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Review Article

The Emerging Role of Flavonoids in the Treatment of Type 2 Diabetes Mellitus: Regulating the Enteroendocrine System

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Abstract

Type 2 diabetes mellitus (T2DM) is a prevalent yet complex metabolic disorder that has shown a rising incidence over the past few decades. Recent research has identified flavonoids as compounds capable of both preventing and managing T2DM through various mechanisms. These mechanisms include enhancing insulin sensitivity, stimulating insulin secretion, modulating intestinal microbiota, inhibiting glucose absorption, and reducing gluconeogenesis. Moreover, numerous studies have suggested that flavonoids may influence gut hormones. Therefore, we propose that flavonoids could serve as effective therapeutic agents for T2DM by modulating intestinal hormone levels. This review aimed to elucidate the potential pathways through which flavonoids may impact T2DM, with a particular emphasis on their role in regulating the enteroendocrine system.

Introduction

Diabetes mellitus (DM) is a common, lifelong chronic metabolic disease and one of the major challenges to global public health. More than half a billion people worldwide are living with diabetes.[1] Type 2 diabetes mellitus (T2DM) accounts for over 90% of all diabetes cases worldwide.[2] The deterioration of insulin sensitivity and beta cell function, increased insulin clearance, high levels of visceral or liver fat, and worsening lipid profiles are key factors in T2DM.[3] Incretin-based therapies not only address these conditions but have also gained popularity recently due to their powerful effects on blood sugar and weight management,[4,5] as well as their enhancement of systemic and liver insulin action.[6] Furthermore, these drugs exert direct protective effects on the heart and kidneys. Novel drugs, such as tirzepatide, retatrutide, and orforglipron, have shown significant advantages in managing T2DM and obesity.[7–9] The gastrointestinal hormone regulatory network is complex and closely related to metabolism. Currently, glucagon-like peptide-1 (GLP-1) has been successfully used in clinical practice, and the success of its dual and even triple agonists in clinical trials highlights the great potential and advantages of gastrointestinal hormones in treating DM.

Keywords: Flavonoids; Type 2 diabetes mellitus; Glucagon-like peptide-1; Dipeptidyl peptidase-IV inhibitors; Glucose-dependent insulinotropic polypeptide; Cholecystokinin; Somatostatin; Peptide YY; Serotonin; Ghrelin.

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Flavonoids, a class of natural substances with diverse phenolic structures, are widely found in the plant kingdom. These natural products are renowned for their health benefits. Recent studies have shown that flavonoids are beneficial for obesity and metabolic syndrome through mechanisms that include regulation of the enteroendocrine system.[10,11] Nevertheless, research exploring the relationship between flavonoids, gut hormones, and diabetes remains limited. Therefore, this study aimed to investigate the potential mechanisms through which flavonoids may influence T2DM by regulating the enteroendocrine system.

Flavonoids: classification, distribution, absorption

In nature, flavonoids are a group of low-molecular-weight phenolic compounds extracted from various plants.[12] To date, more than 10,000 flavonoid compounds have been identified.[13] These compounds have a characteristic structure comprising three central carbon chains containing a total of 15 carbon atoms, forming a basic skeleton represented as C6-C3-C6. The three carbon chains are labeled A, B, and C, corresponding to the C6, C3, and C6 components of the skeleton, respectively.[14] Flavonoids mainly exist in plant cells as C-glycosides or O-glycosides,[15–17] which include seven different types based on modifications to the basic skeleton: flavanols, anthocyanidins, flavanones, flavonols, isoflavones, flavones, and chalcones (see Fig. 1).

Flavonoids are commonly found in various foods. During consumption, polyphenols are released into saliva as food is chewed. Certain compounds, such as quercetin 4′-glucoside and genistin, are rapidly hydrolyzed, with a small portion being absorbed through the oral epithelium.[18] The remaining flavonoids then enter

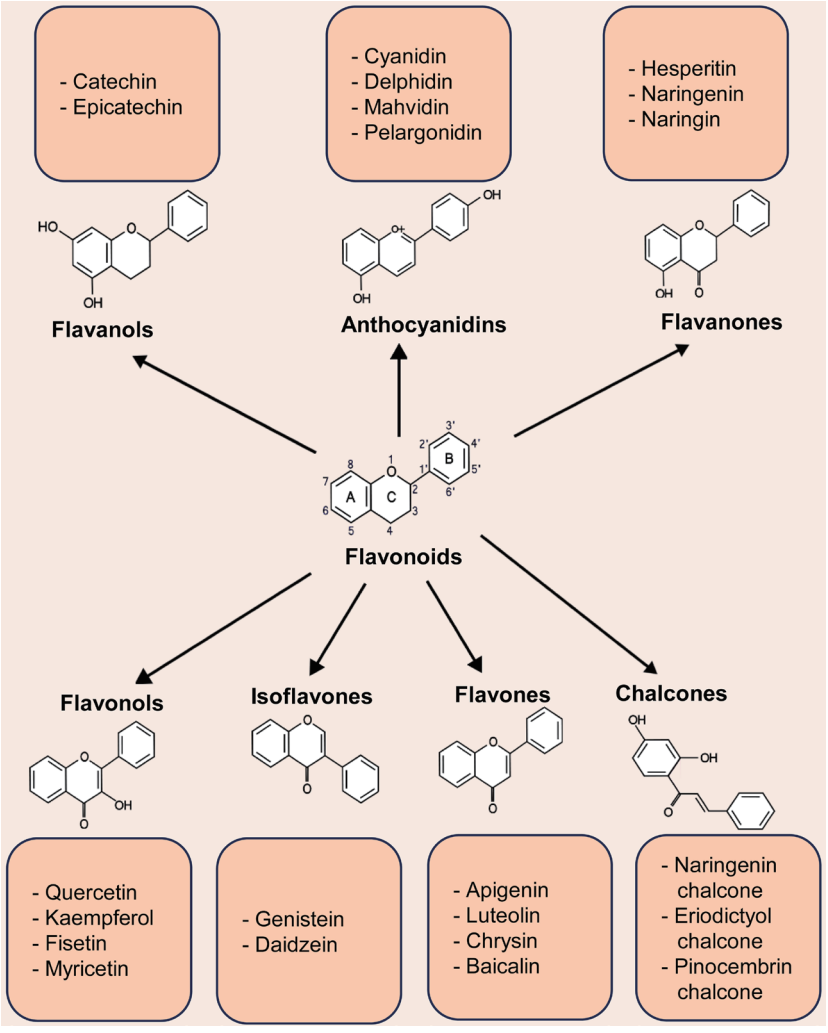

Fig. 1. Structure and classification of flavonoids.

the acidic environment of the stomach, where some oligomers are broken down into smaller units. *In vitro* gastrointestinal digestion leads to partial degradation of proanthocyanidin oligomers into cyanidins.[19] Similarly, during digestion of legumes, phenolics such as anthocyanins degrade into smaller compounds.[20] In the stomach, sugar alcohols such as quercetin are absorbed, while glycosidic forms are not absorbed.[21] In the small intestine, there are no flavonoid-specific receptors on the surface of epithelial cells. Two hypotheses describe how flavonoids are absorbed. The first suggests that flavonoid glycosides are transported into intestinal epithelial cells via the sodium-dependent glucose transporter pathway,[22] enabling their intestinal absorption. The second hypothesis proposes that flavonoid glycosides are hydrolyzed to aglycones by lactase phlorizin hydrolase, after which the aglycones are absorbed through passive diffusion.[23] When unabsorbed metabolites reach the colon, they undergo structural modifications and microbial degradation, forming smaller, easily absorbed phenolic compounds. These metabolites are either absorbed or excreted in urine or feces.[24] Structural modifications such as acylation, glycosylation, de-glycosylation, O-methylation, hydroxylation, halogenation, and sulfation may occur throughout the entire process of intestinal assimilation.[25] Some metabolites, such as phenolic acids, flavonoids, and coumarins, can permeate the intestinal barrier.[26] The type of food matrix also affects flavonoid absorption. Components such as carbohydrates, lipids, proteins, vitamins, and minerals influence bioavailability.[27] *In vitro* gastrointestinal digestion studies have shown that after the addition of a food matrix, anthocyanin levels decrease significantly.[19]

The mechanism of flavonoids on type 2 diabetes

Flavonoids exhibit various biological activities, including anti-diabetic, antioxidant, anti-inflammatory, lipid-regulating, cytotoxic, antibacterial, and anticancer properties.[28,29] Recent *in vitro* and *in vivo* studies have shown that flavonoids possess anti-diabetic effects.[15,28,30,31] The exact mechanisms are illustrated in Figure 2.

Reduction of insulin resistance (IR) and enhancement of insulin secretion

IR is a primary factor affecting glucose metabolism and homeostasis in T2DM. Recent studies suggest that flavonoids may help manage T2DM by reducing IR and enhancing insulin secretion.[28,32]

Several key processes enhance insulin sensitivity: 1) Suppres-

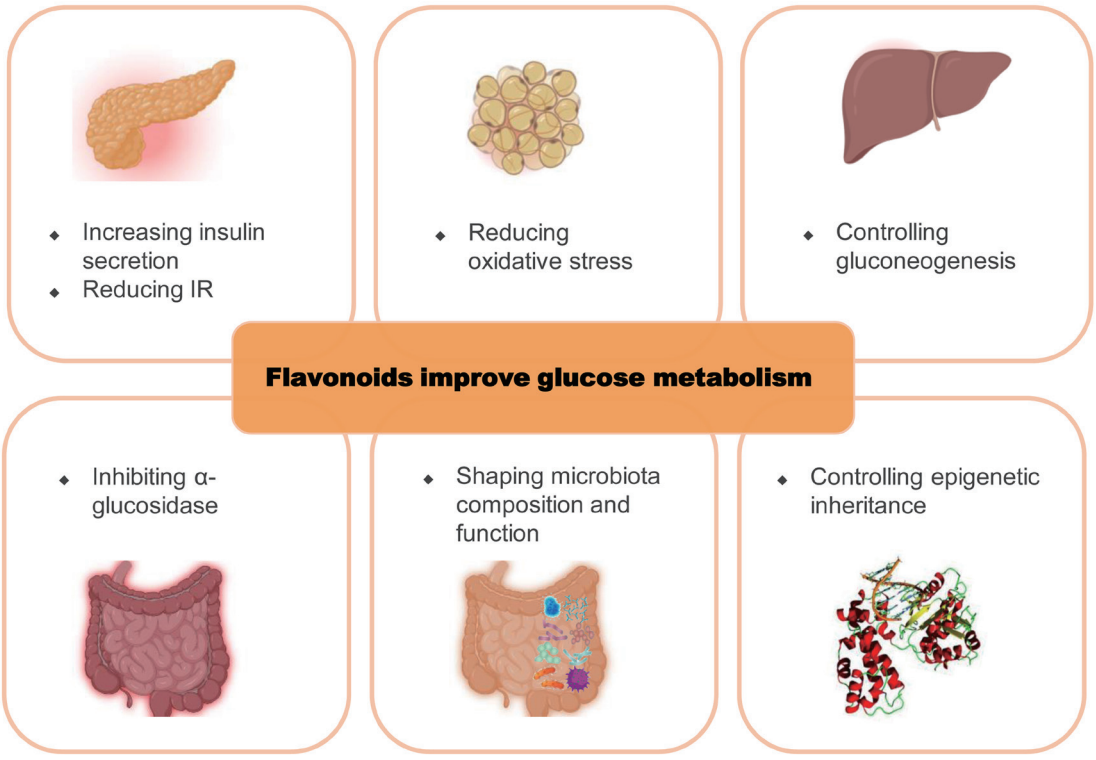

Fig. 2. The traditional pathways of flavonoids regulating T2DM. T2DM, type 2 diabetes mellitus.

sion of protein tyrosine phosphatase 1B increases the phosphorylation of insulin receptor substrate (IRS) 2,[33] improving insulin sensitivity. This effect has been observed with cyanidin-3-O-glucoside in diabetic db/db mice.[34] 2) Plant-derived compounds such as phloretin inhibit peroxisome proliferator-activated receptor γ phosphorylation, which disrupts cyclin-dependent kinase-5 activation, leading to improved insulin sensitivity and glucose uptake.[35] 3) Inhibition of the IKKβ/NFκB signaling pathway reduces inflammatory cytokines, particularly interleukin (IL)-6 and tumor necrosis factor α (TNF-α), improving insulin resistance.[36] This has been demonstrated by bioactive components from Potentilla bifurca.[37] 4) Cyanidin-3-O-glucoside inhibits IRS-1 phosphorylation, reducing TNF-α-induced insulin resistance in adipocytes.[38]

Flavonoids also enhance insulin secretion, contributing to the treatment of T2DM. Trimer procyanidins from cinnamon extracts and epicatechin activate calcium-calmodulin-dependent protein kinase type 2 in pancreatic β-cells, increasing insulin secretion.[39,40] Additionally, cyanidin-3-rutinoside promotes Ca^{2+} influx and upregulates glucose transporter 2 (GLUT2) messenger RNA (mRNA) expression.[41]

Reducing oxidative stress

Mitochondrial dysfunction and endoplasmic reticulum stress, caused by oxidative stress from reactive oxygen species, contribute significantly to insulin secretion issues in T2DM.[15,42–44] Naringin enhances mitochondrial membrane potential and decreases reactive oxygen species levels, helping to improve insulin resistance.[45] Fucoidan protects pancreatic β-cell function by activating the PI3K/AKT signaling pathway and inhibiting inflammation and endoplasmic reticulum stress.[46]

Controlling gluconeogenesis

In T2DM, gluconeogenesis is regulated by enzymes glucose-6-phosphatase and phosphoenolpyruvate carboxykinase.[47,48] Flavonoids such as Baicalin and its metabolites inhibit gluconeogenesis through the AMP-activated protein kinase and PI3K/AKT pathways, reducing GLUT2 expression in insulin-resistant HepG2 cells.[49] Compounds like mulberry anthocyanidin extract and epigallocatechin-3-gallate (EGCG) from green tea enhance glucose consumption and inhibit gluconeogenesis through similar pathways.[50,51] In contrast, quercetin and (-)-EGCG downregulate forkhead box protein O1, reducing the protein levels of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase.[52]

Inhibiting α -glucosidase

Inhibition of α-glucosidase is crucial for maintaining normal blood glucose levels. Apigenin, amentoflavone, and hinoki flavone demonstrate more potent inhibitory effects compared to acarbose.[53] Sadeghi *et al*.[54] showed *in vitro* that the conformation of strychnobiflavone combined with α-glucosidase significantly changes, affecting its catalytic activity. Various flavonoids, including myricetin, rutin, and quercetin, exhibit significant α-glucosidase inhibitory activity, influenced by structural modifications such as hydroxylation and deglycosylation.[55,56]

Shaping microbiota composition and function

Gut microbiota significantly influences systemic glucose metabolism,[57] and imbalances in the microbiota contribute to the development of T2DM through mechanisms such as increased insulin resistance and inflammatory responses.[58,59] An increased Firmicutes/Bacteroidetes ratio is observed in the gut microbiota of patients with T2DM.[60] The novel 6,8-guanidyl luteolin quinone-chromium

Table 1. Subtypes and functions of enteroendocrine cells

Hormones	Cell type	Mainly distributed	Function
GLP-1	L cells	The intestinal	Stimulates insulin secretion, inhibits glucagon secretion, and reduces food intake
GIP	K cells	Small intestine	Stimulates insulin and glucagon secretion, inhibition of gastric acid and other gut hormones secretion
CCK	I cells	Duodenum, jejunum	Regulates gallbladder contraction, stimulates insulin secretion, reduces food intake
Somatostatin	D cells	Gastric fundus, duodenum	Inhibition of insulin and glucagon secretion
PYY	L cells	Ileum, colon	Inhibiting appetite
Serotonin	Enterochromaffin cells	The intestinal	Appetite suppression, regulates intestinal motility, fluid secretion, and vasodilation
Ghrelin	X cells	Gastric antrum	Stimulate appetite, increase gastric emptying and gastrointestinal motility

CCK, cholecystokinin; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; PYY, peptide YY.

coordination (hereinafter referred to as GLQ.Cr) reduces the Firmicutes/Bacteroidetes ratio and enhances glucose metabolism in mice with T2DM, supported by fecal microbiota transplants from the GLQ.Cr group.[61] Pelargonidin-3-O-glucoside reduces hyperglycemia by modulating gut microbiota composition. The composition of gut bacteria is closely linked to blood sugar levels.[62]

Controlling epigenetic inheritance

Epigenetics studies how gene expression is regulated without changing DNA sequences, focusing on processes such as DNA methylation, histone modification, and non-coding RNA.[63,64] Flavonoids, such as tea polyphenols and bioflavonoids, can alter epigenetic inheritance by inhibiting DNA methylation through DNA methyltransferase. This alteration provides valuable insights into the mechanisms underlying diabetes.[65–67]

Enteroendocrine system

The intestinal endocrine system plays a crucial role in food digestion and absorption and functions as a complex endocrine network. This system regulates overall metabolism. However, our understanding of the intestinal endocrine system remains incomplete. In this article, we will focus on gastrointestinal endocrine cells and gut hormones.

Subtypes and functions of enteroendocrine cells (EECs)

The enteroendocrine system releases various hormones that regulate complex physiological processes both inside and outside the intestinal tract, coordinating the body's response to food. Additionally, intestinal hormones affect peripheral tissues and the brain, influencing nutrient intake and distribution.[68] EECs are distributed throughout the epithelial cells from the stomach to the rectum, with different regions producing distinct hormones. There are at least eleven EEC subtypes, including D cells, G cells, enterochromaffin cells, I cells, K cells, enterochromaffin-like cells, L cells, M cells, N cells, S cells, and X/A cells (P/D1 cells in humans). These cells collectively secrete over twenty hormones (see Table 1).[69]

Changes in the enteroendocrine system in T2DM

In T2DM patients, incretin hormone effectiveness is reduced, with esophagogastroduodenoscopy showing lower GLP-1R expression in gastric mucosa biopsies compared to non-T2DM patients, potentially impairing incretin axis function.[70] In severely obese individuals with type 2 diabetes, the density of GLP-1-positive cells in the jejunum is reduced, while the density of other hormone-secreting cells, such as those producing cholecystokinin (CCK), glucose-dependent insulinotropic polypeptide (GIP), and peptide YY (PYY), remains unchanged.[71,72] Additionally, individuals with obesity and T2DM exhibit a diminished ability to produce GLP-1 after meals. This reduction is linked to impaired differentiation of GLP-1 cells and a decrease in mature glucagon precursors.[72] Studies comparing the changes in EEC distribution and hormone gene expression before and after Roux-en-Y gastric bypass (RYGB) surgery in obese T2DM patients and obese individuals with normal blood glucose revealed notable results. After RYGB, the density of positive cells, including those for GLP-1, PYY, CCK, and GIP, increased, whereas gene expression for hormones such as ghrelin, secretin, and GIP decreased.[73] These changes contribute to improved blood glucose levels and metabolic status post-surgery. Additionally, the duodenal-jejunal bypass was shown to prevent long-term deterioration of glucose homeostasis in Goto-Kakizaki (GK) rats while increasing intestinal cell populations co-expressing GIP and GLP-1.[74]

Flavonoids regulate the enteroendocrine system

A growing body of research highlights the effects of flavonoids on gut hormones in EECs. Chlorogenic acid, a phenolic substance found in coffee, improves GLP-1 levels in human plasma.[75] Curcumin, another phenolic compound, enhances GLP-1 secretion in GLUTag mouse enteroendocrine cell lines.[76] Grape seed procyanidins regulate the cell membrane potential of intestinal secretin tumor cell line cells and nutrition-induced intestinal hormone secretion.[77] Soy isoflavones decrease plasma auxin-releasing peptide levels while increasing CCK and PYY levels.[78] In Wistar rats, grape seed proanthocyanidin extract (GSPE) increased GLP-1 and auxin-releasing peptide levels, whereas gallate treatment did not significantly alter these parameters. In contrast, gallic acid tends to elevate CCK levels.[79] Procyanidin dimer B2 promoted PYY release, and catechin upregulated CCK release in pig and human colon cells *in vitro*.[80] Extracts from the leaves of S. gallons reversed diabetes in rats by regulating hormones (e.g., insulin, GLP-1, glucagon) and enzymes (e.g., α-amylase, α-glucosidase).[81] Monomeric flavanols increased ghrelin secretion, which was inhibited

Table 2. The anti-diabetic properties of flavonoids in lab and clinical studies

Compounds	Objects	Mechanistic view	Model	References
C3G; chlorogenic Acid; GSPE; GTC and CCA; hispidulin; quercetin	GLP-1	↑ABC transporter; ↑cAMP/PKA signaling;↓KATP channel; ↑ L- cell differentiation; ↑SGLT-1	Crypt cells; DB/DB mice; GLUTag cells; healthy men; PD mice	80,83–88
Anthocyanins; curcumin; EGCG; enzogenol; hesperetin; lingonberry extract; naringenin; quercetin and coumarin; rottlerone analogues	DPP-4	Molecular docking	Fluid; HepG2 and Hep3B cell lines; simulated body; wistar rats	89–96
Phloretin; green tea polyphenols; GTC and CCA	GIP	↑ or ↓ SGLT-1 and GLUT2	C57-BL/6J male mice; healthy men	87,97,98
Catechin monomers; GSPE	CCK	Bind certain receptors	Crypt cells pig intestines; human colon; postmenopausal women	80,99
CEB; PA; shuidouchi	Somatostatin	↓Gastrin secretion	Human gastric mucosa; rat gastric mucosal tissue	100–102
GSPE; soy isoflavones	PYY	Bind certain receptors; ↑L-cell differentiation	Crypt cells; human colon; pig intestines; postmenopausal women	80,85,103
Luteolin; quercetin; viscum album L	Serotonin	↑TPH-1 expression; ↓MAO-A or MAO-B; antioxidant and anti-inflammatory	Caenorhabditis elegans; galleria mellonella; villus and crypt in diabetic rats	104–106
Echinacoside; emoghrelin; ginkgo ghrelin; K3MG; Q3MG; teaghrelin	Ghrelin	Ghrelin analog	Rat pituitary cells	107,108

The arrow shows an increase (↑) or decrease (↓) in the levels or activities of the analyzed parameters. ABC transporter, adenosine 5′-triphosphate-binding cassette transporters; C3G, cyanidin-3-O-glucoside; cAMP, cyclic adenosine monophosphate; CCA, coffee chlorogenic acids; CCK, cholecystokinin; CEB, extract of curatella americana bark; DPP-4, dipeptidyl peptidase-4; EGCG, epigallocatechin-3-gallate; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; GLUT2, glucose transporters-2; GSPE, grape seed proanthocyanidin extract; GTC, green tea catechins; K3MG, kaempferol 3-O-malonylglucoside; KATP, adenosine 5′-triphosphate-sensitive potassium; MAO-A, monoamine oxidase A; MAO-B, monoamine oxidase B; PA, proanthocyanidin; PD, Parkinson's disease; PKA, protein kinase A; PYY, peptide YY; Q3MG, quercetin 3-O-malonylglucoside; SGLT-1, sodium-glucose co-transporter-1; TPH-1, tryptophan hydroxylase-1.

by GSPE treatment.[82] In conclusion, multiple studies confirm that flavonoids regulate GLP-1, auxin-releasing peptide, PYY, and CCK. However, further exploration is needed to understand the regulation of other gut hormones by flavonoids.

Therapeutic effects of flavonoids in T2DM via EECs

Extensive studies have shown that flavonoids regulate the secretion of intestinal hormones, which are essential for maintaining metabolic homeostasis. They hold significant potential for managing T2DM. The following sections discuss the various intestinal endocrine hormones regulated by flavonoids in T2DM (see Table 2).[80,83–108]

GLP-1

GLP-1 is produced by intestinal endocrine L cells, which promote insulin secretion, inhibit glucagon release, slow gastric emptying, reduce appetite,[109] and lose weight.[110] GLP-1 increases insulin release only in case of hyperglycemia, thus avoiding the risk of hypoglycemia.[111] Research indicates that flavonoids positively affect intestinal health and glucose balance by influencing GLP-1 metabolism, thereby improving glycemic control. Cyanidin-3-O-glucoside increases GLP-1 levels in diabetic mice and may promote GLP-1 secretion by regulating intestinal flora metabolism, particularly key metabolites like short-chain fatty acids, thus supporting intestinal and glucose homeostasis.[83] Flavonoids, including quercetin, luteolin, apigenin, baicalein, and osthole, stimulate GLP-1 secretion without promoting its synthesis. This effect, positively correlated with glucose concentration, is observed with quercetin.[86] Aging decreases GLP-1 mRNA levels in the colon, but this decline can be reversed by GSPE, highlighting its potential therapeutic benefits.[99] Dihydromyricetin stimulates GLP-1 secretion through the cAMP signaling pathway and inhibits dipeptidyl peptidase (DPP)-4 expression in the colon, increasing circulating GLP-1 levels.[112] High-fat feeding disrupts the GLP-1 secretion rhythm in mice, but nobiletin restores it to normal.[113] Quercetin increases GLP-1 secretion at 5 μM, with maximal effectiveness at 50 μM only in the presence of extracellular glucose. Without extracellular glucose, neither quercetin nor luteolin stimulates GLP-1 secretion.[86] Research shows that hispidulin, a flavonoid from medicinal plants, directly stimulates L cells to release GLP-1 through the cAMP signaling pathway, further enhancing blood glucose control. Hispidulin significantly improves blood glucose control, insulin release, and β-cell survival rates in diabetic mice.[88]

DPP IV inhibitors

DPP IV is commonly found in human tissues and organs, including epithelial cells of the liver, intestine, and kidney. It effectively degrades two important glycoregulatory hormones: GIP and GLP-1,[114] protecting them from dissociation.[115,116] DPP-IV inhibitors increase insulin secretion and have gained attention as an important therapeutic strategy for T2DM.[117] Flavonoids inhibit DPP-IV activity in Caco-2 cells by either binding directly to its active site or reducing its expression.[118] This inhibition is positively correlated with the hydrophobicity of glycoside groups, the number of

glycoside hydrogen bonds, and the presence of electron-donating substituents.[118,119] Kalhotra *et al*.[120] also discovered that galanin inhibited DPP-IV activity in a concentration-dependent manner. Citrus bioflavonoids effectively inhibit DPP-IV activity.[121] Epicatechin reduces DPP-IV activity in circulation, while anthocyanins decrease DPP-IV expression in the jejunum.[122] Singh *et al*.[89] demonstrated that plant-derived compounds, quercetin and coumarin, exhibited significantly higher inhibitory activity against DPP-IV compared to sitagliptin, while also providing antioxidant benefits. EGCG, a polyphenol found in tea, also demonstrates strong inhibitory effects on DPP-IV.[90] Proença *et al*.[123] investigated 140 flavonoids on DPP-4 and found that the effectiveness of inhibition was closely related to the position of hydroxyl groups and glycosylation patterns in flavonoid molecules.

GIP

GIP is secreted by intestinal endocrine K cells in the small intestine.[124] Similar to L cells that secrete GLP-1, K cells also produce the sodium-coupled glucose transporter. This transporter is positively associated with the secretion of incretin hormones, which enhance glucose uptake in the intestine.[125] GIP is involved in glucose-dependent insulin-stimulating secretion,[126,127] effect is more pronounced during hyperglycemia.[128,129] However, under lower plasma glucose concentrations, GIP stimulates the secretion of glucagon.[129–132] Thus, it plays a significant role in glycemic management. Certain flavonoids have been found to affect the activity of GIP and may positively impact the treatment of T2DM. In patients with T2DM, GIP expression throughout the intestinal tract is significantly higher than in the non-diabetic control group.[133] Fasting GIP levels are also higher in T2DM patients,[134] although there is no significant difference in postprandial GIP levels.[135] GLP-1 can suppress glucagon secretion, especially at high plasma glucose concentrations, in both normal individuals and those with T2DM.[111,136,137] As previously mentioned, flavonoids can promote GLP-1 expression. It is speculated that flavonoids might inhibit glucagon secretion in T2DM, helping to preserve GIP levels and promote insulin secretion, similar to the effects of dual agonists targeting GLP-1 and GIP receptors. Unfortunately, there is no direct evidence to support this idea. Only a few studies suggest that flavonoids reduce GIP levels. For instance, a study by Yanagimoto and colleagues found that combining catechin with coffee chlorogenic acid significantly increased GLP-1 release while reducing GIP levels.[87] In mice, administering phloretin increased the GLP-1 response and inhibited the GIP response, possibly due to GLUT2 inhibition in K cells.[97] Takahashi *et al*.[98] investigated the effects of catechin-rich tea consumption at various times and found that glucose-dependent insulinotropic peptide levels were significantly lower 30 m after breakfast and dinner in the experimental group compared to the control group.

CCK

CCK is a peptide hormone produced by I cells in the duodenum.[138] It is involved in the regulation of appetite and gastric emptying. CCK is also expressed in islet beta cells in models of obesity and insulin resistance.[139] *In vivo* and *in vitro* studies with transgenic mice overproducing CCK in β-cells showed reduced apoptosis of these cells.[140] In both healthy individuals and those with diabetes, CCK injection can increase insulin release and reduce postprandial hyperglycemia, indicating its potential for diabetes management.[141,142] Exendin-4, a dual-acting CCK1 and GLP-1 receptor agonist, along with novel hybrid peptide analogs such as (Glu-GLN)-CCK-8/exendin-4, offers significant advantages over monotherapy. These agents demonstrate equal or superior therapeutic efficacy compared to combination therapy, significantly enhancing satiety, glucose homeostasis, insulin resistance, and weight management. (Glu-GLN)-CCK-8/exendin-4 improves insulin sensitivity and pancreatic β-cell performance in high-fat-fed mice.[143] Postprandial circulating glucose levels decreased, and circulating insulin levels increased in both healthy postmenopausal women and postmenopausal women with T2DM (six each) after intravenous CCK-8 intervention.[142] These antidiabetic effects are comparable to those of the intestinal hormone GLP-1. *In vitro*, CCK-8 analogs protect islet β-cells from cytokine-induced apoptosis, including IL-1, interferon-γ, and TNF-α, by activating extracellular signal-regulated kinases 1/2 in INS-1E cells. Research has shown that CCK protects human β-cells from apoptosis in both diabetic and transplant scenarios.[144] Flavonoids may regulate food intake and blood sugar levels by influencing CCK secretion. Al Shukor *et al*.[145] demonstrated that various flavonoids, including quercetin, kaempferol, apigenin, rutin, and baicalein, stimulate CCK secretion from intestinal endocrine secretin tumor cell line cells *in vitro*, although their effectiveness varies. Catechin monomers (catechin and epicatechin) in grape seed proanthocyanidin extract (GSPE) enhance CCK secretion in the porcine duodenum, whereas procyanidin dimer B2 does not.[80] This suggests that the biological effects of mixed flavonoid extracts often depend on the actions of individual flavonoid molecules, a relationship that is complex and not fully understood.

Somatostatin

Somatostatin is primarily produced by pancreatic D cells and the gastrointestinal tract, but it is also produced by brain, immune, and neuroendocrine cells in response to various stimuli. It is an endogenous inhibitory regulator that controls development, proliferation, metabolism, secretion, and neural activities.[146] Somatostatin can inhibit the release of insulin and glucagon and suppress the secretion of cholecystokinin, gastrin, and secretin.[147] Flavonoids may affect blood glucose levels in diabetic patients by altering somatostatin secretion. Catechins inhibit somatostatin release by decreasing gastrin secretion in G cells.[148] Similar results were observed when proanthocyanidin was used to treat rat stomach tissues *in vitro*.[100] The mechanisms underlying this inhibition of secretion have not been extensively studied, and its effects on blood glucose regulation remain unclear. While flavonoids influence other gastrointestinal hormones, their impact on blood glucose regulation is still unexplored. Chen *et al*.[149] proposed that high doses of green tea extract (EGCG) might aid in weight loss by inhibiting somatostatin secretion in women with central obesity.

PYY

PYY is a group of components in the neuropeptide Y family and is mainly secreted by L cells in the ileum and colon. PYY exists in two forms: PYY1-36 and PYY3-36. Both forms play a role in regulating food intake. However, PYY1-36 primarily stimulates appetite and promotes weight gain, while PYY3-36 is an intestinal-derived satiety hormone believed to have strong anorectic properties, primarily inhibiting appetite and promoting weight loss.[150] In a study involving 36 healthy postmenopausal women who supplemented with soy isoflavones, total plasma PYY levels increased, while plasma glucose and insulin remained unchanged.[103] The total PYY level in obese patients was lower than in healthy subjects, but it increased significantly six months after obesity surgery (including sleeve gastrectomy and Roux-en-Y gastric bypass). PYY is a key effector in the early restoration of glucose-mediated impaired insu-

lin and glucagon responses after obesity surgery.[151] Within 10-14 days after RYGB surgery, normal glucose metabolism and insulin and glucagon responses were restored in GK rats. This result was replicated by long-term *in vitro* exposure of pancreatic islets from diabetic rats to PYY.[152] A concentration of 100 mg/L of GSPE increases the secretion of PYY in isolated human colon cells.[80] This may occur because GSPE induces cell differentiation into L cells in ileal organoids, which increases PYY hormone secretion by regulating the expression of early-stage transcription factors such as the NeuroD1 gene.[85]

Serotonin

Serotonin, also known as 5-hydroxytryptamine(5-HT), is popularly called the "happy hormone".[153] Circulating serotonin is synthesized mainly in enterochromaffin cells of the entire intestine.[154] Serotonin suppresses appetite in mammals.[155] It also regulates intestinal motility, fluid secretion, and vasodilation, which are related to digestion and absorption.[156] The depletion of central serotonin induces hyperphagia and weight gain in rodents.[157] In the pancreas, serotonin promotes insulin secretion by activating cell surface 5-hydroxytryptamine receptors.[154] Quercetin supplementation enhanced serotonergic function impaired by diabetes, potentially reducing the apoptosis of serotonin-immunoreactive cells.[105] In C. elegans, luteolin decreases fat degradation by promoting serotonin synthesis, which stimulates lipolysis and β-oxidation of fatty acids.[104] This effect may be linked to luteolin's elevation of the rate-limiting enzyme tryptophan hydroxylase-1, which is crucial for serotonin synthesis, as well as the increased mRNA levels of the SER-6 receptor. Additionally, an extract of Viscum album L. elevated serotonin levels by inhibiting monoamine oxidase activity in G. mellonella larvae.[106]

Ghrelin

Ghrelin, a circulating hormone secreted by X cells in the gastric fundus, stimulates appetite and enhances food intake.[158] In contrast to insulin regulation, plasma ghrelin increases during fasting and decreases after meals.[159,160] In both healthy subjects and T2DM subjects, 5 g intravenous glucose administration reduces ghrelin levels, while insulin does not acutely affect plasma ghrelin.[161] Decreased plasma ghrelin activity was significantly associated with hyperinsulinism and insulin resistance in patients with T2DM, and plasma ghrelin concentrations were significantly lower in obese patients.[162] This inhibitory effect was more pronounced in the weight gain group.[163] The difference persisted after adjusting for body mass index and was independent of age.[164] Lin *et al*.[165] studied the effects of Ghsr-/- mice, which lack the ghrelin secretagogue receptor, on obesity and insulin sensitivity. They found that these knockout mice showed improvements in aging-related obesity and insulin resistance due to increased thermogenesis. Sun *et al*.[166] ablated ghrelin in ob/ob mice with leptin deficiency, which failed to rescue the obese phenotype of hyperphagia, indicating that ghrelin was not the root cause of obesity. However, ghrelin can regulate glucose homeostasis by downregulating uncoupling protein 2 expression, enhancing glucose-stimulated insulin secretion, and increasing insulin sensitivity. These studies suggest that ghrelin may be involved in insulin and glucose metabolism, but the exact mechanism remains unclear. Teaghrelins extracted from Oolong tea can induce hunger in rats and stimulate ghrelin secretion in the anterior pituitary cells of rats, potentially acting as agonists of auxin-releasing peptide receptors.[167] Q3MG (quercetin 3-O-malonylglucoside), obtained from mulberry leaves, enhances ghrelin secretion in rat anterior pituitary cells and functions as an agonist for the auxin-releasing peptide receptor.[107] In C57BL/6J mice, phloretin supplementation resulted in a significant increase in ghrelin mRNA levels in both the stomach and hypothalamus, showing a dose-dependent effect.[168] In model rats with non-steroidal anti-inflammatory drugs related enteropathy, ghrelin expression in intestinal tissue was significantly lower than in normal Sprague-Dawley rats, but it markedly improved in the naringin treatment group. These results suggest that naringin significantly promotes ghrelin secretion, possibly due to the reduction of the inflammatory factor TNF-α in intestinal tissue.[169]

So far, many flavonoids have been shown to influence intestinal hormones.[80,106,170] Most research has concentrated on measuring hormone levels and regulating blood sugar and pancreatic function.[28] However, there are currently few studies examining how flavonoids affect hormone secretion in the enteroendocrine system, leading to a limited understanding of the related biochemical pathways.[11,80] To facilitate drug development, well-designed studies are needed to investigate how flavonoids regulate gut hormones and the associated signaling pathways.

Limitations

Flavonoids play a significant role in regulating gut hormones and managing blood sugar levels.[28] However, the molecular structure of natural flavonoids is both complex and variable.[171,172] There is limited evidence that the specific chemical structure of flavonoids directly determines their biological activity or anti-diabetic effects. The same flavonoid molecules can exhibit different effects in different tissues. For instance, EGCG lowers serotonin levels in the colon but raises them in the hippocampus.[173] Additionally, a compound can have multiple anti-diabetic targets, as seen with anthocyanins.[96] This highlights the need for extensive research to identify the specific molecular structures in flavonoids that contribute to their anti-diabetic properties. Furthermore, when studying their therapeutic effects, it is important to consider the safety and potential side effects of long-term or high-dose applications. Recent studies indicate that certain polyphenols, including Galangin, Daidzein, Genistein, Hesperidin, Quercetin, and Resveratrol, may exhibit harmful effects on healthy cells at elevated concentrations.[174] Additionally, Rotenone is known to induce apoptosis in cells.[175] Investigating methods to mitigate these toxic side effects is crucial for advancing diabetes management and addressing its complications.

Conclusions

In conclusion, flavonoids have the potential to control T2DM. This review shows that both *in vivo* and *in vitro* studies suggest flavonoids may help control T2DM by regulating gut hormones. Therefore, additional supplementation of beneficial flavonoids through food or medications may help control or delay the progression of T2DM. Current data will assist medical professionals in understanding how flavonoids regulate gut hormones and their beneficial role in preventing and treating T2DM.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

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