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REVIEW

Modulation of Chronic Inflammation by Quercetin: The Beneficial Effects on Obesity

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Abstract: Obesity has become a major risk factor for the development of chronic diseases such as insulin resistance, type 2 diabetes mellitus, and cardiovascular disease. Moreover, obesity induces chronic inflammation in adipose tissue, liver, skeletal muscle, and the vascular system. Quercetin is the major representative of the flavonoid subclass of flavonols, which is ubiquitously contained within natural plants such as green tea, and vegetables, including onions and apples. Researchers have focused greater attention to the beneficial physiological roles of quercetin, which has anti-oxidative, anti-inflammatory, and anti-fibrotic effects on insulin resistance and atherosclerosis in obesity-related diseases. Also, the anti-inflammatory effects of quercetin on intestinal microbiota have been demonstrated in obesity. In addition, there is increasing evidence that quercetin is associated with epigenetic activities in cancer, and in maternal undernutrition during gestation and lactation. In this review, we focus on the chemical properties of quercetin, its dietary sources in obesity, and its anti-inflammatory effects on insulin resistance, atherosclerosis, intestinal microbiota, and maternal under-nutrition with epigenetic activity.

Keywords: quercetin, inflammation, obesity, insulin resistance, atherosclerosis

Introduction

Obesity has become one of the most prevalent health problems globally and represents a major risk factor for the development of chronic diseases such as insulin resistance, type 2 diabetes mellitus, and cardiovascular disease.[1] Moreover, obesity induces chronic inflammation in adipose tissue, the liver, skeletal muscle, and the vascular system. Chronic inflammation induces release of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), and interleukin-6 (IL-6), and immune cell infiltration is closely associated with the development of insulin resistance through interactions with the insulin signaling pathway in adipose tissue and skeletal muscle[2,3] and is closely linked to the pathogenesis of atherosclerosis in vessel walls.[4]

Quercetin, a flavonoid compound, is found in vegetables and plants such as onions, apples, and green tea. For instance, the dominant onion flavonoids have been determined to be quercetin, quercetin-3-O-β-glucoside (Q3G), quercetin-4′-O-β-glucoside (Q4′G), and quercetin-3,4′-di- O-β-glucoside (Q3,4′G).[5] Interestingly, cooking methods affect the final flavonoid content; total quercetin abundance is increased 1.5-fold by microwave heating for 1 min, whereas the levels of Q4′G are decreased by boiling.[6]

To date, researchers have focused more attention on the beneficial physiological roles of quercetin, which has anti-oxidative, anti-inflammatory, and anti-fibrotic

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effects,[7–9] although quercetin has been reported to have its potential pro-oxidative property in addition to its antioxidative property.[10,11] More interestingly, there is increasing evidence that quercetin is associated with epigenetic changes in cancer[12] and in maternal under-nutrition during gestation and lactation.[13] Therefore, studying the physiological roles of quercetin on chronic inflammation would contribute to preventive and therapeutic applications in obesity-related diseases.

In this review, we focused on chemical properties, dietary sources, and anti-inflammatory effects of quercetin on insulin resistance, atherosclerosis, intestinal microbiota, and maternal under-nutrition with epigenetic activity.

Chemical Structure and Dietary Source of Quercetin

Quercetin is the major representative of the flavonoid subclass of flavonols and is ubiquitously present in plants, fruits, and vegetables. The characteristic structure of flavonoids comprises a basic backbone of flavan, which has a C6-C3-C6 structure in which 2 benzene rings (C6) are bonded by 3 carbons (C3). Flavonols are present in plants as flavonoid-sugar compounds, which are referred to as glycosides in general. Figure 1 illustrates the structures of quercetin aglycone, which lacks a sugar moiety, and of quercetin-β-glucoside, which has been reported to be contained mainly in onions.[14,15]

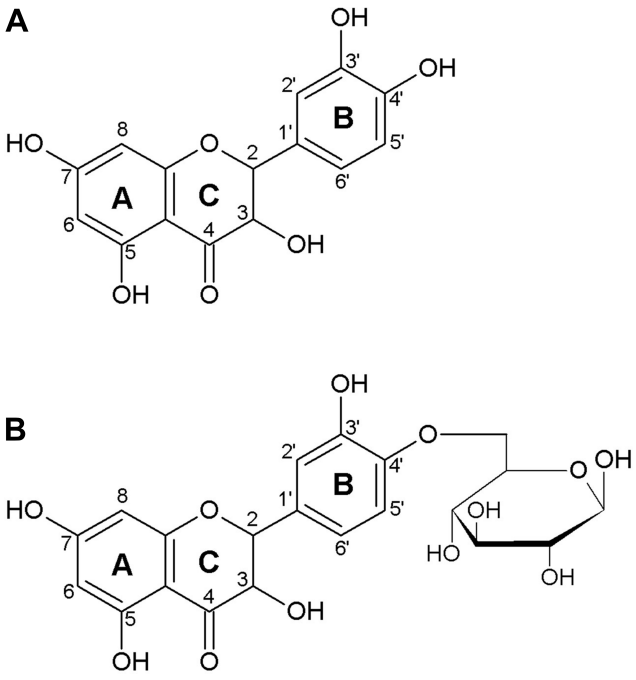

Figure 1 Structure of quercetin aglycon (**A**), and quercetin-4′-O-β-D-glucoside (**B**).

The types and amounts of flavonoids are extremely varied among plants. To date, the levels of quercetin in various foodstuffs have been reported in numerous studies.[16–20] When foods containing quercetin are consumed, the rate of intestinal absorption is higher for quercetin glycosides than aglycon.[21] Hollman et al, who evaluated the bioavailability of quercetin, reported detecting increased concentrations of quercetin in plasma immediately after oral administration of onion and apple supplements.[15] Absorbed quercetin is rapidly metabolized in the liver, and circulates as methyl, glucuronide, and sulfate metabolites.[22] In human healthy adults, 163 diverse metabolites and quercetin conjugates such as quercetin-3-glucuronide, isorhamnetin-3-glucuronide, quercetin diglucuronide, and quercetin-30-sulphate were measured in the plasma after long-term quercetin-containing supplements; especially the concentrations of conjugates increased at the 1000 mg/day dose for 90 days.[23] Therefore, circulating quercetin and its metabolites in peripheral tissues are expected to exhibit bioavailability, resulting in anti-inflammatory effects.

Anti-Inflammatory Effects of Quercetin on Insulin Resistance

Insulin is well known to induce glucose uptake by binding to its receptors on the cell membrane of target organs such as the liver, skeletal muscle, and adipose tissue. When the insulin receptor (IR) is phosphorylated, the phosphorylation of insulin receptor substances (IRS) is increased. IRS activate the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, which is largely responsible for the metabolic action of insulin, as well as the Ras/mitogen-activated protein kinase (MAPK) pathway, which mediates gene expression for insulin's effect.[24] When the PI3K/Akt pathway is activated, glucose transporter 4 (Glut4) expression and translocation are upregulated, promoting the uptake of glucose into cells.[25,26] Insulin resistance is one of the main factors responsible for the onset and progression of diseases such as obesity, diabetes, and atherosclerosis. Insulin resistance is involved in impairment of the PI3K/Akt pathway in target organs such as adipose tissue and skeletal muscle, leading to the downregulation of Glut4 expression and its translocation. In obesity, excessive accumulation of fat in the visceral adipose tissue induces hypertrophy and dysfunction of adipocytes.[27,28] The excessive amount of free fatty acids (FFAs) released from visceral adipose tissue is associated with interference in insulin's action.[29]

Insulin resistance is closely associated with chronic low-grade inflammation through interactions with the insulin signaling pathway in the liver and adipose tissue.[2,3] For instance, elevated levels of proinflammatory cytokines such as TNF-α, MCP-1, and IL-6, and of proinflammatory enzymes such as cyclooxygenases (COXs) and inducible nitric oxide synthase (iNOS) in adipose tissue, skeletal muscle, and neuronal systems, have been demonstrated to lead to the development of insulin resistance.[30,31] In particular, TNF-α is one of the most important proinflammatory mediators which is involved in the development of insulin resistance.[32]

Regarding the anti-inflammatory effects of quercetin on proinflammatory cytokine production, in macrophages and adipocytes, it decreases the expression levels of the inflammatory genes *TNF-α, IL-6, IL-1β*, and *COX-2*, suppressing the activation of nuclear factor (NF-κB) and c-Jun N-terminal kinase (JNK).[33] Dietary quercetin attenuates adipose tissue expansion and decreases the levels of serum *IL-6* and *MCP-1* mRNA in white adipose tissue in high fat diet (HFD)-induced obese mice.[34] In the hypothalamus, quercetin reduces the mRNA expression levels of *TNF-α, MCP-1*, and *IL-1β* in HFD-fed obese mice.[35] Moreover, dietary quercetin and the combination of quercetin and catechin reduce metabolic parameters such as insulin concentrations and insulin resistance (HOMA-IR), and also levels of adipocytokine proteins such as TNF-α, visfatin, and resistin in adipose tissue in HFD-fed mice.[36] The effects of quercetin on proinflammatory enzymes have been investigated in several studies. For example, quercetin inhibits nitric oxide (NO) production and iNOS expression in PC cells treated with dopaminergic neurotoxin 6-hydrooxydopamine, which induces neural damage.[37] In lipopolysaccharide-treated colon epithelial cells, the quercetin 3,7-O-dimethyl ether isolated from herbs downregulates the expression of iNOS and COX-2 proteins.[38] Intraperitoneal treatment with quercetin suppresses increased COX-2 expression in rats with unilateral ureteral obstruction, which is associated with increased inflammation and oxidative stress.[39] Importantly, quercetin may improve insulin resistance through inhibiting the production and expression of proinflammatory cytokines and/or enzymes.

Toll-like receptors (TLRs) are one of the key elements of the immune system, which play central roles in host cell recognition and responses to microbial pathogens.[40] Also, TLRs are known to regulate obesity-related inflammation and insulin resistance.[41] The activation of TLR pathways encourages the production of proinflammatory cytokines through the upregulation of transcription factors such as NF-κB and activated protein 1 (AP-1).[41,42] FAAs released from adipose tissue increases proinflammatory reactions and polarization of M1 macrophages (classically activated macrophages) through upregulation of the TLR4 pathway.[43] In addition, age-associated adipose tissue inflammation is reported to be reduced in TLR4-deficient mice fed HFD.[44] There is evidence to demonstrate that quercetin has potential to regulate inflammation through the TLR4/NF-κB signaling pathway. Interestingly, quercetin treatment decreases cortical inflammation by inhibiting the TLR4/NF-κB signaling pathway in hypoxia-ischemia-induced brain injury in neonatal rats.[45] In addition, the combined treatment of quercetin and catechin inhibits increased levels of proinflammatory mediators, including TNF-α, IL-1β, and COX-2 in lipopolysaccharide (LPS)-stimulated macrophage RAW 264.7 cells, suggesting that the combined treatment may suppress the activation of TLR4-mediated NF-κB and MAPK signaling pathways.[46] Therefore, quercetin contributes to the suppression of proinflammatory mediators through inhibition of the TLR4/NF-κB signaling pathway.

Increased activation of AMP-activated protein kinase (AMPK) may play a role in suppression of proinflammatory mediator expression by inhibiting NF-κB activation.[47] In addition, metformin, which is widely used as an antidiabetic drug, ameliorates chronic low-grade inflammation and modulates macrophage polarization through the activation of AMPK in HFD-fed mice.[48] Moreover, AMPK is closely linked to fibrosis-promoting pathways, as well as inflammation.[49] AMPK activation reduces glomerular TGF-β, collagen, and fibronectin accumulation in several murine models of diabetic kidney disease.[50]

Several studies have revealed that polyphenolic compounds, such as quercetin, resveratrol, and curcumin, enhance the phosphorylation of AMPK.[51] For example, quercetin treatment showed anti-adipogenesis activity through the upregulation of AMPK and acetyl-CoA carboxylase (ACC) phosphorylation in 3T3-L1 preadipocytes.[52] The expression of uncoupling protein 1 (UCP1), which plays an important role in increasing energy expenditure, increased in 3T3-L1 adipocytes treated with quercetin.[53] The authors suggested that quercetin increased the level of UCP1 in adipose tissues, accompanied by AMPK activation, and may lead to the prevention of obesity.[53] In C2C12 myotubes, quercetin ameliorated insulin resistance under inflammatory conditions with activation of AMPK.[54] Quercetin suppresses inflammation by modulating the AMPK pathway as well as the silent information regulator

(Sirt) 1.[55–57] In addition, quercetin reduces macrophage infiltration of adipose tissues, lowers the levels of proinflammatory mediators, and upregulates AMPK phosphorylation and Sirt1 expression in adipose tissues of HFD-fed mice.[55] In a renal ischemia/reperfusion (I/R) animal model, quercetin improves renal I/R injury through upregulation of AMPK phosphorylation and activates autophagy during I/R.[58] When HFD-fed ApoE-/- mice, an animal atherosclerosis model, received quercetin, the levels of TNF-α, IL-1β, and IL-18 and ratios of microtubule-associated protein light chain 3A (LC3) II/I were restored,[59] suggesting that the attenuation of atherosclerosis by quercetin is associated with enhancement of autophagy. Therefore, quercetin may be involved in the resolution of inflammation through upregulation of autophagy activation.

In addition, insulin resistance is closely associated with inflammation and atrophy in skeletal muscle in the obese. In insulin resistance, the production of proinflammatory mediators such as TNF-α, IL-1, and IL-6 is upregulated in skeletal muscle and adipose tissue,[60,61] which consequently leads to impaired insulin action and muscle fiber metabolism.[62,63] Treatment with quercetin suppresses the upregulation of TNF-α and iNOS expression levels and restores the reduction of glucose uptake by L6 myotubes treated with palmitate.[64] In an obese animal model, quercetin suppresses obesity-related skeletal muscle atrophic factors such as MAFbx/atrogin-1 and muscle ring-finger protein 1 (MuRF1), accompanied by increases in heme oxygenase 1 (HO-1) levels, and inactivation of NF-κB.[65] In addition, quercetin reduces macrophage accumulation and levels of inflammatory cytokines (eg, TNF-α and MCP-1) and the mRNA levels of MAFbx/atrogin-1 and MuRF1 in skeletal muscle of HFD-fed obese mice, suggesting that quercetin may prevent obesity-induced skeletal muscle atrophy through suppressing inflammatory responses.[66] Thus, quercetin could contribute to protect against obesity-related skeletal muscle atrophy by suppressing inflammatory mediators and macrophage infiltration in skeletal muscle, leading to improved insulin resistance.

Anti-Inflammatory Effects of Quercetin on Atherosclerosis

Inflammation is closely linked to the pathogenesis of atherosclerosis.[4] Atherosclerosis is known as an inflammatory condition of vessel walls, characterized by infiltration involving mainly macrophage and T-cells; macrophages play key roles in the onset and development of atherosclerosis. As stimulated by lipid deposition, hypertension, and oxidative stress during the early stages of atherosclerosis, monocytes and T-cells migrate from the circulation into the vascular intima to differentiate into macrophages. Macrophages phagocytose oxidized low-density lipoprotein (ox-LDL), and the number of cells is increased. Thereafter, macrophages are transformed into foam cells, which take up excessive ox-LDL. These conditions promote the development of atherosclerosis.[67] Furthermore, macrophages produce pro- and anti-inflammatory cytokines, including IL-1β, and TNF-α, and emerge as a key mediator in the pathogenesis of atherosclerosis.

Quercetin suppresses the formation of ox-LDL-induced RAW264.7 macrophage foam cells, which is a foam cell model, reducing cellular lipid accumulation.[68] These phenomena can be interpreted; quercetin increases autophagy and decreases mammalian Ste20-like kinase 1 (MST1) during atherosclerotic progression.[69] Quercetin improves glucosamine-induced apoptosis and inflammation in human umbilical vein endothelial cells (HUVECs), which represent a model of vascular endothelial injury in the initial stages of atherosclerosis.[70] The combination of quercetin and docosahexaenoic acid (DHA) suppresses mRNA expression and phosphorylation of NF-κB subunits p50 and p65, and ERK1/2 and JNK1/2 in LPS-stimulated RAW264.7 macrophage cells.[71] Cao et al revealed that quercetin reduces otherwise elevated levels of TNF-α, IL-1β, and IL-18, and enhances lowered autophagy activity in HFD-fed ApoE-/- mice.[59] In addition, quercetin reduces the elevated mRNA expression of *TLRs* and *TNF-α* in high cholesterol diet-fed atherosclerotic rats, and quercetin also inhibits the nuclear translocation of NF-κB and release of cytokines in ox-LDL-stimulated human peripheral blood mononuclear cells in vitro, suggesting that quercetin may be a promising agent for the prevention of atherosclerosis.[72] Interestingly, quercetin treatment suppresses the progression of atherosclerosis in ApoE-/- mice by inhibiting dendritic cell activation associated with the development of atherosclerosis through downregulation of CD80, CD86, MHC-II, IL-6, and IL-12 levels.[73]

Clinical Studies Involving Quercetin Supplementation

In randomized clinical trials, participants who were overweight-to-obese patients with pre- and stage 1 hypertension were randomized to receive a dose of 162 mg/day quercetin from onion skin extract for 6 weeks. As a result, no

significant effects were observed in terms of serum C-reactive protein and TNF-α, as well as the levels of glucose, insulin, and HOMA-IR compared to a placebo group.[74] When healthy (pre) hypertensive men and women received quercetin-3-glucoside (160 mg/day) for 4 weeks, the levels of soluble endothelial selectin ($p = 0.03$) and IL-1β ($p = 0.009$), and the *z* score for inflammation ($p = 0.02$) were lower compared to placebo.[75] No effects of supplementation of four quercetin capsules per day containing 100 mg quercetin dihydrate (100 mg/day for 10 weeks) were observed for the inflammatory markers, IL-6 and soluble vascular cell adhesion molecule-1, in healthy male smokers, although quercetin reduced the serum levels of total cholesterol and LDL-cholesterol compared to a placebo group.[76] Women with type 2 diabetes receiving quercetin (500 mg/day for 10 weeks) exhibited reduced systolic blood pressure. However, there were no effects on serum levels of IL-6, TNF-α, and C-reactive protein in comparing the quercetin and placebo groups.[77] In addition, women with polycystic ovary syndrome were assigned to 2 groups of quercetin treatment: 1 g/day (two 500 mg capsules) daily for 12 weeks, and placebo. Quercetin reduced HOMA-IR levels ($p < 0.001$) and slightly increased serum adiponectin compared to a placebo group, the authors suggesting that quercetin supplementation may improve adiponectin-mediated insulin resistance.[78] Furthermore, women with rheumatoid arthritis (RA) were assigned into quercetin (500 mg/day) or placebo groups for 8 weeks. The study's results indicated that there were no effects of quercetin on plasma oxidative and inflammatory status, or systolic and diastolic blood pressure in patients with RA.[79] On the other hand, Javadi et al demonstrated that plasma TNFα levels were significantly decreased in a quercetin group compared to placebo in women with RA allocated into a quercetin (500 mg/day) or placebo group for 8 weeks.[80] Based on previous clinical studies, the effects of quercetin remain unclear. Further studies with various design and sample sizes, and with different quercetin doses, are needed, considering the beneficial effects of quercetin observed in previous animal and cell investigations.

Anti-Inflammatory Effects of Quercetin via Intestinal Microbiota in Obesity

Intestinal microbiota, which exist with a certain diversity in the human gastrointestinal lumen, are also involved in obesity. For instance, it has been revealed in humans and in animal models that obesity is associated with changes in the relative abundance of the two dominant bacterial divisions, the Bacteroidetes and the Firmicutes, with increased levels of Actinobacteria.[81,82] Turnbaugh et al demonstrated that colonization of germ-free mice with microbiota from obese animals resulted in significantly greater increases in total body fat than colonization with a non-obese "lean" microbiota.[83] Although there are some studies indicating that the proportions of intestinal microbiota are different among populations[84] or are not involved in obesity,[85] imbalances and alterations in composition and/or function of intestinal microbiota, so-called "dysbiosis", have been identified to be related to onset and/or development of obesity. In addition, the gut microbiota may be associated with the onset and/or development of atherosclerosis including inflammation and lipid metabolism.[86] For example, berberine isolated from various medicinal plants showed the anti-atherosclerotic effect with the changes in composition and functions of gut microbiota, which is associated with anti-inflammatory and glucose and lipid metabolisms.[87]

In recent years, attention has been focused on the effects of food components such as quercetin on intestinal microbiota in obesity. Etxeberria et al found that quercetin administration in rats effectively alleviates intestinal dysbiosis induced by a high-fat sucrose diet.[88] Quercetin supplementation attenuates the Firmicutes/Bacteroidetes ratio and inhibits the growth of bacterial species associated with diet-induced obesity. In another study, a combination of quercetin and resveratrol was able to ameliorate obesity and reverse the gut microbiota dysbiosis in HFD-fed rats.[89] Moreover, there are recent reports indicating that the relationship between quercetin and gut microbiota is associated with an anti-inflammatory status. *Citrobacter rodentium*-induced colitis in mice is well documented as an animal model of inflammatory bowel disease (IBD). Interestingly, pre-administered quercetin could alleviate *Citrobacter rodentium*-induced colitis, due to quercetin's ability to suppress pro-inflammatory cytokines such as IL-6 and TNF-α, and/or to modify gut microbiota. That is, pre-administration quercetin may enhance population numbers of *Bifidobacterium, Bacteroidetes*, and *Lactobacillus*, and may reduce those of *Fusobacterium* and *Enterococcus*.[90] In in vitro studies, quercetin reduces the levels of inflammatory mediators in LPS-stimulated macrophages by enhancing secretion of anti-inflammatory substances by *Bifidobacterium adolescentis*.[91] Stearic acid is tentatively identified as the anti-inflammatory molecule from *B. adolescentis* stimulated by quercetin.[92]

From these findings of the relationships between quercetin and microbiota, quercetin is expected to play a role in moderating intestinal inflammation in obesity. Indeed, a recent study using a mouse model of nonalcoholic fatty liver disease (NAFLD) associated with obesity demonstrates that quercetin can revert gut dysbiosis and related endotoxemia-mediated TLR4 pathway induction, with subsequent inhibition of inflammasome responses.[93] In addition, it is reported that the atherosclerotic lesions and size of plaques were reduced in mice fed HFD diets with oral quercetin treatment, by the alternation of the composition of the gut microbiota.[94] Quercetin treatment may contribute to mitigate the onset and/or development of atherosclerosis by modulating intestinal microbiota balance. In order to elucidate the anti-inflammatory effects of quercetin in obesity, including atherosclerosis, further investigations regarding intestinal microbiota are needed.

Epigenetic Activities of Quercetin During Inflammation

Epigenetics is referred to as heritable phenotypic alterations in gene expression that are independent of DNA sequence changes.[95,96] Common epigenetic modifications in mammalian cells include changes in DNA methylation, histone modification, and expression of various non-coding microRNAs (miRNAs). DNA methylation is catalyzed by DNA methyltransferases (DNMTs) and is thought to act at promoters so as to induce gene silencing. Histone modifications to specific amino acid residues modulate chromatin structure and gene expression. For example, the histone acetylation state is thought to be adjusted by histone acetyltransferases (HATs) and histone deacetylases (HDACs). miRNAs are known to regulate gene expression post-transcriptionally and function in RNA-silencing.[97]

Studies of epigenetic mechanisms have allowed advances in the understanding of cancer.[98,99] Interestingly, polyphenolic compounds derived from plants seem to exert anti-tumor effects through epigenetic activities.[100,101] Treatment with quercetin upregulates miR-503-5p and miR-6867-5p expression and exhibits the potential for anti-proliferative and anti-inflammatory actions in endometriosis implanted mouse models.[102] Treatment with quercetin decreases global DNA methylation levels and the activity of DNMTs, HDACs, and histone methyltransferases (HMTs) in quercetin-treated HeLa cells, a human cervical cancer cell line.[12] A combination of quercetin and butyrate with chemopreventive activity suppresses human esophageal cancer cell growth and downregulates the expression of DNMT1, NF-κBp65, HDAC1, and Cyclin D1.[103] In addition, quercetin enhances apoptosis by increasing the expression level of Fas ligand through the upregulation of HAT activity in human leukemia HL-60 cells.[104] Thus, quercetin is expected to act as a candidate natural therapeutic agent to prevent cancer through epigenetics activity. The HFD-fed mice showed hypermethylation in the peroxisome proliferator activated-receptor gamma coactivator 1 alpha (PGC-1α) promoter and Pgc-1α mRNA expression, which is a transcriptional coactivator, in skeletal muscle. Conversely, quercetin supplementation reduced the increases in DNA methylation and PGC-1α expression,[105] suggesting that quercetin may regulate PGC-1α expression through DNA methylation in obesity. Moreover, the treatment of quercetin inhibited inflammation in livers of nickel-treated mice by modulating nuclear factor-E2 related factor 2 (Nrf2) nuclear translocation and HO-1 activity and decreased DNMTs activity and DNA methylation level of the Nrf2 DNA.[106] Therefore, quercetin may epigenetically regulate the obesity and inflammation.

There is growing evidence that nutrients may modify epigenetic programs, thus regulating gene expression. For example, maternal under-nutrition or restriction of dietary protein during pregnancy leads to many diseases, including obesity, diabetes, and renal disease in adult offspring.[107–110] Such diseases are closely associated with the development of chronic inflammation. Maternal over-nutrition in utero results in developmental programming of genes involved in obesity, inflammation, and pro-fibrogenic genes in the liver of the offspring.[111] The unfolding pattern of histone H3 lysine 4 trimethylation in children and mothers was associated with human undernutrition.[112] Although quercetin exerts anti-inflammatory action with a wide range of mechanisms of actions, few reports have addressed mechanisms by which quercetin modulates inflammation by regulating epigenetic pathways, which is linked to maternal under-nutrition.

We previously reported that the feeding of quercetin to protein-restricted dams during lactation upregulates AMPK activation in the liver of 23 week-old adult offspring.[113] Significant increases in AMPK-associated phosphorylated ACC and endothelial nitric oxide synthase (eNOS) levels are found in the liver of such adult offspring. Quercetin treatment during lactation may lead to long-term alterations to the AMPK pathway in the liver of

adult offspring of protein-restricted dams. However, whether quercetin treatment during lactation directly activated AMPK in adult offspring remain unclear. The decreased levels of histone acetylation and increased levels of promoter methylation of PGC-1α promoter methylation were correlated with the activity of AMPK in human placenta of diabetic mothers. When diabetic placental explant was treated with metformin, an anti-diabetic drug, AMPK was activated, concomitant with increased H3K27 acetylation and decreased PGC-1α promoter methylation.[114] Thus, because metformin as well as quercetin upregulate the AMPK activation,[51] we hypothesized that quercetin treatment during lactation may activate AMPK via epigenetic regulation.

More interestingly, maternal quercetin intake during lactation may cause long-term alterations to inflammation and autophagy flux in the kidneys of high-fructose-diet fed adult female rat offspring.[13] Maternal quercetin intake during lactation decreases the number of infiltrating macrophages and depresses *IL-6* mRNA levels in the kidneys of adult female offspring fed a high-fructose diet after birth. After inducing obesity in female rats fed a HFD, maternal quercetin treatment improved glucose metabolism, insulin sensitivity, hepatic inflammation, and adipose tissue deposition in the adult offspring of obese dams.[115] On the other hand, maternal quercetin treatment, starting from 3 days before conception until the end of gestation, resulted in increased iron storage and decreased 8-oxo-dG levels in the liver of 12-week old adult murine offspring.[116] In addition, the authors indicated that maternal quercetin treatment increases IL-1β, IL-6, and IL-10 levels in the liver of the adult offspring. Importantly, maternal quercetin intake during gestation and/or lactation may modulate long-term alterations, including inflammatory responses in adult offspring. However, further experiments are required to clarify whether quercetin treatment during gestation and/or lactation contributes to the regulation of epigenetic pathways after birth.

Conclusions and Perspectives

This review provided recent evidence of the anti-inflammatory effects of quercetin. First, quercetin is involved in the attenuation of insulin resistance and atherosclerosis in obesity-related diseases. Insulin resistance is closely associated with the development of chronic low-grade inflammation. Quercetin may improve insulin resistance through inhibiting the production and expression of proinflammatory cytokines and/or enzymes. Importantly, quercetin is associated with inhibition of the TLR4/NF-κB signaling pathway. Based on previous cell culture studies and animal experiments, quercetin treatment is clearly required for preventative and therapeutic applications. However, different studies may also show the effects of quercetin in clinical studies. In this regard, the bioavailability of quercetin in organisms may be variable. It is necessary to establish more comprehensive studies that help to guide clinical studies. Second, some studies have shown the anti-inflammatory effects of quercetin on intestinal microbiota in obesity.

Prebiotics alter the intestinal microbiota and reduce serum levels of IL-6 in children with overweight or obesity.[117] In addition, quercetin treatment may mitigate the onset and/or development of atherosclerosis.[94] Not only quercetin but also a combination of quercetin and prebiotic treatment may contribute to improve chronic inflammation in obesity-related diseases. Third, we summarized that maternal quercetin intake during lactation may exert long-term alterations in inflammation. Several studies have investigated epigenetic modulation mediated by quercetin. Quercetin is thought to act as a candidate therapeutic agent to prevent cancer through epigenetic activities. On the other hand, few reports have addressed suggestions that maternal quercetin exerts anti-inflammatory effects in adult offspring programmed by maternal under-nutrition and over-nutrition through modulation of epigenetic pathways. Further investigations are required to advance our understanding of the effects of maternal quercetin intake during gestation and/or lactation on anti-inflammatory activity in obesity- and age-related diseases.

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Disclosure

The authors declare no conflicts of interest.

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