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Review

Flavonoids for preserving pancreatic beta cell survival and function: A mechanistic review

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ABSTRACT

Although the currently available antidiabetic medications are effective in managing hyperglycemia, vascular complications are common in diabetic patients. Cohort studies have shown preserved beta cell function has a protective role against the development of diabetic complications. Accordingly, beta cell mass and function are important pharmacological targets in the field of diabetes. Growing number of evidence supports the efficacy of flavonoids (e.g., quercetin, kaempferol, luteolin, and epicatechin) for prevention and attenuation of diabetes consequences. The focus of this paper is to give an overview regarding the effects of flavonoids on pancreatic beta cells. Experiments on insulin-releasing cell lines, isolated pancreatic islets, and diabetic animal models have shown that flavonoids strengthen the survival processes and insulin secretory capacity of beta cells. The proposed mechanisms by which flavonoids preserve beta cells survival (against cytokines, glucotoxicity, and lipotoxicity) include inhibition of NF-κB signaling, activation of PI3K/Akt pathway, inhibition of nitric oxide generation, and decrease of reactive oxygen species levels. Improving mitochondrial bioenergetic function and stimulating pathways of insulin secretion (e.g., PLC/PKC and/or cAMP/PKA signaling) are mechanisms by which flavonoids improve the secretory capacity of beta cells. These beneficial effects of flavonoids are of great importance because may protect beta cells of diabetic patients before dramatic dysfunction and degeneration.

1. Introduction

Diabetes mellitus is a chronic metabolic disease characterized primarily by dysregulation of glucose homeostasis leading to hyperglycemia. According to the report by the World Health Organization (November 2017), the global prevalence of adult diabetes is more than 8% and it will be the seventh cause of death in 2030. Based on its etiology and pathology, the disease is generally classified into type-1 diabetes (T1D) and type-2 diabetes (T2D). While patients with T1D show insulin deficiency because of beta cells destruction, T2D is associated with a progressive loss of insulin secretion based on the background of insulin resistance [1]. In both types of diabetes, long-term hyperglycemia leads to multiple functional and structural abnormalities which damage to several organs including the kidneys, nerves, heart, eyes, and lower extremity [2].

Although the currently available medications (e.g., insulin and other anti-hyperglycemic and hypoglycemic drugs) are effective in controlling hyperglycemia, vascular complications occur finally in many diabetic patients [3,4]. Cohort studies have shown a protective role for residual beta cell function against the development of diabetic complications, suggesting the great value of treatments that allow preserving beta cell mass/function over the time [5,6]. It seems that the augmentation of endogenous insulin release has several advantages over exogenous insulin replacement. For example, (1) endogenous insulin is released into portal vein, producing better kinetics for reducing gluconeogenesis than those of subcutaneously injected insulin, (2) the level of endogenous insulin is precisely adjusted according to the amount of glucose loading, and (3) function of alpha cells is under the control of the pulsatile paracrine insulin release [7]. Therefore, preserving beta cell survival in early-diagnosed patients and restoring beta cell mass/function in chronic diabetic patients will be the rationale for long-term treatment of diabetes. Growing number of studies have shown that phytochemicals, particularly flavonoids, have beneficial effects on the prevention and treatment of diabetes [8–11]. In addition, several health-promoting effects have been demonstrated for flavonoids including antioxidant, anti-inflammatory, nephroprotective, and anticancer properties [12–14]. The focus of this paper is to give an overview regarding the possible effects of flavonoids on the survival and function

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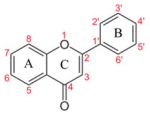
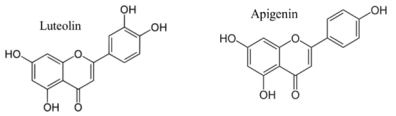
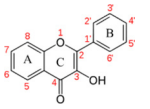
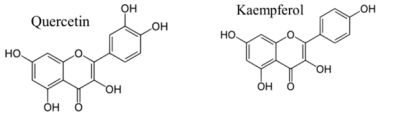
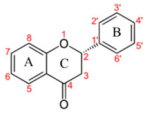
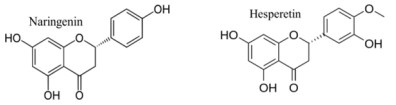
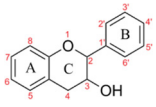
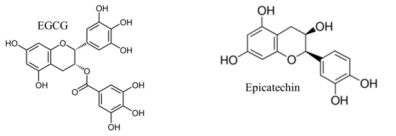
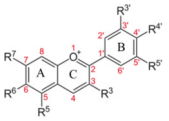
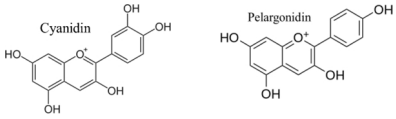
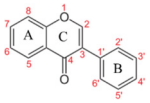
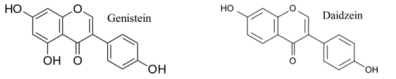
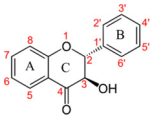
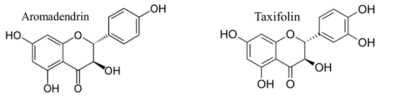
Table 1
Classification, structures, and examples of top natural sources of flavonoids. Neoflavonoids are not shown here, as they are not often found in food plants. EGCG: epigallocatechin gallate.

Subclasses	Description	Structure backbone	Examples	Natural sources
Flavones	2-phenylchromen-4-one			Parsley Oregano Artichokes Green pepper
Flavonols	3-hydroxy-2-phenylchromen-4-one			Capers Parsley Sorrel Radish Onion skin
Flavanones	2,3-dihydro-2-phenylchromen-4-one			Grapefruit Lemons Oranges Lemons
Flavanols	2-phenyl-3,4-dihydro-2H-chromen-3-ol			Green tea Black tea Dark chocolate Blackberries
Anthocyanidins	2-phenyl chromenylium			Elderberry Chokeberry Bilberries Chickpeas
Isoflavones	3-phenylchromen-4-one			Soybean Green bean Mung bean Cowpea
Flavanonols	3-hydroxy-2,3-dihydro-2-phenylchromen-4-one			Larch Chir pine Deodar cedar Milk thistle

of pancreatic beta cells.

2. Flavonoids: natural sources and classification

Flavonoids are a group of natural compounds with polyphenolic structure, widely found in vegetables, fruits, and, as naturally derived colors, added to certain beverages. Most flavonoids comprise two aromatic rings (A and B) connected via a heterocyclic pyrane ring (C). They are categorized into different subclasses based on which carbon of the C ring is connected to B ring and on the degree of oxidation and unsaturation of the C ring. In most flavonoids, the B ring is connected to the C-2 carbon of the C ring. These compounds include flavones, flavonols, flavanols, flavanones, flavanonols, and anthocyanidins (Table 1). Flavonol compounds differ from flavanones by a C-2 to C-3 double bond and a hydroxyl group at the C-3 position. Flavonoids in which the B ring is connected to the C-3 carbon of the C ring are named isoflavones. Those in which the B ring is attached to the C-4 carbon of the C ring are called neoflavonoids [15,16].

Among vegetables, parsley, oregano, artichokes, radish, and pepper contain high amounts of flavones and flavonols. Citrus such as grapefruit, lemon, and orange comprise high levels of flavanones. Different types of tea and berries are rich in flavonols and anthocyanidins, respectively. The isoflavones can be found in cereals and legumes including soybean, green bean, and cowpea [15,17,18]. Flavonoids are found in nature as aglycones, glycosides, methylated derivatives, and oligomers. The glycosidic linkage is usually D-glucose, galactose, arabinose, L-rhamnose, and glucorhamnose, which are typically located in positions 3 or 7 [16]. Some of the best-known glycosides are naringin, rutin, and hesperidin which are glycosides of the flavanone naringenin, flavonol quercetin, and the flavanone hesperetin, respectively [19].

2.1. Bioavailability and metabolism of flavonoids

The chemical structures of flavonoids determine their rate of intestinal absorption, metabolism, and excretion. Given that most of the dietary flavonoids are in the form of glycosides, the attached sugar must be hydrolyzed in the gastrointestinal tract to its more absorbable form. The main enzymes responsible for the hydrolysis include β-glucosidase within the enterocytes and lactase phlorizin hydrolase in the brush-border of these cells [20]. When the sugar moiety is detached, the resulting aglycone flavonoids can be absorbed by diffusion because of their enhanced lipophilicity. Depending on the dose and the type of flavonoid, the intestinal absorption ranges from 0 to 60% [21]. Flavonoids undergo phase II biotransformation reactions in the small intestine and liver. Within the enterocytes, flavonoids are conjugated by sulfotransferases, catechol-*O*-methyltransferase or uridine diphosphate glucuronosyltransferase to sulfated, methylated, or glucuronidated forms. Then, the conjugated compounds are transferred either back to the digestive tract or into the blood by different types of ATP-binding cassette transporters [22,23]. The absorbed compounds are transferred via the portal vein to the liver, where they can be subjected to further modifications such as hydroxylation, methylation/demethylation, and glucuronidation [24]. The resulting metabolites might be excreted into the bile or returned to the systemic circulation and ultimately eliminated by the kidney [21,23]. Despite their high absorption in the small intestine, a considerable amount of a given flavonoid and its metabolites (brought in by the bile) appear in the large intestine where they undergo further transformation (e.g., dehydroxylation and demethylation) by the colonic microbiota. Some of the colonic-derived compounds are absorbed into the bloodstream and circulate throughout the body prior to elimination by the kidney [25]. Pharmacokinetic studies

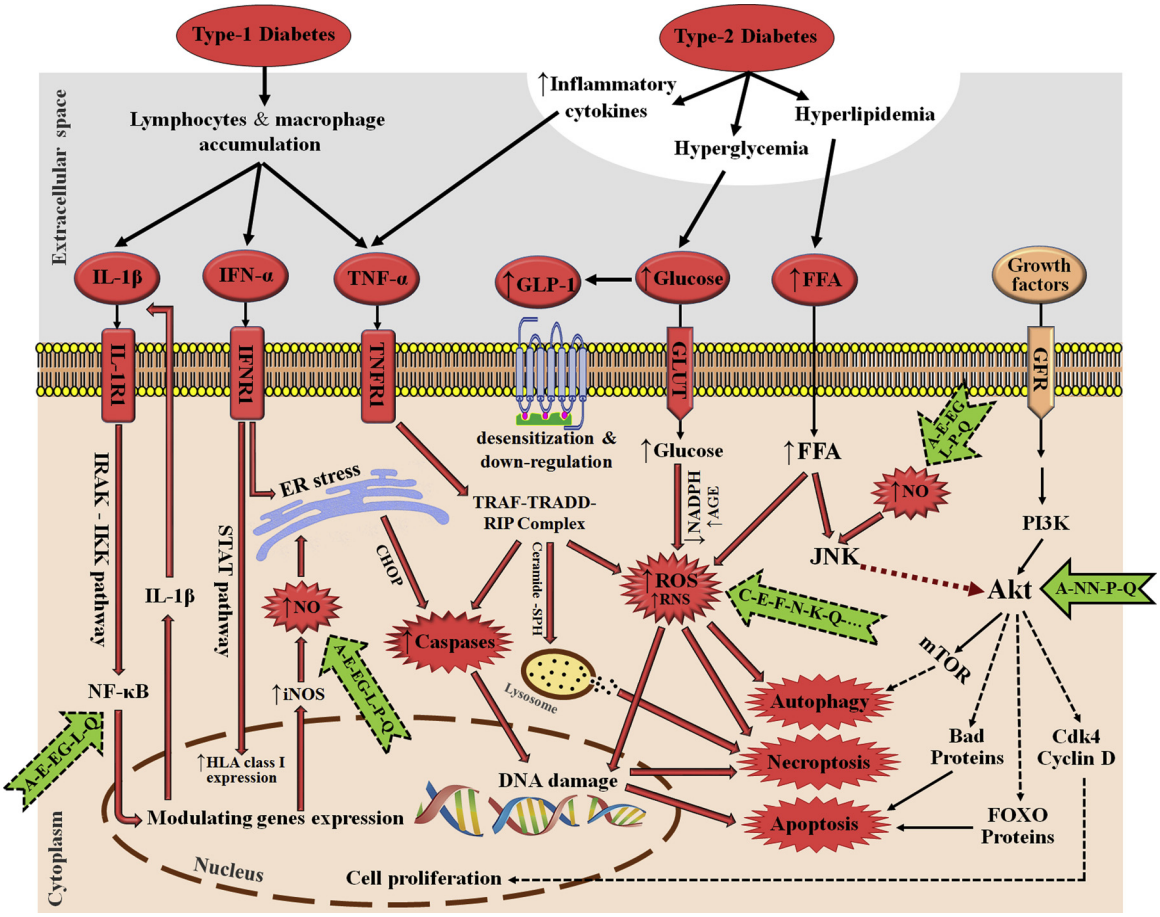


Fig. 1. Mechanisms of beta cell death in diabetes (red pathways) and the main mechanisms by which flavonoids preserve the survival of the cell (green arrows). Inhibitory effects were shown by dotted arrows. The letters inside the green arrows refer to flavonoids (A: apigenin; C: Chrysin; E: epicatechin; EG: epigallocatechin gallate; F: Fisetin; K: kaempferol; L: luteolin; N: Naringin; NN: Naringenin; P: puerarin; Q: quercetin). AGE: advanced glycation end-product; CHOP: CCAAT-enhancer-binding protein homologous protein; ER: endoplasmic reticulum; FFA: free fatty acids: FOXO: Forkhead box class O; GFR: growth factor receptor; GLUT; glucose transporter; GLP-1: glucagon-like peptide 1; IKK: inhibitor of nuclear factor kappa B kinase; IL-1β: interleukin 1β; IL-1R1: interleukin 1 receptor type 1; iNOS: inducible nitric oxide synthase; IRAK: interleukin 1 receptor-associated kinase; JNK: c-Jun N-terminal kinase; mTOR: mammalian target of rapamycin; NF-κB: nuclear factor kappa B; NO: nitric oxide; PI3K: phosphoinositide 3-kinase; RIP: receptor-interacting protein kinase; ROS/RNS: reactive oxygen/nitrogen species; STAT: Signal transducer and activator of transcription; TNF-α: tumor necrosis factor alpha; TNFR1: tumor necrosis factor receptor-1; TRADD: tumor necrosis factor receptor type 1-associated death domain protein; TRAF: TNF receptor-associated factors (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

in humans have reported wide variations in post-ingestion peak plasma concentration (C_{max}, 2 nmol/L to 8 μmol/L) and time to reach C_{max} (T_{max}, 0.3–9.3 h) depending on the type of flavonoids, dose, and intervention duration. Also, elimination half-life ($T_{1/2}$) can be as low as 1.6 h in the case of quercetin-3-*O*-glucuronide or as high as 43 h, as reported for flavone diosmetin [21–23,26].

3. Pancreatic beta cell death in diabetes

Fig. 1 summarizes the underlying mechanisms responsible for beta cell death in diabetes. In T1D, a combination of genetic and environmental parameters initiates autoimmune reactions that lead to lymphocytes and macrophage accumulation in the islets, followed by the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IFN-α. These cytokines, together with the excessive generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) by immune cells, activate intracellular signaling pathways that promote autophagy, apoptosis, or necroptosis [27]. In T2D, insulin resistance and impaired glucose-induced insulin secretion lead to sustained hyperglycemia, hyperlipidemia, and elevated inflammatory cytokines. These trigger oxidative stress, endoplasmic reticulum (ER) stress, and lysosomal destabilization, which stimulate cell death through apoptosis, autophagy, or necroptosis [28,29].

In diabetes, both the extrinsic and intrinsic signaling pathways of apoptosis are involved in beta cell death. The extrinsic pathway is initiated by the binding of death stimuli such as TNF-*α* and Fas ligand (Fas-L) to their cell surface receptors. In the case of TNF-α, its receptor (TNFR-1) triggers a series of intracellular signals that finally leads to the activation of caspases-3 and -7. These caspases cleavage several substrates such as poly (ADP-ribose) polymerase, lamin, and XK-related protein 8, leading to apoptotic changes in beta cells including nuclear condensation, membrane blebbing, and DNA-fragmentation [30]. Activation of TNFR-1 is also capable to start autophagy and necroptosis pathways through the formation of necrosome, a complex that facilitates production of ROS (leading to autophagy) and permeation of the lysosomal membrane (leading to necroptosis). IFN-α and IL-1β can amplify apoptotic pathways in beta cells through inducing ER stress and increasing the level of inflammatory and immunity mediators like Fas-L, nitric oxide (NO), and human leukocyte antigen class I [28,31,32].

The intrinsic pathway of apoptosis is governed by the Bcl-2 protein family, which contains pro-apoptotic (e.g., Bad, Bax and Bak) and anti-apoptotic (e.g., Bcl-x L, Bcl-2, and Bcl-w) members. In response to apoptotic stimuli such as oxidative stress and hypoxia, Bax and Bak permeate mitochondrial outer-membrane, leading to the efflux of

cytochrome c to the cytoplasm. Cytochrome c facilitates stimulation of caspase-9, which in turn promotes apoptosis by activation of caspases-3 and -7 [30].

In diabetes, oxidation of intracellular glucose and FFA generates excessive ROS/RNS, which induces beta cell apoptosis through the intrinsic pathway. Increased levels of intracellular glucose facilitate production of sorbitol by aldose reductase, a reaction that consumes NADPH. Depletion of NADPH decreases the regeneration of reduced glutathione, an important intracellular antioxidant, and therefore makes the cell susceptible to oxidative damage [9]. Increased levels of ROS/RNS can damage proteins and DNA, thereby induces apoptosis or triggers pathways that end with autophagy or necroptosis [28]. Also, chronic exposure of beta cells to elevated levels of FFA leads to ER stress, which triggers apoptosis by enhancing transcription of CCAAT-enhancer-binding protein homologous protein (CHOP) and by activation of caspase-12 and c-Jun N-terminal kinase (JNK), a mitogen-activated protein kinase (MAPK) [33,34]. The activation of JNK by ER stress, cytokines, or oxidative stress results in inhibition of phosphoinositide 3-kinase (PI3K)/ Akt (also known as protein kinase B) pathway. The PI3K/Akt signaling has a key role in the regulation of beta cell mass and function [33,35]. Akt preserves cell survival and proliferation by modulating the activity of the mammalian target of rapamycin (mTOR), Forkhead box (Fox) proteins, Bad proteins, nuclear factor-kappa B (NF-κB), glycogen synthase kinase-3, and cyclin-dependent kinases (CDK) [35].

4. Effects of flavonoids on beta cell survival

Evidence of the effects of flavonoids on beta cell survival falls into two main categories: first, the studies performed on in vivo animal models of diabetes; and second, the experiments conducted on the isolated islets or insulin-secreting cell lines in vitro. Table 2 summarizes the results from studies that evaluated the effects of flavonoids on the survival of beta cells in diabetic animals.

Several independent laboratory studies have shown that quercetin [36–41] and proanthocyanidins [42–44] preserve pancreatic islet morphology and beta cell mass in diabetic rodents. Also, there are a number of reports for the protective effects of other flavonoids such as epicatechin, fisetin, genistein, and naringin against diabetes-induced beta cell degeneration [45–47]. One of the main molecular mechanisms by which flavonoids protect beta cell survival is the suppression of oxidative stress and subsequent inhibition of the caspase cascade and DNA damage (Fig. 1). In diabetic animals, administration of flavonoids increases the antioxidant capacity of beta cells by enhancing both enzymatic (e.g., catalase, glutathione peroxidase, glutathione S transferase, superoxide dismutase) and non-enzymatic (e.g., reduced glutathione) antioxidants [36,38,40,43,44,46,48,49]. The increase of antioxidant capacity inhibits ROS accumulation and lipid peroxidation in beta cells and therefore protects them against autophagy, apoptosis, or necroptosis [36,38,40,43,48–50]. In diabetes, glucotoxicity, lipotoxicity, and chronic oxidative stress are associated with increased expression of pro-apoptotic genes (e.g., caspases) and downregulation of anti-apoptotic genes (e.g., Bcl-2 proteins) in beta cells. Flavonoids have been shown to preserve the survival of beta cells by inhibiting these changes in gene expression [51–54]. For instance, kaempferol preserves the survival of beta cells in high glucose condition by enhancing Bcl-2 expression and reducing caspase-3 level [53]. Similarly, cirsimaritin suppresses STZ-induced beta cell apoptosis by up-regulation of Bcl-2 protein expression and inhibiting the activity of caspase-3, caspase-8, BH3 interacting-domain death agonist, and the DNA repair protein poly (ADP-ribose) polymerase [52].

Cytokines that are released by inflammatory cells around beta cells stimulate the expression of inducible nitric oxide synthase (iNOS) and overproduction of NO, leading to cell damage [28,31,32]. NO may induce ER stress by reducing the level of Ca^{2+} in ER [55]. In addition, NO may activate the JNK pathway and thereby suppress the PI3K/Akt signaling. [56]. NF-κB, a pro-inflammatory transcription factor, plays a key role in cytokine-induced overexpression of iNOS and increase of NO in beta cells [29,57]. It has been shown that the cytoprotective effect of quercetin in beta cells is associated with reduced expression of iNOS, decreased the level of NO, and inhibited translocation of NF-κB [54,58,59]. For example, quercetin counteracts the cholesterol-induced NFκB activation in the pancreas and Min6 beta cell line [54]. Similarly, apigenin, epicatechin, epigallocatechin gallate (EGCG), and luteolin were shown to decrease IL-1β-induced NF-κB activation, iNOS expression, and nitrite production [59–63]. Also, epicatechin was shown to reduce the protein level of JNK in INS-1E beta cells exposed to oxidative stress [64]. The beneficial effects of flavonoids such as proanthocyanidins and EGCG on beta cell survival are correlated with a decrease in markers of ER stress [42,65]. Because mitochondrial-derived ROS plays an important role in the activation of the cytokine-sensitive NF-κB, the antioxidant effect of flavonoids may thus be responsible for inhibition of NF-κB activation and iNOS expression [66]. In addition, flavonoids can increase gene expression of heat shock proteins (e.g., Hsp70) in insulin-producing cells [51]. Up-regulation of hsp70 was shown to potentiate beta cells resistance against NO, ROS, and different toxins including STZ [67].

There are some reports that the protective effect of flavonoids against cytokine-induced beta cells toxicity may also be mediated through activating PI3K/Akt pathway, independent of MAPK or iNOS [68,69]. The isoflavone puerarin was reported to protect beta cells survival against cobalt chloride toxicity through activation of Akt phosphorylation [70]. Similarly, quercetin and naringenin protect beta cells against cytokine-induced apoptosis by increasing the levels of phosphorylated Akt [68]. In the pancreas of diabetic rats, quercetin was found to suppress Cdkn1a (p21) expression induced by STZ and oxidative stress [40]. Cdkn1a inhibits the activity of CDK and thereby prevents cell proliferation by arresting the cell cycle at G1 and S phases [71]. However, long-term exposure to quercetin may suppress PI3K/Akt signaling and inhibit beta cells proliferation [72]. It seems that, in conditions of insulin resistance (e.g., high-fructose feeding), quercetin prevents beta cells proliferation and islet hyperplasia to preserve beta cell mass and function. This effect is mediated through suppression of Akt/FoxO1 phosphorylation [41].

5. Beta cell function in diabetes

The maintenance of glucose homeostasis through secretion of insulin can be considered as the vital function of pancreatic beta cells. Fig. 2 shows the main pathways involved in the initiation, amplification, and inhibition of glucose-stimulated insulin secretion. The increase of blood glucose is the main physiologic trigger of insulin secretion. After entering into beta cells, glucose increases the ratio of ATP to ADP, an event that closes the K_{ATP} channels and therefore depolarizes the cell membrane. This opens voltage-dependent calcium channels, which raises intracellular calcium ($[Ca^{2+}]_i$), leading to the activation of calcium/calmodulin-dependent pathways to initiate exocytosis of insulin granules [73]. The response of beta cells to blood glucose is modulated by different activating and inhibitory signals. The main activating pathways that contribute to sustained and enhanced glucose-stimulated insulin secretion are adenylyl cyclase/cAMP/protein kinase A (PKA) and phospholipase C (PLC)/diacylglycerol/protein kinase C (PKC) cascades [74,75]. Glucagon and some incretin hormones such as glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide (GIP), and vasoactive intestinal polypeptide (VIP) potentiate glucose-induced insulin release through activation of cAMP-dependent pathways. Cholecystokinin (CCK) and acetylcholine (Ach) has a positive impact on insulin gene expression and insulin secretion via the PKC pathway. On the other hand, somatostatin and alpha-2 agonists act via an inhibitory G protein to decrease cAMP level and closing Ca^{2+} channels, which reduce insulin release [73,74]. Incretin hormones are responsible for augmenting insulin response to meals

Table 2
A summary of studies evaluated the effects of flavonoids on pancreatic beta cells in diabetic animals. ALO: alloxan; EGCG: epigallocatechin gallate; FBG: fasting blood glucose; GPx: glutathione peroxidase; GST: glutathione S transferase; NO: nitric oxide; STZ: streptozotocin; SOD: superoxide dismutase; ↓: decrease; ↑: increase.

Flavonoids	Experimental model	Effective dose	Effects on pancreatic islets	Other effects	Ref.
Epicatechin	STZ-induced diabetic rats	30 mg/kg twice a day (6 days)	↓Beta cell degeneration ↑Insulin and glucagon expression ↑Insulin release ↓NO	↓FBG	[45]
EGCG	*db/db* type 2 diabetic mice	10 g per kg of diet (10 weeks)	↑The number and the size of islets ↑Pancreatic insulin content	↑Serum insulin; ↓FBG ↑Glucose tolerance	[65]
Eupatilin	*db/db* type 2 diabetic mice	5 mg and 20 mg per 100 g diet (6 weeks)	↑Pancreatic insulin level	↑Serum insulin ↓FBG and HbA1c ↑Serum adiponectin ↑Hepatic glycogen content	[88]
Fisetin	STZ-induced diabetic mice	10 mg/kg (30 days)	↓Beta cell degeneration ↑Enzymatic antioxidants (↑catalase, ↑SOD, ↑GPx ↑GST)	↑Serum insulin ↓FBG and HbA1c ↓Serum NO ↓Serum oxidative stress indices (↓ lipid peroxidation; ↓glutathione) ↓Serum IL-1β	[46]
Genistein	STZ-induced diabetic mice	250 mg/ kg (4 weeks)	↓ Beta cell apoptosis ↑Beta cell proliferation	↑Serum insulin ↓FBG	[47,89]
Naringenin	STZ-induced diabetic rats	50 mg/ kg (3 weeks)	↑Beta cell number ↓Oxidative stress (↓lipid peroxidation; ↑SOD; ↑catalase; ↑GPx; ↑GST)	↑Serum insulin ↓FBG	[48]
Naringin	STZ-induced diabetic rats	100 mg/ kg (4 weeks)	↑Beta cell number ↓Oxidative stress (↓lipid peroxidation; ↑SOD; ↑catalase; ↑GPx; ↑GST)	↓Serum cytokines (TNF-α, IL-6)	[50]
Proanthocyanidins	STZ- and high carbohydrate/fat diet-induced diabetic rats	250 & 500 mg/kg (16 weeks)	↓Beta cell apoptosis ↑Insulin expression in the pancreas	↑Glucose tolerance	[42]
	ALO-induced diabetic rats	50 & 100 mg/kg (72 h)	↓Oxidative stress (↑glutathione, ↓lipid peroxidation) ↓Nitrate/nitrite content)	↑Serum insulin ↓FBG	[43]
	Cadmium-induced pancreatitis in rats	Pretreatment with 25-100 mg/ kg	↓Beta cell apoptosis ↓Expression of caspases ↑Pancreatic insulin ↓NO ↓Pancreatic TNF-α, IL-1β, and IFN-γ ↓Oxidative stress (↓ROS, ↑glutathione, ↓lipid peroxidation, ↓xanthine oxidase)	↑Serum insulin ↓FBG ↓Serum lipids	[44]
Puerarin	STZ-induced diabetic mice	100 mg/kg (3 days pretreatment)	↑Beta cell mass	↑Serum insulin ↓FBG ↑Glucose tolerance	[70]
Quercetin	STZ-induced diabetic rats	15 mg/kg (4 weeks)	↑Beta cell number ↓Oxidative stress (↓lipid peroxidation, ↑catalase, ↑GPx)	↑Serum insulin ↓FBG ↓Serum NO	[36]
		15 mg/kg (10 days)	↑Beta cell number	↑Serum insulin ↓FBG ↑Glucose tolerance	[37]
		25 mg/kg (30 days)	↓Beta cell apoptosis ↓Oxidative stress (↑SOD; ↓lipid peroxidation, ↑catalase, ↑GPx)	↑Serum insulin ↓FBG ↓Serum NO	[38]
		50 mg/kg (40 days)	↑Beta cell number	↑Serum insulin ↓Hepatic oxidative stress (↓lipid peroxidation)	[39]
	STZ-induced diabetic mice	Diets containing 0.1% or 0.5% quercetin (2 weeks)	↑Beta cell proliferation ↓Oxidative stress (↓lipid peroxidation)	↑Serum insulin ↓FBG	[40]
	Fructose-induced hyperinsulinemia (rats)	100 mg/Kg (4 weeks)	Preserving islet morphology and function	↓FBG ↓Serum insulin ↓Serum leptin	[41]
Rutin	STZ-induced diabetic rats	100 mg/g (45 days)	↑Beta cell number ↓Oxidative stress (↓lipid peroxidation; ↑SOD; ↑GPx; ↑catalase; ↑glutathione)	↑Serum insulin ↓FBG	[49]

[76]. The effect of epinephrine/norepinephrine on alpha 2 receptors is important to inhibit insulin secretion during exercise [77].

In addition to glucose as the primary trigger, FFAs and some amino acids can also modulate insulin secretion from beta cells. Amino acids may increase insulin secretion by enhancing ATP production from the tricarboxylic acid cycle and/or contributing to intracellular calcium increase [78]. FFAs can enhance glucose-induced insulin release in part through diacylglycerol/PKC pathway [74]. However, prolonged exposure of beta cells to FFAs may inhibit insulin gene expression and cause exhaustion of insulin release [74,79].

Dysfunction of beta cells is a major hallmark in the pathogenesis of both types of diabetes. A wide range of environmental conditions (e.g., decreased energy expenditure, increased caloric intake, and over-consumption of saturated fat) cooperate with genetic factors (e.g., PPARγ and c-Kit) to develop pathological alterations which promote beta cell dysfunction [80]. Some of these alterations include insulin resistance, inflammation, immune dysregulation, decreased incretin level/effect, increased sympathetic tone, and oxidative stress.

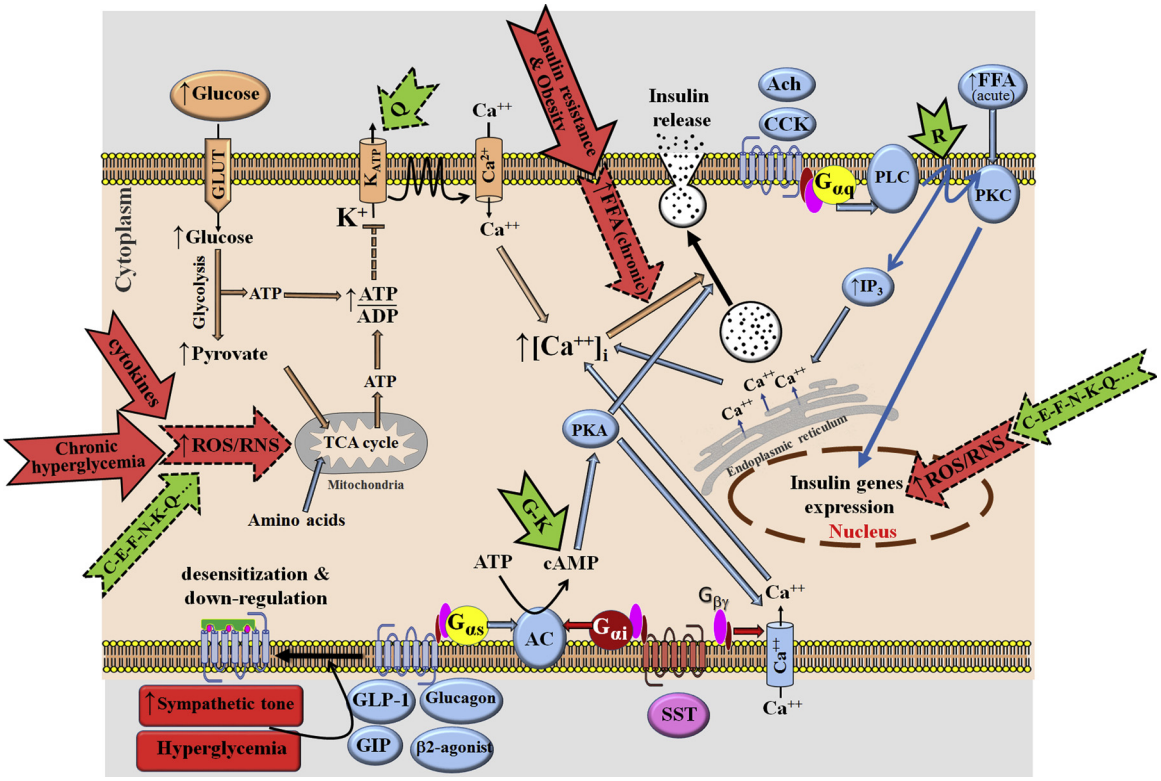


Fig. 2. Effects of diabetes (red arrows) on the insulin secretion from pancreatic beta cells and the main mechanisms by which flavonoids preserve the secretory capacity (green arrows). The triggering and amplifying pathways of insulin secretion in normal condition are shown by orange and blue pathways, respectively. Inhibitory effects were shown by dotted arrows. The letters inside the green arrows refer to flavonoids (C: Chrysin; E: epicatechin; F: Fisetin; G: Genistein; K: kaempferol; L: N: Naringin; Q: quercetin; R: rutin). AC: adenylate cyclase; Ach: acetylcholine; FFA: free fatty acids: GIP: glucose-dependent insulinotropic peptide; GLP-1: glucagon-like peptide 1; GLUT; glucose transporter; IP_3; inositol 1,4,5-trisphosphate; PKA: protein kinase A; PKC: protein kinase C; PLC: phospholipase C; ROS/RNS: reactive oxygen/nitrogen species; SST: somatostatin; TCA: tricarboxylic acid cycle (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

In obese and insulin-resistant patients, elevation of circulating glucose, FFAs, and advanced glycation end products (AGE) induce an inflammatory process within tissues involved in energy homeostasis (liver, fat, muscle, islets). FFAs bind to Toll-like receptors (e.g., TLR2 and TLR4), leading to activation of NF-kB and generation of various pro-inflammatory cytokines, including IL-1β and TNFα [81]. The inflammatory cytokines increase expression of 12-lipoxygenase and NADPH oxidase-1 genes. The increased level of NADPH oxidase can enhance the generation of ROS [82]. Beta cells are highly vulnerable to oxidative stress because of their inherently low antioxidant capacity [83]. The accumulation of ROS and RNS inhibits the electron transport chain in mitochondria leading to reduced ATP production and uncoupling of glucose sensing from insulin secretion [84,85]. In addition, oxidative stress may alter the function of K_{ATP} channels and thereby attenuate insulin release [84].

Also, obesity and high-fat feeding increase the amount of fat within the islets, which provides a long-term source of FFAs for beta cells. Chronic exposure of the cells to FFAs can attenuate insulin release by dissociation of Ca^{2+} channels dependent signaling from insulin secretory machinery [86,87]. In addition, obesity and insulin resistance enhances insulin demand leading to hyperactivity of beta cells which in long-term, results in dysfunctional secretory response to glucose [86].

6. Effects of flavonoids on beta cell function

There is increasing evidence that certain flavonoids such as EGCG, eupatilin, fisetin, genistein, naringenin, proanthocyanidins, puerarin, quercetin, and rutin increase plasma insulin in animal models of diabetes [36–40,43,44,46,48,49,65,70,88,89]. The increase of plasma insulin can be attributed to the preserving survival of beta cells, as described above, and/or the stimulating insulin release. As shown in Table 3, several studies reported that flavonoids enhance glucose-stimulated insulin release and counteract the cytokine-induced beta cell dysfunction. These beneficial effects are mediated through influencing both triggering and amplifying pathways of insulin secretion. Since accumulation of ROS inhibits the electron transport chain in mitochondria and alters the function of K_{ATP} channel [84,85], it is expected that the antioxidant effects of flavonoids can preserve the triggering signaling pathway of insulin release in diabetic beta cells. Consistent with this hypothesis, the stimulatory effect of apigenin, epicatechin, EGCG, and quercetin on insulin secretion from beta cells was shown to be accompanied by a substantial decrease in the level of intracellular ROS [54,58,63,64,90]. Quercetin can recover cytokine- and cholesterol-induced loss of mitochondrial membrane potential (Δψm), a marker of mitochondrial oxidative phosphorylation activity [68]. Similarly, pretreatment of beta cells with apigenin inhibits 2-deoxy-D-ribose-induced attenuation of ΔΨm [90]. The beneficial effects of flavonoids on mitochondria improve its bioenergetic function, which increases ATP production, leading to the closing of K_{ATP} channels and depolarization of cell membrane [53,72,73,91]. Kittle et al. reported a 50% inhibition of K_{ATP} current and a 25 mV depolarization of membrane potential in beta cells treated with quercetin [72]. These effects make flavonoids able to increase $[Ca^{2+}]i$ level that triggers priming of insulin vesicles for exocytosis [92,93].

Some flavonoids also are able to enhance glucose-induced insulin secretion through influencing amplifying pathways including PLC/PKC and cAMP/PKA signaling cascades [53,94,95]. Involvement of the PLC/PKC pathway in insulin secretagogue activity of rutin was demonstrated in the isolated rat pancreatic islets [95]. The insulinotropic effect of genistein and kaempferol was shown to be mediated through activation

Table 3
A summary of studies evaluated effects of flavonoids on the isolated islets or insulin-secreting cell lines in vitro. *t*-BOOH: tert-butylhydroperoxide; dRib: 2-deoxy-D-ribose; EGCG: epigallocatechin gallate; ER: endoplasmic reticulum; ERK: extracellular signal-regulated kinase; GPx: glutathione peroxidase; Inc.: incubation; iNOS: inducible nitric oxide synthase; PKA: protein kinase A; NF-κB: nuclear factor-kappa B; NO: nitric oxide; PI3K: phosphoinositide 3-kinase; PLC: phospholipase C; ROS: reactive oxygen species; SOD: superoxide dismutase; STZ: streptozotocin; ↓: decrease; ↑: increase; ↔: no significant effect; *Only effective concentrations of flavonoids are shown.

Flavonoids	In vitro model	Concentration* and time of inc.	Effects on beta cells	Proposed mechanism	Ref.
Apigenin	Rat insulinoma RINm5F cells	24 h co-inc. with apigenin (25 and 50 μmol/L) and cytokine cocktail	↓Cytokines (IL-1β + IFN-γ)-induced cell death ↓Cytokine-mediated inhibition of insulin secretion	↓NF-κB translocation; ↓NO production	[59]
		60 min pre-inc. with apigenin (5 μmol/L) and 24 in. with STZ (6 mmol/L)	↓STZ-induced cell death	↓Oxidative stress (↓ROS, ↓lipid peroxidation; (↑ catalase, ↑SOD, ↑GPx)	[113]
	Hamster pancreatic HIT-T15 cells	30 min pre-inc. with apigenin (10 μmol/L) and 24 h inc. with dRib (30 mmol/L)	↓dRib-induced cell death	↓Oxidative stress (↓ROS); ↓NF-κB translocation	[90]
Chrysin	Hamster pancreatic HIT-T15 cells	24 h pre-inc. with chrysin (40, 60, and 80 μmol/L) and 24 h inc. with high glucose (50 mmol/L)	↑Insulin content ↓High glucose-induced apoptosis	↓Oxidative stress (↓ROS, ↓lipid peroxidation)	[114]
Cirsimaritin	Rodent INS-1 beta cells	2 h pre-inc. with cirsimaritin (1, 2.5, and 5 μmol/L) and 24 h inc. with STZ (50 μmol/L)	↓STZ-induced apoptosis	↓Oxidative stress (↓ROS); ↓Expression of proapoptotic proteins (e.g., caspase 3 & 8) ↑Expression of anti-apoptotic protein Bcl-2	[52]
Cyanidin-3-glucoside	Rodent INS-1 beta cells	60 min co-inc. with cyanidin-3-glucoside (10 to 250 μg/mL) and glucose (4 or 10 mmol/L)	↑Glucose-induced insulin secretion	–	[115]
Delphinidin-3-glucoside	Rodent INS-1 beta cells	60 min co-inc. with delphinidin-3-glucoside (50 μg/mL) and glucose (4 or 10 mmol/L)	↑Glucose-induced insulin secretion	–	[115]
Epicatechin	Rodent INS-1 beta cells	20 h pre-inc. with epicatechin (5, 10, and 20 μmol/L) and 2 h inc. with *t*-BOOH (50 μmol/L)	↓*t*-BOOH-induced cell death ↑Glucose-induced insulin secretion	↓Oxidative stress (↑glutathione, ↓GPx; ↓ROS)	[64]
	Rat isolated pancreatic islets and rat insulinoma RINm5F cells	60 min pre-inc. with epicatechin (800 μmol/L) and 24 h inc. with IL-1β (100 ρg/mL)	↓IL-1β-induced inhibition of insulin release	↓NO production	[62]
EGCG	Rat insulinoma RINm5F cells	60 min pre-inc. with EGCG (20 and 40 μmol/L) and 24 h inc. with the cytokine cocktail	↑Glucose-induced insulin secretion ↓Cytokine (IL-1β + IFN-γ)-induced cell death	↓NO production ↓ROS Inhibition of the mitochondrial pathway of apoptosis	[63]
		24 h co-inc. with EGCG (50, 100, and 200 μg/mL) and the cytokine cocktail	↓Cytokine (IL-1β + IFN-γ)-induced cell death	↓iNOS expression and NO production; ↓NF-κB activation	[60]
		2 h (insulin assay) or 120 h (viability assay) co-inc. with EGCG (0.1 and 10 μmol/L) and glucose (3.3 or 33 mmol/L)	↑Glucose-induced insulin secretion ↓High glucose-induced cell death	Insulin receptor substrate 2 signaling; AMP-activated protein kinase signaling	[92]
	Mice isolated pancreatic islets and mouse insulinoma MIN6 cells	24 h (isolated islets) or 48 h (MIN6 cells) co-inc. with EGCG (20 μmol/L) and palmitate (0.5 mmol/L)	↓Palmitate-induced apoptosis	↓ER stress ↓Expression of proapoptotic protein caspase-3	[65]
Genistein	Mouse isolated pancreatic islets, rodent INS-1 beta cells, and mouse insulinoma MIN6 cells	30 min co-inc. with genistein (2.5 μmol/L) and high glucose (5.6-16.8 mmol/L)	↑Glucose-induced insulin secretion	Stimulation of cAMP/PKA signaling pathway	[94]
	Human and rat pancreatic islets and rat insulinoma RINm5F cells	24 h co-inc. with genistein (25 and 100 μmol/L) and NaF (5 mmol/L)	At low concentration: ↓NaF-induced islet cell apoptosis; At high concentration: ↑apoptosis	Tyrosine kinase inhibitory effect	[116]
Kaempferol	Human isolated pancreatic islets and rodent INS-1 beta cells	4 days co-inc. with kaempferol (10 μmol/L) and high glucose (20 mmol/L)	↑Glucose-induced insulin secretion ↓High glucose-induced apoptosis	↑cAMP, ↑ATP ↓Expression of proapoptotic proteins (caspase-3); ↑ Expression of anti-apoptotic proteins (Bcl-2)	[53]
	Hamster pancreatic HIT-T15 cells	30 min pre-inc. with kaempferol (10 μmol/L) and 24 h inc. with dRib (20 mmol/L)	↓dRib-induced cell death	↓Oxidative stress (↓ROS, ↓lipid peroxidation)	[117]
Luteolin	Rat insulinoma RINm5F cells	24 h co-inc. with luteolin (25 and 50 μmol/L) and cytokine cocktail	↓Cytokines (IL-1β + IFN-γ)-induced cell death ↓Cytokine-mediated inhibition of insulin secretion	↓NF-κB translocation; ↓NO production	[59]
	Hamster pancreatic HIT-T15 cells	24 h pre-inc. with luteolin (40, 60, and 80 μmol/L) and 24 h inc. with high glucose (50 mmol/L)	↑Insulin content ↓High glucose-induced cell death	↓Oxidative stress (↓ROS, ↓lipid peroxidation)	[114]
	Mouse isolated pancreatic islets and mouse insulinoma MIN6 cells	2 h pre-inc. with luteolin (10 μmol/L) and 24 h inc. with uric acid (5 mg/dL)	↓Uric acid-induced inhibition of insulin secretion	↓NF-κB activity; ↓iNOS expression and NO production	[104]

(*continued on next page*)

Table 3 (*continued*)

Flavonoids	In vitro model	Concentration* and time of inc.	Effects on beta cells	Proposed mechanism	Ref.
Naringenin	Rodent INS-1 beta cells	60 min co-inc. with naringenin (10 nmol/L and 1 μmol/L) and high glucose (16.7 mmol/L)	↑Glucose-induced insulin secretion	↑Akt expression; ↓Expression of proapoptotic proteins (caspase-3); ↑Expression of anti-apoptotic proteins (Bcl-2)	[51]
		24 h co-inc. with naringenin (50 μmol/L) and cytokine cocktail	↓Cytokine (IL-1β + IFN-γ + TNF-α)-induced apoptosis ↔Cytokine-mediated inhibition of insulin secretion	Stimulation of PI3K/Akt signaling pathway	[68]
Pelargonidin	Rodent INS-1 beta cells	60 min co-inc. with pelargonidin (50 μg/mL) and glucose (4 or 10 mmol/L)	↑Glucose-induced insulin secretion	–	[115]
Puerarin	Mice isolated pancreatic islets and mouse insulinoma MIN6 cells	8 h pre-inc. with puerarin (10 μmol/L) and 16 h inc. with cobalt chloride (400 μmol/L)	↓Cobalt chloride-induced apoptosis ↑Glucose-induced insulin secretion	Stimulation of PI3K/Akt signaling pathway	[70]
Quercetin	Rat isolated pancreatic islets and rodent INS-1 beta cells	60 min inc. with quercetin (20 μmol/L)	↑Insulin secretion	↑$[Ca^{2+}]i$	[93]
	Rodent INS-1 beta cells	60 min co-inc. with quercetin (20 μmol/L) and glibenclamide (10 nmol/L), high glucose (8.3 mmol/L), or H_2O_2 (50 μmol/L)	↑Glucose- and glibenclamide-induced insulin secretion ↓H_2O_2-induced cell death	Stimulation of the ERK1/2 signaling pathway	[98]
		30 min co-inc. with quercetin (1 μmol/L) and high glucose (16.7 mmol/L)	↑Glucose-induced insulin secretion	↑Akt expression; ↑Expression of anti-apoptotic proteins (Bcl-2)	[51]
		60 min co-inc. with quercetin (50 μmol/L) and glucose (0 and 20 mmol/L) 48 h inc. with quercetin (50 and 100 μmol/L)	↑Basal- and glucose-stimulated insulin secretion ↓Cell proliferation (long-term exposure)	K_{ATP} channel inhibition and ↑cellular Ca^{2+} Inhibition of PI3K/Akt signaling; ↓iNOS expression	[72]
		24 h co-inc. with quercetin (50 μmol/L) and cytokine cocktail	↓Cytokine (IL-1β + IFN-γ + TNF-α)-induced apoptosis ↔Cytokine-mediated inhibition of insulin secretion	Stimulation of PI3K/Akt signaling pathway	[68]
	Rat insulinoma RINm5F cells	2 h pre-inc. with quercetin (20 μmol/L) and 24 h co-inc. with cytokine cocktail and glucose (2.8 or 16.7 mmol/L)	↓Cytokine (IL-1β + IFN-γ)-induced cell death ↑High glucose-induced insulin secretion	↓ROS ↓NF-κB translocation ↓NO production	[58]
		24 h co-inc. with quercetin (25 and 50 μmol/L) and cytokine cocktail	↓Cytokine (IL-1β + IFN-γ)-induced cell death ↓Cytokine-mediated inhibition of insulin secretion	↓NF-κB translocation; ↓NO production	[59]
	Hamster pancreatic HIT-T15 cells	24 h pre-inc. with quercetin (40, 60, and 80 μmol/L) and 24 h inc. with high glucose (50 mmol/L)	↑Insulin content ↓High glucose-induced cell death	↓Oxidative stress (↓ROS, ↓lipid peroxidation)	[114]
	Mouse insulinoma MIN6 cells	6 h co-inc. with quercetin (10, 50, and 100 μmol/L) and cholesterol (320 μmol/L)	↓Cholesterol-induced apoptosis	↓Oxidative stress (↓ROS, ↓lipid peroxidation, ↑SOD; ↑GPx:); ↓Caspases activation; ↓NFκB translocation	[54]
Rutin	Rat isolated pancreatic islets	10 min inc. with rutin (0.1 ρmol/L)	↑Ca^{2+} uptake	PLC and PKC signaling pathways	[95]
		60 min co-inc. with rutin (50 μg/mL) and STZ (5 mmol/L)	↓STZ-induced inhibition of insulin secretion ↔Basal insulin secretion	↓Oxidative stress	[118]
	Rat insulinoma RINm5F cells	2 h (insulin assay) or 120 h (viability assay) co-inc. with rutin (0.1 and 10 μmol/L) and glucose (3.3 or 33 mmol/L)	↑Glucose-induced insulin secretion ↓High glucose-induced cell death	Insulin receptor substrate 2 signaling; AMP-activated protein kinase signaling	[92]
	Rodent INS-1 beta cells	48 h inc. with rutin (100 μmol/L) 60 min co-inc. with rutin and glucose (0 and 20 mmol/L)	↓Cell proliferation (long-term exposure) ↔Basal- and glucose-stimulated insulin secretion	–	[72]

of the cAMP/PKA pathway [53,94]. Recent studies revealed a cross-talk between the cAMP/PKA and extracellular signal-regulated kinase (ERK) 1/2 signaling pathways in beta cells and compounds that activate cAMP/PKA cascade (e.g., GLP-1) amplify both glucose-stimulated insulin release and ERK1/2 phosphorylation [96,97]. ERK1/2 kinases, in turn, control the protein levels and phosphorylation of cAMP-responsive element-binding protein and therefore play a key role in the regulation of beta cells functions and survival [96]. Therefore, it is rational to expect that flavonoids modulate ERK1/2 signaling pathway in these cells. Studies of Youl et al. and Kittle et al. showed that phosphorylation of ERK1/2 involved in the potentiation of glucose-induced insulin release by quercetin [72,98].

Several studies have suggested that the inhibitory effect of flavonoids on NO production may be involved in their beneficial effects on insulin secretion from beta cells [58,59,62,63]. Protective effect of apigenin, epicatechin, and luteolin against cytokine-mediated inhibition of insulin secretion is accompanied by a decrease of NO level in beta cells [59,62]. Similarly, EGCG and quercetin potentiate glucose-induced insulin secretion concomitant with a decrease in NO production [58,63]. Nevertheless, the role of NO in insulin-releasing mechanisms is still controversial. A number of studies have shown that early phase of glucose-induced insulin release requires endogenous NO [99,100]. On the other hand, some studies have found that exogenous NO inhibited glucose-stimulated insulin release through opening K_{ATP} channels [101,102]. It seems that NO at low concentrations facilitates $[Ca^{2+}]i$ oscillations and insulin secretion induced by glucose, whereas at high concentrations produces inhibitory effects [103]. Flavonoids have the potential to prevent excessive concentration of NO in beta cells exposed to cytokines and other stressor stimuli [58,59,62,63,104].

Most of the in vitro studies that evaluated effects of flavonoids on insulin-secreting cell lines or the isolated islets have used concentrations ranging from 10 nmol/L to 100 μmol/L (Table 3). For example, quercetin could increase glucose-induced insulin secretion at concentrations of 1–20 μmol/L (incubation time: 30–60 min) [51,93,98]. It is important that the concentrations of flavonoids and incubation times used in vitro be translatable into the in vivo conditions. In vivo studies on diabetic animals are often conducted at doses of 10 to 250 mg/kg of flavonoids (Table 2). For example, administration of 15 mg/kg of quercetin to diabetic rats could preserve beta cell mass and increased the level of serum insulin [36,37]. It has been shown that oral administration of quercetin at a dose of 10 mg/kg produces a serum concentration of about 10–17 μmol/L after 30–60 min [105]. Therefore, it seems that the concentrations tested in vitro can be achieved in the bloodstream in vivo by oral administration of flavonoid. Also, as mentioned above, C_{max} values in humans varies between 2 nmol/L and 8 μmol/L, depending on the type of flavonoids and the dose administered [21–23,26], which corresponded well with the concentrations used in vitro.

According to the Food and Drug Administration (FDA) draft guideline for estimating the safe starting dose in clinical trials [106,107], the effective dose in animals may be extrapolated to a human equivalent dose by the following formula:

Human equivalent doses (mg/kg) = Animal dose (mg/kg) × Animal *Km* / Human *Km*.

where the *Km* factor is the result of dividing the body weight (kg) by the body surface area (m^2). The *Km* value is approximately 37, 6, and 3 for an adult human, rat, and mouse, respectively [106,107]. Therefore, the doses of flavonoids showing beneficial effects on beta cells in rats (10–250 mg/kg) are approximately comparable to 1.5–40 mg/kg in human, or 90–2400 mg for a 60 kg person. Although doses up to 500 mg of flavonoids can be practically administrated by a daily oral dosage form, safety concerns should be undertaken. The no observed adverse effect level (NOAEL) of a limited number of flavonoids has been determined in rodents (varies between 75–3000 mg/kg in rats) [108–110] and further studies on this topic are needed.

Lack of clinical trials addressing the effects of flavonoids on pancreatic beta cells is one of the limitations that makes it difficult to draw a definite conclusion on this aspect. Although there are some reports on the efficacy of flavonoids for treating hyperglycemia in diabetic patients [111,112], the antihyperglycemic effect can occur by several mechanisms including decreasing carbohydrate absorption from the small intestine, improving insulin resistance, inhibiting gluconeogenesis, and enhancing insulin release from beta cells [9]. Therefore, to prove that the glucose-lowering effect of flavonoids in diabetic patients is a result of increased insulin secretion, the level of serum c-peptide (as an index of endogenous insulin release) should be determined. As far as we know, no clinical study has yet assessed the effect of a given flavonoid on serum c-peptide in human.

7. Conclusion

Preserving beta cells survival and function in early-stage diabetic patients and restoring beta cells mass/function in the advanced-stage patients are the logical solutions for the treatment of diabetes. Studies using insulin-releasing cell lines, isolated pancreatic islets, and animal models of diabetes support the idea that flavonoids can preserve the function and survival of beta cells. The antioxidant and anti-inflammatory properties of flavonoids as well as their ability to stimulate pro-survival pathways and to inhibit proapoptotic proteins expression contribute to the protective action of these natural compounds against beta cell death induced by cytokines, glucotoxicity, and lipotoxicity in diabetes. Also, improving mitochondrial bioenergetic function and stimulating amplifying pathways of insulin secretion (e.g., cAMP/PKA and PLC/PKC signaling) are likely the main mechanisms by which flavonoids preserve the secretory capacity of beta cells. The beneficial effects of flavonoids may be of great importance for clinical intervention because these compounds display a possibility to protect beta cells of diabetic patients before dramatic dysfunction and degeneration. However, well-designed clinical studies are needed to draw a definite conclusion regarding the beneficial effects of flavonoids on pancreatic beta cells survival and function.

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