Food Polyphenols and Type II Diabetes Mellitus

Subjects: Pharmacology & Pharmacy

Contributor: Rabia Naz, Fatima Saqib, Samir Awadallah, Muqeet Wahid, Muhammad Farhaj Latif, Iram Iqbal, Mohammad S. Mubarak

Type II diabetes mellitus and its related complications are growing public health problems. Many natural products present in our diet, including polyphenols, can be used in treating and managing type II diabetes mellitus and different diseases, owing to their numerous biological properties. Anthocyanins, flavonols, stilbenes, curcuminoids, hesperidin, hesperetin, naringenin, and phenolic acids are common polyphenols found in blueberries, chokeberries, sea-buckthorn, mulberries, turmeric, citrus fruits, and cereals. These compounds exhibit antidiabetic effects through different pathways.

Keywords: type II diabetes mellitus ; polyphenols ; resveratrol ; curcumin

1. Introduction

Phytochemicals and polyphenols in fruits and vegetables have antidiabetic effects [1]. Plant-based nutrients such as vegetables (onion, cabbage, and especially broccoli), fruits (apples, grapes, cherries, pears, and various berries), and grains contain hundreds of different polyphenols [2][3][4]. In this context, some vegetables such as beans, cabbage, onions, and cereals also contain anthocyanidins, whereas red fruits are the primary source of these polyphenols [5]. The plant kingdom contains a large number of polyphenols that fall under the categories of tannins, lignans, stilbenes, phenolic acids, and flavonoids, among others [6]. On the other hand, fruits, spices, grains, vegetables, and other phenolic-rich plant products contain phenolic acids (hydroxycinnamic acids and hydroxybenzoic acid), stilbenes, and lignans [3][4][7]. Phenolics are crucial to fruit quality because they impact the fruit's taste, appearance, and nutritional value [8]. For example, flavonoids may lessen the risk of developing diabetes [6] by maintaining glucose uptake, blood glucose points, and insulin secretion, controlling immune function [9][10]. In this respect, dietary flavonoids demonstrated a significant anti-hyperglycemic-like effect through glucose absorption control [11], a reserve of digestive enzymes [12][13], regulation of intestinal microbiota [14], inhibition of the formation of innovative glycation end products [15], and other mechanisms. Polyphenols may also influence the signaling pathways and ensuing alterations in gene expression [16][17]. By controlling the events of glucose metabolism, hepatic enzymes, and lipid profiles, flavonoids reduce the pathogenesis of diabetes and its complications [18]. Flavone C-glycosides, which can also hinder digestive enzymes and activate insulin signaling, can lessen the production of advanced glycation end products (AGEs) [19]. Accordingly, the consumption of purple carrots, high in anthocyanins (flavonoids) and low in carotenoids, was linked to a decrease in impaired glucose tolerance [20]. Quercetin, a flavonoid, has received the most research attention for its in vivo and cellular anti-diabetic properties in animal and cell models [21], followed by kaempferol [22], luteolin [23], myricetin [24], and naringenin [25]. The most well-known sources of the stilbenes class of polyphenols, including resveratrol, are mulberries, grape skin, and peanuts [26]. The numerous and diverse phytochemicals known as polyphenols contain phenolic rings [9]. In this regard, two aromatic rings are joined by a 3-carbon chain to form an oxygenated heterocyclic ring, and this structure makes up a class of phenolic compounds known as flavonoids [27]. Anthocyanins, flavonols, flavones, isoflavonoids, and syringic acid are flavonoid subclasses connected to diabetes because the consumption of food that contains these compounds lowers the risk of type II diabetes [28].

According to estimates, there will likely be over 300 million cases of type II diabetes worldwide by 2030 [29]. Therefore, medical professionals, academics, and policymakers are taking note of the rising number of fatalities brought on by diabetes, related illnesses, and physiological disorders to promote healthy eating habits [1]. Currently, preventing and treating metabolic syndrome and type II diabetes involves increasing physical activity and decreasing calorie intake [30]. Hyperglycemia is a metabolic disease with multiple underlying origins that necessitate lifetime medication therapy and dietary adjustments. In diabetes management and prevention, herbal supplements are now supported by a growing body of scientific research. Nutritional polyphenols, the most common phytochemical in human diets, have drawn much interest due to growing evidence of their positive effects on humans. Dietary polyphenols aid in the management of type II diabetes and lessen the severity of diabetic complications in animals. The anti-diabetic effects of resveratrol [31][32], curcumin [33], and anthocyanins [34] have been demonstrated in humans. Studies validate that these polyphenols

conducted in vitro and in vivo compounds have anti-inflammatory, antioxidant, chemopreventive, and neuroprotective properties.

2. Resveratrol

Baur and coworkers reported that resveratrol increases the lifespan in high-caloric diet mice by reducing glucose and improving insulin levels. It increased insulin sensitivity in diabetic mice and homeostatic model assessment during glucose tolerance tests [35]. Research findings showed that resveratrol lowers blood insulin levels in animals with hyperinsulinemia and insulin resistance. Rodents with diet-induced hyperinsulinemia were used to demonstrate this effect [36][37][38][39][40]. On the other hand, resveratrol seems to raise blood insulin levels in rodent models of type II diabetes with reduced-cell mass and hypoinsulinemia, as demonstrated in db/db mice [41][42]. The improvement in insulin action lowers blood glucose levels, which prevents glucotoxicity, the harmful effects of hyperglycemia on β-cells [43]. In addition, resveratrol alleviates steatosis and lowers hepatic lipid buildup. Decreased expression of acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS) is linked to these effects [38][39][42][44][45][46][47][48]. It also reduces the expression of fatty acid synthase [49]. According to some published research, resveratrol's effects on FAS and ACC may be mediated by the AMPK/SIRT1 axis [50][51]. It also decreases plasma amylase levels, which increases pancreatic damage. Thus, it prevents pancreatic damage.

In addition, resveratrol increases mitochondrial numbers and citrate synthase activity [52] with reduced caloric and exercise [52][53]. Furthermore, in liver tissue, resveratrol decreases the appearance of pro-inflammatory cytokines [47][54] and increases glutathione peroxidase activity, which decreases oxidative liver damage [55]. Furthermore, resveratrol decreases inflammatory markers, which protect pancreatic β-cells [56]. Findings also demonstrated that resveratrol lessens oxidative stress; reduces islet fibrosis and destruction; restores islet architecture; enhances islet structure and function; and attenuates other worsening changes in db/db mice, a type II diabetes animal model with diminished β-cell mass. Moreover, resveratrol increases the β-cell mass and partially stops β-cell failure [41][42]. Parametric analysis of gene set enrichment (PAGE) showed that resveratrol alters glycolysis, TCA cycle, classic and alternative complement pathways, butanoate, propanoate metabolism, and sterol biosynthesis [35]. In insulin-resistant rodents, resveratrol promotes intracellular glucose transport in rats fed a high-cholesterol and high-fructose diet and given resveratrol larger than those animals not given this supplement [57]. Resveratrol enhances skeletal muscle's ability to absorb insulin-stimulated glucose [58][59].

Resveratrol Effect on Diabetes via GLUT4 Elevation

In insulin-resistant rodents, intracellular glucose transport increases by resveratrol. Within this context, Deng and colleagues indicated that when rats fed on a high-fructose and high-cholesterol diet are given resveratrol in the initial animal studies, they show greater soleus muscle glucose uptake than animals not given this supplement [57]. Similar results were obtained and showed that resveratrol increases skeletal muscle glucose uptake in rats nourished on a high-fat diet [58][60]. Resveratrol increases intracellular glucose transportation in insulin-resistant animals via two GLUT4-related mechanisms. It is well recognized that resveratrol expedites the translocation of GLUT4 to the muscle cells' plasma membranes [57][58], and GLUT4 expression is also increased in animals with insulin resistance in their skeletal muscle [61] and in db/db mice [62]. Moreover, research findings showed improved insulin action by increased intracellular glucose transportation in resveratrol-consuming insulin-resistant animals. In skeletal muscle, resveratrol reduces insulin resistance through various mechanisms, including alterations in metabolism and lipid buildup. In addition, resveratrol encourages mitochondrial biogenesis in rats with diet-induced insulin resistance in their skeletal muscles [63] and improves mitochondrial β-oxidation [59]. Coen and Goodpaster reported that type II diabetes and insulin resistance are exacerbated by increased intramyocellular lipid accumulation, affecting how well insulin works [64].

Resveratrol Effect on Diabetes via SIRT1 Involvement

Kitada et al. [65] reported that variations in the expression and activities of two intracellular controllers are closely related to the beneficial effects of resveratrol on the muscle tissue of insulin-resistant rodents, i.e., SIRT1 and AMPK. The NAD+-dependent histone deacetylase SIRT1 (silent information regulator 1) involves several processes, including inflammation, mitochondrial biogenesis, stress resistance, intracellular metabolism, glucose homeostasis, apoptosis, and others. Since type II diabetic patients have decreased SIRT1 activity and expression, SIRT1 is considered a target for anti-diabetic medications [65][66]. In addition, scientists showed that resveratrol triggers SIRT1 in mammalian tissues [67] and triggers muscle SIRT1 in animals with diet-induced insulin resistance [59]. An increase in the NAD+/NADH ratio is related to this enzyme's activation [63]. Findings also revealed that resveratrol raises the SIRT1 level in the muscle in rodents with genetically stimulated insulin resistance [68]. Deacetylation and activation of PGC-1α are linked to resveratrol-induced upregulation of AMPK in skeletal muscle, possibly via SIRT1-dependent mechanisms [61][65].

Resveratrol Effect on Diabetes via AMPK Activation

Another enzyme involved in the action of resveratrol, besides SIRT1, is AMP-activated protein kinase (AMPK). AMPK controls various physiological functions, such as mitochondrial function, energy metabolism, insulin secretion, and biogenesis [69]. In this regard, McCart reported that AMPK promotes insulin sensitivity and fatty acid oxidation [70]. Furthermore, resveratrol activates AMPK by phosphorylation and acetyl-coA carboxylase [52]. Insulin resistance induced by the diet in animal models is preceded by decreased AMPK activity [71], and insulin resistance is genetically determined [39]. The insulin-sensitizing medicines thiazolidinediones and metformin usually stimulate AMPK in various tissues, even though a direct connection between AMPK initiation and the reduction of insulin resistance in humans has not been established [69]. Resveratrol activates AMPK to these drugs in insulin-resistant animals. Resveratrol also reverses diet-induced insulin resistance in rodents by restoring AMPK phosphorylation [36] and makes AMPK active in skeletal muscle [62].

Resveratrol Effect on Diabetes Involving Mitochondria

Resveratrol reduced the acetylation status of PGC-1α [35], a transcriptional co-activator that regulates the mitochondrial biogenesis mediated by SIRT1 deacetylation [72][73]. In addition, it is believed that in humans, mitochondrial muscle dysfunction speeds up intramuscular lipid deposition and reduces insulin action [74]. Therefore, resveratrol action in muscle tissues appears to depend on the rise in mitochondrial biogenesis caused by a concurrent reduction in intramuscular lipid level [65][66].

Resveratrol Effect on Diabetes via FFA Reduction

Increased release of free fatty acids is identified as a significant factor in the emergence of insulin resistance [75][76] in rodents [39][54][77] with diet-induced insulin resistance. In this respect, resveratrol has been shown to lower pancreatic triglyceride levels in animals fed with high-fat diets [37]. The anti-obesity properties of resveratrol may be connected to its anti-diabetic properties [13][14], with decreased action of lipogenic enzymes (acetyl-CoA carboxylase, glucose-6-P-dehydrogenase, and lipoprotein liPase) [45]. It is well known that having more body fat reduces the effectiveness of insulin and increases the risk of developing type II diabetes in humans [2][78]. Without causing appreciable changes in adiposity, resveratrol may enhance insulin action [79] or decrease body weight [54][68]. By increasing insulin receptor phosphorylation, resveratrol may also enhance insulin signaling in animals with insulin resistance in their skeletal muscles [80] and increased protein levels of IRS-1 [68].

3. Curcumin

Curcumin exhibits anti-inflammatory properties that may aid in controlling diabetes. Curcumin analogs have been identified and are currently the subject of extensive research for their potential roles in diabetes. In this regard, numerous studies on the effectiveness of curcumin in regulating blood glucose in various rodent models have been published. According to Arun and Nalini, curcumin lowers blood sugar, hemoglobin (Hb), and glycosylated hemoglobin levels (HbA1C) [81] and recovers insulin sensitivity [82]. Similarly, Abu-Taweel and coworkers reported that curcumin improves diabetes pathology through various mechanisms, including the control of lipid metabolism; antioxidant activity; and other activities such as antiapoptotic, anti-inflammatory, and antihyperglycemic activities [83]. Research findings indicated that curcumin extract reduces insulin resistance, prevents cell death, delays the onset of diabetes, and enhances cell functions in animal models [84]. Similar results were obtained when 250 mg curcuminoids were used for nine months in pre-diabetic patients not diagnosed with diabetes. Furthermore, Chuengsamarn et al. [33] reported that curcumin improves the overall performance of β-cells with higher homeostasis model assessment (HOMA-β) and lower C reactive protein (CRP). Those who received curcumin experienced higher levels of adiponectin and lower levels of insulin resistance. In the meantime, Wickenberg reported that postprandial serum insulin concentrations increased by 6 g turmeric ingestion without having an appreciable impact on plasma glucose levels [85]. A paper by Gutierres and colleagues showed that giving curcumin for 31 days to STZ-induced diabetic rats reduced the hyperlipidemic and hyperglycemic effects [86]. On the other hand, a different study found curcumin (90 mg/kg BW) with insulin (1 U/day vs. 4 U/day) in STZ-induced rats decreased hyperglycemia, hypercholesterolemia, and biochemical markers of kidney and liver damage while increasing the activity of glutathione peroxidase and superoxide dismutase (hepatic antioxidants) [87].

In addition, curcumin has excellent wound-healing qualities due to its capacity to reduce oxidative stress by removing free radicals [88]; many people with diabetes experience difficulties with wound healing [89]. In this context, Yang and coworkers showed that curcumin can prevent retinal attenuation by enhancing the retina's ultrastructure [90]. By promoting the superoxide dismutase enzyme's expression, curcumin can reduce oxidative stress [91] and the reduction of ROS production, both of which are crucial for treating diseases such as diabetes caused by oxidative stress and inflammation

[92]. Oxidative stress is thought to make diabetes worse, whereas ROS have been proposed to be crucial in diabetes pathogenesis. Curcumin's chemical makeup and anti-oxidative strength allow it to function naturally as a free radical scavenger. Fasting blood glucose (FBG), hemoglobin A1c (HbA1C), estimated average glucose (EAG), and body mass index (BMI) levels were all improved by curcumin in diabetic patients [93]. In this respect, Panahi et al. reported that curcuminoid supplementation has an antioxidant effect in T2DM patients because it reduced malondialdehyde (MDA) and raised serum SOD activity and total antioxidant capacity [94]. Similarly, Jain reported that curcumin diet supplements (50 or 100 mg/kg BW) decrease hyperglycemia and inflammatory processes in STZ-induced diabetic rats by preventing McP-1, HbA1c, TNf-α, IL-6, and lipid peroxidation and suppressing the NF-kB signaling pathway; protecting against inflammation [95]; and restoring normal antioxidant enzymes levels, including catalase, glutathione peroxidase, and SOD [96].

He et al. [97] also reported that curcumin prevents the NF-kB signaling cascade and inflammation. Reduced levels of IL-6 and TNF-a were assessed in STZ-induced diabetic rats with heart damage in a study by Abo-Salem et al. [98]. On the other hand, Arafa showed that curcumin could increase insulin sensitivity by decreasing cholesterol and blood glucose levels [99]. A high curcumin supplement (100 mg/kg) improved insulin intolerance and glucose in gestational diabetes mice by triggering the AMPK pathway [100]. Findings also showed that curcumin treatment significantly decreased superoxide production and NADPH oxidase subunit expression (p67phox, p22phox, and gp91phox) in diabetic rats. This effect may have been caused by curcumin inhibiting the protein kinase C (PKC)-MAPK signaling pathway [101]. Oxidative stress and endoplasmic reticulum (ER) were protected from diabetes by the novel curcumin analog C66, which inhibited JNK activation in diabetes [102]. Additionally, results showed that curcumin significantly increased mitochondrial permeability and decreased palmitate-induced oxidative stress. It did this by causing pancreatic β-cells to secrete more insulin when glucose was present [103]. Pathological complications of diabetes include diabetic nephropathy, diabetic neuropathy, vessel damage, and cardiovascular diseases [104]. In contrast, Panahi et al. [105] reported that taking curcumin (1 g daily) for three months reduces leptin levels and the leptin/adiponectin ratio (an indicator of atherosclerosis) in patients with atherosclerosis; it also increased adiponectin.

4. Quercetin

Quercetin (**Figure 3**) has been proven useful in treating T2D [106]. Research by Pereira and coworkers showed that quercetin interacts with molecular marks in the adipose tissue, liver, skeletal muscle, pancreas, and small intestine to maintain glucose homeostasis [107]. Other studies reported that quercetin treats T2D by reducing hyperglycemia, enzyme levels, liver glucose content, high blood pressure, serum cholesterol levels, and hyperlipidemia, as well as by encouraging weight loss [106][108], lowering blood sugar levels [109][110][111], improving glucose tolerance [109][112] and hepatic glucokinase activity [112], and enhancing the subsequent release of insulin and pancreatic cell regeneration [113][114]. In this respect, research findings revealed that quercetin activates AMPK, which inhibits glycogenic isoenzymes such as phosphoenolpyruvate carboxylase (PEPCK) and glucose-6-phosphatase (G6Pase) to reduce glucose synthesis [111][115] and stimulate protein kinase B (Akt) and skeletal muscle GLUT4 receptors, which in turn activates AMPK in the cell membrane [116]. Pereira confirmed that the GLUT4 transporter controls blood sugar levels by controlling glucose entrance into the cells [107]. In another study, Borghi indicated that by encouraging the GLUT4 translocation to the cell membrane, quercetin administration, GLUT2 expression, and intestinal-sodium-dependent glucose uptake are reduced, thus lowering gastrointestinal absorption of glucose and controlling blood sugar levels [117].

Similarly, Spínola et al. showed that the inhibition of pancreatic-amylase and intestinal-glucosidase decreases starch hydrolysis, slows postprandial hyperglycemia progression, and diminishes the rate of glucose absorption by quercetin usage [118][119]. Another study reported that quercetin improves dyslipidemia caused by a high-fat diet (HFD) in Swiss albino mice [120]. By controlling the levels of c-peptide and HbA1c, quercetin reduced the harm to pancreatic β-cells [121] and decreased lipid levels and insulin resistance [122], thus increasing pancreatic β-cell functions and exerting anti-hyperglycemic activity in diabetic rats [123]. In this respect, 20 µM of quercetin induced a significant increase in insulin secretion by increasing intracellular calcium ions through interaction with L-type Ca^{2+} ion channels in INS-1 β-cells [124], as well as simultaneous transient inhibition of KATP channels [125]. According to these results, quercetin controls glucose metabolism by enhancing glycolysis and reducing gluconeogenesis [126]. Moreover, published research showed that fat accumulation, reduced body weight, dyslipidemia, hyperglycemia, and hyperinsulinemia were significantly improved by quercetin treatment due to improved gene-associated glucose or lipid metabolism in high-fat-fed obese mice [122][127]. In addition to lowering blood sugar and HbA1c levels, Wang et al. found that oral administration of quercetin in multiple doses improved glycogen synthesis, decreased insulin resistance, and lowered glucosidase activity. Furthermore, it decreased oxidative stress, which enhanced pancreatic insulin secretion and helped diabetic patients control their blood glucose levels [102]. In addition, quercetin helps in alleviating diabetic complications by blocking AR [128].

The protein expression of insulin-signaling molecules such as phosphatidylinositol 3-kinases (PI3K) and insulin receptor substrate-1 (IRS-1) can be increased by quercetin, according to studies on STZ-induced diabetic rats; this results in an increase in insulin-mediated glucose uptake [107]. A survey by Ashraf and colleagues showed that quercetin lowers oxidative stress by scavenging ROS and improving the AMP/ATP ratio in clonal pancreatic cells [129]. On the other hand, obesity-related T2DM is associated with fat buildup in the muscles and liver, which triggers the nuclear transcription factor NF-B (NF-B) and Jun N-terminal kinase (JNK) inflammatory pathways [130]; both of these pathways are suppressed by quercetin [131]. In addition, brown adipose tissue releases pro-inflammatory mediators such as IL-8, IL-4, IL-1, IL-6, TNF-α, and histamine in response to high blood glucose levels and improved insulin resistance [132]. These mediators are inhibited by quercetin, which also reduces oxidative stress [133]. Blocking the enzymes lipoxygenase and cyclooxygenase prevents the release of pro-inflammatory mediators such as prostaglandins and leukotrienes [134]. Yao et al. reported in a clinical survey conducted among the Chinese population an inverse relationship between quercetin consumption and the prevalence of T2D [135].

5. Catechins

Kim and colleagues reported that catechins stimulate either GLUT4 transcription or translocation to the plasma membrane in muscle cells and glucose uptake in peripheral tissues. Furthermore, catechins inhibit lipogenesis, glycogen synthesis, and glucose oxidation in liver cells [136]. Similar results were reported by several studies [137][138][139][140][141]. Catechins can also impair glucose transporters on the plasma membrane of intestinal cells, Similarly, epicatechin gallate inhibits the Na^+-dependent glucose transporter in rabbit intestinal brush-border membrane vesicles (SGLT1), demonstrating that epicatechin gallate inhibits SGLT1 [142][143]. Moreover, researchers showed that catechins prevent weight gain and the start of chronic illnesses such as T2D or metabolic syndrome when consumed regularly [144][145]. Similarly, other researchers indicated that epigallocatechin gallate inhibits pancreatic glucosidase in a noncompetitive manner that is reversible [146][147][148]. Moreover, galloylated catechins are more potent than nongalloylated catechins at inhibiting glucosidase and amylase. Depending on their chemical composition, catechins have varying levels of inhibitory power [149].

6. Isoflavones

Findings showed that the consumption of isoflavone decreased the risk of diabetes [150] via glucose uptake inhibition and negligible intestinal carbohydrate absorption [151]. In addition, isoflavones enhance insulin sensitivity and resistance, safeguarding pancreatic β-cells, acting as an anti-inflammatory agent, reducing oxidative stress, and preventing the formation of the Maillard reaction and advanced glycation end products [152]. In this context, Rockwood et al. reported that genistein significantly lowers hyperglycemia in T2D [153][154], increases cell proliferation while decreasing apoptosis [155], and reduces oxidative stress and cardiac inflammation [156]. In contrast, daidzein's preventive effect on reducing hyperglycemia, dyslipidemia, obesity, insulin resistance, inflammation, and other T2D complications has been thoroughly studied. It causes an immunomodulatory effect in mice with diabetes [157][158]. To incorporate several methods to increase flavonoids' antidiabetic activity, numerous strategies have been developed in recent years to use flavonoids in vitro and in vivo models.

7. Hydroxycinnamic Acids

Ferulic Acid

Published research revealed that ferulic acid (FA) lowers hyperglycemia, the lipid profile, creatinine, urea, serum glutamic oxaloacetate transaminases, and serum glutamic pyruvic transaminases while maintaining islet mass in STZ-induced diabetic rats over the course of three weeks [159]. At doses of 0.01 and 0.1% of the standard diet, FA lowered blood glucose levels in STZ-induced diabetic mice. In KK-Ay mice, 0.05% FA significantly lowered blood glucose levels [160]. Similarly, oral administration of FA (10 and 50 mg/kg BW) into STZ-induced diabetic rats demonstrated antioxidant activity; it decreased the levels of lipid peroxidation indicators in the serum, liver, pancreas, and kidney [161]. In this respect, several food items such as tomatoes, berries (such as strawberries), rice husks, and other fruits and vegetables commonly contain FA [162][163]. By increasing plasma insulin levels, glucokinase activity, and liver glycogen synthesis in diabetic rats, FA and sinapic acid effectively decreased blood glucose levels [164][165].

Gallic Acid

Gandhi et al. reported that gallic acid (GA) exhibits antidiabetic properties in animal models lacking insulin or are resistant to insulin [166] by significantly reducing blood sugar, triglyceride, total cholesterol, urea, uric acid, low-density lipoprotein cholesterol, and creatinine while simultaneously raising plasma levels of insulin (16.3 U/mL), C-peptide, and glucose

tolerance [167]. Other researchers showed that GA reduces gluconeogenesis and increases glycolysis, ultimately decreasing hyperglycemia in STZ-induced diabetic rats [168]. Fruits such as grapes and berries contain GA [169][170]; in this regard, researchers found that apple juice and berries might help improve short-term glycemic control [9].

Protocatechuic Acid

Protocatechuic acid (PCA) showed reduced levels of hepatic gluconeogenic enzymes such as fructose-1,6-bisphosphatase, glucose 6-phosphatase (G6Pase), and sorbitol dehydrogenase, as well as increased levels of glucose-6-phosphate dehydrogenase and hexokinase in STZ-induced diabetic rats [171]. These results show that PCA can enhance GLUT4 translocation, adiponectin secretion, and glucose uptake [172]; prodigious amounts of PCA are found in gooseberry, raspberry, blueberry, mulberry, honey, soybeans, and loquat fruit [171].

Ellagic Acid

Ellagic acid (EA) might be a useful dietary supplement to lessen the metabolic changes associated with HFD feeding animals in combination with STZ injection [173]. EA reduces glycation stress, hyperglycemia, inflammation, and hyperinsulinemia and aggravates renal function dose-dependently. In this respect, research findings showed that EA (3.12–50 M) increases the expression of PPAR in L6 myotubes and GLUT4 [174].

Salicylic Acid

Blackberries, cantaloupes, blueberries, dates, grapes, apricots, kiwis, olives, green peppers, radishes, tomatoes, and mushrooms are among the foods that contain salicylic acid in high concentrations. This acid lowers blood concentrations in diabetic Goto-Kakizaki rats [175].

Caffeic Acid

Numerous fruits and vegetables, including blueberries, kiwis, cherries, plums, apples, pears, potatoes, artichokes, cider, and coffee, contain caffeic acid (CA), a phenolic acid [7]. Researchers reported that dietary supplements with CA (0.02% in the diet for five weeks) decrease blood glucose, G6Pase, and phosphoenolpyruvate carboxy kinase activities, accompanied by a decrease in the liver GLUT2 expression and enhanced insulin levels, glucokinase, catalase, glutathione peroxidase, and SOD activities in db/db mice [176]. Additionally, CA significantly lowered the levels of plasma HbA1c [177]. In insulin-resistant rats undergoing a glucose test, administration of CA reduced the elevation of plasma glucose levels. CA also increases the isolated adipocytes' ability to absorb glucose. Moreover, the reduction in plasma glucose appears to be caused by CA's increased glucose utilization [178].

***p*-Coumaric Acid**

Another phytochemical, *p*-coumaric acid, is prevalent in fruits and vegetables, including apples, pears, beans, potatoes, tomatoes, tea, and pineapple [179][180][181]. By changing glucose and lipids' metabolism, *p*-coumaric acid can potentially prevent or treat insulin resistance and T2D [182].

Chlorogenic Acid

Chlorogenic acid (CGA) increases GLUT in skeletal muscle by phosphorylating AKP-activated protein kinase, which enhances the metabolism of lipids and glucose, thus reducing the hazard of diabetes [183]. Evidence suggests that CGA reduces intestinal-sodium-gradient-driven glucose transport and inhibits G6Pase. It increased AMPK phosphorylation and favorable metabolic changes linked to AMPK activation while improving skeletal muscle glucose uptake and lipid profiles [184]. In addition, Bassoli and coworkers reported that inhibiting G6Pase activity prevents the production of hepatic gluconeogenesis [185]. Moreover, it reduced hepatic steatosis and inhibited the expression and activity of G6Pase in the liver [186]. Cherries, apples, kiwis, artichokes, eggplants, plums, and coffee are just a few of the foods that contain CGA, one of the most prevalent phenolic compounds [7]. CGA reduces the effects of retinopathy and other diabetic complications in animals by preventing retinal neo-angiogenesis [187]. Furthermore, enzymes that break down carbohydrates are weakly inhibited by chlorogenic acid [188]. Research findings indicated that CGA inhibits glucosidase activity [189].

***trans*-Cinnamic Acid**

trans-Cinnamic acid (t-CA) is found in numerous food-related plants, fruits, and herbs [190]. Through the involvement of GLUT4, t-CA (1 ng/mL) isolated from Cinnamomum cassia activates insulin-mediated glucose transport [191]. In isolated islets, it significantly increased glucose-enhanced insulin secretion [192]. Daily oral administration of t-CA (80 mg/kg BW) for four weeks decreased hyperglycemia in male albino rats with diabetes induced by alloxan [193]. These results

demonstrate that treatment with t-CA (80 M) increases AMPK activation and adiponectin secretion. Additionally, the inhibitory effect of paclitaxel suggests that t-CA-stimulated signaling in 3T3-L1 adipocytes involves a G-protein-coupled receptor and enhances insulin sensitivity [194].

8. Anthocyanins/Anthocyanidins

Zhou and coworkers reported that anthocyanidins (ACNs) promote health through their antioxidant, anti-inflammatory, and blood-sugar-regulating properties [111]. In this regard, AMPK/ACC/mTOR pathway helps anthocyanin-rich mulberry extract prevent hyperglycemia [195]. Other researchers showed that by managing blood lipid and triglyceride levels, lowering cholesterol, and having low-density cholesterol while raising high-density cholesterol and apolipoprotein, ACNs might reduce insulin resistance [196]. Moreover, anthocyanins stimulated the release of insulin by increasing the appearance of the intracellular Ca^{2+} signaling pathway and the glucose-transport-related gene (Glut2) in mouse islet β-cells. Along this line, purple potato extract with added cyanidin increased insulin secretion [197]. Delphinidin 3-arabinoside anthocyanidins, found in fermented berry beverages, controlled DPPIV and its substrate GLP-1, boosted insulin secretion, and increased the mRNA expression of genes related to insulin receptors [198]. Published work by Graf et al. showed that ACN-rich grape-bilberry juice (AGBJ) supplementation improved several risk factors for diseases linked to obesity in male Fischer rats for ten weeks. Results revealed that AGBJ intervention successfully reduced serum levels of triglycerides and leptin while having no impact on the release of adipokines, adiponectin, glucose, insulin, or non-esterified fatty acids. In addition, AGBJ increased plasma levels of polyunsaturated fatty acids while lowering levels of saturated fatty acids. Overall, the findings suggested that AGBJ might effectively combat metabolic diseases linked to obesity [199]. In STZ-induced T2DM rats, ACNs from purple root vegetables reduced liver damage and oxidative stress and enhanced lipid and blood glucose levels [200].

ACNs act as anti-inflammatory agents by suppressing the expressions of a few inflammatory cytokines crucial to the inflammatory response, including TNF-, IL-6, and IL-1 [201][202][203][204]. Monocyte chemoattractant protein 1 (MCP-1), a chemokine, plays a role in developing diabetes mellitus by controlling leukocyte migration and infiltration [205]. Numerous studies demonstrated that ACNs can lower MCP-1 expression [204][206]. In addition, research findings showed that ACNs could be a potent therapeutic agent to prevent obesity and diabetes because of the changes in AMP-activated protein kinase activation. ACNs decreased the AMP/ATP ratio, which strongly correlated with ACN supplementation. [207]. AMP-activated protein kinase (AMPK) is a critical molecule in the control of glucose metabolism in the liver, white adipose tissue, and skeletal muscle, which is activated by ACNs [200][208][209][210][211]. Activation of AMPK induces GLUT4, thus improving glucose utilization and uptake [211][212]. Moreover, the production of the liver's glucose is decreased when AMPK is activated [213]. Findings confirmed that ACNs could help with obesity, as well as impaired glucose tolerance, insulin resistance, and DM prevention. Cyanidin-3-glucoside (C3G) improved glucose tolerance (GT) and reduced body weight gain in mice fed with a high-fat diet [214]. In this regard, numerous studies demonstrated that ACN-rich blueberries can decrease body weight, enhance lipid profiles, suppress the countenance of inflammatory factors, and increase insulin sensitivity in animal models fed with a high-fat diet [202][215][216][217]. Black elderberry [206], raspberry [218], Aronia melanocarpa [219][220], and black rice [221] are rich in ACN and could improve insulin resistance and lipid metabolism in the liver or serum in obese mice.

Takikawa et al. [208] reported that bilberry extract containing an increased ACN level significantly decreases blood glucose levels in T2DM mice and improves insulin sensitivity. Feeding T2DM mice a diet containing 0%, 5%, or 10% buckwheat sprouts revealed that as the number of buckwheat sprouts in the diet increases, lipids levels and blood glucose improve more noticeably [222]. Similarly, ACNs from the black soybean seed coat could also lessen the harm done to the liver, kidney, and pancreas in STZ-induced T2DM mice [223]. In a different experiment involving animals, giving blueberry ACN extract to T2DM mice improved glucose tolerance and blood glucose levels; reduced polydipsia and polyuria symptoms; and reduced TC, TG, and insulin levels [224]. Ye and colleagues reported that C3G intervention reduces blood sugar and insulin resistance and improves blood sugar and lipid parameters in db/db mice [225]. Furthermore, diabetic db/db mice supplemented with dietary C3G for 5 weeks showed reduced hepatic triglyceride content and steatosis and decreased inflammatory cytokine concentration in the serum [226].

On the other hand, malvidin and ACNs were used in combination with metformin in the treatment of STZ-induced diabetic rats, and the outcomes demonstrated that the combination therapy has more significant relief from insulin resistance, decreased fasting blood glucose, and improved lipid metabolism and serum insulin compared to single therapy [227]. After receiving combined treatment with fenofibrate and ACNs in T2DM patients with postprandial hyperlipidemia, the serum postprandial triglyceride level and LDL cholesterol concentration were pointedly reduced (from black soybeans) [228]. Several studies showed that ACNs can decrease the initiation of pro-inflammatory factors and improve insulin resistance [213][229]. ACNs prevent the stimulation of JNK and NF-B, which lowers the phosphorylation of IRS-1 serine residues and

improves insulin resistance [213][217]. Additionally, it has been demonstrated that ACN can trigger the production of adiponectin, which can potentially reduce insulin resistance [204][230][231]. ACNs increase the efficiency of two enzymatic antioxidants called SOD and catalase (CAT), which shield cells from oxidative damage by catalyzing the conversion of free radicals into hydrogen peroxide [204][232]. Furthermore, the inflammatory response may accelerate the development of DM complications and contribute to insulin resistance, eventually resulting in T2D complications [233]. Cranberries, blackberries, chokeberries, black grapes, gooseberries, bilberries, red raspberries, blueberries, blackcurrants, and strawberries are rich sources of ACNs. Other sources include a variety of other fruits such as peaches, grapes, nectarines, pomegranates, plums, cherries, seeds, and vegetables, i.e., red onions and red lettuce [234].

9. Kaempferol

Kaempferol exhibits anti-oxidative stress anti-hyperglycemic [235], anti-inflammatory [236], and hypolipidemic [237] effects. Inflammatory cytokines, including TNF-α and IL-6, stimulate the c-Jun amino-terminal kinase (JNK) and I-kB kinase-b/nuclear factor-kB (NF-kB) paths in insulin-sensitive organs and inhibit insulin signaling [238]. Similar to an insulin secretagogue, kaempferol enhances insulin secretion. Kaempferol increased plasma insulin levels while lowering the blood glucose level in STZ-induced diabetic rats [239]. Kaempferol directly activates mitochondrial calcium uptake (MCU) in a concentration-dependent manner. An amount of 1 µM can trigger the pancreatic β-cell secretion/metabolism/coupling and closely dual the uptake of mitochondrial Ca^{2+} [240][241]. With an increase in cAMP, Ca^{2+}, and glutathione (GSH) levels, kaempferol raises glucagon-like peptide 1 (GLP-1) and insulin levels [242]. In this respect, Fang et al. showed that in 3T3-L1 adipocytes, kaempferol enhances insulin-dependent glucose uptake [243]. Kaempferol also lowers blood glucose levels by boosting GCK levels and enhancing glycogen synthesis [22].

An imbalance in the making and utilization of glucose leads to disorders of glucose metabolism. Hepatic IR plays a significant role in fasting hyperglycemia. In this regard, abnormal glucose-metabolism-regulating enzyme levels, such as phosphoenolpyruvate carboxykinase, PC, glucokinase (GCK), and glucose-6-phosphatase, are a hallmark of hepatic IR (PEPCK). Blood sugar levels directly affect how GCK is activated and inactivated. Activation of GCK is thus a probable target for diabetes treatment [244]. Kaempferol (50 mg/kg/day), administered orally to mice, significantly reduces hyperglycemia by reactivating hexokinase and inhibiting PC and gluconeogenesis [235]. A direct rise in the activity of Akt and inhibition of PC are additional components of the mechanism by which kaempferol inhibits hepatic gluconeogenesis [22], as Akt phosphorylates and suppresses FOXO1 transcription when insulin signaling is activated, ultimately suppressing PEPCK and G6P expression [245][246]. As part of its anti-inflammatory effects, kaempferol prevents the hepatic inhibitor IkB kinase/NF-kB pathway and restores Akt activity [247]. To create phosphatidylinositol (3,4,5)-triphosphate, insulin first binds to the insulin receptor on the cell's outer surface, causing tyrosine phosphorylation of the insulin receptor substrate (PIP3). Protein kinase C (PKC) and P70 ribosomal S6 kinase (S6K) are both activated by PIP3 after Akt, a 3-phospholipid-dependent protein kinase I, is activated [248].

The physiological effects of insulin are significantly influenced by Akt-dependent phosphorylation. GSK3a/b is first inactivated by Akt-induced phosphorylation, which then causes dephosphorylation and activation of glycogen synthase [249]. To control the intracellular GLUT4 vesicle movement to the cell membrane and boost glucose uptake, Akt phosphorylates the 160 kDa TBC1D4/AS160 substrate [250][251]. To have an anti-inflammatory effect, kaempferol constrains the hepatic Ik-B kinase/NF-kB pathway and increases Akt activity [247]. Adipose tissues, the liver, and the muscles exhibit increased AMPK and ACC phosphorylation in response to kaempferol [252][253]. For the treatment of diabetes, AMPK activation is an important pharmacological target. In this context, thiazolidinediones (TZDs) and metformin have been recognized as AMPK activators [254]. Foods high in kaempferol can lower postprandial glucose levels and decrease carbohydrate absorption. Changes in the intestinal microbiota play a significant role in metabolic syndrome, type II diabetes, and obesity [255]. Additionally, kaempferol decreases the relative richness of thick-walled flora, boosts bacteroides, lowers blood lipid and glucose levels, and enhances IR in C57BL/6 obese mice [256]. The excellent autophagy enhancer kaempferol reduces ER stress, promotes intracellular lipid degradation, and guards against lipotoxic damage to β-cells [257]. To maintain intracellular balance, autophagy is well-defined as an intracellular lysosomal degradation process of defective proteins, macromolecules, damaged organelles, and toxic aggregates [258]; disorders of autophagy are linked to IR, obesity, and T2DM [259]. In another study, Varshney and coworkers reported that through AMPK mTOR signaling, treatment with 10 µM kaempferol increased lipid droplet co-localization with lysosomes and autophagosomes in cells and decreased ectopic lipid buildup and ER stress [260]. Chronic hyperglycemia in diabetes eventually destroys the mitochondrial function, activates nicotinamide adenine dinucleotide phosphate oxidase, and increases the production of ROS [261]. The excellent antioxidant effect of kaempferol can prevent excessive ROS from damaging β-cells. Kaempferol protects pancreatic β-cells from oxidative damage in diabetes [262]. In the kidney, liver, heart tissues, and erythrocytes of diabetic rats, kaempferol significantly increases membrane-bound ATPase activity [263]. This is

yet another way that kaempferol protects β-cells. Natural plants such as ginkgo biloba, galangal, and pueraria have been used for a long time, especially in Asia, and are good sources of kaempferol. In addition, it can be found in foods such as tomatoes, beans, gooseberries, grapes, cabbage, cauliflower, and strawberries [423

10. Hesperetin

Hesperidin effectively reduces pancreatic β-cell dysfunction and programmed cell death in diabetic rat models, as well as the expression of the 78-kDa glucose-regulated protein (GRP78) [264]. Additionally, by upregulating the anti-apoptotic cell lymphoma extra-large (Bcl-xL) and downregulating the BCL2-linked X-protein, hesperidin as an apoptosis regulator successfully modulated the expressions of apoptosis regulatory proteins (Bax) [264]. Additionally, by controlling AMPK-mediated p300 inactivation, hesperetin and naringenin protected pancreatic β-cells in both in vitro and in vivo models [265]. The apoptosis of pancreatic β-cells is influenced by the initiation of the MAPK and FoxO1/PPAR signaling pathways [266] and may accelerate the development of type II diabetes and insulin resistance [267]. Furthermore, phosphorylation of the MAPK activates NF-kB, causing the release of pro-inflammatory cytokines [268]. Research findings indicated that hesperetin metabolites reduce inflammation by preventing the phosphorylation of NF-B and MAPK. Finally, it is worth mentioning that hesperidin is most prevalent in citrus fruit [269].

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