplementation lowers blood pressure in patient associated with hypertension. The number of studies have shown quercetin being associated with a lower mortality rate and incidence of heart attack for test subjects who regularly ingested the antioxidant flavonoid. Quercetin causes the breakdown of fatty deposits and cholesterol, supports healthy systolic and diastolic blood pressure. It also helps to prevent heart attack and stroke.

Because of anti-inflammatory and anti-oxidative property, quercetin seems to be effective for blood vessel and heart related disorders. During an in vitro study on isolated rat arteries, quercetin in its a-glycan form has been demonstrated to be a vasodilator. Studies done in animal and some human populations show that various types of flavonoids (for example - quercetin, resveratrol and catechins,) can help reduce the risk of atherosclerosis, which is a dangerous condition caused by plaque building up within the arteries. One of the primary risk factors for experiencing a heart attack or stroke is cut-off blood flow in the arteries, which is why cardiac arrest is less likely among people who eat a nutrient-packed diet. In fact, red wine is good for the heart, because quercetin as a natural constituent in it. Quercetin is the leading active ingredient in red wine extract, that's why red wine is good for heart, which is interconnected with healthier heart function.

Antidiabetic Effect of Quercetin[15,16]

Diabetes mellitus is a metabolic disorder causing hyperglycemia. Numerous studies reported that anti-diabetic activity of antioxidants explains about the involvement of oxidative stress in the pathobiology of diabetes mellitus. According to some studies, anti-diabetic effect was owing to its antagonistic effect to prevent a decrease of pancreatic activity of antioxidant enzymes induced by STZ. Studies also show that oral administration of quercetin (100 mg/kg) significantly decreased serum glucose levels at 60 and 90 min after an oral ingestion of starch (1 g/kg). These results indicate hypoglycemic activity of quercetin in animal model of diabetes mellitus. Quercetin at the dose of 25mg/kg orally as well as 10 mg/kg

intraperitoneally has produced the significant peak reduction in serum glucose level in Type I &Type II diabetic rats. The mechanism of action of quercetin as anti-diabetic drug needs to be studied in detail.

The antidiabetic feature of quercetin involve the stimulation of glucose uptake which in skeletal muscles has resulted in the translocation of glucose transporter 4 (GLUT4) through an MAPK insulin-dependent mechanism.

Quercetin has been shown to play a important role in improving renal functioning in diabetic nephropathic rats by blocking the overexpression of CTGF and TGF-β1. Results showed that rats treated with quercetin, overexpression of CTGF and TGF-β1 was reduced in the renal tissues in streptozotocin induced diabetic Sprague-Dawley rats. Moreover, rats treated with quercetin observed a reduction in their weight ratio of kidney and body. Additional qualities of quercetin in-vitro has shown to produce an effective block against lens aldose reductase and additionally prevents polyol accumulation. In humans, quercetin has shown its effectiveness by decreasing the seriousness of jolting pain, numbness, and irritation for patients with type 2 diabetes neuropathy.

Neurological effects[17]

Quercetin is neurotoxic as well as neuroprotective. When used in combination to fish oil, it has been reported to behave as a neuroprotector in rat brain. Quercetin has been reported to show inhibitory effect against acetylcholinesterase and therefore, beneficial effects are possible to notice against neurodegenerative diseases (example, Alzheimer's disease). Moreover, quercetin is reported to reduce the oxidative stress induced by 6-hydroxydopamine in neurons from the brain striatum of rats. A study on healthy P19 neurons reported that quercetin treatment lead to depletion in intracellular glutathione contents which can affect working of nervous system.

Antiviral activity[18,19]

Extensive research on quercetin demonstrated antiviral activity. Viral diseases are a growing threat for human health. Effective action of quercetin has also been seen against various viruses. Recently, quercetin has reported its inhibitory effect against *in-vitro* replication of dengue virus. In in-vivo studies quercetin-7-rhamnoside was found effective against porcine epidemic diarrhea virus and Quercetin-3-O-β-D-glucuronide has been reported to be effective against influenza-A virus. In-vitro study of quercetin reveal that quercetin caused a

concentration-dependent reduction in the infectivity herpes simplex virus type 1 (HSV-1), polio-virus type 1, and respiratory syncytial virus (RSV) and parainfluenza virus type 3 (Pf-3). Direct viricidal activity of baicalein and quercetin against Japanese encephalitis was reported with IC50 = 212.1 µg/mL. Quercetin significantly decreased the production of infectious HCV particles; the viral genome replication and specific infectivity of the newly produced viral particles and proved to be effective against hepatitis C virus.

Anti-Inflammatory Effect of Quercetin[20,21,22,23]

Anti-inflammatory properties have been seen in extracts from *Mexican oregano*, mechanism involving decrease in production of nitric oxide (NO) and reactive oxygen species (ROS). Similarly, many phenolic compounds are observed to inhibit production and secretion of proinflammatory cytokines. At low concentrations, quercetin (less than 50 μM) stimulated IL-10 anti-inflammatory cytokine IL-10. In RAW 264.7 cells quercetin at less than 10 μM inhibited the production of iNOS, NO, IL-6, TNF-α, monocyte chemoattractant protein-1 (MCP-1), and COX-2 by inhibiting NF-κB activation.

Recently, quercetin exhibited significant blocking of proinflammatory cytokines in cultured fibroblasts. The level of TNF-α and NO were inhibited by 10–25 μM quercetin.. In-vivo effects of quercetin are seen as, 10 μM quercetin downregulated the production of COX-2, NO and the Nuclear Factor-kappa B (NF-κB). 25 μM quercetin blocked IL-1β, IL-6, IFN-γ, and TNF-α secretion in human whole blood (HWB) induced by LPS. Finally, In LPS-stimulated RAW 264.7 microphages the secretion of IL-6 and TNF-α was reduced by 50 and 100 μM, while at 25 and 50μM it is proved to be the most coherent blocker of TNF-α secretion in macrophages. The reduction in protein level of NF-κB, IL-1β, IL-6, and TNF-α and pancreatic histopathological damage are the effects exhibited by quercetin. Quercetin can also inhibit proinflammatory cytokines. A six-week regimen of 150 milligrams of quercetin taken daily by human subjects significantly lowered cytokine TNF-α serum concentrations. Example of quercetin's inhibitory qualities include inhibition in *in-vitro* production of lipoxygenase (LOX) and cyclooxygenase (COX) which are known to be induced by inflammation.

Hepatoprotective activity[24,25,26,27]

Animal studies have revealed quercetin’s hepatoprotective effects from a variety of hepatotoxic insults, including carbon tetrachloride (CCl4), acetaminophen etc. Hepato-protectivity was then observed by the decrease in plasma concentration of alanine

aminotransferase. Oxidative damage induced by ethanol in rat hepatocytes has been reported to be curable with the quercetin administration Hepato-protectivity of quercetin suggests that its administration may be helpful to prevent liver damage, thus quercetin may be a suitable natural product as hepatoprotective agent. Studies reveal that quercetin decreases liver damage in mice with Non-Alcoholic Steatohepatitis. Quercetin in hepatic ischemic reperfusion injured rats attenuates oxidative stress and modulates the expressions of iNOS, eNOS, and NOSTRIN. Quercetin plays a significant role in hepatic fibrosis by inhibiting hepatic stellate cell activation and reducing autophagy via TGF-beta1/Smads and PI3/Akt pathways. Quercetin has also been outlined for its preventive effect on the reproductive system of embryonic chicken. Literature also reveals anti-obesity use of quercetin.

Antioxidant activity[28,29,30,31]

Quercetin is proposed to be used as chelating agent in the chelation therapy treatment for the removal of toxic metal ions, quercetin-cadmium complexes has also been reported to have higher stability constant (Kf) value. The antioxidant potential of quercetin is attributed to free radical scavenging activity and quercetin is capable of scavenging ROS. During in vivo study, it has been reported that methanolic extract of Hetero-cainuloides containing quercetin can effectively reduce oxidative damage caused by CCl_4.

During in vitro studies quercetin has been capable of inhibiting cataract formation caused by oxidative stress in rat eye lens cultured proving its antioxidant property. Recently, in vivo study, it has been reported that oxidative damage caused by an industrial compound CCl_4 can be effectively reduced using the methanolic extract of Hetero-cainuloides containing quercetin. Moreover, Quercetin reported its antioxidant behavior against the oxidative stress induced by streptozotocin-induced diabetes mellitus in rats at a dose of 25-50 mg/kg. In another study, in vivo inhibitory effect against tert-butyl-hydroperoxide caused lipid peroxidation in human sperm cells has been reported by quercetin.

Dosing[1,31,32]

The appropriate dose of quercetin depends on factors such as the patient's age, health, and many other conditions. It is better to keep in mind that natural products are not always safe and dosages are important. One should be sure to follow directions given on product labels and consult your pharmacist or physician before using.

Disease	Dose	Function
Neuroprotective	25-100mg/kg	Alzheimer's disease
Cardiovascular		It modulates the production of endothelin-1 & nitric oxide, Improve endothelial function &thereby lead to beneficial cardiovascular effect.
Cancer	1mg/kg	Effective in breast cancer and suppress tumor growth. It works at the cellular level interfering with the process that transforms healthy cells into malignant cancer cell.
Blood pressure	730mg	Reduces blood pressure in hypertensive patients
Renal injury	2mg/kg	Quercetin ameliorates ferric nitrilotriacetate-induced Oxidative renal dysfunction in rats.
Diabetes mellitus		iNOS expression NF-kB factor produced due to oxidative stress was reduced by quercetin in streptozotocin-induced diabetic rats.
Arthritis	750mg/day	Convincing against inflammation and quite effective Arthritic pain.
Asthma	100uM	Potent for respiratory infections, provide relief for asthmatic patients by relaxing smooth muscle.
Anti-inflammatory	10mg/kg	It improves the inflammatory status in obese Zucker rats.

Drug Interactions[32,33]

Antibiotics (Quinolone antibiotics)interacts with Quercetin

Taking quercetin along with antibiotics decreases the efficiency of some antibiotics. According to studies, scientists think quercetin might prevent antibiotics from killing bacteria. Some of the antibiotics that might interact with quercetin include ciprofloxacin, norfloxacin, sparfloxacin, trovafloxacin, and grepafloxacin.

Medications which are moved by pumps in cells (P-glycoprotein Substrates) interacts with Quercetin

Some formulations are moved by pumps in cells. Quercetin makes this pump less active and increase the absorption of drug by this route. This can lead to unnecessary unwanted side effects by the drug.

Drugs that may interfere include diltiazem, verapamil, digoxin, cyclosporine, saquinavir, amprenavir, nelfinavir, loperamide, quinidine, paclitaxel, vincristine, etoposide, cimetidine, ranitidine, fexofenadine, ketoconazole, itraconazole, and others.

Medications changed by the liver (Cytochrome P450 2C8 substrates) interacts with Quercetin

Previous of taking quercetin talk to your doctor, if you take any medications that are changed by the liver. Quercetin can interfere with the procedure of such medications which are broken down by liver and their active metabolite plays a role in pharmacotherapy. Administration of quercetin along with these drugs should be avoided as it may lead to increase the therapeutic effect and/or side effects of the original drug.

Some medications that are changed by the liver along with the substrate are mentioned in the table given below.

(Cytochrome P450 2C8 substrates)	(Cytochrome P450 2C9 substrates)	(Cytochrome P450 3A4 substrates)	(Cytochrome P450 2D6substrates)
Rosiglitazone	Tolbutamide	Omeprazole, lansoprazole	Amitriptyline
Repaglinide	Phenytoin	Verapamil, propranolol	Codeine
Verapamil	Ibuprofen	Indinavir	Haloperidol
Paclitaxel	Glipizide	Ketoconazole, itraconazole	Metoprolol
Docetaxel	Diclofenac	Cyclosporine	Venlafaxine
Amiodarone	Celecoxib	Clarithromycin	Risperidone
	Warfarin	Lovastatin	Ondansetron

CONCLUSION

From this review we conclude that quercetin has beneficial effects in various diseases and disorders. Thus, it can prove to be potent drug in many diseases such as Diabetes mellitus, hypertension and hepatotoxicity mainly because of its antioxidant and anti-inflammatory property. Perhaps, mechanism of action in cardiovascular diseases and as hepatoprotective is yet to be checked and has good future scope. As previously mentioned quercetin can act as immunomodulator an therefore can be effective as anti-cancer drug and hence requires detailed study to be done.

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