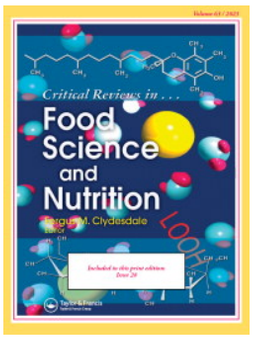

Critical Reviews in Food Science and Nutrition

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/bfsn20

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To cite this article: Lei Yan, Mostafa Vaghari-Tabari, Faezeh Malakoti, Soheila Moein, Durdi Qujeq, Bahman Yousefi & Zatollah Asemi (2023) Quercetin: an effective polyphenol in alleviating diabetes and diabetic complications, Critical Reviews in Food Science and Nutrition, 63:28, 9163-9186, DOI: 10.1080/10408398.2022.2067825

To link to this article: https://doi.org/10.1080/10408398.2022.2067825

Published online: 25 Apr 2022.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
2023, VOL. 63, NO. 28, 9163–9186
https://doi.org/10.1080/10408398.2022.2067825

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REVIEW

Quercetin: an effective polyphenol in alleviating diabetes and diabetic complications

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ABSTRACT

Various studies, especially in recent years, have shown that quercetin has beneficial therapeutic effects in various human diseases, including diabetes. Quercetin has significant anti-diabetic effects and may be helpful in lowering blood sugar and increasing insulin sensitivity. Quercetin appears to affect many factors and signaling pathways involved in insulin resistance and the pathogenesis of type 2 of diabetes. TNFα, NFKB, AMPK, AKT, and NRF2 are among the factors that are affected by quercetin. In addition, quercetin can be effective in preventing and ameliorating the diabetic complications, including diabetic nephropathy, cardiovascular complications, neuropathy, delayed wound healing, and retinopathy, and affects the key mechanisms involved in the pathogenesis of these complications. These positive effects of quercetin may be related to its anti-inflammatory and anti-oxidant properties. In this article, after a brief review of the pathogenesis of insulin resistance and type 2 diabetes, we will review the latest findings on the anti-diabetic effects of quercetin with a molecular perspective. Then we will review the effects of quercetin on the key mechanisms of pathogenesis of diabetes complications including nephropathy, cardiovascular complications, neuropathy, delayed wound healing, and retinopathy. Finally, clinical trials investigating the effect of quercetin on diabetes and diabetes complications will be reviewed.

KEYWORDS

Quercetin; inflammation; diabetes; wound healing

1. Introduction

Diabetes is a common disease all over the world but it is more prevalent in developed countries. In general, diabetes is divided into two categories: type 1 diabetes mellitus and type 2 diabetes mellitus. However, diabetes can also occur in some conditions, such as pregnancy or poisoning by certain chemicals. Laboratory indicators for the diagnosis of diabetes include fasting plasma glucose greater than or equal to 126 mg/dl, two-hour plasma glucose greater than or equal to 200 mg/dl, and glycosylated hemoglobin (HbA1c) greater than or equal to 6.5%. Type 1 diabetes mellitus is an autoimmune disease in which the B cells of the pancreas langerhans islets, which produce insulin, are destroyed, so the patient needs insulin injections to survive. This disease occurs at a young age and accounts for about 5 to 10% of cases. Type 2 diabetes mellitus is associated with obesity and a sedentary lifestyle. This disease also has hereditary aspects. Type 2 diabetes accounts for about 90 to 95% of all cases of diabetes and is more prevalent in developed countries. The present article also focuses on type 2 diabetes and its complications. In this disease, the B cells of the langerhans islets are healthy, but the problem is insulin resistance. Insulin resistance occurs primarily in adipose tissue, skeletal muscle, and liver. Insulin resistance is described as a condition in which cells are unable to respond properly to insulin. Therefore, glucose uptake from the blood is impaired. The pancreas increases insulin secretion to alleviate this impairment. However, insulin resistance may lead to dysfunction of pancreatic β cells and impaired insulin secretion. A wide range of factors including sedentary lifestyle, drugs such as corticosteroids, chronic inflammatory conditions, and some diseases such as PCOS and some genetic loci are associated with insulin resistance. Diabetes can be considered a very serious health challenge. More than one million deaths per year occur due to diabetes. In 2017, the global prevalence rate of type 2 diabetes was estimated at 6059 cases per 100,000. It is estimated that this rate will increase to 7079 per 100,000 in 2030 (Khan et al. 2020). The complications of diabetes are not limited to one organ and involve various organs of the body including the heart, kidneys, brain, and eyes. Some of the complications

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of diabetes are very common. For example, the prevalence of diabetic nephropathy is estimated to be between 6% and 51% in various studies (Hicks and Selvin 2019). Treatment of diabetes and prevention of its complications is an active field of research.

In recent years, polyphenolic compounds have been considered as potentially useful compounds in the treatment of diabetes complications due to their anti-oxidant and anti-inflammatory properties. It seems that dietary polyphenols have beneficial effects in the management of diabetes in various ways such as attenuating the intestinal absorption of carbohydrates, enhancing insulin secretion and sensitivity (Aryaeian, Sedehi, and Arablou 2017). Polyphenolic compounds have also been considered as useful compounds for the treatment of diabetes complications (Borges et al. 2016; Naseri et al. 2019). One of these polyphenolic compounds is quercetin. A significant number of studies have focused on the anti-diabetic effects of quercetin and the benefits of this polyphenolic compound in the treatment of diabetic complications. In this review article, we tried to review the most interesting results of these studies.

2. Quercetin: A polyphenol with therapeutic properties

Quercetin is a derivative of quercetum and a component of flavonols. Flavonols are a subclass of flavonoids. Flavonoid compounds are a group of natural compounds, have a phenolic ring in their structure and are often found in vegetables (Maleki Dana et al. 2021). Onions, chili peppers, spinach, apples, and asparagus are among the most important nutritional sources of quercetin (Dabeek and Marra 2019). Mean flavonols intake among the European population (18 to 64 years) is estimated at 23 ± 2 mg/d. In some countries, including Spain and the Czech Republic, it is lower (15 and 16 mg/d respectively) and in others, including Ireland and the Netherlands, much higher (38 and 31 mg/d respectively) (Vogiatzoglou et al. 2015). In a study of the adult female population in northern China, the mean flavonol intake was reported to be 16 · 29 mg/d (Sun et al. 2015). Therefore, it seems that the average intake of flavonols varies from country to country. This amount of flavonols intake cannot be considered appropriate amount. Some studies have reported a very interesting association between the use of flavonols, including quercetin, and a reduced risk of various human diseases. For example, a meta-analysis has shown that there is an inverse relationship between high flavonol intake and stroke risk in men (Wang et al. 2014). The results of another meta-analysis suggest that high intake of flavonols may be associated with reduced risk of death from coronary heart disease (Huxley and Neil 2003). In a clinical trial performed on 150 people with metabolic syndrome traits, it was shown that quercetin supplementation could reduce systolic blood pressure and oxidized LDL, however, no significant effect was reported on serum TNFα and CRP levels (Egert et al. 2009).

Quercetin also appears to have anti-cancer effects. In addition to a significant number of studies in cellular and animal models that have shown the anti-cancer effects of quercetin, some clinical studies have reported an inverse relationship between quercetin consumption and the risk of some cancers. For example, one study found an inverse association between high quercetin intake and the risk of noncardia gastric adenocarcinoma (Ekström et al. 2011). Quercetin also appears to have antiviral effects, with the results of a meta-analysis suggesting that quercetin may reduce viral load and mortality rates in lower respiratory tract infections (Brito et al. 2021). Quercetin may also have positive effects on kidney function, neuronal protection, and hepatocyte protection (Yang et al. 2018; Khan et al. 2019; Chen et al., 2021). The question may now be what are the characteristics of quercetin that have such a wide range of positive effects on health? Although many dimensions of molecular mechanisms are not yet known, based on the available findings, these positive effects can be attributed to the anti-oxidant and anti-inflammatory properties of quercetin. It seems that quercetin can enhance the expression of NRF2 and its translocation to the nucleus (Ramyaa, Krishnaswamy, and Padma 2014). NRF2 is a transcription factor. Under normal circumstances, this transcription factor is retained by Keap1 in the cytoplasm and subjected to ubiquitination and subsequent degradation in the proteasome. Under conditions of oxidative stress, NRF2 goes to the nucleus and is involved in enhancing the expression of antioxidant genes (Deshmukh et al. 2017; Vaghari-Tabari et al. 2020). Quercetin can also attenuate iNOS expression and reduce NO production (Comalada et al. 2006). Therefore, it seems that quercetin can have a significant effect on strengthening the anti-oxidant system and prevent oxidative damage. Studies have shown that quercetin can reduce the expression of NFKB (Ramyaa, Krishnaswamy, and Padma 2014), which is a central factor in the inflammatory process. In addition, quercetin appears to attenuate COX2 expression, reduce the release of TNFα, IL-6, IL1-B, and IL-8 following LPS stimulation, and reduce MCP-1 and ICAM-1 expression (Comalada et al. 2006; Ramyaa, Krishnaswamy, and Padma 2014; Cheng et al. 2019; Xiong et al. 2019). All of these are pro-inflammatory cytokines and key factors involved in the inflammatory process. Quercetin can not only attenuate the production of pro-inflammatory cytokines, but also appears to potentiate the production of IL-10, which has anti-inflammatory properties (Comalada et al. 2006; Milenković et al., 2010). All these findings indicate that quercetin is an effective anti-inflammatory compound. In addition, quercetin has effects on some of the cellular signaling pathways. These effects have varied in different diseases and conditions, as if quercetin acts as an intelligent regulator for the health of the body.

Some studies have shown that quercetin suppresses the phosphorylation of AKT and STAT3 and enhances the expression of PTEN, a negative regulator of the PI3K/AKT signaling pathway (Maurya and Vinayak 2017; Zhu, Zhou, and Zhao 2017). In addition, quercetin inhibitory effects on MAPK, mTOR, and B-catenin signaling pathways have been reported by various studies (Lu et al. 2015; Seo et al. 2015; Ren et al. 2016). In addition, the link between quercetin and a number of miRNAs has been elucidated. For example,

quercetin appears to attenuate the activation of the NFKB and JNK signaling pathways in LPS-treated lung cell models by attenuating miR-221 expression (Wang et al. 2019). Each of the above properties, from anti-oxidant effects to anti-inflammatory effects and effects on cellular signaling pathways, may be related to the beneficial health effects of quercetin reported in human studies. For example, quercetin appears to have protective effects against alzheimer disease with several mechanisms such as enhancing NRF2 translocation to the nucleus, increasing glutathione and SOD levels, decreasing levels of inflammatory mediators such as TNFα and IL1-B, attenuating TLR4/NFKB signaling, and reducing ROS production, and attenuation of the mitochondrial apoptotic pathway (Zhang et al. 2020). It seems that the beneficial effects of quercetin on the cardiovascular system are probably due to its anti-oxidant and anti-inflammatory properties. A study has shown that quercetin weakens the effect of ox-LDL in activating NFKB and enhancing IL6 production (Bhaskar, Shalini, and Helen 2011). The molecular mechanisms of the beneficial effects of quercetin on the liver and kidney are also somewhat known. The results of a study on mouse models showed that the protective effect of quercetin against alcohol-induced liver damage may be related to its inhibitory effects on the PI3K/AKT, NFKB, and STAT3 signaling pathways (Zhu, Zhou, and Zhao 2017). Another study showed that quercetin inhibited renal fibrosis possibly through inhibiting mTOR and β-catenin signaling (Ren et al. 2016). Inhibitory effects of quercetin on the PI3K/AKT and mTOR signaling pathways are also involved in the anti-cancer properties of quercetin (Gulati et al. 2006; Shen et al. 2016). All of the above indicates that quercetin has beneficial therapeutic effects in various human diseases and affects a wide range of events and factors involved in various diseases ranging from redox balance to inflammation and cellular signaling pathways. In the following, we will focus specifically on the anti-diabetic effects of quercetin and its related mechanisms, after reviewing some key point regarding oxidative stress and inflammation roles in insulin resistance and type2 of diabetes.

3. Oxidative stress, inflammation and typ2 of diabetes: A brief overview

Before discussing the anti-diabetic effects of quercetin, it is necessary to have a very brief overview of the role of oxidative stress and inflammation in insulin resistance and type 2 of diabetes. As mentioned in the introduction, in type 1 diabetes, which is an autoimmune disease, there is destruction of pancreatic B cells and consequent defect in insulin secretion. In type 2 diabetes, autoimmunity is not involved, but hyperglycemia occurs due to insulin resistance which can eventually lead to dysfunction of pancreatic B cells and impaired insulin secretion. Insulin receptors) IR), which have four subunits and tyrosine kinase activity, are present on the surface of tissues that store carbohydrates in the form of glycogen or triacylglycerol, including liver, skeletal muscle, and adipose tissue, and mediate insulin signaling. Binding of insulin to these receptors causes auto-phosphorylation of these receptors in some tyrosine residues, which pave the way for the recruitment and phosphorylation of IRS adapter molecules. The phosphorylation of IRS1 and IRS2 molecules enables these molecules to activate PI3K. The activation of PI3K eventually leads to phosphorylation and activation of AKT. AKT plays a key role in the translocation of GLUT4 to the membrane surface (Keane et al. 2015; Sayem et al. 2018). GLUT4 brings glucose into the cell and thus insulin exerts its effect in this way. Therefore, it is obvious that any disruption in all stages of the aforementioned process, from mutations in the IRS to mutations in various components of the PI3K/AKT signaling pathway or any factor that can disrupt this process, reduces insulin sensitivity (Keane et al. 2015). Inflammation and oxidative stress have an interesting relationship with insulin resistance and play an important role in the pathogenesis of diabetes. These events are key players in the development of diabetes complaints, as well. It seems that, hyperglycemia by various mechanisms increases the production of ROS and creates conditions of oxidative stress that the discussion of the details of these mechanisms is beyond the scope of this article. Potentiation of mitochondrial NADPH oxidase activity, higher NO levels, and xanthine oxidase activity are among the most important of mechanisms (Pitocco et al. 2013; Adela et al. 2015). In addition, glucose auto-oxidation and the production of AGEs play a significant role in the production of ROS (Keane et al. 2015). Oxidative stress can disrupt insulin signaling and increase insulin resistance. In addition, oxidative stress can also cause diabetes complications such as, retinopathy, nephropathy, and neuropathy (Asmat, Abad, and Ismail 2016). Oxidative stress plays a role in insulin resistance in various ways.

For example, there is some evidence for the role of oxidative stress in the loss of IRS-1 through a p38MAPK-dependent signaling mechanism (Archuleta et al. 2009). There is also a close link between oxidative stress and inflammation. The inflammatory process is a key player in insulin resistance and diabetes. NFKB signaling plays a pivotal role in inflammation. It appears that oxidative stress may impair IRS-1 phosphorylation and PI3K activation through NFKB activation (Ogihara et al. 2004). A study of mice fed a high-fat diet also found that the lack of NRF2 boosted NFKB signaling and induced insulin resistance in the liver (Liu, Mei, et al. 2016). From these results, the possibility of strengthening the anti-oxidant defense on weakening inflammation and insulin resistance is inferred. Interestingly, in the hearts of diabetic patients and mouse models, NRF2 expression is significantly reduced while ERK phosphorylation is increased. ERK appears to enhance oxidative stress and insulin resistance by attenuating NRF2 activity (Tan et al. 2011). Oxidative species such as NO have the ability to enhance TNFα production. TNFα plays a very destructive role in the development of insulin resistance and is considered one of the links between obesity and diabetes, because, obesity develops a subclinical form of inflammation that is associated with increased levels of pro-inflammatory cytokines, including TNFα. This subclinical inflammation may be due to increased number of M1 macrophages and other immune cells such as B and T lymphocytes in adipose

tissue (Appari, Channon, and McNeill 2018; Tsalamandris et al. 2019). It should be noted that M1 macrophages are considered as pro-inflammatory phenotype and M2 macrophages are considered as anti-inflammatory phenotype of macrophages (Moein et al. 2019). It seems that TNFα can exert a detrimental effect on insulin signaling in various ways. It appears that this cytokine converts IRS-1 to an inhibitor of IR tyrosine kinase activity by inducing phosphorylation of some serine residues in IRS-1 (Hotamisligil et al. 1996). JNK, a transcription factor that can be activated by TNFα, also appears to be involved in IRS-1 serine phosphorylation, leading to impaired IR mediated tyrosine phosphorylation of IRS-1 (Aguirre et al. 2000). On the other hand, TNFα seems to be able to boost hormone-sensitive lipase activity in adipose tissue and increase blood free fatty acid levels (Keane et al. 2015). Free fatty acids can in turn boost IRS-1 serine phosphorylation and impair insulin signaling and glucose uptake in the skeletal muscle (Den Hartogh et al. 2020). Besides, it seems that TNFα can also attenuate AMPK signaling, thereby causing insulin resistance in the skeletal muscle (Steinberg et al. 2006). It should be noted that AMPK acts as an energy sensor and enhances glucose uptake and fatty acid oxidation when energy needs are required, while weakening glucose and lipid production processes (Long and Zierath 2006).

In addition to TNFα, white adipose tissue secretes other pro-inflammatory cytokines, such as IL-6 and IL-1 as well as adipokines, including adiponectin and resistin, which are involved in insulin resistance. For example, IL6 appears to disrupt insulin signaling by inducing SOCS-3 expression, which is capable of inhibiting insulin signaling (Rehman et al. 2017). Inflammation plays a key role in the impairment of pancreatic β cells function, which may occur in type 2 of diabetes. One of the important mechanisms that appear to be involved in the dysfunction and apoptosis of pancreatic B cells is a mechanism dependent on IL1, NFKB, and NO, which is another aspect of the association between inflammation, oxidative species, and diabetes. In this mechanism, IL-1R signaling activates NFKB in β cells. NFKB affects the expression of iNOS and enhances NO production. NO appears to be involved in β cells dysfunction and apoptosis (Keane et al. 2015). There is also an interesting link between gut microbiota and inflammation, which seems to be very important in the pathogenesis of type 2 diabetes. Various studies have shown that changes in the composition of gut bacteria can lead to subclinical inflammation in type 2 diabetes. The population of beneficial bacteria such as Akkermansia muciniphila and Faecalibacterium prausnitzii seems to be significantly reduced in patients with type 2 diabetes compared to healthy individuals, while the population of Escherichia coli is significantly increased (Ghaemi et al. 2020). These changes in bacterial composition can weaken the gut barrier. The surface of the gut epithelium is covered by a layer of mucus named the mucosal barrier or gut barrier. This gut barrier prevents over-infiltration of intestinal lumen bacteria into the underlying layers. The strength of this intestinal barrier depends on the tight junctions between adjacent epithelial cells. Akkermansia muciniphila can increase occludin expression, a key protein in tight junctions, enhance tight junctions, reduce intestinal permeability, and improve glucose tolerance in mouse models of diabetes (Chelakkot et al. 2018). It seems that microbial anti-inflammatory molecule (MAM), a metabolite of Faecalibacterium prausnitzii, may also strengthen the gut barrier in type 2 diabetes by increasing the expression of zona occludens 1 (ZO-1), another important protein of tight junctions (Xu et al. 2020). Therefore, reducing the population of these bacteria may weaken the gut barrier in type 2 diabetes. Besides, it appears that E. coli can lyse mucin and weaken the intestinal barrier by secreting a metabolic enzyme called StcE (Yang, Wei, et al. 2021). Damage to the intestinal barrier can cause some components of intestinal bacteria called pathogen-associated molecular patterns (PAMPs) to enter the circulation, which can cause systemic inflammation in type 2 of diabetes. One of the most important of these PAMPs is LPS, which is located on the surface of gram-negative bacteria (Yang, Wei, et al. 2021).

Metabolic endotoxemia, which is referred to some conditions such as elevated plasma LPS levels, appears to play an important role in stimulating inflammation and pathogenesis of type 2 of diabetes. LPS can be detected by Toll-like receptor 4 (TLR-4) of macrophages, which leads to the activation of macrophages and the production of high levels of inflammatory mediators including TNF-α, IL6, IL-1β, and MCP-1. These inflammatory mediators can also induce other immune cells, which can lead to enhanced inflammation in tissues, including metabolically important tissues. A high-fat diet can also enhance the production of intestinal chylomicrons and facilitate the transport of LPS from the intestinal lumen to other tissues (Cani et al. 2012; Yang, Wei, et al. 2021). As mentioned above, inflammatory mediators, especially TNF-a, play a very destructive role in insulin resistance and the pathogenesis of type 2 diabetes. In addition, some intestinal bacteria whose populations appear to be reduced in type 2 of diabetes, including Akkermansia muciniphila, have anti-inflammatory properties. For example, Akkermansia muciniphila appears to reduce serum levels of TNF-α and LPS in diabetic rats. On the other hand, this bacterium seems to be able to induce IL-10, which is a cytokine with anti-inflammatory properties (Zhang et al. 2018; Gurung et al. 2020). Therefore, changing the composition of intestinal bacteria that can cause damage to the intestinal barrier can also be a key player in enhancing inflammation in type 2 of diabetes. The results reviewed above may justify the results of a study that showed an increase in the population of bacteria with inflammatory properties (e.g., Bacteroides caccae, Lactobacillus ruminis, and Bacteroides caccae) and a decrease in the population of anti-inflammatory bacteria (e.g., Butyrivibrio and Faecalibacterium prausnitzii) may be involved in the development of type 2 of diabetes (Kulkarni, Devkumar, and Chattopadhyay 2021). Given the above, which is only a summary of the role of inflammation and oxidative stress in insulin resistance and pathogenesis of type 2 of diabetes, it seems that further studies on inflammation and oxidative stress can be helpful in finding appropriate treatment approaches for more effective treatment of type2 diabetes. It is possible that natural compounds with strong anti-oxidant

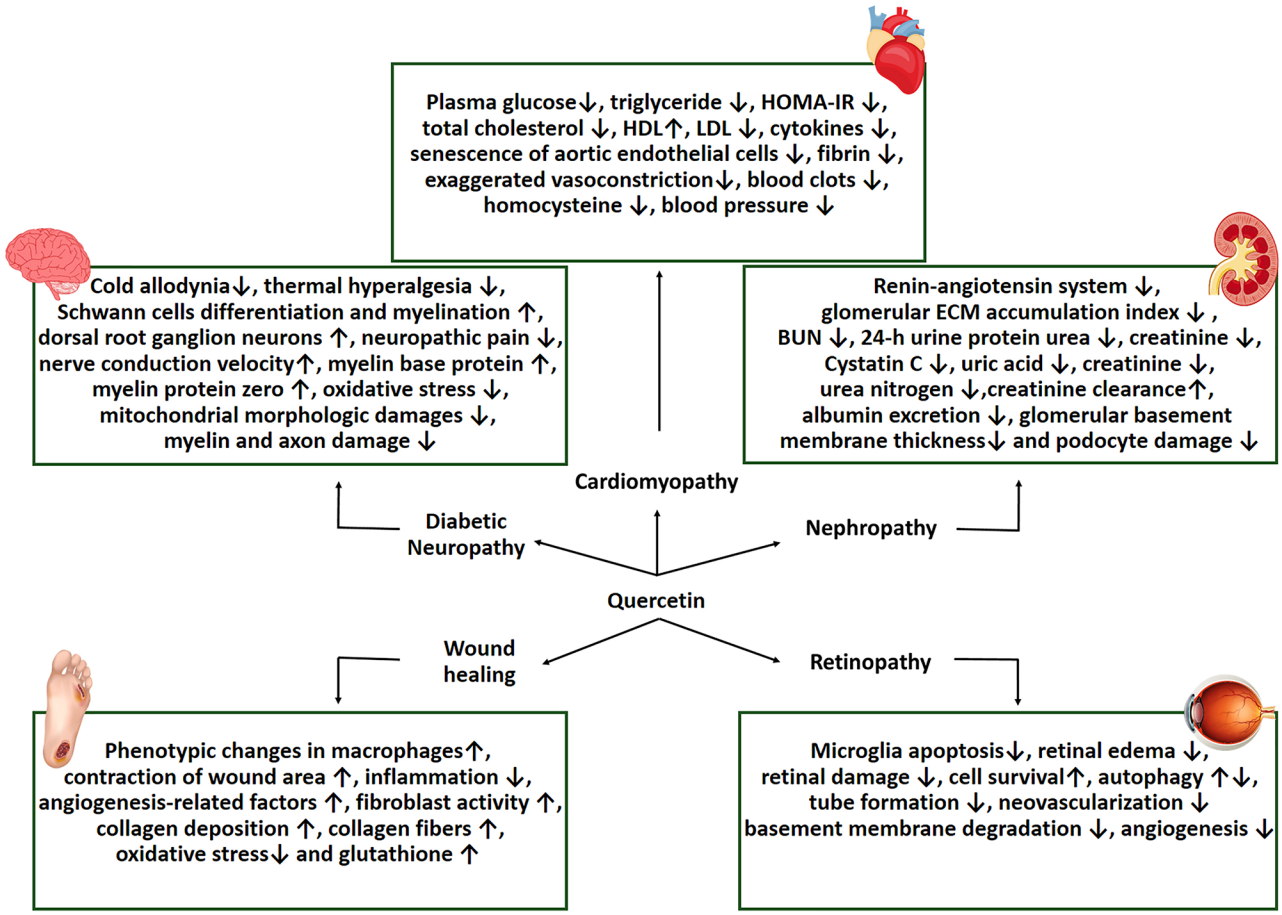

Figure 1. Oxidative stress and inflammation are the main players in diabetic condition. In this regard quercetin as an anti-inflammatory and anti-oxidative agent plays its anti-diabetic roles through affecting these pathways.

and anti-inflammatory properties may be helpful in the treatment of diabetes. Quercetin is one of these compounds that appears to have significant anti-diabetic effects, which will be discussed in the next section (Figure 1).

4. The anti-diabetic effects of quercetin

Limited epidemiological studies have been performed on the relationship between dietary quercetin intake and diabetes risk, and different results have been reported. A study of the American population published 16 years ago found no significant association between quercetin intake and type2 of diabetes (Song et al. 2005). However, a recent study of the Chinese adult population found an inverse relationship between quercetin intake and the prevalence of type 2 diabetes (Yao, Du, et al. 2019). Although more epidemiological studies in different communities are needed to clarify the relationship between dietary quercetin intake and diabetes risk, various animal models studies and clinical investigations have shown that quercetin has an anti-diabetic effect, possibly due to its anti-inflammatory and anti-oxidant properties as well as its effects on various cellular signaling pathways. For example, a study on STZ-induced diabetes rat models showed that quercetin could lower glucose levels significantly. In addition, the findings of this study showed that quercetin increased the activity of sirtuin-1, catalase, and superoxide dismutase in renal tissue while decreasing MDA and NFKB levels (Iskender et al. 2017). It should be noted that MDA is an indicator of lipid peroxidation and high levels of MDA indicate oxidative stress. Given the destructive role of NFKB and the oxidative stress mentioned above, these findings can be considered very important. A recent study on Arbor Acre (AA) broilers models showed that quercetin supplementation had a significant effect on lowering fasting blood glucose and fasting insulin. In this study, in which hyperglycemia was induced by streptozotocin (STZ) administration in AA broilers, it was also shown that quercetin supplementation could reduce MDA and NO levels, attenuate PI3K, AKT, GSK-3β, and insulin receptor (IR) expression, and upregulate insulin receptor substrate 1 (IRS-1). In this study, no significant effect of quercetin was observed on reducing MCP-1 and IL-6, but quercetin increased TNFα level (Ying et al. 2020). Given the highly destructive role of NO in the pathogenesis of diabetes and pancreatic β cell dysfunction mentioned above, the effect of quercetin in reducing NO can be very important and further studies should be performed on this issue. The effects of quercetin on IR and AKT expression are inconsistent with the effects of quercetin on lowering fasting glucose and insulin in this study. Also, some results of this study contradict the results of some other studies, which

suggest the possibility of a complex mechanism in the anti-diabetic effects of quercetin.

Another study on STZ-induced diabetic rats showed that treatment with quercetin at 100 mg/kg b.w, reduces the degeneration of pancreatic tissue cells. This study also showed that treatment with quercetin could increase insulin and TNFα levels and decrease MDA levels (Dokumacioglu et al. 2018). However, in another study on high fat diet/STZ-induced diabetic rats, quercetin 0.1% had no significant effects on reducing fasting glucose, insulin resistance index (HOMA-IR) and plasma insulin, but found that quercetin 0.1% significantly increases the expression of GLUT4 and insulin receptors in skeletal muscle. This study also showed that treatment with quercetin 0.1% could reduce MDA and TNFα levels. (Jung et al. 2011). These results may support the hypothesis that quercetin increases glucose uptake by cells. This hypothesis is further reinforced by the results of another study which showed that quercetin could somewhat attenuate the effect of TNFα on inducing insulin resistance in skeletal muscle cells and improve glucose uptake, possibly, through activating the AKT and AMPK signaling pathways and suppressing the NFKB signaling and the NO/iNOS system (Dai et al. 2013). In the previous section, we mentioned the suppressive effect of TNFα on AMPK, which acts as an energy sensor in boosting glucose uptake and oxidation of fatty acids. Therefore, it seems that quercetin weakens one of the important mechanisms of insulin resistance by weakening this suppressive effect. The results of a study performed on PCOS rat models also show the effect of quercetin on increasing insulin sensitivity. This study demonstrated that quercetin could significantly reduce the levels of IL-1B, IL6, TNFα, blood insulin, fasting blood glucose, and insulin resistance index (HOMA-IR). The results of this study suggest that quercetin may reduce insulin resistance in PCOS rat models by attenuating TLR4/NFKB signaling (Wang et al. 2017). Because, as mentioned in the introduction, PCOS is one of the diseases that seems to be associated with insulin resistance, further studies, especially clinical studies, are needed to investigate the effects of quercetin on insulin resistance in PCOS. The results of a very interesting study suggest that the effect of quercetin on glucose uptake is conditional, so that under normal conditions quercetin attenuates the effect of insulin on glucose disposal in skeletal muscle, while in inflammatory conditions it improves insulin function (Liu, Mei, et al. 2016). Therefore, it can be hypothesized that quercetin in obese people who may have subclinical inflammation may have a significant effect on increasing insulin sensitivity and controlling diabetes. This hypothesis needs to be further investigated in a clinical study. It is also necessary to evaluate the effect of quercetin on the efficacy of drugs such as metformin, which are prescribed to diabetic patients to increase insulin sensitivity.

The results of the studies reviewed above on the effect of quercetin on TNFα are contradictory and some indicate a decreasing effect and some an increasing effect. In interpreting these contradictory results, factors such as the animals' diet and the concentrations of quercetin should be considered. However, further studies, preferably clinical investigations in diabetic and obese patients, are necessary to elucidate the effect of quercetin on TNFα levels. TNFα may play a role in the regulation of glucose uptake by quercetin under normal conditions and inflammatory conditions. Several other hypotheses can be made for the contradictory effects of quercetin on TNFα reported by various studies. Therefore, one of the most interesting topics for future studies is to investigate the relationship between quercetin, TNFα, and glucose uptake under normal and inflammatory conditions. It seems that the effect of quercetin on boosting NRF2 mentioned in the previous sections also plays a role in weakening insulin resistance and lowering glucose. In a study of mouse models of type 2 of diabetes, it was shown that treatment with low or high doses of quercetin could enhance NRF2 expression and has positive effects on lowering glucose and weakening insulin resistance (Yang, Wei, et al. 2021). In addition, quercetin appears to attenuate ERK phosphorylation in adipocytes (Ahn et al. 2008). In the previous section, we mentioned the possible role of ERK in enhancing oxidative stress and insulin resistance by suppressing NRF2 activity. It was also mentioned that IL6 may impair insulin signaling by inducing SOCS3. It seems that quercetin can weaken the expression of SOCS3 in the liver (Khodarahmi et al. 2019). Quercetin also affects the polarization of macrophages in adipose tissue. A very interesting study on high-fat diet mice showed that quercetin inhibits the recruitment of immune cells into adipose tissue, shifts the polarization of adipose tissue macrophages to M2 macrophages, reduces levels of pro-inflammatory cytokines including TNFα, IL6, and MCP-1, attenuates insulin resistance, and increases glucose uptake by adipocytes (Dong et al. 2014). Quercetin can also affect the composition of intestinal bacteria. In the previous section, we mentioned the reduction of Akkermansia population in type 2 diabetes and the anti-inflammatory properties of this bacterium. The results of a study in mice on a high-fat diet showed that supplementation with 0.05% quercetin for 6 weeks could increase the relative frequency of Akkermansia, reduce blood glucose levels, plasma insulin levels, and enhance insulin sensitivity (Tan et al. 2021). Besides, quercetin can disrupt E.coli's cell wall and membrane, and supplementation with quercetin may reduce the population of E.coli in the cecum of AA broiler chickens (Wang et al. 2018). It seems that quercetin can increase the expression of some proteins in narrow intestinal junctions, including occludin and Claudin-4, and enhance gut barrier function (Amasheh et al. 2008; Xu et al. 2021). Thus, that the regulation of gut microbiota by natural compounds like quercetin can be a practical approach for diabetes management (Li, Xu, et al. 2019; Meng et al. 2019).

Therefore, it seems that quercetin affects almost all the key mechanisms of insulin resistance, which were briefly mentioned in the previous sections, and has strong anti-diabetic properties that are related to its anti-oxidant and anti-inflammatory properties. The results reviewed above suggest that quercetin can be further studied as a natural product to increase insulin sensitivity and type 2 of diabetes prevention and treatment (Figure 1).

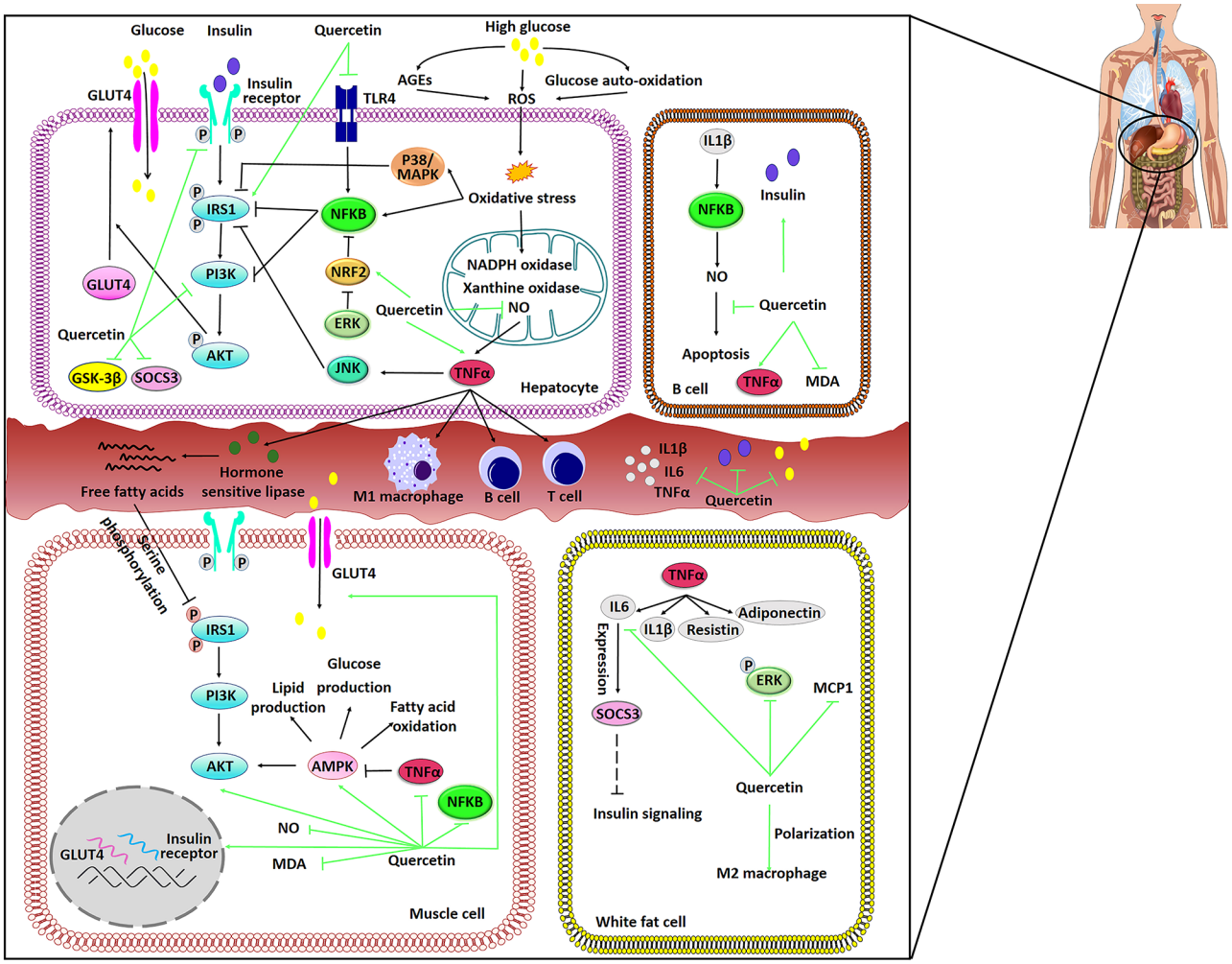

Figure 2. Quercetin protective mechanisms of action in diabetic complications.

5. Quercetin and complications of diabetes

As mentioned in the introduction, the complications of diabetes are not limited to one organ and may involve several organs. Oxidative stress and inflammation play key roles in diabetic complications. Therefore, compounds with anti-oxidant and anti-inflammatory properties, including quercetin, can be considered for the prevention and treatment of diabetes complications. In the previous section, the effects of quercetin on increasing insulin sensitivity and glycemic control were discussed, and based on the results of reviewed studies, quercetin has significant anti-diabetic properties. In this section, we will discuss the effects of quercetin in the prevention and treatment of diabetes complications on various organs, including the kidneys, cardiovascular system, nervous system and eyes (Figure 2).

5.1. Quercetin and diabetic nephropathy

Renal complications are very common in diabetes and diabetic nephropathy is one of the most common kidney diseases which can lead to end-stage renal disease (ESRD). Diabetic nephropathy is associated with structural and functional changes in the kidney. Structural changes in the glomerulus can include mesangial expansion, thickening of the basement membrane, and glomerulosclerosis. In tubules, hypertrophy, atrophy, interstitial fibrosis, and arteriolar hyalinosis are among the structural changes (Lim 2014). Diabetic nephropathy is associated with hyper-filtration and albuminuria, which can exacerbate renal dysfunction (Kanwar et al. 2008). The disease has a very complex pathogenesis and several mechanisms are involved in the pathogenesis of this disease, the discussion of the details of these mechanisms is beyond the scope of this article. Briefly, interactions between metabolic and hemodynamic factors are involved in the pathogenesis of diabetic nephropathy, and the role of renin-angiotensin system, AGEs, inflammation, and oxidative stress, is very important.

Glucose reabsorption in the proximal tubule is performed by sodium-dependent glucose transporters. These transporters can cotransport glucose and sodium into the circulation. Therefore, hyperglycemia, which is accompanied by an increase in the load of filtered glucose, reduces the delivery of sodium to maculadensa, which is involved in regulating blood pressure, leading to activation of the renin-angiotensin system, which results in increased glomerular blood pressure and renal hyper-filtration (DeFronzo, Reeves, and Awad 2021). As mentioned in the previous

sections, hyperglycemia is associated with increased production of AGEs. AGEs can bind to the collagen and proteins that make up the glomerular basement membrane, disrupting the glomerular barrier, increasing permeability, and enhancing the passage of proteins (Zelmanovitz et al. 2009). AGEs can activate key players involved in the pathogenesis of diabetic nephropathy such as PKC, TGF-β, and NFKB (Kanwar et al. 2008; Soldatos and Cooper 2008). Each of these factors plays a destructive role in the pathogenesis of diabetic nephropathy. PKC may be involved in basement membrane impairment and albuminuria.(Soldatos and Cooper 2008) TGF-B1 is involved in the accumulation of extracellular matrix in the mesangium and causes glomerulosclerosis and interstitial fibrosis. In general, it can be considered a cytokine with fibrogenic and hypertrophic effects in diabetic nephropathy (Chang et al. 2016). NFKB can enhance the expression of inflammation-related genes such as adhesion molecules, pro-inflammatory cytokines, and chemoattractants (Donate-Correa et al. 2020). MCP-1 is among the chemotaxis molecules that enhance the recruitment of monocytes from the circulation. ICAM-1 is one of the adhesion molecules and its upregulation in endothelial cells plays a key role in infiltration of mononuclear cells into the kidney. CSF-1 is involved in enhancing monocyte/macrophage proliferation, differentiation, and activation. Active macrophages can produce pro-inflammatory and pro-fibrotic cytokines, and potentiate oxidative stress by producing ROS, which can lead to promotion of inflammation, progressive fibrosis, and glomerular filtration impairment (Lim 2014). Pro-inflammatory cytokines, including TNFα, IL-6, and IL-18, play a highly destructive role in the pathogenesis of diabetic nephropathy. IL18 is involved in the pathogenesis of diabetic nephropathy by various mechanisms, such as enhancing ICAM-1 expression, pro-inflammatory cytokines, and stimulating apoptosis. Elevated IL-6 levels are associated with glomerular basement membrane thickness, mesangium expansion, and elevated fibronectin levels. TNFα is associated with changes in endothelial cell permeability that can lead to decreased GFR. TNFα also raises ROS levels within the kidney cells, which can cause changes in the glomerular capillary wall and increase UAE (Donate-Correa et al. 2020).

Inflammatory events associated with changes in the composition of intestinal bacteria and increased intestinal permeability mentioned in the previous section may also be involved in damaging podocytes and endothelial cells, and play an important role in the pathogenesis of diabetic nephropathy (Wang et al. 2021). The oxidative stress that occurs in hyperglycemic conditions and discussed earlier may play an important role in the induction of angiotensin II and the synthesis of TGF-B, fibronectin, and type IV collagen, which are key factors in the development of glomeruloesclerosis (Zelmanovitz et al. 2009). NRF2, which is involved in strengthening anti-oxidant defenses, has a protective role against pathological changes in glomeruli (Donate-Correa et al. 2020). It seems that NRF2 can inhibit TGF-B1 and attenuate the production of extracellular matrix and activation of NRF2 has been suggested as a therapeutic approach in slowing the progress of diabetic nephropathy (Jiang et al. 2010; Zheng et al. 2011). Although what has been reviewed above is a summary of the most important mechanisms involved in the pathogenesis of diabetic nephropathy, it clearly demonstrates the destructive role of inflammation and oxidative stress in the pathogenesis of this disease. Quercetin as an anti-oxidant and anti-inflammatory compound with significant anti-diabetic properties discussed above has beneficial effects in improving diabetic nephropathy. Quercetin in addition to its anti-diabetic effects, which can be effective in controlling hyperglycemia and preventing the renal complications of diabetes, affects all the important mechanisms involved in the pathogenesis of diabetic nephropathy. For example, it seems that quercetin can attenuate the renin-angiotensin system by attenuating angiotensin-converting enzyme (ACE) activity (Parichatikanond, Pinthong, and Mangmool 2012). Immunohistochemical examination of the kidney tissue of rat models of diabetic nephropathy showed that quercetin could reduce the expression of AGEs around the capsule and tubular basement membrane (Tang et al. 2020). A study of diabetic rat models showed that TGF-β and CTGF expression increased in kidney tissue, but quercetin administration could attenuate these over-expressions (Lai, Zhang, and Yang 2012). Given the destructive role of TGF-B in the pathogenesis of diabetic nephropathy mentioned above, these findings could be very important and suggest that quercetin may be able to enhance renal function in diabetic nephropathy by impairing TGF-B expression, so further studies are needed. It seems that quercetin can attenuate the effect of hyperglycemia in upregulating NFKB and MCP-1 in mesangial cells and exert a suppressive effect on these key inflammatory factors (Chen et al. 2012). Another study in diabetic rats showed that quercetin could reduce the glomerular ECM accumulation index and attenuate the expression of NF-κB p65 in kidney tissue. In this study, it was also shown that quercetin had a significant effect on reducing BUN and 24-h urine protein, which indicates the positive effect of quercetin on improving renal function (Chen et al. 2013).

A study on diabetic rats showed that quercetin could attenuate ICAM-1 expression in the endothelium, reduce the infiltration of inflammatory cells into kidney tissue, alleviate pathological injury to kidney tissue, and improve kidney function (Tong et al. 2017). A study of diabetic rat models showed that quercetin could significantly reduce AGEs levels in kidney tissue and serum levels of TNFα and IL-6. This study also showed that quercetin significantly reduced serum levels of urea, creatinine, and cystatin C (Alnahdi et al. 2017), indicating a positive effect on improving renal function and protecting against diabetic nephropathy. Another study of rat models showed that quercetin at a dose of 100 ml/kg was able to significantly reduce IL-18 and IL-1B levels in the serum and kidney tissue. In this study, it was also shown that quercetin at a dose of 100 ml/kg has a significant effect on reducing serum levels of uric acid, creatinine, and urea nitrogen and also significantly increases creatinine clearance (Wang et al. 2012). These results suggest that some of the protective effects of quercetin in diabetic nephropathy may be due to the remarkable

anti-inflammatory properties of quercetin. Due to the role of oxidative stress in the induction of fibrogenic factors such as TGFB, as well as the close association of oxidative stress with the inflammatory process, the anti-oxidant properties of quercetin may be related to its protective effects against diabetic nephropathy. A study of diabetic rats showed that four weeks of quercetin treatment at 10 mg/kg per day had a significant effect on reducing MDA levels and increasing GSH, catalase, and SOD levels in kidney tissue. This study, like the previous studies, showed that quercetin has positive effects on increasing creatinine clearance and reducing serum creatinine and nitrogen urea levels as well as reducing albumin excretion (Anjaneyulu and Chopra, 2004). Therefore, it seems that strengthening the anti-oxidant system and weakening oxidative stress by quercetin play a role in attenuating diabetic nephropathy. Quercetin appears to attenuate the production of superoxide anion in kidney cells and also has positive effects in preventing glomerulosclerosis in diabetic nephropathy (Gomes et al. 2014). Another study in rat models of diabetic nephropathy showed that quercetin increased GSH and SOD levels in kidney tissue and decreased MDA levels. A similar pattern was observed in the blood. The findings of this study also showed that quercetin attenuates the TGF-B/Smads signaling pathway. The results of histological examination of this study also showed that quercetin reduces the thickness of the glomerular basement membrane and attenuate podocyte damage (Gao et al. 2018). These findings clearly show the positive effects of quercetin on diabetic nephropathy and its possible association with the anti-oxidant properties of quercetin. The effect of quercetin on boosting NRF2 mentioned in the previous sections may also play a role in boosting anti-oxidant defense and the protective effects of quercetin in diabetic nephropathy, which need to be investigated in future studies.

In addition, the possible role of intestinal barrier weakening and related inflammation in endothelial cell damage and the pathogenesis of diabetic nephropathy (Wang et al. 2021), the possible increase in the population of bacteria such as E. coli and shigella in the gut of patients with diabetic kidney disease (He et al. 2022), and the effects of quercetin in damaging E. coli and increasing the population of bacteria with anti-inflammatory properties (Wang et al. 2018; Tan et al. 2021), suggest that the effects of quercetin on intestinal bacteria may also be related to the beneficial effects of quercetin on diabetic nephropathy. This hypothesis needs to be analyzed in future studies. In overall, quercetin appears to have protective effects against diabetic nephropathy by attenuating the key destructive mechanisms involved in the pathogenesis of the disease, and the anti-inflammatory and anti-oxidant properties of quercetin may be very important in this regard.

5.2. Quercetin and cardiac complications of diabetes

Cardiovascular disease is the most common cause of death among diabetics. Diabetes greatly increases the risk of cardiovascular disease, and the risk of death from cardiovascular disease in adults with diabetes in the United States was estimated to be 1.7 times higher than in adults without diabetes (Leon and Maddox 2015). Diabetes affects a variety of risk factors that play a key role in the pathogenesis of cardiovascular disease. One of the most important of these risk factors is dyslipidemia. Numerous clinical studies have shown increased levels of total cholesterol and triglycerides levels in patients with type 2 of diabetes (Singla et al. 2009; Ramazani, Qujeq, and Moazezi 2019). Decreased HDL levels and increased LDL levels have also been reported in diabetic patients (Singla et al. 2009). Elevated LDL has been reported even in pre-diabetic patients compared to healthy individuals (Fardipour et al. 2020). LDL is an important player in the pathogenesis of atherosclerosis. Briefly, the uptake of oxidized LDL (OX-LDL) by macrophages may initiate the formation of atherosclerotic lesions. The inflammatory process causes these lesions to develop, eventually forming a lipid center with a significant cholesteryl ester content that is surrounded by a large number of macrophages and inflammatory cells. The structure is also covered by a cap made of endothelial connective tissue. Advanced lesions may also contain calcium deposits. Cap destruction and plaque rupture can trigger the coagulation process, leading to clot formation, obstruction, and acute coronary syndrome. Anti-oxidants such as tocopherol, ascorbate, and beta-carotene appear to prevent LDL oxidation and impair the progression of atherosclerosis (Jialal and Fuller 1993).

Elevated fatty acid levels in the diabetic patients mentioned above play a very destructive role in dyslipidemia. Increasing free fatty acids and glucose in the liver reduces the breakdown of apoB100 and enhances VLDL secretion. In type 2 of diabetes, it appears that apoB48 production in the intestine is also accelerated. High levels of triglycerides in diabetics may potentiate CETP activity, which increases the exchange of triglycerides and cholesteryl esters between triglyceride-rich lipoproteins and HDL and LDL. These events lead to the production of triglyceride-rich HDL, which has a short plasma half-life. Triglyceride-rich LDLs are also degraded by lipoprotein lipase and liver lipase, which reduces LDL size (Wu and Parhofer 2014). Small LDLs are highly atherogenic particles. There may also be detrimental effects of AGEs, inflammation, and oxidative stress on HDL function, leading to HDL dysfunction in diabetes (Srivastava 2018). On the other hand, insulin resistance in diabetes is associated with increased levels of PAI-1 and fibrinogen and enhanced coagulation (Cheung and Li 2012). In addition, insulin resistance appears to be associated with elevated homocysteine levels, an important risk factor for cardiovascular disease (Meigs et al. 2001; Ebrahimpour, Vaghari-Tabari, et al. 2018). Hypertension is another risk factor for cardiovascular disease that is so common in diabetics that it is estimated that 60% of patients with type 2 of diabetes have hypertension (Matheus et al. 2013). Discussing why diabetes increases the risk of hypertension requires another review article. In summary, increased renin-angiotensin system activity, endothelial dysfunction due to oxidative stress and inflammation, and enhanced sodium reabsorption due to insulin resistance and increased

insulin concentrations are probably the most important causes of hypertension in diabetes (Ohishi 2018; Petrie, Guzik, and Touyz 2018). In addition to the aforementioned events, inflammation and oxidative stress also have destructive effects on heart cells. Diabetic cardiomyopathy is a ventricular disorder that is independent of coronary heart disease. Renin-angiotensin system disorders, systemic metabolic disorders, oxidative stress and inflammation are also involved in the pathogenesis of this disease. These events can cause interstitial fibrosis of the heart tissue, impaired diastole, and ultimately impaired cardiac systole, with complex mechanisms that are beyond the scope of this article but have been discussed elsewhere (Jia, Whaley-Connell, and Sowers 2018). Pro-inflammatory cytokines, including TNFα, IL6, and MCP-1, are involved in cardiac fibrosis and diastolic dysfunction. AGEs also play a destructive role in cardiac fibrosis by stimulating the NFKB signaling, which leads to an increase in pro-inflammatory cytokines. In addition, in diabetic heart tissue, the polarization of M2 macrophages is weakened and the polarization of M1 macrophages, which are involved in cardiac fibrosis, is enhanced (Jia, Whaley-Connell, and Sowers 2018).

It seems that stimulation of the immune system by intestinal bacteria, whose role in the pathogenesis of diabetes was mentioned in the previous sections, is also involved in the development of cardiovascular diseases, and an interesting association between plasma levels above 50 pg/ml of endotoxin and an increased risk of cardiovascular disease has been reported (Wiedermann et al. 1999; Miele et al. 2015). An inverse association between plasma levels of atherogeniclysophosphatidylcholine (LPC 18: 1) and some gut bacteria including Actinobacteria and Cyanobacteri has been reported in mice on a high-fat diet (Nie et al. 2019). Decreased populations of bacteria with anti-inflammatory properties such as Faecalibacterium and increased populations of Escherichia-Shigella have also been reported in patients with coronary artery disease (Zhu et al. 2018). As mentioned in the previous sections, oxidative stress and inflammation are closely related (Jia, Whaley-Connell, and Sowers 2018). Oxidative spices appear to be involved in cardiomyocyte apoptosis. For example H2O2 can be involved in hypertrophy and cardiomyocyte apoptosis by inducing the ERK1/2 MAPK, JNK, p38MAPK, and AKT signaling pathways (Kayama et al. 2015). What has been reviewed above, which is only a summary of current knowledge, clearly demonstrates the destructive role of oxidative stress and inflammation in the cardiac complications of diabetes. Therefore, it is possible that quercetin with its anti-oxidant and anti-inflammatory properties can be effective in preventing and improving the cardiac complications of diabetes. Studies to date have shown promising results. For example, a study of mouse models of type 2 diabetes showed that quercetin at low (0.04%) and high (0.08%) doses could lower plasma glucose and triglyceride levels, as well as insulin resistance index values (HOMA-IR) also decreases after treatment with quercetin. The results of this study also showed that supplementation with high doses of quercetin could reduce total cholesterol levels and increase HDL levels (Jeong et al. 2012). The results of a study on the Japanese female population showed that there was an inverse relationship between dietary quercetin intake, LDL and total plasma cholesterol levels (Arai et al. 2000). In addition, the results of a clinical trial have shown that quercetin supplementation significantly reduces plasma OX-LDL levels in overweight and metabolic syndrome subjects (Egert et al., 2009). In addition to reducing the concentration of OX-LDL, quercetin also appears to impair its atherogenic effects. One study showed that quercetin could inhibit the induction of TLR2 and TLR4 expression by OX-LDL and modulate the TLR-NFKB signaling, which reduces the production of cytokines such as IL6 and ultimately attenuates inflammation (Bhaskar, Shalini, and Helen 2011).

In fact, quercetin may attenuate the inflammatory process stimulated by OX-LDL, which plays a key role in atherosclerosis, so further studies are needed. In addition, quercetin appears to attenuate the effect of OX-LDL in enhancing the senescence of aortic endothelial cells (Jiang et al. 2020), indicating the beneficial effects of quercetin on vascular endothelial cells. Quercetin also appears to have anticoagulant properties. The results of a study showed that quercetin can inhibit the activity of thrombin and FXa and attenuate the formation of fibrin and blood clots (Choi, Kim, and Kim 2016). Quercetin may also regulate homocysteine metabolism, which is an important risk factor for cardiovascular disease. One study showed that quercetin can reduce serum homocysteine levels in methionine-enriched diet rats (Meng et al. 2013). It seems that the effect of quercetin on reducing homocysteine levels is due to the effect of quercetin on enzymes involved in homocysteine metabolism and enhancing remethylation and transsulfuration (Meng et al. 2015). Quercetin also appears to have beneficial effects in lowering blood pressure. The results of a clinical trial have shown that quercetin can reduce systolic blood pressure in overweight patients with metabolic syndrome traits (Egert et al., 2009). The results of a study on rat models of diabetes suggest that the effect of quercetin on lowering systolic blood pressure is probably age-dependent, so that in 6-month-old rats quercetin can lower systolic blood pressure, but in 1-year-olds rats are ineffective (Ferenczyova et al., 2020). The results of another study in animal models have shown that quercetin may inhibit the exaggerated vasoconstriction induced by diabetes and has positive effects on lowering blood pressure. The results of this study also showed that quercetin could attenuate leukocyte infiltration, endothelial pyknosis, and collagen deposition, and these effects may be associated with decreased TNFα levels and the inhibitory effect of quercetin on aortic NF-κB (Mahmoud et al. 2013). The effects of quercetin on intestinal bacteria may also be associated with a reduction in some risk factors for cardiovascular disease. The results of a study in mice on a high-fat diet showed that quercetin could increase the population of some intestinal bacteria, including Actinobacteria and Cyanobacteria, and lower intestinal levels of cholesterol, lysophosphatidic acids, and 18: 1 LPC (Nie et al. 2019). The inverse relationship between Actinobacteria, Cyanobacteria, and 18: 1 LPC was noted earlier. Quercetin also has effects on reducing the population of E. coli and increasing some bacteria with anti-inflammatory

properties, and it is necessary to study the relationship between these effects and cardiovascular complications of diabetes in the future.

It seems that quercetin can retard the progression of diabetic cardiomyopathy by amplifying SIRT1 and AMAPK, enhancing the expression of catalase and superoxide dismutase in cardiac tissue, and reducing MDA and NFKB levels (Li et al. 2017). In fact, quercetin appears to counteract the destructive role of oxidative stress and inflammation in diabetic cardiomyopathy. One study on hyperglycemic rats also showed that quercetin could improve cardiac diastolic dysfunction. This study showed that quercetin could attenuate high-cholesterol-induced oxidative stress through various mechanisms, such as inhibiting reduction of GSH/GSS ratio and enhancing NRF2 nuclear translocation (Castillo et al. 2018). Rutin, a metabolite of quercetin, also has positive effects on diabetic cardiomyopathy and appears to reverse myocardial hypertrophy, attenuate extracellular collagen deposition, reduce oxidative damage, inhibit fibrosis, and improve myocardial function (Huang et al. 2017). In general, it seems that quercetin can have beneficial effects on reducing the cardiac complications of diabetes, both by reducing the risk factors for coronary heart disease and retarding diabetic cardiomyopathy, which can be further studied.

5.3. Quercetin and diabetic neuronal complications

Diabetic neuropathy is another important complication of diabetes. Diabetic neuropathy is very common. In a study of the American patient population, it was reported that 66% of patients with type 1 of diabetes and 59% of patients with type 2 of diabetes have some form of neuropathy (Dyck et al. 1993). Diabetic neuropathies have differences in clinical manifestations and risk factors as well as pathophysiology and can be said to be heterogeneous. Neuropathic syndromes can be categorized according to the type of nerves they affect, such as sensory, motor, and autonomic, the site of neuronal damage, such as focal, multifocal, and generalized, and the duration of the disease, such as acute or chronic (Yang, Sloan, et al. 2019). Duration of diabetes and hemoglobin A1c levels are the most important predictors of diabetic neuropathy. Diabetic neuropathy can be associated with symptoms such as falls and pain and reduces the quality of life (Feldman et al. 2019). The pathogenesis of diabetic neuropathy is still unclear and has many unknown dimensions. It seems that the hyperglycemia and dyslipidemia that occur in diabetes and discussed above can weaken the support of neurons by Schwann cells and microvessels. Inflammatory signals and oxidative species may be involved in demyelination and decreased density of myelinated fibers, leading to neuronal damage and decreased nerve conduction velocity.

On the other hand, inflammatory signals and oxidative stress play a role in micro-vascular damage, which leads to reduced blood flow to the nerves (Yang, Sloan, et al. 2019). Future studies will undoubtedly shed light on the wide range of mechanisms of the pathogenesis of diabetic neuropathy. Changes in the composition of intestinal bacteria have also been reported in patients with diabetic neuropathy compared to healthy individuals, but the association of these changes with the pathogenesis of the disease is not yet clear. an increase in Escherichia-Shigella and a decrease in Faecalibacterium are among of these changes (Wang, Qiu, et al. 2020). These findings may raise the hypothesis of the involvement of inflammation resulting from changes in the composition of intestinal bacteria in the pathogenesis of peripheral diabetic neuropathy, which needs to be investigated in future studies. Type2 of diabetes appears to increase the risk of Alzheimer disease, an important neurodegenerative disease (Chatterjee and Mudher 2018). Various mechanisms may be associated with this increased risk, one of the most important of which is the stimulatory effects of insulin resistance on Aβ accumulation and tau protein hyperphosphorylation. Insulin may be involved in the secretion of amyloid-beta out of the cell and inhibit the accumulation of amyloid-beta inside the cell. Disrupted insulin signaling can impair the processing of amyloid-beta precursor protein peptides (AβPP) and disrupt AβPP-Aβ clearance in the brain. Insulin resistance also has destructive effects on tau protein. Insulin resistance in the brain is associated with increased GSK-3β activity. Increased GSK-3β activity may be involved in tau hyper-phosphorylation, which leads to misfolding of this protein and fibril aggregation (Kim 2019). Tau and Aβ toxicities are probably associated with oxidative stress, and oxidative stress may play an important role in the signaling changes and pathogenesis of Alzheimer disease (Giraldo et al. 2014). The inflammatory process is also involved in the pathogenesis of Alzheimer disease, and there is a hypothesis that inflammation is a downstream effect of the accumulation of Aβ and tau (Zotova et al. 2010). It seems that quercetin can be helpful in improving the neurological complications of diabetes, and studies have been conducted in this field that is very important due to the high prevalence of diabetic neuropathy. One study showed that the quercetin content of Allium cepa Lam. leaves have protective effects against diabetic neuropathy (Dureshahwar, Mubashir, and Une 2017). In a study of diabetic rats, quercetin treatment at 10 mg/kg for 4 weeks (starting treatment 4 weeks after induction of diabetes by STZ) had significant effects in attenuating cold allodynia and thermal hyperalgesia (Anjaneyulu and Chopra, 2004).

It seems that quercetin can alleviate high glucose induced Schwann cells' damage, possibly through enhancing autophagy. The results of this study showed that under high glucose conditions the proliferation of Schwann rat cells is attenuated and the expression of autophagic markers including Beclin-1 and LC3 is reduced, while quercetin can rescue the proliferative and autophagic activity of these cells (Qu et al. 2014). A study published in 2020 has shown that the combination of quercetin with hirudin and cinnamaldehyde can have significant effects on enhancing the differentiation and myelination of Schwann cells under high glucose condition. The results of this study suggest that the protective effects of this combination are due to the inhibitory effect on ERK signaling (Liu et al. 2020). Another study showed that this combination also had a protective effect on the dorsal root

ganglion neurons in high glucose conditions. The results of this study showed that this protective effect is due to reduced expression of NFKB, TNFα, and IL-6, enhanced expression of NRF2 and attenuated apoptosis (Shi et al. 2017). From these results, it can be concluded that weakening inflammation and strengthening the anti-oxidant system may be an effective way to protect neurons in diabetes. Furthermore, quercetin appears to attenuate P2X 4 receptor expression, which is linked with neuropathic pain and is associated with the P38MAPK signaling pathway in the dorsal root ganglia, and may have a positive effect on improving diabetic neuropathic pain (Yang, Sloan, et al. 2019). The positive effects of quercetin on diabetic neuropathic pain also appear to be associated with the inhibition of the mTOR/p70S6K signaling (Wang, Qiu, et al. 2020). This signaling pathway is probably involved in neuropathic pain. In the previous sections, the effect of quercetin on AMPK was mentioned. This effect also appears to be associated with the attenuation of diabetic peripheral neuropathy. A recent study in showed that quercetin administration could improve nerve conduction velocity and increase the expression of myelin base protein and myelin protein zero. The results of this study also showed that quercetin can reduce high glucose-induced oxidative stress and attenuate mitochondrial morphologic damages. In addition, quercetin increased the expression of SIRT1, NRF1, AMPK, and PGC-1α, in hyperglycemic conditions. The results of this study suggest that quercetin may be able to attenuate peripheral diabetic neuropathy by modifying abnormality of mitochondria by enhancing the AMPK/PGC-1α signaling (Zhang et al. 2021).

The results of a very interesting study on diabetic rat models suggest that the positive effects of quercetin on peripheral diabetic neuropathy may also be related to the effects of quercetin on the composition of intestinal bacteria. The results of this study showed that quercetin attenuates oxidative stress and myelin and axon damage, possibly through reducing the abundance of some pathogenic bacteria (f_Porphyromonadaceae, f_Oxalobacteraceae, g_Oxalobacter, and g_Klebsiella) that are directly related to peripheral diabetic neuropathy and the production of oxidative species and increasing the abundance of probiotic bacteria (p_Actinobacteria and c_Actinobacteria) which are inversely correlated with diabetic neuropathy and oxidative species levels (Xie et al. 2020). Given the evidence for the association between intestinal bacteria and diabetes, further studies on the association between the effects of quercetin on intestinal bacteria, AMPK, and peripheral diabetic neuropathy may be helpful. Another study on rat models of diabetes showed that administration of quercetin for 8 weeks at doses of 20 and 40 mg/kg could significantly increase nerve conduction velocity in motor and sensory nerves. The results of this study also showed that quercetin reduced MDA and neural nitrite levels, inhibited the decrease in neural levels of SOD and GSH following diabetes, and reduced TNFα and IL-1B levels in the sciatic nerve (Kandhare et al., 2012). These results may also indicate that the anti-oxidant and anti-inflammatory properties of quercetin may be a key factor in the neuroprotective effects of quercetin in diabetes. Quercetin also appears to have beneficial effects on memory function in diabetes. The results of a study performed on diabetic rat models showed that quercetin has ameliorative effects on memory dysfunction (Bhutada et al. 2010). Another study showed that quercetin supplementation in the form of superparamagnetic iron oxide nanoparticles (QC-Fe3O4 NPs) had better effects on improving memory function in diabetic rats compared to free quercetin (Ebrahimpour, Vaghari-Tabari, et al. 2018). Quercetin appears to be able to attenuate Aβ1–42 aggregation by enhancing macroautophagy and proteasomal degradation (Regitz, Dußling, and Wenzel 2014). The results of one study showed that quercetin reduces the toxic effects of Abeta (1-42) in hippocampal cultures, possibly by attenuating oxidative stress (Ansari et al. 2009). The effects of quercetin on boosting AMPK activity also appear to be helpful in preventing Alzheimer disease. The results of one study showed that quercetin may attenuate tau hyper-phosphorylation by enhancing AMPK activation and ER stress suppression (Chen et al. 2016). Based on the above findings, it seems that quercetin due to its role in metabolic regulation and regulation of signaling pathways and anti-inflammatory and anti-oxidant properties may be a useful natural product to prevent and improve the neurological complications of diabetes.

5.4. Quercetin and delayed wound healing in diabetes

Another complication of diabetes is impaired wound healing, leading to diabetic ulcers, which are common in the foot area. It is estimated that diabetic foot ulcers affect about 15% of diabetic patients and are the leading cause of amputation in these patients (Brem and Tomic-Canic 2007). The molecular mechanism of wound healing is very broad. Briefly, after skin injury, the homeostasis phase begins. The formation of fibrin clot occurs at this phase (Goodarzi, Maniati, and Qujeq 2019). The clot and the wound environment secrete pro-inflammatory cytokines and growth factors such as TGF-B. When the bleeding stops, the inflammatory cells migrate to the wound site and the inflammatory phase begins. Neutrophils can clear cellular debris and invasive microbes in the wound area. Macrophages play a very important role in wound healing. These cells initially enhance the recruitment and activation of leukocytes by secreting cytokines. Macrophages also play a role in clearing apoptotic cells. Macrophages then undergo a phenotype alteration and reparative phenotype is formed. Reparative phenotype can stimulate fibroblasts, keratinocytes, and angiogenesis leading to enhancement of tissue regeneration (Guo and Dipietro 2010). In the proliferation phase, events such as angiogenesis, re-epithelialization, collagen synthesis, and ECM formation are occurred. Collagen remodeling and vascular maturation are among the events of the remodeling phase (Guo and Dipietro 2010). In diabetes, different stages of the wound healing process may be disrupted. Hyperglycemia and oxidative stress appear to affect macrophage polarization. Impaired regulation of macrophage polarization is one of the main causes of impaired wound healing in diabetic patients. Other events such as prolongation of the inflammatory phase and continuous production of pro-inflammatory cytokines, impaired angiogenesis,

impaired migration and proliferation of fibroblasts and keratinocytes, dysfunction of neutrophils and impaired production of growth factors are among the events that may be associated with delayed wound healing in diabetes. Hypoxia due to narrowing of the vessels and glycation of hemoglobin, which impair the supply of oxygen and nutrients to the tissues, may also be other reasons for delayed wound healing in diabetes (Patel et al. 2019). However, the exact etiology of wound healing impairment in diabetes is still unclear. Some studies have shown that quercetin can be helpful in healing diabetic wounds. A study of diabetic rats showed that topical quercetin ointment could have positive effects on wound healing (Ahmad et al. 2017).

A study of diabetic rat models showed that quercetin may potentiate phenotypic changes in macrophages toward M2 macrophages, thereby having a beneficial effect on accelerating wound healing in diabetes. The results of this study showed that quercetin treatment could enhance contraction of wound area, reduce pro-inflammatory cytokine levels including TNFα and IL-6, increase IL-10 levels which has anti-inflammatory properties, increase angiogenesis-related factors levels, including VEGF-a, decrease iNOS levels, which is M1 macrophages marker; increase Msr-1 and Arg-1 levels, which are markers of M2 macrophages; and enhance collagen deposition and fibroblast activity (Fu et al. 2020). Another study using topical quercetin ointment reported a similar one. This study showed that quercetin could reduce TNFα and IL-1B levels and boost VEGF and TGF-β1 and IL-10 expression in diabetic wound tissue (Kant et al. 2021). Therefore, these results suggest that the positive effect of quercetin on accelerating wound healing in diabetes is probably due to the anti-inflammatory properties of quercetin and enhanced polarization of macrophages toward the M2 phenotype. Further studies on the effect of quercetin topical ointments on wound healing in diabetic patients seem to be very useful. Some studies have also shown that the combination of quercetin and laser therapy may have beneficial effects on wound healing in diabetes. One study in diabetic rats showed that quercetin treatment with oral gavage and low-level laser therapy could increase collagen fibers in injured skin, reduce TNF-α and IL-1β levels, attenuate oxidative stress, and increase glutathione and IL-10 levels (Ahmed et al. 2018). Therefore, it seems that combining quercetin with other therapeutic approaches can be a good way to accelerate wound healing in diabetes. Some studies in recent years have also suggested the use of nanoparticles to improve the penetration of quercetin into the wound (Choudhary et al. 2020). Undoubtedly, with the expansion of studies in all the above fields, from identifying the mechanism of action to appropriate delivery methods, we can hope for the clinical application of quercetin to accelerate wound healing in diabetes in the future.

5.5. Quercetin and diabetic retinopathy

Among diabetic complications diabetic retinopathy as an asymptomatic disorder has triggered one-third of diabetic society and is the underlying cause of blindness which reduces the patient's standard of living (Antonetti, Silva, and Stitt 2021). Diabetic retinopathy has irreversible retinal damages because initial symptoms manifest in advanced stages. As a neurovascular complication, it has both vascular and neuronal abnormalities which leads to the onset of clinical characteristics including microaneurysms, hemorrhages, hard exudates, capillary loss, retinal vascular leakage, diabetic macular edema (DME), and neovascularization (Lee, Wong, and Sabanayagam 2015; Rodríguez et al. 2019). There are two classes of diabetic retinopathy; non-proliferative DR (NPDR) and proliferative DR (PDR) (Abu et al. 2016). Further detail is beyond the main purpose of this article. Normal amount of ROS are responsible for regulating physiological processes, including cell metabolism, proliferation, immune system, and vascular remodeling. However, ROS accumulation as the most important cause of diabetic retinopathy is associated with oxidative stress, inflammation, and angiogenesis (Ola, Al-Dosari, and Alhomida 2018). High glucose concentration in diabetic patients can develop retinal complication in two major ways; first, when glucose is high, ROS generation enhances significantly which leads to the activation of different pathways and subsequently diabetic retinopathy (Hammes 2018; Kang and Yang 2020). Secondly, during hyper-glycaemia, glucose interacts with macromolecules and creates AGEs which has the capacity to bind to different cell types and cause vessels elasticity disregulation, ECM abnormalities, and inflammatory signaling pathways activation, resulting in diabetic retinopathy progression (Zong, Ward, and Stitt 2011; Sahajpal et al. 2019). Oxidative stress, inflammation, apoptosis, and autophagy are the main victims in diabetic retinopathy (Dehdashtian et al. 2018). In addition to reactive oxygen species (ROS) increase in diabetes which occurs as a result of disruptions in glucose homeostasis and NADPH oxidase (Nox) 2 and Nox 4 overexpression, anti-oxidant enzymes appear to be reduced in these cases (Dehdashtian et al. 2018). Furthermore, ROS accumulation leads to elevating the demand for more energy and autophagy creates the opportunity to degrade different elements in purpose of maintaining homeostasis (Rosa et al. 2016). In this regard, it is not surprising that autophagy markers experience a significant rise in diabetic retinopathy (Lopes de Faria et al. 2016).

The elevation of both apoptotic mediators, including cytochrome c, caspase-3, p53, and Bax, as well as inflammatory mediators, including IL-1β, IL-18, TNF-α, ICAM1 (intercellular adhesion molecule 1), VCAM1 (vascular cell adhesion molecule), NF-kB, and PTEN are accompanied by diabetic retinopathy progression (Khalfaoui, Lizard, and Ouertani-Meddeb 2008; Choudhuri et al. 2015; Lin et al. 2016; Tien et al. 2017; Rübsam, Parikh, and Fort 2018; Yao, Du, et al. 2019; ValdezGuerrero et al. 2021). In addition, there are different inflammasomes subtypes which are able to recognize stress and danger signals; Nucleotide binding oligomerization domain-like receptors 3 (NLRP3) is one of them and has three domains including central, C terminal, and N terminal domains which are vital for NLRP3 innate immunity activity. In NLRP3 inflammasome, the adaptor-apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) can recruit caspase-1

which is associated with IL-1β and IL-18 activation (Kelley et al. 2019). This complex has been identified in retinal cells and its overexpression is observed in diabetic retinopathy cases (Chaurasia et al. 2018; Raman and Matsubara 2020). Mechanistically, when the concentration of glucose is high, ROS production rises leading to the indirect activation of NLRP3 inflammasome. Overall, huge number of studies has proved that since prolonged activation of this inflammasome and its downstream effectors result in diabetic retinopathy, triggering this complex can be a selective approach to alleviate diabetic retinopathy (Lu et al. 2018; Li, Xu, et al. 2019; Raman and Matsubara 2020; Wang, Qiu, et al. 2020). High mobility group box 1 (HMGB1) takes part in inflammatory responses and during stresses like high glucose concentration it can interact with toll-like receptor 4 (TLR4) in order to phosphorylate and activate the NFkB pathway and subsequently produce inflammatory cytokines (Steinle 2020). In addition, HMGB1/TLR4/NF-κB can also stimulate NLRP3 inflammasome and the production of caspase-1, IL-1β, and IL-18 (Chai et al. 2021). Since different studies have been investigated the overexpression of HMGB1, NF-κB, and NLRP3 inflammasome in diabetic retinopathy, researchers have been looking forward to find therapeutic strategies for this disorder based on targeting these factors (Chai et al. 2020; Liang et al. 2020; Nebbioso et al. 2020; Shen et al. 2020). Moreover, heme oxygenase-1 (HO-1) has anti-oxidant, anti-inflammatory, and anti-apoptotic properties which can be found in retinal cells (Fan et al. 2012). Generally, this enzyme plays an underlying role in returning the normal homeostasis after stresses. On the other side, diabetic retinopathy was considered as a microvascular complication, while nowadays it has been introduced as a neurovascular complication (Gangaputra et al. 2013). Neurotrophic factors like retinal brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF) play pivotal role in neuronal cell survival (Park et al. 2008). By considering the fact that retinal neurovascular unit has an important role in the homeostasis maintenance like vascular density and permeability, any dysregulation in this unit can cause retinopathy in diabetic cases. One of the most important factors in this unit is vascular endothelial growth factor (VEGF) which is essential for the generation of new blood vessels. Retinal hypoxia potentiates VEGF up-regulation, angiogenesis, and diabetic retinopathy progression (Ji et al. 2021). Blood retinal barrier (BRB) breakdown leads to plasma leakage to retina which is overall associated with swelling and hypoxia. Matrix metalloproteinases (MMPs) as endopeptidases are involved in ECM degradation. Therefore, MMPs imbalance not only negatively affects vascular permeability and BRB junction complex but also takes part in neovascularization (Drankowska et al. 2019). Tight junctions are also responsible for preserving membrane polarization, cell morphology, and growth. BRB disruption is related to tight junction proteins dysregulation which eventually results in retinal vasculopathy and diabetic retinopathy (Rudraraju, Narayanan, and Somanath 2020). The hypothesis of the role of inflammation due to altered intestinal bacterial composition in the pathogenesis of diabetic retinopathy has also been proposed (Jiao et al. 2021). Some studies have also reported a decrease in some bacteria with anti-inflammatory properties such as Faecalibacterium and Bifidobacterium and an increase in pathogenic bacteria such as E. coli and Enterobacter in patients with diabetic retinopathy (Das et al. 2021). However, reported changes in the composition of intestinal bacteria, including decreased Escherichia-Shigella and increased Akkermansia in patients with diabetic retinopathy compared with healthy individuals (Das et al. 2021; Huang et al. 2021), justify the need for further studies to draw accurate conclusions.

A huge number of studies have been introduced natural agents as the effective therapeutic strategies for alleviating pathological processes in diabetic retinopathy (Jeenger et al. 2015; Nabavi et al. 2016; Bungau et al. 2019; Ahmad and Hoda 2020; Matos et al. 2020). One of these agents is quercetin which plays its anti-diabetic retinopathy's functions through the regulation of different mechanisms (Bungau et al. 2019). In the following we will shed more light on the protective effect of quercetin on diabetic retinopathy. The amount of inflammatory cytokines like TNF-α and IL-1β rises in diabetic retinopathy which is accompanied by NF-kB and caspase-3 activation and pathological consequences. Given the destructive role of these inflammatory elements, a study observed that six months quercetin therapy in diabetic rat models can prohibit the release of cytokines and the activation of NF-kB and caspase-3 dose dependently, resulting in microglia apoptosis inhibition. Moreover, quercetin has the capacity to reduce retinal edema and induce anti-oxidant enzymes, leading to retinal damage protection (Kumar et al. 2014). The protective effects of miR-29b in diabetic retinal cells have been reported widely. For example, Triptolide and resveratrol have the capacity to prevent diabetic retinopathy through up regulation of miR-29b (Zeng et al. 2017; Han et al. 2020). In line with these demonstrations, a study examined the association between quercetin and miR-29b in adult retinal pigment epithelial cell line-19 (ARPE-19) cells during high glucose stress. During such stress condition, p-AKT and miR-29b expression reduce while PTEN, p-p65 and IκBα expression level enhance which over all leads to PTEN/AKT and NF-κB activation and cell apoptosis. Encouraging results showed that the application of 30 μM quercetin exerts anti-apoptotic effects and improves cell viability due to its negative effects on the expression level of p53, Bax, and caspase-3 as well as positive effects on CyclinD1, CDK4, and Bcl-2. Moreover, quercetin up-regulates miR-29b expression in order to activate the AKT pathway and suppress the NF-κB pathway, conducting to cell survival. Collectively, quercetin plays its protective role against retinal cell death and diabetic retinopathy progression in miR-29b dependent manner (Wang, Qiu, et al. 2020). The release of Cytochrome c causes caspase-3 activation and DNA fragmentation. BDNF can interact with tropomyosin-related kinase B (TrkB) receptor and then activate the Akt signaling which leads to cell survival and stop apoptosis. Mohammad S. Ola et al observed that quercetin application in diabetic rats with retinal complication can enhance the BDNF–TrkB/Akt-synaptophysin signaling

pathway and also prevent apoptosis through the activation of Bcl-2 and the suppression of cytochrome c and caspase-3 activation (Ola et al. 2017). Another study also confirmed the neuroprotective effect of quercetin in a zebra fish model which suffers diabetic retinopathy (Wang, Qiu, et al. 2020). Encouraging evidence shows that inflammatory elements, including NLRP3 inflammasome, LC3, and Beclin-1, autophagy, angiogenesis, and migration give a rise in human retinal microvascular endothelial cells (HRMECs) during high glucose concentration while quercetin can reverse these pathophysiologic characteristics through affecting them negatively (Li, Mao, et al. 2021). Experimental analysis showed that the expression level of HO-1 and HMGB1 decreases and increases in diabetic retinopathy patients respectively (Nebbioso et al. 2020; Wu, Zhu, and Zhou 2020). An interesting study evaluated the effect of quercetin on these factors and found that this polyphenol can reduce HMGB1/TLR4/NF-κB/NLRP3 inflammasome/IL-1β/IL-18 axis and angiogenesis factors like VEGF and sICAM-1 while it increases the expression of neurotrophic factors, BDNF and NGF, and also HO-1. This study also revealed that quercetin exerts these functions in HO-1 dependent manner because HO-1 inhibition reversed the effects of quercetin on diabetic retinopathy rat models (Chai et al. 2021). Studies focused on the interconnection between quercetin and the angiogenesis in diabetic retinopathy (Sulaiman, Basavarajappa, and Corson 2014).

Experimental evidence on human microvascular endothelial cells showed that quercetin, especially its derivate (8MQPM), appears to suppress angiogenesis and tube formation through VEGFR-2 downregulation and its downstream signaling pathways like ERK1/2, Akt and JNK activation/phosphorylation (Lupo et al. 2019). Relatively, some studies are investigated the cross talk between MMPs especially MMP-9 and VEGF in diabetic retinopathy (Ishizaki et al. 2006; Abu et al. 2016); because basement membrane degradation is essential in the formation of new vessels and diabetic retinopathy progression. In this regard, a study observed one of the diabetic retinopathy protective mechanisms of action of quercetin is that this natural component has the capacity to reduce MMP-9 and VEGF and also their negative functions in retina in diabetic rats (Chen et al. 2017). Another study compared the function of VEGF and quercetin treatment in Retinal Photoreceptor Cells and found that when cells were treated by VEGF, the expression of ICAM1, VCAM1, MMP2 and MMP9 as well as NF-kB/p65 subunit nuclear translocation and MAPKs activation increases while the expression of IKKα and β-catenin and Zona occludins-1 decreases. Quercetin has the capacity to reverse the VEGF inflammatory functions through the inhibition of the NF-kB, MAPK and Akt pathways (Lee et al. 2017). Quercetin also is one of the main components of Xueshuantong Capsule which exerts positive effects on diabetic retinopathy treatment via alleviating neovascularization and macular edema (Xing et al. 2019; Li, Li, and Zheng 2020; Yao et al. 2021). An in-vitro study declared that quercetin appears to protect tight junction proteins via up-regulation of autophagy. For example, it stops the translocation of ZO-1 from cytomembrane to cytoplasm; Quercetin does this function in autophagy dependent manner, because autophagy inhibition reverses tight junction proteins protective effect of this natural agent (Li, Mao, et al. 2021). Overall, it has been declared that quercetin protects against diabetic retinopathy development through its anti-inflammatory, anti-apoptosis, anti-angiogenesis pathways. Therefore, this fact has been obtained from studies that quercetin is effective in retinal cells integrity and it can be a proper candidate for retinal diseases treatment like diabetic retinopathy (Fernandez-Gonzalez, Mas-Sanchez, and Garriga 2021). However, further studies are required to evaluate the effectiveness of this phytochemical in human diabetic retinopathy cases. One of the interesting topics of future studies can be the study of the effects of quercetin on the composition of intestinal bacteria in patients with diabetic retinopathy and the relationship between these effects and the benefits of quercetin in relieving diabetic retinopathy.

6. Clinical evidences regarding usefulness of quercetin in diabetes

What has been mentioned above is often the result of studies on animal models that clearly show that quercetin is a natural product with anti-diabetic effects that is also useful in preventing and reducing the complications of diabetes. Some clinical studies have also confirmed the effects of quercetin, which has raised hopes for the clinical use of quercetin in the treatment of diabetes. However, some other clinical studies have not reported significant effects in this regard. In a clinical trial performed on patients with type 2 of diabetes, quercetin supplementation at a dose of 250 mg/day was performed for 8 days. The results of this study showed that quercetin has no significant effect on lowering blood sugar and weakening insulin resistance. However, the results of this study showed that quercetin supplementation significantly improves total antioxidant capacity and significantly reduces ox-LDL levels (Mazloom et al. 2014). However, some studies on PCOS patients have shown that quercetin supplementation at a dose of 1000 mg/day for 12 weeks could significantly reduce fasting plasma glucose levels and insulin resistance index (HOMA-IR) (Rezvan et al. 2016; Khorshidi et al. 2018). In a clinical trial performed on women with type2 of diabetes, it was shown that quercetin supplementation at a dose of 500 mg/day for 10 weeks had a significant effect on reducing TNFα and IL-6 levels (Zahedi et al. 2013). Given the destructive role of TNFα in insulin resistance discussed in the previous sections, it is necessary to investigate the relationship between the effect of quercetin on reducing TNFα levels and HOMA-IR. The results of a clinical trial performed on overweight to obese patients with pre- and stage 1 hypertension showed that quercetin supplementation at 162 mg/day for 6 weeks had no significant effect on reducing fasting plasma glucose levels and HOMA-IR (Brüll et al., 2017). The results of the subgroup analysis of a meta-analysis performed on randomized controlled trials

suggest that quercetin supplementation at doses of ≥500 mg/day for 8 weeks or more may be useful in reducing fasting plasma glucose levels in patients with metabolic syndrome. In addition, this meta-analysis concluded that insulin levels were reduced in studies that performed quercetin supplementation at doses of ≥500 mg/day and included patients less than 45 years of age (Ostadmohammadi et al. 2019). Therefore, it seems that more clinical studies should be performed on the effect of quercetin supplementation on fasting glucose levels and insulin resistance. Although very limited clinical studies have been performed on the effect of quercetin on the renal complications of diabetes, quercetin seems to have positive effects in this regard.

A clinical trial performed on patients with diabetic kidney disease showed that quercetin supplementation at 1000 mg/day plus dasatinib at 100 mg/day for three days had significant effects on reducing pro-inflammatory cytokine levels, including IL6 and IL −1. In addition, the results of this study showed that fibroblast growth factor (FGF) −2 and GM-CSF also tend to decrease following quercetin supplementation plus dasatinib (Hickson et al., 2019). In the previous sections, we briefly mentioned the destructive role of these cytokines and growth factors in the pathogenesis of diabetic nephropathy. Another clinical trial in pre-hyperuricaemic males showed that quercetin supplementation at 500 mg/day for 4 weeks could significantly reduce serum uric acid levels but had no significant effect on fasting plasma glucose levels, blood pressure and urinary excretion of uric acid (Shi and Williamson 2016). Some clinical investigations have also shown that quercetin has beneficial effects in reducing some of the risk factors for cardiovascular disease. Some clinical trial studies have shown that quercetin supplementation at doses of 150 mg/day for 6 weeks in patients with metabolic syndrome and 250 mg/day for 8 weeks in patients with type 2 diabetes has a significant effect on lowering ox-LDL (Egert et al., 2009; Mazloom et al. 2014). However, there are different results regarding the effect of quercetin on lipid profile. The results of a meta-analysis of clinical studies showed that quercetin had no significant effect on lipid profile (Huang et al. 2020), while the results of another meta-analysis of clinical trials conducted exclusively on patients with metabolic syndrome and related disorders showed that quercetin supplementation had a positive effect in lowering total cholesterol, LDL-C and CRP levels (Tabrizi et al., 2020). Different results have been reported regarding the effect of quercetin on blood pressure, as well. While some clinical trial studies have shown that quercetin supplementation has a positive effect on lowering systolic blood pressure (Egert et al., 2009; Zahedi et al. 2013), other studies have shown that quercetin supplementation does not have a significant effect on lowering systolic blood pressure (Dower et al. 2015; Bondonno et al. 2016). It should be noted that the first batch of the above studies have been performed on patients with type 2 diabetes or individuals with metabolic syndrome traits. Therefore, it is possible that quercetin is more effective in lowering blood pressure, LDL-C, and total cholesterol in diabetic patients or patients with metabolic syndrome. More clinical trials should be performed on diabetic patients and healthy individuals to investigate this possibility. In addition, clinical trials in diabetic patients to evaluate the effect of quercetin on other risk factors of cardiovascular disease, including homocysteine levels, may be helpful. Regarding the positive effects of quercetin in diabetic neuropathy, a clinical trial study on patients with diabetic neuropathy has shown that QR-333, a topical quercetin-containing compound, has positive effects in reducing jolting pain, numbness, and irritation and improving quality of life (Valensi et al. 2005).

The positive effects of quercetin on wound healing in diabetes mentioned in the previous section have also been shown in clinical studies. In a clinical study on diabetic patients with lower limb skin wound, it was shown that topical application of nanohydrogels containing quercetin and oleic acid can significantly reduce wound healing time (Gallelli et al. 2020). Although limited clinical studies have been performed to evaluate the effect of quercetin on the complications of diabetes, the results of these limited studies reviewed above indicate that quercetin may be useful in ameliorating the complications of diabetes and can confirm the promising results of animal models and in-vitro studies reviewed in the previous sections. Further clinical studies in the future will undoubtedly reveal more dimensions of the beneficial effects of quercetin in diabetes.

7. Conclusion and future direction

Oxidative stress and inflammation play an important role in insulin resistance, pathogenesis of type 2 of diabetes and pathogenesis of diabetes complications including nephropathy, cardiovascular complications, neuropathy, delayed wound healing, and retinopathy. Quercetin, a powerful anti-inflammatory and anti-oxidant compound, may play an important role in improving insulin sensitivity and lowering blood sugar. Quercetin can improve kidney function in animal models of diabetes, reduce the risk factors of cardiovascular disease including ox-LDL and hypertension, improve memory function in diabetes, alleviate hyperglycemia-induced Schwann damage, and improve diabetic neuropathy. Quercetin may accelerate wound healing in diabetes by potentiating macrophage polarization toward M2 macrophages, weakening inflammation, and enhancing TGF-B and VEGF expression. Quercetin exerts its protective role against diabetic retinopathy through the down-regulation of inflammation, apoptosis, and angiogenesis as well as inducing neurotrophic factors. Limited clinical studies have examined the effect of quercetin on diabetes and its complications. Some of these studies have reported conflicting results that may be due to differences in population and dose used. However, the results of some clinical trials have shown that quercetin has positive effects in lowering ox-LDL, systolic blood pressure, improving diabetic neuropathy, diabetic retinopathy, and accelerating wound healing in diabetes. Many of the positive results of quercetin in animal model studies have not yet been clinically evaluated. For example, the effect of quercetin supplementation on kidney function and kidney tissue in diabetic patients has not yet been extensively studied clinically.

Topical quercetin ointments that have been shown to be effective in treating diabetic peripheral neuropathy and accelerating wound healing in diabetes need further and more extensive clinical studies. In addition to clinical studies, more animal model studies are needed because the effects of quercetin on many of the different mechanisms and signaling pathways involved in the pathogenesis of diabetes and its complications are still unclear.

Acknowledgements

The Authors would like to thanks Clinical Research Development Unit, Shohada Hospital, Tabriz University of Medical Sciences for kind supports.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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References

Abu, El-Asrar, A. M., M. M. Siddiquei, M. I. Nawaz, G. De Hertogh, G. Mohammad, K. Alam, A. Mousa, and G. Opdenakker. 2016. Coexpression of heparanase activity, cathepsin l, tissue factor, tissue factor pathway inhibitor, and mmp-9 in proliferative diabetic retinopathy. *Molecular Vision* 22:424–35.

Adela, R., S. K. Nethi, P. K. Bagul, A. K. Barui, S. Mattapally, M. Kuncha, C. R. Patra, P. N. Reddy, and S. K. Banerjee. 2015. Hyperglycaemia enhances nitric oxide production in diabetes: A study from south Indian patients. *Plos ONE* 10 (4):e0125270. doi: 10.1371/journal.pone.0125270.

Aguirre, V., T. Uchida, L. Yenush, R. Davis, and M. F. White. 2000. The c-Jun NH(2)-terminal kinase promotes insulin resistance during association with insulin receptor substrate-1 and phosphorylation of Ser(307). *The Journal of Biological Chemistry* 275 (12):9047–54. doi: 10.1074/jbc.275.12.9047.

Ahmad, I., and M. Hoda. 2020. Attenuation of diabetic retinopathy and neuropathy by resveratrol: Review on its molecular mechanisms of action. *Life Sciences* 245:117350. doi: 10.1016/j.lfs.2020.117350.

Ahmad, M., M. Sultana, R. Raina, N. K. Pankaj, P. K. Verma, and S. Prawez. 2017. Hypoglycemic, hypolipidemic, and wound healing potential of quercetin in streptozotocin-induced diabetic rats. *Pharmacognosy Magazine* 13 (Suppl 3):S633–S639. doi: 10.4103/pm.pm_108_17.

Ahmed, O. M., T. Mohamed, H. Moustafa, H. Hamdy, R. R. Ahmed, and E. Aboud. 2018. Quercetin and low level laser therapy promote wound healing process in diabetic rats via structural reorganization and modulatory effects on inflammation and oxidative stress. *Biomedicine & Pharmacotherapy* 101:58–73. doi: 10.1016/j.biopha.2018.02.040.

Ahn, J., H. Lee, S. Kim, J. Park, and T. Ha. 2008. The anti-obesity effect of quercetin is mediated by the AMPK and MAPK signaling pathways. *Biochemical and Biophysical Research Communications* 373 (4):545–9. doi: 10.1016/j.bbrc.2008.06.077.

Alnahdi, H. S., N. O. Ayaz, A. M. Mohamed, I. A. Sharaf, and N. M. Alshehri. 2017. Modulating impacts of quercetin and/or lactoferrin on diabetic nephropathy and cardiomyopathy induced rats. *International Journal of Pharmaceutical Research & Allied Sciences* 6 (2):128-137.

Amasheh, M., S. Schlichter, S. Amasheh, J. Mankertz, M. Zeitz, M. Fromm, and J. D. Schulzke. 2008. Quercetin enhances epithelial barrier function and increases claudin-4 expression in Caco-2 cells. *The Journal of Nutrition* 138 (6):1067–73. doi: 10.1093/jn/138.6.1067.

Anjaneyulu, M., and K. Chopra. 2004. Quercetin attenuates thermal hyperalgesia and cold allodynia in STZ-induced diabetic rats. *Indian Journal of Experimental Biology* 42 (8):766–9.

Anjaneyulu, M., and K. Chopra. 2004. Quercetin, an anti-oxidant bioflavonoid, attenuates diabetic nephropathy in rats. *Clinical and Experimental Pharmacology & Physiology* 31 (4):244–8. doi: 10.1111/j.1440-1681.2004.03982.x.

Ansari, M. A., H. M. Abdul, G. Joshi, W. O. Opii, and D. A. Butterfield. 2009. Protective effect of quercetin in primary neurons against Abeta(1-42): Relevance to Alzheimer's disease. *The Journal of Nutritional Biochemistry* 20 (4):269–75. doi: 10.1016/j.jnutbio.2008.03.002.

Antonetti, D. A., P. S. Silva, and A. W. Stitt. 2021. Current understanding of the molecular and cellular pathology of diabetic retinopathy. *Nature Reviews. Endocrinology* 17 (4):195–206. doi: 10.1038/s41574-020-00451-4.

Appari, M., K. M. Channon, and E. McNeill. 2018. Metabolic regulation of adipose tissue macrophage function in obesity and diabetes. *Antioxidants & Redox Signaling* 29 (3):297–312. doi: 10.1089/ars.2017.7060.

Arai, Y., S. Watanabe, M. Kimira, K. Shimoi, R. Mochizuki, and N. Kinae. 2000. Dietary intakes of flavonols, flavones and isoflavones by Japanese women and the inverse correlation between quercetin intake and plasma LDL cholesterol concentration. *The Journal of Nutrition* 130 (9):2243–50. doi: 10.1093/jn/130.9.2243.

Archuleta, T. L., A. M. Lemieux, V. Saengsirisuwan, M. K. Teachey, K. A. Lindborg, J. S. Kim, and E. J. Henriksen. 2009. Oxidant stress-induced loss of IRS-1 and IRS-2 proteins in rat skeletal muscle: Role of p38 MAPK. *Free Radical Biology and Medicine* 47 (10):1486–93. doi: 10.1016/j.freeradbiomed.2009.08.014.

Aryaeian, N., S. K. Sedehi, and T. Arablou. 2017. Polyphenols and their effects on diabetes management: A review. *Medical Journal of the Islamic Republic of Iran* 31:134. doi: 10.14196/mjiri.31.134.

Asmat, U., K. Abad, and K. Ismail. 2016. Diabetes mellitus and oxidative stress-a concise review. *Saudi Pharmaceutical Journal: SPJ : The Official Publication of the Saudi Pharmaceutical Society* 24 (5):547–53. doi: 10.1016/j.jsps.2015.03.013.

Bhaskar, S., V. Shalini, and A. Helen. 2011. Quercetin regulates oxidized LDL induced inflammatory changes in human PBMCs by modulating the TLR-NF-κB signaling pathway. *Immunobiology* 216 (3):367–73. doi: 10.1016/j.imbio.2010.07.011.

Bhutada, P., Y. Mundhada, K. Bansod, C. Bhutada, S. Tawari, P. Dixit, and D. Mundhada. 2010. Ameliorative effect of quercetin on memory dysfunction in streptozotocin-induced diabetic rats. *Neurobiology of Learning and Memory* 94 (3):293–302. doi: 10.1016/j.nlm.2010.06.008.

Bondonno, N. P., C. P. Bondonno, L. Rich, E. Mas, S. Shinde, N. C. Ward, J. M. Hodgson, and K. D. Croft. 2016. Acute effects of quercetin-3-o-glucoside on endothelial function and blood pressure: A randomized dose-response study. *The American Journal of Clinical Nutrition* 104 (1):97–103. doi: 10.3945/ajcn.116.131268.

Borges, C. M., A. Papadimitriou, D. A. Duarte, J. M. Lopes de Faria, and J. B. Lopes de Faria. 2016. The use of green tea polyphenols for treating residual albuminuria in diabetic nephropathy: A double-blind randomised clinical trial. *Scientific Reports* 6:28282. doi: 10.1038/srep28282.

Brem, H., and M. Tomic-Canic. 2007. Cellular and molecular basis of wound healing in diabetes. *The Journal of Clinical Investigation* 117 (5):1219–22. doi: 10.1172/jci32169.

Brito, J. C. M., W. G. Lima, L. P. B. Cordeiro, and W. S. Cruz Nizer. 2021. Effectiveness of supplementation with quercetin-type flavonols for treatment of viral lower respiratory tract infections: Systematic

review and meta-analysis of preclinical studies. *Phytotherapy Research* 35 (9):4930–42. doi: 10.1002/ptr.7122.

Brüll, V., C. Burak, B. Stoffel-Wagner, S. Wolffram, G. Nickenig, C. Müller, P. Langguth, B. Alteheld, R. Fimmers, P. Stehle, et al. 2017. No effects of quercetin from onion skin extract on serum leptin and adiponectin concentrations in overweight-to-obese patients with (pre-)hypertension: A randomized double-blinded, placebo-controlled crossover trial. *European Journal of Nutrition* 56 (7):2265–75. doi: 10.1007/s00394-016-1267-0.

Bungau, S., M. M. Abdel-Daim, D. M. Tit, E. Ghanem, S. Sato, M. Maruyama-Inoue, S. Yamane, and K. Kadonosono. 2019. Health benefits of polyphenols and carotenoids in age-related eye diseases. *Oxidative Medicine and Cellular Longevity* 2019:9783429. doi: 10.1155/2019/9783429.

Cani, P. D., M. Osto, L. Geurts, and A. Everard. 2012. Involvement of gut microbiota in the development of low-grade inflammation and type 2 diabetes associated with obesity. *Gut Microbes* 3 (4):279–88. doi: 10.4161/gmic.19625.

Castillo, R. L., E. A. Herrera, A. Gonzalez-Candia, M. Reyes-Farias, N. de la Jara, J. P. Peña, and C. Carrasco-Pozo. 2018. Quercetin prevents diastolic dysfunction induced by a high-cholesterol diet: Role of oxidative stress and bioenergetics in hyperglycemic rats. *Oxidative Medicine and Cellular Longevity* 2018:7239123. doi: 10.1155/2018/7239123.

Chai, G., S. Liu, H. Yang, G. Du, and X. Chen. 2020. Nlrp3 blockade suppresses pro-inflammatory and pro-angiogenic cytokine secretion in diabetic retinopathy. *Diabetes, Metabolic Syndrome and Obesity : targets and Therapy* 13:3047–58. doi: 10.2147/dmso.s264215.

Chai, G. R., S. Liu, H. W. Yang, and X. L. Chen. 2021. Quercetin protects against diabetic retinopathy in rats by inducing heme oxygenase-1 expression. *Neural Regeneration Research* 16 (7):1344–50. doi: 10.4103/1673-5374.301027.

Chang, A. S., C. K. Hathaway, O. Smithies, and M. Kakoki. 2016. Transforming growth factor-β1 and diabetic nephropathy. *American Journal of Physiology. Renal Physiology* 310 (8):F689–F696. doi: 10.1152/ajprenal.00502.2015.

Chatterjee, S., and A. Mudher. 2018. Alzheimer's disease and type 2 diabetes: A critical assessment of the shared pathological traits. *Frontiers in Neuroscience* 12:383. doi: 10.3389/fnins.2018.00383.

Chaurasia, S. S., R. R. Lim, B. H. Parikh, Y. S. Wey, B. B. Tun, T. Y. Wong, C. D. Luu, R. Agrawal, A. Ghosh, A. Mortellaro, et al. 2018. The NLRP3 inflammasome may contribute to pathologic neovascularization in the advanced stages of diabetic retinopathy. *Scientific Reports* 8 (1):2847. doi: 10.1038/s41598-018-21198-z.

Chelakkot, C., Y. Choi, D. K. Kim, H. T. Park, J. Ghim, Y. Kwon, J. Jeon, M. S. Kim, Y. K. Jee, Y. S. Gho, et al. 2018. Akkermansia muciniphila-derived extracellular vesicles influence gut permeability through the regulation of tight junctions. *Experimental & Molecular Medicine* 50 (2):e450. doi: 10.1038/emm.2017.282.

Chen, B., T. He, Y. Xing, and T. Cao. 2017. Effects of quercetin on the expression of MCP-1, MMP-9 and VEGF in rats with diabetic retinopathy. *Experimental and Therapeutic Medicine* 14 (6):6022–6. doi: 10.3892/etm.2017.5275.

Chen, J., X. Deng, N. Liu, M. Li, B. Liu, Q. Fu, R. Qu, and S. Ma. 2016. Quercetin attenuates tau hyperphosphorylation and improves cognitive disorder via suppression of ER stress in a manner dependent on AMPK pathway. *Journal of Functional Foods* 22:463–76. doi: 10.1016/j.jff.2016.01.036.

Chen, L., J. Liu, G. Mei, H. Chen, S. Peng, Y. Zhao, P. Yao, and Y. Tang. 2021. Quercetin and non-alcoholic fatty liver disease: A review based on experimental data and bioinformatic analysis. Food and chemical toxicology: An international journal published for the. *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 154:112314. doi: 10.1016/j.fct.2021.112314.

Chen, P., J. Chen, Q. Zheng, W. Chen, Y. Wang, and X. Xu. 2013. Pioglitazone, extract of compound danshen dripping pill, and quercetin ameliorate diabetic nephropathy in diabetic rats. *Journal of Endocrinological Investigation* 36 (6):422–7. doi: 10.3275/8763.

Chen, P., Q. Shi, X. Xu, Y. Wang, W. Chen, and H. Wang. 2012. Quercetin suppresses NF-κB and MCP-1 expression in a high glucose-induced human mesangial cell proliferation oliferation model. *International Journal of Molecular Medicine* 30 (1):119–25. doi: 10.3892/ijmm.2012.955.

Cheng, S.-C., W.-C. Huang, J.-H. S. Pang, Y.-H. Wu, and C.-Y. Cheng. 2019. Quercetin inhibits the production of il-1β-induced inflammatory cytokines and chemokines in ARPE-19 cells via the mapk and NF-κB signaling pathways. *International Journal of Molecular Sciences* 20 (12):2957. doi: 10.3390/ijms20122957.

Cheung, B. M., and C. Li. 2012. Diabetes and hypertension: Is there a common metabolic pathway? *Current Atherosclerosis Reports* 14 (2):160–6. doi: 10.1007/s11883-012-0227-2.

Choi, J. H., K. J. Kim, and S. Kim. 2016. Comparative effect of quercetin and quercetin-3-o-β-d-glucoside on fibrin polymers, blood clots, and in rodent models. *Journal of Biochemical and Molecular Toxicology* 30 (11):548–58. doi: 10.1002/jbt.21822.

Choudhary, A., V. Kant, B. L. Jangir, and V. G. Joshi. 2020. Quercetin loaded chitosan tripolyphosphate nanoparticles accelerated cutaneous wound healing in wistar rats. *European Journal of Pharmacology* 880:173172. doi: 10.1016/j.ejphar.2020.173172.

Choudhuri, S., I. H. Chowdhury, S. Das, D. Dutta, A. Saha, R. Sarkar, L. K. Mandal, S. Mukherjee, and B. Bhattacharya. 2015. Role of NF-κB activation and VEGF gene polymorphisms in VEGF up regulation in non-proliferative and proliferative diabetic retinopathy. *Molecular and Cellular Biochemistry* 405 (1–2):265–79. doi: 10.1007/s11010-015-2417-z.

Comalada, M., I. Ballester, E. Bailón, S. Sierra, J. Xaus, J. Gálvez, F. S. de Medina, and A. Zarzuelo. 2006. Inhibition of pro-inflammatory markers in primary bone marrow-derived mouse macrophages by naturally occurring flavonoids: Analysis of the structure-activity relationship. *Biochemical Pharmacology* 72 (8):1010–21. doi: 10.1016/j.bcp.2006.07.016.

Dabeek, W. M., and M. V. Marra. 2019. Dietary quercetin and kaempferol: Bioavailability and potential cardiovascular-related bioactivity in humans. *Nutrients* 11 (10):2288. doi: 10.3390/nu11102288.

Dai, X., Y. Ding, Z. Zhang, X. Cai, L. Bao, and Y. Li. 2013. Quercetin but not quercitrin ameliorates tumor necrosis factor-alpha-induced insulin resistance in C2C12 skeletal muscle cells. *Biological & Pharmaceutical Bulletin* 36 (5):788–95. doi: 10.1248/bpb.b12-00947.

Das, T., R. Jayasudha, S. Chakravarthy, G. S. Prashanthi, A. Bhargava, M. Tyagi, P. K. Rani, R. R. Pappuru, S. Sharma, and S. Shivaji. 2021. Alterations in the gut bacterial microbiome in people with type 2 diabetes mellitus and diabetic retinopathy. *Scientific Reports* 11 (1):2738. doi: 10.1038/s41598-021-82538-0.

DeFronzo, R. A., W. B. Reeves, and A. S. Awad. 2021. Pathophysiology of diabetic kidney disease: Impact of SGLT2 inhibitors. *Nature Reviews. Nephrology* 17 (5):319–34. doi: 10.1038/s41581-021-00393-8.

Dehdashtian, E., S. Mehrzadi, B. Yousefi, A. Hosseinzadeh, R. J. Reiter, M. Safa, H. Ghaznavi, and M. Naseripour. 2018. Diabetic retinopathy pathogenesis and the ameliorating effects of melatonin; involvement of autophagy, inflammation and oxidative stress. *Life Sciences* 193:20–33. doi: 10.1016/j.lfs.2017.12.001.

Den Hartogh, D. J., F. Vlavcheski, A. Giacca, and E. Tsiani. 2020. Attenuation of free fatty acid (FFA)-induced skeletal muscle cell insulin resistance by resveratrol is linked to activation of AMPK and inhibition of mTOR and p70 S6K. *International Journal of Molecular Sciences* 21 (14):4900. doi: 10.3390/ijms21144900.

Deshmukh, P., S. Unni, G. Krishnappa, and B. Padmanabhan. 2017. The Keap1-Nrf2 pathway: Promising therapeutic target to counteract ROS-mediated damage in cancers and neurodegenerative diseases. *Biophysical Reviews* 9 (1):41–56. doi: 10.1007/s12551-016-0244-4.

Dokumacioglu, E., H. Iskender, T. M. Sen, I. Ince, A. Dokumacioglu, Y. Kanbay, E. Erbas, and S. Saral. 2018. The effects of hesperidin and quercetin on serum tumor necrosis factor-alpha and interleukin-6 levels in streptozotocin-induced diabetes model. *Pharmacognosy Magazine* 14 (54):167–73. doi: 10.4103/pm.pm_41_17.

Donate-Correa, J., D. Luis-Rodríguez, E. Martín-Núñez, V. G. Tagua, C. Hernández-Carballo, C. Ferri, A. E. Rodríguez-Rodríguez, C.

Mora-Fernández, and J. F. Navarro-González. 2020. Inflammatory targets in diabetic nephropathy. *Journal of Clinical Medicine* 9 (2):458. doi: 10.3390/jcm9020458.

Dong, J., X. Zhang, L. Zhang, H. X. Bian, N. Xu, B. Bao, and J. Liu. 2014. Quercetin reduces obesity-associated ATM infiltration and inflammation in mice: A mechanism including AMPKα1/SIRT1. *Journal of Lipid Research* 55 (3):363–74. doi: 10.1194/jlr.M038786.

Dower, J. I., J. M. Geleijnse, L. Gijsbers, P. L. Zock, D. Kromhout, and P. C. Hollman. 2015. Effects of the pure flavonoids epicatechin and quercetin on vascular function and cardiometabolic health: A randomized, double-blind, placebo-controlled, crossover trial. *The American Journal of Clinical Nutrition* 101 (5):914–21. doi: 10.3945/ajcn.114.098590.

Drankowska, J., M. Kos, A. Kościuk, P. Marzęda, A. Boguszewska-Czubara, M. Tylus, and A. Święch-Zubilewicz. 2019. MMP targeting in the battle for vision: Recent developments and future prospects in the treatment of diabetic retinopathy. *Life Sciences* 229:149–56. doi: 10.1016/j.lfs.2019.05.038.

Dureshahwar, K., M. Mubashir, and H. D. Une. 2017. Quantification of quercetin obtained from *Allium cepa* Lam. Leaves and its effects on streptozotocin-induced diabetic neuropathy. *Pharmacognosy Research* 9 (3):287–93. doi: 10.4103/pr.pr_147_16.

Dyck, P. J., K. M. Kratz, J. L. Karnes, W. J. Litchy, R. Klein, J. M. Pach, D. M. Wilson, P. C. O'Brien, L. J. Melton, 3rd, and F. J. Service. 1993. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: The rochester diabetic neuropathy study. *Neurology* 43 (4):817–24. doi: 10.1212/wnl.43.4.817.

Ebrahimpour, A., M. Vaghari-Tabari, D. Qujeq, S. Moein, and Z. Moazezi. 2018. Direct correlation between serum homocysteine level and insulin resistance index in patients with subclinical hypothyroidism: Does subclinical hypothyroidism increase the risk of diabetes and cardio vascular disease together? *Diabetes & Metabolic Syndrome* 12 (6):863–7. doi: 10.1016/j.dsx.2018.05.002.

Ebrahimpour, S., A. Esmaeili, and S. Beheshti. 2018. Effect of quercetin-conjugated superparamagnetic iron oxide nanoparticles on diabetes-induced learning and memory impairment in rats. *International Journal of Nanomedicine* ume 13:6311–24. doi: 10.2147/IJN.S177871.

Egert, S., A. Bosy-Westphal, J. Seiberl, C. Kürbitz, U. Settler, S. Plachta-Danielzik, A. E. Wagner, J. Frank, J. Schrezenmeir, G. Rimbach, et al. 2009. Quercetin reduces systolic blood pressure and plasma oxidised low-density lipoprotein concentrations in overweight subjects with a high-cardiovascular disease risk phenotype: A double-blinded, placebo-controlled cross-over study. *British Journal of Nutrition* 102 (7):1065–74. doi: 10.1017/S0007114509359127.

Ekström, A. M., M. Serafini, O. Nyrén, A. Wolk, C. Bosetti, and R. Bellocco. 2011. Dietary quercetin intake and risk of gastric cancer: Results from a population-based study in Sweden. *Annals of Oncology: Official Journal of the European Society for Annals of Oncology* 22 (2):438–43. doi: 10.1093/annonc/mdq390.

Fan, J., G. Xu, T. Jiang, and Y. Qin. 2012. Pharmacologic induction of heme oxygenase-1 plays a protective role in diabetic retinopathy in rats. *Investigative Ophthalmology & Visual Science* 53 (10):6541–56. doi: 10.1167/iovs.11-9241.

Fardipour, S., S. Moein, S. H. Teshnizi, M. Khaytian, and D. Qujeq. 2020. Evaluation of MASP1, CMPF and UA serum levels in pre-diabetic subjects in comparison to normal individuals for early diagnosis of subjects with pre-diabetes, a case-control study. *Journal of Diabetes & Metabolic Disorders* 19 (2):1593–8. doi: 10.1007/s40200-020-00697-9.

Feldman, E. L., B. C. Callaghan, R. Pop-Busui, D. W. Zochodne, D. E. Wright, D. L. Bennett, V. Bril, J. W. Russell, and V. Viswanathan. 2019. Diabetic neuropathy. *Nature Reviews. Disease Primers* 5 (1):41. doi: 10.1038/s41572-019-0092-1.

Ferenczyova, K., B. Kalocayova, L. Kindernay, M. Jelemensky, P. Balis, A. Berenyiova, A. Zemancikova, V. Farkasova, M. Sykora, L. Tothova, et al. 2020. Quercetin exerts age-dependent beneficial effects on blood pressure and vascular function, but is inefficient in preventing myocardial ischemia-reperfusion injury in Zucker diabetic fatty rats. *Molecules (Basel, Switzerland)* 25 (1):187. doi: 10.3390/molecules25010187.

Fernandez-Gonzalez, P., A. Mas-Sanchez, and P. Garriga. 2021. Polyphenols and visual health: Potential effects on degenerative retinal diseases. *Molecules (Basel, Switzerland)* 26 (11):3407. doi: 10.3390/molecules26113407.

Fu, J., J. Huang, M. Lin, T. Xie, and T. You. 2020. Quercetin promotes diabetic wound healing via Switching Macrophages From M1 to M2 Polarization. *The Journal of Surgical Research* 246:213–23. doi: 10.1016/j.jss.2019.09.011.

Gallelli, G., E. Cione, R. Serra, A. Leo, R. Citraro, P. Matricardi, C. D. Meo, F. Bisceglia, M. C. Caroleo, S. Basile, et al. 2020. Nano-hydrogel embedded with quercetin and oleic acid as a new formulation in the treatment of diabetic foot ulcer: A pilot study. *International Wound Journal* 17 (2):485–90. doi: 10.1111/iwj.13299.

Gangaputra, S., J. F. Lovato, L. Hubbard, M. D. Davis, B. A. Esser, W. T. Ambrosius, E. Y. Chew, C. Greven, L. H. Perdue, W. T. Wong, et al. 2013. Comparison of standardized clinical classification with fundus photograph grading for the assessment of diabetic retinopathy and diabetic macular edema severity. *Retina (Philadelphia, Pa.)* 33 (7):1393–9.,doi: 10.1097/IAE.0b013e318286c952.

Gao, F., X. He, S. Liang, S. Liu, H. Liu, Q. He, L. Chen, H. Jiang, and Y. Zhang. 2018. Quercetin ameliorates podocyte injury via inhibition of oxidative stress and the TGF-β1/Smad pathway in DN rats. *RSC Advances* 8 (62):35413–21. doi: 10.1039/C8RA07935H.

Ghaemi, F., A. Fateh, A. A. Sepahy, M. Zangeneh, M. Ghanei, and S. D. Siadat. 2020. Intestinal microbiota composition in iranian diabetic, pre-diabetic and healthy individuals. *Journal of Diabetes and Metabolic Disorders* 19 (2):1199–203. doi: 10.1007/s40200-020-00625-x.

Giraldo, E., A. Lloret, T. Fuchsberger, and J. Viña. 2014. Aβ and tau toxicities in Alzheimer's are linked via oxidative stress-induced p38 activation: Protective role of vitamin E. *Redox Biology* 2:873–7. doi: 10.1016/j.redox.2014.03.002.

Gomes, I. B., M. L. Porto, M. C. Santos, B. P. Campagnaro, T. M. Pereira, S. S. Meyrelles, and E. C. Vasquez. 2014. Renoprotective, anti-oxidative and anti-apoptotic effects of oral low-dose quercetin in the C57BL/6J model of diabetic nephropathy. *Lipids in Health and Disease* 13:184. doi: 10.1186/1476-511x-13-184.

Goodarzi, G., M. Maniati, and D. Qujeq. 2019. The role of micrornas in the healing of diabetic ulcers. *International Wound Journal* 16 (3):621–33. doi: 10.1111/iwj.13070.

Gulati, N., B. Laudet, V. M. Zohrabian, R. Murali, and M. Jhanwar-Uniyal. 2006. The antiproliferative effect of quercetin in cancer cells is mediated via inhibition of the PI3K-Akt/PKB pathway. *Anticancer Research* 26 (2A):1177–81.

Guo, S., and L. A. Dipietro. 2010. Factors affecting wound healing. *Journal of Dental Research* 89 (3):219–29. doi: 10.1177/0022034509359125.

Gurung, M., Z. Li, H. You, R. Rodrigues, D. B. Jump, A. Morgun, and N. Shulzhenko. 2020. Role of gut microbiota in type 2 diabetes pathophysiology. *EBioMedicine* 51:102590. doi: 10.1016/j.ebiom.2019.11.051.

Hammes, H. P. 2018. Diabetic retinopathy: Hyperglycaemia, oxidative stress and beyond. *Diabetologia* 61 (1):29–38. doi: 10.1007/s00125-017-4435-8.

Han, F., J. Zhang, K. Li, W. Wang, and D. Dai. 2020. Triptolide protects human retinal pigment epithelial ARPE-19 cells against high glucose-induced cell injury by regulation of miR-29b/PTEN. *Archives of Physiology and Biochemistry* 30:1–7. doi: 10.1080/13813455.2020.1797101.

He, X., J. Sun, C. Liu, X. Yu, H. Li, W. Zhang, Y. Li, Y. Geng, and Z. Wang. 2022. Compositional alterations of gut microbiota in patients with diabetic kidney disease and type 2 diabetes mellitus. *Diabetes, Metabolic Syndrome and Obesity : Targets and Therapy* 15:755–65. doi: 10.2147/dmso.s347805.

Hicks, C. W., and E. Selvin. 2019. Epidemiology of peripheral neuropathy and lower extremity disease in diabetes. *Current Diabetes Reports* 19 (10):86. doi: 10.1007/s11892-019-1212-8.

Hickson, L. J., L. Langhi Prata, S. A. Bobart, T. K. Evans, N. Giorgadze, S. K. Hashmi, S. M. Herrmann, M. D. Jensen, Q. Jia, K. L. Jordan,

et al. 2019. Senolytics decrease senescent cells in humans: Preliminary report from a clinical trial of dasatinib plus quercetin in individuals with diabetic kidney disease. *EBioMedicine* 47:446–56. doi: 10.1016/j.ebiom.2019.08.069.

Hotamisligil, G. S., P. Peraldi, A. Budavari, R. Ellis, M. F. White, and B. M. Spiegelman. 1996. IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-alpha- and obesity-induced insulin resistance. *Science (New York, N.Y.)* 271 (5249):665–8. doi: 10.1126/science.271.5249.665.

Huang, H., D. Liao, Y. Dong, and R. Pu. 2020. Effect of quercetin supplementation on plasma lipid profiles, blood pressure, and glucose levels: A systematic review and meta-analysis. *Nutrition Reviews* 78 (8):615–26. doi: 10.1093/nutrit/nuz071.

Huang, R., Z. Shi, L. Chen, Y. Zhang, J. Li, and Y. An. 2017. Rutin alleviates diabetic cardiomyopathy and improves cardiac function in diabetic apoeknockout mice. *European Journal of Pharmacology* 814:151–60. doi: 10.1016/j.ejphar.2017.08.023.

Huang, Y., Z. Wang, H. Ma, S. Ji, Z. Chen, Z. Cui, J. Chen, and S. Tang. 2021. Dysbiosis and implication of the gut microbiota in diabetic retinopathy. *Frontiers in Cellular and Infection Microbiology* 11:646348. doi: 10.3389/fcimb.2021.646348.

Huxley, R. R., and H. A. Neil. 2003. The relation between dietary flavonol intake and coronary heart disease mortality: A meta-analysis of prospective cohort studies. *European Journal of Clinical Nutrition* 57 (8):904–8. doi: 10.1038/sj.ejcn.1601624.

Ishizaki, E., S. Takai, M. Ueki, T. Maeno, M. Maruichi, T. Sugiyama, H. Oku, T. Ikeda, and M. Miyazaki. 2006. Correlation between angiotensin-converting enzyme, vascular endothelial growth factor, and matrix metalloproteinase-9 in the vitreous of eyes with diabetic retinopathy. *American Journal of Ophthalmology* 141 (1):129–34. doi: 10.1016/j.ajo.2005.08.066.

Iskender, H., E. Dokumacioglu, T. M. Sen, I. Ince, Y. Kanbay, and S. Saral. 2017. The effect of hesperidin and quercetin on oxidative stress, NF-κB and SIRT1 levels in a STZ-induced experimental diabetes model. *Biomedicine & Pharmacotherapy* 90:500–8. doi: 10.1016/j.biopha.2017.03.102.

Jeenger, M. K., S. Shrivastava, V. G. Yerra, V. G. Naidu, S. Ramakrishna, and A. Kumar. 2015. Curcumin: A pleiotropic phytonutrient in diabetic complications. *Nutrition (Burbank, Los Angeles County, Calif.)* 31 (2):276–82. doi: 10.1016/j.nut.2014.06.015.

Jeong, S. M., M. J. Kang, H. N. Choi, J. H. Kim, and J. I. Kim. 2012. Quercetin ameliorates hyperglycemia and dyslipidemia and improves antioxidant status in type 2 diabetic db/db mice. *Nutrition Research and Practice* 6 (3):201–7. doi: 10.4162/nrp.2012.6.3.201.

Ji, L., H. Tian, K. A. Webster, and W. Li. 2021. Neurovascular regulation in diabetic retinopathy and emerging therapies. *Cellular and Molecular Life Sciences : CMLS* 78 (16):5977–85. doi: 10.1007/s00018-021-03893-9.

Jia, G., A. Whaley-Connell, and J. R. Sowers. 2018. Diabetic cardiomyopathy: A hyperglycaemia- and insulin-resistance-induced heart disease. *Diabetologia* 61 (1):21–8. doi: 10.1007/s00125-017-4390-4.

Jialal, I., and C. J. Fuller. 1993. Oxidized LDL and antioxidants. *Clinical Cardiology* 16 (4 Suppl 1):I6–9. doi: 10.1002/clc.4960161304.

Jiang, T., Z. Huang, Y. Lin, Z. Zhang, D. Fang, and D. D. Zhang. 2010. The protective role of Nrf2 in streptozotocin-induced diabetic nephropathy. *Diabetes* 59 (4):850–60. doi: 10.2337/db09-1342.

Jiang, Y. H., L. Y. Jiang, Y. C. Wang, D. F. Ma, and X. Li. 2020. Quercetin attenuates atherosclerosis via modulating oxidized LDL-induced endothelial cellular senescence. *Frontiers in Pharmacology* 11:512. doi: 10.3389/fphar.2020.00512.

Jiao, J., H. Yu, L. Yao, L. Li, X. Yang, and L. Liu. 2021. Recent insights into the role of gut microbiota in diabetic retinopathy. *Journal of Inflammation Research* 14:6929–38. doi: 10.2147/jir.s336148.

Jung, J. Y., Y. Lim, M. S. Moon, J. Y. Kim, and O. Kwon. 2011. Onion peel extracts ameliorate hyperglycemia and insulin resistance in high fat diet/streptozotocin-induced diabetic rats. *Nutrition & Metabolism* 8 (1):18. doi: 10.1186/1743-7075-8-18.

Kandhare, A. D., K. S. Raygude, V. Shiva Kumar, A. R. Rajmane, A. Visnagri, A. E. Ghule, P. Ghosh, S. L. Badole, and S. L. Bodhankar. 2012. Ameliorative effects quercetin against impaired motor nerve function, inflammatory mediators and apoptosis in neonatal streptozotocin-induced diabetic neuropathy in rats. *Biomedicine & Aging Pathology* 2 (4):173–86. doi: 10.1016/j.biomag.2012.10.002.

Kang, Q., and C. Yang. 2020. Oxidative stress and diabetic retinopathy: Molecular mechanisms, pathogenetic role and therapeutic implications. *Redox Biology* 37:101799. doi: 10.1016/j.redox.2020.101799.

Kant, V., B. L. Jangir, M. Sharma, V. Kumar, and V. G. Joshi. 2021. Topical application of quercetin improves wound repair and regeneration in diabetic rats. *Immunopharmacology and Immunotoxicology* 43 (5):536–53. doi: 10.1080/08923973.2021.1950758.

Kanwar, Y. S., J. Wada, L. Sun, P. Xie, E. I. Wallner, S. Chen, S. Chugh, and F. R. Danesh. 2008. Diabetic nephropathy: Mechanisms of renal disease progression. *Experimental Biology and Medicine (Maywood, N.J.)* 233 (1):4–11. doi: 10.3181/0705-mr-134.

Kayama, Y., U. Raaz, A. Jagger, M. Adam, IN. Schellinger, M. Sakamoto, H. Suzuki, K. Toyama, J. M. Spin, and P. S. Tsao. 2015. Diabetic cardiovascular disease induced by oxidative stress. *International Journal of Molecular Sciences* 16 (10):25234–63. doi: 10.3390/ijms161025234.

Keane, K. N., V. F. Cruzat, R. Carlessi, P. I. de Bittencourt, Jr., and P. Newsholme. 2015. Molecular events linking oxidative stress and inflammation to insulin resistance and β-cell dysfunction. *Oxidative Medicine and Cellular Longevity* 2015:181643. doi: 10.1155/2015/181643.

Kelley, N., D. Jeltema, Y. Duan, and Y. He. 2019. The NLRP3 inflammasome: An overview of mechanisms of activation and regulation. *International Journal of Molecular Sciences* 20 (13):3328. doi: 10.3390/ijms20133328.

Khalfaoui, T., G. Lizard, and A. Ouertani-Meddeb. 2008. Adhesion molecules (ICAM-1 and VCAM-1) and diabetic retinopathy in type 2 diabetes. *Journal of Molecular Histology* 39 (2):243–9. doi: 10.1007/s10735-007-9159-5.

Khan, H., H. Ullah, M. Aschner, W. S. Cheang, and E. K. Akkol. 2019. Neuroprotective effects of quercetin in Alzheimer's disease. *Biomolecules* 10 (1):59. doi: 10.3390/biom10010059.

Khan, M., M. J. Hashim, J. K. King, R. D. Govender, H. Mustafa, and J. A. Kaabi. 2020. Epidemiology of type 2 diabetes – Global burden of disease and forecasted trends. *Journal of Epidemiology and Global Health* 10 (1):107–11. doi: 10.2991/jegh.k.191028.001.

Khodarahmi, A., A. Eshaghian, F. Safari, and A. Moradi. 2019. Quercetin mitigates hepatic insulin resistance in rats with bile duct ligation through modulation of the STAT3/SOCS3/IRS1 signaling pathway. *Journal of Food Science* 84 (10):3045–53. doi: 10.1111/1750-3841.14793.

Khorshidi, M., A. Moini, E. Alipoor, N. Rezvan, S. Gorgani-Firuzjaee, M. Yaseri, and M. J. Hosseinzadeh-Attar. 2018. The effects of quercetin supplementation on metabolic and hormonal parameters as well as plasma concentration and gene expression of resistin in overweight or obese women with polycystic ovary syndrome. *Phytotherapy Research: PTR* 32 (11):2282–9. doi: 10.1002/ptr.6166.

Kim, H. G. 2019. Cognitive dysfunctions in individuals with diabetes mellitus. *Yeungnam University Journal of Medicine* 36 (3):183–91. doi: 10.12701/yujm.2019.00255.

Kulkarni, P., P. Devkumar, and I. Chattopadhyay. 2021. Could dysbiosis of inflammatory and anti-inflammatory gut bacteria have an implications in the development of type 2 diabetes? A pilot investigation. *BMC Research Notes* 14 (1):52. doi: 10.1186/s13104-021-05466-2.

Kumar, B., S. K. Gupta, T. C. Nag, S. Srivastava, R. Saxena, K. A. Jha, and B. P. Srinivasan. 2014. Retinal neuroprotective effects of quercetin in streptozotocin-induced diabetic rats. *Experimental Eye Research* 125:193–202. doi: 10.1016/j.exer.2014.06.009.

Lai, P. B., L. Zhang, and L. Y. Yang. 2012. Quercetin ameliorates diabetic nephropathy by reducing the expressions of transforming growth factor-β1 and connective tissue growth factor in streptozotocin-induced diabetic rats. *Renal Failure* 34 (1):83–7. doi: 10.3109/0886022x.2011.623564.

Lee, M., S. Yun, H. Lee, and J. Yang. 2017. Quercetin mitigates inflammatory responses induced by vascular endothelial growth factor in mouse retinal photoreceptor cells through suppression of

nuclear factor kappa B. *International Journal of Molecular Sciences* 18 (11)2497. doi: 10.3390/ijms1811:.

Lee, R., T. Y. Wong, and C. Sabanayagam. 2015. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. *Eye and Vision (London, England)* 2:17. doi: 10.1186/s40662-015-0026-2.

Leon, B. M., and T. M. Maddox. 2015. Diabetes and cardiovascular disease: Epidemiology, biological mechanisms, treatment recommendations and future research. *World Journal of Diabetes* 6 (13):1246–58. doi: 10.4239/wjd.v6.i13.1246.

Li, B. Y., X. Y. Xu, R. Y. Gan, Q. C. Sun, J. M. Meng, A. Shang, Q. Q. Mao, and H. B. Li. 2019. Targeting gut microbiota for the prevention and management of diabetes mellitus by dietary natural products. *Foods* 8 (10)440. doi: 10.3390/foods8100:.

Li, C., X. Zhao, H. Zheng, and F. Cai. 2017. GW28-e0635 quercetin retards progression of diabetic cardiomyopathy through modulations of SIRT1 and AMP-activated protein kinase. *Journal of the American College of Cardiology* 70 (16):C63–C64. doi: 10.1016/j.jacc.2017.07.217.

Li, D. L., L. Mao, Q. Gu, F. Wei, and Y. Y. Gong. 2021. Quercetin protects retina external barrier from oxidative stress injury by promoting autophagy. *Cutaneous and Ocular Toxicology* 40 (1):7–13. doi: 10.1080/15569527.2020.1860082.

Li, H., B. Li, and Y. Zheng. 2020. Exploring the mechanism of action compound-Xueshuantong capsule in diabetic retinopathy treatment based on network pharmacology. *Evidence-Based Complementary and Alternative Medicine : eCAM* 2020:8467046. doi: 10.1155/2020/8467046.

Li, R., L. Chen, G. M. Yao, H. L. Yan, and L. Wang. 2021. Effects of quercetin on diabetic retinopathy and its association with nlrp3 inflammasome and autophagy. *International Journal of Ophthalmology* 14 (1):42–9. doi: 10.18240/ijo.2021.01.06.

Li, S., H. Yang, and X. Chen. 2019. Protective effects of sulforaphane on diabetic retinopathy: Activation of the nrf2 pathway and inhibition of NLRP3 inflammasome formation. *Experimental Animals* 68 (2):221–31. doi: 10.1538/expanim.18-0146.

Liang, W. J., H. W. Yang, H. N. Liu, W. Qian, and X. L. Chen. 2020. HMGB1 upregulates NF-kB by inhibiting IKB-α and associates with diabetic retinopathy. *Life Sciences* 241:117146. doi: 10.1016/j.lfs.2019.117146.

Lim, A. 2014. Diabetic nephropathy – Complications and treatment. *International Journal of Nephrology and Renovascular Disease* 7:361–81. doi: 10.2147/ijnrd.s40172.

Lin, X., X. Zhou, D. Liu, L. Yun, L. Zhang, X. Chen, Q. Chai, and L. Li. 2016. Microrna-29 regulates high-glucose-induced apoptosis in human retinal pigment epithelial cells through pten. *In Vitro Cellular & Developmental Biology. Animal* 52 (4):419–26. doi: 10.1007/s11626-015-9990-z.

Liu, D., X. C. Liang, Y. Sun, Y. N. Wu, and H. Zhang. 2020. Combination of quercetin, hirudin and cinnamaldehyde promotes schwann cell differentiation and myelination against high glucose by inhibiting ERK signaling pathway. *Chinese Journal of Integrative Medicine* 26 (8):591–8. doi: 10.1007/s11655-020-2721-7.

Liu, K., F. Mei, Y. Wang, N. Xiao, L. Yang, Y. Wang, J. Li, F. Huang, J. Kou, B. Liu, et al. 2016. Quercetin oppositely regulates insulin-mediated glucose disposal in skeletal muscle under normal and inflammatory conditions: The dual roles of AMPK activation. *Molecular Nutrition & Food Research* 60 (3):551–65. doi: 10.1002/mnfr.201500509.

Liu, Z., W. Dou, Z. Ni, Q. Wen, R. Zhang, M. Qin, X. Wang, H. Tang, Y. Cao, J. Wang, et al. 2016. Deletion of nrf2 leads to hepatic insulin resistance via the activation of NF-κB in mice fed a high-fat diet. *Molecular Medicine Reports* 14 (2):1323–31. doi: 10.3892/mmr.2016.5393.

Long, Y. C., and J. R. Zierath. 2006. Amp-activated protein kinase signaling in metabolic regulation. *The Journal of Clinical Investigation* 116 (7):1776–83. doi: 10.1172/jci29044.

Lopes de Faria, J. M., D. A. Duarte, C. Montemurro, A. Papadimitriou, S. R. Consonni, and J. B. Lopes de Faria. 2016. Defective autophagy in diabetic retinopathy. *Investigative Opthalmology & Visual Science* 57 (10):4356–66. doi: 10.1167/iovs.16-19197.

Lu, L., Q. Lu, W. Chen, J. Li, C. Li, and Z. Zheng. 2018. Vitamin D3 protects against diabetic retinopathy by inhibiting high-glucose-induced activation of the ROS/TXNIP/NLRP3 inflammasome pathway. *Journal of Diabetes Research* 2018:8193523. doi: 10.1155/2018/8193523.

Lu, Q., X. J. Ji, Y. X. Zhou, X. Q. Yao, Y. Q. Liu, F. Zhang, and X. X. Yin. 2015. Quercetin inhibits the mTORC1/p70S6K signaling-mediated renal tubular epithelial-mesenchymal transition and renal fibrosis in diabetic nephropathy. *Pharmacological Research* 99:237–47. doi: 10.1016/j.phrs.2015.06.006.

Lupo, G., M. T. Cambria, M. Olivieri, C. Rocco, N. Caporarello, A. Longo, G. Zanghì, M. Salmeri, M. C. Foti, and C. D. Anfuso. 2019. Anti-angiogenic effect of quercetin and its 8-methyl pentamethyl ether derivative in human microvascular endothelial cells. *Journal of Cellular and Molecular Medicine* 23 (10):6565–77. doi: 10.1111/jcmm.14455.

Mahmoud, M. F., N. A. Hassan, H. M. El Bassossy, and A. Fahmy. 2013. Quercetin protects against diabetes-induced exaggerated vasoconstriction in rats: Effect on low grade inflammation. *PloS One* 8 (5):e63784. doi: 10.1371/journal.pone.0063784.

Maleki Dana, P., F. Sadoughi, Z. Asemi, and B. Yousefi. 2021. Anti-cancer properties of quercetin in osteosarcoma. *Cancer Cell International* 21 (1):349. doi: 10.1186/s12935-021-02067-8.

Matheus, A. S., L. R. Tannus, R. A. Cobas, C. C. Palma, C. A. Negrato, and M. B. Gomes. 2013. Impact of diabetes on cardiovascular disease: An update. *International Journal of Hypertension* 2013:653789. doi: 10.1155/2013/653789.

Matos, A. L., D. F. Bruno, A. F. Ambrósio, and P. F. Santos. 2020. The benefits of flavonoids in diabetic retinopathy. *Nutrients* 12 (10):3169. doi: 10.3390/nu12103169.

Maurya, A. K., and M. Vinayak. 2017. Quercetin attenuates cell survival, inflammation, and angiogenesis via modulation of AKT signaling in murine t-cell lymphoma. *Nutrition and Cancer* 69 (3):470–80. doi: 10.1080/01635581.2017.1267775.

Mazloom, Z., S. M. Abdollahzadeh, M. H. Dabbaghmanesh, and A. Rezaianzadeh. 2014. The effect of quercetin supplementation on oxidative stress, glycemic control, lipid profile and insulin resistance in type 2 diabetes: A randomized clinical trial. *Journal of Health Sciences and Surveillance System* 2:8–14.

Meigs, J. B., P. F. Jacques, J. Selhub, D. E. Singer, D. M. Nathan, N. Rifai, R. B. D'Agostino, Sr., and P. W. Wilson. 2001. Fasting plasma homocysteine levels in the insulin resistance syndrome: The framingham offspring study. *Diabetes Care* 24 (8):1403–10.,doi: 10.2337/diacare.24.8.1403.

Meng, B., W. Gao, J. Wei, L. Pu, Z. Tang, and C. Guo. 2015. Quercetin increases hepatic homocysteine remethylation and transsulfuration in rats fed a methionine-enriched diet. *BioMed Research International* 2015:815210. doi: 10.1155/2015/815210.

Meng, B., W. Gao, J. Wei, J. Yang, J. Wu, L. Pu, and C. Guo. 2013. Quercetin reduces serum homocysteine level in rats fed a methionine-enriched diet. *Nutrition (Burbank, Los Angeles County, Calif.)* 29 (4):661–6. doi: 10.1016/j.nut.2012.10.012.

Meng, J. M., S. Y. Cao, X. L. Wei, R. Y. Gan, Y. F. Wang, S. X. Cai, X. Y. Xu, P. Z. Zhang, and H. B. Li. 2019. Effects and mechanisms of tea for the prevention and management of diabetes mellitus and diabetic complications: An updated review. *Antioxidants (Basel, Switzerland)* 8 (6):170. doi: 10.3390/antiox8060170.

Miele, L., V. Giorgio, M. A. Alberelli, E. De Candia, A. Gasbarrini, and A. Grieco. 2015. Impact of gut microbiota on obesity, diabetes, and cardiovascular disease risk. *Current Cardiology Reports* 17 (12):120. doi: 10.1007/s11886-015-0671-z.

Milenković, M., N. Arsenović-Ranin, Z. Stojić-Vukanić, B. Bufan, D. Vučićević, and I. Jančić. 2010. Quercetin ameliorates experimental autoimmune myocarditis in rats. *Journal of Pharmacy & Pharmaceutical Sciences: A Publication of the Canadian Society for Pharmaceutical Sciences. Journal of Pharmacy & Pharmaceutical Sciences: A Publication of the Canadian Society for Pharmaceutical Sciences, Societe Canadienne Des Sciences Pharmaceutiques* 13 (3):311–9. doi: 10.18433/j3vs3s.

Moein, S., M. Vaghari-Tabari, D. Qujeq, M. Majidinia, S. M. Nabavi, and B. Yousefi. 2019. Mirnas and inflammatory bowel disease: An

interesting new story. *Journal of Cellular Physiology* 234 (4):3277–93. doi: 10.1002/jcp.27173.

Nabavi, S. F., A. J. Barber, C. Spagnuolo, G. L. Russo, M. Daglia, S. M. Nabavi, and E. Sobarzo-Sánchez. 2016. Nrf2 as molecular target for polyphenols: A novel therapeutic strategy in diabetic retinopathy. *Critical Reviews in Clinical Laboratory Sciences* 53 (5):293–312. doi: 10.3109/10408363.2015.1129530.

Naseri, R., F. Farzaei, S. Fakhri, F. F. El-Senduny, M. Altouhamy, R. Bahramsoltani, F. Ebrahimi, R. Rahimi, and M. H. Farzaei. 2019. Polyphenols for diabetes associated neuropathy: Pharmacological targets and clinical perspective. *Daru : journal of Faculty of Pharmacy, Tehran University of Medical Sciences* 27 (2):781–98. doi: 10.1007/s40199-019-00289-w.

Nebbioso, M., A. Lambiase, M. Armentano, G. Tucciarone, V. Bonfiglio, R. Plateroti, and L. Alisi. 2020. The complex relationship between diabetic retinopathy and high-mobility group box: A review of molecular pathways and therapeutic strategies. *Antioxidants (Basel, Switzerland)* 9 (8):666. doi: 10.3390/antiox9080666.

Nie, J., L. Zhang, G. Zhao, and X. Du. 2019. Quercetin reduces atherosclerotic lesions by altering the gut microbiota and reducing atherogenic lipid metabolites. *Journal of Applied Microbiology* 127 (6):1824–34. doi: 10.1111/jam.14441.

Ogihara, T., T. Asano, H. Katagiri, H. Sakoda, M. Anai, N. Shojima, H. Ono, M. Fujishiro, A. Kushiyama, Y. Fukushima, et al. 2004. Oxidative stress induces insulin resistance by activating the nuclear factor-kappa B pathway and disrupting normal subcellular distribution of phosphatidylinositol 3-kinase. *Diabetologia* 47 (5):794–805. doi: 10.1007/s00125-004-1391-x.

Ohishi, M. 2018. Hypertension with diabetes mellitus: Physiology and pathology. *Hypertension Research : official Journal of the Japanese Society of Hypertension* 41 (6):389–93. doi: 10.1038/s41440-018-0034-4.

Ola, M. S., M. M. Ahmed, S. Shams, and S. S. Al-Rejaie. 2017. Neuroprotective effects of quercetin in diabetic rat retina. *Saudi Journal of Biological Sciences* 24 (6):1186–94. doi: 10.1016/j.sjbs.2016.11.017.

Ola, M. S., D. Al-Dosari, and A. S. Alhomida. 2018. Role of oxidative stress in diabetic retinopathy and the beneficial effects of flavonoids. *Current Pharmaceutical Design* 24 (19):2180–7. doi: 10.2174/1381612824666180515151043.

Ostadmohammadi, V., A. Milajerdi, E. Ayati, F. Kolahdooz, and Z. Asemi. 2019. Effects of quercetin supplementation on glycemic control among patients with metabolic syndrome and related disorders: A systematic review and meta-analysis of randomized controlled trials. *Phytotherapy Research* 33 (5):1330–40. doi: 10.1002/ptr.6334.

Parichatikanond, W., D. Pinthong, and S. Mangmool. 2012. Blockade of the renin-angiotensin system with delphinidin, cyanin, and quercetin. *Planta Medica* 78 (15):1626–32. doi: 10.1055/s-0032-1315198.

Park, K. S., S. S. Kim, J. C. Kim, H. C. Kim, Y. S. Im, C. W. Ahn, and H. K. Lee. 2008. Serum and tear levels of nerve growth factor in diabetic retinopathy patients. *American Journal of Ophthalmology* 145 (3):432–7. doi: 10.1016/j.ajo.2007.11.011.

Patel, S., S. Srivastava, M. R. Singh, and D. Singh. 2019. Mechanistic insight into diabetic wounds: Pathogenesis, molecular targets and treatment strategies to pace wound healing. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie* 112:108615. doi: 10.1016/j.biopha.2019.108615.

Petrie, J. R., T. J. Guzik, and R. M. Touyz. 2018. Diabetes, hypertension, and cardiovascular disease: Clinical insights and vascular mechanisms. *The Canadian Journal of Cardiology* 34 (5):575–84. doi: 10.1016/j.cjca.2017.12.005.

Pitocco, D., M. Tesauro, R. Alessandro, G. Ghirlanda, and C. Cardillo. 2013. Oxidative stress in diabetes: Implications for vascular and other complications. *International Journal of Molecular Sciences* 14 (11):21525–50. doi: 10.3390/ijms141121525.

Qu, L., X. Liang, B. Gu, and W. Liu. 2014. Quercetin alleviates high glucose-induced Schwann cell damage by autophagy. *Neural Regeneration Research* 9 (12):1195–203. doi: 10.4103/1673-5374.135328.

Raman, K. S., and J. A. Matsubara. 2020. Dysregulation of the NLRP3 inflammasome in diabetic retinopathy and potential therapeutic targets. *Ocular Immunology and Inflammation* 11:1–9. doi: 10.1080/09273948.2020.1811350.

Ramazani, M., D. Qujeq, and Z. Moazezi. 2019. Assessing the levels of l-carnitine and total antioxidant capacity in adults with newly diagnosed and long-standing type 2 diabetes. *Canadian Journal of Diabetes* 43 (1):46–50. e41. doi: 10.1016/j.jcjd.2018.03.009.

Ramyaa, P., R. Krishnaswamy, and V. V. Padma. 2014. Quercetin modulates OTA-induced oxidative stress and redox signalling in hepF2 cells – Up regulation of Nrf2 expression and down regulation of NF-κB and COX-2. *Biochimica et Biophysica Acta* 1840 (1):681–92. doi: 10.1016/j.bbagen.2013.10.024.

Regitz, C., L. M. Dußling, and U. Wenzel. 2014. Amyloid-beta ($A\beta_{1}4_{2}$)-induced paralysis in *Caenorhabditis elegans* is inhibited by the polyphenol quercetin through activation of protein degradation pathways . *Molecular Nutrition & Food Research* 58 (10):1931–40. doi: 10.1002/mnfr.201400014.

Rehman, K., M. Akash, A. Liaqat, S. Kamal, M. I. Qadir, and A. Rasul. 2017. Role of interleukin-6 in development of insulin resistance and type 2 diabetes mellitus. *Critical Reviews in Eukaryotic Gene Expression* 27 (3):229–36. doi: 10.1615/CritRevEukaryotGeneExpr.2017019712.

Ren, J., J. Li, X. Liu, Y. Feng, Y. Gui, J. Yang, W. He, and C. Dai. 2016. Quercetin inhibits fibroblast activation and kidney fibrosis involving the suppression of mammalian target of rapamycin and β-catenin signaling. *Scientific Reports* 6:23968. doi: 10.1038/srep23968.

Rezvan, N., A. Moini, L. Janani, K. Mohammad, A. Saedisomeolia, M. Nourbakhsh, S. Gorgani-Firuzjaee, M. Mazaherioun, and M. J. Hosseinzadeh-Attar. 2016. Effects of quercetin on adiponectin-mediated insulin sensitivity in polycystic ovary syndrome: A randomized placebo-controlled double-blind clinical trial. *Hormone and Metabolic Research* 49 (02):115–21. doi: 10.1055/s-0042-118705.

Rodríguez, M. L., S. Pérez, S. Mena-Mollá, M. C. Desco, L, and Ortega, Á. 2019. Oxidative stress and microvascular alterations in diabetic retinopathy: Future therapies. *Oxidative Medicine and Cellular Longevity* 2019:4940825. doi: 10.1155/2019/4940825.

Rosa, M. D., G. Distefano, C. Gagliano, D. Rusciano, and L. Malaguarnera. 2016. Autophagy in diabetic retinopathy. *Current Neuropharmacology* 14 (8):810–25. doi: 10.2174/1570159x14666160321122900.

Rübsam, A., S. Parikh, and P. E. Fort. 2018. Role of inflammation in diabetic retinopathy. *International Journal of Molecular Sciences* 19 (4):942. doi: 10.3390/ijms19040942.

Rudraraju, M., S. P. Narayanan, and P. R. Somanath. 2020. Regulation of blood-retinal barrier cell-junctions in diabetic retinopathy. *Pharmacological Research* 161:105115. doi: 10.1016/j.phrs.2020.105115.

Sahajpal, N. S., R. K. Goel, A. Chaubey, R. Aurora, and S. K. Jain. 2019. Pathological perturbations in diabetic retinopathy: Hyperglycemia, ages, oxidative stress and inflammatory pathways. *Current Protein & Peptide Science* 20 (1):92–110. doi: 10.2174/1389203719666180928123449.

Sayem, A., A. Arya, H. Karimian, N. Krishnasamy, A. Ashok Hasamnis, and C. F. Hossain. 2018. Action of phytochemicals on insulin signaling pathways accelerating glucose transporter (GLUT4) protein translocation. *Molecules (Basel, Switzerland)* 23 (2):258. doi: 10.3390/molecules23020258.

Seo, M. J., Y. J. Lee, J. H. Hwang, K. J. Kim, and B. Y. Lee. 2015. The inhibitory effects of quercetin on obesity and obesity-induced inflammation by regulation of MAPK signaling. *The Journal of Nutritional Biochemistry* 26 (11):1308–16. doi: 10.1016/j.jnutbio.2015.06.005.

Shen, X., Y. Si, Z. Wang, J. Wang, Y. Guo, and X. Zhang. 2016. Quercetin inhibits the growth of human gastric cancer stem cells by inducing mitochondrial-dependent apoptosis through the inhibition of PI3K/AKT signaling. *International Journal of Molecular Medicine* 38 (2):619–26. doi: 10.3892/ijmm.2016.2625.

Shen, Y., H. Cao, F. Chen, Y. Suo, N. Wang, and X. Xu. 2020. A cross-sectional study of vitreous and serum high mobility group box-1 levels in proliferative diabetic retinopathy. *Acta Ophthalmologica* 98 (2):e212–e216. doi: 10.1111/aos.14228.

Shi, Y., X. C. Liang, H. Zhang, Q. Sun, Q. L. Wu, and L. Qu. 2017. Combination of quercetin, cinnamaldehyde and hirudin protects rat dorsal root ganglion neurons against high glucose-induced injury through Nrf-2/HO-1 activation and NF-κB inhibition. *Chinese Journal of Integrative Medicine* 23 (9):663–71. doi: 10.1007/s11655-017-2405-0.

Shi, Y., and G. Williamson. 2016. Quercetin lowers plasma uric acid in pre-hyperuricaemic males: A randomised, double-blinded, placebo-controlled, cross-over trial. *The British Journal of Nutrition* 115 (5):800–6. doi: 10.1017/s0007114515005310.

Singla, S., K. Kaur, G. Kaur, H. Kaur, J. Kaur, and S. Jaswal. 2009. Lipoprotein (a) in type 2 diabetes mellitus: Relation to LDL:HDL ratio and glycemic control. *International Journal of Diabetes in Developing Countries* 29 (2):80–4. doi: 10.4103/0973-3930.53125.

Soldatos, G., and M. E. Cooper. 2008. Diabetic nephropathy: Important pathophysiologic mechanisms. *Diabetes Research and Clinical Practice* 82 Suppl 1:S75–S79. doi: 10.1016/j.diabres.2008.09.042.

Song, Y., J. E. Manson, J. E. Buring, H. D. Sesso, and S. Liu. 2005. Associations of dietary flavonoids with risk of type 2 diabetes, and markers of insulin resistance and systemic inflammation in women: A prospective study and cross-sectional analysis. *Journal of the American College of Nutrition* 24 (5):376–84. doi: 10.1080/07315724.2005.10719488.

Srivastava, R. 2018. Dysfunctional HDL in diabetes mellitus and its role in the pathogenesis of cardiovascular disease. *Molecular and Cellular Biochemistry* 440 (1-2):167–87. doi: 10.1007/s11010-017-3165-z.

Steinberg, G. R., B. J. Michell, B. J. van Denderen, M. J. Watt, A. L. Carey, B. C. Fam, S. Andrikopoulos, J. Proietto, C. Z. Görgün, D. Carling, et al. 2006. Tumor necrosis factor alpha-induced skeletal muscle insulin resistance involves suppression of amp-kinase signaling. *Cell Metabolism* 4 (6):465–74. doi: 10.1016/j.cmet.2006.11.005.

Steinle, J. J. 2020. Role of HMGB1 signaling in the inflammatory process in diabetic retinopathy. *Cellular Signalling* 73:109687. doi: 10.1016/j.cellsig.2020.109687.

Sulaiman, R. S., H. D. Basavarajappa, and T. W. Corson. 2014. Natural product inhibitors of ocular angiogenesis. *Experimental Eye Research* 129:161–71. doi: 10.1016/j.exer.2014.10.002.

Sun, C., H. Wang, D. Wang, Y. Chen, Y. Zhao, and W. Xia. 2015. Using an FFQ to assess intakes of dietary flavonols and flavones among female adolescents in the suihua area of northern china. *Public Health Nutrition* 18 (4):632–9. doi: 10.1017/s1368980014000780.

Tabrizi, R., O. R. Tamtaji, N. Mirhosseini, K. B. Lankarani, M. Akbari, S. T. Heydari, E. Dadgostar, and Z. Asemi. 2020. The effects of quercetin supplementation on lipid profiles and inflammatory markers among patients with metabolic syndrome and related disorders: A systematic review and meta-analysis of randomized controlled trials. *Critical Reviews in Food Science and Nutrition* 60 (11):1855–68. doi: 10.1080/10408398.2019.1604491.

Tan, Y., T. Ichikawa, J. Li, Q. Si, H. Yang, X. Chen, C. S. Goldblatt, C. J. Meyer, X. Li, L. Cai, et al. 2011. Diabetic downregulation of Nrf2 activity via ERK contributes to oxidative stress-induced insulin resistance in cardiac cells in vitro and in vivo. *Diabetes* 60 (2):625–33. doi: 10.2337/db10-1164.

Tan, Y., C. C. Tam, M. Rolston, P. Alves, L. Chen, S. Meng, H. Hong, S. Chang, and W. Yokoyama. 2021. Quercetin ameliorates insulin resistance and restores gut microbiome in mice on high-fat diets. *Antioxidants (Basel, Switzerland)* 10 (8):1251. doi: 10.3390/antiox10081251.

Tang, L., K. Li, Y. Zhang, H. Li, A. Li, Y. Xu, and B. Wei. 2020. Quercetin liposomes ameliorate streptozotocin-induced diabetic nephropathy in diabetic rats. *Scientific Reports* 10 (1):2440. doi: 10.1038/s41598-020-59411-7.

Tien, T., J. Zhang, T. Muto, D. Kim, V. P. Sarthy, and S. Roy. 2017. High glucose induces mitochondrial dysfunction in retinal müller cells: Implications for diabetic retinopathy. *Investigative Opthalmology & Visual Science* 58 (7):2915–21. doi: 10.1167/iovs.16-21355.

Tong, F., S. Liu, B. Yan, X. Li, S. Ruan, and S. Yang. 2017. Quercetin nanoparticle complex attenuated diabetic nephropathy via regulating the expression level of icam-1 on endothelium. *International Journal of Nanomedicine* 12:7799–813. doi: 10.2147/ijn.s146978.

Tsalamandris, S., A. S. Antonopoulos, E. Oikonomou, G. A. Papamikroulis, G. Vogiatzi, S. Papaioannou, S. Deftereos, and D. Tousoulis. 2019. The role of inflammation in diabetes: Current concepts and future perspectives. *European Cardiology* 14 (1):50–9. doi: 10.15420/ecr.2018.33.1.

Vaghari-Tabari, M., M. Majidinia, S. Moein, D. Qujeq, Z. Asemi, F. Alemi, R. Mohamadzadeh, N. Targhazeh, A. Safa, and B. Yousefi. 2020. Micrornas and colorectal cancer chemoresistance: New solution for old problem. *Life Sciences* 259:118255. doi: 10.1016/j.lfs.2020.118255.

ValdezGuerrero, A. S., J. C. Quintana-Pérez, M. G. Arellano-Mendoza, F. J. Castañeda-Ibarra, F. Tamay-Cach, and D. Alemán-González-Duhart. 2021. Diabetic retinopathy: Important biochemical alterations and the main treatment strategies. *Canadian Journal of Diabetes* 45 (6):504–11. doi: 10.1016/j.jcjd.2020.10.009.

Valensi, P., C. L. Devehat, J. L. Richard, C. Farez, T. Khodabandehlou, R. A. Rosenbloom, and C. LeFante. 2005. A multicenter, double-blind, safety study of QR-333 for the treatment of symptomatic diabetic peripheral neuropathy. A preliminary report. *Journal of Diabetes and Its Complications* 19 (5):247–53. doi: 10.1016/j.jdiacomp.2005.05.011.

Vogiatzoglou, A., A. A. Mulligan, M. A. Lentjes, R. N. Luben, J. P. Spencer, H. Schroeter, K. T. Khaw, and G. G. Kuhnle. 2015. Flavonoid intake in European adults (18 to 64 years). *PloS One* 10 (5):e0128132. doi: 10.1371/journal.pone.0128132.

Wang, C., Y. Pan, Q. Y. Zhang, F. M. Wang, and L. D. Kong. 2012. Quercetin and allopurinol ameliorate kidney injury in STZ-treated rats with regulation of renal NLRP3 inflammasome activation and lipid accumulation. *PloS One* 7 (6):e38285. doi: 10.1371/journal.pone.0038285.

Wang, C., Z. Qu, L. Kong, L. Xu, M. Zhang, J. Liu, and Z. Yang. 2019. Quercetin ameliorates lipopolysaccharide-caused inflammatory damage via down-regulation of miR-221 in WI-38 cells. *Experimental and Molecular Pathology* 108:1–8. doi: 10.1016/j.yexmp.2019.03.002.

Wang, P., T. Wang, X. Zheng, W. Cui, J. Shang, and Z. Zhao. 2021. Gut microbiota, key to unlocking the door of diabetic kidney disease. *Nephrology (Carlton, Vic.)* 26 (8):641–9. doi: 10.1111/nep.13874.

Wang, R., Z. Qiu, G. Wang, Q. Hu, N. Shi, Z. Zhang, Y. Wu, and C. Zhou. 2020. Quercetin attenuates diabetic neuropathic pain by inhibiting mTOR/p70s6K pathway-mediated changes of synaptic morphology and synaptic protein levels in spinal dorsal horn of db/db mice. *European Journal of Pharmacology* 882:173266. doi: 10.1016/j.ejphar.2020.173266.

Wang, S., S. Du, Y. Lv, W. Wang, and F. Zhang. 2020. Elevated microRNA-20b-3p and reduced thioredoxin-interacting protein ameliorate diabetic retinopathy progression by suppressing the NLRP3 inflammasomes. *IUBMB Life* 72 (7):1433–48. doi: 10.1002/iub.2267.

Wang, S., S. Du, W. Wang, and F. Zhang. 2020. Therapeutic investigation of quercetin nanomedicine in a zebrafish model of diabetic retinopathy. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie* 130:110573. doi: 10.1016/j.biopha.2020.110573.

Wang, S., J. Yao, B. Zhou, J. Yang, M. T. Chaudry, M. Wang, F. Xiao, Y. Li, and W. Yin. 2018. Bacteriostatic effect of quercetin as an antibiotic alternative in vivo and its antibacterial mechanism in vitro. *Journal of Food Protection* 81 (1):68–78. doi: 10.4315/0362-028X.JFP-17-214.

Wang, X., H. Li, H. Wang, and J. Shi. 2020. Quercetin attenuates high glucose-induced injury in human retinal pigment epithelial cell line ARPE-19 by up-regulation of miR-29b. *Journal of Biochemistry* 167 (5):495–502. doi: 10.1093/jb/mvaa001.

Wang, Y., X. Ye, D. Ding, and Y. Lu. 2020. Characteristics of the intestinal flora in patients with peripheral neuropathy associated with type 2 diabetes. *The Journal of International Medical Research* 48 (9):300060520936806. doi: 10.1177/0300060520936806.

Wang, Z., D. Zhai, D. Zhang, L. Bai, R. Yao, J. Yu, W. Cheng, and C. Yu. 2017. Quercetin decreases insulin resistance in a polycystic ovary syndrome rat model by improving inflammatory microenvironment. *Reproductive Sciences (Thousand Oaks, Calif.)* 24 (5):682–90. doi: 10.1177/1933719116667218.

Wang, Z. M., D. Zhao, Z. L. Nie, H. Zhao, B. Zhou, W. Gao, L. S. Wang, and Z. J. Yang. 2014. Flavonol intake and stroke risk: A

meta-analysis of cohort studies. *Nutrition (Burbank, Los Angeles County, Calif.)* 30 (5):518–23. doi: 10.1016/j.nut.2013.10.009.

Wiedermann, C. J., S. Kiechl, S. Dunzendorfer, P. Schratzberger, G. Egger, F. Oberhollenzer, and J. Willeit. 1999. Association of endotoxemia with carotid atherosclerosis and cardiovascular disease: Prospective results from the Bruneck study. *Journal of the American College of Cardiology*. 34 (7):1975–81. doi: 10.1016/S0735-1097(99)00448-9.

Wu, L., and K. G. Parhofer. 2014. Diabetic dyslipidemia. *Metabolism: clinical and Experimental* 63 (12):1469–79. doi: 10.1016/j.metabol.2014.08.010.

Wu, R., Z. Zhu, and D. Zhou. 2020. VEGF, apelin and HO-1 in diabetic patients with retinopathy: A correlation analysis. *BMC Ophthalmology* 20 (1):326. doi: 10.1186/s12886-020-01593-9.

Xie, J., W. Song, X. Liang, Q. Zhang, Y. Shi, W. Liu, and X. Shi. 2020. Protective effect of quercetin on streptozotocin-induced diabetic peripheral neuropathy rats through modulating gut microbiota and reactive oxygen species level. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie* 127:110147. doi: 10.1016/j.biopha.2020.110147.

Xing, W., Y. Song, H. Li, Z. Wang, Y. Wu, C. Li, Y. Wang, Y. Liu, W. Wang, and J. Han. 2019. Fufang xueshuantong protects retinal vascular endothelial cells from high glucose by targeting yap. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie* 120:109470. doi: 10.1016/j.biopha.2019.109470.

Xiong, G., W. Ji, F. Wang, F. Zhang, P. Xue, M. Cheng, Y. Sun, X. Wang, and T. Zhang. 2019. Quercetin inhibits inflammatory response induced by LPS from porphyromonas gingivalis in human gingival fibroblasts via suppressing NF-κB signaling pathway. *BioMed Research International* 2019:6282635. doi: 10.1155/2019/6282635.

Xu, B., W. Qin, Y. Xu, W. Yang, Y. Chen, J. Huang, J. Zhao, and L. Ma. 2021. Dietary quercetin supplementation attenuates diarrhea and intestinal damage by regulating gut microbiota in weanling piglets. *Oxidative Medicine and Cellular Longevity* 2021:6221012. doi: 10.1155/2021/6221012.

Xu, J., R. Liang, W. Zhang, K. Tian, J. Li, X. Chen, T. Yu, and Q. Chen. 2020. Faecalibacterium prausnitzii-derived microbial anti-inflammatory molecule regulates intestinal integrity in diabetes mellitus mice via modulating tight junction protein expression. *Journal of Diabetes* 12 (3):224–36. doi: 10.1111/1753-0407.12986.

Yang, G., J. Wei, P. Liu, Q. Zhang, Y. Tian, G. Hou, L. Meng, Y. Xin, and X. Jiang. 2021. Role of the gut microbiota in type 2 diabetes and related diseases. *Metabolism: clinical and Experimental* 117:154712. doi: 10.1016/j.metabol.2021.154712.

Yang, H., G. Sloan, Y. Ye, S. Wang, B. Duan, S. Tesfaye, and L. Gao. 2019. New perspective in diabetic neuropathy: From the periphery to the brain, a call for early detection, and precision medicine. *Frontiers in Endocrinology* 10:929. doi: 10.3389/fendo.2019.00929.

Yang, H., Y. Song, Y. N. Liang, and R. Li. 2018. Quercetin treatment improves renal function and protects the kidney in a rat model of adenine-induced chronic kidney disease. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research* 24:4760–6. doi: 10.12659/msm.909259.

Yang, L., S. YanYu, L. GuoHao, L. Qi, W. YuXiang, and D. YuSong. 2021. Antagonistic effect of quercetin against oxidative pancreatic injury in diabetic rats via nrf2 pathway. *Shipin Kexue/Food Science* 42 (5):208–14.

Yang, R., L. Li, H. Yuan, H. Liu, Y. Gong, L. Zou, S. Li, Z. Wang, L. Shi, T. Jia, et al. 2019. Quercetin relieved diabetic neuropathic pain by inhibiting upregulated P2X4 receptor in dorsal root ganglia. *Journal of Cellular Physiology* 234 (3):2756–64. doi: 10.1002/jcp.27091.

Yao, H., D. Xin, Z. Zhan, and Z. Li. 2021. Network pharmacology-based approach to comparatively predict the active ingredients and molecular targets of compound xueshuantong capsule and hexuemingmu tablet in the treatment of proliferative diabetic retinopathy. *Evidence-Based Complementary and Alternative Medicine: eCAM* 2021:6642600. doi: 10.1155/2021/6642600.

Yao, Y., J. Du, R. Li, L. Zhao, N. Luo, J. Y. Zhai, and L. Long. 2019. Association between ICAM-1 level and diabetic retinopathy: A review and meta-analysis. *Postgraduate Medical Journal* 95 (1121):162–8. doi: 10.1136/postgradmedj-2018-136102.

Yao, Z., Y. Gu, Q. Zhang, L. Liu, G. Meng, H. Wu, Y. Xia, X. Bao, H. Shi, S. Sun, et al. 2019. Estimated daily quercetin intake and association with the prevalence of type 2 diabetes mellitus in Chinese adults. *European Journal of Nutrition* 58 (2):819–30. doi: 10.1007/s00394-018-1713-2.

Ying, L., M. T. Chaudhry, F. Xiao, Y. Mao, M. Wang, B. Wang, S. Wang, and Y. Li. 2020. The effects and mechanism of quercetin dietary supplementation in streptozotocin-induced hyperglycemic arbor acre broilers. *Oxidative Medicine and Cellular Longevity* 2020:9585047. doi: 10.1155/2020/9585047.

Zahedi, M., R. Ghiasvand, A. Feizi, G. Asgari, and L. Darvish. 2013. Does quercetin improve cardiovascular risk factors and inflammatory biomarkers in women with type 2 diabetes: A double-blind randomized controlled clinical trial. *International Journal of Preventive Medicine* 4 (7):777–85.

Zelmanovitz, T., F. Gerchman, A. P. Balthazar, F. C. Thomazelli, J. D. Matos, and L. H. Canani. 2009. Diabetic nephropathy. *Diabetology & Metabolic Syndrome* 1 (1):10. doi: 10.1186/1758-5996-1-10.

Zeng, K., Y. Wang, N. Yang, D. Wang, S. Li, J. Ming, J. Wang, X. Yu, Y. Song, X. Zhou, et al. 2017. Resveratrol inhibits diabetic-induced Müller cells apoptosis through microrna-29b/specificity protein 1 pathway. *Molecular Neurobiology* 54 (6):4000–14. doi: 10.1007/s12035-016-9972-5.

Zhang, L., Q. Qin, M. Liu, X. Zhang, F. He, and G. Wang. 2018. Akkermansia muciniphila can reduce the damage of gluco/lipotoxicity, oxidative stress and inflammation, and normalize intestine microbiota in streptozotocin-induced diabetic rats. *Pathogens and Disease* 76 (4): 1–8. doi: 10.1093/femspd/fty028.

Zhang, Q., W. Song, B. Zhao, J. Xie, Q. Sun, X. Shi, B. Yan, G. Tian, and X. Liang. 2021. Quercetin attenuates diabetic peripheral neuropathy by correcting mitochondrial abnormality via activation of AMPK /PGC-1α pathway in vivo and in vitro. *Frontiers in Neuroscience* 15:636172. doi: 10.3389/fnins.2021.636172.

Zhang, X. W., J. Y. Chen, D. Ouyang, and J. H. Lu. 2020. Quercetin in animal models of Alzheimer's disease: A systematic review of preclinical studies. *International Journal of Molecular Sciences* 21 (2):493. doi: 10.3390/ijms21020493.

Zheng, H., S. A. Whitman, W. Wu, G. T. Wondrak, P. K. Wong, D. Fang, and D. D. Zhang. 2011. Therapeutic potential of Nrf2 activators in streptozotocin-induced diabetic nephropathy. *Diabetes* 60 (11):3055–66. doi: 10.2337/db11-0807.

Zhu, M., X. Zhou, and J. Zhao. 2017. Quercetin prevents alcohol-induced liver injury through targeting of PI3K/Akt/nuclear factor-κB and STAT3 signaling pathway. *Experimental and Therapeutic Medicine* 14 (6):6169–75. doi: 10.3892/etm.2017.5329.

Zhu, Q., R. Gao, Y. Zhang, D. Pan, Y. Zhu, X. Zhang, R. Yang, R. Jiang, Y. Xu, and H. Qin. 2018. Dysbiosis signatures of gut microbiota in coronary artery disease. *Physiological Genomics* 50 (10):893–903. doi: 10.1152/physiolgenomics.00070.2018.

Zong, H., M. Ward, and A. W. Stitt. 2011. Ages, rage, and diabetic retinopathy. *Current Diabetes Reports* 11 (4):244–52. doi: 10.1007/s11892-011-0198-7.

Zotova, E., J. A. Nicoll, R. Kalaria, C. Holmes, and D. Boche. 2010. Inflammation in Alzheimer's disease: Relevance to pathogenesis and therapy. *Alzheimer's Research & Therapy* 2 (1):1. doi: 10.1186/alzrt24.