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QUERCETIN AND METABOLIC SYNDROME

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ABSTRACT

Quercetin is an important and one of the most researched flavonoid for its biological activities both in clinical and preclinical studies. Experimental studies on quercetin suggest its potential in the amelioration of metabolic syndrome and its components. Present review is an overview of quercetin potential in the amelioration of metabolic syndrome.

KEYWORDS: Quercetin, metabolic syndrome, insulin resistance, obesity, inflammation, gene expression.

INTRODUCTION

Metabolic syndrome (MS) is collection of several factors that responsible for myocardial infarction such as obesity, dyslipidemia, hypertension, insulin resistance, glucose intolerance and obesity related inflammation.[1–3] The prevalence of these factors increases the susceptibility for diabetes and myocardial infarction.[4] It has been found that there is high prevalence of metabolic syndrome in urban India.[5,6] Thus MS suffering individual must be treated to avoid the further complications of diabetes and myocardial infarction. During the past several years there have a continuous research in this field such as new therapeutic targets, noval mechanism, new leads that are specific on their action and also fewer or no side effects have been achieved. Though, several mechanistic targets and drug candidate have been explored the treatment with single candidate has not been achieved.

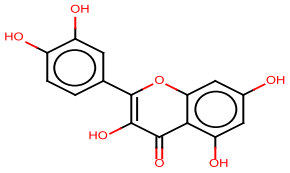
In the research for the drug management several phytoconstituents has shown their potential in countering the MS and its components. In particular, flavonoids are most extensively researched category of phytoconstituents and have gained fair share of recognition because of preclinical and clinical investigation on the compound that lead to their emergence in amelioration of hypercholesterolemia, hypertriglyceridemia, obesity, insulin resistance and hypertension.[7]

In general, flavonoids are poly-phenolic, secondary metabolites present in several of our dietary plants that are often consumed by us such as fruit juice, wine, tea, dark chocolate, cereals, legumes and olive oil etc which contribute to beneficial health effects.[8] Structurally, flavonoids are diphenyl propanes in which linear carbon chain (C6-C3-C6) form closed pyran ring with one of the two benzene rings. Flavonoids are thus 15 carbon compounds arranged to form three rings with extensive substitution and oxidation that provides structural and functional peculiarity to these flavonoids. Depending upon the substitution and oxidation in heterocyclic pyran ring, flavonoids can be broadly divided into seven subclasses such as flavonols, flavones, flavanones, flavanols, flavanonols, isoflavones, catechins, anthocyanidins and anthocyanins.[9]

In particular, quercetin belongs to the flavonol subgroup of flavonoids, with other members of this subgroup such as myricetin, galangin, kaempferol and fisetin etc. It is present in abundance in several vegetables and fruits such as onions, broccoli, tomato, red cabbage, fennel, apples, apricots, cherries, blueberries, grapes, semambu leaves, papaya shoots, black and green tea.[10] Several plants that are effective in amelioration of MS such as Fenugreek seed polyphones which has insulin sensitizing actions quercetin was detected as an important polyphenols component in a rat model.[11] Quercetin treatment to rats that showed metabolic syndrome showed improvement in the altered cardiovascular and hepatic factors[12] and was also shown to ameliorate metabolic syndrome and inflammation in obese Zucker rats.[13]

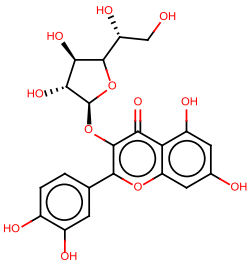
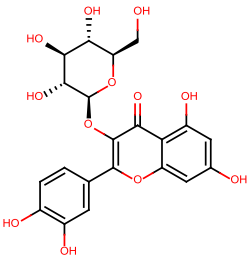
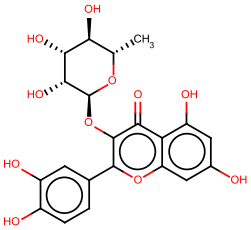
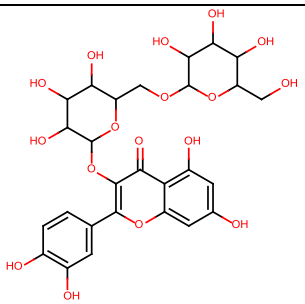
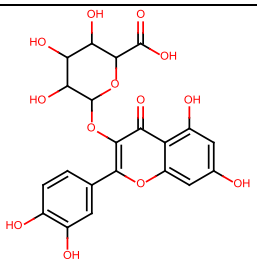
The name quercetin has been inspired word “quercetum” the name used for “oak forest” and is in use since 1857. Its IUPAC name is 3, 5, 7, 3´, 4´ pentahydroxyflvanone **(1)** and is an auxin transport inhibitor in plants. As far as its solubility is concerned it is soluble in lipids and alcohol, poorly soluble in hot water and insoluble in cold water. However, the quercetin glycosides formed generally on replacement of OH at position 3 by sugar such as rhamnose, glucose or rutinose results in increased water solubility compared to quercetin

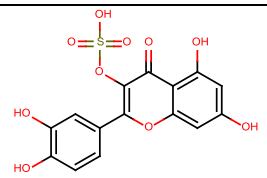
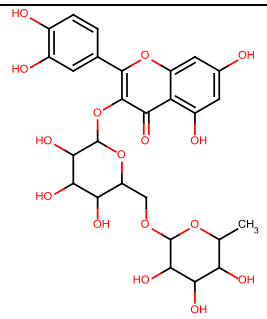
aglycone and change several other pharmacokinetic parameters.[14] Some important quercetin derivatives are given in Table 1.



Quercetin (1).

Table 1. Some important quercetin derivatives for metabolic syndrome.

S. No	Derivatives of quercetin	Structure
1	Pentamethylquercetin	
2	Isoquercetin (Quercetin 3-O-β-D-glucopyranoside)	
3	Quercitrin (Quercetin 3-rhamnoside)	
4	Quercetin 3-O-gentiobioside	
5	quercetin-3-O-β-D-glucuronide (Querciturón)	

6	Quercetin 3-O-sulfate	
7	Quercetin 3-rutinoside	

QUERCETIN AND INSULIN RESISTANCE

Chronic intake of excessive calories in addition to the lack of physical activity leads to increased fat synthesis and deposition of fat in non-adipose tissues causing insulin resistance.[15] In particular, insulin resistance signify the condition in which peripheral organs such as skeleton muscle cells, liver and adipose tissue becomes unresponsive to the insulin action, resulting in decreased glucose intake and increased glucose output.[16]

Quercetin (50 µM) treatment to L6 skeletal muscle cells, human HepG2 and murine H4IIE hepatocytes for 18 h stimulated AMPK, increased GLUT4 translocation in cultured rat L6 skeletal muscle cells. It was also observed that quercetin induce hepatic AMPK activation and inhibits glucose-6-phosphatase in H4IIE hepatocytes. Moreover, quercetin exhibits capacity, though mildly, to enhance glycogen synthase in HepG2 hepatocytes which is a rate-limiting enzyme for glycogen synthesis.[17] In earlier study Eid et al. showed that quercetin glycoside (quercetin-3-O-glycosides) at the consecration of 50 muM for 18 h treatment, stimulated glucose uptake by 38 to 59% in the absence of insulin treatment. Moreover, it was observed that aglycone part of quercetin glycoside at very low concentration (25-100 µM) stimulated glucose uptake by 37% probably due to AMPK activation that facilitate GLUT4 translocation to cell membrane. In quercetin treated isolated mitochondria, aglycone part of quercetin glycoside inhibits ATP synthase which was shown to 34 and 79% at 25 and 100 µM, respectively suggesting hydrolysis of glycoside to aglycone is necessary for activity.[18]

Activity of quercetin glycosides in amelioration of insulin resistance is enhanced in the presence of other agents. For instance, fructooligosaccharide augment benefits of quercetin glycoside (quercetin-3-O-β-glucoside) on insulin sensitivity and plasma total cholesterol. It increased quercetin absorption in sucrose-fed rats to enhance bioavailability of quercetin.[19] Moreover other glucose transporters are also under the influence of quercetin treatment. For instance, Mathur et al. reported *Psidium guajava* Linn. leaf extract containing quercetin up to 9.9% w/w to regulate expression of hepatic GLUT-2 and attenuate early onset of insulin resistance on fructose administration.[20] Besides regulating expression of glucose transporter, quercetin also ameliorated fatty acids induced insulin resistance and up-regulates cellular antioxidants level in oleic acid induced steatosis in HepG2 cells[21] and also in non alcoholic fatty liver disorder (NAFLD) cell model.[22] Besides, these direct effects in insulin sensitivity quercetin play a role in lowering of increased cytokines content in the state of insulin resistance. For instance, Chuang et al. reported that quercetin treatment to primary human adipocytes attenuated TNFα mediated insulin resistance and inflammation which was comparable to resveratrol treatment.[23] Moreover in another study Dai et al. showed quercetin effects in amelioration of TNF-α induced insulin resistance in C2C12 skeletal muscle cells.[24]

Henagan et al. reported that dietary incorporation of quercetin increases PGC1α expression in skeletal muscle, improves mitochondrial function and attenuates insulin resistance in mice.[25] In earlier study by Henagan et al. showed effects of dietary quercetin and quercetin-rich red onion extract to affect skeletal muscle mitochondria and insulin sensitivity.[26] Besides, having potential activity, its efficacy is enhanced by other agents. For example, quercetin rich *Psidium guajava* juice when combined with trehalose reduces autophagy, apoptosis and pyroptosis formation in the kidney and pancreas of Type II Diabetic Rats.[27]

QUERCETIN IN OBESITY

Obesity is the result of the increased calorie intake than energy expenditure. This is due to the combined effect of sedentary life style and intake of high calorie fast foods besides other environmental and genetic factors. Experimental studies have shown that chronic dietary intake of quercetin alleviates hepatic fat accumulation associated with consumption of a Western-style diet in C57/BL6J mice.[28] Moreover, monosodium glutamate, the most used flavor enhancer, is associated with increased prevalence of metabolic syndrome.[29] It was

found that pentamethylquercetin (quercetin derivative) generates beneficial effects in monosodium glutamate-induced obesity in mice and in C2C12 myotubes via AMPK activation.[30]

Other quercetin derivatives such as quercetin 3-O-gentiobioside and isoquercitrin reduces blood glucose and serum insulin levels and improve glucose tolerance in obese mice. Moreover, isoquercitrin and quercetin-3-O-gentiobioside treated mice showed reduction in cholesterol levels. It was also observed that ethanolic extract of Okhra inhibited the expression of nuclear receptor transcription factor PPARγ, which is an important regulator of lipid and glucose homeostasis. Furthermore, ethanolic extract of Okhra and quercetin 3-O-gentiobioside have shown antioxidant activity *in-vitro.*[31]

In *in-vitro* model of normal and insulin resistant 3T3-L1 cells, quercetin inhibited AS160 phosphorylation and therefore inhibited insulin-mediated GLUT4 translocation. Moreover, in inflammatory 3T3-L1 cells showing insulin resistance, quercetin facilitated insulin signaling by inhibiting IKKβ phosphorylation and restores the insulin-mediated AS160 phosphorylation facilitating the GLUT4 translocation. Hence, quercetin had different effects on glucose uptake in insulin resistant and basal conditions which were related to its regulation of AMPK activity.[32]

Guo et al. showed quercetin and quercetin-3-O-glucuronide are equally effective in ameliorating endothelial insulin resistance and has shown their effects through inhibition of reactive oxygen species-associated inflammation.[33]

Quercetin is one of the abundant flavonoid in onion. In high fat diet/streptozotocin-induced diabetic rats it has been found that extreact prepared from the peel ameliorate hyperglycemia and insulin resistance.[34] Besides, quercetin as an excellent antioxidative properties and have been implicated in the amelioration of dyslipidemia and hyperglycemia in type 2 diabetic db/db mice.[35]

QUERCETIN AND INFLAMMATION

Inflammation is another important component of metabolic syndrome. Chronic obesity induces the inflammatory conditions characterized by increased inflammatory factors in serum and blood.

Pfeuffer et al. reported effect of quercetin on endothelial function and inflammation which are different traits of the metabolic syndrome in men that varied in APOE isoforms.[36] In a double blind cross-over study with APOE genotype on 49 male subjects, the quercetin (150 mg/d 8 weeks) followed by 3 week washout period, significantly decreased waist circumference ($P = 0.004$), postprandial systolic blood pressure ($P = 0.044$) and postprandial triacylglycerol concentrations whereas HDL-cholesterol concentrations increased after quercetin and decrease the increased levels of TNFα ($P = 0.024$).[36] The study by Zhang et al. suggests that quercetin inhibits AMPK/TXNIP activation and reduces inflammatory lesions that improve insulin signaling defect in the hypothalamus of high fructose-fed rats.[37] This study is of significance since in hypothalamus AMPK activation is not desired condition.

Mahmoud et al. showed that quercetin protects against low grade inflammation and vasoconstriction in diabetic rats[38] and also protects against skeletal muscle inflammation and atrophy induced by obesity.[39] Zhang et al. reported that in nonalcoholic fatty liver disease of rats, quercetin affects IL-18 content in serum, improved insulin resistance.[40] Quercetin reduces obesity-associated ATM inflammation and infiltration in mice and activation of AMPKα1/SIRT-1 pathway was proposed by Dong et al for effects of quercetin.[41] The study by Anhe et al. suggests that quercetin decreases inflammatory response and increases insulin action in skeletal muscle of ob/ob mice and in L6 myotubes.[42] Overman et al. also suggests that Quercetin attenuates inflammation in human macrophages and adipocytes exposed to macrophage-conditioned media.[43] These studies suggest quercetin potential in the amelioration of inflammation which is the consequence of obesity and contribute in insulin resistance.

QUERCETIN AS GENE EXPRESSION REGULATOR

On treatment to C57BL/6N mice that were fed a high-fat diet, quercetin derivatives isolated from mulberry leaves downregulated gp91phox expression (Liver gene expression), downregulated expression of FAS and GPAT (involved in lipid metabolism) and upregulate PPAR-α (related to β-oxidation). Moreover, it was observed that quercetin treatment downregulate expression of G6Pase and L-PK while showed increased expression of GK.[44] The study suggest that quercetin control translation of mRNA that have role in glucose metabolism.

Moreover microRNAs, which are post-transcriptional gene regulators, their expression have been implicated in several biological functions and their abnormal expression and/or function in the immune system have been linked to multiple human diseases such as inflammatory disorders, specifically inflammatory bowel disease and cancers.[45] Quercetin has been reported to regulate microRNA expression and ameliorate inflammation. For instance, in high fat fed mice, quercetin treatment (6 week) downregulated mRNA expression of inflammatory genes, C-reactive protein, interleukin-6, monocyte chemoattractant protein 1 and acyloxyacyl hydrolase. Moreover, quercetin treatment increased the expression of redox factor 1 that inturn regulate nuclear factor κB signaling. Furthermore, hepatic miR-122 and miR-125b concentrations were also increased by quercetin supplementation.[46] All these

effects of the quercetin in stimulation of genes improve insulin resistance and several other parameters of MS.

It was reported by Joven et al. that plant-derived polyphenols regulate expression of miRNA paralogs miR-103/107 and miR-122 and prevent diet-induced fatty liver disease in hyperlipidemic mice.[47] In high-fat induced obesity in mice, quercetin treatment significantly resists any weight gain and any increase in white adipose tissue content, decrease serum lipids, triglyceride and cholesterol content. Quercetin treatment altered the expression of several genes related to fat metabolism such as Pon1, Fnta, Pparg, Apoa4, Aldh1b1, Abcg5, Acaca, Gpam, Cd36, Fdft1 and Fasn. In conclusion quercetin prevents HFD-induced obesity in C57B1/6 mice and its anti-obesity effects may be related to the regulation of lipogenesis at the level of transcription.[48]

Quercetin role in amelioration of inflammation in macrophage can be associated with obesity and obesity induced inflammatory state that finally leads to insulin resistance. It has been reported that quercetin (0.l%) supplementation along with high fat diet to C57BL/6 mice for seven weeks, improve insulin sensitivity, improve glucose intolerance in mice and attenuated any rise in weight. Moreover, quercetin treatment increases GLUT-4 translocation and PKB signal, stimulate AMPK phosphorylation, lowered pro-inflammatory cytokines in epididymus epithelial tissue.[41] It has been found that the effect of quercetin can be enhanced by making quercetin more lipophilic. For instance, acylation of quercetin-3-O-glucoside with eicosapentaenoic acid was more effective than quercetin-3-O-glucoside on treatment to lipopolysaccharides (LPS) induced inflammation of THP-1 derived macrophages to reduce tumor necrosis factor-alpha (TNF-α), nuclear factor-kappa B (NF-κB), prostaglandin 2 (PGE2) and cyclo-oxygenase (COX)-2 levels. In in-vivo models of high fat fed mice the acylated quercetin-3-O-glucoside was more effective in reducing the serum concentrations of interleukin (IL)-6, C-reactive protein (CRP) and interferon-gamma (IFN-γ).[49]

Quercetin effectiveness is more on differentiang adipocytes than to mature cells. For instance, in mature and differentiating 3T3-L1 preadipocytes when exposed for 24 hours with low doses (0.1-10 μM) of quercetin it was observed that at doses of 0.5 to 10 μM to differentiating adipocytes reduced triacylglycerol content. Specifically, at low concentration of 1 μM, quercetin reduced C/EBPβ, PPARγ gene expression and SREBP1 protein levels. In addition, quercetin (10 μM) reduced lipoprotein lipase (LPL), Peroxisome proliferate activate receptor gamma (PPARγ) and sterol regulatory element binding protein (SREBP1c) expression. In mature adipocytes, high dose of quercetin (10 μM) was shown to reduce triacylglycerol content and fatty acid synthetase (FAS) gene expression.[50]

QUERCETIN IN HYPERTENSION

Quercetin potential for its antihypertensive activatiy has been compile by Perez-Vizcaino et al. in their review "Antihypertensive effects of the flavonoid quercetin".[51] In addition, on supplementation onion skin extract (with 162 mg/d quercetin) lowered the ambulatory blood pressure in hypertensive patients.[52] It has been reported that quercetin's antihypertensive effects in men, on giving a single dose of quercetin (1095 mg), suggests for some other mechanism irrespective of effect on angiotensin converting enzyme (ACE activity), nitric oxide bioavailability and endothelin 1 (ET-1).[53] In another double-blind, placebo-controlled, randomized, crossover study antihypertensive effects of quercetin (730 mg quercetin/d for 28 days) were reported without any effect on oxidative stress.[54] Clinical trial studies also suggests that quercetin reduced systolic blood pressure significantly without any significant effect on inflammatory biomarker and other cardiovascular risk factors.[55] In contrast, cardioprotective effects of tea, which have quercetin as an important component along with epicatechin, contribute in attenuation of inflammation in endothelial function.

QUERCETIN AND METABOLIC ENZYME REGULATION.

Quercetin derivative has shown inhibition potential in enzymes related to diabetes and hypertension. For instance, 2-Chloro-1,4-naphthoquinone derivative of quercetin inhibits aldose reductase.[56] Guerrero et al, investigated quercetin potential against angiotensin converting enzyme (ACE) inhibition at IC_{50} value of 43 μM.[57] On molecular docking by Auto Dock Vina and PyRx, the analysis suggests for quercetin binding affinity to ACE enzyme in terms of binding energy as low as -8.5 kcal/mol.[58] Balasuriya et al. reported that quercetin-3-O-glucoside and quercetin-3-O-glucuronic acid inhibited ($p<0.05$) ACE activity. Two quercetin metabolites (quercetin-3-O-sulfate and quercetin-3-O-glucuronic acid) isolated from flavonoid-rich apple peel extract significantly ($p<0.05$) inhibited ACE enzyme of human umbilical vein endothelial cell (HUVEC) model.[59]

LIMITATION OF QUERCETIN IN METABOLIC SYNDROME

Besides, all the encouraging studies there are also some limitation. For instance, on insuction of diet-induced obesity in C57BL/6J mice, Stewart et al. reported failure of dietary quercetin to alter the progression of insulin resistance among tissues.[60] Romero et al. reported absence of any antihypertensive effect of quercetin in adult spontaneously hypertensive rats.[61] Adenosine in combination with quercetin, induce insulin resistance in high fat diet-fed mice.[62] Arias et al. reported quercetin potential in attenuation of insulin resistance however fails to show any decrease in fat accumulation and adipose tissue content effect on treatment with skeletal muscle.[63] Moreover, it is reported that quercetin doesnot contribute significantly in cardioprotection role and amelioration of insulin resistance effect of cocoa and tea,

however suggests for epicatechin may in part contribute to the by improving insulin resistance.[64] However, in another study supplementation quercetin and epicatechin improve several biomarkers of endothelial dysfunction and inflammation.[65]

BIOAVAILABILITY OF QUERCETIN

Phytoconstituents efficacy is depenent upon their bioavailability which is under the influence of several endogenous and exogenous factors. Kawabata et al suggested that on ingestion of vegetables and fruits containing quercetin glycosides, metabolised and absorbed and then is circulated as conjugates in the blood. The major metabolite of quercetin is quercetin-3-O-β-D-glucuronide which is hydrophilic in nature get distributed throughout the body and exert several beneficial effects in tissues. It has been observed that hydrophilic quercetin-3-O-β-D-glucuronide get deconjugated to hydrophobic quercetin aglycone at injured sites which, in turn, may improve the pathological conditions such as inflammation.[66] Quercetin bioavailability is generally poor and also varies between different subjects depending upon their age, gender, glycosylation, presence of other sugar moieties, fibre content of food and dietary fat content.[67] Quercetin bioavailability is influenced by other drugs. For instance, deficiency of vitamin C increased quercetin biovailability in humans.[68] Moreover, fat content in the diet increases quercetin absorption and thus bioavailability in overweight individuals.[69] As already mentioned sugar moiety of quercetin-glucosides increases bioavailability in humans and also when subjected to α-oligoglucosylation. It has been found that quercetin on supplementation with dietary sources is more bioavailable than it's glucosides in humans and this is probably due to food matrix.[70]

CONCLUSION

Though several *in-vitro* and *in-vivo* studies suggests quercetin potential in amelioration of different components of metabolic syndrome, clinical trial studies are fewer and those reported fails to suggest the potentiality of quercetin in metabolic syndrome. Possibly, the reason could be the bioavalability issue of quercetin and its glycosides. Further, studies to synthesize different derivative of quercetin that have better pharmacokinetics profile and at the same time effective are warranted. Moreover prodrug approach for enhancing the absorption of quercetin and modification of quercetin formulation are other areas of research. However, inclusions of the more of quercetin containing dietary foods should be included in the diet of metabolic syndrome subjects could be an effective strategy to counter some of the MS components effectively. This will help in, as evident from experimental studies, to counter insulin resistance, increase of insulin sensitivity, attenuation of obesity induced inflammation, lower hypertension, all of which are different components of MS.

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