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Plant-Derived Phytochemicals as Natural GLP-1 Receptor Agonists: A Review of Evidence and Potential for Veterinary Applications

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Abstract | This review underscores the encouraging role of phytochemicals derived from plants as natural agonists of the glucagon-like peptide-1 receptor (GLP-1R) in the treatment of diabetes mellitus. Despite substantial progress in the development of pharmacological agents for managing diabetes mellitus in farm animals, no definitive cure has been established to date. Current veterinary therapeutic options, including insulin analogs, sulfonylureas, biguanides, α-glucosidase inhibitors, thiazolidinediones, meglitinides, sodium–glucose cotransporter-2 (SGLT2) inhibitors, and incretin-based therapies such as glucagon-like peptide-1 receptor (GLP-1R) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, have improved glycemic control in companion and experimental animals. However, long-term use of these agents is often associated with undesirable side effects, reduced treatment compliance, and increased costs, which may limit their routine application in veterinary practice. Among these therapies, GLP-1R agonists are gaining attention in veterinary endocrinology due to their multifaceted benefits, including improved glucose homeostasis, weight regulation, and potential cardioprotective effects in animals. Nevertheless, their limitations particularly high cost, injectable administration, and gastrointestinal side effects emphasize the urgent need for alternative or adjunctive strategies suitable for veterinary medicine. In this context, medicinal plants and their bioactive phytochemicals have emerged as promising candidates. Recognized for their accessibility, affordability, and relatively favorable safety profiles, phytochemicals are being explored as modulators of key metabolic pathways in animals. Importantly, accumulating evidence suggests that certain plant-derived compounds may act as natural GLP-1R agonists, offering comparable metabolic benefits to synthetic drugs. This review underscores the encouraging role of phytochemicals derived from plants as natural agonists of the glucagon-like peptide-1 receptor (GLP-1R) in the treatment of diabetes mellitus. Traditional antidiabetic treatments, while effective, face limitations due to side effects, high costs, and diminished long-term effectiveness. Research from experimental and preclinical studies suggests that bioactive substances such as berberine, geniposide, curcumin, ginsenosides, and thymoquinone can boost GLP-1 secretion, promote insulin release, enhance glucose tolerance, and safeguard pancreatic ß-cells from oxidative harm. It is recommended to conduct additional in vivo studies and controlled clinical trials to validate the efficacy, safety, and pharmacokinetics of phytochemicals functioning as GLP-1R agonists in veterinary medicine. It is crucial to establish standardized extraction methods, conduct phytochemical profiling, and optimize dosages to ensure the reproducibility and reliability of therapeutic outcomes.

Keywords | Diabetes mellitus, Veterinary Applications, Glucagon-like peptide-1 receptor agonist, Phytochemicals

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INTRODUCTION

Diabetes mellitus is one of the most prevalent endocrine disorders in companion animals, particularly in dogs and cats, and its management remains a considerable challenge in veterinary practice. Current therapeutic options are largely limited to insulin administration, dietary modification, and weight control. While effective in many cases, insulin therapy is associated with several limitations, including the risk of hypoglycemia, variability in glycemic response across species, high costs, and the requirement for lifelong daily injections that can reduce owner compliance. Furthermore, incretin-based therapies, such as GLP-1 receptor agonists and DPP-4 inhibitors, which have shown significant benefits in human diabetes management, are not widely approved or optimized for veterinary use. Species-specific differences in disease pathogenesis add further complexity; for instance, canine diabetes is often characterized by insulin deficiency resembling type 1 diabetes, whereas feline diabetes more closely parallels type 2 diabetes with insulin resistance. These differences hinder the straightforward translation of human therapeutic strategies to veterinary patients.

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, defective insulin action, or both, leading to impaired glucose uptake by peripheral tissues and accumulation of glucose in the bloodstream. Diabetes was first described in 1500 BC, although its pathophysiology remained poorly understood until much more recently (Karamanou *et al*., 2016). Today, DM is considered one of the major noncommunicable diseases, with well-established diagnostic criteria. According to Singh *et al.* (2024), diagnosis of DM can be confirmed by one or more of the following: fasting plasma glucose (FPG) ≥ 7.0 mmol/L (126 mg/dl); 2-hour plasma glucose ≥ 11.1 mmol/L (200 mg/dl) during a 75 g oral glucose tolerance test (OGTT); glycated hemoglobin (HbA1c) ≥ 6.5% (48 mmol/mol); or random plasma glucose ≥ 11.1 mmol/L (200 mg/dl) in the presence of classic hyperglycemic symptoms.

Non-modifiable risk factors for DM include age, sex, ethnicity, and genetic predisposition. Individuals aged 65 years and older show a higher prevalence of prediabetes, although many cases of both type 1 (T1DM) and type 2 diabetes (T2DM) remain undetected during the prediabetic stage. Monogenic diabetes, though rare, has also been described; neonatal diabetes occurs in approximately 1 in 100,000 to 500,000 live births and is frequently misdiagnosed as T1DM due to insufficient insulin secretion in infancy (Reddy, 2017).

Over time, DM has been classified into four major categories (Solis-Herrera *et al*., 2015). Type 1 diabetes mellitus (T1DM): An autoimmune condition typically presenting in childhood, characterized by autoimmune destruction of pancreatic β-cells, resulting in absolute insulin deficiency. Type 2 diabetes mellitus (T2DM):The most common form, accounting for nearly 90% of all cases, caused primarily by insulin resistance in peripheral tissues, often in the presence of compensatory hyperinsulinemia. Gestational diabetes mellitus (GDM): A form of glucose intolerance emerging during mid-to-late pregnancy, associated with pregnancy-induced insulin resistance, which may result in adverse maternal outcomes and fetal overgrowth due to hyperglycemia crossing the placenta. Other specific types of diabetes: A heterogeneous group including monogenic forms, pancreatic exocrine diseases, endocrinopathies, infections, drug- or chemically induced diabetes, and post-surgical diabetes.

Complications of diabetes mellitus

Metabolic dysregulation in DM leads to a wide spectrum of pathophysiological alterations affecting multiple organ systems, thereby imposing a substantial health burden (Kasper *et al*., 2008). The disease is a major cause of morbidity and mortality worldwide, primarily due to its vascular complications. Microvascular complications include diabetic retinopathy, nephropathy, and neuropathy, while macrovascular complications involve accelerated atherosclerosis and damage to large blood vessels, contributing to cardiovascular disease, stroke, and peripheral arterial disease (Vlad and Timar, 2012).

Nephropathy

Diabetic nephropathy (DN) is the leading cause of end-stage renal disease worldwide, affecting 40% of patients with T2DM (Alicic *et al*., 2017; Thipsawat, 2021). Normally, 162–180 g of glucose is filtered daily by the glomeruli, with SGLT2 and SGLT1 reabsorbing 90% and 10%, respectively (Pecoits-Filho *et al*., 2016; Gronda *et al*., 2020). When plasma glucose exceeds 180 mg/dL, reabsorption is saturated, resulting in glycosuria (Abiola *et al*., 2024).

Neuropathy

Peripheral neuropathy, present in 50% of diabetic patients, is a major contributor to foot ulcers (Dyck *et al*., 1993; Börü *et al*., 2004; Cade, 2008). It predominantly affects lower extremities, causing sensory, motor, and autonomic dysfunction (Berger *et al*., 2004). Experimental studies suggest that GLP-1 receptor agonists may improve nerve function and reduce neuropathic pain (Sango *et al*., 2022).

Cardiovasculer disease

CVD is the leading cause of death in DM, driven by hyperglycemia, insulin resistance, and dyslipidemia, which accelerate atherosclerosis and increase risk of myocardial

infarction, stroke, and heart failure (Einarson *et al*., 2018; Schmidt, 2019). Achieving HbA1c <7% significantly reduces this risk (Abiola *et al*., 2024).

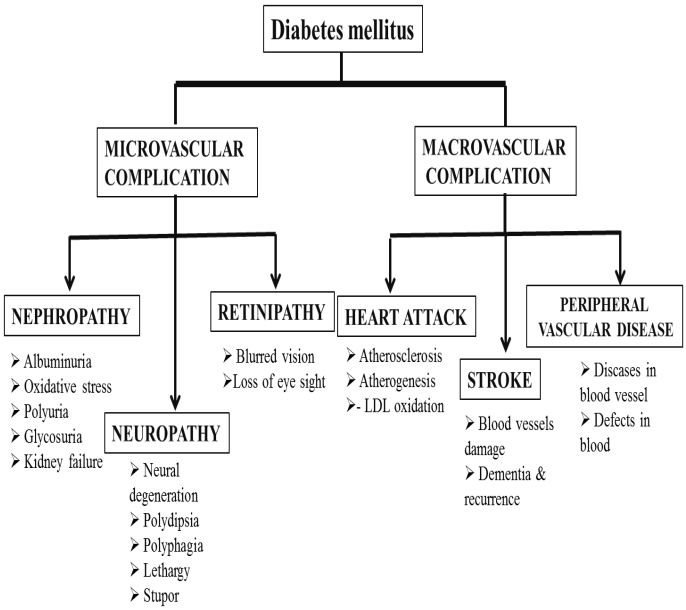

Figure 1: Diabetes-related macrovascular and microvascular problems (Naveen and Baskaran, 2018).

Obesity

Obesity is a multifactorial, relapsing disease strongly associated with T2DM, CVD, and cancer (Lobstein *et al*., 2022). Up to 50% of patients remain undiagnosed during the prediabetic stage (Han and Cho, 2014). Bariatric surgery remains the most effective intervention for sustained weight loss and glycemic control (Arterburn *et al*., 2020).

Liver dysfunction

Non-alcoholic fatty liver disease (NAFLD), including non-alcoholic steatohepatitis (NASH), is highly prevalent in T2DM, affecting more than half of patients (Younossi *et al*., 2019). NASH has become a leading indication for liver transplantation worldwide (Cholankeril and Ahmed, 2018).

Cancer

Both T1DM and T2DM are linked to increased cancer risk, particularly hepatocellular, pancreatic, gastrointestinal, renal, bladder, breast, and endometrial cancers (Atchison *et al*., 2011; Boyle *et al*., 2012; Tsilidis *et al*., 2015; Cignarelli *et al*., 2018). Some evidence also associates insulin therapy with elevated cancer risk (Karlstad *et al*., 2013).

GLP-1 in diabetes mellitus: Mechanisms and therapeutic applications

GLP-1 in diabetes management

Incretin-based therapies provide a novel and promising approach for managing type 2 diabetes mellitus (T2DM). Unlike conventional antidiabetic drugs, they stimulate insulin secretion without causing weight gain or hypoglycemia. Among incretins, glucagon-like peptide-1 (GLP-1) has emerged as the most critical hormone, though its action is rapidly terminated by dipeptidyl peptidase-4 (DPP-4) (Singh *et al*., 2015). Patients with T2DM often exhibit reduced incretin responses, making GLP-1 receptor agonists (GLP-1RAs) valuable therapeutic options (Abiola and Oluyemi *et al*., 2024; Alfaris *et al*., 2024). Agents such as exenatide and liraglutide have demonstrated efficacy in lowering glycated hemoglobin either alone or in combination with other antidiabetic therapies, while showing minimal risk of hypoglycemia and favorable effects on weight. Given GLP-1's short half-life (2–3 min), the development of stable GLP-1RAs has become essential for clinical use (Singh *et al*., 2015).

Mechanisms of GLP-1 receptor agonists

GLP-1 plays a multifaceted role in glucose regulation. It suppresses glucagon secretion from pancreatic α-cells, thereby lowering hepatic glucose output, and enhances insulin sensitivity in skeletal muscle by improving microvascular recruitment (Richards *et al*., 2014). It also delays gastric emptying, which attenuates postprandial glucose excursions. GLP-1 receptors (GLP-1Rs) are expressed in islet β-cells, the central nervous system (CNS), and peripheral tissues, linking GLP-1 action to both metabolic and energy balance regulation (Drucker, 2018; Alfaris *et al*., 2024). Although CNS GLP-1Rs are not essential for endogenous glucose control, peripheral GLP-1 signaling through the portal vein sensor plays a crucial role in insulin responses (Malbert *et al*., 2021). In T2DM, the decline in incretin effect is mainly due to impaired gastric inhibitory polypeptide (GIP) activity (Nauck *et al*., 1993). While GLP-1 secretion remains intact, its functional action is reduced, leading to diminished insulinotropic effects, insulin resistance, and possible GLP-1 receptor down regulation a phenomenon referred to as GLP-1 resistance (Calanna *et al*., 2013).

GLP-1R intracellular signaling

The GLP-1 receptor, first cloned in pancreatic islets over two decades ago (Thorens, 1992), is a seven-transmembrane G protein-coupled receptor (GPCR) of the secretin receptor family (Mayo *et al*., 2003). Upon GLP-1 binding, intracellular cyclic adenosine monophosphate (cAMP) levels rise, activating protein kinase A (PKA) and exchange proteins directly activated by cAMP (EPAC). These signaling cascades promote insulin secretion and β-cell gene expression (MacDonald *et al*., 2002; Seino and Shibasaki, 2005; Baggio and Drucker, 2007; Holst, 2007; Cho *et al*., 2014). GLP-1R activation inhibits ATP-sensitive potassium (KATP) channels through PKA and EPAC pathways (Light *et al*., 2002; Nakazaki *et al*., 2002;

Shiota *et al*., 2002; Kang *et al*., 2006). Increasing β-cell glucose sensitivity by promoting depolarization (Holz *et al*., 1993). It also enhances L-type calcium channel activity (Yada *et al*., 1993; Britsch *et al*., 1995) and non-specific cation channel activation as seen in Figure 2 (Holz *et al*., 1995; Leech and Habener, 1997), facilitating insulin exocytosis. Emerging evidence suggests similar signaling in GLP-1R–expressing neurons in the hippocampus and hypothalamus, linking GLP-1 to central regulation of energy balance (Beak *et al*., 1998; Gilman *et al*., 2003; Hayes *et al*., 2011).

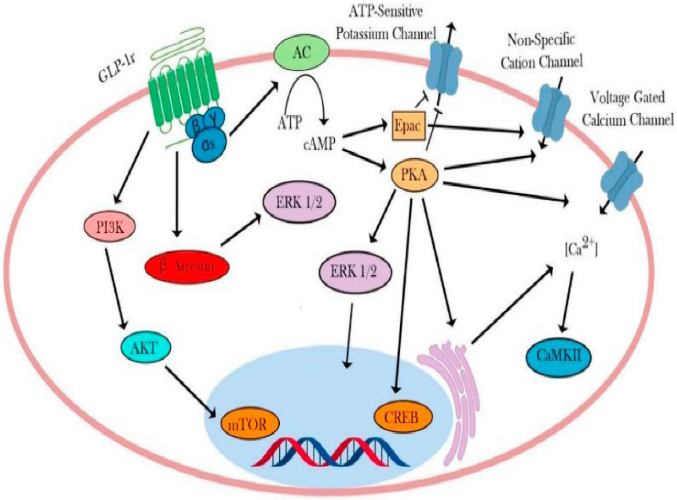

Figure 2: GLP-1R-regulated signaling (Smith *et al*., 2019).

GLP-1–BASED THERAPEUTICS

GLP-1RAs including exenatide, lixisenatide, liraglutide, albiglutide, dulaglutide, and semaglutide are well-established for T2DM treatment and, in higher doses, for obesity management (Collins and Costello, 2024). They are especially recommended in patients intolerant to metformin, or in those with HbA1c ≥1.5% above target, particularly when associated with cardiovascular or renal disease (Burcelin and Gourdy, 2017; Gourgari *et al*., 2017; Hunt *et al*., 2019). Their benefits extend to weight loss through central and peripheral mechanisms including vagal-mediated effects on gastric motility and modulation of leptin signaling (Drucker, 2018; Hasib, 2020; Liu *et al*., 2020). Structurally, they are classified as either exendin-4–based (e.g., exenatide, lixisenatide) or human GLP-1–based (e.g., liraglutide, dulaglutide, albiglutide, semaglutide) (Collins and Costello, 2024). Novel dual agonists such as tirzepatide (GLP-1/GIP) show strong efficacy, though some candidates like taspoglutide were discontinued due to safety concerns (Madsbad, 2016). Despite their success, challenges remain regarding tolerability and high cost (Sanford, 2014; Janzen *et al*., 2016; Hinnen, 2017).

DPP-4 INHIBITORS AS COMPLEMENTARY STRATEGY

Dipeptidyl peptidase-4 (DPP-4) is a membrane-bound and soluble enzyme expressed in the gastrointestinal tract, liver, kidney, vascular endothelium, and plasma, where it cleaves peptides with alanine or proline at the second N-terminal position (Duez *et al*., 2012). GLP-1 and GIP are key physiological substrates of DPP-4. Preclinical studies demonstrated that genetic deletion or pharmacological inhibition of DPP-4 enhances glucose tolerance, increases GLP-1/GIP levels, boosts insulin secretion, reduces food intake, and improves energy expenditure (Marguet *et al*., 2000; Conarello *et al*., 2003). In diabetic animal models, DPP-4 inhibitors improved insulin production, reduced hyperglycemia, and enhanced insulin sensitivity (Pederson *et al*., 1998; Pospisilik *et al*., 2002). These findings support their therapeutic value in augmenting incretin action and improving glucose homeostasis.

MEDICINAL PLANTS IN DIABETES MANAGEMENT

Plant-based diets include a wide variety of phytochemicals, they offer a promising natural approach to the control of type 2 diabetes. The significance of a diet high in plant-based foods (fruits, vegetables, spices, and condiments) in the prevention and treatment of diabetes mellitus has been emphasized by numerous epidemiological studies. Such natural products are widely available, reasonably priced, and typically free of side effects, in contrast to conventional drugs. Incorporating plant-based foods into the daily diet provides numerous health advantages, including assisting in the management of weight in obese people and reducing the hyperglycemia seen in DM (Ansari *et al*., 2024). Management of DM with a particular focus on the promising potential of plant-based foods. Despite major advances in therapeutic strategies over the past three decades, clinical outcomes remain suboptimal (Kooti *et al*. 2016). Conventional treatments, including biguanides that inhibit hepatic gluconeogenesis and α-glucosidase inhibitors that delay intestinal carbohydrate absorption, have demonstrated efficacy but are often associated with limitations such as toxicity, adverse effects, and the development of drug resistance (Hui *et al*., 2005; Kooti *et al*., 2016) For example, nearly 44% of patients lose responsiveness to sulfonylureas within six years of therapy (Kooti *et al*., 2016). Moreover, conventional glucose-lowering medications fail to adequately control associated metabolic complications such as hyperlipidemia (Dey *et al*., 2002). These concerns underscore the need for safer, more sustainable alternatives. Medicinal plants, also referred to as phytomedicinals, are increasingly recommended as complementary or alternative options in diabetes management (Kooti *et al*., 2015). They can be used wholly or partially in different forms such as teas, tinctures, or extracts. The use of plants in medicine has a long historical background; for instance, willow (*Salix* sp.) has been used therapeutically for over 6000 years (Haj-Zaroubi *et al*., 2024).

Importantly, salicylic acid isolated from willow bark in 1820 led to the development of aspirin, highlighting the potential of natural products as sources of synthetic drugs (Carmona and Pereira, 2013). Beyond their therapeutic roles, medicinal plants provide additional benefits through bioactive phytochemicals that act as functional foods or nutraceuticals. These compounds not only contribute to disease prevention but also enhance overall health and nutritional status. Various classes of phytochemicals such as phenolic acids, flavonoids, phytoestrogens, carotenoids, phytosterols, phytostanols, and organosulfur compounds (e.g., allium derivatives and glucosinolates) have been linked to the prevention and management of chronic diseases including diabetes, cardiovascular disorders, and cancer (Oz and Kafkas, 2017).

It is cleared that some compounds (e.g., geniposide) are reported to act directly at GLP-1R (cell assays), while others raise circulating GLP-1 by promoting secretion (L-cell stimulants) or reducing degradation (DPP-4 inhibition). These are different mechanisms and can produce different downstream effects.

Group of chemical substances found in plants

Plant-based diets that incorporate medicinal plants, abundant in bioactive compounds, have attracted considerable interest for their potential role in the prevention and management of chronic diseases, particularly diabetes. Phytochemicals, including flavonoids, anthocyanins, carotenoids, saponins, tannins, and polyphenols, are present in a diverse array of plant-based foods such as fruits, vegetables, legumes, and whole grains, and are crucial in diabetes management. These compounds assist in regulating blood sugar levels through various mechanisms, which may include enhancing insulin sensitivity or secretion, inhibiting enzymes responsible for carbohydrate breakdown, and decreasing glucose production in the liver. Additionally, they promote gut health, stimulate the release of glucoregulatory or satiating hormones from the gut, mitigate inflammation, and counteract oxidative stress, all of which are vital for improving overall metabolic function and preventing diabetes (Elkhalifa *et al*., 2021). Although plant secondary metabolites are not uniformly classified, they are often categorized based on their structural characteristics, as shown in Figure 3. These groups include alkaloids, terpenoids, saponins, carotenoids, and phenolic compounds (Abiola *et al*. 2024).

Figure 3 summarizes the multifaceted ways in which phytochemicals may influence the GLP-1 pathway. These natural compounds can stimulate endogenous GLP-1 release from L-cells, inhibit enzymatic degradation by DPP-4, or act directly as GLP-1 receptor agonists on pancreatic β-cells. In addition, several phytochemicals activate downstream signaling cascades (PI3K/Akt, FOXO1) that promote insulin secretion, B-cell survival, and improved glucose uptake. Unlike synthetic incretin therapies, which usually target a single mechanism, phytochemicals appear to exert pleiotropic effects at multiple levels of the incretin axis, potentially offering synergistic benefits. This mechanistic diversity suggests a rationale for investigating phytochemicals as adjunctive therapies in veterinary diabetes, though careful validation in species-specific models is required.

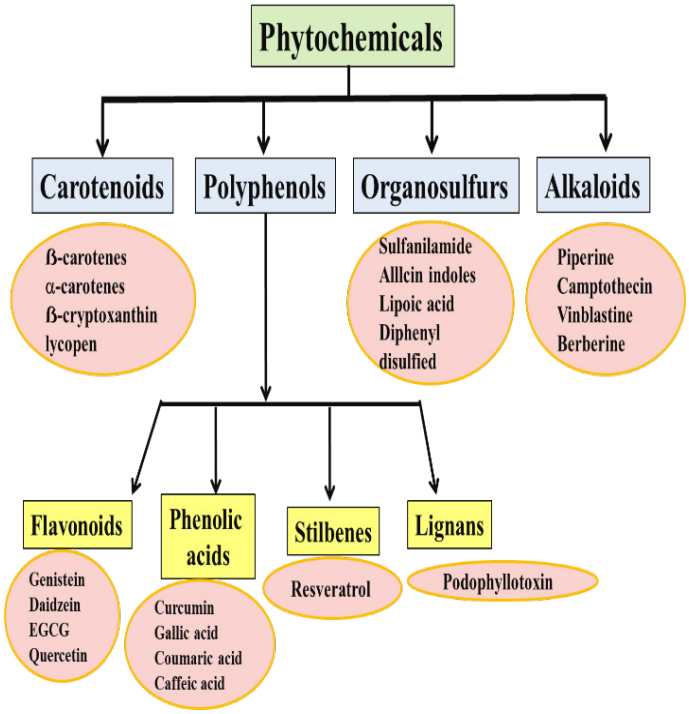

Figure 3: Phytochemical classes (Srivastava *et al*., 2103).

Potential mechanisms of GLP-1 secretion induced by phytochemicals

Phytochemicals found in plant-based diets can offer considerable advantages in the management of diabetes by improving insulin sensitivity, decreasing oxidative stress, and controlling blood sugar levels through the modulation of various antidiabetic mechanisms. This positions them as a promising natural complement to conventional therapies aimed at enhancing metabolic health, providing a pharmacological overview of the effects of commonly utilized medicinal plant-based diets. A pharmacological overview of the effects of commonly utilized medicinal plant-based diets. Emerging evidence suggests that phytochemicals may stimulate GLP-1 release by activating its receptor on gut enteroendocrine cells. This process involves multiple intracellular signaling pathways mediated by key proteins such as transient receptor potential (TRP) channels, phospholipase C beta 2 (PLCβ2), gustducin (a G protein), and the inositol 1, 4, 5-trisphosphate receptor type 3 (IP3R3). These mechanisms collectively increase intracellular Ca^{2+} levels, leading to membrane

depolarization and subsequent GLP-1 secretion (Singh *et al*., 2015). Figure 4 provides a schematic representation of how GLP-1 ultimately enhances insulin release from pancreatic β-cells (Abiola *et al*., 2024).

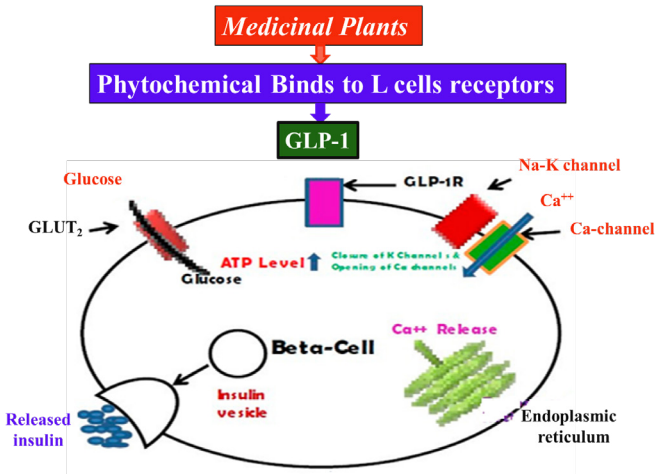

Figure 4: Mechanism of phytochemicals to induce GLP-1 (Singh *et al*., 2015).

Figure 4 summarizes the integrated effects of phytochemicals on GLP-1 biology and glucose homeostasis. These compounds not only stimulate GLP-1 secretion and prevent its degradation, but also activate GLP-1 receptors to enhance insulin release and β-cell survival. In addition, downstream effects include reduced hepatic gluconeogenesis, improved skeletal muscle glucose uptake, modulation of lipid metabolism, and anti-inflammatory protection. This multi-target profile distinguishes phytochemicals from conventional drugs, offering a potentially broader therapeutic impact in diabetes management. However, the pleiotropic actions illustrated also emphasize the need for careful evaluation of efficacy, dosing, and safety across different veterinary species.

The Glucagon-Like Peptide-1 (GLP-1) agonist plays a significant role in maintaining glucose homeostasis by regulating insulin secretion and inhibiting glucagon release, while also promoting slower gastric emptying. This review examines natural products that influence the GLP-1 pathway, highlighting several promising options for diabetes management. Plant-derived natural products have demonstrated encouraging effects on the GLP-1 agonist pathway. For instance, compounds such as berberine, sourced from various plants, have been found to enhance GLP-1 secretion and improve insulin sensitivity. Additionally, ginsenosides derived from ginseng and curcumin extracted from turmeric exhibit similar beneficial activities (Kolhe *et al*., 2025). The Glucagon-Like Peptide-1 (GLP-1) pathway (Figure 5) plays a vital role in the regulation of glucose homeostasis and has emerged as a significant target for diabetes therapy. GLP-1 is an incretin hormone released by the L-cells of the small intestine in reaction to the consumption of nutrients, especially carbohydrates and fats (Müller *et al*., 2019). It operates through various mechanisms that work together to sustain normal blood glucose levels. To begin with, GLP-1 promotes insulin secretion by attaching to GLP-1 Receptors (GLP-1R) located on pancreatic beta cells. This interaction triggers the adenylate cyclase-cAMP-Protein Kinase A (PKA) signaling pathway, which results in the phosphorylation of proteins that play a role in insulin exocytosis. Furthermore, GLP-1 stimulates the Phosphatidylinositol-3-Kinase (PI3K) pathway, which increases beta cell responsiveness to glucose, thereby boosting insulin secretion in a glucose-dependent fashion (Nadkarni *et al*., 2014; Nauck et al., 2021).

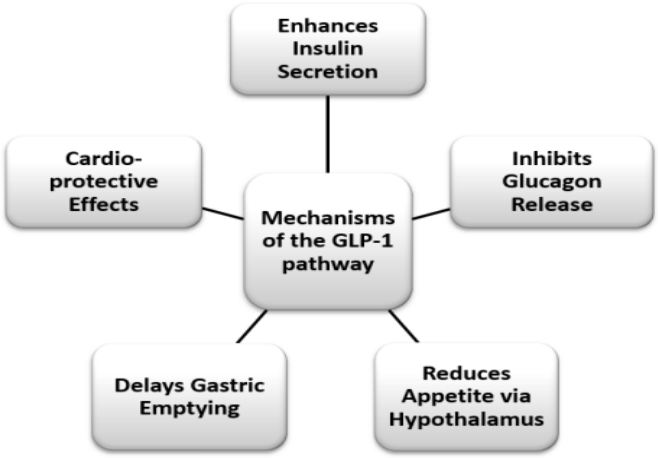

Figure 5: Mechanisms of the GLP-1 pathway (Kolhe *et al*., 2025).

Figure 5 illustrates the broader spectrum of phytochemical actions in diabetes beyond GLP-1 modulation. In addition to stimulating incretin secretion and preventing its degradation, phytochemicals enhance β-cells survival and insulin release, suppress a-cell glucagon output, and improve glucose handling in peripheral tissues through GLUT-4 upregulation. Moreover, their antioxidant and anti-inflammatory effects contribute to β-cell preservation and improved metabolic control. Collectively, these diverse mechanisms highlight the potential of phytochemicals as multitarget agents for diabetes management, though translational validation in veterinary species remains limited.

Role of medicinal plants in enhancing GLP-1 levels

Medicinal plants represent a promising source for the development of novel therapeutic agents targeting diabetes mellitus and related disorders (Singh *et al*., 2015). Globally, approximately 400 plant species and 700 herbal formulations are traditionally used for the treatment of diabetes (Ivorra *et al*., 1989; Grover *et al*., 2002). The

antidiabetic effects of these plants are attributed to several mechanisms, including: regeneration of pancreatic β-cells, stimulation of insulin secretion, enhancement of glucose uptake by muscle and adipose tissues, suppression of hepatic gluconeogenesis, and inhibition of intestinal β-glucosidase activity (Prabhakar and Doble, 2011). More recently, certain medicinal plants have been identified as potential modulators of GLP-1 activity, thereby expanding their therapeutic relevance in diabetes management (Yogisha and Raveesha, 2010; Hussein *et al*., 2011).

Guirgis *et al*. (2021) investigate the biochemical and molecular impacts of Moringa oleifera (MO) and Ficus sycomorus (FLE) on streptozotocin-induced diabetic rats, comparing their effects to those of metformin. This comparison is achieved through the assessment of the expression levels of β-actin, glucose transporter GLUT2, GLUT4, and insulin receptor genes across the studied groups. Additionally, the study involves measuring fasting blood glucose and insulin levels both prior to and following the induction of STZ, as well as quantitatively estimating serum cholesterol, triglyceride (TG) levels, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and the activity of certain antioxidant enzymes such as glutathione peroxidase and catalase, alongside lipid peroxidation in plasma. The findings indicate that MO and FLE exhibit significant anti-diabetic potential in diabetic albino mice, which may be linked to their anti-inflammatory properties. The findings indicate that MO and FLE exhibit significant anti-diabetic potential in diabetic albino rats. Recently, Bashir *et al*. (2024) assessed the impact of the watery leaf extract of Urtica dioica on cardiac parameters related to diabetes mellitus (DM) in Wistar rats. The animals (N= 25) were divided into four groups: An untreated normal control group (n=8) receiving distilled water; a diabetic control group (n=7) induced with alloxan (120 mg/kg); and two diabetic treatment groups receiving Urtica dioica extract at 250 mg/kg (n=5) or 500 mg/kg (n=5). The data indicated that the diabetic group experienced a decrease in heart rate, leading to bradyarrhythmia. Following treatment with 250 mg/kg of UD, an improvement in heart rate was observed. Furthermore, increasing the UD concentration to 500 mg/kg resulted in a further elevation of the heart rate to normal levels.

Table 1: Most important medicinal plants induce GLP-1.

Common Name	Part used	Phytochemicals	Mechanism of action	References
Agave (*Agave tequilana* Gto., Agavaceae)	Roots	Agave fructan	Agave fructans increased the concentration of far precursors and induced GLP-1.	Urias *et al*., 2008
Barberry (*Berberis vulgaris*, Berberidaceae)	Roots, rhizomes	Berberine	Berberine has an antidiabetic impact via promoting glycolysis and raising insulin secretion. Additionally, berberine raises levels of GLP-1 and glucose transporter-4 (GLUT-4).	Cicero and Tartagni, 2012
Bitter melon (*Momordica charantia*, Cucurbitaceae)	Fruit	Karavilagenine E	Mice given a single dose of WES orally for 30 minutes showed higher serum GLP-1, insulin, and lower glucose, suggesting that WES also promoted GLP-1 secretion in vivo.	Huang *et al*., 2013
Cinnamon tree (*Cinnamomum zeylanicum*, Lauraceae)	Bark	Cinnamon	Three grams of cinnamon raised GLP-1 levels and decreased postprandial serum insulin without appreciably changing blood glucose levels.	Hlebowicz *et al*., 2009
Gardenia (*Gardenia jasminoides*, Rubiaceae)	Fruit	Geniposide (GP)	By activating the glucagon-like peptide 1 receptor (GLP-1R) in INS-1 cells, geniposide improves glucose-stimulated insulin production and inhibits oxidative stress-induced neuron death.	Liu *et al*., 2012
Korean Pine (Pinus koraiensis, Pinaceae)	Seeds	Free fatty acids (FFA) and triglycerides (TG)	GLP-1 increased 60 minutes after the introduction of pine nuts.	Pasman *et al*., 2008
Little dragon (*Artemisia dracunculus* L., Asteraceae)	Leaves	Tarrallin	Additionally, the extract was demonstrated to enhance glucagon-like peptide (GLP1) binding to its receptor in vitro	Ribnicky *et al*., 2006
Mango Mangifera (indica, Anacardiaceae)	Leaves	-	For type 2 diabetes, Mangifera indica increases GLP-1 and inhibits DPP-4.	Yogisha and Raveesha, 2010
Mate tea (Ilex paraguariensis, Aquifoliaceae)	Leaves	Matesaponin, 3,5-Odicaffeoyl-D-quinic acid, mate-saponin 2	GLP-1 levels significantly increased upon acute administration of mate's main ingredients. GLP-1 levels were significantly elevated by compounds (3,5-O-dicaffeoyl-D-quinic acid and matesaponin 2, respectively) and alinolenic acid.	Hussein *et al*., 2011

Table 2: GLP-1R agonists of Plant-based phytochemicals (Abiola et al., 2024).

The plants	Compound's name	Actions and techniques		References
Cynanchum marnierianum Rauh	Pregnane glycoside	*In vitro*	Increases the secretion of GLP-1	Tsoukalas *et al.*, 2016
Curcuma longa L.	Curcumin	*In vitro*	Enhanced secretion of GLP-1	Takikawa *et al.*, 2013
Panax ginseng C.A. Mey	Saponins and Ginsenoside	*In vitro* and *in vivo*	Proglucagon gene expression upregulation and glucose-induced GLP-1	Liu *et al.*, 2012
Agave tequilana F.A.C. Weber	Fructans	*In vivo*	Enhanced lipid glucose metabolism through proglucagon induction	Urias-Silvas *et al.*, 2008
Nigella sativa L.	Thymoquinone, Dithymoquinone	*In vivo*	Possible activation of pancreatic β-cells leading to decreased hepatic gluconeogenesis and insulin secretion	Benhaddou *et al.*, 2008
Zingiber officinale Roscoe	6-gingerol	*In vivo*	Improved resistance to glucose and support for the glucose-induced release of insulin	Samad *et al.*, 2017
Artemisia dracunculus L.	Tarralin	*In vitro*	Decreases glucagon secretion	Ribnicky *et al.*, 2006
Gardenia Jasminoides J. Ellis	Geniposide	*In vivo*	Akt and FOXO1 phosphorylation in INS-1 cells	Liu *et al.*, 2012
Berberis vulgaris	Berberine	*In vivo*	Promotes glycolysis and raises insulin production.	Cicero and Tartagni, 2012
Berberis aristata	Berberine	*In vivo*	Controls glucose homeostasis by lowering oxidative stress and gluconeogenesis.	Potdar *et al.*, 2012
Bacopa monnieri (L.) Wettst.	Bacosine	*In vivo*	Peripheral glucose consumption and defense against oxidative damage	Ghosh *et al.*, 2011
Anoectochilus roxburghii	Kinsenoside	*In vivo*	Repair of damage to pancreatic β cells	Zhang *et al.*, 2007
Hibiscus sabdariffa L.	Delphinidin		GLP-1 elevation in the pancreas and ileum	Kartinah *et al.*, 2019
Hoodia gordonii (Masson)	Gordonoside F	*In vivo*	Causes GLP-1 to be released through GPR119	Zhang *et al.*, 2015
Momordica charantia	Cucurbiracin	*In vivo*	Promotes the release of insulin and increases plasma GLP-1.	Zhang *et al.*, 2015
Rheum palmatum L.	Emodin	*In vivo* and *in vitro*	Elevated release of GLP-1 in plasma	Wang *et al.*, 2020

Based on the studies collated here, berberine and ginsenosides present the most consistent preclinical evidence for GLP-1 pathway modulation (multiple *in vivo* and mechanistic reports). Geniposide and tarralin merit further study given receptor-level or in vivo glycaemic signals, respectively. Many other listed phytochemicals have only in vitro or single short-term animal evidence and therefore remain preliminary. The best medicinal plants is berberine and ginsenosides, and the Mechanistically interesting but less tested is geniposide and tarralin.

GLP-1 AND PHYTOCHEMICALS

Extensive research has investigated the mechanisms by which phytochemicals exert antidiabetic effects, particularly their ability to modulate GLP-1 activity (Abiola *et al.*, 2024), as shown in Table 2. For instance, Cicero and Tartagni (2012) examined the effects of berberine, an isoquinoline alkaloid derived from the roots and rhizomes of Berberis vulgaris. Their findings demonstrated that berberine enhanced insulin secretion, stimulated glycolysis, and significantly increased both GLP-1 and glucose transporter-4 (GLUT-4) expression in rats treated with 500 mg/kg body weight (Abiola *et al.*, 2024). Similarly, geniposide, a phytochemical isolated from Gardenia jasminoides fruit, was reported to potentiate glucose-stimulated insulin secretion via direct activation of the GLP-1 receptor (GLP-1R) in INS-1 pancreatic β-cells, while also protecting neurons from oxidative stress-induced apoptosis (Liu *et al.*, 2012; Zhang *et al.*, 2021). Moreover, tarralin, a bioactive compound from Artemisia dracunculus leaves, demonstrated improved GLP-1 binding affinity to its receptor in vitro, and oral administration at 500 mg/kg significantly improved glycemic outcomes in KK-Aγ diabetic mice (Ribnicky *et al.*, 2006).

Phytochemicals engage with the incretin system in ways that are fundamentally different from traditional GLP-

1-based medications. In contrast to synthetic GLP-1 receptor agonists, which function as stable receptor mimetics, phytochemicals have the capacity to affect various levels of the GLP-1 pathway concurrently. For instance, certain compounds like berberine and ginsenosides promote the secretion of endogenous GLP-1 from intestinal L-cells, thus enhancing the physiological release of hormones in response to nutrients. Other compounds, such as flavonoids, curcuminoids, and polyphenols, inhibit dipeptidyl peptidase-4 (DPP-4), which slows the degradation of GLP-1 and extends the action of the hormone. A smaller subset, including geniposide, has been noted to function as direct GLP-1 receptor agonists, thereby mimicking incretin activity at the receptor level. Beyond these incretin-specific effects, numerous phytochemicals display pleiotropic effects such as antioxidant properties, anti-inflammatory signaling, and protection of β-cells which may work synergistically with incretin enhancement to improve glycemic control. This complex interaction pattern is a significant differentiator from single-target pharmaceuticals and highlights the potential of phytochemicals as complementary or adjunctive treatments in the management of diabetes.

It is insight from Table 2 that the strongest and clearest dose evidence is Urtica dioica extract and the promising but under-documented is bitter melon (acute GLP-1 rise shown, but no mg/kg listed), meanwhile, the remaining extracts show positive signals but lack standardized dosing data, extract composition, or replication in multiple models.

GLP-1 RECEPTOR AGONIST SIDE EFFECTS

The most frequent adverse events of GLP-1 receptor agonists are gastrointestinal, particularly nausea and diarrhea, which affect up to 50% of patients but usually diminish with continued therapy; about 4% of patients discontinue treatment due to persistent nausea (Ratner *et al*., 2006; Buse *et al*., 2009; Filippatos *et al*., 2015). Concerns have been raised regarding pancreatic safety, as animal studies reported histopathological changes and an increased risk of ancreatitis, although clinical evidence remains inconclusive (Lee *et al*., 2011; Yu *et al*., 2012; Mondragon *et al*., 2014). Injection-site reactions, such as erythema and pruritus, are also observed, particularly with long-acting formulations (Madsbad *et al*., 2011; Filippatos *et al*., 2015). Cardiovascular outcomes from meta-analyses showed no significant increase in major adverse events, though a mild rise in heart rate has been consistently reported (Monami *et al*., 2011; Robinson *et al*., 2013; Katout *et al*., 2014) Other less common adverse effects include hypersensitivity reactions, endocrine disturbances, musculoskeletal disorders, renal effects, and rare reports of malignancy or overdose (Filippatos *et al*., 2015).

CONCLUSION AND RECOMMENDATIONS

This review underscores the encouraging role of phytochemicals derived from plants as natural agonists of the glucagon-like peptide-1 receptor (GLP-1R) in the treatment of diabetes mellitus. Traditional antidiabetic treatments, while effective, face limitations due to side effects, high costs, and efficacy. Research from experimental and preclinical studies suggests that bioactive substances such as berberine, geniposide, curcumin, ginsenosides, and thymoquinone can boost GLP-1 secretion, promote insulin release, enhance glucose tolerance, and safeguard pancreatic β-cells from oxidative damage. These results highlight the therapeutic promise of phytochemicals as cost-effective, accessible, and safer alternatives or supplements to synthetic GLP-1R agonists in both veterinary and medical fields. Nevertheless, the variation in phytochemical composition, differences in extraction techniques, and the absence of standardized dosing protocols underscore the necessity for additional scientific validation.

It is recommended to conduct additional *in vivo* studies and controlled clinical trials to validate the efficacy, safety, and pharmacokinetics of phytochemicals functioning as GLP-1R agonists in veterinary medicine. It is crucial to establish standardized extraction methods, conduct phytochemical profiling, and optimize dosages to guarantee the reproducibility and reliability of therapeutic results. Moreover, further molecular research should explore the intracellular pathways by which phytochemicals influence GLP-1 secretion and receptor signaling.

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NOVELTY STATEMENT

This review emphasizes the potential of phytochemicals derived from plants as natural GLP-1 receptor agonists for managing diabetes mellitus within the field of veterinary medicine. In contrast to traditional antidiabetic treatments, these bioactive substances provide affordable, accessible, and safer alternatives, along with the benefit of influencing various metabolic pathways. By thoroughly assessing recent findings from experimental and preclinical research, this article underscores the distinctive function of phytochemicals in promoting GLP-1 secretion, enhancing glucose tolerance, and safeguarding pancreatic β-cells. The innovation lies in the incorporation of phytochemical-based approaches into veterinary endocrinology, setting the stage for the future development of plant-derived

therapeutics as economical and sustainable solutions for diabetes management in animals.

AUTHOR'S CONTRIBUTION

Mohamed M.A. Hussein: Conceptualization, supervision, critical revision of the manuscript. Amany I. Ahmed: Data collection, literature review, drafting of the manuscript. Hend Saeed Syam: Data interpretation, figure and table preparation, editing and formatting of the manuscript. All authors contributed to the writing and approval of the final version of the manuscript.

Generative AI and AI-assisted technology statement

All authors of this work declare that generative AI technologies including large language models (e.g., ChatGPT, Copilot) and text-to-image generators were not utilized in any capacity during the preparation, writing, or editing of this manuscript.

Conflict of interest

The authors have declared no conflict of interest.

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