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Review Article

Natural Bioactives Targeting the GLP-1 Pathway: A Promising Approach for Diabetes Management

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ABSTRACT

Diabetes, a disorder that is becoming more and more common in the world; however, it affects over 400 million people worldwide. Despite considerable growth in diabetes management, most patients often suffer from a significant number of adverse effects and complications of current treatment plans. Therefore, the best action would be collaborating differently for exploring new therapeutic possibilities. The Glucagon-Like Peptide-1 (GLP-] agonist has a huge role in glucose homeostasis which control insulin secretion and inhibits the release of glucagon with prompts slow gastric emptying. This review covers natural products that modulate the GLP-1 path, presenting a few hope-giving possibilities in diabetes care. Natural products related to plants have shown promising effects on the GLP-1 agonist pathway. Compounds like berberine, from a variety of plants, have been observed to increase GLP-1 secretion with an increase in insulin sensitivity. Ginsenosides from ginseng and curcumin from turmeric have similar activities. This article reviews the mechanisms by which these natural products alter the GLP-1 pathway. It also surveys some expected benefits of the used compounds in diabetic therapy, such as drastically reduced side effects and extra health benefits of anti-inflammatory and antioxidant properties. Henceforth, natural modulators of the GLP-1 pathway seem to aim an excellent and promising new direction for the care of diabetes.

Keywords: GLP-1 Pathway, Diabetes Mellitus, Natural Products, Phytochemicals, Insulin Secretion.

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INTRODUCTION

Diabetes mellitus is a chronic and complex metabolic disorder characterized by persistent hyperglycemia, resulting from either the inadequate production of insulin by the pancreas (Type 1 diabetes) or the body's inability to effectively use the insulin produced (Type 2 diabetes).[1-3] Type 2 Diabetes (T2DM) is the most common form, accounting for approximately 90-95% of all diabetes cases.[4] The global prevalence of diabetes has been rising at an alarming rate, with current estimates indicating that over 400 million people are affected worldwide. Projections suggest that this number could exceed 700 million by 2045 if current trends continue.

The increasing prevalence of diabetes is driven by various factors, including aging populations, urbanization, unhealthy diets, sedentary lifestyles, and rising obesity rates.[5] The economic burden of diabetes is substantial, encompassing direct medical costs and indirect costs such as lost productivity and disability.[6,7] Despite significant advances in diabetes management, achieving optimal glycemic control remains a challenge for many patients. Current therapeutic options, including oral hypoglycemic agents, insulin therapy, and newer drug classes like GLP-1 receptor agonists and SGLT2 inhibitors, have improved outcomes but are not without limitations.[8,9] These limitations include adverse effects such as hypoglycemia, gastrointestinal disturbances, weight gain and in some cases, high costs and the inconvenience of injectable administration. Moreover, long-term complications such as cardiovascular disease, neuropathy, nephropathy, and retinopathy continue to pose significant health risks for individuals with diabetes.[10,11] Therefore there is a critical need for continued research into novel therapeutic approaches that can provide more effective, safer and more affordable options

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for diabetes management. Natural products have emerged as a promising area of study offering potential alternatives with diverse pharmacological properties and fewer side effects.[12] Traditional medicinal plants and dietary sources rich in bioactive compounds such as flavonoids, terpenoids, alkaloids, and saponins have shown promise in modulating various pathways involved in glucose homeostasis including the GLP-1 pathway.[13]

Investigating the potential of natural products to modulate the GLP-1 pathway represents a particularly exciting possibility for diabetes research. GLP-1, an incretin hormone, enhances insulin secretion, inhibits glucagon release, slows gastric emptying and promotes satiety, making it a key target for improving glycemic control and managing diabetes.[14] Natural GLP-1 modulators could offer a complementary approach to existing therapies, potentially enhancing their efficacy and reducing side effects.[15]

The Glucagon-Like Peptide-1 (GLP-1) pathway (Figure 1) is critical in regulating glucose homeostasis and has become an important target for diabetes treatment. GLP-1 is an incretin hormone secreted by the L-cells of the small intestine in response to nutrient intake, particularly carbohydrates and fats.[14] It exerts its effects through multiple mechanisms that collectively help maintain normal blood glucose levels. Firstly, GLP-1 enhances insulin secretion by binding to GLP-1 Receptors (GLP-1R) on pancreatic beta cells. This binding activates the adenylate cyclase-cAMP-Protein Kinase A (PKA) signaling pathway, leading to the phosphorylation of proteins involved in insulin exocytosis. Additionally, GLP-1 activates the Phosphatidylinositol-3-Kinase (PI3K) pathway, enhancing beta cell sensitivity to glucose, thus increasing insulin secretion in a glucose-dependent manner.[15,16]

Secondly, GLP-1 inhibits glucagon release by binding to receptors on pancreatic alpha cells. Since glucagon promotes glycogenolysis and gluconeogenesis in the liver, its inhibition results in decreased hepatic glucose production, thereby lowering blood glucose levels. Thirdly, GLP-1 delays gastric emptying, slowing the rate at which food leaves the stomach and enters the small intestine.[17] This controlled absorption of glucose into the bloodstream leads to a more gradual rise in blood glucose levels and enhances satiety, reducing appetite and aiding in weight management.[18]

Furthermore, GLP-1 acts on the hypothalamus to promote satiety, decreasing food intake and assisting in weight loss, which is particularly beneficial for individuals with diabetes. Additionally, emerging research suggests that GLP-1 has cardioprotective effects, improving endothelial function, reducing inflammation and protecting against ischemic injury, which is advantageous given the increased cardiovascular risk in diabetes patients.[17]

In Type 2 Diabetes (T2DM), the efficacy of the GLP-1 pathway can be diminished due to a reduced incretin effect, contributing to impaired insulin secretion and uncontrolled hyperglycemia. Pharmacological agents such as GLP-1 receptor agonists and Dipeptidyl Peptidase-4 (DPP-4) inhibitors have been developed to enhance the activity of the GLP-1 pathway.[19] GLP-1 receptor

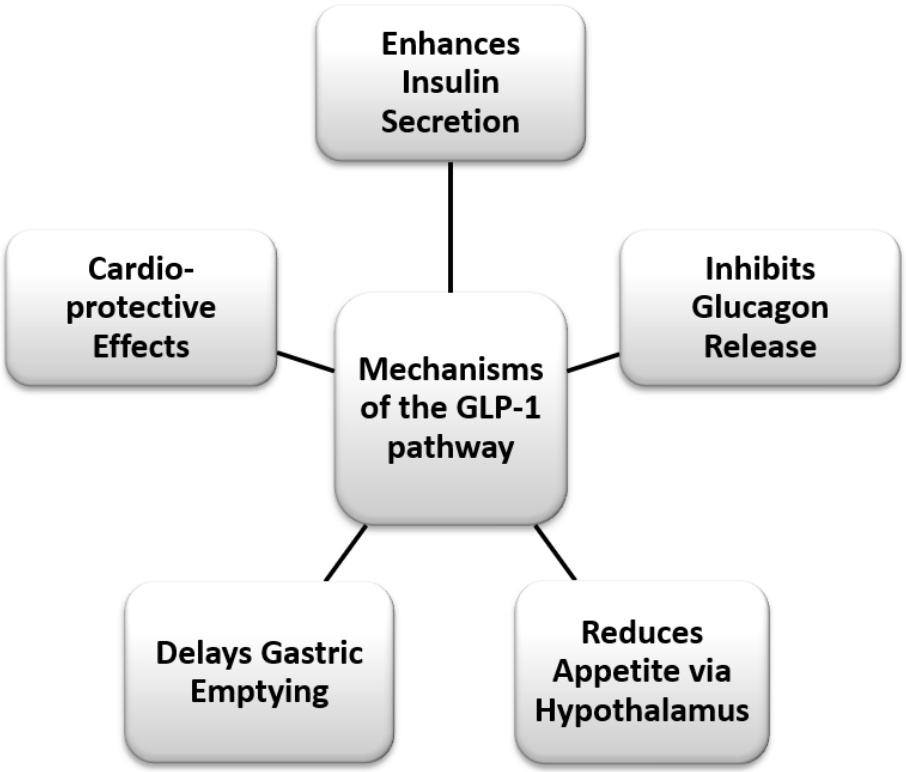


Figure 1: Mechanisms of the GLP-1 pathway.

agonists, such as exenatide, liraglutide and semaglutide, mimic the action of endogenous GLP-1, providing sustained effects on insulin secretion, glucagon suppression, gastric emptying, and satiety. DPP-4 inhibitors, such as sitagliptin, saxagliptin, and linagliptin, inhibit the enzyme DPP-4 that degrades GLP-1, thus increasing the levels and prolonging the action of GLP-1.[20] Hence, the GLP-1 pathway's multifaceted role in glucose regulation makes it a valuable target for diabetes therapy, improving glycemic control and reducing the risk of complications.

Berberine

Found in several plants like *Berberis vulgaris* (barberry), berberine (Figure 2a) has been garnered attention for its potential therapeutic effects in managing diabetes mellitus. Berberine has been shown to increase the secretion of GLP-1 from intestinal L-cells (Table 1).[21] GLP-1 is an incretin hormone that enhances insulin secretion in response to nutrient intake, inhibits glucagon release, slows gastric emptying and promotes satiety.[22] By increasing GLP-1 secretion, berberine contributes to improved glucose control following meals, reducing postprandial hyperglycemia. Upon secretion, GLP-1 binds to GLP-1 receptors (GLP-1R) on pancreatic beta cells. This binding activates several signaling pathways within the beta cells, including the adenylate cyclase-cAMP-Protein Kinase A (PKA) pathway and the Phosphatidylinositol-3-Kinase (PI3K) pathway.[23] Through pathways result GLP-1 binds to its receptors on pancreatic beta cells, initiating signaling pathways that promote insulin secretion in a glucose-dependent manner and inhibit glucagon release, thereby reducing hepatic glucose production. These actions contribute to improved postprandial glucose control and overall glycemic regulation.[22,24] Additionally, berberine has been reported to enhance insulin sensitivity in peripheral tissues, facilitating glucose uptake and utilization.[22] Berberine has been reported to enhance insulin sensitivity in peripheral tissues, such as skeletal muscle and adipose tissue. This improvement in insulin sensitivity allows tissues to respond more effectively to insulin, facilitating glucose uptake and utilization.[25] Beyond its effects on the GLP-1 pathway, berberine exhibits anti-inflammatory and antioxidant properties.[26] Chronic low-grade inflammation and oxidative stress play significant roles in the pathogenesis of insulin resistance and beta cell dysfunction in diabetes. Berberine's anti-inflammatory and antioxidant effects may help mitigate these factors, contributing to its overall beneficial effects on glucose metabolism.[27] Clinical studies have demonstrated that berberine supplementation can effectively lower fasting blood glucose levels and HbA_{1c} levels in individuals with Type 2 diabetes, underscoring its potential as a natural therapeutic agent.[28,29] Continued research into berberine's mechanisms and its optimal clinical applications holds promise for enhancing diabetes treatment strategies with natural compounds.

Capsaicin

(Figure 2b) its active compound in chili peppers,[30] influences the GLP-1 pathway primarily by activating Transient Receptor Potential Vanilloid 1 (TRPV1) channels (Table 1). This activation triggers the release of GLP-1 from enteroendocrine L-cells in the gut, boosting levels of this incretin hormone. Enhanced GLP-1 then promotes glucose-dependent insulin secretion from pancreatic β-cells, aiding in glucose regulation. Capsaicin's anti-inflammatory and antioxidant effects also protect pancreatic cells and improve insulin sensitivity, contributing to overall metabolic health.[31,32] Capsaicin activates Transient Receptor Potential Vanilloid 1 (TRPV1) channels, which are present in the gastrointestinal tract. This activation triggers the release of GLP-1 from enteroendocrine L-cells, enhancing GLP-1 levels in the bloodstream.[33,34] By increasing GLP-1 secretion, capsaicin indirectly promotes insulin secretion from pancreatic β-cells. This effect is glucose-dependent, ensuring that insulin release is regulated according to blood sugar levels. Capsaicin may also enhance insulin sensitivity, improving glucose uptake by tissues.[35] Capsaicin has anti-inflammatory and antioxidant properties that protect β-cells from damage and improve their function. By reducing inflammation, it supports a healthier environment for insulin signaling and glucose metabolism.[36] Preclinical studies on capsaicin have found that it effectively increases GLP-1 secretion and enhances glucose regulation in animal models. These studies have demonstrated that capsaicin's activation of TRPV1 channels can lead to improved insulin secretion and better blood sugar control. Additionally, capsaicin's anti-inflammatory and antioxidant properties have shown protective effects on pancreatic β-cells, supporting overall metabolic health and indicating potential therapeutic benefits for managing diabetes and obesity.[37,38]

Quercetin

A flavonoid abundantly found in various fruits, vegetables and grains has garnered interest for its potential therapeutic effects in diabetes management particularly through its interaction with the Glucagon-Like Peptide-1 (GLP-1) pathway.[39] Quercetin (Figure 2c) has been shown to stimulate the secretion of GLP-1 from intestinal L-cells. (Table 1) GLP-1 is an incretin hormone that enhances insulin secretion in response to nutrient intake and inhibits glucagon release.[40] By increasing GLP-1 secretion, quercetin promotes enhanced glucose-stimulated insulin secretion from pancreatic beta cells, leading to improved glucose control following meals. Secretion, GLP-1 binds to GLP-1 Receptors (GLP-1R) on pancreatic beta cells. This binding activates several intracellular signaling pathways, including the adenylate cyclase-cAMP-Protein Kinase A (PKA) pathway and the Phosphatidylinositol-3-Kinase (PI3K) pathway.[41] These pathways contribute to increased insulin secretion and inhibition of glucagon release. Quercetin has been reported to enhance insulin sensitivity in peripheral tissues, such as skeletal muscle

and adipose tissue.[42] Improved insulin sensitivity allows tissues to utilize glucose more effectively, thereby reducing blood glucose levels and improving overall metabolic health.[43]

Myricetin

A flavonoid bioactive compound found in various fruits, vegetables, and medicinal plants.[44,45] It has gained significant attention for its role in modulating the Glucagon-Like Peptide-1 (GLP-1) pathway, which is essential in glucose metabolism and diabetes management. Myricetin (Figure 2d) enhances GLP-1 secretion and activity, contributing to improved insulin sensitivity and glucose regulation (Table 1). It exerts its effects through antioxidant and anti-inflammatory mechanisms, protecting pancreatic β-cells from oxidative stress. Myricetin can stimulate the secretion of GLP-1 from enteroendocrine L-cells in the intestine. This secretion is often triggered through the activation of signaling pathways such as the cyclic Adenosine Monophosphate (cAMP) pathway, which amplifies GLP-1 release in response to nutrient intake.[46] GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4). Myricetin may inhibit DPP-4 activity, thereby extending the half-life of GLP-1 and enhancing its physiological effects. By inhibiting this enzyme, myricetin ensures prolonged GLP-1 activity in the bloodstream.[47]

GLP-1 stimulates insulin secretion from pancreatic β-cells in a glucose-dependent manner. Myricetin helps improve insulin sensitivity and secretion by promoting β-cell function, which is crucial for maintaining blood glucose levels.[48] Oxidative stress and inflammation negatively impact pancreatic β-cells and overall glucose metabolism. Myricetin has potent antioxidant and anti-inflammatory properties that protect β-cells from damage and maintain proper insulin signaling, indirectly supporting GLP-1 activity.[49] When GLP-1 binds to its receptor on pancreatic β-cells, it activates intracellular pathways such as the cAMP/Protein Kinase A (PKA) pathway and the Phosphatidylinositol 3-Kinase (PI3K) pathway. These pathways promote insulin secretion and β-cell survival. Myricetin may enhance these signaling pathways, boosting GLP-1's overall effectiveness.[47]

Luteolin

A flavonoid present in herbs like parsley and celery,[49,50] Luteolin (Figure 2e) has been found to stimulate the secretion of GLP-1 from enteroendocrine L-cells in the gut. These cells are responsible for the release of GLP-1 in response to nutrient intake, particularly carbohydrates. By increasing GLP-1 secretion, luteolin helps boost the body's insulinotropic response, promoting insulin secretion in a glucose-dependent manner (Table 1). This enhanced secretion of GLP-1 helps regulate postprandial

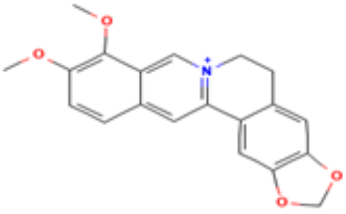
Table 1: Phytoconstituents Modulating the GLP-1 Pathway.

Class	Phyto constituent	Biological Source	Family	Mechanism of GLP-1 Modulation
Alkaloids	Berberine	Berberis (*Berberis vulgaris*)	Berberidaceae	Boosts GLP-1 secretion and inhibits DPP-4 enzyme.
	Capsaicin	Chili Pepper (*Capsicum annuum*)	Solanaceae	Activates TRPV1 channels, enhancing GLP-1 release.
Flavonoids	Quercetin	Apples, Onions	Rosaceae	Enhances GLP-1 secretion and inhibits degradation enzymes.
	Myricetin	Berries, Red Onions	Myrtaceae	Increases GLP-1 release and inhibits DPP-4 activity.
	Luteolin	Celery (*Apium graveolens)*	Apiaceae	Stimulates GLP-1 secretion and reduces oxidative stress.
	Genistein	Soybean (*Glycine max*)	Fabaceae	Enhances GLP-1 secretion and improves insulin sensitivity.
Polyphenols	Curcumin	Turmeric (*Curcuma longa*)	Zingiberaceae	Stimulates GLP-1 secretion, providing anti-inflammatory effects.
	Resveratrol	Grapes (*Vitis vinifera*)	Vitaceae	Increases GLP-1 levels and insulin sensitivity.
	Epigallo catechin gallate	Green Tea (*Camellia sinensis*)	Theaceae	Enhances GLP-1 secretion and pancreatic β-cell protection.
Aromatic aldehyde	Cinnamaldehyde	Cinnamon (*Cinnamomum verum*)	Lauraceae	Increases GLP-1 secretion and improves glucose metabolism.
Saponins	Ginsenosides	Ginseng (*Panax ginseng*)	Araliaceae	Modulates GLP-1 pathway, improving insulin release.

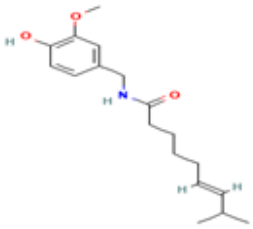
(after-meal) glucose levels, preventing hyperglycemia, which is a characteristic issue in diabetes.[51] After being secreted, GLP-1 binds to its Receptor (GLP-1R) on pancreatic beta cells, triggering the adenylate cyclase-cAMP-Protein Kinase A (PKA) signaling pathway. Luteolin enhances this interaction, leading to an increase in insulin secretion from the beta cells. This is crucial for lowering blood sugar levels, as insulin promotes glucose uptake into cells, particularly muscle and fat cells, where glucose can be used for energy or stored. This helps reduce blood glucose levels and improves overall glycemic control in diabetic patients.[52] In addition to stimulating insulin, GLP-1 inhibits glucagon release from pancreatic alpha cells. Glucagon is responsible for raising blood glucose levels by stimulating hepatic glucose production. Luteolin, by enhancing the GLP-1 pathway, contributes to the suppression of glucagon secretion. This decreases glucose production in the liver and helps maintain balanced blood glucose levels, particularly between meals or during fasting periods.[53] Beyond its role in modulating GLP-1 secretion and action, luteolin has been found to improve insulin sensitivity in peripheral tissues such as skeletal muscle and adipose tissue. Insulin sensitivity refers to the efficiency with which cells respond to insulin, allowing for more effective glucose uptake from the bloodstream. By improving insulin sensitivity, luteolin helps to reduce insulin resistance, a major feature of T2DM. This improved sensitivity, in conjunction with enhanced GLP-1 activity, allows for better glucose regulation.[54] Chronic inflammation and oxidative stress are major contributors to insulin resistance and beta-cell dysfunction in diabetes. Luteolin is known for its potent anti-inflammatory and antioxidant properties. It reduces the levels of pro-inflammatory cytokines such as TNF-α and IL-6, which are elevated in diabetic patients. By lowering inflammation and oxidative stress, luteolin protects pancreatic beta cells and supports the proper functioning of the GLP-1 pathway. This, in turn, aids in the maintenance of healthy beta cells and promotes better glucose regulation in the long term.[55] Luteolin has been shown to protect pancreatic beta cells from apoptosis (cell death) induced by oxidative stress and inflammatory damage. By preserving beta cell function, luteolin ensures continued insulin production and secretion, which is essential for maintaining glycemic control. The protective effects of luteolin on beta cells contribute to the overall effectiveness of the GLP-1 pathway in managing blood sugar levels in diabetic patients.[56] Luteolin modulates the GLP-1 pathway by stimulating GLP-1 secretion, enhancing insulin release, inhibiting glucagon production, and improving insulin sensitivity. By influencing multiple aspects of glucose regulation, luteolin offers a comprehensive approach to managing Type 2 diabetes. Its potential for preserving beta cell function and improving glycemic control[57] makes it a promising candidate for natural diabetes therapy. Further research on luteolin's molecular mechanisms could lead to its inclusion as an adjunctive treatment in diabetes care.

Genistein

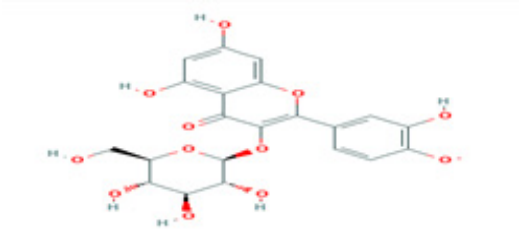
Found in soybeans and soy products,[58] genistein (Figure 2f) has been studied for its potential to increase GLP-1 secretion and improve glucose homeostasis. Genistein has been shown to enhance the secretion of GLP-1 from enteroendocrine L-cells in the intestinal tract. These cells release GLP-1 in response to food intake, especially carbohydrates and fats (Table1).[59] By promoting GLP-1 secretion, genistein helps boost the insulinotropic effect of GLP-1, meaning it stimulates insulin release from pancreatic beta cells in a glucose-dependent manner. This enhanced GLP-1 secretion helps in regulating postprandial glucose levels, preventing the sharp rise in blood sugar levels after meals, which is a major issue in individuals with T2DM. After GLP-1 is secreted, it binds to its Receptor (GLP-1R) on the surface of pancreatic beta cells, triggering a signaling cascade that result in the production and release of insulin. Genistein enhances the activation of GLP-1R, which in turn amplifies the downstream signaling through the adenylate cyclase-cAMP-Protein Kinase A (PKA) pathway. This activation leads to an increase in insulin secretion, which promotes the uptake of glucose by cells, thereby lowering blood glucose levels. The ability of genistein to enhance GLP-1R activity is critical for improving glucose metabolism in diabetic patients.[60] Genistein also plays a role in reducing glucagon secretion from pancreatic alpha cells. Glucagon is a hormone that raises blood glucose levels by stimulating the liver to produce glucose (gluconeogenesis). GLP-1 naturally suppresses glucagon secretion, and genistein enhances this effect by boosting GLP-1 activity. By inhibiting glucagon secretion, genistein helps reduce hepatic glucose production, particularly during fasting states, leading to improved blood glucose control. DPP-4 is an enzyme that degrades GLP-1, thereby limiting its insulinotropic and glucagonostatic effects. Genistein has been shown to inhibit DPP-4 activity, which prolongs the half-life of GLP-1 in circulation. By inhibiting DPP-4, genistein ensures sustained insulin secretion and suppression of glucagon, allowing for better blood glucose regulation. This DPP-4 inhibition also enhances the overall efficacy of the GLP-1 pathway in managing T2DM.[61] Insulin resistance, a hallmark of T2DM, occurs when the body's cells become less responsive to insulin, leading to elevated blood sugar levels. Genistein has been shown to improve insulin sensitivity, particularly in peripheral tissues such as skeletal muscle and adipose tissue. By improving the cells' responsiveness to insulin, genistein helps facilitate glucose uptake from the bloodstream. This, combined with enhanced GLP-1 activity, allows for better regulation of blood glucose levels in diabetic individuals.[62] Genistein exerts protective effects on pancreatic beta cells, which are responsible for producing and secreting insulin. Oxidative stress and inflammation often lead to beta-cell dysfunction in diabetes. Genistein, with its antioxidant and anti-inflammatory properties, helps protect beta cells from damage, thereby preserving their function. This preservation of beta-cell function is crucial for maintaining insulin production



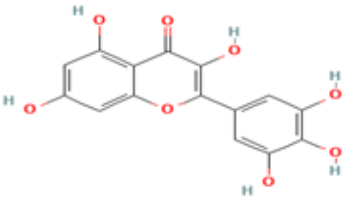
a. Berberine



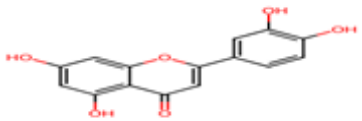
b. Capsaicin



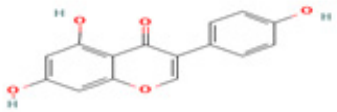
c. Quercetin



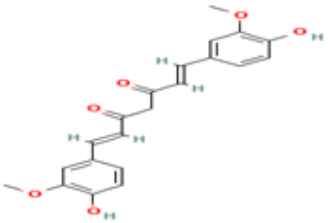
d. Myricetin



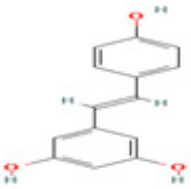
e. Luteolin



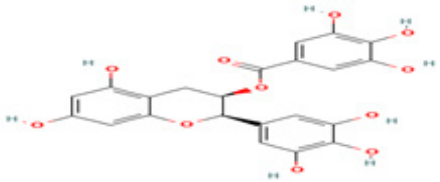
f. Genistein



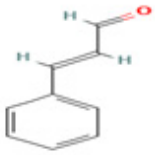
g. Curcumin



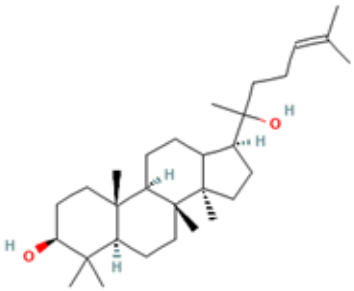
h. Resveratrol



i. Epigallo catechin gallate



j. Cinnamaldehyde



k. Ginsenosides

Figure 2: Phytoconstituents modulate GLP-1 pathway.

and ensuring the proper functioning of the GLP-1 pathway in the long term.[63] Chronic inflammation and oxidative stress are closely linked to insulin resistance and beta-cell dysfunction in diabetes. Genistein has potent anti-inflammatory and antioxidant properties that reduce the levels of pro-inflammatory cytokines (such as TNF-α and IL-6) and scavenge free radicals. By reducing inflammation and oxidative stress, genistein helps maintain the integrity of pancreatic beta cells and supports the proper functioning of the GLP-1 pathway. This anti-inflammatory action also contributes to improved insulin sensitivity and better overall glucose control.[64] Several preclinical and clinical studies have demonstrated genistein's ability to modulate the GLP-1 pathway and improve glycemic control. In animal models of diabetes, genistein has been shown to increase GLP-1 secretion, enhance insulin sensitivity, and reduce blood glucose levels. Studies have also suggested that genistein supplementation can improve insulin resistance, lower fasting glucose levels, and promote better glycemic control in individuals with T2DM.[65,66] Genistein modulates the GLP-1 pathway by stimulating GLP-1 secretion, enhancing GLP-1 receptor activation, inhibiting glucagon release, and improving insulin sensitivity. By inhibiting DPP-4, genistein prolongs the action of GLP-1, ensuring sustained insulinotropic and glucagonostatic effects. Its antioxidant, anti-inflammatory, and AMPK-activating properties further enhance its role in glucose regulation. Through these mechanisms, genistein presents a promising natural approach for the management of Type 2 diabetes mellitus. Further studies are needed to explore its full therapeutic potential and possible clinical applications.

Curcumin

Derived from turmeric (Curcuma longa) curcumin[67] has anti-inflammatory properties and may enhance GLP-1 secretion. Curcumin (Figure 2g) has been found to promote the secretion of GLP-1 from intestinal L-cells (Table 1). GLP-1 is an incretin hormone that is released in response to nutrient ingestion. Once released, it enhances insulin secretion from pancreatic beta cells in a glucose-dependent manner, meaning that insulin is secreted only when blood glucose levels are high, minimizing the risk of hypoglycemia. Curcumin stimulates GLP-1 secretion, leading to improved insulin responses postprandially (after meals), which helps in lowering post-meal blood glucose spikes.[68] GLP-1 after its release binds to its receptors (GLP-1R) present on pancreatic beta cells. This receptor activation initiates multiple intracellular signaling pathways, including the adenylate cyclase-cAMP-Protein Kinase A (PKA) and the Phosphatidylinositol-3-Kinase (PI3K) pathways. These pathways promote insulin biosynthesis and secretion from beta cells. Curcumin enhances this signaling cascade, improving insulin production and release in response to high glucose levels.[69] Additionally, activation of GLP-1 receptors inhibits glucagon release from alpha cells, reducing hepatic glucose output, and contributing to better glycemic control.[70] Curcumin has been shown to improve insulin sensitivity, especially in peripheral tissues such as skeletal muscle and adipose tissue. By modulating the GLP-1 pathway, curcumin enhances the effectiveness of insulin, enabling better glucose uptake and utilization by cells. This results in reduced insulin resistance, a key problem in Type 2 Diabetes (T2DM), and helps maintain normal blood glucose levels.[71] Another important aspect of curcumin's action involves the inhibition of DPP-4, an enzyme responsible for degrading GLP-1. By inhibiting DPP-4, curcumin prolongs the half-life of GLP-1, enhancing its effects on glucose metabolism. This results in sustained insulin secretion, delayed glucagon release, and improved postprandial glucose regulation.[72] GLP-1 also influences gastric emptying, slowing the rate at which food moves from the stomach into the intestines. Curcumin by modulating GLP-1 activity may delay gastric emptying, leading to slower absorption of glucose and preventing sharp postprandial increases in blood glucose levels. This effect contributes to better overall glycemic control and helps reduce the risk of postprandial hyperglycemia.[73] Chronic low-grade inflammation and oxidative stress are major contributors to the progression of diabetes and its complications, such as insulin resistance and beta-cell dysfunction.[74] Curcumin is well-known for its potent anti-inflammatory and antioxidant properties. It reduces the levels of pro-inflammatory cytokines (such as TNF-α, IL-6, and IL-1β) and inhibits oxidative stress, which, in turn, preserves beta-cell function and improves insulin sensitivity. By reducing inflammation and oxidative damage, curcumin helps maintain the integrity of the GLP-1 pathway and enhances its regulatory effects on glucose metabolism.[75] Curcumin has also been shown to activate AMP-activated Protein Kinase (AMPK), a key regulator of cellular energy balance. AMPK activation improves insulin sensitivity, enhances glucose uptake in muscle and adipose tissue, and inhibits hepatic gluconeogenesis (the production of glucose in the liver). By activating AMPK, curcumin complements the action of the GLP-1 pathway, creating a synergistic effect that further enhances glucose regulation and overall metabolic health.[76] Several preclinical and clinical studies support curcumin's role in diabetes management. In animal models of diabetes, curcumin administration has been shown to improve glucose tolerance, increase insulin secretion, and reduce fasting blood glucose levels.[77] Moreover, curcumin has been found to decrease oxidative stress and inflammation, which are key factors in the progression of insulin resistance and beta-cell dysfunction in T2DM. In clinical trials, curcumin supplementation has been associated with improved glycemic control, reduced insulin resistance, and lower HbA_{1c} levels (a marker of long-term glucose control).[78] Curcumin's ability to stimulate GLP-1 secretion, enhance insulin sensitivity, inhibit DPP-4 activity, and exert anti-inflammatory and antioxidant effects makes it a promising natural compound for the management of Type 2 diabetes. By targeting multiple mechanisms within the GLP-1 pathway, curcumin helps to improve glucose regulation, reduce insulin resistance, and preserve pancreatic beta-cell function.

Resveratrol

Found in grapes, red wine, and berries,[79] has been shown to increase GLP-1 secretion and improve insulin sensitivity.[80,81] Resveratrol (Figure 2h) has been shown to enhance the secretion of GLP-1 from intestinal L-cells. GLP-1 is an incretin hormone that promotes insulin secretion from pancreatic beta cells in response to nutrient intake (Table 1). By boosting GLP-1 levels, resveratrol helps to improve postprandial (after meal) glucose control. The increased GLP-1 secretion augments the body's ability to secrete insulin in a glucose-dependent manner, ensuring that insulin is released only when blood glucose levels are elevated, thus reducing the risk of hypoglycemia.[82,83] Once released, GLP-1 binds to its Receptors (GLP-1R) present on pancreatic beta cells. This receptor activation initiates intracellular signaling cascades, particularly through the adenylate cyclase-cAMP-Protein Kinase A (PKA) and Phosphatidylinositol-3-Kinase (PI3K) pathways. These pathways enhance insulin biosynthesis and exocytosis, promoting the release of insulin. Resveratrol supports this process by amplifying the insulinotropic action of GLP-1, resulting in improved insulin secretion in response to rising blood glucose levels. Additionally, activation of GLP-1 receptors on alpha cells inhibits the secretion of glucagon, a hormone that raises blood glucose by promoting glucose production in the liver. This glucagon suppression contributes to better glycemic control by reducing hepatic glucose output.[84,85] Resveratrol has been shown to improve insulin sensitivity, especially in peripheral tissues such as skeletal muscle and adipose tissue. Insulin sensitivity refers to how effectively cells respond to insulin and take up glucose from the blood.[86] By enhancing insulin sensitivity, resveratrol helps tissues utilize glucose more efficiently, lowering blood glucose levels. The improvement in insulin sensitivity also reduces insulin resistance, which is a major feature of Type 2 Diabetes (T2DM).[87] Dipeptidyl Peptidase-4 (DPP-4) is an enzyme responsible for the rapid degradation of GLP-1. Resveratrol has been shown to inhibit the activity of DPP-4, thereby extending the half-life of GLP-1 in the circulation.[88] By prolonging GLP-1's activity, resveratrol allows for sustained insulin secretion, improved glucagon suppression, and better regulation of postprandial blood glucose levels. This dual action-enhancing GLP-1 secretion and inhibiting its degradation-makes resveratrol particularly effective in modulating the incretin system for diabetes management.[89] The GLP-1 pathway also influences gastric emptying, which is the rate at which food exits the stomach and enters the small intestine. Resveratrol, by increasing GLP-1 secretion, can slow gastric emptying, leading to delayed glucose absorption. This results in a slower rise in postprandial blood glucose levels, which helps to prevent large glucose spikes after meals. Controlling these spikes is crucial in the management of diabetes, as it reduces the burden on pancreatic beta cells and improves long-term glycemic control.[90] Chronic inflammation and oxidative stress are key drivers of insulin resistance and beta-cell dysfunction in diabetes. Resveratrol is well-known for its potent anti-inflammatory and antioxidant effects. By reducing oxidative stress and inhibiting inflammatory pathways, resveratrol preserves beta-cell function and improves insulin sensitivity. This is important for maintaining the integrity of the GLP-1 pathway, as inflammation and oxidative damage can impair incretin signaling and glucose regulation.[91,92] Resveratrol also exerts its anti-diabetic effects by activating key metabolic regulators such as SIRT1 and AMPK. SIRT1 is a deacetylase enzyme involved in regulating energy metabolism, and its activation improves insulin sensitivity and glucose metabolism.[93] AMPK is a central regulator of cellular energy balance that promotes glucose uptake in muscle tissues and inhibits hepatic glucose production. Resveratrol's activation of SIRT1 and AMPK complements its effects on the GLP-1 pathway, enhancing overall glucose regulation and metabolic health.[94] Preclinical studies and clinical trials have demonstrated resveratrol's potential in improving glycemic control. Animal models of diabetes have shown that resveratrol increases GLP-1 secretion, enhances insulin sensitivity, and reduces fasting blood glucose levels. Additionally, studies have reported that resveratrol supplementation improves insulin resistance, lowers HbA_{1c} (a marker of long-term blood glucose control), and decreases markers of inflammation and oxidative stress.[95] Resveratrol's ability to modulate the GLP-1 pathway, enhance insulin sensitivity, inhibit DPP-4 activity and exert anti-inflammatory effects makes it a promising natural compound for diabetes therapy. By targeting multiple mechanisms within the GLP-1 system, resveratrol helps improve glycemic control, reduce insulin resistance and preserve pancreatic beta-cell function.[96] Continued research into resveratrol's mechanisms and its potential for clinical use may provide new insights into its role in integrative diabetes management strategies.

Epigallocatechin Gallate (EGCG)

Found in green tea, EGCG (Figure 2i) has been studied for its potential to enhance GLP-1 secretion and improve glucose tolerance.[97-99] EGCG has been shown to stimulate the secretion of GLP-1 from intestinal L-cells, which are triggered by the presence of nutrients. GLP-1 is an incretin hormone that helps in regulating blood sugar levels by enhancing insulin secretion from pancreatic beta cells (Table 1).[100] The ability of EGCG to promote GLP-1 release leads to an increase in insulin secretion, especially after meals, improving postprandial glucose control. This insulinotropic effect of GLP-1 is glucose-dependent, which means insulin is secreted only when blood glucose levels are high, reducing the risk of hypoglycemia.[101] Once GLP-1 is secreted, it binds to GLP-1 Receptors (GLP-1R) on the surface of pancreatic beta cells. This receptor binding triggers intracellular signaling cascades, particularly through the adenylate cyclase-cAMP-Protein Kinase A (PKA) pathway.[102] EGCG enhances this pathway, leading to increased insulin biosynthesis and secretion. Additionally, the activation of GLP-1 receptors by EGCG also suppresses glucagon secretion from pancreatic alpha cells.

Glucagon raises blood glucose by promoting glucose production in the liver, and its inhibition by EGCG helps to reduce hepatic glucose output, thereby contributing to better blood sugar control. EGCG is known to inhibit Dipeptidyl Peptidase-4 (DPP-4), an enzyme responsible for degrading GLP-1. DPP-4 inhibition increases the half-life of GLP-1, prolonging its insulinotropic effects. By preventing GLP-1 degradation, EGCG allows for sustained GLP-1 activity, leading to prolonged insulin secretion and enhanced suppression of glucagon. This DPP-4 inhibition complements EGCG's ability to stimulate GLP-1 secretion, further improving glycemic control in diabetic patients.[103] EGCG also enhances insulin sensitivity in peripheral tissues such as skeletal muscle and adipose tissue. Insulin sensitivity refers to how effectively cells respond to insulin and take up glucose from the blood. By improving insulin sensitivity, EGCG allows for more efficient glucose uptake and utilization by cells, thereby lowering blood glucose levels. This reduction in insulin resistance is a key therapeutic goal in managing Type 2 diabetes. The improvement in insulin sensitivity, combined with enhanced GLP-1 secretion, creates a synergistic effect in regulating blood sugar.[104] GLP-1 slows down gastric emptying, which delays the absorption of nutrients and glucose into the bloodstream. EGCG, by enhancing GLP-1 levels, can indirectly slow gastric emptying, leading to a more gradual increase in postprandial glucose levels. This helps prevent sharp glucose spikes after meals, contributing to improved glycemic control and reducing the overall burden on pancreatic beta cells.[105] Chronic inflammation and oxidative stress are major factors in the development and progression of insulin resistance and beta-cell dysfunction in diabetes. EGCG is a powerful antioxidant and anti-inflammatory agent. It reduces oxidative stress by neutralizing free radicals and inhibits the production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β. By reducing inflammation and oxidative damage, EGCG preserves beta-cell function and helps maintain the integrity of the GLP-1 pathway further supporting glucose homeostasis.[106] EGCG has also been shown to activate AMP-activated Protein Kinase (AMPK), a key regulator of cellular energy balance. AMPK activation enhances glucose uptake in muscle cells and suppresses hepatic glucose production. By activating AMPK, EGCG supports the action of the GLP-1 pathway in improving insulin sensitivity and regulating glucose levels, making it a valuable multi-target agent in the management of diabetes.[107] Several preclinical and clinical studies support the anti-diabetic effects of EGCG through the modulation of the GLP-1 pathway. Animal studies have shown that EGCG administration increases GLP-1 levels, enhances insulin secretion, and improves glucose tolerance. In studies, green tea consumption (rich in EGCG) has been associated with improved insulin sensitivity, lower fasting blood glucose levels, and reduced HbA_{1c} levels (a long-term marker of blood sugar control). Additionally, EGCG's antioxidant and anti-inflammatory properties have been shown to protect pancreatic beta cells from damage caused by oxidative stress and inflammation, which are common in diabetes,[108] EGCG's ability to stimulate GLP-1 secretion, inhibit DPP-4, improve insulin sensitivity, delay gastric emptying, and exert anti-inflammatory and antioxidant effects makes it a promising natural compound for diabetes management.[109] By modulating the GLP-1 pathway, EGCG helps regulate blood glucose levels, enhance insulin secretion, and reduce insulin resistance, making it a valuable addition to diabetes treatment strategies. Ongoing research into the molecular mechanisms of EGCG and its potential therapeutic applications may further solidify its role as a natural agent in diabetes care.

Cinnamaldehyde

The active compound in cinnamon[110,111] has shown GLP-1 stimulating effects and may improve insulin sensitivity. Cinnamaldehyde (Figure 2j) promotes the secretion of GLP-1 from enteroendocrine L-cells in the intestine (Table 1). These cells are responsible for releasing GLP-1 in response to food intake, especially carbohydrates and fats. By enhancing GLP-1 secretion, cinnamaldehyde amplifies the body's natural insulinotropic response, stimulating insulin release from pancreatic beta cells in a glucose-dependent manner. This ensures that insulin is only secreted when blood glucose levels rise, thus improving postprandial (after meal) glucose control and reducing the risk of hypoglycemia.[112] Once GLP-1 is secreted, it binds to its Receptors (GLP-1R) on pancreatic beta cells. Cinnamaldehyde enhances this interaction, leading to increased activation of the adenylate cyclase-cAMP-Protein Kinase A (PKA) pathway. This activation boosts insulin biosynthesis and promotes the exocytosis of insulin granules. The enhanced insulin secretion helps cells to take up more glucose from the bloodstream, lowering blood sugar levels and improving overall glycemic control. In addition to stimulating insulin secretion, GLP-1 inhibits glucagon secretion from pancreatic alpha cells. Glucagon is a hormone that increases blood glucose by promoting hepatic glucose production. Cinnamaldehyde, through its modulation of the GLP-1 pathway, suppresses glucagon release, reducing glucose production by the liver. This contributes to a more balanced glucose homeostasis by limiting the rise of blood sugar between meals and during fasting states.[113] DPP-4 is an enzyme that degrades GLP-1, thereby reducing its activity in the body. Cinnamaldehyde has been shown to inhibit DPP-4 prolonging the half-life of GLP-1 in circulation. This extended activity allows for sustained insulin secretion and glucagon suppression, improving the overall efficiency of glucose regulation. The inhibition of DPP-4 by cinnamaldehyde enhances the action of GLP-1, making it more effective in managing postprandial glucose spikes.[114] Beyond stimulating GLP-1 secretion and insulin release, cinnamaldehyde improves insulin sensitivity in peripheral tissues, such as skeletal muscle and adipose tissue. Improved insulin sensitivity allows cells to respond more effectively to insulin, enhancing glucose uptake from the bloodstream. This action reduces insulin resistance,

a hallmark of T2DM, and improves glycemic control. The combination of enhanced GLP-1 secretion and improved insulin sensitivity creates a synergistic effect that helps to lower blood glucose levels more efficiently.[115] GLP-1 slows gastric emptying, delaying the absorption of glucose from the gastrointestinal tract. Cinnamaldehyde, by enhancing GLP-1 secretion, can indirectly slow down gastric emptying. This delay in gastric emptying leads to a more gradual rise in blood sugar after meals, preventing large postprandial glucose spikes, which are harmful in diabetes management. By modulating this process, cinnamaldehyde reduces the stress on pancreatic beta cells and promotes more stable blood sugar control throughout the day.[116] Chronic inflammation and oxidative stress are major contributors to insulin resistance and beta-cell dysfunction in diabetes. Cinnamaldehyde possesses strong anti-inflammatory and antioxidant properties, which help to reduce oxidative stress and inhibit the production of pro-inflammatory cytokines. By lowering inflammation and oxidative damage, cinnamaldehyde preserves the function of pancreatic beta cells and supports the effectiveness of the GLP-1 pathway. This is critical in preventing the progression of diabetes and protecting against diabetes-related complications.[117,118] Cinnamaldehyde also activates AMP-activated Protein Kinase (AMPK), a key regulator of energy balance in the body. AMPK activation enhances glucose uptake in peripheral tissues, such as muscle and fat cells, and inhibits glucose production in the liver. This dual action complements the effects of the GLP-1 pathway by improving glucose utilization and reducing blood sugar levels. The activation of AMPK further enhances insulin sensitivity, making cinnamaldehyde a powerful agent in improving overall metabolic health in diabetics.[119] Preclinical studies have demonstrated the efficacy of cinnamaldehyde in improving glucose metabolism through the GLP-1 pathway. In animal models of diabetes, cinnamaldehyde administration has been shown to increase GLP-1 levels, enhance insulin secretion, and improve insulin sensitivity. Additionally, studies have reported a reduction in fasting blood glucose levels and improved glucose tolerance following cinnamaldehyde treatment. These findings highlight the potential of cinnamaldehyde as a natural agent for modulating the GLP-1 pathway in diabetes therapy.[120,121] Cinnamaldehyde's ability to modulate the GLP-1 pathway, stimulate insulin secretion, inhibit glucagon release, and improve insulin sensitivity makes it a promising natural compound for diabetes management. By enhancing the secretion and action of GLP-1, inhibiting DPP-4, and reducing oxidative stress, cinnamaldehyde helps regulate blood glucose levels and improve overall metabolic health. Its multi-targeted mechanism offers a holistic approach to managing Type 2 diabetes, reducing the risk of complications and improving long-term glycemic control. Further research into cinnamaldehyde's mechanisms may pave the way for its use as an adjunctive therapy in diabetes care.

Ginsenosides

Active compounds found in ginseng,[122,123] ginsenosides (Figure 2k) have been investigated for their potential to modulate GLP-1 secretion and improve glucose metabolism. Ginsenosides, particularly ginsenoside Rb1, have been shown to stimulate the secretion of GLP-1 from enteroendocrine L-cells in the intestine. These cells release GLP-1 in response to the presence of nutrients, especially carbohydrates and fats (Table 1). Ginsenosides enhance this secretion, leading to an increase in circulating GLP-1 levels, which in turn promotes insulin secretion from pancreatic beta cells. This insulinotropic effect helps to maintain postprandial (after meal) glucose control by stimulating insulin release when blood glucose levels rise, reducing hyperglycemia.[124,125] Once GLP-1 is secreted, it binds to its receptors (GLP-1R) on the surface of pancreatic beta cells. Ginsenosides enhance this receptor activation, triggering downstream signaling pathways, such as the adenylate cyclase-cAMP-Protein Kinase A (PKA) pathway. This activation leads to the enhanced production and release of insulin, which facilitates glucose uptake by cells, lowering blood sugar levels. Additionally, this signaling cascade promotes beta-cell survival and improves their function, which is critical in preventing beta-cell exhaustion often seen in T2DM.[126,127] GLP-1 not only stimulates insulin secretion but also suppresses glucagon release from pancreatic alpha cells. Glucagon is a hormone that increases blood sugar by stimulating hepatic glucose production. By enhancing the GLP-1 pathway, ginsenosides help inhibit glucagon secretion, which in turn reduces glucose production by the liver. This dual effect of stimulating insulin release while suppressing glucagon secretion improves overall glucose homeostasis and helps maintain normal blood sugar levels, especially in individuals with T2DM.[128] DPP-4 is an enzyme that rapidly degrades GLP-1, limiting its effectiveness. Ginsenosides have been shown to inhibit the activity of DPP-4, thereby extending the half-life of GLP-1 in circulation. This prolongs the insulinotropic and glucagonostatic effects of GLP-1, leading to sustained insulin secretion and glucagon suppression. By inhibiting DPP-4, ginsenosides enhance the overall efficacy of the GLP-1 pathway in controlling blood glucose levels and preventing glucose spikes after meals.[129] In addition to their effects on GLP-1 secretion and action, ginsenosides improve insulin sensitivity in peripheral tissues such as skeletal muscle and adipose tissue. Insulin sensitivity refers to how responsive cells are to the effects of insulin, particularly in glucose uptake. By enhancing insulin sensitivity, ginsenosides allow cells to more efficiently absorb glucose from the bloodstream, reducing insulin resistance-a key feature of T2DM. This improvement in insulin sensitivity, coupled with the enhanced GLP-1 activity, creates a synergistic effect in controlling blood sugar levels.[130,131] Ginsenosides have been shown to protect pancreatic beta cells from oxidative stress and inflammation, which are common contributors to beta-cell dysfunction in diabetes. This protective effect is crucial in maintaining the viability and function of beta

cells, which are responsible for producing insulin. By reducing oxidative damage and inflammation, ginsenosides help preserve the function of the GLP-1 pathway and ensure sustained insulin secretion. This preservation of beta-cell function is essential for long-term glycemic control in diabetic patients.[132] Chronic inflammation and oxidative stress play significant roles in the progression of diabetes. Ginsenosides possess strong antioxidant and anti-inflammatory properties, which help reduce the levels of pro-inflammatory cytokines such as TNF-α and IL-6, while also scavenging free radicals. By mitigating inflammation and oxidative stress, ginsenosides protect the GLP-1 pathway and beta cells from damage, thereby supporting better insulin secretion and glucose regulation.[133,134] Ginsenosides also act on the liver to reduce glucose production by suppressing gluconeogenesis (the production of glucose from non-carbohydrate sources). This is partly due to the glucagonostatic effect mediated by the enhanced GLP-1 activity. By reducing hepatic glucose output, ginsenosides contribute to better blood glucose control; especially during fasting states when the liver typically produces glucose to maintain energy balance.[135] Ginsenosides also activate AMP-activated protein Kinase (AMPK), a key regulator of energy homeostasis. AMPK activation increases glucose uptake in muscle cells and inhibits hepatic glucose production, which aligns with the glucose-lowering effects of GLP-1. The combination of AMPK activation and GLP-1 modulation by ginsenosides enhances glucose utilization and improves insulin sensitivity, further supporting the management of T2DM.[136] Several animal and cell culture studies have demonstrated the efficacy of ginsenosides in improving glucose metabolism through the GLP-1 pathway. In diabetic animal models, ginsenoside administration has been shown to increase GLP-1 secretion, improve insulin sensitivity, and reduce fasting blood glucose levels. Studies are also beginning to show the potential benefits of ginseng extracts rich in ginsenosides in managing blood sugar levels and improving glycemic control in people with T2DM.[137,138] Ginsenosides modulate the GLP-1 pathway by stimulating GLP-1 secretion, enhancing GLP-1 receptor activation, inhibiting glucagon release, and improving insulin sensitivity. By inhibiting DPP-4[139] and protecting beta cells from oxidative damage, ginsenosides extend the activity of GLP-1 and support better glucose regulation. The anti-inflammatory, antioxidant, and glucose-lowering properties of ginsenosides make them a promising natural therapy for diabetes management.

CONCLUSION

Natural products that modulate the GLP-1 pathway present promising therapeutic potential for the treatment of diabetes. Bioactive compounds such as curcumin, berberine, quercetin, resveratrol and capsaicin have demonstrated their ability to enhance GLP-1 secretion, inhibit its degradation, and improve insulin sensitivity through various mechanisms. These natural agents not only support glucose homeostasis but also provide protective effects against oxidative stress and inflammation, promoting pancreatic β-cell health. While preclinical studies are encouraging, further clinical research is essential to validate their efficacy, safety, and long-term benefits, paving the way for integrative and complementary approaches in diabetes management.

ABBREVIATIONS

GLP-1: Glucagon-Like Peptide-1; **T2DM:** Type 2 Diabetes Mellitus; **DPP-4:** Dipeptidyl Peptidase-4; **PKA:** Protein Kinase A; **PI3K:** Phosphatidylinositol-3-Kinase; **TRPV1:** Transient Receptor Potential Vanilloid 1; **AMPK:** AMP-Activated Protein Kinase; **HbA_{1c}:** Hemoglobin A1c (a marker of long-term glucose control); **TNF-α:** Tumor Necrosis Factor-alpha; **IL-6:** Interleukin-6; **IL-1β:** Interleukin-1 beta; **EGCG:** Epigallocatechin Gallate; **GLP-1R:** Glucagon-Like Peptide-1 Receptor; **SIRT1:** Sirtuin 1.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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