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Narrative Review

Role of Flavonoids in Diabetes

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ABSTRACT

Type 2 diabetes (T2D) and obesity are known as important chronic diseases in the world. A common mechanism of pathogenesis in both diseases is the dysregulation of the insulin-signaling pathway that is essential to maintain an appropriate levels of glucose. Flavonoids are naturally occurring phenolic compounds that exist many foods including in fruits, vegetables and seeds. Accumulating lines of evidence showed a preventive role for the flavonoids against T2D and obesity, and at present, these compounds are suggested as crucial potential chemopreventive agents. In this review we summarized *in vitro* and *in vivo* investigations evaluating data related to the effects of flavonoids and flavonoid-rich foods on the regulation of the insulin-signaling pathway during T2D and obesity. Interestingly, few human investigations have assessed the modulatory effect of these phenolic compounds at molecular level on the insulin regulation. In this regard, it is also important to be considered that the underlying mechanism of the flavonoids is not fully clarified and that an appropriate dosage to reach a positive effects on health status has not been characterized yet. More studies will be required to clarify all these critical inconsistencies and will approve the use of flavonoids to prevent, delay or improve the treatment of T2D and obesity.

Keywords: Antioxidant, anti-inflammatory, flavonoid, type 2 diabetes, obesity, body mass index, insulin, treatment.

Introduction

Current life style is one of the most important risk factor of increased prevalence of common metabolic diseases such as type 2 diabetes (T2D) and obesity. Indeed, both diseases are known as the most common chronic diseases in nearly all regions which can lead to an international health burden. According to the World Health Organization (WHO), the prevalence of diabetes has risen from 108 million in 1980 to 422 million in 2014, and the incidence of obesity has increased in a similar way (1, 2).

The underlying mechanisms of T2D and obesity is very different, but dysregulation of the insulin signaling process, which is present in T2D, is also a common complication in obesity; in this regard, accumulating lines of evidence proposes that obesity increases the risk for developing insulin resistance and T2D, among other pathologies (3). Under these conditions of impaired insulin signaling, the glucose homeostasis is disrupted and the main peripheral tissues involved in this systemic glucose dynamic are affected, i.e., mainly liver, adipose tissue and skeletal muscle. It should be considered that common drugs are not appropriately effective in regulating a long-term

glucose control in most cases. Therefore, at present, it is known that the most efficient approach to prevent or delay T2D and obesity is the increase of activity and improvements in dietary habits. In this regard, flavonoids, which are natural dietary compounds found in vegetables and fruits, have attracted a great attraction due to their lack of toxicity and potential ability to act as highly effective chemopreventive compounds against T2D and obesity (4, 5). In this review, we aimed to summarize the molecular basis of the chemopreventive activity of flavonoids related to insulin signaling during T2D and obesity. Furthermore, the limited current existing evidence on the association between these natural compounds and insulin sensitivity based on human clinical trials is explained.

Underlying Mechanisms of Insulin Signaling in Diabetes and Obesity

Under normal conditions, the circulating glucose is transported into β-pancreatic cells of the islets of Langerhans by the glucose transporter (GLUT)-2 resulting in insulin secretion. Then, the hormone binds to its specific cell surface receptor (insulin receptor, IR) and the insulin signaling process is triggered. This stimulation causes the phosphorylation of the insulin receptor substrates (IRS)-1 and -2, which is correlated with the activation of both the phosphatidylinositol 3-kinase (PI3K)-AKT/protein kinase B (PKB) mechanism and the Ras-mitogen-activated protein kinase (MAPK) process. The PI3K/AKT mechanism is crucial for the most metabolic activities of insulin. Tyrosine phosphorylated IRS-1 binds and triggers the lipid kinase PI3K that then initiates a serine/threonine kinases cascade, including AKT. Finally, the initiation of this process leads to an increased translocation of the insulin-responsive GLUTs to the plasma membrane, and the enhanced glucose uptake in the skeletal muscle and adipose organs (6, 7). In the liver, the stimulation of the PI3K/AKT process results in the initiation of glycogen production and the suppression of gluconeogenesis. Furthermore, the MAPK mechanism is significant for the effects of insulin on cell growth (mitogenesis, cell differentiation, motility and survival), and it does not have a role in mediating the metabolic actions of the hormone. Taken together, it becomes clear that the exact regulation of the insulin signaling is important for maintaining the glucose homeostasis and health. Insulin-mediated signaling regulates the glycemia by modulating the synthesis of glucose in the liver through the glycogenolysis and gluconeogenesis during fasting, and with its uptake in feeding times into the skeletal muscle through the glycogen production and glucose metabolism, and to a much lesser extent into the adipose organs. Indeed, changes in the insulin production and signaling result in an imbalanced metabolism that predisposes to different disorders. Therefore, the impaired function of β-cells during oxidative stress and the impaired response of peripheral tissues to insulin (insulin resistance) cause a situation of hyperglycemia and hyperinsulinemia in combination with a chronic low-grade of inflammation (8, 9).

All these changes are present in T2D, which is known by the decrease of the β-cell activity and worsening of insulin resistance. Moreover, insulin resistance is a marker of obesity, and it has been proposed that unbalanced lipid metabolism, dysbiosis, chronic inflammation and dysregulation of signaling mechanisms (insulin route) have role in the development of the insulin production in this disease. Furthermore, a link between obesity and T2D has been approved (10).

During insulin resistance, the primary defect is that, in the insulin signaling mechanism, the autophosphorylation of IR is less responsive to the hormone. Therefore, the downstream cellular action of insulin is significantly decreased or impaired. Furthermore, during insulin resistance in the skeletal muscle and adipose tissue, the glucose uptake is not carried out correctly because of the declined AKT activity that results in decreased GLUT-4 expression and translocation; therefore, the decreased AKT levels are associated with a reduced glycogen production in the skeletal muscle (10). In a similar way, during insulin resistance, the hepatic AKT function decreases and that results in both upregulation of forkhead box protein O1 (FOXO1) and improvement of gluconeogenesis, as well as to the decrease of glycogen production. Significantly, the accumulation of visceral adipose tissue results in an increase secretion of free fatty acids (FFA), which interferes with the insulin signaling by improving protein kinases such as protein kinase C (PKC), MAPK, c-Jun N-terminal kinase (JNK) and inhibitor of nuclear factor κB kinase β (IκB-β). Furthermore, the low-grade of inflammation related to the situation of insulin

resistance leads to an increased synthesis and release of pro-inflammatory cytokines (tumor necrosis factor [TNF]-α, interleukin [IL]-6, etc.) that in turn suppresses the insulin signaling process (10, 11).

Taken together, insulin signaling change is a common marker in T2D and obesity. Both pathologies are known as the most common chronic disorders in almost all regions, and contribute to an increasing international health burden. Therefore, there is a necessary requirement to continue working on the delay and prevent of these diseases, being the dietary suggestions a very promising and economic approach. In this regard, flavonoids, which are natural compounds, have been receiving a rising attention.

Dietary Flavonoids

Flavonoids are plant secondary compounds widely found in fruits, vegetables and seeds, as well as in their derived foods such as cocoa, coffee, tea, soy-based foods and red wine. Plants produce flavonoids for their protection against microbial destruction, oxidation injury and UV damage; moreover, they make the odors, color and taste of foods. Structurally, flavonoids are included into the group of phenolic compounds as they have a basic polyphenolic structure consisting of two benzene rings (A and B) connected by an oxygenated heterocyclic ring (C). Depending on the functional groups exist on the C-ring (methyl, hydroxyl, glycan, acetyl or others), the degree of C-ring oxidation and the connection position of B-ring, flavonoids are classified into six different subclasses, namely flavones, flavanones, flavonols, flavanols, isoflavones andanthocyanidins (12, 13). At the same time, individual compounds from each subclass are structurally detected by different patterns of hydroxylation and conjugation of the phenolic rings. However, flavonoids also occur as oligomers and polymers (i.e., tannins), and are classified as condensed tannins (also known as proanthocyanidins or procyanidins) or hydrolysable tannins. Most flavonoids exist in foods as a glycoside-bound form, which contributes to their complexity and the large number of individual molecules that have been detected. Indeed, more than 9000 flavonoids have been reported, even though, at present, compounds belonging to this group are still being introduced (14, 15).

Although the consumption of flavonoids by foods may be different among regions, it has been estimated that their mean total intake in Western regions is about 435 mg/day and may even increase in cases with diets rich in plant-based compounds. However, the biological function of flavonoids not only depend on their intake, but also on their bioavailability. Once consumed, the absorption, metabolism and excretion of flavonoids in the human body affect their potential bioactivity. Taken together, in the small intestine, flavonoids are metabolized and produce sulfates, glucuronides, and methylated metabolites, which are more soluble in water. Then, the conjugated compounds pass to the portal vein and liver, where they undergo further phase II metabolism before entering into the blood and being excreted in the urine. Certain plasma compounds can also be secreted in the bile to the duodenum and can be reabsorbed, increasing their half-life in the systemic circulation. Generally, pure flavonoids and its conjugated forms are identified in plasma at nM or low μM concentrations after the regular ingestion of flavonoids or flavonoid-rich foods (16, 17). Furthermore, the colon has a crucial role in the bioavailability of dietary flavonoids, since a relatively high rate of these natural metabolites is not absorbed in the small intestine. These unabsorbed flavonoids pass without any changes to the large intestine, where they are commonly metabolized by the microbiota into a variety of small phenolic acids and aromatic metabolites that can easily be absorbed in the colon. These derived colonic compounds can be identified in plasma at higher concentrations than those of pure flavonoids and their conjugated compounds. Therefore, parent compounds and their metabolites, as well as the colonic metabolites produced by the gut microbiota are knows as the major contributors to the biological functions of flavonoids. Scientific interest in flavonoids has considerably increased in recent years with different investigations supporting their beneficial effects on metabolic disorders such as T2D and obesity. These natural foods and their metabolites make a number of biological activities such as antioxidant and anti-inflammatory functions that confer them different health-promoting characteristics. Furthermore, flavonoids have the ability to directly interact with proteins such as key cellular receptors or components of signaling mechanisms, thus affecting numerous activities in different cells and

organs. Accordingly, flavonoids can decrease insulin resistance in insulin-sensitive cells through different mechanisms, including the regulation of the insulin signaling mechanism. Under physiological and pathological conditions, these natural foods can affect the production of insulin from the β-pancreatic cells and initiate the insulin signaling mechanism to maintain the glucose homeostasis (18, 19).

Moreover, flavonoids may have a role to preserve the normal levels of glucose through the initiation of the glucose uptake in insulin-sensitive tissues and the regulation of the hepatic glucose output and release. Similarly, under physiological situations in hepatic and renal tissues, this mentioned effect was related to both the activation of the IR-IRS-1 and-2- PI3K/AKT mechanism and glucose uptake together with increased levels of GLUT-2, and the prevention of glucose synthesis. In a similar way, in adipocytes the incubation with different flavonoids stimulated the IR-IRS-PI3K/AKT mechanism and the glucose uptake by decreasing the translocation of GLUT-4. Cocoa procyanidins (PCs) have also been reported to mimic the insulin activity in human primary skeletal muscle cells. Cocoa PCs initiate the glycogen production, the glucose uptake and the function of the PI3K/AKT mechanism. Similarly, the flavonoid epigallocatechin-3-O-gallate (EGCG) directly promoted the translocation of GLUT4 to the plasma membrane and increased the glucose uptake through the PI3K/AKT signaling mechanism in L6 skeletal muscle cells. All this points to a potential preventive function for these phenolic compounds against different chronic diseases, including T2D and obesity, whilst in a healthy condition the insulin-like function has been correlated with an improvement of the hormone mechanism. Taken together, in this study we aimed to review the molecular basis of the preventive function of flavonoids associated with insulin signaling in T2D and obesity (12, 20, 21).

Effects of Flavonoids on Insulin Signaling in T2D

T2D is the most common metabolic disease that affects more than 400 million people in the world and its prevalence has been increasing continuously, reaching epidemic rate with a great social and health burden (22-24). It is a complex metabolic disease characterized by persistent increased blood glucose due to the progressive insulin deficiency (beta-cell dysfunction) on the background of insulin resistance. In diabetes, intrinsic genetic and epigenetic risk factors, as well as extrinsic factors, including increased levels of lipids, glucose, or amino acids, can affect the insulin signaling pathway in insulin-sensitive cells, causing insulin resistance. Different scientific investigations have shown that flavonoids may have a role in prevention or amelioration of the insulin resistance in diabetes by their function in modulation of the insulin signaling mechanism in classical target tissues such as liver, muscle, and adipose tissue. These activities have widely been shown in both *in vitro* and *in vivo* animal studies (4).

Liver has a major role in regulation of the balance of glucose homeostasis; however, in diabetes, the activity of insulin to initiate downstream metabolic activities is impaired, causing changes in the hepatic metabolism. Dietary flavonoids may increase insulin sensitivity in diabetes by having role of insulin sensitizers. For instance, flavonoids such as rutin (23 µg/mL) and quercetin (6 µg/mL) have been shown to overcome the high-glucose-induced insulin resistance in hepatic FL83B cells by improving AKT phosphorylation, causing enhanced GLUT-2 translocation and glucose uptake. Similarly, a cocoa flavonoid extract (1 µg/mL) and its main flavonoid epicatechin (EC) (10 µM) can decrease the insulin desensitization in glucose-induced insulin-resistant HepG2 cells by decreasing IRS-1 serine phosphorylation and increasing tyrosine phosphorylated levels of IR, IRS-1 and IRS-2, and triggering both the PI3K/AKT mechanism and AMP-activated protein kinase (AMPK). Similar findings were reported with a swertisin rich flavonoid fraction both in insulin resistance hepatic cells and in high fat diet (HFD)-fed and streptozotocin (STZ)-induced type 2 diabetic rats, as well as with the flavonoid tangeretin in (db/db) diabetic mice (25-27). The hepatic insulin sensitizing effect of tangeretin and cocoa flavonoids has also been correlated with their potential to diminish the MAPKs mechanism. On the contrary, the flavonoid myricetin up-regulated p-IR, p-IRS1 and p-AKT in the liver of HFD-fed and STZ-induced type 2 diabetic rats by suppressing the function and expression of PTP1B, the tyrosine phosphatase that negatively modulates the insulin signal transduction. Interestingly, the impaired insulin mechanism in the liver improves gluconeogenesis and diminishes glycogen

production. In this regard, it has been reported that flavonoids can regulate several genes associated with the glucose metabolism through the IRS/PI3K/AKT mechanism. The levels of glycogen and glycolytic enzymes were increased, whilst the expression of phosphoenolpyruvate carboxykinase (PEPCK) and glucose 6-phosphatase (G6Pase) was decreased in the liver of diabetic animals that were treated with isoquercetin (40 mg/kg bw) for 45 days. In a similar way, consumption of a diet rich in cocoa flavonoids (10%) prevented the inactivation of the glycogen synthase kinase (GSK3)-β mechanism and increased the phosphorylation levels of glycogen synthase (GS) in the liver of Zucker diabetic fatty (ZDF) rats, thus preserving the glycogen content. Furthermore, cocoa consumption decreased the expression levels of the gluconeogenic enzyme PEPCK and positively modulated those of glucokinase (GK), thus suppressing the hepatic glucose synthesis. Moreover, treatment of db/db diabetic mice with a mulberry anthocyanin extract decreased liver glycogen content, and that was in line with alterations in the phosphorylation of GSK3β and FOXO1, suggesting that these changes seemed to be due to gluconeogenesis suppression (28).

In diabetic patients, the insulin pathway in the skeletal muscle is also compromised, causing a lack of glucose consumption. The flavonoid myricitrin has been reported to activate the IRS 1/PI3K/AKT/GLUT4 pathway in both L6 muscle cells exposed to high glucose and in the soleus muscle of rats with T2D, increasing proving the consumption of glucose in the diabetic milieu. An investigation performed with diabetic animals revealed that the treatment with the flavonoid amentoflavone for 2 months enhanced the level of phosphorylated AKT and the expression of GLUT-4 in the skeletal muscle, and that was correlated with an improved peripheral glucose consumption and with a hypoglycemic characteristics (29, 30). In a similar way, supplementation with a mulberry leaf flavonoid extract or with the flavonoid phloretin upregulated IRS-1, PI3K and p-AKT levels in the skeletal muscle of type 2 diabetic rats. This process was correlated with the stimulation of GLUT-4 expression and its translocation, and with an enhancement in the insulin sensitivity. Interestingly, the combination of phloretin with metformin, the first-line treatment, revealed better findings in the initiation of the insulin pathway than each of those compounds alone. Metformin is considered to improve the insulin sensitivity through the regulation of AMPK, whereas flavonoids can perform their beneficial roles, at least partially, through the initiation of the insulin mechanism, suggesting the interest of using flavonoids as adjuvants of classical therapies for the treatment of T2D. Other flavonoids such as chrysin or an extract of mulberry anthocyanin have also revealed to recover the glycogen content in the skeletal muscle of diabetic animals through initiation of the PI3K/AKT mechanism (29, 30).

Regarding the adipose tissue, the supplementation with an açai seed extract (rich in catechin, epicatechin and polymeric proanthocyanidins) increased the insulin sensitivity and decreased plasma glucose and lipid levels in type 2 diabetic animals together with an increase in p-AKT and GLUT-4 expression both in muscle and adipose tissue. Similar findings were shown in ob/ob diabetic mice supplemented with the flavonoid nobiletin. Furthermore, the oral administration of citrus fruit peel extracts and its constituting flavonoids naringin, naringenin, hesperidin and quercetin at a dose of 100 mg/kg bw for one month significantly improved the suppressed mRNA expressions of GLUT-4 and IRβ-subunit in the adipose tissue of nicotinamide (NA)/streptozotocinSTZ/NA-induced type 2 diabetic rats. Accordingly, the recovered insulin sensitivity in the adipose tissue had potent anti-hyperglycemic and anti-hyperlipidemic effects in STZ/NA-induced diabetic rats (31).

Interestingly, flavonoids have also approved their therapeutic characteristics for complications related to diabetes by improving the impaired insulin pathway in other non-classical targets such as the endothelium, kidney, and brain. In the endothelium, under hyperglycemic situations, the inefficiency of the IR/AKT/endothelial nitric oxide synthase (eNOS) mechanism causes a reduced nitric oxide (NO) synthesis and the consequent endothelium-dependent relaxation of the aorta, which is closely correlated with diabetic vascular complications. It has been revealed that catechin (50 mg/kg/day) supplementation in STZ-induced diabetic mice decreased diabetic endothelial dysfunction through the stimulation of endothelial PI3K and the following activation of eNOS and NO production. Furthermore, insulin resistance in the kidney has also been associated with the renal injury and the development of diabetic nephropathy. Indeed,

impaired insulin pathway in the kidney has been correlated with increased glucose uptake and apoptosis, which can significantly affect the kidney activity (32). Similarly, the flavonoid epicatechin (EC) and the microbial metabolite dihydroxyphenylacetic acid (DHPAA) decreased the dysfunction of renal cells treated with high glucose through the suppression of the insulin signaling blockade and the regulation of glucose homeostasis via AKT and AMPK. In line with this, supplementation with luteolin for one month decreased the renal damage in STZ-induced diabetic mice through enhancement of the phosphorylation of IR, PI3K and AKT in the kidney. Furthermore, insulin receptors are also expressed in the brain where insulin is crucial for glucose homeostasis. Diabetic situations change the insulin mediated PI3K-AKT pathway in neuronal cells and decrease the brain glucose metabolism, which in turn increases the risk of dementia, including Alzheimer disease, and can cause the diabetic encephalopathy. Flavonoids such as quercetin and naringenin, which can cross the blood–brain barrier, are able to produce glucose transporters and other key components of the insulin mechanism in the brain of STZ-induced diabetic rats, supporting a neuroprotective characteristic (33).

Taken together, the findings achieved in *in vitro* and animal studies suggest that dietary flavonoids can regulate the insulin pathway in peripheral tissues and, therefore, improve the insulin resistance in T2D. A number of investigations have also assessed the role of the intake of flavonoid-rich compounds in cases with T2D; however, there are not studies providing findings on their role in the insulin pathway at molecular level. Indeed, only few investigations have assessed the role of flavonoids in the insulin sensitivity in cases with T2D, and the findings achieved have been inconsistent. In a study performed for one year on diabetic women, the daily intake of flavonoid-enriched chocolate containing 850 mg of flavanols and 100 mg of isoflavones caused a significant decrease in insulin resistance evaluated by the homeostatic model investigation for insulin resistance (HOMA-IR) index. Similarly, the consumption of a decaffeinated green tea extract making a daily dose of 856 mg of EGCG for four months made a significant decrease in HOMA-IR index in type 2 diabetic patients. On the other hand, other investigations have shown that the acute and the short-term receive of cocoa flavonoids had no role in insulin sensitivity in diabetic cases. Therefore, supplementation with silybin-beta-cyclodextrin for 6 months can decrease the insulin resistance (HOMA-IR) in cases with T2D (differences were not significant). In a similar way, in a clinical trial, diabetic cases supplemented with a grape seed extract (600 mg/day) for one month revealed beneficial effects on decreasing the fasting glucose, but effects on HOMA-IR index were not important (34).

Effects of Dietary Flavanols on Insulin Signaling in Obesity

According to WHO, 39% of adult people (≥18 years-old) were overweight in 2016, and 13% of adults were obese, and more significantly, 38 million children under the age of 5 were overweight or obese in 2019. Obesity is known by an abnormal increase of fat tissues in the white adipose tissue (WAT) and in peripheral important tissues. Diabetes is initiated by an imbalance between the energy intake and expenditure, and the dysfunctionality of the adipose tissue is correlated with impaired lipid metabolism, impaired adipose tissue expandability, and adipocyte hypertrophy. All these impairments in the adipose tissue and peripheral tissues are important for the development of the insulin resistance, and have widely been investigated at molecular level in insulin-responsive tissues and organs). Similarly, therapeutic interventions aimed at decreasing insulin resistance should render protective characteristics against obesity. Accordingly, dietary supplementations to introduce healthful food choices, as increasing fruit and vegetable intake, which are rich in flavonoids, could cause body weight reduction and improved metabolic condition, and thus, to the prevention of obesity. Until now, few clinical trials are available investigating for health benefits associated with the insulin pathway of flavonoids in obese subjects, and most of studies comes from *in vitro* and *in vivo* investigations in which main target organs for the disease, such as adipose tissue and other classical insulin-sensitive peripheral tissues (skeletal muscle and liver) have been evaluated (35).

In cultured adipocytes, cyanidin-3-O-glucoside (C3G) (5–10 µM) decreased palmitic acid (PA)-induced insulin resistance. Therefore, C3G decreased the lipid accumulation and improved the insulin resistant situation by increasing p-(Tyr895)-

IRS-1, p85-PI3K and p-AKT values and decreasing p-(Ser307)-IRS-1 levels. Furthermore, C3G pre-treatment increased GLUT-1 values in 3T3-L1 cells. In a similar way, a hydroalcoholic extract rich in flavonoids from *Lampaya medicinalis* Phil. (HEL) could restore the IRS-1/AKT/AS160 mechanism in cultured adipocytes. Pre-incubation of cells with HEL (0.1 µg/mL) for 2 h followed by PA treatment (16 h) averted the decrease in p-(Tyr612)-IRS-1, p-AKT and p-AS160 levels, as well as the diminution in the glucose consumption (36).

In high-fat diet (HFD) fed rats, the consumption of EGCG (3.2 g/kg food) for four months increased the insulin signaling mechanism in the adipose tissue by decreasing p-IRS- 1 values and improving the levels of p85-PI3K and GLUT-4. Furthermore, EGCG decreased the body weight, several metabolic parameters (i.e., FFA, fasting insulinemia, fasting glycemia, HOMA-IR, glucose infusion rate) and decreased the inflammatory situation present in obese HFD fed animals; indeed, the increase of activity of the insulin signaling pathway in the adipose tissue was correlated with the attenuated inflammation induced by EGCG. Similarly, an improvement in the insulin resistance condition was connected with a mitigation of the inflammation and an improvement of the redox status and metabolic situation, including lipid metabolism, in obese mice receiving nobiletin, an anthocyanidin-rich grape skin extract (GSE) or hydroxytyrosol. Regarding the insulin pathway, nobiletin increased p-AKT and GLUT 4 levels in WAT of HFD fed mice, and GSE stimulated the IR-IRS-1-PI3K-AKT mechanism, and increased GLUT-4 levels in the epididymal adipose tissue and gastrocnemius skeletal muscle of obese mice (37, 38).

Accordingly, EGCG consumption to triglyceride-infused rats improved insulin resistance in WAT and soleus skeletal muscle by enhancement of p-AKT, p-AMPK and GLUT-4 levels, and decreasing p-(Ser307)-IRS-1, PKCθ translocation and oxidative stress. Raspberry consumption (rich in anthocyanins and ellagitannins) also improved the insulin sensitivity in HFD fed mice by regulating the insulin signaling mechanism, as decreased p-(Ser307)-IRS-1 and p-(Ser676)- PKCθ levels, and increased p-AKT and GLUT-4 values in the inguinal WAT. Furthermore, raspberry-rich diet diminished WAT hypertrophy, macrophage infiltration and inflammation, and induced beige adipogenesis through the increase of p-AMPK, peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α, sirtuin (SIRT)-1, uncoupling protein (UCP)-1, cytochrome c, and FNCD/irisin levels (39, 40).

Notably, opposite roles have been reported for genistein on insulin sensitivity under normal and inflammatory situations in the adipose tissue. Therefore, in healthy mice after a glucose load genistein diminished the IRS-1/AKT mechanism, decreased GLUT-4 levels and increased p-AMPK values in the adipose tissue. However, under a proinflammatory condition and after a glucose load decreased the levels of p-(Tyr)-IRS-1, p-AKT, GLUT-4 and IκB kinase (IKK), as well as increased values of p-(Ser307)-IRS-1 and p-AMPK were identified in the adipose tissue. These findings were clarified by the major effects of AMPK, which has a role in the anti-inflammatory effect of genistein, causing the beneficial effect against insulin resistance (41).

Skeletal muscle is also an significant target for assessing the effects of flavonoids against insulin resistance during obesity. Baicalin improved obesity-induced insulin resistance in C2C12 cultured myotubes and in mice fed with HFD. Incubation of cells with this flavone (100, 200 and 400 µM) for 12 h increased p-AKT, p-Akt substrate of 160 kDa (AS160), GLUT-4, p-p38 and PGC-1α levels, as well as mRNA peroxisomal proliferator-activated receptor (PPAR)-γ and GLUT-1 values. In a similar way, in HFD fed mice receiving 50 mg/kg baicalin daily, AKT/AS160/GLUT-4 and p38/PGC-1α/GLUT-4 mechanisms were initiated, and contributed to reverse the insulin resistance, insulin intolerance and hyperglycemia in the skeletal muscle. An improvement in the IRS-1/AKT/PI3K mechanism, GLUT-4 levels and glucose consumption was seen when incubating L6 myotubes with phloretin previously exposed to PA (400 µM, 12 h), being this beneficial role more pronounced when the natural phenol was combined with metformin. In a similar way, da Costa et al. (38) and Arunkumar et al. (42) have shown an upregulation in the IRIRS-1-PI3K-AKT mechanism, increased p-AMPK and GLUT-4 levels, and decreased values of p-ribosomal protein S6 kinase beta-1 (S6K1) in the skeletal muscle and epididymal adipose tissue of obese mice receiving a grape seed extract (GSE) and genistein,

respectively. EGCG also decreased the insulin resistance through the improvement of the insulin signaling and redox balance, the activation of GLUT-4 translocation and the AMPK pathway, as well as by the prevention of PKC in the soleus muscle and WAT of rats infused for two days with a triglyceride emulsion that increases FFA levels. Furthermore, green tea polyphenols attenuated the insulin resistance by initiating the insulin mechanism in the soleus muscle and improved the metabolic condition in obese Zucker rats (43).

Mechanistically, the administration of green tea polyphenols prevented the suppression of IRS-1/AKT pathway and increased GLUT-4 levels, which was correlated with a decreased function of PKCθ. All these molecular alterations cause an insulin-stimulated glucose uptake and decreased lipid accumulation. Flavanol-rich lychee extract (oligonol) supplementation also improved HFD-induced insulin resistance through the inhibition of the inflammation in the tibialis anterior and gastrocnemius muscles and in the liver of mice. Oligonol consumption prevented the blockage of the insulin mechanism in the gastrocnemius by upregulating the levels of IRS-1, p-(Tyr608)-IRS-1, p AS160, and increasing p-AMPK and SIRT-1 values. These regulatory characteristics were associated with an improved insulin resistance and to a diminution of the intramuscular lipid content in the skeletal muscle. In the liver, oligonol also ameliorated the insulin sensitivity through the decrease of p-GSK3 and p-phosphatase and tensin homolog (PTEN), and decreased the intracellular lipid content by preventing mammalian target of rapamycin (mTOR)/sterol modulatory element-binding protein 1 (SREBP-1) mediated lipogenesis. Furthermore, oligonol decreased the adipocyte size (epididymal adipose tissue), as well as leptin and resistin levels through the down-regulation of PPARγ. All these beneficial regulatory effects have a role in improving the metabolic condition of the animals (glycemia, insulinemia, etc.) and to improve the inflammatory condition. In contrast, in the skeletal muscle of HFD fed mice supplemented with quercetin, Stewart et al. (44) showed no effects on insulin resistance as p-AKT levels, PI3K values and function, and triglyceride (TG) content remained unchanged in this tissue. As mentioned above, the liver has an important role in preserving glucose homeostasis, contributing to maintain the insulin sensitivity, also during obesity (45).

In a similar way, aspalathin-enriched green rooibos (GRE) prevented PA-induced insulin resistance in C3A hepatic cells and ameliorated the insulin sensitivity in obese rats. GRE increased the phosphorylated levels of AKT and AMPK, as well as total levels of GLUT-2 *in vitro*. Furthermore, GRE improved both glucose and lipid metabolism through the modulation of the FOXO1/carnitine palmitoyltransferase I (CPT1) mechanism and by increasing the uptake of both glucose and lipids in C3A cells. A reversion in the blockage of the IRS-1/AKT/PI3K mechanism, as well as increased GLUT-4 levels and glucose uptake were seen when incubating stimulated-PA BRL-3A cells with phloretin (50 µM). These beneficial findings were more pronounced when this natural compound was combined with the anti-diabetic agent metformin (46). Likewise, in obese insulin-resistant rats, GRE administration upregulated relevant genes involved in the insulin signaling mechanism and glucose metabolism, namely *Insr*, *Irs1*, *Irs2*, *Pi3k* and *Ampk*. Consumption of a genistein-rich diet to high fat-high-fructose fed mice ameliorated the hepatic insulin resistance by abolishing the increased p-(Ser)-IRS-1 and -2 levels and p-S6K1, as well as through the initiation of IR, IRS-1 and -2, PI3K, AKT and AMPK. Furthermore, in these mice, genistein decreased lipid accumulation through the down-regulation of lipogenic genes and the upregulation of lipolytic genes. Similarly, EGCG and both aqueous and ethanolic-rich phenolic extracts from seeds of *Lepidium sativum* improved the condition of insulin resistance in the liver of HFD fed rats by preventing the blockage of the insulin mechanism (IR/IRS/AKT/mTOR/p70S6K) (46); this amelioration was connected with an improvement of the pro-inflammatory and redox imbalance (increase in the enzymatic antioxidant functions). Accordingly, the prevention of both oxidative and endoplasmic reticulum stress in HFD-fed-mice induced by purple sweet potato color (anthocyanin) and hydroxytyrosol cause the attenuation of the hepatic insulin resistance. Indeed, both natural agents restored the IRS-1/PI3K/AKT insulin pathway, as well as glucose and lipid metabolism in the liver of HFD-fed mice. An improvement of the insulin resistance and endoplasmic reticulum stress was also seen in hepatic cultured cells exposed to palmitic acid and incubated with hydroxytyrosol (47). Similarly, consumption of *Vitis vinifera* L. grape skin extract (rich in anthocyanidins) for three months in HFD

fed mice decreased insulin resistance, hyperglycemia and lipid accumulation in the liver. Mechanistically, p-IRS-1, p-AKT, PI3K and GLUT-2 levels increased in animals receiving the skin grape compound, suggesting an improvement in the blockage of the insulin mechanism induced by HFD. Furthermore, lipogenic proteins (SREBP1c) were upregulated and the lipolytic pathway (LKB1-AMPK) was down-regulated, which was associated with the inhibition of hepatic steatosis. Blueberry consumption also ameliorated the insulin sensitivity and decreased insulin resistance in HFD fed rats. These beneficial characteristics were associated with decreased levels of p-(Ser307)-IRS-1 and HOMA-IR, and were seen in conjunction with a decreased inflammation, alterations in gut microbiota composition and ameliorated gut integrity. On the contrary, quercetin-enriched foods initially (3 weeks of treatment) exacerbated the detrimental characteristics caused by the administration of a HFD in the liver of mice, whilst by the end of the investigation (two months of treatment), both HFD fed animal groups were equally compromised (48).

In addition, in obesity, flavonoids perform beneficial roles related to the insulin pathway on non-classical insulin-targeted tissues, such as the endothelium and brain. Therefore, luteolin (10 and 100 μM) increased the insulin sensitivity in human umbilical vein endothelial (HUVEC) cells exposed to palmitic acid through the restoration of the p-IRS-1 values and the stimulation of the AKT/eNOS mechanism, causing an enhanced NO synthesis. Moreover, luteolin decreased the PA-induced inflammation in HUVEC cells and increased the insulin-mediated endothelium-dependent relaxation in aortic rings from healthy rats. Similarly, purple sweet potato color consumption (500 mg/kg/day for 11 weeks) improved the insulin resistance in the hippocampus of HFD fed mice, as mitigated the suppression of the IRS-1/PI3K/AKT mechanism. This beneficial role was also correlated with a reduced glycemia, apoptosis and inflammatory situation, improved glucose tolerance and improved cognitive impairment (49).

Most human studies aimed to assess the effect of flavonoids on obesity have investigated clinical markers related to this disease, such as body weight, body mass index (BMI) and lipid profile. A more decreased number of investigations have shown the roles of these natural foods on insulin resistance by providing indexes associated with this condition during obesity, namely HOMA-IR and Quantitative Insulin Sensitivity Check Index (QUICKI). In this regard, in a clinical trial, subjects received a controlled diet with blackberries (600 g/day containing 1500 mg flavonoids) or a calorie and carbohydrate matched amount of gelatin to be consumed within 12 h. An improved HOMA-IR and insulin sensitivity together with an improved fat oxidation was shown. In a similar way, Kosen-cha, a pecan-rich diet (15% of total calories) and pomegranate juice (500 mL/day containing 842.5 mg polyphenols) decreased the insulin resistance (HOMA-IR) after the intervention. This effect was along with decreased values of insulinemia, glycemia and homeostasis model evaluation of β-cell activity (HOMA-B), and improved blood pressure (BP) and lipid profile. Nevertheless, other interventional investigations have not shown a regulation of the insulin resistance condition in overweight/obese cases receiving flavanol-rich foods. Therefore, in a clinical trial in which polyphenol-rich dark chocolate was daily administered for one month, HOMA-IR and QUICKI indexes were unchanged (50, 51). A significant decrease in the body weight, systolic BP and diastolic BP was seen, whilst no differences were identified for the waist circumference and lipid profile. Similarly, orange juice and green tea consumption did not improve HOMA-IR in overweight cases. Orange juice improved the lipid profile, the immune response, the inflammatory condition and the antioxidant capacity without regulating the body composition. In contrast, the green tea decreased the body weight and insulinemia, and, as the orange juice, improved the lipid profile (50, 51).

Notably, Ormazabal et al. (52) investigated in visceral adipose tissue from normal and obese cases the insulin responsiveness after protocatechuic acid incubation (100 μM, 24 h). This phenolic compound is easily produced by the metabolism of the microbiota after anthocyanin intake, and it was approved that this compound can decrease the insulin resistance by increasing p-Tyr-IRS-1 and p-AKT levels in the visceral adipose tissue from obese subjects. Furthermore, protocatechuic acid decreased the PTP1B function and the inflammation (decreased p-p65 nuclear factor kappa B [NF-κB] and IL-6 levels). Taken together, in spite of the few number of investigations assessing the effect of flavonoids

against insulin resistance during obesity at molecular level, the studies suggest that these natural foods may be promising compounds for improving the change in the response of the hormone and other complications related to this disease. More investigations are required, especially in humans, to reveal the effects of these natural foods on insulin pathways during obesity.

Conclusions and Future Perspectives

Based on the investigations summarized in this study, the possible mechanisms of action initiated by flavonoids in association with the insulin mechanisms have been reported in *in vitro* and *in vivo* studies of T2D and obesity. Taken together, flavonoids perform their beneficial roles against these pathologies through the regulation of key elements of the insulin signal transduction mechanism and the modulation of glucose transport, being these effects related to a decreased insulin resistance, and both improved insulin sensitivity and glucose tolerance. However, it is interesting to consider that at present, few investigations have assessed some favorable insulin-sensitizing effects, and even a lower number of studies have investigated the effects of these flavonoids on the insulin pathway at molecular level. Thus, further studies, and especially more well-controlled interventional human investigations, are essential to truly estimate the ability of flavonoids in terms of insulin-mimetic and insulin sensitizing characteristics, elucidation of the molecular pathway and targets of these natural compounds in relation to the insulin signaling mechanism, and definition of optimal doses. All this findings would allow disclosing how to achieve a positive effect from these natural compounds to prevent, delay or contribute to the prevention and treatment of T2D and obesity.

Declarations

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Author Contribution

Seyedeh Parisa Manavi: Study design, data collection, writing draft of study.

Tara Amiri: Study design, data collection, writing draft of study.

Mohammad Javad Mozafaryan: Study design, data collection, writing draft of study.

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Conflict of interest

There is no conflict of interest.

Data Availability

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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