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Role of quercetin in the prevention and treatment of diseases: Mini review

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Abstract. Quercetin is the most abundant flavonoid and one of the most important antioxidant of plant origin. The aim of the review was to describe quercetin and its role in the prevention and treatment of diseases. Articles were searched from internet databases using the following search words; quercetin, oxidative stress, quercetin and liver disease, quercetin and kidney disease, quercetin and hyperglycemia. The articles that met the selection criteria were used to describe quercetin and its role in the prevention and treatment of different diseases. The result showed that flavonoids are generally found at higher concentrations in outer layers of fruits and vegetables, onion has more quercetin than blackcurrants, broccoli, black grapes and apple. Quercetin and quercetin rich diets are used in the treatment and prevention of hyperglycemia, cardiovascular and kidney diseases, liver damage and nervous system disorders. In conclusion, quercetin is a naturally occurring flavonoid, more abundant in fruits and vegetables and are used in the treatment and prevention of many diseases.

Keywords: Quercetin; Flavonoid; Oxidative stress; Disease.

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Introduction

Quercetin (3,3',4',5,7-pentahydroxyflavone) is a flavonol, one of the six subclasses of flavonoid compounds, it is insoluble in cold water, poorly soluble in hot water but quite soluble in alcohol and lipids (Kelly, 2011). Quercetin is the most abundant flavonoid, widely distributed throughout the plant kingdom and one of the most important antioxidant of plant origin (Crozier et al., 2009; Brüll et al., 2015). They occur naturally in fruits and vegetables including apples, berries, grapes, onions, brassica vegetables, shallots, tea and tomatoes (Kelly, 2011). Oxidative stress occur as a results of imbalance between

the generations of reactive oxygen species/free radicals and endogenous antioxidant systems. Free radicals and reactive oxygen species (ROS) are formed under normal physiological conditions but become deleterious when not eliminated by the endogenous systems. ROS are major sources of primary catalysts that initiate in vivo and in vitro oxidation and create oxidative stress which results in numerous diseases such as cancer (Kinnula and Crapo, 2004), Alzheimer's disease (Smith et al., 2000) Parkinson's disease (Bolton et al., 2000), alcohol induced liver disease (Arteel, 2003) and diabetes (Rajeshkumar, 2010). Oxygen derived free radicals such as superoxide anions, hydroxyl radicals and hydrogen peroxide are cytotoxic and can cause tissue injuries or increases the severity (Jainu and Devi, 2005). Excessive amount of ROS is harmful because they initiate bimolecular oxidation which causes oxidative stress that eventually results in malfunction of cells. In addition, oxidative stress causes inadvertent enzyme activation and oxidative damage to cellular system (Wiseman and Halliwell, 1996)

Antioxidants are molecule capable of slowing or preventing the oxidation of other molecules. Oxidation is a chemical reaction that transfers electrons from a substance to an oxidizing agent. Oxidation reactions can produce free radicals, which start chain reactions that damage cells. Antioxidants terminate these chain reactions by removing free radical intermediates, and inhibit other oxidation reactions by being oxidized themselves. Therefore, antioxidants are reducing agents, examples are thiols, quercetin, ascorbic acid or polyphenols (Kawsar et al., 2014). Although oxidation reactions are crucial for life, they can also be damaging; hence, plants and animals maintain complex systems of multiple types of antioxidants, such as glutathione, quercetin, vitamin C, and vitamin E as well as enzymes such as catalase, superoxide dismutase and various peroxidases. Low levels of antioxidants, or inhibition of the antioxidant enzymes causes oxidative stress and may damage cells. Free radicals are chemical species associated with an odd number or unpaired electron. They are neutral, short lived, unstable and highly reactive substances. They are capable of attacking the healthy cells of the body, causing them to lose their structure and function. Cell damage caused by free radicals appears to be a major contributor to aging and diseases such as cancer, cardiovascular disease, liver diseases, diabetes mellitus, inflammation, renal failure, and brain disorders. In order to protect the cells and organs of the body against reactive oxygen species, humans have developed a highly sophisticated and complex antioxidant protection system that functions synergistically to neutralize free radicals (Kawsar et al., 2014). The aim of the review was to describe quercetin and its role in the prevention and treatment of diseases.

Materials and methods

Articles were searched from the Directory of Open Access Journals, Google Scholar, PubMed, Science Direct and Scopus using key words such as quercetin, oxidative stress, quercetin and liver disease, quercetin and kidney disease, quercetin and diabetes, quercetin and cardiovascular disease, quercetin and nervous system injury. The articles were selected and reviewed base on the following criteria:

i. Articles on quercetin from different sources.
ii. Articles that described the role of quercetin in the prevention and treatment of different diseases.
iii. Articles on antioxidant and oxidative stress.

Fifty one (51) articles from different databases met the selection criteria and were selected for the review.

The articles were used to describe quercetin and its role in the prevention and treatment of different diseases.

Results

Quercetin

Quercetin is widely distributed in the plant kingdom and has a wide range of uses. Most of the dietary intake of quercetin-type flavonols is as quercetin glycosides. The most common are quercetin linked to one or two glucose molecules (quercetin glucosides) and quercetin linked to rutinose (quercetin rutinoside). The aglycone form of quercetin is not as abundant as the flavonol glycoside form. Two of the most important food sources of aglycone form of quercetin are onions and shallots, quercetin in shallot flesh is about 99.2% quercetin glucosides and 0.8% quercetin aglycone while the dry shallot skin consist of 83.3% quercetin aglycone and 16.7% quercetin glucosides (Wiczkowski, et al., 2008). The flesh of onions contains mostly quercetin glucosides, with only trace amounts of quercetin aglycone while the skin and outermost layers of an onion have much more quercetin aglycone (Smith et al., 2003).

Flavonoids are classified into 13 different categories (Croft, 1998). Flavonoids serve as chemo-preventers in foods, they play a role as antioxidants preventing the rancidity development in lipids before consumption or during digestion processes. They increase intestinal transit time, protect intestinal microflora, can increase up take of some beneficial constituents from the diet, and reduce the level of food mutagens and carcinogens (Stavric et al., 1997). There are seven major flavonoid compounds in onions; Quercetin aglycone, quercetin monoglucoside, quercetin diglucoside, isorhamnetin (a methylether of quercetin), isorhamnetin monoglucoside, rutin and kaempferol (Park and Lee, 1996). Quercetin diglucoside and monoglucoside account for up to 93% of the total flavonol content in onion (Lombard et al., 2002). Flavonoids are generally found at higher concentrations in outer layers of fruits and vegetables (Tsushida and Suzuki, 1996), therefore peeling results in their great loss. After homelike peeling red onions contained 79% of the original total content of quercetin-4'-glucoside and only 27% of the anthocyanins (Gennaro et al., 2002). Onion has more quercetin (300 mg/kg) than blackcurrants (40 mg/kg), broccoli, black grapes and apple (30 mg k/g) (Hollman and Arts, 2000).The total quercetin content in the dry onion skins is significantly higher than that in the edible parts. However the levels of quercetin glucosides in the dry outer skins are less than 10% of the levels in fleshy and partly dried scales. The probable mechanism is that quercetin is formed by deglucosidation of quercetin glucosides on the border between drying and dried brown areas on individual scales (Takahama & Hirota, 2000). About 90% of the total quercetin of each scale is confined to the epidermal tissue, and the rest in the storage tissue. The total content of quercetin is higher in the upper part of an onion as compared with the lower part (Trammell and Peterson, 1976).

Many studies have reported the preventive and therapeutic role of quercetin from different fruits and vegetables on various organs and tissues of the body in humans, cell lines and animal models. Quercetin was reported to protect the liver, kidney and heart of Wistar rats from doxorubicin induced toxicity (Jambhulkar et al., 2014).

Effect of quercetin on hyperglyceamia

Quercetin rich diet was reported to significantly reduce plasma glucose and blood glycated hemoglobin in diabetic mice compared to controls, it had no significant influence on plasma insulin level but significantly decrease the activities of small intestinal maltase activity (Kim et al., 2011). Therefore,

quercetin may be effective in controlling post prandial and fasting blood glucose levels in diabetic patients. Bakhshaeshi et al. (2012) reported the preventive effect of quercetin derived from Allium cepa on the liver of streptozotocin-induced diabetic rats, they showed that quercetin reduced the number of apoptotic cells in the liver suggesting it role in the prevention of liver damage that occur as a result of diabetes. Treatment of streptozotocin-induced diabetic rats with quercetin result in decreased blood glucose levels and reduction in the activities of ALT and AST as compared with untreated diabetic rats having high blood glucose levels due to impaired metabolism (Kilicarslam and Donmez, 2016).

Zhang et al. (2016) reported that administration of quercetin from Toona sinensis leaves (QTL) to diabetic mice significantly reduces the serum levels of glucose, insulin, total cholesterol, ALT, AST, triglycerides and low density lipoprotein-cholesterol compared with untreated diabetic mice. It further reduce oxidative stress as determined by lipid peroxidation and nitric oxide content as a result, decrease the rate of liver injury that occur in diabetic state. QTL also suppressed the diabetes-induced activation of p65/NF-kB pathways, caspase-3 and caspase-9 levels in the liver as well as decrease in the levels of cellular organelle injury in the hepatocytes of diabetic rats. Quercetin significantly reduce fasting blood glucose and malondialdehyde (MDA) levels in diabetic rats compared to diabetic controls. The mRNA levels of HSP27, HSP70, HSF-1 and glucose-6-phosphate was also significantly decreased while the expression of glycokinase was significantly increased in response to quercetin (Hemmanti et al., 2018). This findings suggest that the therapeutic effect of quercetin could be through increase in transcript level of glucokinase that simultaneously decrease the expression of glucose-6-phosphate and stress protein (Hemmanti et al., 2018).

Effect of quercetin on liver disease

Bile duct obstruction in rats causes a decrease in hepatic and mitochondrial thiobarbituric acid reactive substances (TBARS), collagen concentration and fibrosis but administration of quercetin to the biliary obstructed rats resulted in reduced liver oxidative damage, ductal proliferation, fibrosis and a decrease in TBARS and collagen concentration, suggesting that quercetin can be used to preserve liver function in patients with biliary obstruction (Peres et al., 2000). Quercetin was reported to have protective effect on the liver of rats with Non-alcoholic steatohepatitis (NASH). There was a significant decrease in hepatic damage enzymes, lipo-peroxidation, DNA damage and a lower micro-vesicular steatosis in NASH rats treated with 50 mg/kg quercetin compared to untreated NASH rats (Marcolin et al., 2013). Liposomal quercetin was reported to inhibit concavalin-A induced acute hepatitis and hepatic fibrosis. The probable mechanism was the ability of quercetin to modulate antinuclear factor kappa-light-chain-enhancer of activated B cells(NF-kB) and transforming growth factor beta (TGF-β) production suggesting that liposomal quercetin can be a potent substance in the treatment of patients with liver damage and liver fibrosis (Wan et al., 2014).

Earlier study by Ashkani-Esfahani et al. (2016). Showed the protective effect of quercetin on thioacetamide-induced acute liver damage in Sprague-Dawley rats. Rats that received 350 mg/kg thoacetamide (TAA) plus 300 mg/kg quercetin intraperitoneally had a significant decrease in the level of ALT, AST and NH4 with lower piecemeal necrosis and encephalopathy compared with rats treated with 350 mg/kg TAA only. The levels of AST, ALT, total bilirubin and triglycerides were reduced in alcohol-induced liver injured mice treated with

quercetin (Zhu et al., 2017). It also increased the activities of SOD, GPx and suppressed IL-1β, IL-6, IL-10 and inducible nitric oxide synthase. Quercetin also suppressed the protein expression levels of B-cell lymphoma (Bcl)-2, caspase-3, poly ADP-ribose polymerase and signal transducer and activator of transcription (STAT) 3 phosphorylation, nuclear factor (NF)-kB and protein kinase B (Akt) Phosphorylation levels in alcohol-induced liver injured mice. These results suggest that the role of quercetin against alcohol-induced liver injury was through the phosphoinositide 3-kinase/Akt/NF-kB and STAT 3 pathway.

Wu et al. (2017) reported that quercetin was able to reduce bile duct ligation and carbon tetrachloride (CCl4) liver cirrhosis in mice by inhibiting extracellular matrix formation and regulating matrix metallopeptidase (MMP)-9 and tissue inhibitor of metalloproteinase (TIMP)-1. The mechanism through which quercetin attenuate liver damage was by suppressing the TGF-β1/smad signaling pathway and activating the P13k/Akt signaling pathway to inhibit autophagy. Quercetin prevents hepatic fibrosis by decreasing the rate of activation of hepatic stellate cell and inhibiting autophagy through the regulation of crosstalk between TGF-β1/smad and P13/Akt pathway. Li et al. (2018) conduction a research to investigate the impact of quercetin on macrophages activation and polarization. BALB/c mice were induced liver fibrosis using CCl4 for 8 weeks and concomitantly treated with 50 mg/kg quercetin. Quercetin was shown to ameliorate liver inflammation, fibrosis and inhibit HSCs activation. It also inhibit macrophage activation and M1 Polarization as well as decreased the mRNA expression of M1 macrophages markers such as TNF-α, IL-1β, IL-6 and nitric oxide synthase 2. Quercetin reduces CCl4-induced liver inflammation and fibrosis in mice through the inhibition of macrophages infiltration and modulating M1 macrophages polarization via targeting Notch 1 pathway.

Effect of quercetin on kidney disease

Quercetin treatment signifying reduce diabetic nephropathy (DN) in hypercholesterolemic mice by decreasing serum levels of glucose and triglycerides and normalizing the glomerulosclerosis index and the kidney and body weight (Gomes et al., 2015). Quercetin administration ameliorate kidney fibrosis and macrophage accumulation in kidney with obstructive nephropathy (Ren et al., 2016).

Quercetin administration in rats with 5/6 nephrectomy was able to reduce the plasma level of malondialdehyde (MDA), increase glutathione peroxidase (GPx) activity and reduce the degree of fibrosis in kidney tissue as compared with untreated 5/6 nephrectomized rats (Layal et al., 2017). Flavonoids prevent renal injuries associated with arterial hypertension by decreasing blood pressure and acting on the renal parenchyma. This is due to flavonoid interference with multiple signaling pathways known to produce renal injury and are independent of their blood pressure lowering effect (Vargas et al., 2018). Flavonoid consumption also prevent the adverse effect of high fat diet, type 1 and 2 diabetes on kidney function.

Effect of quercetin on gastric disorders

High dietary intake of quercetin is inversely associated to the risk of non-cardia gastric adenocarcinoma, the protection appears to be particularly strong in women exposed to oxidative stress (Estrom et al., 2011). There was a significant reduction in the lesion index in the stomach of indomethacin-induced gastric ulcerated rats treated with 50 mg/kg of quercetin as compared with untreated rats. Also a significant increase in protein bound carbohydrate

complexes and nucleic acids was observed with significant decrease in volume of gastric juice, pepsin concentration and acid output in the rats treated with 50 mg/kg of quercetin as compared to the untreated ones (Shakeerabanu et al., 2011). This suggest that the gastro-protective effect of quercetin might be due to its cytoprotective nature. Pre-treatment of indomethacin-induced gastric ulcerated diabetic rats with quercetin caused a significant decrease in gastric ulcer index, MDA, IL-6, TNF-α and p53 levels with concomitant increase in SOD activity when compared with normal and diabetic rats treated with indomethacin alone (Khaleel et al., 2015).

Alkushi and Elsawy (2017) reported that quercetin can protect gastric mucosa against indomethacin-induced gastric ulceration than famotidine by the observed decrease in ulcer index, with mild inflammatory cell infiltration in the stomach of rats treated with 50 mg/kg of quercetin as compared with those of rats treated with 50 mg/kg famotidine.

Effect of quercetin on the nervous system disorders

Pretreatment of primary hippocampal cultures with quercetin significantly reduce Aβ (1-42)-induced cytotoxicity, protein oxidation lipid peroxidation and apoptosis in cultured neurons (Ansari et al., 2009). These findings suggest that quercetin may provide a promising approach for the prevention and treatment of neurodegenerative diseases. Quercetin glycosides rutin and isoquercetin were reported to have neuroprotective effect against 6-OHDA-induced rat pheochromocytoma (PC-12) cells by significantly increasing the activities of catalase, superoxide dismutase, Glutathione peroxidase and glutathione that were reduced by 6-OHDA in PC-12 cells (Magalingam et al., 2016). There was no significant difference in the activation of glutathione peroxidase and glutathione enzymes between rutin and isoquercetin signifying that the two glycosides are equally important in protecting PC-12 cells against 6-OHDA toxicity. Both rutin and isoquercetin suppressed lipid peroxidation, MDA generation and prevented cell damage in 6-OHDA-induced neurotoxic PC-12 cells. Quercetin supplementation in diabetic and non-diabetic rats reported were to have neuroprotective effect by preventing glial and neuronal loss and the presence of reduced neuronal and glial body areas (Souza et al., 2017). This suggest that quercetin have the capacity of preventing cellular damages associated with long term diabetes mellitus. Yang et al. (2018) showed that quercetin (50 mg/kg) was able to suppress azodothymidine (AZT)-induced neuroinflammation by significantly inhibiting the expression of microglial and astrocytic markers induced by 100 mg/kg AZT in the mouse cortex, hippocampus and spinal cord. Co-administration of quercetin with AZT also attenuates the up-regulation of pro-inflammatory cytokines.

Effect of quercetin on cardiovascular disease

Philippine red *Allium cepa* was reported to decrease the serum level of LDL-cholesterol in Wistar rats (Pinedi and Calzada, 2013). They suggested the flavonoid content of the red Allium cepa to be responsible for the decrease in the serum level of LDL-cholesterol and that Allium cepa may decrease the risk of atherosclerosis. Onion skin quercetin at 162 mg/d was capable of decreasing blood pressure in hypertensive patients suggesting a cardio-protective effect of quercetin but without effect on the mechanistic parameters (Brüll et al., 2015). Quercetin was reported to reduce the force of contraction of porcine pulmonary arteries by limiting calcium release from the sarcoplasmic reticulum with no effect on voltage-operated channel (Banerjee, 2015). The transcriptional activity of nuclear factor

of transcription kappa B (NF-KB) and serum levels of interleukin 1β and Tissue necrosis factor-α (TNF-α) were decreased by quercetin in patinets with coronary artery disease as compared with untreated controls (Chekalina et al., 2018).

Quercetin was reported to significantly reduce the carcinogen activity of some cooked food mutagens including bay-region diol epoxides of benzo[a] pyrene and heterocyclic amines, these carcinogens reduce activation by cytochrome P-450 dependent mixed-function oxidases; quercetin inhibits these oxidases in vitro (Morris, 2001).

Conclusion

Quercetin is a naturally occurring flavonoid, it is more abundant in fruits and vegetables. Onion contain more quercetin than blackcurrants, broccoli, black grapes and apple. The total quercetin content in the dry onion skin is significantly higher than that in the edible parts. Quercetin is used in the treatment and prevention hyperglycemia, kidney disease, liver disease, cardiovascular disease and nervous system disorders.

Conflicts of interest

Authors declare that they have no conflict of interests.

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