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QUERCETIN AS AN IMPORTANT NUTRACEUTICAL AND MEDICINAL AGENT

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Abstract

Quercetin is one of the most important flavonoids of polyphenols group and widely distributed in varieties of fruits, vegetables, leaves, and grains. It has been used as a nutraceutical for the mitigation of various ailments such as antihypertension, anti-diabetes, anti-arthritis, anticancer, anti-inflammatory, and antiaging. This review focuses on the quercetin as an herbal product and its application in nutraceutical for the benefit in hepato-toxicity & also for various diseases. Various literatures claimed it to be nutraceutical and beneficial in various disorders therefore as Medicinal Chemist we investigated and compiled it for the readers. We observed that quercetin is associated with certain issues such as thermolability, photosensitivity, poor bioavailability, low water solubility and chemically. These limitations have created a hurdle in the path of drug formulation and development. The researchers and pharmaceutical scholars have developed various formulations like liposomes, cubosomes, nanoparticles, and cocrystals. This review article presents the importance of quercetin as a nutraceutical as well as a herbal agent in the management of various disorders, particularly as an antioxidant and anti-inflammatory.

Key words: Quercetin, Antioxidant, Neutraceutical, Hepato-protective, Cardio-protective.

Introduction

Quercetin is 3, 3',4', 5,7-pentahydroxyflavone, as one of the most important flavonoids from polyphenol group and widely distributed in varieties of fruits, vegetables, leaves and grains (Fig. 1). It has been used as a nutraceutical as well as herbal medicine for the management of various ailments such as antihypertension (Edwards, 2007), anti-diabetes (Jeong, 2012), anti-arthritis (Gardi, 2015), anticancer (Yoshida, 1992), anti-inflammatory(Comalada, 2005), anti-aging(Chondrogianni *et al*., 2010), anti-microbial (Nitiema, 2012), anti-thrombotic (Lee, 2013), wound healing and anti-viral property(Ohnishi, 1993). The average daily requirement of quercetin is 16 mg/day(M. K. Kim, Park, Yeo, Choo, & Chong, 2009). This poorly water-soluble quercetin can interact with sodium-dependent glucose transport receptors in mucosal epithelial and is absorbed by the small intestine. It also prevents free radical generations and protects from cell injury as revealed in *in- vitro* model study(Gee, DuPont, Rhodes, & Johnson, 1998). It also protects from ultraviolet radiations (Patil, Mallaiah, & Patil, 2013). Out of five hydroxyl functional groups in quercetin, three hydroxyl groups at position 3, 3' & 4' are responsible for its antioxidant property. The presence of 5 hydroxyl group can act as both hydrogen acceptor and hydrogen donor whereas two hydrogen acceptor is the aromatic cyclic oxygen and keto group(Vasisht *et al*., 2016; Veverka *et al*., 2015). The existence of phenolic hydroxyl functional moiety in flavonoids has a property to denote hydrogen atoms to radicals and thus act as a free radicals' chain terminator (Kapoor *et al*., 2017). It is photo-stable in propylene glycol solution rather than in creams. It is oxidized and degraded in alkaline solution even if protected from light but stable in non-nucleophilic solvents(Dall'Acqua, Miolo, Innocenti, & Caffieri, 2012).

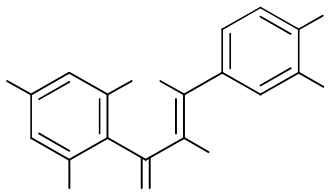

Fig. 1 : Chemical structure of quercetin.

Hepatoprotective mechanism and drug delivery approaches

During the liver inflammation and injury, the potent liver enzymes level like ALT, AST, GGT, ALP, and bilirubin level are usually increased beyond their normal level and thus affects the basic metabolism pathways. The antioxidant liver enzyme like SOD, GSH and GPx level is raised while the MDA level is decreased and generates reactive oxygen species (ROS) radicals and causes hepatotoxicity (Roy *et al*., 2012; Sarma *et al*., 2017; Sarma *et al*., 2018; Satija *et al*., 2018). Quercetin is considered as one of the potential medicinal agents for the prevention and treatment of hepatotoxicity as it has been reported in various literature through its antioxidant and anti-inflammatory action (Chellappan *et al*., 2019). It inhibits the production of inflammatory species such as ROS, TNF, IL-1, and also p38 whereas promotes SOD, GSH, GPx level leading to antioxidant, hepatoprotective and apoptotic effect (Fig. 2)(Chen, 2010). Quercetin is thermolabile, photosensitive (Dall'Acqua *et al*., 2012), less water soluble and chemically

unstable in neutral and alkaline medium (Juhi *et al*., 2012). Poor bioavailability and absorption are also associated with it (Peter *et al*., 1997). These limitations have created a hurdle in the path of drug formulation and development. The researchers and pharmaceutical scholars have developed various formulations like liposomes, cubosomes, nanoparticles, and cocrystals to solve these issues (Table 1).

Evelyn B. Rodriguez *et al.* (2019), have prepared the nano-liposomal encapsulation of quercetin which has an improvement in its stability and bioactivity.

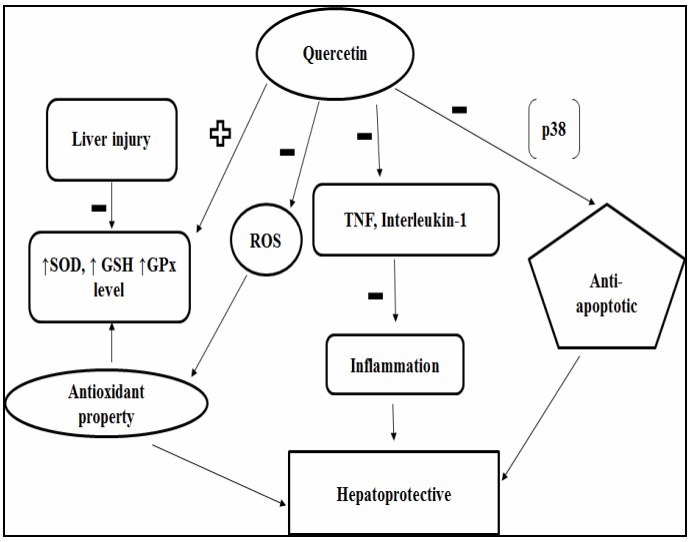

Fig. 2 : Hepatoprotective mechanism of quercetin

The formulation was prepared by using rice bran phospholipids. The formulation was stable for 6 months at 4 °C and 5 months at 27°C without any degradation in its antioxidant property. The 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging activity was enhanced by 1004-fold of nano-liposomal quercetin. At the same time, anti-angiogenic activity was also improved by 2-5-folds(Rodriguez, Almeda, Vidallon, & Reyes, 2019). Jeon *et al.* (2015), have reported the improved stability of quercetin by liposomes formulation by multi-layered deposition using L-α-phosphatidylcholine, chitosan, cholesterol, & di-hexadecyl phosphate. The permeability of drug in multi-layered liposome was higher than uncoated liposomes (Jeon, Yoo, & Park, 2015)

Xiaohe Li *et al.* (2019), have prepared the nano-formulation of quercetin with cellulose nanofiber as a carrier and has found improved dietary and antioxidant activity than a pure form of quercetin. The pure form of quercetin has low solubility, bioavailability, and stability problem due to which the nanoformulation technique was used to overcome this issue. This formulation also had a high loading quercetin capacity & encapsulation efficiency of 78.91% and 88.77% respectively (Li *et al*., 2019). Cortesi *et al.* (2017),had prepared the monoolein aqueous dispersion of quercetin for drug delivery to overcome the solubility issue of active drug quercetin. In this method, glyceryl monoolein, sodium cholate, 2,2 diphenyl-picrylhydrazyl & Folin-Ciocalteau were used in the preparation of formulation. This technique was also useful to overcome the solubility problem of quercetin (Cortesi *et al*., 2017). Poulosea *et al.* (2018), had prepared the quercetin cubosomes by incorporating glyceryl monooleate by assisted the ultrasonication method.

They developed this formulation to overcome the stability issues and entrapment efficiency of tropical formulation gels or creams (Khursheed *et al*., 2019). The entrapment efficiency was improved up to 87.43 ±0.07 % and found to be useful as a skin protective tropical delivery system (Pooja *et al*., 2018). The nano-phytosomes of quercetin had 98 % entrapment efficiency along with enhanced physical stability and bioavailability (Kumari *et al*., 2012). The incorporation of cholesterol in the formulation enhanced the stability of cubosomes formulation and bioavailability of drug was also improved (Rasaie, Ghanbarzadeh, Mohammadi, & Hamishehkar, 2014). Kakran *et al.* (2012), have prepared the nanocrystals of quercetin by bead milled technique under high pressure (Riyaz *et al*., 2018). To prevent agglomeration and to improve stability of nanocrystals, it was stored in a freeze drier or in a freeze (Kakran *et al*., 2012).

Table 1 : Drug delivery approaches of quercetin.

Delivery approache	Chemicals used	Reason for selection	Outcomes	Ref.
Nano-liposomal	Rice bran phospholipid	To enhance the stability and bioavailability of quercetin	1004-fold raised in DPPH radical scavenging property. 2-5-fold increase in anti-angiogenic property. Stability increased for 5 months at 27 °C	(Rodriguez *et al*., 2019)
Liposome	L-α-phosphatidylcholine, chitosan, cholesterol, dihexadecyl phosphate, quercetin	To improve the stability of quercetin	Enhanced quercetin stability by liposome formulation	(Jeon *et al*., 2015)
Nano-formulation	Cellulose nanofiber (carrier)	Low water solubility & low bioavailability	Improved dietary & antioxidant activity than quercetin	(X. Li *et al*., 2019)
Aqueous dispersion	Glyceryl mono-oleate, sodium cholate, Folin-Ciocalteau's phenol quercetin, 2,2 diphenyl-picrylhydrazyl)	Low solubility	Monoolein aqueous dispersions improve the solubility problem	(Cortesi *et al*., 2017)

Quercetin Cubosomes	Glyceryl monooleate, quercetin	To enhance entrapment efficiency, the stability of quercetin	87.43 ±0.07 % entrapment efficiency, chances to make skin protective gels or cream	(Pooja Poulosea *et al*., 2018)
Nano Phytosomes	Cholesterol, phosphatidylcholine, quercetin	Stability & bioavailability problems	Cholesterol enhanced the physical stability for 3 weeks & entrapment efficiency by 98 %	(Rasaie *et al*., 2014)
Nano crystals	Quercetin	Stability issue	Improved physical stability by nano crystals	(Kakran *et al*., 2012)

Quercetin as Neutraceutical

Quercetin is chemically 3,5,7-trihydroxy-2-(3,4-dihydroxyphenyl)-4Hchromen-4-one, a most potent flavonoid present in many dietary foods and vegetables like caper, black chokeberry, onion, tomatoes, broccoli, apples, tea, red wine etc. and among which dock leaves (86.20 mg/kcal) and coriander leaves (52.90 mg/kcal) contains the largest amount of quercetin content (Table 2) (Ay *et al*., 2016). It has low water aqueous solubility and bioavailability, chemically unstable and has short biological half-life (Cai, Fang, Dou, Yu, & Zhai, 2013). The stability of quercetin is influenced by temperature, pH, oxygen, water, and metal ions. It is also unstable at alkaline pH (Moon, Wang, DiCenzo, & Morris, 2008). It is lipophilic in nature and highly soluble in dimethyl sulfoxide. An only a small amount of oral quercetin is absorbed into the circulation. Quercetin has basically two parts: quercetin glucoside and quercetin aglycone. It is found in various forms such as quercetin galactosides (in apples), quercetin arabinosides (in berries), quercetin-3-rutinosides (capers), etc. Quercetin and its conjugate metabolites are also potent in protecting erythrocytes from membranous damage caused by smoking or unhygienic air environmental conditions. Table 2 represents the various concentration of quercetin presents in the different food source. The concentration of quercetin may vary according to the climate, soil, harvesting, processing, extraction, and other parameters influencing it. Capers: It is considered as the richest source of quercetin-containing nutraceuticals. It is also a nutritional food source belonging to family Capparaceae with various medicinal values(Vincenza Romeo, Marisa Ziino, Daniele Giuffrida, Cettina Condurso, & Verzera, 2007). Lovage leaves (family Apiaceae) also contains a rich source of quercetin, possessing different medicinal properties widely grown in Asia and Africa region(Serkan Sertel, Tolga Eichhorn, Peter K. Plinkert, & Efferth, 2011).

Table 2 : Quercetin concentration in dietary source (Ay *et al*., 2016).

S. No.	Fruits & vegetables source	Quercetin (mg/100 g)	S. No.	Fruits & vegetables source	Quercetin (mg/100 g)
1.	Capers, raw	234	14.	Chokeberry, raw	19
2.	Lovage, leaves, raw	170	15.	Sweet potato leaves	17
3.	Dock, raw	86	16.	Cranberries	15
4.	Radish leaves	70	17.	Asparagus	14
5.	Rocket, wild	66	18.	Lingonberries	13
6.	Carob fiber	58	19.	Oregano, fresh	7
7.	Cilantro leaves, raw	53	20.	Crowberries, raw	5
8.	Dill weed, fresh	55	21.	Blackberries, raw	4
9.	Peppers, yellow wax, raw	51	22.	Apples	4
10.	Fennel leaves	49	23.	Blueberries, raw	4
11.	Juniper berries, ripe	47	24.	Blueberries, raw	4
12.	Juniper berries, ripe	47	25.	Cherries, sweet, raw	2
13.	Watercress, raw	30	26.	Grapes, black	2

Quercetin glycoside is absorbed mainly through sodium-dependent glucose transporter 1 (SLGT1), but it is not the same with quercetin aglycone. The non-glycoside type of quercetin is less absorbed as a comparison to that of aglycone & glucosides form (Erlund, 2004). The bioavailability of quercetin depends upon the solubility of the vehicle used for the administration. The water solubility of quercetin is 1.53-12.5 mg/L at its gastrointestinal pH levels (pH). In a pig animal study, it has been found that dietary fat improved the quercetin bioavailability. Quercetin bioavailability is also improved by ingestion of quercetin with short-chain fructo-oligosaccharides (FOS)(Kaşıkcı & Bağdatlıoğlu, 2016). The average daily intake of quercetin is 16-23 mg/day. It also observed to interact with various drugs as represented in Table 3, such as felodipine, estrogens, cyclosporine, quinolone, cisplatin, digoxin and leading to side effects (Kaur *et al*., 2014; Kaur *et al*., 2017; Kaur *et al*., 2018).

We represented Table 4 for the drug-induced hepatotoxicity which can be treated by quercetin as nutraceuticals. Qader *et al.* (2014), have reported the protective effect of quercetin against isoniazid & rifampicin-induced hepatotoxicity in rats model. Isoniazid and rifampicin is the first line anti-tubercular drug for the treatment and prevention of tuberculosis .and hepatotoxicity is the major problem associated with these drugs (Khurana *et al*., 2012, Khurana *et al*., 2013, Kaur *et al*., 2014, Mishra *et al*. 2019a; Mishra *et al*., 2019b; Singh *et al*., 2008). The hepatotoxicity induced by these drugs is overcome by the

concurrent use of quercetin and decreases the elevated enzyme level like aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Quercetin has a defensive mechanism comprising antioxidant molecules and antioxidant enzymes which act symbiotically to detoxify the oxidative injury by means of oxygen free radicals(Gulala Ibrahim Qader, RoshnaShawkat Aziz, ZheenAorahman Ahmed, ZanaFaeq Abdullah, & Hussain, 2014). In the literature, David *et al.* (2011), have reported hepatoprotective action of quercetin in preventing thioacetamide-induced liver injury in rats. The increased in the liver enzymes like aspartate aminotransferase (AST), alanine aminotransferase (ALT) and other thioacetamide-induced hepatotoxicity were reduced by the quercetin intake to their normal level through regulation of oxidative and apoptosis pathways. Thus quercetin ameliorates the hepatotoxic effects in rat models (de David *et al*., 2011).

Mishra *et al.* (2013), have described the beneficial effects of quercetin on chloroquine induced oxidative stress and hepatotoxicity in mice by decreasing the raised liver enzymes level of aspartate aminotransferase (AST), alanine aminotransferase (ALT. These enzymes are evaluated as the key factor for liver damage and necrosis. The damage occurred in the liver due to oxidative stress and other factors are minimized by quercetin through free radical scavenging property and another relevant pathway in reducing the hepatotoxicity induced by chloroquine (Kumar Mishra, Singh, & Rath, 2013).

In another research article, Olayinka *et al.* (2014), have reported the protective effect of quercetin on melphalan induced hepatic and renal toxicity like increase in the liver enzymes like alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) and plasma bilirubin, urea and creatine level. Quercetin prevents all these by its antioxidant and free radical scavenging property (Peerzada *et al*., 2018). Hepatic glutathione S-transferase (GST) is an enzyme involved in the detoxification of most of the ingested xenobiotics in the liver and form an important component of antioxidant defense action (Olayinka, Ore, Ola, & Adeyemo, 2014). Like-wise another author Pal *et al.* (2010), have described the carotenoids hepatoprotective activity induced by isoniazid-rifampicin in a rat model (Amini *et al*., 2017; Bansal *et al*., 2015; Bashary *et al*., 2019; Chatterjee *et al*., 2018). They reported that carotenoids had best hepatoprotective activity at dose of 10mg/kg body weight per day by reducing the raised level of liver enzymes: serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase (ALP) and bile level through termination of peroxyl radical-mediated reactions and free radical scavenging activity. Carotenoids are fat-soluble compounds and most frequently used as a diet. It protects the liver from toxins both in-vitro and in-vivo model by the reduction of reactive free metabolites through their antioxidant property It also reverses the liver enzymes level to their normal level(Pal, Rana, Vaiphei, & Singh, 2010).

Akdemir *et al.* (2018), have reported the casticin and myricetin hepatoprotective action induced by methotrexate on liver injury in the rat model. Methotrexate increases the malondialdehyde (MDA) level and decreases the antioxidant enzymes level such as superoxide dismutase (SOD), catalase & glutathione peroxidase (GPX) which are responsible for keeping the liver to their normal stage. This hepatoprotective action is reversed and maintained by casticin and myricetin through its anti-inflammatory, free radical scavenging activity and antioxidant defense mechanism (Eki Nci-Akdemi R *et al*., 2018).

Nathiya *et al.* (2015) have described in their literature the hepatoprotective activity of hesperidin induced by isoniazid, rifampicin & pyrazinamide in rats. They found fruitful result towards hepatotoxicity induced by such first-line antitubercular drugs. The elevated liver enzymes (aspartate transaminase, alkaline phosphatase, gamma-glutamyl transferase, alanine transaminase, lactate dehydrogenase, lipid peroxidase, malondialdehyde) and antioxidant enzymes: SOD, catalase, GR, GSH and GST, were reversed to their normal level by the scavenging activity of Hesperidin towards reactive oxygen species and sparing of endogenous antioxidant enzymes. It also protects the peroxidation of polyunsaturated lipids present in the plasma membrane and other sub-cell organelles (Nathiya *et al*., 2015). Quercetin has been also reported as a combination therapy with other nutraceuticals in hepatic and cardiac protection (Table 4). The authors Panda *et al.* (2012), have reported the combined effects of quercetin and atenolol in cardioprotective in rats model induced by isoproterenol - induced cardiotoxicity. The combination of quercetin and atenolol has potent cardioprotective action rather than individual effects by decreasing the raised levels of serum creatine kinase MB (CK-MB), LDH, glutamate pyruvate transaminase, and malondialdehyde (MDA) enzymes and increasing the free radicals scavenging liver enzymes like superoxide dismutase (SOD) and catalase (CAT). These SOD and CAT enzymes are also responsible for the liver protective through its antioxidant and free radicals scavenging properties (Panda *et al*., 2012).

Table 3 : Drug interaction with quercetin.

Name of drug	Remarks	Ref.
Felodipine	Inhibits enzymes responsible for breaking down into inactive forms. Increases the chances of side effects (especially with grapefruits & its juice).	(Miniscalco, Lundahl, Regårdh, Edgar, & Eriksson, 1992)
Estrogens	Grapefruits/juice (Quercetin) increases the estradiol level in the blood. Women taking estradiol should avoid taking quercetin containing fruits and vegetables.	(Schubert, Cullberg, Edgar, & Hedner, 1994)
Cyclosporine	Decreases the cyclosporine blood levels as compared with water.	(Hsiu *et al*., 2002)
Quinolone	Quercetin acts as competitive inhibitors to quinolones.	(Hilliard *et al*., 1995)
Cisplatin	Increases the chance of genotoxicity.	(Cross, Tilby, Chipman, Ferry, & Gescher, 1996)
Digoxin	Quercetin may promote chances of accumulation of digoxin in blood and increases the toxicity and side effects.	(Wang, Chao, Hsiu, Wen, & Hou, 2004)

Table 4 : Drug interaction with quercetin.

Name of Nutraceuticals	Drug-induced hepatotoxicity	Outcomes	Ref.
Quercetin	Isoniazid & Rifampicin	Decrease AST & ALP level. Improves the histopathological profile of liver through antioxidant activity	(Gulala Ibrahim Qader *et al.*, 2014)
Quercetin (50mg/kg i.p.)	Thioacetamide (in rats)	Decrease the increased level of serum aspartate amino transferase (AST) and alanine aminotransferase (ALT). By modulating the oxidative stress and apoptosis pathway	(de David *et al.*, 2011)
Quercetin	Chloroquine (antimalarial drug)	Chloroquine-induced hepatotoxicity at higher was reduced by the quercetin administration through oxidative pathways and decreased the raised level of liver function enzymes	(Kumar Mishra *et al.*, 2013)
Quercetin	Melphalan	Quercetin decreases the increased level of melphalan induced toxicities like plasma bilirubin, urea, creatine, liver enzymes like ALP, ALT, AST, and Gamma-glutamyl transferase.	(Olayinka *et al.*, 2014)
Quercetin	Methotrexate	Methotrexate decreases the liver enzymes level like AST, ALP, ALT & GGT, blood glucose level, hemoglobin, total protein and renal markers like urea and creatine level.	(Eki Nci-Akdemi R *et al.*, 2018)
Quercetin	Ciprofloxacin	Quercetin ameliorates the hepatotoxicity induced by ciprofloxacin through its free radical scavenging property. Malondialdehyde (MDA) levels are reduced and antioxidant enzyme levels are increased by quercetin treatment. Quercetin reduces the release of reactive oxygen species (ROS)& interferon-c from leucocytes.	(Taslidere *et al.*, 2016)
Quercetin & Arginine	Gold nanoparticles induced hepatotoxicity	Increased level of total proteins, malondialdehyde and liver enzymes like alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transferase & aspartate aminotransferase are improved by the co-administration of Quercetin and arginine. The antioxidant property reduces the inflammatory mediators, inhibit oxidative stress, cytokine production, and inhibit DNA fragmentation by increased wound DNA synthesis.	(Abdelhalim, Moussa, & Qaid, 2018)
Quercetin	Atenolol	Better cardioprotective effect than individual drug. Synergistic effect prevents the accumulation of lipid peroxides & free radicals protection. The combined effect decreases CR MB, LDH & SGPT level and protects cardiac damage.	(Panda *et al.*, 2012)
Quercetin	Amlodipine	Adds up the cardioprotective action of amlodipine. Improves cardiac electrophysiologic functions like adenosine triphosphate (ATP) & glutathione (GSH). Reduces plasma creatine kinase (CK), cardiac thiobarbituric acid reactive substance (TBARS) and nitrite content and thus acts as cardioprotective.	(Ahmed, Salem, Attia, & El-Sayed, 2009)
Quercetin	Atorvastatin	Acts through antioxidative stress, antithrombotic mechanism, and free radical scavenging mechanism. Synergistic effect on cardiac protection	(Zaafan, Zaki, El-Brairy, & Kenawy, 2013)
Quercetin	Trimetazidine	Possess synergetic anti-ischemic activity. Prevents against oxygen free radical generation through antioxidant and anti-inflammatory action. Maintains and improves myoglobin and cardiac troponin level by quercetin.	(Yaseen, Shaban, El-Odemi, El-Fiky, & Shebl, 2017)
Quercetin	Simvastatin	10mg/kg of quercetin decreases the bioavailability of simvastatin to a notable level. But quercetin does not alter the AUC, T_{max} or half-life of simvastatin.	(Cermak, Wein, Wolffram, & Langguth, 2009)

The authors Ahmed *et al.* (2009), had reported the enhancement in the cardioprotective action of amlodipine by quercetin in ischemia/reperfusion injury in a rat model. Ischemia/reperfusion causes enhancement in the level of plasma creatinine kinase (CK), cardiac thiobarbituric acid, reactive substances (CT BARS) and raised nitrate/nitrite content whereas decreased in glutathione (GSH) and adenosine triphosphate (ATP) level (Harjit *et al.*, 2016). The combination of these two is very potent in maintaining these level through its antioxidant, anti-apoptotic and metal chelating activities (Ahmed *et al.*, 2009).

Likewise, Zaafan *et al.* (2013), had reported the cardiac protective combination of atorvastatin and quercetin as antilipidemic and nutraceuticals combinations in isoprenaline-induced myocardial infarction in the rat model. Isoprenaline induction causes the change in the cardiac impairment and raises the level of serum creatine kinase (CK-MB), cardiac troponin (cTn-1), oxidative biomarkers, interleukins (IL-10), TNF-α, malondialdehyde (MDA) and nitrite content whereas decreases the level of glutathione(GSH). The combination of atorvastatin and quercetin maintains and normalizes to their normal level (Zaafan *et al*., 2013).

The authors Burczynski *et al.* (2013) had reported the hepatoprotective activity of d-cis Diltiazem and silymarin through its free radical scavenging property by reducing reactive oxygen species (ROS), boosting ATP levels and decreasing Bax mRNA and Bax levels. Silymarin reduces the raised intracellular Ca^{2+} levels through its modulation and thus protects from liver damage. The d-cis diltiazem only possesses antioxidant property rather than l-cis diltiazem. The hepatoprotective activity of diltiazem and silymarin are dose specific and do not increase with the increase in dose concentration (diltiazem dose: 2.5 to 10 μM & silymarin dose: 1000 μM) (Burczynski, 2013).

In the literature, Haleagrahara *et al.* (2018), have reported a combination of quercetin and methotrexate in the treatment of inflammation and joint pain caused by autoimmune rheumatoid arthritis. Quercetin decreases joint inflammation by decreasing the cytokines levels and matrix metalloproteinase(Haleagrahara *et al*., 2018).

Similarly, Raffoul-Orozco *et al.* had explained the combination effect of pravastatin in lipid profile and found that monotherapy had better effects than on combination therapy on decreasing the lipid profile level. But their combination had good euglycemic (maintain the normal blood glucose level) and anti-obesogenic (reducing obesity) effect along reducing the hepatic toxic effects of pravastatin. Naringenin had been found to be a good hepato-protectant against pravastatin(Raffoul-Orozco *et al*., 2018).

Likewise, another author, Cermak *et al.* (2009), described the quercetin effect on the bioavailability of simvastatin and found that the 10mg/kg of quercetin decreases the bioavailability of simvastatin without affecting the AUC of time curve, time to obtain maximum concentration and half-life in a pig model. The high doses of quercetin did not increase the plasma level of simvastatin and its active metabolites in pigs(Cermak *et al*., 2009).

Pharmaceutical uses

Protects liver damage: Rojas *et al.* (2016), have reported the hepatoprotective activity of quercetin against hepatitis C virus either of the mechanism by decreasing viral gene replication or reducing the production of infectious virus or by inhibiting diacylglycerol acyltransferase (DGAT). It is very useful for preventing from hepatitis C virus and reduces internal ribosomal entry at the site of activity and finally inhibits hepatitis C virus replication. DGAT is the microsomal enzymes responsible for triglycerides biosynthesis and main host factor for hepatitis C virus infection. It has been also reported that quercetin is found to be safe at a dose of 5 g/day (Rojas *et al*., 2016).

Neuroprotective: Quercetin is rich in the antioxidant-containing compound and several studies have reported on the neuroprotective effect of it (Javed *et al*., 2018, Singh *et al*. 2011). For example, oral quercetin (0.5-50 mg/kg) is known to have a neuroprotective effect on rodents induced by various neurotoxic agents due to its free radical scavenging property and anti-inflammatory activity (Khan *et al*., 2018). It has shown neuroprotective effect against metals like lead, mercury, tungsten, and other neurotoxic causing agents. Several researchers have also found that quercetin ameliorates the Alzheimer disease, Parkinson disease(Khan *et al*., 2018; Teles *et al*., 2018) and other neurodegenerative diseases induced by various agents in animal models(Teles *et al*., 2018). Neurodegeneration occurs due to several factors like age-related degeneration process, oxidative stress, excessive production or insufficient neutralization of free radicals and formation of free radicals (Tripathy *et al*., 2011). The neuroprotective action against oxidative damage and cell death results due to the stimulation of the Nrf2-ARE pathway. The paraoxonase-2(PON2) pathway exert an antioxidant effect and prevents the atherosclerosis process and also in neuroprotection(Costa, Garrick, Roquè, & Pellacani, 2016). It also exerts the neuroprotective activity by boosting the Glo-1 function in central nerve cell under chronic HG conditions that may be mediated by the stimulation of the Nrf2/ARE pathway(Kale *et al*., 2018; Liu *et al*., 2018).

Protects from diabetes: Umathe *et al.* (2099), have reported that quercetin (10 mg/kg oral) does not alter the pharmacokinetic property of pioglitazone when they are co-administered rather improves the bioavailability of nitrous oxide in diabetic rat aortas(Umathe, Dixit, Vaghasiya, & Jain, 2009). It has been found to be useful for the treatment of diabetes induced by streptozotocin and acts through either increasing insulin secretion or enhancing glucose uptake (Chauhan *et al*. al, 2017, Vyas *et al*, 2017, Vyas *et al*., 2019, Yeshi *et al*., 2017). It has been reported that it is also useful for treating diabetic cataracts by suppressing aldose reductase enzymes level(Shetty, Rashmi, Rajan, Sambaiah, & Salimath, 2004).

Improves memory function: Quercetin has been found to improve memory function in animal models (Khan *et al*., 2018; Li *et al*., 2015). Yao *et al.* (2010), have reported quercetin (5 mg/kg i.p. for 14 days in rats) effectiveness in improving the cognitive defects in an animal model through its neuroprotective mechanism of action. It also inhibits the sodium channel influx and reverses the LTP (Long Term Potentiation) deficiency induced by ischemia(Yao, Han, Zhang, & Yang, 2010).

Protects ocular surfaces in dry eye disease: Quercetin and resveratrol on tropical application protect the ocular surfaces in dry eye diseases problems. Dry eye disease is a condition characterized by increased cell apoptosis in conjunctiva along with a decrease in tear production. About 8-14% of worldwide populations are affected by such problems and very are formulations have been made so far. e.g. Cyclosporine, Lifitegrast. But quercetin and resveratrol have been found to a potent nutraceutical for the treatment and prevention in animal model suffering from such eye disease problems (Abengózar-Vela *et al*., 2018).

An antiviral agent: It is very useful in the treatment of influenza A virus in a very minute concentration. (7.76

micrograms) showing the inhibitory action in the early stage of influenza virus H5N1, H1N1 and also shows synergistic action with influenza vaccines. It shows that combination therapy enhances the antiviral therapeutic of this agent, reduced toxicity with fewer toxic effects (Wu *et al*., 2016). Similarly, in another patent report, it has been described quercetin effectiveness towards the treatment of Japanese Encephalitis virus at a dose of 50 µg/ml (Johari, Kianmehr, Mustafa, Abubakar, & Zandi, 2012).

Bioenhancer: The author Narade and Pore have reported that quercetin (10 mg) can be used as a bioenhancer carrier in *ex vivo* permeability of an anticancer drug berberine chloride, improving its bioavailability and reducing the dose(Narade & Pore, 2019).

Anti-aging agents: Chondrogianni *et al.* (2010), have reported the anti-aging activity of quercetin (5 mg/ml) and quercetin caprylate (5-10 mg/ml) for increasing the lifespan of cells, increasing their survival & viability. It is mainly concerned with the activation of proteasome & reducing tyrosinase levels through its antioxidant activity and free scavenging property (Sunil *et al*., 2019). It enhances the elasticity and decreases the wrinkles forming cells on tropical applications(Chondrogianni *et al*., 2010)

Cancer protective: Several types of research have been done to show the anti-cancer activity of quercetin. It inhibits the proliferative phases of cancerous cells (e.g. colorectal cancer, prostate cancer, liver cancer, pancreatic cancer, and lung cancer) by modulating its cellular process(Cincin *et al*., 2014; H. Kim *et al*., 2013). It also prevents cancer cells formation induced by various drugs and oxidative stress through its anti-oxidant property(Anandam & Selvamuthukumar, 2014).

Ultraviolet prevention: Inal and Kahraman have reported the oxidative stress induced by ultraviolet light and its protective effects done by quercetin in a dose of 50 mg/kg in the rat model. During the oxidative stress, ROS, MDA, and SOD levels are raised and level of antioxidant liver enzymes decreases causing inflammation, injury, and cell necrosis due to which hepatotoxicity and cancer cells become most prominent to occur(Kahraman & Inal, 2002). To prevent from such oxidative stress induced by UV lights, quercetin flavonoid is very useful in controlling and preventing such conditions(Inal & Kahraman, 2000). Casagrannde *et al.* (2006), have also reported a tropical protective effect of quercetin against oxidative stress induced by UV light in hairless mice model. It is very useful in preventing from UV light causing cancer and other skin related problems caused by UV radiations(Casagrande *et al*., 2006).

Asthma: Several animal studies have reported for the treatment and prevention of asthma at a dose of 10-20mg/kg. Quercetin reduces the production of inflammatory cells, histamines and pro-inflammatory mediator responsible allergic conditions, asthma. It also reduces transcriptase expression factors GATA 3 (also known as an erythroid transcription factor) which is responsible for Th2 cell growth and differentiation (Mehta *et al*., 2018). Epithelial thickness, subepithelial smooth muscle thickness & goblet cell number are also reduced by intake of quercetin(Rogerio AP & ABM, 2017).

Cardiovascular disease prevention: Quercetin is very useful for preventing and treating cardiovascular diseases such as hypertension, atherosclerosis, congestive heart failure, ischemia, heart attack, etc. At a dose of 730 mg/kg for 4 weeks, quercetin reduces blood pressure (7 mm Hg/ 5 mm Hg) and treats hypertensive patients(Edwards, 2007).

Furthermore quercetin has been explored by preparing different dosage forms, which can be beneficial for its wide application.

Conclusions

Quercetin, a flavonoid component of polyphenols has hepatoprotective, anticancer, antiaging, and anti-microbial properties in addition to being a nutraceutical. The decreased levels of SOD, GPx and GSH are elevated by its anti-oxidant & anti-inflammatory properties. The inceptions of sophisticated technology in the pharmaceutical field have increased its solubility, bioavailability, and permeability without compromising its efficacy using novel drug delivery systems. It is proposed to be effective in hepatoprotection, cardio-protection as well as shown neuroprotective effect against metals like lead, mercury, tungsten, and other neurotoxic causing agents. Quercetin has been also reported as a combination therapy with other nutraceuticals for hepatic and cardiac protection suggesting its potential in combination therapies.

Conflict of interest

Authors have no conflict of interest for this study.

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