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Endoplasmic reticulum stress in pancreatic β-cell dysfunction: The potential therapeutic role of dietary flavonoids

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ABSTRACT

Diabetes mellitus (DM) is a global health burden that is characterized by the loss or dysfunction of pancreatic β-cells. In pancreatic β-cells, endoplasmic reticulum (ER) stress is a fact of life that contributes to β-cell loss or dysfunction. Despite recent advances in research, the existing treatment approaches such as lifestyle modification and use of conventional therapeutics could not prevent the loss or dysfunction of pancreatic β-cells to abrogate the disease progression. Therefore, targeting ER stress and the consequent unfolded protein response (UPR) in pancreatic β-cells may be a potential therapeutic strategy for diabetes treatment. Dietary phytochemicals have therapeutic applications in human health owing to their broad spectrum of biochemical and pharmacological activities. Flavonoids, which are commonly obtained from fruits and vegetables worldwide, have shown promising prospects in alleviating ER stress. Dietary flavonoids including quercetin, kaempferol, myricetin, isorhamnetin, fisetin, icariin, apigenin, apigetrin, vitexin, baicalein, baicalin, nobiletin hesperidin, naringenin, epigallocatechin 3-O-gallate hesperidin (EGCG), tectorigenin, liquiritigenin, and acacetin have shown inhibitory effects on ER stress in pancreatic β-cells. Dietary flavonoids modulate ER stress signaling components, chaperone proteins, transcription factors, oxidative stress, autophagy, apoptosis, and inflammatory responses to exert their pharmacological effects on pancreatic β-cells ER stress. This review focuses on the role of dietary flavonoids as potential therapeutic adjuvants in preserving pancreatic β-cells from ER stress. Highlights of the underlying mechanisms of action are also presented as well as possible strategies for clinical translation in the management of DM.

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1. Introduction

Diabetes mellitus (DM) is one of the silent killers globally (WHO, 2019). According to the International Diabetes Federation (IDF), the global report for adults living with DM was estimated to be approximately 537 million, with a death rate and cost implication of 6.7 million and US 966 billion dollars respectively (IDF, 2021). African region has the highest proportion of undiagnosed cases and currently accounts for more than 24 million cases in the global report and estimated prevalence rate of 55 million by 2045 (IDF, 2021). This metabolic disorder is characterized by abnormally high blood sugar levels from the loss of functional pancreatic β cells, resulting in defective insulin secretion and/or action on target tissues. The inability of insulin-producing β-cells to compensate for increased metabolic demand and stress in diabetic conditions contributes to the decline of β-cells function and survival. The early steps in the biosynthetic pathway of insulin take place in the endoplasmic reticulum (ER), and pancreatic islet β-cells contain large and well-developed ER with molecular chaperones where proinsulin is folded and assembled (Oakes and Papa, 2015). Regardless of the robust nature of ER in pancreatic β-cells, a large number of fractions of proinsulin are misfolded due to genetic and environmental perturbations, thereby making the molecular biosynthesis and folding of proinsulin in the ER of pancreatic β-cells a stressful event. ER stress in DM is associated with accumulation of misfolded insulin proteins and it is aggravated by DM predisposing factors such as hyperglycemia, hyperlipidemia, oxidative stress or calcium dysregulation in the ER. (Ghosh et al., 2019; Herlea-Pana et al., 2021; Oakes and Papa, 2015). As a corollary, the compromised functional capacity of ER during insulin biosynthesis has been implicated in the formation of conformationally altered products, progressive β-cells dysfunction and apoptosis, and early onset of diabetes in mice (Ghosh et al., 2019; Herbach et al., 2007). Therefore, maintenance of ER homeostasis in response to a constantly changing physiologic environment in β-cells is of crucial importance.

To ensure fidelity of protein folding and maintain protein homeostasis under stressed conditions in the ER lumen, pancreatic β-cells limits the production of insulin and activate the unfolded protein response (UPR), an evolutionary conserved stress response mechanism with both survival and apoptotic outcomes (Fig. 1). The UPR enhances secretory performance and creates adaptive programs to relieve the load of unfolded or misfolded proteins to promote cell survival or maladaptively trigger destructive programs that promote apoptosis of damaged cells (Xin et al., 2018). Dual outcomes of the UPR exists depending on the intensity and duration of ER stress. At manageable levels of ER stress, the UPR reduces mRNA translation of secretory proteins, promotes ER-associated protein degradation (ERAD), and transcriptional induction of genes encoding proteins that increase polypeptide refolding (Fink et al., 2018). However, at irremediable ER stress, UPR transitions from adaptive cellular remodeling to pro-apoptotic cell death signaling. Considering the role of the ER in the pathogenesis of DM, pharmacologic intervention to ameliorate pathologic alterations in ER functional capacity in pancreatic β-cells could be a promising therapeutic strategy for DM.

Although modern medicine and pharmaceutical industry could provide means for the management of DM, certain plant derived compounds could be an alternative to modern treatments for DM. Allopathic treatments for DM may present with undesirable side effects, thereby encouraging the use of plant-derived compounds, which have potential to reduce ER stress signaling and pancreatic β-cells function (Ghorbani

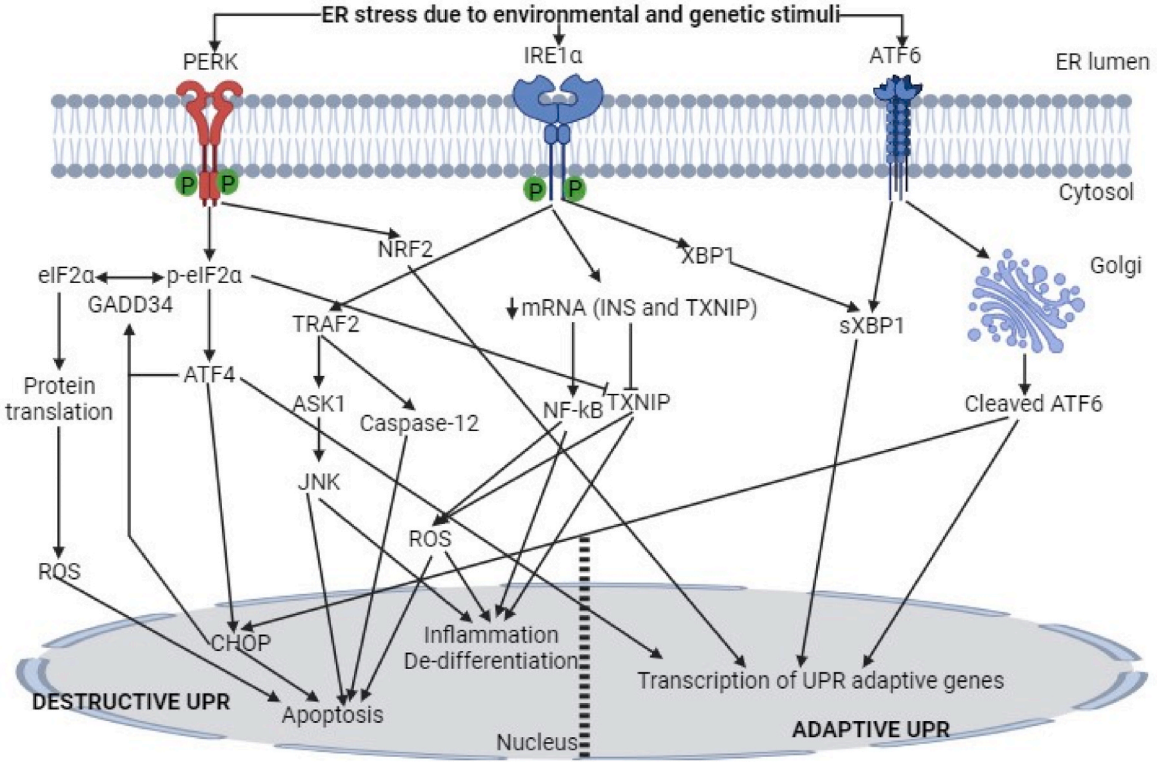


Fig. 1. The survival and apoptotic mechanisms of ER stress-activated UPR. ER stress induces UPR in three major pathways involving the activation of the transcription factors XBP-1, ATF4, and ATF6. Combinatorial outputs from these three transcription factors/ER stress sensors over time determine the cell fate outcomes under ER stress. During ER stress, adaptive UPR mechanisms reinstate cellular homeostasis. During unmitigated ER stress, the adaptive mechanisms morph into destructive outputs to cause β-cell apoptosis. ASK1. Apoptosis signal-regulating kinase 1, ATF6, Activating transcription factor 6; CHOP, C/EBP homologous protein; eIF2α; eukaryotic translation initiation factor 2-alpha; GADD34, growth arrest- and DNA damage-inducible gene 34; IRE1α; Inositol-requiring enzyme-1α; INS, insulin; JNK, c-Jun NH_2-terminal protein kinase; $NF\text{-}_{K}B$, nuclear factor kappa B; NRF2, nuclear factor erythroid 2-related factor 2; PERK, protein kinase RNA-like endoplasmic reticulum kinase; PI3K, phosphoinositide 3-kinases; ROS; reactive oxygen species; TRAF2, TNF receptor associated factor 2; TXNIP, Thioredoxin-interacting protein; XBP1, X-box binding protein 1. Figure created with BioRender.com.

et al., 2019). Flavonoids are naturally occurring secondary metabolites of the phenylpropanoid pathway with various biological activities. Flavonoids consist of phenolic rings with variations in the arrangement of different side groups, including hydroxyl, alkyl, and glycosidic groups attached to the polyphenolic skeleton (Kim et al., 2010). Studies have reported the inverse relationship between the consumption of flavonoids and DM incidences (Ghorbani, 2017; Hussain et al., 2020). Moreover, several experimental evidence have shown flavonoids to modulate ER stress signaling and UPR through their pleiotropic effects, including modulating UPR, lipid metabolism, oxidative stress, and pro-inflammatory cytokines (Keylani et al., 2023; Kim et al., 2010). However, their potential application in maintaining pancreatic β-cells ER homeostasis remains vague. Therefore, we shed light on the background to pancreatic β-cells' fate in DM and review the understanding of flavonoids as potential modulators of ER-induced pancreatic β-cells dysfunction. We also provide insights into the underlying mechanisms of action from preclinical studies as well as offer recommendations for clinical application.

2. Pancreatic β-cell fate in diabetes mellitus

The pancreatic β-cells are essential endocrine cell types that regulate glycemic levels by integrating several signals and releasing insulin in response to changing metabolic demands. Chronic dysglycemia induces the loss of β-cell differentiation, changes stimulus-secretion coupling, promotes β-cell apoptosis, and upregulates the expression of under-expressed genes in normal β-cells (Ghosh et al., 2019). Available studies suggest that a progressive decline of functional insulin-producing β-cell mass over a long period, which results in loss of viable β-cells with an adequate number, size, and efficient insulin-producing capacity, and β-cell decompensation are considered shared features in patients with all forms of diabetes (Aguayo-Mazzucato et al., 2019; Aguayo-Mazzucato and Bonner-Weir, 2018; Remedi and Emfinger, 2016). As the loss of functional β-cell mass features prominently in all types of DM (Wang and Kaufman, 2012), a research effort to understand the mechanisms of β-cell failure and β-cell survival to compensate for insulin resistance and loss of β-cell mass is imperative.

There are fundamental differences in the pathophysiology of Type 1 DM (T1DM) and Type 2 DM (T2DM) that have significant implications on the initial phases of β-cell dysfunction and eventual fate. In T1DM, a combination of genetic and environmental factors triggers molecular crosstalk between immune cells or their cytokines (tumor necrosis factor (TNF)-α, and interferon (IFN)-γ) and β-cells, leading to cytokine-induced β-cell stress, dysfunction and ultimately death (Eizirik et al., 2009). Moreover, increased nitric oxide and free radicals as well as disruption of calcium homeostasis play pathophysiological role in immune-mediated pancreatic β-cell damage in T1DM (Eizirik et al., 2020). This necessitates lifelong exogenous insulin therapy and to successfully manage T1DM, strategies must be developed to abrogate the autoimmune attack and restore appropriate insulin release from β-cells. In T2DM, which is characterized by relative insulin deficiency and insulin resistance, prolonged metabolic stress, hyperglycemia and high levels of free fatty acids (FFA) causes progressively impaired insulin secretion, β-cell dysfunction, and failure. A combination of lifestyle modifications, pharmacological therapy, and individualized monitoring is employed to successfully manage T2DM. However, despite recent advances in research, no pharmacotherapy, including insulin could prevent or reverse the loss or dysfunction of pancreatic β cells to abrogate DM progression.

Although different biological mechanisms contribute to the loss of sustainable β-cells function, the actual correlation of decreased β-cell mass to pancreatic β-cell dysfunction remains unclear and debated. The ER of pancreatic β-cells might be subjected to unbearable levels of stress during protein folding to induce apoptosis as the different types of diabetes progress (Eizirik et al., 2020). The induction of the ER stress affects proinsulin folding, cellular maintenance of ER proteostasis, and β-cell fate, especially in terms of insulin secretion and β-cell mass. Dedifferentiation, autophagy, and apoptosis of β-cell are major pathophysiological mechanisms contributing to the loss of functional β-cell mass, and consequently β-cell failure in T1DM and T2DM (Bilekova et al., 2021; Marchetti and Masini, 2009; Muralidharan et al., 2021; Talchai et al., 2012). Dedifferentiation can cause the fate conversion of pancreatic β-cells to lose their identity and specialized function of glucose response and insulin secretion. Available evidence from preclinical and clinical studies suggests that cell dedifferentiation is a risk factor for the loss of functional β-cell mass in T2DM (Cinti et al., 2016; Wang et al., 2014; Weir et al., 2013). Autophagy, a physiologic process for organelle quality control, can morph into a destructive cellular response mechanism during diabetes to contribute to pancreatic β-cells loss (Hur et al., 2010; Mbara et al., 2021). The limited antioxidant status and glycolytic capacity of the β-cells lead to oxidative stress, which can uncouple glucose sensing from insulin secretion (Talchai et al., 2012). The resulting glucotoxicity and elevated reactive oxygen species (ROS) may impair the regenerative capacity of β-cells and result in apoptosis of β-cells. Therefore, the research focus should be geared toward understanding the mechanisms to enhance β-cell survival and recovering functional endogenous β-cell mass as an early intervention in preventing the disease progression.

3. Endoplasmic reticulum stress (ER) and the unfolded protein response (UPR)

The ER plays a central role in coordinating protein biosynthesis, folding, and quality control of soluble and transmembrane proteins to their native conformations in all eukaryotic cells. In the ER lumen, newly synthesized proteins undergo various posttranslational modifications, including hydroxylation, glycosylation, lipidation, and disulfide bond formation by ER-resident molecular chaperones, glycosylating enzymes, oxidoreductases, and cofactors to catalyze protein-folding and maturation. Professional secretory cells such as pancreatic β-cells, hepatocytes, and B lymphocytes, which are more physiologically prone to protein folding overload than other cells, require a balanced ER environment (Scheuner and Kaufman, 2008; Yong et al., 2021). Both physiological and pathological stresses in the ER contribute to an imbalance between protein-folding demand and protein-folding capacity to cause ER stress. The UPR is triggered in an attempt to cope with ER stress and reinstate normal appropriate protein folding and metabolic processes in the cells by suppressing protein translation, stimulating chaperone synthesis, and stimulating the ERAD to degrade misfolded proteins (Wang and Kaufman, 2012).

The UPR is transduced downstream of three ER transmembrane signaling protein sensors, namely inositol requiring enzyme 1-α (IRE1-α), activating transcription factor 6 (ATF6), and protein kinase RNA-like ER kinase (PERK) (Walter and Ron, 2011). The three transmembrane signal transducers collaborate to induce gene expression programs and cytosolic responses that increase protein folding capacity and mitigate the burden of unfolded proteins. These "first responders" contain ER luminal domains, transmembrane regions, and cytosolic domains that activate transcriptional and translational remodeling of ER and promote adaptive means to resolve ER stress in the cell. Specifically, ATF6, a member of basic leucine zipper (bZIP) transcription factors, cleaves in the plane of the ER membrane during ER stress and translocates to the nucleus to regulate numerous UPR target genes that encode ER protein folding activities. The serine/threonine kinases, IRE1α and PERK undergo a conformational change to produce specific transcription factors —XBP1 and ATF4, respectively, that trans-activate genes necessary for boosting ER secretory function. XBP1s regulates the transcription of several different genes, including those involved in ERAD, protein translocation into the ER, lipid synthesis, and protein folding. While ATF4 modulates the gene expression of that regulate amino acid metabolism, redox homeostasis, protein synthesis, autophagy, and apoptosis (Hetz and Papa, 2018).

Apart from catalyzing the processing of XBP1s mRNA through its RNase activity under ER stress, IRE1α can act as a molecular scaffold for adaptor and modulator proteins through the UPR to enhance its activity and signal transduction with other stress pathways (Hetz and Glimcher, 2009; Liu et al., 2000). In its cytosolic RNase domain, IRE1α facilitates endonucleolytic cleavage and degradation of mRNAs, ribosomal RNAs, and microRNAs to regulate glucose metabolism, stress, inflammation, and apoptosis, via regulated IRE1α-dependent decay (RIDD) (Hetz and Papa, 2018). Although with distinct molecular mechanisms and kinetics, the oligomerization state of IRE1α may play a significant role in the RNase activity of XBP1 and RIDD-regulated mRNA splicing.

Activated PERK phosphorylates the eukaryotic translation initiation factor 2α (eIF2α) to inhibit protein synthesis (at the level of translation initiation) during ER stress, thereby maximizing the efficiency of the protein-folding machinery in the ER (Harding et al., 2000). The phosphorylation of eIF2α is the core event for several other stress pathways known as the "integrated stress response," in which activated PERK and other specific kinases reduce protein flux into the ER (Pakos-Zebrucka et al., 2016). However, a non-canonical translation initiation bypasses eIF2α phosphorylation using an internal ribosome entry site (IRES) element or upstream open reading frames (uORFs) to allow the selective translation of the mRNA encoding the transcription factor ATF4. ATF4 translation also promotes transcriptional activation of the pro-apoptotic factors, including growth arrest and DNA damage-inducible protein 34 (GADD34) and CCAAT/enhancer-binding protein homologous protein (CHOP), to induce oxidative stress, protein synthesis, autophagy, and apoptosis (Moriguchi et al., 2019). GADD34 is part of a phosphatase complex that facilitates the dephosphorylation of eIF2α to restore protein translation.

The transcription factor ATF6, which has a luminal "sensing" domain and a cytosolic transcription transactivation domain is activated by the ER chaperone, GRP78, as well as protein disulfide isomerases (PDIs) (Haze et al., 1999). Upon ER stress, ATF6 is cleaved to an active N-terminus cytosolic fragment (ATF6N) by S1P and S2P proteases in the Golgi apparatus. The cleavage product is transported into the nucleus where it acts as a transcription factor to induce ER chaperones, ERAD components, the pro-apoptotic factor CHOP, and several other homeostatic effectors (Sicari et al., 2019; Wu et al., 2007).

The transcriptional output of these UPR transducers is regulated based on the physiological state of the ER molecular chaperone, binding immunoglobulin protein/glucose-regulated protein 78 (BiP/GRP78), which serves as the master regulator and marker for ER stress and UPR activation. In non-stressed mammalian cells, BiP binds to the luminal domains of the UPR sensors, maintaining them in an inactive form. In stressed conditions, BiP dissociates from the ER stress sensors and preferentially binds to nascent or unfolded proteins to initiate UPR activation. However, recent studies suggest a BiP-independent mechanism in which misfolded protein directly activates these UPR sensors (Hetz and Papa, 2018; Hetz et al., 2020; Oakes and Papa, 2015). The chaperone activity of BiP correlates with the demand for insulin and appears to be essential in β-cell physiology. Underexpression of BiP activity induces constitutive ER stress and β-cell dysfunction and reduced insulin secretion (Fritz et al., 2014; Zhang et al., 2009). Conversely, the overexpression of BiP has been linked to the maintenance of pancreatic β-cell ER homeostasis, proliferation of β-cells, and increased insulin secretion, thus leading to β-cell survival (Ittner et al., 2014; Lindahl et al., 2014).

In chronic irremediable ER stress, when the adaptive responses to restore proteostasis are overwhelmed, these UPR sensors/effectors switch from adaptive to maladaptive signaling programs, culminating in apoptosis. UPR-induced apoptosis could be beneficial or detrimental depending on the context and duration of ER stress. It could be a stringent but definitive quality control mechanism during irremediable ER stress since eliminating highly stressed cells would prevent them from producing potentially defective secretory products. However, UPR-induced apoptosis could result in the progression of various diseases and organ failure due to the loss of functional cell mass (Ghosh et al., 2019).

Although the precise machinery that regulates UPR-induced apoptosis under irreversible ER stress conditions remains to be determined, numerous pro-apoptotic mechanisms have been proposed to contribute to apoptosis. Among such mechanisms include the transcriptional induction of the pro-apoptotic factors CHOP and components of the B cell lymphoma protein 2 (BCL-2) protein family by ATF4 (Galehdar et al., 2010), endonucleolytic decay of essential ER components and miRNAs by excessive RIDD activity (Han et al., 2009; Hetz et al., 2020), as well as dysregulated Ca^{2+} signaling, excessive oxidative stress, and proteotoxicity (Ren et al., 2021; Urra et al., 2018).

4. Effects of endoplasmic reticulum stress on pancreatic β-cell function

Pancreatic β-cells are prone to disruption of ER homeostasis due to high secretory burden and relative complexity of folding proinsulin into insulin. Several environmental, and physiological factors modulate ER homeostasis in pancreatic β-cells. ER/UPR exerts a dual physiologic role on β-cells as protein homeostasis regulators under physiological conditions and as inducers of apoptosis and β-cells dysfunction during chronic stress. Chronic ER stress, apart from impairing insulin production and transitioning cell adaptation to cell death programs, induces oxidative stress, inflammatory responses, and dedifferentiation and dysregulates calcium homeostasis and ERAD in β cells. In remediable stress, UPR modulates the expression of genes involved in insulin biosynthesis and acts as a gatekeeper to ensure that the right amount of insulin is produced to meet the body's demand (Boland et al., 2017; Chen et al., 2017). This regulatory role maintains glucose homeostasis and prevents over- or underproduction of insulin. However, the ER folding capacity and catalytic function of important ER resident chaperones such as PDI, ERp57, and GRP94 can be compromised during chronic ER stress-induced hyperglycemia due to increased insulin biosynthesis to compensate for the increased metabolic demand (Boland et al., 2017). This ultimately overwhelms the β-cell's insulin secretory capacity, thereby decreasing insulin release in response to glucose stimulation. Acute ER stress stabilizes ER protein folding capacity and increases β-cell proliferation through survival pathways and cell replication.

Conversely, as mentioned earlier, irremediable ER stress can trigger β-cell apoptosis, resulting in a decline in β-cell mass and exacerbating glucose dysregulation. This loss of β-cells can further disrupt the biosynthesis and secretion of insulin and other components of the secretory machinery, leading to β-cell failure and the development of diabetes. This is evidenced by gain-of-function and loss-of-function studies on the physiology of UPR transducers in β-cells in preclinical and clinical settings. For instance, the homozygous deletion in mice of Perk (also known as Eif2ak3) and PERK gene mutation in patients with neonatal DM causes β-cell failure (Delépine et al., 2000; Harding et al., 2001). In patients with T2DM, β-cell ER stress leads to elevated apoptosis and increased protein levels of p58IPK, ATF3, and CHOP (indicators of PERK signaling), as well as BiP and XBP1 (Laybutt et al., 2007; Marchetti et al., 2007). Furthermore, the genetic knock-in of the homozygous non-phosphorylatable (Ser51Ala) mutant in eIF2α also causes β-cell failure in a mouse model similar to Perk deletion (Back et al., 2009; Scheuner et al., 2001), suggesting the regulatory role of eIF2α phosphorylation by PERK in β-cell function.

Moreover, the PERK-PI3K-AKT cascade serves as an adaptive mechanism that prevents apoptosis (Ren et al., 2021). The second UPR transducer, ATF6, plays a crucial role in β-cell function by activating distinct signaling elements, leading to the induction of autophagy, abrogation of apoptosis, and reduction of ROS levels. The deletion of ATF6 in mice fed a high-fat diet reduced pancreatic insulin content and increased the development of diabetes (Usui et al., 2012). Moreover, single-nucleotide polymorphisms in ATF6 are linked with increased susceptibility to T2DM in several human populations (Meex et al., 2007; Thameem et al., 2006). Although there is no report on IRE1 mutations in

patients with monogenic diabetes, the β-cells of Ire1 null-mice developed β-cell failure and diabetes due to impaired proinsulin synthesis (Hassler et al., 2015). Evidently, IRE1α-mediated Xbp1 splicing is required to maintain β-cell integrity and induce gene products required for the translocation and processing of preproinsulin to the ER during proinsulin biosynthesis (Lee et al., 2011; Yong et al., 2021). Similarly, IRE1α, just like the PERK and ATF6 signaling branches, has been shown to induce autophagy, suppress the generation of ROS, and prevent apoptosis by activating multiple signaling mechanisms (Ho et al., 2012; Urra et al., 2020).

While UPR maintains β-cell integrity through its adaptive programs, chronic ER stress can engender destructive UPR output to compromise β-cell function. For example, the anti-cancer agent imatinib abrogated and reversed diabetes by modulating the UPR to reduce ER stress-induced apoptosis in new-onset T1DM mice (Louvet et al., 2008; Morita et al., 2017). By blocking the interaction between IRE1α and the non-receptor ABL tyrosine kinases at the ER membrane, imatinib suppresses IRE1α's endoribonuclease (RNase) activity to attenuate pro-apoptotic terminal UPR signaling in β-cells. Transcriptional dysregulations of UPR pathways impair β-cell function as its associated with pancreatic aging (Li et al., 2021), local inflammation (O'Neill et al., 2013), and glucotoxicity (Maedler et al., 2002) in human and animal T2DM models.

Furthermore, unresolved ER stress could hyperactivate IRE1α RNase to lose its target specificity and promote multiple downstream destructive outcomes, including oxidative stress, sterile inflammation, and β-cells dedifferentiation through regulated endonucleolytic decay of RNAs. This IRE1α-induced hyperactivation can induce loss of ER-localized mRNAs encoding structural and enzymatic components of the ER protein-folding machinery (Ghosh et al., 2019). For instance, the loss of the redox protein, peroxiredoxin 4 (PRDX4) by IRE1α-induced hyperactivation predisposes β-cells to elevated ROS generated through oxidative folding of pro-insulin (Mehmeti et al., 2014; Zhang et al., 2019). Hyperactivated IRE1α strengthens thioredoxin-interacting protein (TXNIP) mRNA stability, which concomitantly induces NLRP3 inflammasome in β-cells (Oslowski et al., 2012), just as the loss of IRE1α expression impaired postnatal β-cell maturation, and results in dedifferentiation of adult β-cells in β-cells of mice (Lee et al., 2020).

Acute ER stress promotes β-cells secretory function by maintaining robust glucose-responsive Ca^{2+} signaling. Reports have shown that UPR mediators enhance glucose-stimulated insulin secretion (GSIS) and ER Ca^{2+} homeostasis to maintain β-cell ER calcium health by enhancing Ca^{2+} influx entry and sarco-endoplasmic reticulum Ca^{2+} ATPase 2b (SERCA2b) activity, which ensures appropriate insulin release in response to glucose levels (Kirkpatrick et al., 2011; Sharma et al., 2021; Wang, R. et al., 2013). However, unresolved chronic ER stress dysregulates Ca^{2+} homeostasis, triggering calcium leakage from the ER into the cytoplasm, thereby disrupting insulin secretion and overall β-cell function.

The UPR activated during acute ER stress enhances the transcription of genes encoding ER-resident protein-folding enzymes and ER-associated degradation (ERAD) machinery's efficiency, which evacuates misfolded proteins and promotes ER function by upregulating the expression of components involved in ERAD (Travers et al., 2000), enhancing proteasome activity (McCracken and Brodsky, 2003), and chaperone-mediated ERAD (Stolz and Wolf, 2010). For instance, PERK could initiate various types of autophagy and balance redox homeostasis in the pancreas by activating EIF2A and ATF4, thereby preventing ROS-mediated build-up of misfolded proteins in the ER lumen (Ghosh et al., 2019; Ren et al., 2021). Conversely, irremediable ER stress has the opposite effect on the ERAD machinery, thereby resulting in the accumulation of toxic protein aggregates, impaired proteasomal degradation, and reduced efficiency, further aggravating ER stress.

Overall, ER stress-induced pancreatic β-cells dysfunction is a critical pathological factor in the development and progression of diabetes. Thus, further research should be geared toward understanding the underlying mechanisms and therapeutic modulation of UPR on β-cell function to preserve β-cell health and function in diabetes and related metabolic disorders.

5. Flavonoids

Dietary flavonoids, which are major constituents of our daily diets, are polyphenolic secondary metabolites biosynthesized via the Shikimate and acetate pathways, usually found in fruits, vegetables, and other plant species (Shen et al., 2022) (Fig. 2). They are well-known in folkloric and modern medicine for the treatment of various diseases, including DM. This is corroborated by their numerous biological activities, which make them good candidates and pharmaceutical leads for the development of new drugs against several diseases. Dietary flavonoids consist of a 2-phenyl-benzo-pyrane backbone bound to a 3-carbon unit (C_6–C_3–C_6) heterocyclic pyran ring and are classified into subtypes based on the oxidation degree of the central heterocyclic ring. Their structural composition such as the degree of polymerization, hydroxylation, and conjugation, plays a significant role in the biological activity of dietary flavonoids. Dietary flavonoids are mostly stored as conjugates in glycosides in the cell vacuole of plants, as glycosylation increases their solubility in water. The common sugar components linked with these aglycones are mainly D-glucose and L-rhamnose, attached at the C-3 or C-7 position (Habtemariam, 2019). Growing evidence suggests the efficacy of dietary flavonoids in enhancing survival pathways and inhibiting death signals in pancreatic β-cells (Ghorbani et al., 2019; Pinent et al., 2008; Soares et al., 2017).

Dietary flavonoids, especially flavonols, flavones, and flavonones have potent pharmacological effects and are possible future therapeutic candidates to mitigate ER stress-mediated β-cells dysfunction. Dietary flavonoids have the physiological role of inducing or inhibiting ER

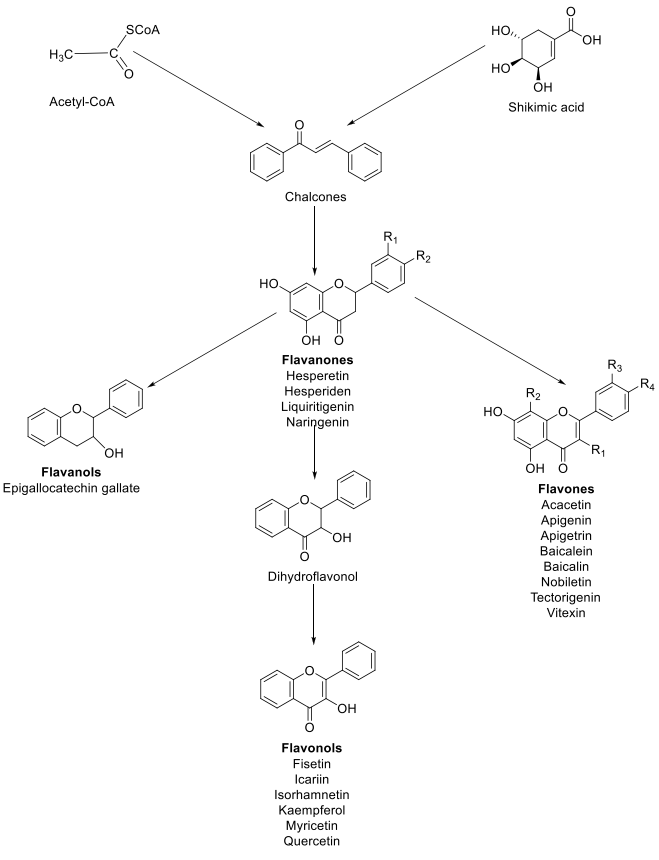


Fig. 2. Schematic of the biosynthesis of representative flavonoids with potential therapeutic effects against endoplasmic reticulum stress in pancreatic β-cell.

stress-mediated apoptosis in pancreatic β-cells depending on the cell type, dose, nature and duration of ER stress (Ghorbani et al., 2019). Owing to their diverse chemical structures, dietary flavonoids exert pleiotropic effects on the pancreas and modulate β-cell function by stimulating insulin secretion and increasing cell proliferation directly or indirectly (Mbara et al., 2022b; Pinent et al., 2008). Although their precise mechanisms of action remain unclear, the modulation of UPR signaling has been suggested from experimental evidence to play a key role in alleviating ER stress (Pandey et al., 2017, 2019; Tang et al., 2017). Below, the beneficial effects of selected dietary flavonoids on modulating ER stress-mediated diseases in various organs of the body using mouse models is reviewed (Table 1).

6. Molecular mechanisms of flavonoids in pancreatic beta cell dysfunction

The molecular mechanisms of dietary flavonoids on ER homeostasis and UPR can vary depending on the specific flavonoid compound to modulate various cellular processes, signaling pathways, and their associated molecules that interfere with ER stress in islet cell physiology. These mechanisms include direct binding with ER stress signaling components, chaperone protein induction, regulation of transcription factors, mediators of glucolipotoxicity, and mitochondrial homeostasis, mitigation of oxidative stress, modulation of autophagy, apoptosis, intermediary metabolism, and anti-inflammatory effects (Kraskiewicz and FitzGerald, 2012) (Fig. 3).

Table 2 summarizes the mechanisms of action and the pharmacological effects of dietary flavonoids on cellular signaling pathways and molecular targets implicated in the induction of ER stress in pancreatic β-cells.

6.1. Flavonols

6.1.1. Quercetin

The dietary polyphenolic flavonoid quercetin has potent bioactivities and a good safety profile and occurs ubiquitously in many plants, such as buckwheat, onion, apples, and tea (Mbara et al., 2022a). Quercetin has known antioxidant properties that suppress free-radical formation from resonance-stabilized phenoxyl radicals, owing to its structural features. Quercetin improves endothelial function and, consequently, recovery of β-cells by suppressing ER stress-mediated oxidative stress in diabetic rats (Suganya et al., 2018a). Treatment with quercetin decreased immunoreactivity to CHOP and ET-1 and stimulated the expression of the proangiogenic factor VEGF and its receptor (VEGF-R2), in pancreatic tissues. In another study, quercetin was shown to ameliorate endothelial dysfunction in experimental diabetes by relieving ER stress in a co-culture system of immortalized endothelial cells and rat pancreatic β-cells (Suganya et al., 2018b). ER stress plays a pathophysiological role in diabetic complications by suppressing nitric oxide (NO) production by endothelial nitric oxide synthase (eNOS) in vascular endothelial cells to inhibit the secretion of insulin in β-cells (Kuboki et al., 2000). By upregulating the eNOS expression, quercetin modulates NO production to maintain vascular homeostasis in endothelial cells, thereby favoring insulin secretion from pancreatic β-cells. Treatment with quercetin significantly improved the endothelial-pancreatic β-cells communication and abrogated apoptosis by reducing the expression of the ER markers, GRP78 and CHOP, and levels of ROS and phosphoproteins involved in MAPK signaling (Suganya et al., 2018b), suggesting a beneficial role in glycoprotein trafficking and molecular chaperone activity of pancreatic β-cells. Quercetin has been shown to activate the cytosolic, catalytic, effector domain of yeast IRE1 RNase and enhances affinity for ADP at the nucleotide-binding cleft (Wiseman et al., 2010). This allosteric regulation results in a conformational change at the dimer interface of the IRE1 kinase extension nuclease (KEN) domain that promotes the interaction between IRE1 protomers in the plane of the ER membrane. Hence, this implies that quercetin could act as an effective

Table 1
Overview of mouse models of reviewed dietary flavonoids for the treatment of various ER-related diseases.

S/N	Flavonoids	Organs/animal	Target	Disease condition	References
1	Acacetin	Liver	ATF6 and CHOP	Non-alcoholic fatty liver disease	Jiang et al. (2023)
2	Apigenin	Liver and visceral fats	p-PERK, GRP78, p-eIF2a, and CHOP	Obesity	Wu et al. (2021)
3	Baicalein	Spinal cord	GRP78, ATF4, CHOP, and CASP12	Ischemia-reperfusion Injury	Wu et al. (2020)
5	EGCG	Brain	GRP78, CHOP, cleaved-caspase-12 and caspase-3.	Alzheimer's disease	Du et al. (2018)
		Ovaries	GRP78 and XBP1	Reproductive system disorder	Hegde et al. (2020)
6	Fisetin	Liver	ROS, GRP78 and CHOP	NAFLD	Dai et al. (2022)
		Heart	PERK, eIF2α, IRE1, XBP1 and CHOP	Cardiomyopathy	Ge et al. (2019)
8	Hyperoside	Heart	BiP, CHOP and Nrf2	Cardiac ischemia-reperfusion injury	Hou et al. (2016)
9	Icariin	Spinal cord	ATF6, IRE1α, GRP78, XBP1 and eIF2α	Neuronal apoptosis	Li et al. (2019)
10	Isorhamnetin	Lungs	CHOP, GRP78, p-PERK, and p-eIF2α)	Pulmonary fibrosis	Zheng et al. (2019)
11	Kaempferol	Lungs	XBP-1 and IRE1α	Chronic airways diseases	Park et al. (2015)
		Liver	Grp78 and CHOP	Liver failure	Wang et al. (2019)
13	Naringenin	Brain	p-eIF2α, ATF4, and CHOP	Brain injury	Deng et al. (2021)
		Peritoneal macrophages	GRP78, XBP-1 and ATF6	Atherosclerosis	Xu et al. (2019)
		Kidney	GRP78, CHOP, Nrf2 and HO-1; ATF4 and CHOP	Renal Ischemia-Reperfusion Injury; nephrotoxicity	(Zhang et al., 2022; Khan et al., 2022
15	Quercetin	Brain	PERK, IRE-1α, ATF6,	Diabetic encephalopathy	(Hu et al., 2020; Chen

(continued on next page)

Table 1 (*continued*)

S/N	Flavonoids	Organs/animal	Target	Disease condition	References
			eIF2α, BIP and PDI		et al., 2016)
16	vitexin	Liver	CHOP, GRP-78, CHOP and eIF2α, GRP78 and ATF4	NAFLD	Jiang et al. (2022)

regulator of proteostasis to ensure the proper folding of error-prone medically important mutant proteins in the ER of pancreatic β-cells.

Moreover, quercetin has been shown to stimulate the endoribonuclease activity of IRE1, which is involved in the activation of AMPK and AMPK-dependent pathways in pancreatic β-cells in response to NO-induced stress (Meares et al., 2011). This signaling pathway is crucial for maintaining cellular metabolism and initiating prosurvival autophagy in tissues with high metabolic activity, such as the pancreatic β-cells, because it regulates the activity of critical proteins, such as acetyl-CoA carboxylase, PGC-1α, and mTORC (Mbara et al., 2021). The quercetin derivative, hyperoside has been reported to be the bioactive compound responsible for the beneficial effects of *Zanthoxylum bungeanum* on pancreatic β-cell survival and insulin secretion *in vivo* (Zhang et al., 2021). Oral administration of hyperoside restored structural integrity and pancreatic β-cell function of diabetic mice by inhibiting MAPK signaling, intracellular Ca^{2+} concentration, and TXNIP expression, suggesting its therapeutic potential for managing inflammation-induced protein misfolding. Thus, the clinical merits of quercetin concerning its feasibility, efficacy, safety, and tolerability need to be established and employed to alleviate β-cell dysfunction.

6.1.2. *Kaempferol*

Kaempferol, another dietary flavonol with well-known anti-oxidative and anti-inflammatory effects, is relatively abundant in various plants such as grapefruit, cabbage, kale, and some edible berries. Kaempferol has been reported to have protective effects and improve pancreatic β-cells secretory function in T2DM animal models (Elekofehinti et al., 2020; Zhang et al., 2013). Kaempferol activates autophagy, an adaptive response to quell ER stress in lipid-induced pancreatic β-cell apoptosis by modulating the AMPK/mTOR signaling pathway (Varshney et al., 2017). In a similar study to evaluate the effect of kaempferol on autophagic turnover in pancreatic β-cell's lipid metabolism, treatment with Kaempferol triggers lipophagy and alleviates ER stress-induced β-cell dysfunction by downregulating the transcription factor, CHOP, and activating AMPK/mTOR signaling pathway (Varshney et al., 2018). This abrogation of lipid-activated ER stress through AMPK-mediated lipophagy suggests the cytoprotective role of kaempferol in pancreatic β-cell lipid metabolism. Furthermore, kaempferol has been shown to

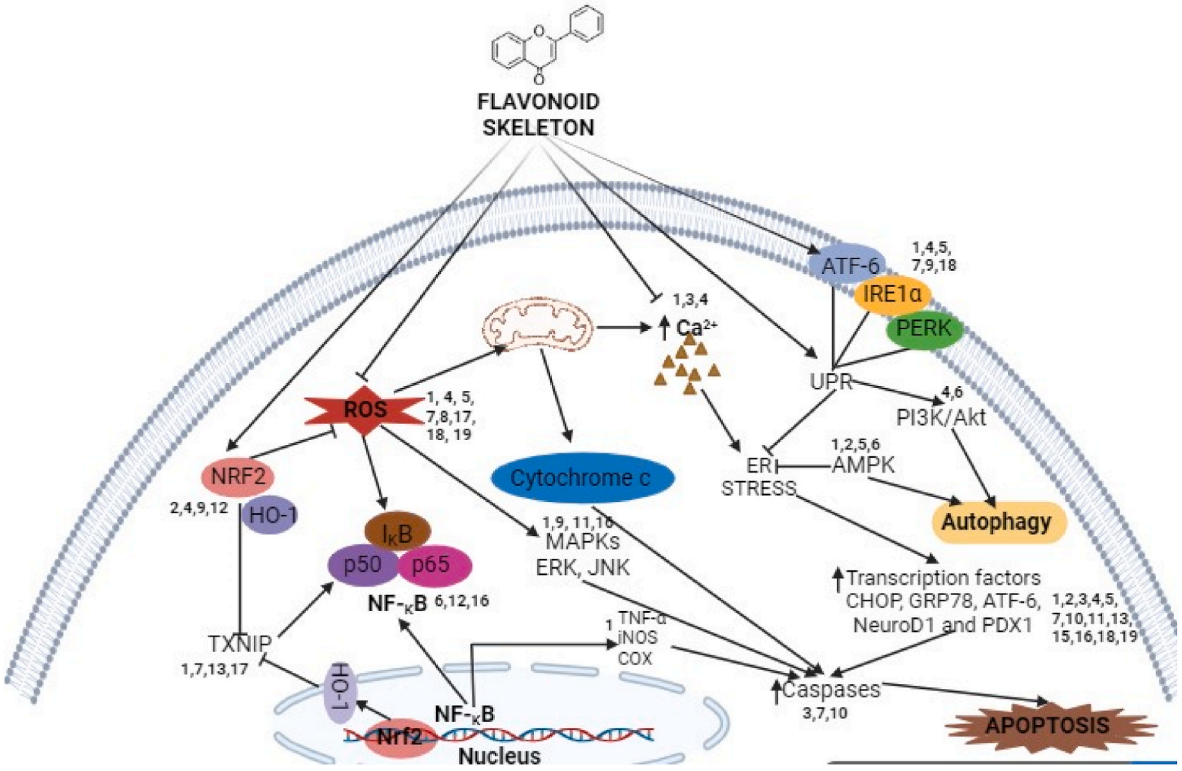
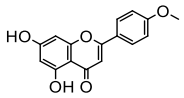
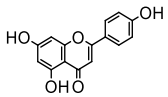
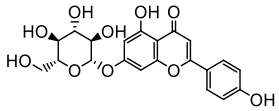
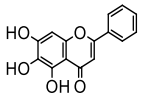
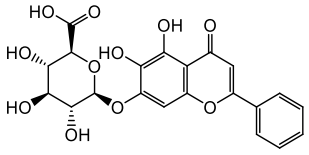
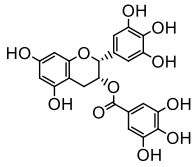
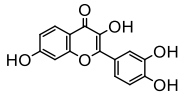
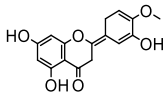
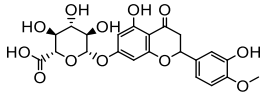
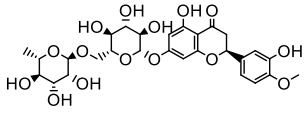
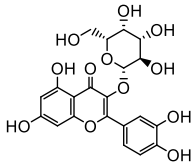


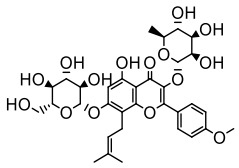
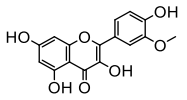
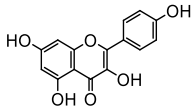
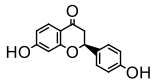
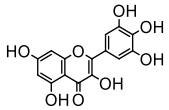
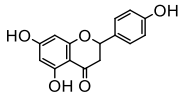
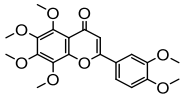
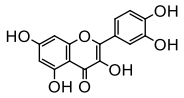
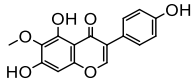
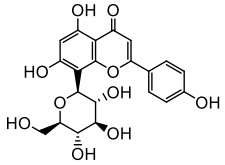
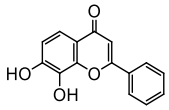
Fig. 3. The major molecular targets of dietary flavonoids to preserve pancreatic β-cells from ER stress. The potential mechanisms involved are primarily through the modulation of UPR transcription factors, upregulation of Nrf2/HO-1 and AMPK/PI3K/Akt signaling and suppression of ROS, MAPK signaling, TXNIP, NF-κB and Ca^{2+} overload. 1–19 represent the different dietary flavonoids in the relevant regulatory pathways: (1) quercetin (2) kaempferol (3) myricetin (4) isorhamnetin (5) fisetin (6) icariin (7) apigenin (8) apigetrin (9) baicalein (10) baicalin (11) nobiletin (12) vitexin (13) hesperidin (14) hesperetin (15) epigallocatechin gallate (16) tectorigenin (17) naringenin (18) liquiritigenin (19) acacetin. AMPK, AMP-activated protein; kinaseAkt, protein kinase-β; ATF6, Activating transcription factor 6; CHOP, C/EBP homologous protein; COX, cyclooxygenase; eIF2α; eukaryotic translation initiation factor 2-alpha; ERK, extracellular signal-regulated kinases; GADD34, growth arrest- and DNA damage-inducible gene 34; GRP78, glucose-regulated protein; HO-1, heme oxygenase 1; iNOS, inducible nitric oxide synthase; IRE1α; Inositol-requiring enzyme-1α; JNK, c-Jun NH_2-terminal protein kinase; MAPKs. mitogen-activated protein kinases; NeuroD1, neurogenic differentiation 1; NF-κB, nuclear factor kappa B; NRF2, nuclear factor erythroid 2-related factor 2; PDX1, pancreatic and duodenal homeobox 1; PERK, protein kinase RNA-like endoplasmic reticulum kinase; PI3K, phosphoinositide 3-kinases; ROS; reactive oxygen species; TNFα, tumour necrosis factor alpha; TXNIP, Thioredoxin-interacting protein; XBP1, X-box binding protein 1. UPR, unfolded protein response. Figure created with BioRender.com.

Table 2
The mechanisms of action of dietary flavonoids in regulating ER stress in pancreatic β-cells.

S/N	Flavonoid/structure	Mechanism(s)	Function	References
1	Acacetin 	↑AMPK ↑CAT,↑SOD,↑GPx ↓Ca^{2+}, ↓CHOP	↓ Oxidative stress and inflammation ↓ lipotoxicity in pancreatic cells	Song et al. (2022) (Wang et al., 2022)
2	Apigenin 	↓CHOP, ↓cleaved caspase 3, ↓TXNIP ↑ IRE1	↓ ER stress-induced β-cell apoptosis. ↑ Cytoplasmic ligand modulation of IRE1	Ihim et al. (2023) (Wiseman et al., 2010)
3	Apigetrin 	↓XBP1, ↓Ca^{2+}, ↓GRP78, ↓PERK, ↓eIF2α, ↓ATF6, ↓CHOP ↑ Antioxidants (SOD, CAT, GSH)	↓ β-cell dysfunction and apoptosis ↓ islets tissue damage	Zhang et al. (2020) (Abdulrasheed-Adeleke et al., 2023)
4	Baicalein 	↑ERK, ↑HO-1	↓ lipotoxicity in pancreatic cells	Kwak et al. (2017)
5	Baicalin 	↓ BIP, ↓XBP1s, ↓CHOP, ↓caspase-9, ↓cleaved-caspase-3, ↓TNF-α and ↓IL-6,	↓Inflammatory cytokines and cell damage in severe acute pancreatitis	Yang et al. (2020)
6	EGCG 	↑NeuroD1 ↓CHOP ↑PDX-1	↓Pancreatic β-cell impairment induced by ethanol. ↑Impaired β-cell function	Wu et al. (2016) (Zhu et al., 2022)
7	Fisetin 	↑AMPK/mTOR, ↑ATF6, ↑ATF4, and ↑PERK ↑ Antioxidants (SOD, CAT, GPx, and GST) ↓ NF-κB	↑Autophagy in β-cells ↓ Oxidative stress and inflammation	Jia et al. (2019) (Prasath et al., 2013)
8	Hesperetin 	↑AMPK ↓TXNIP	↓ Pancreatic β-cell damage	Wang et al. (2021)
9	Hesperetin 7-glucuronide 	↓TNF-α ↓NF-kB	↓ Inflammation to promote pancreatic β-cell survival	Fraga et al. (2023)
10	Hesperidin 	↓GRP78 ↓CHOP ↓TNF-α ↑SOD and ↑GPx	↓ β-cell apoptosis	Hanchang et al. (2019)
11	Hyperoside 	↓ TXNIP, ↓ ROS, ↓ Ca^{2+}	↓ Pancreatic β-cells ER-mediated apoptosis	Zhang et al. (2021)

(*continued on next page*)

Table 2 (*continued*)

S/N	Flavonoid/structure	Mechanism(s)	Function	References
12	Icariin 	↑ AMPK ↑PI3K/Akt ↓ NF-κB	↑ GSIS and preserving β-cells. ↑Insulin secretion and reduce β-cell apoptosis. ↓β-cell apoptosis.	Li et al. (2020) (Zhang and Qiu, 2020) (Zhong et al., 2018)
13	Isorhamnetin 	↑Nrf2 ↑HO-1 ↓ CHOP ↓ GRP78 ↑PKCε ↓XBP-1, ↓ATF6, ↓CHOP	↓ Oxidative stress ↓ ER stress ↑ Islet cell survival ↑ Insulin secretion in pancreatic islets	Yang et al. (2014) (Li et al., 2023; Zheng et al., 2019) Kvezereli et al. (2008) Rodríguez-Rodríguez et al. (2015)
14	Kaempferol 	↑ AMPK, ↓ mTOR ↑ AMPK, ↓ mTOR ↓ CHOP ↓ GRP78, ↑ Nrf2	↑ Autophagy to sustain pancreatic β-cell mass and function. ↑ Autophagy to improve ER stress and lipid mobilization in pancreatic β-cells. ↓ ER stress to alleviate pancreatic dysfunction and insulin resistance.	Varshney et al. (2017) (Varshney et al., 2018) (Elekofehinti et al., 2020)
15	Liquiritigenin 	↑Akt and ↓PERK, ↓ eIF-2a, and ↓CHOP	↓ lipotoxicity in pancreatic cells	Han et al. (2019)
16	Myricetin 	↑ CDK5, ↑ SERCA2b ↓ hIAPP, ↓ ROS	↓ Mitochondrial dysfunction and apoptosis ↑ insulin secretion by protecting pancreatic β-cells	Karunakaran et al. (2019a) (Dubey et al., 2021)
17	Naringenin 	↓TNF-α ↓NF-kB	↓ Inflammation to promote pancreatic β-cell survival	Fraga et al. (2023)
18	Nobiletin 	preventing JNK activation ↓CHOP	↑ Insulinotropic and anti-apoptotic effects in β-cells ↓ β-cell apoptosis	Takii et al. (2017) (Binh et al., 2020)
19	Quercetin 	↓ CHOP, ↓ NO•, ↓ GRP78, ↓ ROS, ↑ IRE1 ↑ IRE1 ↑ AMPK	↓ ER stress, ↓ Oxidative and nitrosative stress ↑ Cytoplasmic ligand modulation of IRE1 activity ↑Endoribonuclease activity of IRE1	(Suganya et al., 2018a, 2018b) (Wiseman et al., 2010) (Meares et al., 2011)
20	Tectorigenin 	↑ERK ↑PDX1	↓Glucolipotoxicity in islet β-cell	Yao et al. (2020)
21	Vitexin 	↑ Nrf2 and ↓NF-κB	↓ oxidative stress and inflammation to prevent apoptosis in pancreatic β-cells	Ganesan et al. (2020)
22	7,8-Dihydroxyflavone 	↓GRP78 ↓CHOP	↓Inflammation and ER stress	Sahin et al. (2022)

suppress the Keap1 inhibitive effect on nuclear factor erythroid 2-related factor 2 (Nrf2) signaling to restore glucose homeostasis in diabetic rats. This is suggested to be responsible for the ameliorative effects of methanolic leaf extract of *Cymbopogon citratus* against streptozotocin (STZ)-induced ER stress in rats through transcriptional induction of Nrf2 (Elekofehinti et al., 2020), a known master regulator of redox balance, survival, function and proliferation of β-cells (Baumel-Alterzon et al., 2021). These cases demonstrate the prospects of kaempferol as a useful phytochemical for improving β-cell health, pending large-scale randomized clinical studies and rigorous validation approaches.

6.1.3. Myricetin

Myricetin (3, 5, 7, 3′, 4′, 5′-hexahydroxyflavonol), a dietary molecule with a known safety profile is commonly used as a bioactive ingredient and additive in many foods (Song et al., 2021). Myricetin, just like its analog quercetin, modulates several biological processes that may contribute to its beneficial effects on pancreatic β-cell function and turnover. Initiation of the mitochondria-dependent apoptotic pathway and ER stress are key pathologic mechanisms involved in progressive deterioration of β-cell function. Myricetin relieves ER stress and mitochondrial oxidative damage in β-cells by suppressing cyclin-dependent kinase 5 (CDK5), a key regulator of apoptosis and cell survival, as well as upregulating SERCA2b and other apoptosis-related proteins (Karunakaran et al., 2019a). Similarly, treatment with myricetin improved ER stress-induced mitochondrial dysfunction and susceptibility to apoptosis in β-cells by inhibiting CDK5 and regulating Ca^{2+} signaling (Karunakaran et al., 2019b). The suppression of CDK5 has been associated with nuclear exclusion of pancreatic duodenal homeobox protein-1 (Pdx1) and transcriptional induction of SERCA2b to trigger ER stress. Myricetin also protected β-cells from thapsigargin-induced ER stress by preventing SIRT1 degradation (Karunakaran et al., 2019b), indicating its inhibitory and stimulatory effects on apoptosis and autophagy respectively to alleviate ER stress-related organ damage. Treatment with myricetin in β-cells inhibited the activation of the JNK pathway caused by thapsigargin, which, in turn, helps to stabilize Bcl-2, suggesting its beneficial role in alleviating apoptosis and maintaining Ca^{2+} homeostasis in β-cells. Furthermore, myricetin has been shown to exhibit significant anti-apoptotic properties by effectively reducing the Bax/Bcl-2 ratio in pyridinium-induced β-cell apoptosis (Han et al., 2022; Harithpriya et al., 2023).

Myricetin has been shown to abrogate amyloid-mediated ER stress by inhibiting the aggregation of human islet amyloid polypeptide (hIAPP) (Dubey et al., 2021). Myricetin interacts with the amyloidosis core to prevent hIAPP fibrillization, and/or disaggregates previously formed fibrils into harmless substances. Moreover, myricetin improved β-cell function in hIAPP-exposed islets by restoring glucose-stimulated insulin secretion, suggesting its beneficial effects in the treatment of T2DM. Although research on the potential role of myricetin in alleviating ER stress in pancreatic β-cells is ongoing (Dubey et al., 2021; Karunakaran et al., 2019a), more evidence from preclinical and clinical studies is required to establish its efficacy and optimal dosages for therapeutic purposes.

6.1.4. Isorhamnetin

Isorhamnetin is a monomethoxyflavonol and a metabolite of quercetin, found naturally in a variety of plants and plant-based foods. Despite having similar structures, isorhamnetin exhibits different physiological properties from its aglycone parent, quercetin, in terms of scavenging radicals, enzymatic activity, and vasodilation (Jiang et al., 2019). Isorhamnetin has known antioxidant effects of activating Nrf2/heme oxygenase-1 (HO-1) and PI3K/Akt pathways (Li et al., 2023; Yang et al., 2014), leading to the aversion of ER stress and apoptosis in pancreatic β-cells. By activating Protein kinase C epsilon (PKCε), it is argued that isorhamnetin could suppress the expression of GRP78, leading to cytoprotection of islet β-cells by relieving them of ER stress-induced intracellular Ca^{2+} overload, ROS production, and apoptosis (Kvezereli et al., 2008). Moreover, Zheng et al. (2019) reported the suppression of CHOP and GRP78 protein expression by isorhamnetin against pulmonary ER stress in mice. Isorhamnetin glycosides from *Opuntia ficus-indica* ameliorated ER stress, improved insulin sensitivity and insulin secretion, as well as metabolic abnormalities in obese animals by reducing the mRNA expression levels of diverse biomarkers of ER stress and lipogenesis, including ATF6, XBP1, CHOP, SREBP1, FAS, and SCD1 (Rodríguez-Rodríguez et al., 2015). The transcriptional suppression of these genes suggests that isorhamnetin could be a promising therapeutic intervention for the treatment of lipotoxic ER stress in pancreatic β-cells.

6.1.5. Fisetin

Fisetin (3,7,3′,4′-tetrahydroxyflavone) is a natural flavonoid found mostly in vegetables and fruits, such as cucumber, onion, apple, and strawberry, with numerous pharmacological activity (Jia et al., 2019; Mbara et al., 2022a). The antioxidant activity of fisetin is a prominent characteristic that may contribute to its beneficial effects by normalizing the antioxidant status of pancreatic β-cells in the ER-resident protein-folding machinery (Prasath et al., 2013). Fisetin induces autophagy in response to ER stress by enhancing AMPK/mTOR signaling and activating stress-induced transcription factor p8, which in turn modulates the expression of ATF6, ATF4, and PERK through the p53/PKC-α signaling pathway (Jia et al., 2019; Mbara et al., 2022a). Moreover, fisetin has been shown to enhance antioxidant enzyme status and insulin secretion while inhibiting inflammation in the pancreas of diabetic rats, thus leading to alleviation of diabetic-associated complications (Prasath et al., 2013), suggesting its prospects in alleviating ROS-mediated β-cells injury.

6.1.6. Icariin

The flavonol glycoside, icariin is the major component of the Chinese herb Yin Yang Huo (*Epimedii herba*) that has a long-established therapeutic profile in metabolic syndrome (Fu et al., 2015). Icariin is considered to have ameliorative effects on pancreatic β-cells health by modulating various molecular pathways to maintain cellular homeostasis. The substitutable prenyl group at C-8 that enriches the structural and biological diversity, and the propensity to be metabolized into glucuronide conjugates of isoflavonoids and flavonoid aglycones could be responsible for the pharmacological effects of icariin (Qian et al., 2012). Icariin activates phosphorylated AMPK (p-AMPK), leading to the abrogation of the loss of pancreatic islet cells and alleviation of the severity of diabetes in rats (Li et al., 2020), suggesting its beneficial role in improving glucose-stimulated insulin secretion (GSIS), proliferation, and survival of pancreatic β-cells. Icariin has been shown to improve insulin secretion and reduce β-cell apoptosis in uric acid-induced pancreatic β-cell injury by activating PI3K/Akt, suggesting its role in alleviating metabolic dysfunction associated with T2DM (Zhang and Qiu, 2020). Icariin inhibits NF-κB's nuclear translocation and the expression of pro-inflammatory cytokines, leading to the blockade of immune cells activation and abrogation of cytokine-induced β-cell apoptosis (Zhong et al., 2018), suggesting a potential therapeutic role in the management of T1DM-related ER stress. Owing to the beneficial therapeutic effects and molecular mechanisms as evidenced by pre-clinical studies, further clinical studies are needed to consider icariin as a complementary therapy for managing ER stress in the pancreas.

6.2. Flavones

6.2.1. Apigenin and apigetrin

Apigenin (4′, 5, 7, -trihydroxy flavone), belonging to the flavone subclass of flavonoids, is the aglycone of several glycosides present in various fruits and vegetables. The pharmacological properties of apigenin have positioned it as a viable option for treating various disease conditions. Additionally, its affordability and minimal risk side effects have further enhanced its potential application. Several prior studies have demonstrated the beneficial effects of apigenin in alleviating ER stress in several organs of the body (Choi et al., 2010; Wu et al., 2021). Recently, Ihim et al. (2023) reported that apigenin has protective effects on INS-1 β-cells against ER stress-mediated apoptosis. In INS-1 β-cells, apigenin alleviated thapsigargin-induced ER stress by inhibiting the expression of CHOP, cleaved caspase-3, and TXNIP, suggesting its protective role against β-cell apoptosis in the treatment of T2DM. Apigenin, just as quercetin has been shown to activate IRE1 nuclease activity and splicing of XBP1 (Wiseman et al., 2010). Similarly, the apigenin derivative, apigetrin, activates XBP1 and other ER stress biomarkers, as well as mitigates oxidative stress and calcium dyshomeostasis in STZ-induced pancreatic β cell damage *in vitro* (Zhang et al., 2020), suggesting a

cytoprotective role in restoring redox balance and ER function in diabetic condition. In a recent report, apigetrin restores β-cells integrity and improves insulin secretion through a redox-dependent signaling mechanism (Abdulrasheed-Adeleke et al., 2023). This indicates that the beneficial role of apigetrin in ER function could be because of its antioxidant effects, and its structural similarity with apigenin, which has the same pharmacological effects (Isoda et al., 2014). Therefore, the potential effects of these flavones on pancreatic β-cells ER function need to be considered in further studies.

6.2.2. Baicalein and baicalin

Baicalein, and its glycoside baicalin, the major bioactive compounds isolated from the root of *Scutellaria baicalensis*, have been reported to improve β-cell function (Baradaran Rahimi et al., 2021; Kwak et al., 2017). Baicalein relieves ER stress in palmitate-induced β-cell dysfunction and improves insulin secretion by activating extracellular signal-regulated kinases (ERK) - HO-1 cellular defensive mechanism (Kwak et al., 2017). HO-1 is an anti-inflammatory molecule that is activated by numerous stressors such as endotoxin, cytokines, and oxidants in the catabolism of heme to carbon monoxide (CO), biliverdin, and iron (Lazarus et al., 2022). The protective effect of baicalein on β-cell ER stress appears to be partly because of its known antioxidant and anti-inflammatory activity, which is evident by increased production of CO and the upregulation of Nrf2/ARE-dependent HO-1 expression. Moreover, baicalin, a major constituent of the Chinese herbal formula, Chaiqin chengqi, alleviates cellular ER stress-mediated apoptosis and inflammatory response in an animal model of acute kidney injury caused by acute pancreatitis by suppressing the protein expression levels of BIP, XBP1s, CHOP, caspase-9, and cleaved-caspase-3 in the kidney cells (Yang et al., 2020). While these prospects are promising, available evidence are still in the preclinical stage and requires further studies, including rigorous clinical trials, to promote its translation in managing pancreatic β cells ER stress-related conditions in humans.

6.2.3. Nobiletin

The polymethoxyflavonoid, nobiletin occurs predominantly in the peels of citrus fruits. Nobiletin, just like other flavonoids, has known antioxidant, anti-inflammatory, and antidiabetic effects (Lee et al., 2010). Nobiletin has been shown to exert insulinotropic effects and abrogate ER stress-mediated β-cell apoptosis in pancreatic β-cells by preventing JNK activation, suggesting a cytoprotective role in oxidative stress-mediated tissue damage (Takii et al., 2017). Similarly, a recent report by the same authors shows that nobiletin increased pancreatic insulin content and protects against β-cell loss in mouse models of obesity and diabetes (Kaneko et al., 2022), indicating the maintenance of adaptive UPR responses in islet cells. Moreover, nobiletin and its analogs suppress β-cell death and exert cytoprotective effects against tunicamycin-induced ER stress through transcriptional repression of *chop* mRNA stress in mouse pancreatic β-cells (Binh et al., 2020), suggesting a promising role in the fidelity of insulin processing.

6.2.4. Vitexin

Vitexin, a glycoside of apigenin, improves insulin signaling and mitigates β-cells susceptibility to oxidative stress in the pancreas by stimulating Nrf2 and inhibiting NF-κB activity (Ganesan et al., 2020), suggesting its beneficial role in various diseases associated with oxidative stress and inflammation. The beneficial effects of vitexin appear to be because of its antioxidant and anti-inflammatory activity, which abrogates ROS and pro-inflammatory mediators generated by PDI, ER oxidoreductases, and UPR sensors in the ER (Eckard et al., 2014; McCullough et al., 2001).

6.3. Flavanones

6.3.1. Hesperidin and hesperetin

Hesperidin and its aglycone, hesperetin, are citrus fruits-derived flavonoids with many reported biological functions (Mbara et al., 2022a). Hesperidin improves pancreatic β-cell dysfunction in streptozotocin-activated apoptotic UPR in diabetic rat models by inhibiting GRP78 and CHOP (Hanchang et al., 2019), suggesting a beneficial role in modulating UPR initiation and apoptosis activation. Hesperetin plays a pivotal role in protecting β-cells from hyperglycemia-induced apoptosis *in vivo* and *in vitro* by suppressing histone acetylation through AMPK-dependent degradation of TXNIP (Wang et al., 2021). This suggests that hesperetin could regulate nutrient flux (especially insulin overload) to ER of pancreatic β-cells, thereby, relieving β-cells from ER stress by extrapancreatic mechanisms of enhancing glucose uptake in peripheral tissues. Hesperetin 7-glucuronide modulates protein expression of different cellular processes, including cell adhesion, cell signaling, metabolism, inflammation, and protein processing in ER pathways to alleviate pancreatic β-cells dysfunction under hyperglycemia-induced ER stress (Fraga et al., 2023).

6.4. Flavanols

6.4.1. Epigallocatechin gallate

Epigallocatechin Gallate (EGCG), the main constituent of green tea, has known therapeutic effects on DM. EGCG is suggested to mitigate ER stress in islet cells by modulating transcription factors (Johnson et al., 2014; Wu et al., 2016). EGCG alleviates ethanol-induced apoptosis in pancreatic β-cells by upregulating the transcription factor NeuroD1 and epigenetic silencing CHOP expression (Wu et al., 2016). Treatment with EGCG restored the activity of Neurod1 on the CHOP promoters by deacetylation of histone H4 in ethanol-treated cells. Thus, EGCG could be a viable candidate to prevent cellular injury of β-cells due to ethanol epigenetic effects. Similarly, EGCG improves impaired β-cell function in T2DM animal model by upregulating PDX-1 (Zhu et al., 2022), a transcriptional regulator of SERCA2b gene, which regulates ER Ca^{2+} homeostasis (Johnson et al., 2014), and β-cell susceptibility to ER stress (Sachdeva et al., 2009), suggesting its prospect in the maintenance of ER health of β-cells.

6.5. Other dietary flavonoids

Other dietary flavonoids, including their oxidation and polymerization products such as tectorigenin, acacetin, liquiritigenin, and 7,8-hydroxyflavone have cytoprotective effects on β-cells' ER stress (Bae et al., 2018; Sahin et al., 2022; Wang et al., 2022; Yao et al., 2020). Tectorigenin, a methoxyisoflavone found in many plants has various pharmacological activities such as antidiabetic, antimutagenic, estrogenic, hypolipidemic, anti-tumor, hepatoprotective, anticarcinogenic anti-inflammatory, and antioxidant properties (Han et al., 2012). Tectorigenin reduces ER stress, conserves islet mass, and rescues β-cells from glucolipotoxic-induced apoptosis *in vitro* and *in vivo* by stimulating the ERK signaling and promoting the expression of PDX1 in islet β-cells (Yao et al., 2020), suggesting its potential role in islet β-cell regeneration and proliferation. Moreover, the inhibitory effects of tectorigenin on ROS-associated inflammation by blocking IKKβ/NF-κB phosphorylation and JNK activation (Wang, Q. et al., 2013), could be argued to be a therapeutic pathway to alleviate β-cells ER stress. However, the mechanisms of action of tectorigenin in pancreatic β-cells ER health are far from being fully understood and require more experimental and clinical data validation.

Naringenin, the aglycone form of the main bitter flavonoid naringin, predominant in citrus fruits possesses numerous biological activities such as antioxidant, anti-inflammatory, antiproliferative, anti-dyslipidaemic, and antidiabetic effects (Mbara et al., 2022a; Nyane et al., 2017). Naringenin exerts a protective effect on pancreatic β-cells by blocking histone acetylation, which in turn regulates the inhibition of TXNIP (Wang et al., 2021). Although, the authors reported the protective effects of naringenin to be independent of their direct antioxidant activity, such protective effects on β-cells health could be expected in

further studies owing to its prominent antioxidant activities (Rajappa et al., 2019) and metformin-like effects (Nyane et al., 2017).

The dietary flavonoid, liquiritigenin isolated from the roots of the genus *Glycyrrhiza* is a known estrogen receptor β agonist (Mersereau et al., 2008), used in the treatment of many ailments, including diabetes. Treatment with liquiritigenin reduces ER stress response and preserves β-cells from apoptosis induced by the lipotoxic effects of accumulated fats in cells by activating Akt and reducing PERK, phosphorylated eIF-2a, and CHOP expression *in vitro* (Bae et al., 2018). The protective mechanism of liquiritigenin on β-cells ER stress may be attributed in part to its estrogen receptor agonistic effects mediated by extranuclear estrogen receptors, which inhibit GRP78 expression and ROS generation (Han et al., 2019). Thus, further mechanistic studies, especially on the relationship between the estrogenic effects of tectorigenin and pancreatic β-cells UPR sensors are necessary to understand the potential therapeutic application of tectorigenin in ER stress-related conditions.

Acacetin, (5,7-dihydroxy-4-methyl flavone) is a natural flavone found in many plant species with remarkable antioxidant, anti-inflammatory, anti-tumor, vasodilating, and antibacterial effects (Singh et al., 2020; Sun et al., 2018). Acacetin is suggested to have cytoprotective effects on β-cells ER stress by its antioxidant and anti-inflammatory effects and by promoting AMPK phosphorylation (Song et al., 2022). Acacetin alleviates lipotoxicity and relieves ER stress-mediated cell apoptosis in pancreatic cells by upregulating the endogenous antioxidant enzymes and downregulating CHOP expression (Wang et al., 2022), suggesting a beneficial role in preventing β-cells dysfunction and loss in diabetes and obesity. Similarly, the acacetin analog, 7,8-Dihydroxyflavone improved metabolic abnormalities, inflammation, and ER stress *in vivo* by downregulating GRP78 and CHOP expression (Sahin et al., 2022). This suggests that acacetin and its analogs could be potential candidates for ameliorating ERS-induced metabolic disorders in the pancreas but requires to be corroborated with further preclinical and clinical evidence.

7. Clinical considerations

Preclinical evidence has shown the numerous pharmacological effects of dietary flavonoids in preserving β-cells function. Given that flavonoids are secondary metabolites that cannot be synthesized by the human body, the consumption of flavonoids as dietary supplements for the management of DM and its complications has been a common lifestyle practice. This practice has gained so much prominence that some of these flavonoids have been subjected to clinical trials for the prevention and/or treatment of metabolic syndrome (NCT05243238), cardiovascular diseases (NCT00677599), prediabetes (NCT06005142), diabetic nephropathies (NCT03325322), and diabetic neuropathies (NCT05247034, NCT01307917, NCT05243238).

However, despite the promising future of dietary flavonoids from preclinical evidence in the management of ER stress in the pancreas, some grey areas of concern persist. Pharmacokinetic issues such as low bioavailability due to low permeability, food or drug interactions, poor solubility, poor oral and systemic absorption, extensive first-pass effect, and glucuronidation in the liver and intestine, as well as lack of pharmacodynamic reproducibility, have hampered the translation of flavonoids as approved drugs for clinical use (Mbara et al., 2022a; Zhao et al., 2019). Hence, developing strategies to abrogate these absorption barriers of dietary flavonoids would be of utmost importance. As previously mentioned, the majority of the studies on the pharmacological role of dietary flavonoids in ER stress of the pancreas were obtained from preclinical studies. In these studies, dietary flavonoids were administered at metabolically unrealistic high concentrations either as solubilized inorganic solvents *in vitro* or usually intraperitoneally (i.p.) to laboratory animals *in vivo*. This poses a challenge to the oral route administration of dietary flavonoids, which is the most preferred for successful clinical translation, considering patient compliance, convenience, cost-effectiveness, and extended time of drug administration, to attain the desired therapeutic plasma concentration (Sharma et al., 2004). Therefore, much still needs to be done to understand the precise estimates of dietary flavonoid intake through the data from *in vitro*, animal, clinical, observational as well as randomized intervention studies.

The bioavailability of dietary flavonoids can be affected by the innate physicochemical properties and their biological interaction in the systemic circulation. For instance, the formation of geometrically planar structures from the C2–C3 double bond of flavones and flavonols affects their structure–permeation relationship and reduces solubility to result in slow dissolution rates and consequently poor absorption (Chuang et al., 2017; Zhao et al., 2019). As a result, a significant portion of these flavonoids may not be absorbed into the bloodstream at effective levels, and consequently, hampers their translation into patient-compliant drugs. Thus, strategies that enhance target delivery, solubility, dissolution rate, and permeability and prevent the degradation or metabolism of flavonoids such as bioenhancers, structural modification (e.g., prodrugs, glycosylation), and pharmaceutical innovations (e.g., carrier complexes, nanotechnology, cocrystals) can be employed to address the challenge of oral bioavailability of flavonoids.

Moreover, the bioavailability of dietary flavonoids can vary among individuals due to genetic differences and flavonoid-microbiome pharmacology. These different genetic predispositions and microbial metabolisms of flavonoids in the gut should be taken into account when interpreting studies that investigate the effects of dietary flavonoids. Therefore, further pharmacogenomic studies on the structure-activity relationship of flavonoids are required to understand the interactions between interindividual variability and flavonoid bioavailability, which would contribute to explaining the role of genetic factors on dietary flavonoid metabolism. Furthermore, more research should be geared towards understanding the regulatory mechanisms of dietary flavonoids-gut microbiota interactions, which would contribute toward research in precision nutrition. There should be careful consideration of flavonoid–food or drug interaction as flavonoids either precipitate or complexes with other food or drug components to reduce its bioavailability (Basheer and Kerem, 2015). These interactions may affect the transport and/or disposition of free drugs, which could in some cases lead to adverse effects or therapy failures by elevating the concentration in the blood. Flavonoids are known modulators of xenobiotics-metabolizing enzymes such as cytochrome P450 enzymes (Baby et al., 2021; Fukasawa et al., 2007), and drug transporters such as P-glycoprotein (P-gp) and organic anion transporting polypeptides (OATPs) (Shirasaka et al., 2009), since both proteins share a substantial overlap in substrate specificity. It has been reported that grapefruit juice is a potent inhibitor of intestinal and hepatic CYP3A4 and an inducer of drug efflux by P-glycoprotein transporters (Soldner et al., 1999). Naringin, a major flavonoid of grapefruit, has been shown to affect drug disposition and alter the plasma concentration of co-administered drugs by suppressing cytochrome P-450 (CYP) 3A4 enzyme, and OATP 1A2 *in vitro* (Bailey et al., 2007; Choi and Kang, 2008) and in humans (Dresser et al., 2005), suggesting a potential role in affecting the pre-systemic metabolism and bioavailability of many drugs. Therefore, the coadministration of flavonoids with conventional drugs could elicit a botanical-drug interaction, which could be harnessed to modulate the activity of these proteins and improve their pharmacokinetic profiles.

Additionally, better monitoring of the metabolism and interactions of dietary flavonoids with conventional drugs can be elucidated using metabolomics and other-omics approaches. The stability of flavonoids is another concern for its clinical application. Previous studies have shown the susceptibility of flavonoids to chemical degradation upon exposure to oxygen, temperature, pH, and ultraviolet rays (Zhou and Zhang, 2022). These physicochemical parameters affect the yield of flavonoids from biological sources as well as play a critical role in their efficient extraction and isolation. However, structural modifications by chemical, enzymatic, or chemo-enzymatic reactions such as glycosylation and acylation can be employed to not only enhance their stability but also

the solubility of flavonoids. Although flavonoids are generally considered phytocompounds with excellent safety profiles, the issue of toxicity could arise because to exact the desired pharmacological effects, flavonoids need to be taken in high doses to augment the inherent problem of poor bioavailability. It is worth mentioning that flavonoids at high doses could trigger pro-oxidative reactions in the presence of redox-active metals (Eghbaliferiz and Iranshahi, 2016), which could have a pathophysiologic role in pancreatic β-cell function. However, it could be possible that the pro-oxidant effects of flavonoids could reduce immature, damaged, and misfolded proteins from pancreatic β-cells by triggering apoptosis at irremediable ER stress, indicating its beneficial role. Either way, the jury is still out there, but does not negate the need for large-scale randomized clinical studies to determine the safe dose for humans in the management of ER stress in the pancreas.

In order to increase translatability, the potential role of some dietary flavonoids alone or in combination with conventional treatment regimens in managing DM and its associated complications has been subjected to clinical trials. The Beni-Suef University has completed and recently published an interventional clinical trial NCT05243238) in which the effects of either hesperidin (1 g/day for 12 weeks) or diosmin (1 g/day for 12 weeks) or a combination of both on 129 patients with metabolic syndrome and diabetic neuropathy receiving oral hypoglycemics were evaluated (Osama et al., 2023). By the completion of the trial, the authors reported that the combination of both flavonoids had superior efficacy in alleviating metabolic syndrome and diabetic neuropathy than oral supplementation with either hesperidin or diosmin alone. The FLAVO trial by the University of East Anglia (NCT00677599), is another completed clinical trial. The trial involves a year-long intervention with flavonoids (found in cocoa and soy) on 152 postmenopausal women with type 2 diabetes who are at high risk of cardiovascular disease. The study aims to determine whether these flavonoids are more effective in reducing the risk of cardiovascular disease than standard therapy with statin by comparing it with a placebo chocolate bar that does not contain flavonoids. Although the study was completed in April 2010, the results of the trial have not been published yet.

An ongoing trial from the São Paulo State University (NCT06005142) is enrolling 80 participants diagnosed with prediabetes and being treated with metformin (1000 mg/day), in which eriomin will be administered at a dose of 250 mg/day for 12 weeks. This trial aims at evaluating the effects of eriomin associated with metformin on glycemic control, insulin resistance, and other metabolic, inflammatory, and clinical parameters in pre-diabetic patients. Another ongoing phase II trial, which is currently on hold and estimated to enroll 30 participants is the one held by the Mayo Clinic (NCT03325322). This study aims to evaluate the effect of fisetin (20 mg/kg/day, orally for 2 consecutive days) on adipose tissue-derived mesenchymal stem/stromal cell function, kidney function, markers of inflammation, and physical function in patients with advanced chronic kidney disease monitored for 12 months.

An ongoing clinical trial (NCT05247034) commissioned by a research group from Anahuac University, aimed at evaluating the biochemical, clinical profile, and somatosensory profile of cocoa (a dietary supplement with a high content of flavonoids) on peripheral and autonomic diabetic neuropathy. In this study, 5 participants suffering from T2DM, and diabetic neuropathy were enrolled to verify whether a daily intake of 500 mg of cocoa for 12 weeks could alleviate these conditions. Similarly, another trial on diabetic neuropathy was completed in September 2012 by the Texas Tech University Health Sciences Center (NCT01307917), which enrolled 80 adolescents, divided equally into healthy and diabetic groups (T1DM or T2DM), received a capsule containing 500 mg of flavonoids or a placebo for 14 days, twice a day. This trial aims to measure flavonoid effects on urine nitric oxide, and proinflammatory factors in patients with DM to ascertain whether flavonoids with anti-inflammatory and antioxidant activities could be used to prevent endothelial dysfunction and the development and progression of nephropathy. Unfortunately, the results of this study have not been published yet. While some of these studies have reported promising results, further confirmation of the findings, including well-designed randomized controlled trials with larger sample sizes and longer durations, is needed to establish the efficacy and safety of dietary flavonoids in managing diabetes. Moreover, it is important to understand the circulating concentration of these dietary flavonoids in blood and how they match with experimental concentrations. However, there is a dearth of data in this regard, and it can be challenging to achieve due to differences in absorption, metabolism, and elimination of flavonoids, as well as the study conditions and model systems (Chakraborty et al., 2012; Fiorani et al., 2003; Kanakis et al., 2005).

8. Conclusion

It is evident given the strong correlation between hyperglycemia and accumulation of misfolded/unfolded protein, the use of phytopharmaceuticals as better candidates to target ER stress in the pancreas is imperative for the treatment of diabetes and its complications. Flavonoids are important secondary metabolites of plants that exhibit a variety of beneficial bioactivities. Evidence from experimental studies supports the therapeutic efficacy of dietary flavonoids in preserving pancreatic β-cell function. Apart from their broad bioactivities, dietary flavonoids have excellent safety profiles and are cheaper than synthetic drugs. Dietary flavonoids have garnered attention as potential therapeutic adjuvants in the management of ER stress-induced pancreatic β-cell dysfunction. Antioxidant, anti-inflammatory, and ER stress-modulating properties have been identified as key factors that contribute to their potential beneficial role in the preservation of β-cell function. As such, these compounds are increasingly being recognized as a promising avenue for developing novel therapeutic approaches for managing pancreatic β-cell dysfunction. However, data from human studies are lacking and the clinical application of flavonoids requires careful consideration of dosing, individual variability, and potential drug interactions. Therefore, there is a need for further research to establish the effectiveness and develop personalized approaches that integrate flavonoid-rich dietary choices or supplements into comprehensive treatment strategies for ER stress-related conditions in the pancreas.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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