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Recent advances in understanding the anti-diabetic actions of dietary flavonoids

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Abstract

Flavonoids are polyphenolic compounds that are abundant in fruits and vegetables and increasing evidence demonstrates a positive relationship between consumption of flavonoid-rich foods and disease prevention. Epidemiological, in vitro and animal studies support the beneficial effects of dietary flavonoids on glucose and lipid homeostasis. It is encouraging that the beneficial effects of some flavonoids are at physiological concentrations and comparable to clinically-used anti-diabetic drugs; however, clinical research in this field and studies on the anti-diabetic effects of flavonoid metabolites are limited. Flavonoids act on various molecular targets and regulate different signaling pathways in pancreatic β -cells, hepatocytes, adipocytes, and skeletal myofibers. Flavonoids may exert beneficial effects in diabetes by (i) enhancing insulin secretion and reducing apoptosis and promoting proliferation of pancreatic β -cells, (ii) improving hyperglycemia through regulation of glucose metabolism in hepatocytes, (iii) reducing insulin resistance, inflammation and oxidative stress in muscle and fat, and (iv) increasing glucose uptake in skeletal muscle and white adipose tissue. This review highlights recent findings on the anti-diabetic effects of dietary flavonoids, including flavan-3-ols, flavanones, flavonols, anthocyanidins, flavones, and isoflavones, with particular emphasis on the studies that investigated the cellular and molecular mechanisms involved in the beneficial effects of the compounds.

Keywords

diabetes; flavonoids; insulin; glucose; β -cells; liver; fat; muscle; hyperglycemia; polyphenols; islets; pancreatic β -cells

Diabetes mellitus (DM) is increasing globally and now affects 7% of the world's adult population [1]. DM is a complex metabolic disorder that results from defects in insulin secretion, action, or a combination of both [2]. There are two major classifications of DM. Type 1 DM (T1D) is associated with complete or near-total insulin deficiency related to autoimmune-mediated destruction of pancreatic β -cells, and Type 2 DM (T2D) is associated

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with variable degrees of insulin resistance, impaired insulin secretion, moderate to severe β -cell apoptosis and increased hepatic glucose production [2]. In the United States, about 8.3% of the total population have diabetes and an additional 79 million adults have prediabetes [3], a condition where the blood glucose levels are higher than normal but not high enough to be diagnosed as diabetes (i.e., fasting blood glucose ≥ 100 mg/dL and < 126 mg/dL). A recent modeling study estimated that 52% of the population in the United States will have diabetes or prediabetes by 2020 [4].

Regulation of glucose homeostasis

Insulin and glucagon are the primary hormones that maintain glucose homeostasis by tightly controlling blood glucose concentrations following ingestion of a carbohydrate-rich meal. Most starch molecules are digested in the upper gastrointestinal tract, hydrolyzed into monosaccharides and absorbed into the blood stream through various glucose transporters (GLUT) [5], proteins located on basolateral (facing the bloodstream) or apical membranes (facing the lumen) of epithelial cells. From the circulation, glucose is transported into pancreatic β -cells of the islets of Langerhans through GLUT2 and its oxidation leads to insulin secretion, through a mechanism involving closure of ATP-sensitive potassium channels, membranepolarization followed by voltage-dependent calcium influx and subsequent exocytosis of insulin granules [5]. Insulin-mediated signaling lowers blood glucose by: (i) enhancing the uptake of glucose in peripheral tissues (skeletal muscle, adipose tissue and kidney) through translocation of GLUT4 vesicles to the plasma membrane, (ii) promoting glucose utilization/storage in the liver (e.g., glycogenesis for storage as glycogen), and (iii) inhibiting lipolysis and promoting lipogenesis in white adipose tissue (WAT) [5]. When blood glucose concentrations decline, glucagon is secreted from α -cells of pancreatic islets. Glucagon raises blood glucose by (i) promoting glucose production and release in the liver (e.g., glycogenolysis and gluconeogenesis) [5], and (ii) increasing lipolysis and release of free fatty acids (FFAs) from adipose tissue. Hence compounds that target glucose-regulating processes in the pancreas, liver, skeletal muscle, or adipose tissues can affect glucose homeostasis.

Insulin is used in treating T1D and many oral hypoglycemic agents are used in the treatment of T2D [1]. The four important classes of oral hypoglycemic drugs are sulphonylureas, biguanides, thiazolidinediones (TZDs), and α -glucosidase inhibitor. In addition, some of the more recently approved drugs such as glucagon-like peptide-1 agonists, dipeptidyl peptidase-IV inhibitors, and amylin analogues are also used in the management of diabetes [1]. Due to adverse side effects and alleviation of symptoms while not targeting the cause, there have been persistent efforts to identify potential compounds that can “cure” DM, for example by stimulating β -cell regeneration and preventing apoptosis, leading to a return of endogenous control of glucose homeostasis. Naturally occurring plant compounds are attractive candidates because they are abundant in nature, inexpensive to produce and may have fewer side-effects than currently used pharmaceutical compounds.

Flavonoids

Flavonoids represent a large class of at least 6,000 phenolic compounds found in fruits, vegetables, herbs, cocoa, chocolate, tea, soy, red wine, and other plant food and beverage products [6]. Structurally, flavonoids consist of 2 aromatic rings (A and B rings) linked by a 3-carbon chain that forms an oxygenated heterocyclic ring (C ring). Flavonoids are classified as flavan-3-ols, flavanones, flavonols, anthocyanidins, flavones, and isoflavones based on differences in generic structure of the C ring, functional groups on the rings, and the position at which the B ring is attached to the C ring. Within each subclass, individual compounds are characterized by specific hydroxylation and conjugation patterns [7].

The intake of flavonoids by U.S. adults is dominated by flavan-3-ols, followed by flavanones, flavonols, anthocyanidins, flavones, and isoflavones [8]. Epidemiological studies and meta-analyses suggested an inverse relationship between the consumption of flavonoid-rich diets and development of many aging-associated diseases including cancers, cardiovascular disease, diabetes, osteoporosis, and neurodegenerative disorders [9, 10]. Numerous *in vitro* and animal studies also support a beneficial effect of dietary flavonoids on glucose homeostasis [5, 11–18]. Flavonoids were shown to regulate carbohydrate digestion, insulin secretion, insulin signaling, and glucose uptake in insulin-sensitive tissues through various intracellular signaling pathways [5]. A recent study evaluated the relationship between dietary intake of different flavonoid subclasses (flavonols, flavones, flavanones, flavan-3-ols, and anthocyanins) and T2D [19]. This study involved 3 prospective cohort studies including nearly 200,000 US men and women and reported that a higher consumption of anthocyanins, particularly from blueberries, apples, and pears, was consistently associated with a lower risk of diabetes [19]. In addition, flavonols, flavan-3-ols, and total flavonoids were also shown to be inversely associated with diabetes risk in individual cohorts though results were not consistent across all cohorts [19]. In this review we focus on recent findings related to the anti-diabetic effects of dietary flavonoids with a focus on studies that investigate the cellular and molecular mechanisms involved.

Flavan-3-ols

Flavan-3-ols are present in many fruits, teas, cocoa, and chocolate. They exist as monomers (epicatechin and catechin) or oligomers (proanthocyanidins). Catechin and epicatechin are the main flavan-3-ols in fruits and cocoa, whereas epicatechin gallate (ECG), gallocatechin, epigallocatechin (EGC), and epigallocatechin gallate (EGCG) are found in tea, grapes and seeds of certain leguminous plants [20].

Numerous studies reported anti-diabetic effects of flavan-3-ols, especially EGCG, in animal and cell-culture studies. Cai *et al.* evaluated the effect of EGCG on glucose-induced toxicity in a rat pancreatic β -cell line, rat insulinoma (RIN)-m5F cells, and showed that EGCG (0.1 and 10 μ M) treatment improved insulin secretory function and viability of β -cells under conditions of glucotoxicity. These effects were at least partly mediated through increased expression of insulin receptor (IR) substrate-2 (IRS2), Akt, the forkhead box protein O1 (FoxO1) and pancreatic duodenal homeobox1 (PDX-1) [11]. In addition, EGCG improved mitochondrial function by enhancing the mass and functional integrity of mitochondria in high glucose exposed pancreatic β -cells [11]. IRS proteins are important mediators of insulin action, with downstream insulin signaling regulating β -cell survival and proliferation [11]. Indeed, disruption of IRS2 was shown to impair peripheral insulin signaling and pancreatic β -cell function and cause T2D in mice [21]. Akt is an essential component in IRS signaling, and Akt activation and subsequent FoxO1 phosphorylation are negatively affected by glucolipotoxicity [22]. The PDX-1 is a master regulator of transcription in β -cells and its expression is critical to the development of pancreas and normal β -cell function in adults. The FoxO1 plays an essential role in regulating cellular proliferation and protection against apoptosis through inducing expression of NeuroD and MafA in β -cells [23]. Thus EGCG may act through multiple components of the insulin signaling cascade to improve β -cell function.

EGCG was also shown to protect insulin-producing β -cells from pro-inflammatory cytokine-induced cytotoxicity, where treatment with EGCG partially restored glucose-stimulated insulin secretion (GSIS) and preserved cell viability [24]. Bcl-2 protein prevents oxidative stress and regulates mitochondrial transitional pore opening by opposing the effect of Bax thereby blocking cytochrome c release and inhibiting caspase activity [24–26]. EGCG treatment may protect β -cells from cytokine-stimulated apoptosis by modulating Bcl-2 expression and by suppressing Bax translocation from the cytosol to mitochondria [24].

EGCG and ECG also have beneficial effects on fatty acid-induced insulin resistance in skeletal muscle [27]. Increased plasma FFAs play a critical role in exacerbating insulin resistance and therefore pathogenesis of T2D [28, 29]. Skeletal muscle consumes nearly 70% of plasma glucose and perturbations to skeletal muscle insulin sensitivity, such as serine phosphorylation of insulin signaling components, disrupt blood glucose homeostasis [27, 30]. FFAs, perhaps through initiation of protein kinase C (PKC) or c-jun amino terminal kinase (JNK) signaling pathways, increase IRS1 Ser307 phosphorylation, which reduces the ability of IRS1 to activate phosphoinositide 3-kinase (PI3K) and Akt [27, 30]. Increased PKC activation enhances Ser307 phosphorylation of IRS1, which reduces its tyrosine phosphorylation leading to reduced binding affinity of IRS1 to IR [27]. Indeed, Ser307 phosphorylation is an important marker of fatty acid-associated insulin resistance [27]. Further, this can lead to the downregulation of the PI3K/Akt signaling pathway and reduced insulin-stimulated glucose uptake. FFAs also induce cell apoptosis through suppression of the mitogen activated protein kinase (MAPK) cascade [27].

Adenosine monophosphate-activated protein kinase (AMPK), an energy sensing molecule highly conserved from yeast to all animals, is increasingly recognized as a master regulator of whole body energy homeostasis [31]. AMPK is a heterotrimeric protein kinase composed of a catalytic subunit (AMPK α) and two regulatory subunits (β and γ) that sense low cellular energy levels by monitoring changes in the AMP:ATP ratio. AMP binding to the γ subunit induces a conformational change that allows AMPK α to be phosphorylated at its threonine residue (Thr 172) by the AMPK-activating protein kinase (LKB1). At the whole body level, AMPK integrates stress responses, nutrient and hormonal signals to the control of food intake, energy expenditure, and substrate utilization. At the cellular level, activated AMPK inhibits hepatic gluconeogenesis [32], promotes fatty acid oxidation [31], and regulates mitochondrial biogenesis [33]. To do so, AMPK α directly regulates the activity of acetyl CoA carboxylase (ACC) and the peroxisome proliferator-activated receptor gamma coactivator-1 β (PGC-1 β) [34–36], two of the most important cellular metabolic regulators. Specifically, AMPK α phosphorylates and inhibits the activity of ACC, the rate limiting enzyme for fatty acid synthesis [34, 35], while it directly phosphorylates and activates PGC-1 β [37], which controls the expression of many genes related to lipid oxidation and mitochondrial biogenesis [38, 39]. In addition, activation of AMPK increases GLUT4 expression and membrane translocation in skeletal muscle [40], thereby improving glucose uptake. Obesity and insulin resistance are always accompanied by impairment in fuel metabolism, a leading pathogenic factor for T2D. Several lines of evidence have shown that pharmacological activation of AMPK improves blood glucose homeostasis and lipid profile in insulin-resistant rodents [41]. Therefore, AMPK is emerging as an attractive target for developing strategies to treat T2D. Indeed, recent studies have shown that AMPK is one of the targets of major insulin sensitizing drugs, such as metformin and TZDs [42].

EGCG and ECG protect C2C12 mouse myoblast cells against FFA-induced insulin resistance by acting through multiple signaling pathways. EGCG treatment was associated with (i) inhibition of PKC activation and enhanced AMPK cascade that blocked IRS1 serine phosphorylation, (ii) activated AMPK and other kinases such as ERK1/2 and p38 MAPK which are essential for the maximal stimulation of glucose uptake in response to insulin [43, 44], and (iii) suppressed lipid accumulation via the AMPK/ACC signaling pathway [27, 30]. However, it is unknown if these catechins act as direct AMPK activators.

It is increasingly recognized that chronic, low-grade tissue inflammation is involved in the pathogenesis of diabetes. Therefore, preventing chronic inflammation may delay or prevent the development of diabetes. Recently it was reported that EGCG treatment delayed the onset of T1D in non-obese diabetic (NOD) mice [13], an autoimmune-mediated T1D animal model. EGCG (0.05 % in drinking water) increased plasma insulin levels and survival rate

and lowered glycosylated hemoglobin (A1C) concentrations in NOD mice, while the concentrations of anti-inflammatory cytokine IL-10 were increased [13]. Furthermore, EGCG (1 and 10 μ M) improved the viability of β -cells chronically exposed to a cocktail of proinflammatory cytokines, which was partly mediated through inhibition of caspase-3 [13]. Therefore, the protective effects of EGCG against the development of T1D could be mediated through anti-inflammatory actions in a variety of cell types.

EGCG supplementation at pharmacological doses (1% in diet) improved glucose intolerance in obese *db/db* mice [45]. EGCG exerted several beneficial effects in *db/db* mice such as improved glucose tolerance, increased GSIS, reduced number of pathologically modified islets, increased number and size of islets, enhanced pancreatic endocrine area, and reduction in islet endoplasmic reticulum (ER) stress markers [45]. ER stress is associated with insulin resistance and β -cell dysfunction in *db/db* mice and in islets obtained from T2D patients [46]. EGCG was shown to preserve islet morphology in EGCG treated *db/db* mice by reducing the expression of ER stress marker Ddit3 and its downstream targets Ppp1r15a and Cdkn1a [45]. Mitochondrial fatty acid transporter carnitine palmitoyltransferase I (L-Cpt-1) expression is induced in β -cells chronically exposed to fatty acids, and reduced L-Cpt-1 expression is proposed to positively affect GSIS [47]. Interestingly, EGCG reduced islet expression levels of L-CptI [45], suggesting that EGCG may improve insulin secretion from pancreatic β -cells.

The Goto-Kakizaki rat, a non-obese T2D animal model, exhibits enhanced oxidative stress, impaired glucose metabolism, and decreased mitochondrial content in skeletal muscle [48]. The key molecules of the mitochondrial autophagy pathway such as LC3B, Beclin1 and DRP1 are induced in the skeletal muscle of these rats [48]. Further, reactive oxygen species (ROS) were proposed to activate ERK and/or JNK and induce autophagy in skeletal muscle [48]. EGCG (100 mg/kg/day by gavage for 3 months) significantly reduced the expression levels of Beclin1 and DRP1 in skeletal muscle. EGCG regulated mitochondria-involved autophagy and ameliorated excessive muscle autophagy through down-regulation of the ROS/ERK/JNK-p53 pathway. EGCG also improved glucose metabolism and reduced oxidative stress in Goto-Kakizaki rats [48].

Collectively, EGCG can elicit a number of changes that are associated with beneficial effects on diabetes, including improvements in insulin secretion, glucose uptake, insulin resistance, glucose tolerance, oxidative stress, inflammation, and mitochondrial function. EGCG appears to act through multiple signaling pathways to exert these beneficial effects in diabetes.

Flavanones

Naringin and hesperidin, the two major flavanones, are rich in citrus fruits, with naringin responsible for the bitter flavors of grapefruit. Naringin has been reported to possess antioxidant, anti-diabetic, lipid-lowering, anti-atherogenic, and anti-inflammatory activities [18, 49, 50]. Both naringin and naringenin (the aglycone form of naringin) have been extensively studied in recent years [51–55].

In a streptozotocin (STZ)-induced model of diabetes in male albino rats, daily oral administration of 50 mg/kg hesperidin or naringin for one month ameliorated hyperglycemia and oxidative stress [56]. Dietary supplementation of hesperidin and naringin (200 mg/kg) was also associated with anti-hyperglycemic effects in C57BL/KsJ-*db/db* mice after 5 weeks of treatment [18]. In a similar study, 7-week old *db/db* mice that consumed diets supplemented with either hesperidin or naringin (200 mg/kg diet) for 5 weeks, displayed reductions in blood glucose levels, increases in plasma insulin and leptin concentrations, hepatic glucokinase (GK) activity and glycogen content, and attenuations in activity of

hepatic glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK), as compared to control animals [57]. GK, which is a regulatory enzyme of glycolysis, shows reduced activity, while PEPCK and G6Pase, key enzymes of gluconeogenesis, are elevated, in diabetes, due to hepatic insulin resistance leading to reduced glucose utilization and storage and increased glucose production and release [58, 59]. Thus, the anti-diabetic effects of naringin and hesperidin may primarily be due to reduction of hepatic glucose output via suppression of PEPCK and G6Pase expression, although the mechanism underlying the improvements in hepatic insulin sensitivity by these compounds are still unknown [18].

Glucose transport in different tissues is undesirably altered in diabetes and may be affected by anti-diabetic compounds. GLUT2 plays a key role in hepatic glucose output and is elevated in diabetic animals [59]. GLUT4 is the primary insulin-dependent transporter and is highly expressed in skeletal muscle and WAT [60]. GLUT4 overexpression in adipocytes improves glycemic control by ameliorating insulin resistance in diabetic *db/db* mice [60]. Insulin resistance is associated with reduced insulin-dependent glucose uptake in skeletal muscle and fat, and uncontrolled glucose release from the liver. Hesperidin and naringin treatment was associated with reduced protein expression of GLUT2 in the liver and enhanced expression of GLUT4 in WAT [18]. Hesperidin and naringin treatment also led to the activation of PPAR in liver and fat of diabetic *db/db* mice [18]. In addition to inducing fat cell differentiation, PPAR also improves glucose homeostasis by stimulating GLUT4 production and inhibiting PEPCK and G6Pase. Thus, hesperidin and naringin may improve hyperglycemia in T2D by regulating gene expression of glucose-regulating enzymes which may be mediated via PPAR, a major target of T2D drugs.

Sharma *et al.* determined the effect of oral administration of naringin (25, 50 and 100 mg/kg body weight) on metabolic parameters and β -cell function in T2D diabetic rats, where diabetes was induced through high-fat (HF) diet feeding coupled to low-dose STZ injection [61]. Naringin dose dependently ameliorated hyperglycemia, hyperinsulinemia and insulin resistance, and improved β -cell function. Further, naringin attenuated ER distention and preserved β -cell function in diabetic rats by maintaining an adequate pool of insulin secretory granules [61]. Heat shock proteins (HSP) are ubiquitous molecular chaperones induced in response to stressful conditions and protect cells against hyperglycemia, inflammation and oxidative stress [61–63]. Activation of PPAR and HSP ameliorated insulin resistance and diabetic complications by inhibiting NF- κ B and JNK activation [61, 62, 64, 65]. Naringin treatment was associated with increased expression of PPAR, HSP-72, and HSP-27 in the liver of diabetic rats [61]. Naringin also increased the phosphorylation of IRS1 (Tyr162) without alteration in the total IRS1 protein expression in liver which may be mediated via the increased expression of HSPs and PPAR [51]. Interestingly, the beneficial effect of naringin was comparable to rosiglitazone, one of the TZDs [61].

Collectively, these studies show the anti-diabetic properties of naringin and hesperidin, which may at least be partially mediated through the regulation of PPAR, although it is unclear if hesperidin and naringin are direct PPAR agonists. However, there is presently lack of data from clinical studies testing the anti-diabetic potential of these flavanones, which are needed to determine whether dietary intake of naringin or hesperidin is effective in the prevention or treatment of diabetes in humans.

Anthocyanidins

Anthocyanidins are widely distributed in the human diet through berries, fruits, vegetables, and red wine [17]. They are responsible for fruit and floral colors [66]. Anthocyanins have also received considerable attention due to their purported health benefits and potent antioxidant capabilities. However, challenges for using these compounds as nutraceuticals or

pharmaceuticals are that these compounds have low bioavailability as compared to other classes of flavonoids and the physiological mechanisms underlying the beneficial effects on health from dietary intake of anthocyanidins are unknown [67, 68]. More than 635 anthocyanin compounds have been identified, including the unmodified versions (anthocyanidin) as well as those modified by sugar and acetyl group attachments (anthocyanins) [68]. The six most commonly occurring anthocyanidins are cyanidin, delphinidin, malvidin, peonidin, pelargonidin, and petunidin [69]. In general, substantial studies reported the anti-obese and anti-diabetic effects of anthocyanins in various animal models [68]. Interestingly, the observed anti-diabetic action by this class of flavonoid seems beyond their antioxidant property.

Bilberries are one of the richest sources of anthocyanins [17]. Takikawa *et al.* evaluated the metabolic effects of bilberry extract (BBE) (27g BBE containing 10g anthocyanin/ kg diet) in mice with T2D [17]. Dietary BBE improved hyperglycemia and insulin sensitivity in diabetic mice by targeting AMPK, GLUT4, and metabolic enzymes. BBE increased total AMPK and phosphorylation of AMPK at Thr 172 and subsequently increased GLUT4 in WAT and skeletal muscle of diabetic mice, consistent with reports that activation of AMPK was shown to increase the expression of GLUT4 by an insulin-independent mechanism [70]. BBE downregulates the expression of gluconeogenic enzymes such as PEPCK and G6Pase and suppressed glucose flux into the blood [17]. Additionally, ACC, the key enzyme for fatty acid synthesis that is downstream of AMPK, was inactivated, whereas PPAR α , acyl-CoA oxidase, and carnitine palmitoyltransferase-1A were upregulated in the liver of BBE-supplemented diabetic mice [17]. Recently retinol-binding protein 4 (RBP4), an adipocytokine, was linked to obesity and insulin resistance [71], and it was proposed that targeting RBP4 may provide a treatment for T2D. Diabetic mice treated with BBE displayed reduced abundance of RBP4 in mesenteric fat [17]. These results further show that anthocyanins regulate glucose homeostasis by favorably modifying lipid metabolism.

In line with the above study, the anti-diabetic effect of anthocyanins extracted from black soybean seed coats was investigated in STZ-induced diabetic rats [72]. Soybean seed coats are rich in cyanidin, delphinidin and petunidin, where they reside as glycosides [73]. Anthocyanin extract (containing 72% cyanidine-3-glycoside, 20% delphinidin-3-glucoside, and 6% petunidin-3-glucoside) treatment (50 mg/kg for 30 days) by gavage ameliorated insulin resistance, increased serum insulin concentrations, and improved tissue glucose utilization in T1D rats [72]. Anthocyanins enhanced GLUT4 translocation to plasma membranes of skeletal muscle and thereby enhanced glucose uptake. Anthocyanins also improved insulin signaling by stimulating IR phosphorylation, leading to a greater tyrosine kinase activity in the β -subunit of the IR [72]. Moreover, anthocyanins increased β -cell viability and improved cellular function by protecting islet cells against apoptosis through up-regulation of Bcl-2 proteins, down-regulation of Bax, and cleavage of caspase-3 proteins in diabetic rats [72]. Further, the extract used in this study contains known amount of glycosides of anthocyanidins, the major bioactive components of berries. Interestingly, many of those observed effects of anthocyanins were reported to be stronger than those of glibenclamide, a pharmaceutical anti-diabetic agent.

Similarly, beneficial effects of an anthocyanidin mixture were reported in a study that used a HF diet-induced diabetic animal model. Four-week old C57Bl/6 mice were fed a HF diet (60 % kcal) for 6 weeks and supplementation of the diet with an anthocyanidin mixture (delphinidin, cyanidin and pelargonidin 3-O-galactosides; 1 g/kg diet) purified from *C. mas* reduced triglyceride content in the liver, increased plasma insulin levels, and preserved pancreatic islet architecture as compared with mice that consumed the un-supplemented HF diet [74]. The mice that consumed HF diet displayed enlarged islets with irregular structure and insulin staining, whereas islets from mice that consumed anthocyanidins resembled

those of the control mice [74]. In a similar study, 4-week old C57Bl/6J males were fed HF or control diet, some of which were supplemented at 2 g/kg of diet with purple corn color (PCC), a common food coloring ingredient that contains high amounts of cyanidin-3-O- β -D-glucoside [75]. After 12 weeks on the diets, mice that consumed the HF diet supplemented with PCC exhibited reduced body weight, liver triglycerides, blood glucose, insulin and leptin, and decreased lipogenic gene expression in liver and fat [75]. Dietary intake of PCC-supplemented diet reduced adiposity and improved overall glucose homeostasis and lipid metabolism [75].

There has also been interest in the anti-diabetic properties of Canadian lowbush blueberry (*Vaccinium angustifolium*), a fruit also used in traditional medicine that is rich in anthocyanin content [76]. Martineau et al. reported that blueberry plant extracts exerted beneficial effects in a variety of cell-based assays, with anthocyanidins-containing fruit extract being the only plant component that stimulated β -cell proliferation [77]. Several years later, it was reported that these effects were also observed in an in-vivo model [76].

It should be noted that anthocyanins in general have very low bioavailability (less than 1% of an oral dose in the serum) and they undergo changes in molecular conformation in response to pH [76]. For these reasons, Grace et al. dissolved various blueberry extracts and pure anthocyanins in Labrasol, a microemulsifying agent used to improve bioavailability of drug delivery [76]. Six-week old C57Bl/6J mice were fed a low fat or HF diet for 12 weeks, after which they were subjected to a single oral gavage after a 4-hour fasting [76]. At 6 hours post-ingestion, 500 mg/kg of phenolic-rich fractionated blueberry extract (287 mg/g total anthocyanins) and anthocyanin-rich fractionated blueberry extract (595 mg/g total anthocyanins), led to a 33 and 51% reduction in blood glucose concentrations, respectively, whereas metformin led to 27% reduction [76]. The malvidin glycosides are the most abundant anthocyanins in lowbush blueberry extracts and pure malvidin-3-O-glucoside (300 mg/kg BW) treatment reduced 34% of blood glucose in HF fed mice [76]. The anti-diabetic effects of delphinidin-3-O-glucoside [78], and delphinidin 3-sambubioside-5-glucoside, the major anthocyanins in Chilean blackberry (*Aristotelia chilensis*) were also reported in subsequent studies [79].

Bayberry fruit extract (BFE), which is rich in cyanidin-3-glucoside, was shown to protect against oxidative stress-induced pancreatic damage [80]. Pre-treatment of β -cells with BFE (containing 0.5 μ M cyanidin-3-glucoside) inhibited hydrogen peroxide-induced cell death, mitochondrial ROS production, and cell necrosis [80]. BFE also up-regulated PDX-1 gene expression associated with the increased levels of insulin-like growth factor-II gene transcript and insulin [80]. Further, administration of BFE (150 μ g of Cyanidin-3-glucoside/10 g of body weight twice per day) significantly reduced blood glucose and improved glucose tolerance in STZ-induced diabetic mice [80].

In addition to the above studies which focused on anthocyanidin mixtures (containing known amount of anthocyanidins or anthocyanins), there are few studies that specifically focused on the pure anthocyanidin or their glycosides. Pelargonidin (3 mg/kg, ip, single dose) was shown to restore glucose tolerance and serum insulin and antioxidant enzyme concentrations in STZ-induced diabetic rats [81]. These results were quite dramatic, given that a single moderate dose of pelargonidin completely reversed diabetes within a week and the beneficial effects were still observed 5 weeks later [81].

The bioactive components of most berries and cherries exist as glycosides of anthocyanidins. In traditional Chinese medicine, dried cherries from *Cornus* spp. have been used as a therapeutic strategy to combat diabetes [82]. The bioactive components of *Cornus* fruits are anthocyanins such as cyanidin-, delphinidin-, and pelargonidin glycosides [83, 84].

The effect of anthocyanidins and anthocyanins extracted from *Cornus mas* fruits on insulin secretion in rodent pancreatic β -cells (INS-1) was reported in a recent study [83]. A 60-minute treatment of INS-1 cells with different anthocyanins and anthocyanidins revealed that cyanidin-3-glucoside and delphinidin-3-glucoside augmented GSIS, while cyanidin-3-galactoside, pelargonidin-3-galactoside, and aglycones cyanidin, delphinidin, pelargonidin, malvidin, and petunidin had negligible to marginal effects on GSIS [83]. Consistently, cyanidin-3-glucoside (50 μ M) and its metabolite protocatechuic acid were shown to increase glucose uptake and GLUT4 membrane translocation in human and murine adipocytes [85]. Further, cyanidin-3-glucoside increased nuclear PPAR α activity and expressions of adiponectin and GLUT4. It was proposed that cyanidine-3-glucoside and its metabolite may exert insulin-like activity by regulating the internalization of glucose through the PPAR signaling pathway [85].

Dietary cyanidin 3-glucoside (0.2% in diet) was shown to improve fasting glucose and insulin sensitivity in both HF diet fed and obese *db/db* mice [86]. Further it also reduced the serum concentrations and mRNA abundance of inflammatory cytokines such as TNF α , interleukin-6, and monocyte chemoattractant protein-1, and suppressed macrophage infiltration in adipose tissue [86]. FoxO1 is one of the important transcriptional mediators of insulin signaling in many cells including pancreatic β -cells [87], adipocytes [88], and hepatocytes [89]. FoxO1 is regulated differentially in the fasted and fed state by its phosphorylation and intracellular localization. FoxO1 induces the expression of gluconeogenic enzymes in the fasted state by its nuclear translocation whereas in the fed state insulin induced Akt-mediated phosphorylation of FoxO1 leads to the suppression of gluconeogenesis [86]. In the fed state, dietary cyanidin 3-glucoside was shown to down-regulate G6Pase and PEPCK by enhancing the phosphorylation of Akt and FoxO1 and by decreasing the nuclear translocation of FoxO1 in liver and adipose tissues of HF diet-fed and *db/db* mice [86]. Moreover, cyanidin 3-glucoside treatment decreased JNK activation and promoted phosphorylation and nuclear exclusion of FoxO1. Guo et al. proposed that cyanidin 3-glucoside exerts anti-diabetic effects by modulating the JNK/FoxO1 signaling pathway and the related inflammatory adipokines [86].

In line with the above *in vitro* and *in vivo* studies, the anti-diabetic effects of anthocyanins were also reported in human intervention trials and cohort studies. Dietary supplementation with blueberry extracts improved insulin sensitivity in obese, non-diabetic, insulin resistant participants [90]. Further, berry puree (made from bilberries, blackcurrants, cranberries and strawberries) delayed and attenuated the glycemic response in healthy subjects [91]. A study that analyzed data from 3 prospective cohort studies involving 200,000 US men and women [19] reported an inverse association between consumption of anthocyanins/anthocyanin-rich foods and T2D [19]. In the same study, in secondary analyses of individual anthocyanins, a strongest association for cyanidin was observed whereas weaker association for delphinidin, malvidin, peonidin, and petunidin. Pelargonidin was not inversely associated with diabetes risk.

Collectively, anthocyanins and its glycosides alone or in combination improve glucose homeostasis by influencing β -cell mass and function, insulin sensitivity, glucose uptake, and insulin signaling animal models. Moreover, there appears to be a strong association between anthocyanin intake and healthy glucose regulation in humans.

Flavonols

Flavonols are the most common flavonoids and are dispersed throughout the plant kingdom with the exception of algae and fungi. The main dietary flavonols are kaempferol, quercetin, fisetin, isorhamnetin, and myricetin that are mainly found as glycosides [66]. Some

flavonols, such as fisetin, were reported to be activators of sirtuins [92] and inhibitors of DNA methyltransferase enzymes [93].

Fisetin is a tetrahydroxyflavone found in fruits and vegetables. The anti-diabetic effect of fisetin was reported in a study conducted with STZ-induced diabetic rats [94]. Fisetin oral treatment (10 mg/kg body weight/day for 30 days) reduced blood glucose and A1C levels and increased plasma insulin concentrations. Fisetin increased the activities of hexokinase, pyruvate kinase, glucose-6-phosphate dehydrogenase whereas suppressed the activities of lactate dehydrogenase, G6Pase, fructose-1,6-biphosphatase in hepatic and renal tissues of STZ-diabetic rats [94]. Further, fistein treatment increased the glycogen content and the activity of glycogen synthase whereas it suppressed glycogen phosphorylase, suggesting that fisetin may improve glucose homeostasis by modulating these regulatory enzymes of carbohydrate metabolism [94]. However, it is unclear how fisetin increases plasma insulin levels in insulin-dependent diabetic rats.

We recently reported the cytoprotective effects of kaempferol in clonal INS-1E β -cells and pancreatic human islets under conditions of glucotoxicity and lipotoxicity [14]. We found that kaempferol dose-dependently improved cell viability and suppressed apoptosis in β -cells and pancreatic human islets with kaempferol exerting maximal effects at 10 μ M [14]. Consistent with our findings, others showed that kaempferol (10 μ M) protected insulin-secreting HIT-T15 cells from 2-deoxy-D-ribose toxicity, an effect that was mediated through suppression of lipid peroxidation. In addition, kaempferol improved the synthesis and secretion of insulin in β -cells and islets [14]. It is well documented that activation of the cAMP/PKA and PI3K/Akt pathways protects β -cells from apoptosis [14, 95–97]. The cAMP-mediated signaling was associated with many beneficial effects on β -cells, such as amplification of GSIS, regulation of insulin gene expression, and promotion of β -cell survival, all of which were attenuated by chronic hyperglycemia or hyperlipidemia [14, 98–100]. Kaempferol suppressed high glucose- or high palmitate-induced caspase-3 activity and prevented the glucotoxicity- or lipotoxicity-induced down-regulation of anti-apoptotic proteins Akt and Bcl-2 [14, 101]. High glucose or high palmitate diminished the production of intracellular cAMP, PKA activation, and cAMP response element-binding protein (CREB) phosphorylation in β -cells and islets [14, 101], which play a critical role in the cytoprotective effect of kaempferol of the islets. We further demonstrated that kaempferol upregulates PDX-1, which is responsible for the improved cellular function associated with enhanced β -cell survival and function, including improved cAMP signaling and anti-apoptotic protein expression [101]. This observation is very interesting as many structurally related flavonoid compounds have no such effect on PDX-1. These findings demonstrate that kaempferol may be a novel anti-diabetic agent, given the critical roles of PDX-1 in β -cell proliferation and normal function and the evidence that PDX-1 reduction impairs glucose homeostasis in both rodents and human. However, the biological relevance of these in vitro findings is not clear, and there is presently no study showing that this flavonol exerts an anti-diabetic effect in vivo.

Eid *et al.* investigated the effects of quercetin-rich extract from the berry *Vaccinium vitis idaea* and active principle components of the berries on glucose uptake in C2C12 myoblasts [16]. Berry extract was shown to stimulate an insulin-independent AMPK pathway in muscle cells and mildly inhibit adenosine diphosphate (ADP)-stimulated oxygen consumption in isolated mitochondria [16]. It is interesting to note that this mechanism is analogous to that of metformin. Further, quercetin derivatives (quercetin-3-O-glucoside and quercetin-3-O-galactoside) and quercetin aglycone isolated from berry extract, enhanced insulin-independent glucose uptake and stimulated AMPK in muscle cells. However, ATP synthase in isolated mitochondria was inhibited only by quercetin aglycone indicating that the removal of the carbohydrate moiety is required for this activity [16]. This study

suggested that quercetin and its derivatives are the major bioactive components of berry that are responsible for the activation of AMPK and subsequent stimulation of glucose uptake in muscle cells. However the dosage of quercetin and its derivatives (50 μ M) used in this study may be too high to be physiologically achievable.

The anti-diabetic effect of quercetin was also investigated in STZ-induced diabetic mice [102]. Dietary supplementation with quercetin (0.5% in diet for two weeks) lowered blood glucose and enhanced serum insulin concentrations in STZ-induced diabetic mice. Further, quercetin supplementation up-regulated the genes associated with cell proliferation and survival in the liver [102]. Quercetin inhibits *Cdkn1a* expression leading to the recovery of cell proliferation in liver and pancreas [102]. In a subsequent study, intraperitoneal (i.p.) injection of quercetin (10 or 15 mg/kg body weight for 10 days) to STZ-induced diabetic rats reduced hyperglycemia and improved glucose tolerance, increased hepatic glucokinase activity, reduced plasma cholesterol and triglycerides, and preserved islet mass [103]. Consistently, another study confirmed that i.p. injection of quercetin has a protective effect against pancreatic islet damage in STZ-induced diabetic rats [104]. In addition, quercetin supplementation (0.04% in diet) was shown to reduce blood glucose and improve insulin resistance in obese diabetic mice [105], suggesting that this flavonol may exert anti-diabetic effects in T2D.

Few studies focused on the direct effect of quercetin on insulin secreting cells. Quercetin (20 μ M) potentiated GSIS and protected INS-1 cells against oxidative stress through the ERK1/2 pathway [106]. Not only quercetin but also its glycoside quercitrin was shown to protect clonal β -cells against cytokine-induced cell death [107]. Both quercetin and quercitrin improve GSIS, inhibit oxidative stress and suppress nitric oxide accumulation which is associated with the reduced expression of inducible nitric oxide synthase (iNOS) and suppressed translocation of nuclear-factor κ B (NF- κ B) [107]. Further they attenuate mitochondrial apoptosis in RINm5F cells by suppressing cytochrome c release [107] and it was suggested that quercetin and quercitrin can prevent β -cell death via suppression of NF- κ B [107].

The control of postprandial hyperglycemia is an important component of diabetes management. One such strategy is to reduce intestinal digestion of complex carbohydrates by inhibiting intestinal membrane-bound α -glucosidases, which hydrolyze oligosaccharides, disaccharides, and trisaccharides to glucose. Li *et al.* evaluated the inhibitory effect of quercetin, isoquercetin, and rutin (quercetin-3-O-rutinoside) isolated from tartary buckwheat bran on α -glucosidases in a cell free system and compared their effects with an α -glucosidase inhibitor acarbose [108], an anti-diabetic drug used to treat T2D. It was found that all three flavonoids form complexes with α -glucosidases through hydrophobic binding and inhibit the enzyme activity, with quercetin exerting more potent effect than that of acarbose [108]. However, it is unclear whether this inhibitory effect of quercetin on α -glucosidases is specific, which is important for nutritional or pharmacological use of this compound to reduce postprandial glucose load, because it was found that some α -glucosidase inhibitors such as acarbose also cause inhibition of α -amylase [109–111], resulting in undigested starch entering the large intestine and getting fermented by bacteria present there [110, 112], which cause abdominal discomfort, diarrhea, and flatulence [111, 113].

In summary, the hypoglycemic effect of quercetin was reported in various animal studies whereas there are limited studies on the anti-diabetic effects of fistein, kaempferol, and rutin. Quercetin may exert its anti-diabetic effects in diabetic animals by inhibiting intestinal starch digestion and hepatic glucose production, improving skeletal muscle uptake of glucose, as well as protecting against pancreatic islet damage. However, the detailed

mechanism explaining the anti-diabetic action of quercetin needs to be further determined. In addition, it is unclear whether dietary intake of this flavonol or others in this class of flavonoid can improve energy metabolism and glucose homeostasis in humans.

Flavones

Flavones are found in celery, parsley and many herbs [66]. The major dietary flavones are apigenin and luteolin. For hundreds of years, plants containing apigenin, such as passion flower and chamomile, have been used in traditional medicine to treat a variety of ailments and apigenin has been recognized as a potential chemopreventive agent [114]. However, studies testing the anti-diabetic effect of this flavone are very limited. In alloxan-induced insulin-dependent diabetic mice, oral infusion of apigenin (0.78 mg/kg body weight) for 10 days reversed the reduction in hepatic antioxidants, such as catalase, superoxide dismutase and glutathione, and it was suggested that flavones have free-radical scavenging activity, similar to other flavonoid compounds [115]. Apigenin treatment also reduced hyperglycemia, hepatic G6Pase and serum cholesterol in alloxan-induced diabetic mice, while increasing serum insulin, in comparison to control diabetic mice [115]. Similarly, i.p. administration (4 mg/kg BW) of apigenin to STZ-induced diabetic rats resulted in a significant anti-hyperglycemic effect [116]. In HIT-T15 clonal β -cells, apigenin treatment (10 μ M) attenuated 2-Deoxy-D-ribose-induced apoptosis, due to its antioxidant effect and protective action against mitochondrial impairment by improving mitochondrial membrane potential [117]. Similarly, apigenin and luteolin treatment protected RIN cells from interleukin-1 β and interferon- γ -induced apoptosis, through inhibition of NF- κ B activation and iNOS expression [118]. However, it is unclear whether the antioxidant and cytoprotective properties of flavones in cultured β -cells also confer similar protective effects to islets in vivo.

While it is unknown, to the best of our knowledge, whether apigenin has an anti-diabetic effect in T2D, it was reported that in HepG2 hepatocytes, apigenin increased phosphorylation of AMPK [119]. Surprisingly, this effect of apigenin is 200 times the potency of that elicited by metformin [119], a well-known activator of AMPK. Consistently, apigenin was also found to inhibit ACC phosphorylation and prevent lipid accumulation in HepG2 cells exposed to high glucose and this effect of apigenin is dependent of AMPK [119]. Given these data, it is tempting to speculate that apigenin may have beneficial effects on dyslipidemia and diabetes by regulating the AMPK-dependent energy metabolism, an aspect that should be further investigated.

In vitro studies showed that luteolin is an effective maltase inhibitor ($IC_{50}=2.3$ mM), with kaempferol, chrysin and galangin exerting less potent inhibition [120]. The inhibition by luteolin, however, was much less effective than acarbose, and doses of up to 200 mg/kg did not suppress monosaccharide production in the gut of rats, suggesting that luteolin may not be an effective substitute for acarbose [120]. Luteolin was demonstrated to improve insulin sensitivity and enhance Akt2 phosphorylation in adipocytes via activation of PPAR γ [121] whereas another study reported that luteolin inhibited adipogenesis and PPAR γ expression [122]. Hence further studies are needed to confirm the specific effects of luteolin on PPAR γ .

Altogether, there are a limited number of studies on the anti-diabetic effects of flavones and their signaling mechanisms as compared to other flavonoids. Findings from in vitro studies that flavones protect β -cell function and activates the signaling pathways promoting fuel metabolism and insulin sensitization in hepatocytes and adipocytes suggest that flavones may have potential to exert an anti-diabetic effect in vivo.

Isoflavones

Isoflavones are found mainly in leguminous plants and Chinese herb medicines *Genista tinctoria* Linn and *Sophora subprostrata* Chun et T.Chen [123]. The major dietary isoflavones are daidzein and genistein, which are present primarily in soy foods [66]. A number of human, animal, and cell-culture studies reported the anti-diabetic effects of genistein [124–133]. Dietary supplementation of genistein led to improved glucose metabolism and insulin levels in T1D animals [123, 134]. An earlier study suggested that genistein exerts anti-diabetic effects by improving plasma lipids [135], thereby increasing insulin sensitivity. Consistent with this, a recent study confirmed that mice fed a soy-supplemented diet (containing approximately 198 ppm daidzein and 286 ppm genistein) from conception to adulthood displayed an improved lipid profile and glucose metabolism [125]. In this study, soy intake led to increased phosphorylation of AMPK and favorable metabolic changes associated with AMPK activation, including phosphorylation and inactivation of ACC, enhanced mitochondrial biogenesis and expression of genes involved in peroxisomal fatty acid oxidation, and increased glucose uptake in skeletal muscle [125]. This is consistent with other reports attributing the beneficial effects of dietary soy to activation of AMPK in peripheral tissues, similar to other flavonoids [125]. However, the physiological effects of specific flavonoids in soy were not evaluated in this study and the effects may have been due to isoflavones or other constituents of the soy protein. In contrast to these results, data from many previous studies have demonstrated only either a moderate positive effect [126–129] or a neutral effect [136–139] of dietary intake of isoflavones on plasma lipid profile, suggesting that the anti-diabetic action of isoflavones may not be ascribed to their potential hypolipidemic effect. Indeed, recent findings indicated that isoflavone administration lowered plasma glucose even though plasma lipid profile or insulin sensitivity was unaffected in obese and diabetic animals [140]. Therefore, there is the possibility that the effects of an isoflavone mix, genistein, or soy protein may affect metabolism differently in vivo.

Dietary supplementation of genistein or daidzein (0.02% in diet) has been shown to prevent diabetes onset and improve glucose homeostasis in non-obese diabetic (NOD) mice by preserving pancreatic β -cell function [130]. There was an increased insulin/glucagon ratio, insulin staining in β -cells and C-peptide concentration in NOD mice that consumed genistein or daidzein [130]. In this study, isoflavone supplementation was also associated with suppression of activity of the gluconeogenic enzymes PEPCK and G6Pase, as well as α -oxidation of fatty acids, and increased lipogenesis in the liver [130]. Recently we reported the beneficial effect of genistein in a non-genetic mouse model that shares the metabolic characteristics of human T2D with insulin resistance and reduced β -cell mass and function. Specifically, about middle-aged mice that ingested diets containing 250 mg/kg genistein displayed reduced fasting glucose and twice the β -cell mass as compared to the control [131]. Consistent with this observation, genistein improved hyperglycemia, glucose tolerance, and circulating insulin concentrations with significant enhancement of islet β -cell proliferation, survival, and mass in STZ-induced diabetic mice [12].

Emerging studies provide evidence that genistein directly affects β -cell proliferation, GSIS, and β -cell apoptosis. Several studies found that genistein stimulates insulin secretion from clonal β -cells [141] and islets [132, 133], while other studies found an inhibitory effect on insulin secretion [142, 143]. The reason for this discrepancy is not clear. Nevertheless, the concentrations (>30 M) used in most of these studies are well above those physiologically achievable by dietary means (<5 M). In a number of recent studies to investigate the direct effects of genistein on β -cells [12, 144, 145], it was demonstrated that genistein enhanced GSIS and β -cell mass in clonal insulin-secreting cell lines (INS-1 and MIN6), fresh mouse and human islets, and mouse models of T1D and T2D, at a range of physiologically achievable concentrations (10 nM to 5 μ M) [131, 144–146]. Interestingly, genistein induced

the protein expression of cyclin D1, a major cell-cycle regulator required for growth in β -cells [12].

Genistein may exert its effect on β -cells by acting through multiple signaling pathways. In a recent study, activation of Calmodulin kinase II (CaMK II) and Ca^{2+} signaling was shown to play a significant role in genistein-induced potentiation of insulin secretion [147]. Genistein (5 μM) was also shown to prevent cytokine-induced pathological alterations in β -cell function through suppression of the NF- κB , ERK-1/2 and JAK/STAT pathways [148]. Interestingly, the mitogenic and insulinotropic effects of genistein in β -cells are not related to its known activities as an antioxidant, estrogen receptor agonist or protein tyrosine kinase inhibitor, but are mediated via activation of the cAMP/PKA cascade [144]. Genistein induced the proliferation of both INS1 and human islet β -cells through activation of the cAMP/PKA-dependent ERK1/2 signaling pathway [12]. This result is different from a previous study where genistein was shown to suppress ERK1/2 [148]. While the exact reason for this discrepancy is unknown, this could be due to the difference in the experimental design and it also indicates that genistein can act differentially on ERK1/2. The effect of genistein on β -cell proliferation may be structure-specific, and the hydroxyl group at the 5C position on the A ring may be crucial for the unique effect of genistein, because equol and 17 β -estradiol which lack 5C hydroxyl group fail to exert such an effect [124]. While there are many *in vitro* and animal studies in this field, human studies investigating the effect of genistein on glucose homeostasis are limited [124]. A recent intervention trial showed that daily isoflavone intake (100 mg of aglycones) for one year improved insulin sensitivity and blood lipid parameters in post-menopausal women with T2D [149]. However, in another trial, consumption of isoflavones (132 mg) for 3 months did not improve plasma A1C, blood glucose, and insulin in postmenopausal women with T2D [150]. This disparity could be due to the difference in the treatment dosage and duration.

Collectively, genistein exerts its beneficial effects on glucose homeostasis by influencing β -cell mass and function, and insulin signaling in animal models. Genistein appears to target the cAMP/PKA pathway although the specific ligand-receptor interaction controlling this signaling pathway is still unknown. While these findings are encouraging, there are few clinical studies that support the hypoglycemic effect of genistein and therefore further research is clearly warranted.

Conclusions

Epidemiological, animal, and *in vitro* studies support the anti-diabetic effects of many dietary flavonoids. Dietary flavonoids exert their anti-diabetic effects by targeting various cellular signaling pathways in pancreas, liver, skeletal muscle, and WAT. Flavonoids exert their effects by influencing β -cell mass and function, as well as energy metabolism and insulin sensitivity in peripheral tissues. Most of the studies discussed in this review also focused on the specific signaling pathways involved in the effects of flavonoids on glucose homeostasis. Anti-diabetic effects of flavonoids may be due to antioxidant, enzyme inhibition, receptor agonist or antagonist activity or through novel mechanisms yet to be elucidated. It is encouraging that some of the flavonoids are comparable in function to the clinically used anti-diabetic drugs and that novel anti-diabetic effects are continuously identified. Emerging evidence indicates that some metabolites of dietary flavonoids act through multiple components of signaling cascades to exert their modulatory effects in different cell types [66]. However, studies on the anti-diabetic effects of metabolites of dietary flavonoids are scarce and it is therefore presently unknown whether certain metabolites from ingested flavonoids may mediate various biological actions of their parent molecules, which is an interesting question. In addition, studies on the structure-activity relationships of flavonoids are needed to precisely understand whether and how flavonoid

molecules interact with the cellular components. Finally, carefully designed human trials are required to further evaluate the potential of some dietary flavonoids to prevent or treat T2D.

Abbreviations

ACC	Acetyl Co-A carboxylase
ADP	Adenosine diphosphate
AMPK	Adenosine monophosphate-activated protein kinase
ATP	Adenosine triphosphate
BBE	Bilberry extract
BFE	Bayberry fruit extract
CaMK II	Calmodulin kinase II
cAMP	cyclic Adenosine mono phosphate
CREB	cAMP response element-binding protein
DM	Diabetes Mellitus
ECG	Epicatechin gallate
EGC	Epigallocatechin
EGCG	Epigallocatechin gallate
ER	Endoplasmic reticulum
FFA	Free fatty acid
FoXO1	Forkhead box protein O1
G6Pase	Glucose-6-phosphatase
GK	Glucokinase
GLUT	Glucose transporter
GSIS	Glucose-stimulated insulin secretion
HSP	Heat shock proteins
i.p.	Intraperitoneal
IR	Insulin receptor
IRS	Insulin receptor substrate
JNK	c-jun amino terminal kinase
L-cpt-1	Carnitine palmitoyltransferase I
LKB1	AMPK-activating protein kinase
MAPK	Mitogen activated protein kinase
NF- B	Nuclear-factor- B
NOD	Non-obese diabetic mice
PDX-1	Pancreatic duodenal homeobox-1
PEPCK	Phosphoenolpyruvate carboxykinase
PGC-1	Peroxisome proliferator-activated receptor gamma coactivator-1-

PKC	Protein kinase C
PPAR	peroxisome proliferator activated receptor
RBP4	Retinol binding protein-4
RIN cells	Rat insulinoma cells
ROS	Reactive oxygen species
STZ	Streptozotocin
T1D	Type 1 Diabetes Mellitus
T2D	Type 2 Diabetes Mellitus
TNF	Tumor necrosis factor
TZD	Thiazolidinedione
WAT	White adipose tissue

References

- Philippe J, Raccach D. Treating type 2 diabetes: how safe are current therapeutic agents? *Int J Clin Pract.* 2009; 63:321–332. [PubMed: 19196370]
- Akkati S, Sam KG, Tungha G. Emergence of promising therapies in diabetes mellitus. *J Clin Pharmacol.* 2011; 51:796–804. [PubMed: 20705952]
- Fonseca VA, Kirkman MS, Darsow T, Ratner RE. The American Diabetes Association diabetes research perspective. *Diabetes.* 2012; 61:1338–1345. [PubMed: 22618769]
- UnitedHealth Center for Health Reform & Modernization. The united states of diabetes: challenges and opportunities in the decade ahead. Working paper 5. 2010 Nov.
- Hanhineva K, Torronen R, Bondia-Pons I, Pekkinen J, Kolehmainen M, Mykkanen H, et al. Impact of dietary polyphenols on carbohydrate metabolism. *Int J Mol Sci.* 2010; 11:1365–1402. [PubMed: 20480025]
- Manach C, Scalbert A, Morand C, Remesy C, Jimenez L. Polyphenols: food sources and bioavailability. *Am J Clin Nutr.* 2004; 79:727–747. [PubMed: 15113710]
- Beecher GR. Overview of dietary flavonoids: nomenclature, occurrence and intake. *J Nutr.* 2003; 133:3248S–3254S. [PubMed: 14519822]
- Chun OK, Chung SJ, Song WO. Estimated dietary flavonoid intake and major food sources of U.S. adults. *J Nutr.* 2007; 137:1244–1252. [PubMed: 17449588]
- Graf BA, Milbury PE, Blumberg JB. Flavonols, flavones, flavanones, and human health: epidemiological evidence. *J Med Food.* 2005; 8:281–290. [PubMed: 16176136]
- Arts IC, Hollman PC. Polyphenols and disease risk in epidemiologic studies. *Am J Clin Nutr.* 2005; 81:317S–325S. [PubMed: 15640497]
- Cai EP, Lin JK. Epigallocatechin gallate (EGCG) and rutin suppress the glucotoxicity through activating IRS2 and AMPK signaling in rat pancreatic beta cells. *J Agric Food Chem.* 2009; 57:9817–9827. [PubMed: 19803520]
- Fu Z, Zhang W, Zhen W, Lum H, Nadler J, Bassaganya-Riera J, et al. Genistein induces pancreatic beta-cell proliferation through activation of multiple signaling pathways and prevents insulin-deficient diabetes in mice. *Endocrinology.* 2010; 151:3026–3037. [PubMed: 20484465]
- Fu Z, Zhen W, Yuskavage J, Liu D. Epigallocatechin gallate delays the onset of type 1 diabetes in spontaneous non-obese diabetic mice. *Br J Nutr.* 2011; 105:1218–1225. [PubMed: 21144096]
- Zhang Y, Liu D. Flavonol kaempferol improves chronic hyperglycemia-impaired pancreatic beta-cell viability and insulin secretory function. *Eur J Pharmacol.* 2011; 670:325–332. [PubMed: 21914439]
- Zhu W, Jia Q, Wang Y, Zhang Y, Xia M. The anthocyanin cyaniding-3-O-beta-glucoside, a flavonoid, increases hepatic glutathione synthesis and protects hepatocytes against reactive oxygen

- species during hyperglycemia: Involvement of a cAMP-PKA803 dependent signaling pathway. *Free Radic Biol Med*. 2012; 52:314–327. [PubMed: 22085656]
16. Eid HM, Martineau LC, Saleem A, Muhammad A, Vallerand D, Benhaddou-Andaloussi A, et al. Stimulation of AMP-activated protein kinase and enhancement of basal glucose uptake in muscle cells by quercetin and quercetin glycosides, active principles of the antidiabetic medicinal plant *Vaccinium vitis-idaea*. *Mol Nutr Food Res*. 2010; 54:991–1003. [PubMed: 20087853]
 17. Takikawa M, Inoue S, Horio F, Tsuda T. Dietary anthocyanin-rich bilberry extract ameliorates hyperglycemia and insulin sensitivity via activation of AMP-activated protein kinase in diabetic mice. *J Nutr*. 2010; 140:527–533. [PubMed: 20089785]
 18. Jung UJ, Lee MK, Park YB, Kang MA, Choi MS. Effect of citrus flavonoids on lipid metabolism and glucose-regulating enzyme mRNA levels in type-2 diabetic mice. *Int J Biochem Cell Biol*. 2006; 38:1134–1145. [PubMed: 16427799]
 19. Wedick NM, Pan A, Cassidy A, Rimm EB, Sampson L, Rosner B, et al. Dietary flavonoid intakes and risk of type 2 diabetes in US men and women. *Am J Clin Nutr*. 2012; 95:925–933. [PubMed: 22357723]
 20. Erdman JW Jr, Balentine D, Arab L, Beecher G, Dwyer JT, Folts J, et al. Flavonoids and heart health: proceedings of the ILSI North America Flavonoids Workshop, May 31-June 1, 2005, Washington, DC. *J Nutr*. 2007; 137:718S–737S. [PubMed: 17311968]
 21. Withers DJ, Gutierrez JS, Towery H, Burks DJ, Ren JM, Previs S, et al. Disruption of IRS-2 causes type 2 diabetes in mice. *Nature*. 1998; 391:900–904. [PubMed: 9495343]
 22. Kim SJ, Winter K, Nian C, Tsuneoka M, Koda Y, McIntosh CH. Glucose-dependent insulinotropic polypeptide (GIP) stimulation of pancreatic beta-cell survival is dependent upon phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB) signaling, inactivation of the forkhead transcription factor Foxo1, and down827 regulation of bax expression. *J Biol Chem*. 2005; 280:22297–22307. [PubMed: 15817464]
 23. Buteau J, Accili D. Regulation of pancreatic beta-cell function by the forkhead protein FoxO1. *Diabetes Obes Metab*. 2007; 9 Suppl 2:140–146. [PubMed: 17919188]
 24. Zhang Z, Ding Y, Dai X, Wang J, Li Y. Epigallocatechin-3-gallate protects pro831 inflammatory cytokine induced injuries in insulin-producing cells through the mitochondrial pathway. *Eur J Pharmacol*. 2011; 670:311–316. [PubMed: 21925162]
 25. Li D, Ueta E, Kimura T, Yamamoto T, Osaki T. Reactive oxygen species (ROS) control the expression of Bcl-2 family proteins by regulating their phosphorylation and ubiquitination. *Cancer sci*. 2004; 95:644–650. [PubMed: 15298726]
 26. Low IC, Chen ZX, Pervaiz S. Bcl-2 modulates resveratrol-induced ROS production by regulating mitochondrial respiration in tumor cells. *Antioxid Redox Signal*. 2010; 13:807–819. [PubMed: 20367277]
 27. Deng YT, Chang TW, Lee MS, Lin JK. Suppression of free fatty acid-induced insulin resistance by phytopolyphenols in C2C12 mouse skeletal muscle cells. *J Agric Food Chem*. 2012; 60:1059–1066. [PubMed: 22191431]
 28. Boden G. Role of fatty acids in the pathogenesis of insulin resistance and NIDDM. *Diabetes*. 1997; 46:3–10. [PubMed: 8971073]
 29. Boden G, Chen X, Capulong E, Mozzoli M. Effects of free fatty acids on gluconeogenesis and autoregulation of glucose production in type 2 diabetes. *Diabetes*. 2001; 50:810–816. [PubMed: 11289046]
 30. Dong Z. Effects of food factors on signal transduction pathways. *Biofactors*. 2000; 12:17–28. [PubMed: 11216482]
 31. Steinberg GR, Kemp BE. AMPK in Health and Disease. *Physiol Rev*. 2009; 89:1025–1078. [PubMed: 19584320]
 32. Bergeron R, Previs SF, Cline GW, Perret P, Russell RR 3rd, Young LH, et al. Effect of 5-aminoimidazole-4-carboxamide-1-beta-D-ribofuranoside infusion on in vivo glucose and lipid metabolism in lean and obese Zucker rats. *Diabetes*. 2001; 50:1076–1082. [PubMed: 11334411]
 33. Jorgensen SB, Wojtaszewski JF, Viollet B, Andreelli F, Birk JB, Hellsten Y, et al. Effects of alpha-AMPK knockout on exercise-induced gene activation in mouse skeletal muscle. *FASEB J*. 2005; 19:1146–1148. [PubMed: 15878932]

34. Carling D, Sanders MJ, Woods A. The regulation of AMP-activated protein kinase by upstream kinases. *Int J Obes (Lond)* (2005). 2008; 32(Suppl 4):S55–S59.
35. Witczak CA, Sharoff CG, Goodyear LJ. AMP-activated protein kinase in skeletal muscle: from structure and localization to its role as a master regulator of cellular metabolism. *Cell Mol Life Sci*. 2008; 65:3737–3755. [PubMed: 18810325]
36. Jager S, Handschin C, St-Pierre J, Spiegelman BM. AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC-1 α . *Proc Natl Acad Sci USA*. 2007; 104:12017–12022. [PubMed: 17609368]
37. Canto C, Gerhart-Hines Z, Feige JN, Lagouge M, Noriega L, Milne JC, et al. AMPK regulates energy expenditure by modulating NAD⁺ metabolism and SIRT1 activity. *Nature*. 2009; 458:1056–1060. [PubMed: 19262508]
38. Wu Z, Puigserver P, Andersson U, Zhang C, Adelmant G, Mootha V, et al. Mechanisms controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1. *Cell*. 1999; 98:115–124. [PubMed: 10412986]
39. Puigserver P, Wu Z, Park CW, Graves R, Wright M, Spiegelman BM. A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. *Cell*. 1998; 92:829–839. [PubMed: 9529258]
40. Holmes BF, Kurth-Kraczek EJ, Winder WW. Chronic activation of 5'-AMP-activated protein kinase increases GLUT-4, hexokinase, and glycogen in muscle. *J Appl Physiol*. 1999; 87:1990–1995. [PubMed: 10562646]
41. Zhang BB, Zhou G, Li C. AMPK: an emerging drug target for diabetes and the metabolic syndrome. *Cell Metab*. 2009; 9:407–416. [PubMed: 19416711]
42. Yu LF, Qiu BY, Nan FJ, Li J. AMPK Activators as Novel Therapeutics for Type 2 Diabetes. *Curr Top Med Chem*. 2010
43. Lemieux K, Konrad D, Klip A, Marette A. The AMP-activated protein kinase activator AICAR does not induce GLUT4 translocation to transverse tubules but stimulates glucose uptake and p38 mitogen-activated protein kinases α and β in skeletal muscle. *FASEB J*. 2003; 17:1658–1665. [PubMed: 12958172]
44. Green CJ, Macrae K, Fogarty S, Hardie DG, Sakamoto K, Hundal HS. Counter-modulation of fatty acid-induced pro-inflammatory nuclear factor κ B signalling in rat skeletal muscle cells by AMP-activated protein kinase. *Biochem J*. 2011; 435:463–474. [PubMed: 21323644]
45. Ortsater H, Grankvist N, Wolfram S, Kuehn N, Sjöholm A. Diet supplementation with green tea extract epigallocatechin gallate prevents progression to glucose intolerance in db/db mice. *Nutr Metab (Lond)*. 2012; 9:11. [PubMed: 22333133]
46. Laybutt DR, Preston AM, Akerfeldt MC, Kench JG, Busch AK, Biankin AV, et al. Endoplasmic reticulum stress contributes to beta cell apoptosis in type 2 diabetes. *Diabetologia*. 2007; 50:752–763. [PubMed: 17268797]
47. Rubi B, Antinozzi PA, Herrero L, Ishihara H, Asins G, Serra D, et al. Adenovirus894 mediated overexpression of liver carnitine palmitoyltransferase I in INS1E cells: effects on cell metabolism and insulin secretion. *Biochem J*. 2002; 364:219–226. [PubMed: 11988095]
48. Yan J, Feng Z, Liu J, Shen W, Wang Y, Wertz K, et al. Enhanced autophagy plays a cardinal role in mitochondrial dysfunction in type 2 diabetic Goto-Kakizaki (GK) rats: ameliorating effects of (-)-epigallocatechin-3-gallate. *J Nutr Biochem*. 2012; 23:716–724. [PubMed: 21820301]
49. Jeon SM, Park YB, Choi MS. Antihypercholesterolemic property of naringin alters plasma and tissue lipids, cholesterol-regulating enzymes, fecal sterol and tissue morphology in rabbits. *Clin Nutr*. 2004; 23:1025–1034. [PubMed: 15380892]
50. Kim HJ, Oh GT, Park YB, Lee MK, Seo HJ, Choi MS. Naringin alters the cholesterol biosynthesis and antioxidant enzyme activities in LDL receptor-knockout mice under cholesterol fed condition. *Life sci*. 2004; 74:1621–1634. [PubMed: 14738906]
51. Goldwasser J, Cohen PY, Yang E, Balaguer P, Yarmush ML, Nahmias Y. Transcriptional regulation of human and rat hepatic lipid metabolism by the grapefruit flavonoid naringenin: role of PPAR α , PPAR γ and LXR α . *PloS One*. 2010; 5:e12399. [PubMed: 20811644]

52. Jung UJ, Kim HJ, Lee JS, Lee MK, Kim HO, Park EJ, et al. Naringin supplementation lowers plasma lipids and enhances erythrocyte antioxidant enzyme activities in hypercholesterolemic subjects. *Clin Nutr.* 2003; 22:561–568. [PubMed: 14613759]
53. Seo HJ, Jeong KS, Lee MK, Park YB, Jung UJ, Kim HJ, et al. Role of naringin supplement in regulation of lipid and ethanol metabolism in rats. *Life sci.* 2003; 73:933–946. [PubMed: 12798418]
54. Wilcox LJ, Borradaile NM, de Dreu LE, Huff MW. Secretion of hepatocyte apoB is inhibited by the flavonoids, naringenin and hesperetin, via reduced activity and expression of ACAT2 and MTP. *J Lipid Res.* 2001; 42:725–734. [PubMed: 11352979]
55. Borradaile NM, de Dreu LE, Barrett PH, Huff MW. Inhibition of hepatocyte apoB secretion by naringenin: enhanced rapid intracellular degradation independent of reduced microsomal cholesteryl esters. *J Lipid Res.* 2002; 43:1544–1554. [PubMed: 12235187]
56. Mahmoud AM, Ashour MB, Abdel-Moneim A, Ahmed OM. Hesperidin and naringin attenuate hyperglycemia-mediated oxidative stress and proinflammatory cytokine production in high fat fed/streptozotocin-induced type 2 diabetic rats. *J Diabetes Complications.* 2012
57. Jung UJ, Lee MK, Jeong KS, Choi MS. The hypoglycemic effects of hesperidin and naringin are partly mediated by hepatic glucose-regulating enzymes in C57BL/KsJ927 db/db mice. *J Nutr.* 2004; 134:2499–2503. [PubMed: 15465737]
58. Munoz MC, Barbera A, Dominguez J, Fernandez-Alvarez J, Gomis R, Guinovart JJ. Effects of tungstate, a new potential oral antidiabetic agent, in Zucker diabetic fatty rats. *Diabetes.* 2001; 50:131–138. [PubMed: 11147778]
59. Friedman JE, Sun Y, Ishizuka T, Farrell CJ, McCormack SE, Herron LM, et al. Phosphoenolpyruvate carboxykinase (GTP) gene transcription and hyperglycemia are regulated by glucocorticoids in genetically obese db/db transgenic mice. *J Biol Chem.* 1997; 272:31475–31481. [PubMed: 9395482]
60. Gibbs EM, Stock JL, McCoid SC, Stukenbrok HA, Pessin JE, Stevenson RW, et al. Glycemic improvement in diabetic db/db mice by overexpression of the human insulin-regulatable glucose transporter (GLUT4). *J Clin Invest.* 1995; 95:1512–1518. [PubMed: 7706456]
61. Sharma AK, Bharti S, Ojha S, Bhatia J, Kumar N, Ray R, et al. Up-regulation of PPARgamma, heat shock protein-27 and -72 by naringin attenuates insulin resistance, beta-cell dysfunction, hepatic steatosis and kidney damage in a rat model of type 2 diabetes. *The Br J Nutr.* 2011; 106:1713–1723.
62. Chung J, Nguyen AK, Henstridge DC, Holmes AG, Chan MH, Mesa JL, et al. HSP72 protects against obesity-induced insulin resistance. *Proc Natl Acad Sci USA.* 2008; 105:1739–1744. [PubMed: 18223156]
63. Morimoto RI. Cells in stress: transcriptional activation of heat shock genes. *Science.* 1993; 259:1409–1410. [PubMed: 8451637]
64. Michalik L, Wahli W. Involvement of PPAR nuclear receptors in tissue injury and wound repair. *J Clin Invest.* 2006; 116:598–606. [PubMed: 16511592]
65. Serisier S, Leray V, Poudroux W, Magot T, Ouguerram K, Nguyen P. Effects of green tea on insulin sensitivity, lipid profile and expression of PPARalpha and PPARgamma and their target genes in obese dogs. *Br J Nutr.* 2008; 99:1208–1216. [PubMed: 18053305]
66. Crozier A, Jaganath IB, Clifford MN. Dietary phenolics: chemistry, bioavailability and effects on health. *Nat Prod Rep.* 2009; 26:1001–1043. [PubMed: 19636448]
67. Yang M, Koo SI, Song WO, Chun OK. Food matrix affecting anthocyanin bioavailability: review. *Curr Med Chem.* 2011; 18:291–300. [PubMed: 21110799]
68. He J, Giusti MM. Anthocyanins: natural colorants with health-promoting properties. *Annu Rev Food Sci Technol.* 2010; 1:163–187. [PubMed: 22129334]
69. Ghosh D, Konishi T. Anthocyanins and anthocyanin-rich extracts: role in diabetes and eye function. *Asia Pac J Clin Nutr.* 2007; 16:200–208. [PubMed: 17468073]
70. Hardie DG. Role of AMP-activated protein kinase in the metabolic syndrome and in heart disease. *FEBS lett.* 2008; 582:81–89. [PubMed: 18022388]

71. Yang Q, Graham TE, Mody N, Preitner F, Peroni OD, Zabolotny JM, et al. Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. *Nature*. 2005; 436:356–362. [PubMed: 16034410]
72. Nizamutdinova IT, Jin YC, Chung JI, Shin SC, Lee SJ, Seo HG, et al. The anti-diabetic effect of anthocyanins in streptozotocin-induced diabetic rats through glucose transporter 4 regulation and prevention of insulin resistance and pancreatic apoptosis. *Mol Nutr Food Res*. 2009; 53:1419–1429. [PubMed: 19785000]
73. Choung MG, Baek IY, Kang ST, Han WY, Shin DC, Moon HP, et al. Isolation and determination of anthocyanins in seed coats of black soybean (*Glycine max* (L.) Merr.). *JJ Agric Food Chem*. 2001; 49:5848–5851.
74. Jayaprakasam B, Olson LK, Schutzki RE, Tai MH, Nair MG. Amelioration of obesity and glucose intolerance in high-fat-fed C57BL/6 mice by anthocyanins and ursolic acid in Cornelian cherry (*Cornus mas*). *J Agric Food Chem*. 2006; 54:243–248. [PubMed: 16390206]
75. Tsuda T, Horio F, Uchida K, Aoki H, Osawa T. Dietary cyanidin 3-O-beta-D-glucoside-rich purple corn color prevents obesity and ameliorates hyperglycemia in mice. *J Nutr*. 2003; 133:2125–2130. [PubMed: 12840166]
76. Grace MH, Ribnicki DM, Kuhn P, Poulev A, Logendra S, Yousef GG, et al. Hypoglycemic activity of a novel anthocyanin-rich formulation from lowbush blueberry, *Vaccinium angustifolium* Aiton. *Phytomedicine*. 2009; 16:406–415. [PubMed: 19303751]
77. Martineau LC, Couture A, Spoor D, Benhaddou-Andaloussi A, Harris C, Meddah B, et al. Anti-diabetic properties of the Canadian lowbush blueberry *Vaccinium angustifolium* Ait. *Phytomedicine*. 2006; 13:612–623. [PubMed: 16979328]
78. Murray MT. Bilberry (*Vaccinium myrtillus*). *Am J Nat Med*. 1997; 4:17–21.
79. Rojo LE, Ribnicki D, Logendra S, Poulev A, Rojas-Silva P, Kuhn P, et al. In vitro and in vivo anti-diabetic effects of anthocyanins from Maqui Berry (*Aristotelia chilensis*). *Food Chem*. 2012; 131:387–396.
80. Sun CD, Zhang B, Zhang JK, Xu CJ, Wu YL, Li X, et al. Cyanidin-3-glucoside-rich extract from Chinese bayberry fruit protects pancreatic beta cells and ameliorates hyperglycemia in streptozotocin-induced diabetic mice. *J Med Food*. 2012; 15:288–298. [PubMed: 22181073]
81. Roy M, Sen S, Chakraborti AS. Action of pelargonidin on hyperglycemia and oxidative damage in diabetic rats: implication for glycation-induced hemoglobin modification. *Life sci*. 2008; 82:1102–1110. [PubMed: 18440560]
82. Yamahara J, Mibu H, Sawada T, Fujimura H, Takino S, Yoshikawa M, et al. [Biologically active principles of crude drugs. Antidiabetic principles of corni fructus in experimental diabetes induced by streptozotocin (author's transl)]. *Yakugaku zasshi : J Pharma Soc Japan*. 1981; 101:86–90.
83. Jayaprakasam B, Vareed SK, Olson LK, Nair MG. Insulin secretion by bioactive anthocyanins and anthocyanidins present in fruits. *J Agric Food Chem*. 2005; 53:28–31. [PubMed: 15631504]
84. Seeram NP, Schutzki R, Chandra A, Nair MG. Characterization, quantification, and bioactivities of anthocyanins in *Cornus* species. *J Agric Food Chem*. 2002; 50:2519–2523. [PubMed: 11958615]
85. Scazzocchio B, Vari R, Filesi C, D'Archivio M, Santangelo C, Giovannini C, et al. Cyanidin-3-O-beta-glucoside and protocatechuic acid exert insulin-like effects by upregulating PPARgamma activity in human omental adipocytes. *Diabetes*. 2011; 60:2234–2244. [PubMed: 21788573]
86. Guo H, Xia M, Zou T, Ling W, Zhong R, Zhang W. Cyanidin 3-glucoside attenuates obesity-associated insulin resistance and hepatic steatosis in high-fat diet-fed and db/db mice via the transcription factor FoxO1. *J Nutr Biochem*. 2012; 23:349–360. [PubMed: 21543211]
87. Nakae J, Biggs WH 3rd, Kitamura T, Caveness WK, Wright CV, Arden KC, et al. Regulation of insulin action and pancreatic beta-cell function by mutated alleles of the gene encoding forkhead transcription factor Foxo1. *Nat Genet*. 2002; 32:245–253. [PubMed: 12219087]
88. Nakae J, Kitamura T, Kitamura Y, Biggs WH 3rd, Arden KC, Accili D. The forkhead transcription factor Foxo1 regulates adipocyte differentiation. *Dev cell*. 2003; 4:119–129. [PubMed: 12530968]
89. Matsumoto M, Pocai A, Rossetti L, Depinho RA, Accili D. Impaired regulation of hepatic glucose production in mice lacking the forkhead transcription factor Foxo1 in liver. *Cell Metab*. 2007; 6:208–216. [PubMed: 17767907]

90. Stull AJ, Cash KC, Johnson WD, Champagne CM, Cefalu WT. Bioactives in blueberries improve insulin sensitivity in obese, insulin-resistant men and women. *J Nutr.* 2010; 140:1764–1768. [PubMed: 20724487]
91. Torronen R, Sarkkinen E, Tapola N, Hautaniemi E, Kilpi K, Niskanen L. Berries modify the postprandial plasma glucose response to sucrose in healthy subjects. *Br J Nutr.* 2010; 103:1094–1097. [PubMed: 19930765]
92. Howitz KT, Bitterman KJ, Cohen HY, Lamming DW, Lavu S, Wood JG, et al. Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan. *Nature.* 2003; 425:191–196. [PubMed: 12939617]
93. Lee WJ, Shim JY, Zhu BT. Mechanisms for the inhibition of DNA methyltransferases by tea catechins and bioflavonoids. *Mol Pharmacol.* 2005; 68:1018–1030. [PubMed: 16037419]
94. Prasath GS, Subramanian SP. Modulatory effects of fisetin, a bioflavonoid, on hyperglycemia by attenuating the key enzymes of carbohydrate metabolism in hepatic and renal tissues in streptozotocin-induced diabetic rats. *Eur J Pharmacol.* 2011; 668:492–496. [PubMed: 21816145]
95. Granata R, Settanni F, Gallo D, Trovato L, Biancone L, Cantaluppi V, et al. Obestatin promotes survival of pancreatic beta-cells and human islets and induces expression of genes involved in the regulation of beta-cell mass and function. *Diabetes.* 2008; 57:967–979. [PubMed: 18162507]
96. Jetton TL, Lausier J, LaRock K, Trotman WE, Larmie B, Habibovic A, et al. Mechanisms of compensatory beta-cell growth in insulin-resistant rats: roles of Akt kinase. *Diabetes.* 2005; 54:2294–2304. [PubMed: 16046294]
97. Li L, El-Kholy W, Rhodes CJ, Brubaker PL. Glucagon-like peptide-1 protects beta cells from cytokine-induced apoptosis and necrosis: role of protein kinase B. *Diabetologia.* 2005; 48:1339–1349. [PubMed: 15902400]
98. Roger B, Papin J, Vacher P, Raoux M, Mulot A, Dubois M, et al. Adenylyl cyclase 8 is central to glucagon-like peptide 1 signalling and effects of chronically elevated glucose in rat and human pancreatic beta cells. *Diabetologia.* 2011; 54:390–402. [PubMed: 21046358]
99. Philippe J, Missotten M. Functional characterization of a cAMP-responsive element of the rat insulin I gene. *J Biol Chem.* 1990; 265:1465–1469. [PubMed: 2153135]
100. Pugazhenth S, Nesterova A, Sable C, Heidenreich KA, Boxer LM, Heasley LE, et al. Akt/protein kinase B up-regulates Bcl-2 expression through cAMP-response element-binding protein. *J Biol Chem.* 2000; 275:10761–10766. [PubMed: 10753867]
101. Zhang Y, Zhen W, Maechler P, Liu D. Small molecule kaempferol modulates PDX-1 protein expression and subsequently promotes pancreatic beta-cell survival and function via CREB. *J Nutr Biochem.* 2012
102. Kobori M, Masumoto S, Akimoto Y, Takahashi Y. Dietary quercetin alleviates diabetic symptoms and reduces streptozotocin-induced disturbance of hepatic gene expression in mice. *Mol Nutr Food Res.* 2009; 53:859–868. [PubMed: 19496084]
103. Vessal M, Hemmati M, Vasei M. Antidiabetic effects of quercetin in streptozotocin1061 induced diabetic rats. *Comp Biochem Physiol C Toxicol Pharmacol.* 2003; 135C:357–364. [PubMed: 12927910]
104. Coskun O, Kanter M, Korkmaz A, Oter S. Quercetin, a flavonoid antioxidant, prevents and protects streptozotocin-induced oxidative stress and beta-cell damage in rat pancreas. *Pharmacol Res.* 2005; 51:117–123. [PubMed: 15629256]
105. Jeong SM, Kang MJ, Choi HN, Kim JH, Kim JI. Quercetin ameliorates hyperglycemia and dyslipidemia and improves antioxidant status in type 2 diabetic db/db mice. *Nutr Res Pract.* 2012; 6:201–207. [PubMed: 22808343]
106. Youl E, Bardy G, Magous R, Cros G, Sejalon F, Virsolvy A, et al. Quercetin potentiates insulin secretion and protects INS-1 pancreatic beta-cells against oxidative damage via the ERK1/2 pathway. *Br J Pharmacol.* 2010; 161:799–814. [PubMed: 20860660]
107. Dai X, Ding Y, Zhang Z, Cai X, Li Y. Quercetin and quercitrin protect against cytokine-induced injuries in RINm5F beta-cells via the mitochondrial pathway and NF-kappaB signaling. *Int J Mol Med.* 2013; 31:265–271. [PubMed: 23138875]
108. Li YQ, Zhou FC, Gao F, Bian JS, Shan F. Comparative evaluation of quercetin, isoquercetin and rutin as inhibitors of alpha-glucosidase. *J Agri Food Chem.* 2009; 57:11463–11468.

109. Reuser AJJ, Wisselaar HA. An evaluation of the potential side-effects of α -glucosidase inhibitors used for the management of diabetes mellitus. *Eur J Clin Invest.* 1994; 24:19–24. [PubMed: 8001622]
110. Madar Z. The Effect of Acarbose and Miglitol (BAY-M-1099) on Postprandial Glucose Levels Following Ingestion of Various Sources of Starch by Nondiabetic and Streptozotocin-Induced Diabetic Rats. *J Nutr.* 1989; 119:2023–2029. [PubMed: 2695605]
111. van de Laar FA, Lucassen PL, Akkermans RP, van de Lisdonk EH, Rutten GE, van Weel C. Alpha-glucosidase inhibitors for patients with type 2 diabetes: results from a Cochrane systematic review and meta-analysis. *Diabetes care.* 2005; 28:154–163. [PubMed: 15616251]
112. Murai A, Iwamura K, Takada M, Ogawa K, Usui T, Okumura J-I. Control of postprandial hyperglycaemia by galactosyl maltobionolactone and its novel anti-amylase effect in mice. *Life sci.* 2002; 71:1405–1415. [PubMed: 12127161]
113. Bressler R, Johnson D. New pharmacological approaches to therapy of NIDDM. *Diabetes care.* 1992; 15:792–805. [PubMed: 1600838]
114. Patel D, Shukla S, Gupta S. Apigenin and cancer chemoprevention: progress, potential and promise (review). *Int J Oncol.* 2007; 30:233–245. [PubMed: 17143534]
115. Panda S, Kar A. Apigenin (4',5,7-trihydroxyflavone) regulates hyperglycaemia, thyroid dysfunction and lipid peroxidation in alloxan-induced diabetic mice. *J Pharm Pharmacol.* 2007; 59:1543–1548. [PubMed: 17976266]
116. Rauter AP, Martins A, Borges C, Mota-Filipe H, Pinto R, Sepodes B, et al. Antihyperglycaemic and protective effects of flavonoids on streptozotocin-induced diabetic rats. *Phytother Res.* 2010; 24(Suppl 2):S133–S138. [PubMed: 20309949]
117. Suh KS, Oh S, Woo JT, Kim SW, Kim JW, Kim YS, et al. Apigenin attenuates 2-deoxy-D1101 ribose-induced oxidative cell damage in HIT-T15 pancreatic beta-cells. *Biol Pharm Bull.* 2012; 35:121–126. [PubMed: 22223348]
118. Kim EK, Kwon KB, Song MY, Han MJ, Lee JH, Lee YR, et al. Flavonoids protect against cytokine-induced pancreatic beta-cell damage through suppression of nuclear factor kappaB activation. *Pancreas.* 2007; 35:e1–e9. [PubMed: 18090225]
119. Zang M, Xu S, Maitland-Toolan KA, Zuccollo A, Hou X, Jiang B, et al. Polyphenols stimulate AMP-activated protein kinase, lower lipids, and inhibit accelerated atherosclerosis in diabetic LDL receptor-deficient mice. *Diabetes.* 2006; 55:2180–2191. [PubMed: 16873680]
120. Matsui T, Kobayashi M, Hayashida S, Matsumoto K. Luteolin, a flavone, does not suppress postprandial glucose absorption through an inhibition of α 1111 glucosidase action. *Biosci Biotechnol Biochem.* 2002; 66:689–692. [PubMed: 12005074]
121. Ding L, Jin D, Chen X. Luteolin enhances insulin sensitivity via activation of PPARgamma transcriptional activity in adipocytes. *J Nutr Biochem.* 2010; 21:941–947. [PubMed: 19954946]
122. Park HS, Kim SH, Kim YS, Ryu SY, Hwang JT, Yang HJ, et al. Luteolin inhibits adipogenic differentiation by regulating PPARgamma activation. *Biofactors.* 2009; 35:373–379. [PubMed: 19353690]
123. Veitch NC. Isoflavonoids of the leguminosae. *Nat Prod Rep.* 2007; 24:417–464. [PubMed: 17390003]
124. Gilbert ER, Liu D. Anti-diabetic functions of soy isoflavone genistein: mechanisms underlying its effects on pancreatic beta-cell function. *Food Funct.* 2012
125. Cederroth CR, Vinciguerra M, Gjinovci A, Kuhne F, Klein M, Cederroth M, et al. Dietary phytoestrogens activate AMP-activated protein kinase with improvement in lipid and glucose metabolism. *Diabetes.* 2008; 57:1176–1185. [PubMed: 18420492]
126. Anthony MS, Clarkson TB, Hughes CL Jr, Morgan TM, Burke GL. Soybean isoflavones improve cardiovascular risk factors without affecting the reproductive system of peripubertal rhesus monkeys. *J Nutr.* 1996; 126:43–50. [PubMed: 8558324]
127. Anthony MS, Clarkson TB, Bullock BC, Wagner JD. Soy protein versus soy phytoestrogens in the prevention of diet-induced coronary artery atherosclerosis of male cynomolgus monkeys. *Arterioscler Thromb Vasc Biol.* 1997; 17:2524–2531. [PubMed: 9409223]

128. Clarkson TB, Anthony MS, Williams JK, Honore EK, Cline JM. The potential of soybean phytoestrogens for postmenopausal hormone replacement therapy. *Proc Soc Exp Biol Med*. 1998; 217:365–368. [PubMed: 9492349]
129. Washburn S, Burke GL, Morgan T, Anthony M. Effect of soy protein supplementation on serum lipoproteins, blood pressure, and menopausal symptoms in perimenopausal women. *Menopause*. 1999; 6:7–13. [PubMed: 10100174]
130. Choi MS, Jung UJ, Yeo J, Kim MJ, Lee MK. Genistein and daidzein prevent diabetes onset by elevating insulin level and altering hepatic gluconeogenic and lipogenic enzyme activities in non-obese diabetic (NOD) mice. *Diabetes Metab Res Rev*. 2008; 24:74–81. [PubMed: 17932873]
131. Fu Z, Gilbert ER, Pfeiffer L, Zhang Y, Fu Y, Liu D. Genistein ameliorates hyperglycemia in a mouse model of nongenetic type 2 diabetes. *Appl Physiol Nutr Metab*. 2012; 37:480–488. [PubMed: 22509809]
132. Sorenson RL, Brelje TC, Roth C. Effect of tyrosine kinase inhibitors on islets of Langerhans: evidence for tyrosine kinases in the regulation of insulin secretion. *Endocrinology*. 1994; 134:1975–1978. [PubMed: 8137766]
133. Jonas JC, Plant TD, Gilon P, Detimary P, Nenquin M, Henquin JC. Multiple effects and stimulation of insulin secretion by the tyrosine kinase inhibitor genistein in normal mouse islets. *Br J Pharmacol*. 1995; 114:872–880. [PubMed: 7773549]
134. Yang W, Wang S, Li L, Liang Z, Wang L. Genistein reduces hyperglycemia and islet cell loss in a high-dosage manner in rats with alloxan-induced pancreatic damage. *Pancreas*. 2011; 40:396–402. [PubMed: 21206328]
135. Mezei O, Banz WJ, Steger RW, Peluso MR, Winters TA, Shay N. Soy isoflavones exert antidiabetic and hypolipidemic effects through the PPAR pathways in obese Zucker rats and murine RAW 264.7 cells. *J Nutr*. 2003; 133:1238–1243. [PubMed: 12730403]
136. Nestel PJ, Yamashita T, Sasahara T, Pomeroy S, Dart A, Komesaroff P, et al. Soy isoflavones improve systemic arterial compliance but not plasma lipids in menopausal and perimenopausal women. *Arterioscler Thromb Vasc Biol*. 1997; 17:3392–3398. [PubMed: 9437184]
137. Hodgson JM, Puddey IB, Beilin LJ, Mori TA, Croft KD. Supplementation with isoflavonoid phytoestrogens does not alter serum lipid concentrations: a randomized controlled trial in humans. *J Nutr*. 1998; 128:728–732. [PubMed: 9521635]
138. Simons LA, von Konigsmark M, Simons J, Celermajer DS. Phytoestrogens do not influence lipoprotein levels or endothelial function in healthy, postmenopausal women. *Am J Cardiol*. 2000; 85:1297–1301. [PubMed: 10831943]
139. Squadrito F, Altavilla D, Morabito N, Crisafulli A, D'Anna R, Corrado F, et al. The effect of the phytoestrogen genistein on plasma nitric oxide concentrations, endothelin-1 levels and endothelium dependent vasodilation in postmenopausal women. *Atherosclerosis*. 2002; 163:339–347. [PubMed: 12052481]
140. Ali AA, Velasquez MT, Hansen CT, Mohamed AI, Bhathena SJ. Modulation of carbohydrate metabolism and peptide hormones by soybean isoflavones and probiotics in obesity and diabetes. *J Nutr Biochem*. 2005
141. Ohno T, Kato N, Ishii C, Shimizu M, Ito Y, Tomono S, et al. Genistein augments cyclic adenosine 3'5'-monophosphate(cAMP) accumulation and insulin release in MIN6 cells. *Endocr Res*. 1993; 19:273–285. [PubMed: 7508378]
142. Jones PM, Persaud SJ. Tyrosine kinase inhibitors inhibit glucose-stimulated insulin secretion. *Biochem Soc Trans*. 1994; 22:209S. [PubMed: 7525376]
143. Persaud SJ, Harris TE, Burns CJ, Jones PM. Tyrosine kinases play a permissive role in glucose-induced insulin secretion from adult rat islets. *J Mol Endocrinol*. 1999; 22:19–28. [PubMed: 9924176]
144. Liu D, Zhen W, Yang Z, Carter JD, Si H, Reynolds KA. Genistein acutely stimulates insulin secretion in pancreatic beta-cells through a cAMP-dependent protein kinase pathway. *Diabetes*. 2006; 55:1043–1050. [PubMed: 16567527]
145. Fu Z, Liu D. Long-term exposure to genistein improves insulin secretory function of pancreatic beta-cells. *Eur J Pharmacol*. 2009; 616:321–327. [PubMed: 19540219]

146. Babu PV, Si H, Fu Z, Zhen W, Liu D. Genistein prevents hyperglycemia-induced monocyte adhesion to human aortic endothelial cells through preservation of the cAMP signaling pathway and ameliorates vascular inflammation in obese diabetic mice. *J Nutr.* 2012; 142:724–730. [PubMed: 22399524]
147. Lee SJ, Kim HE, Choi SE, Shin HC, Kwag WJ, Lee BK, et al. Involvement of Ca²⁺/calmodulin kinase II (CaMK II) in genistein-induced potentiation of leucine/glutamine-stimulated insulin secretion. *Mol Cells.* 2009; 28:167–174. [PubMed: 19756396]
148. Kim EK, Kwon KB, Song MY, Seo SW, Park SJ, Ka SO, et al. Genistein protects pancreatic beta cells against cytokine-mediated toxicity. *Mol Cell Endocrinol.* 2007; 278:18–28. [PubMed: 17881116]
149. Curtis PJ, Sampson M, Potter J, Dhatariya K, Kroon PA, Cassidy A. Chronic ingestion of flavan-3-ols and isoflavones improves insulin sensitivity and lipoprotein status and attenuates estimated 10-year CVD risk in medicated postmenopausal women with type 2 diabetes: a 1-year, double-blind, randomized, controlled trial. *Diabetes care.* 2012; 35:226–232. [PubMed: 22250063]
150. Gonzalez S, Jayagopal V, Kilpatrick ES, Chapman T, Atkin SL. Effects of isoflavone dietary supplementation on cardiovascular risk factors in type 2 diabetes. *Diabetes care.* 2007; 30:1871–1873. [PubMed: 17468359]

Figure. Dietary flavonoids exert their anti-diabetic effects by targeting various cellular signaling pathways in pancreas, liver, skeletal muscle, and white adipose tissues (↑ : Increase, ↓ : Decrease, +: Stimulate).

Table 1

The anti-diabetic properties and the underlying mechanisms of dietary flavonoids

Flavonoid	Function	<i>In vitro</i> or <i>in vivo</i> model	Mode of action	Ref.
1. Flavon-3-ols				
EGCG	Viability	-cells	IRS2 Akt FoxO1 PDX-1	[11]
EGCG	Apoptosis Glucose uptake	-cells	Bcl-2 Mitochondrial translocation of Bax	[24]
EGCG	Protect muscle cells against FFA induced insulin resistance	C2C12 muscle cells	AMPK activation PKC activation IRS1 serine phosphorylation ERK1/2 activation p38 MAPK activation ACC signaling pathway	[27]
EGCG	Delay the onset of T1D	NOD mice	IL-10	[13]
EGCG	Preserve islet morphology	<i>db/db</i> mice	Ddit3 Ppp1r15a Cdkn1a	[45]
EGCG	Mitochondrial function Excessive muscle autophagy	T2D mice	Down-regulation of ROS- ERK/JNK-p53 pathway	[48]
2. Flavanones				
Naringin or hesperidin	Hyperglycemia	STZ-induced diabetic mice		[56]
Naringin	Hyperglycemia Plasma insulin Leptin	<i>db/db</i> mice	PEPCK and G6Pase expression	[57]
Hesperidin or Naringin	GLUT2 (liver) GLUT4 (WAT)	<i>db/db</i> mice	PPAR	[18]
Naringin	Hyperglycemia cell function	T2D mice	PPAR HSP-72 HSP-26 Maintain adequate pool of insulin secretory granules	[61]
3. Anthocyanidins				
Bilberry anthocyanins	Hyperglycemia insulin sensitivity GLUT4 (WAT and muscle)	T2D mice	Total AMPK AMPK phosphorylation PEPCK and G6Pase expression Acetyl Co-A carboxylase PPAR Acyl-CoA oxidase CPT-1A RBP4	[17]
Black soybean anthocyanins	GLUT4 (muscle) cell viability cell apoptosis	STZ-induced diabetic rats	IR phosphorylation Bcl-2 Bax Caspase-3	[72]
Anthocyanin mixture	Plasma insulin Preserve pancreatic islets	HF induced diabetic mice		[74]
Purple corn color anthocyanidin	Insulin Leptin Adipocyte hypertrophy	HF fed mice	Lipogenic gene expression	[75]

Flavonoid	Function	<i>In vitro or in vivo</i> model	Mode of action	Ref.
Blue berry anthocyanins	hyperglycemia	HF fed mice		[76]
Bayberry fruit anthocyanins	cell viability cell apoptosis GSIS	INS-1 cells	PDX-1 Insulin like growth factor II	[80]
Delphinidin-3-glucoside	GSIS	INS-1 cells		[83]
Cyanidin-3-glucoside and its metabolite Protocatechuic acid	Glucose uptake GLU4 expression Adiponectin	Human and murine adipocytes	PPAR	[85]
Pelargonidin	Glucose tolerance Serum insulin Antioxidant enzymes	STZ-induced diabetic rats		[81]
Cyanidin-3-glucoside	Fasting glucose Insulin sensitivity Inflammatory cytokines	<i>db/db</i> mice and HF-fed obese mice	Phosphorylation of Akt, FoxO1 Nuclear translocation of FoxO1 JNK activation	[86]
4. Flavonols				
Fistein	Hyperglycemia Glycosylated Hb	STZ-induced diabetic rat	PEPCK and G6Pase	[94]
Kaempferol	Secretion of insulin cell apoptosis	INS-1E cells and pancreatic human islets	Akt Bcl-2 cAMP signaling PKA activation CREB phosphorylation PDX-1 Caspase-3	[14]
Quercetin rich extract Quercetin-3-Oglucoside, Q-3-O-galactoside	Glucose uptake	C2C12 muscle cells	AMPK	[16]
Quercetin	Hyperglycemia Insulin Cell proliferation in liver and pancreas	STZ-induced diabetic mice	Cdkn1a	[102]
Quercetin	Hyperglycemia Improve insulin resistance	<i>db/db</i> mice		[105]
Quercetin	GSIS	INS-1 cells	ERK1/2 pathway	[106]
Quercetin and its glucoside quercitrin	GSIS Cell viability	Rat insulinoma cells	iNOS Nuclear translocation of NF B Cytochrome C release from mitochondria	[107]
Quercetin, isoquercetin, rutin	Inhibit -glucosidase	Cell free system		[108]
5. Flavones				
Apigenin	Hyperglycemia Hepatic antioxidant enzymes	Alloxan - diabetic mice		[115]
Apigenin	Hyperglycemia	STZ- induced diabetic mice		[116]
Apigenin	Apoptosis	HIT-T15 clonal -cells		[117]
Apigenin, luteolin	Apoptosis	Rat insulinoma cells	iNOS NF B activation	[118]
Apigenin	GLUT4	HepG2 hepatocytes	AMPK phosphorylation	[119]
6. Isoflavones				
Genistein and daidzein	Improve glucose homeostasis	NOD mice	PEPCK and G6Pase	[130]

Flavonoid	Function	<i>In vitro or in vivo</i> model	Mode of action	Ref.
Genistein	Hyperglycemia -cell mass	T2D mice		[131]
Genistein	Insulinotropic effect	INS-1 MIN-6 Human islet -cells	Activation of cAMP/PKA- dependent ERK1/2 signaling pathway Cyclin D1	[12]
Genistein	Hyperglycemia Glucose tolerance Insulin -cell proliferation, survival and mass	STZ-induced diabetic mice	Activation of cAMP/PKA- dependent ERK1/2 signaling pathway	[12]
Genistein	Insulin secretion	INS-1 cells	CaMK II and Ca ²⁺ signaling	[147]
Genistein	-cell function	RINm5F (RIN) cells	NF- κ B, ERK1/2 and JAK/ STAT pathway	[148]