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REVIEW

Pharmacological and Clinical Studies of Medicinal Plants That Inhibit Dipeptidyl Peptidase-IV

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Abstract: Dipeptidyl peptidase IV (DPP-IV) is an enzyme responsible for the degradation of the incretin hormone glucagon-like peptide-1 (GLP-1). DPP-IV plays a significant role in regulating blood glucose levels by modulating the activity of GLP-1. In the context of diabetes, DPP-IV inhibitors effectively block the activity of DPP-IV, hence mitigating the degradation of GLP-1. This, in turn, leads to an extension of GLP-1's duration of action, prolongs gastric emptying, enhances insulin sensitivity, and ultimately results in the reduction of blood glucose levels. Nonetheless, reported adverse events of DPP-IV inhibitors on T2DM patients make it essential to understand the activity and mechanism of these drugs, particularly viewed from the perspective of finding the effective and safe add-on medicinal plants, to be implemented in clinical practice. This review is intended to bring forth a thorough overview of plants that work by reducing DPP-IV activity, from computational technique, enzymatic study, animal experiments, and studies in humans. The articles were searched on PubMed using "Plants", "DPP-IV", "DPP-IV inhibitor", "GLP-1", "Type 2 diabetes", "diabetes", "in silico", "in vitro", "in vivo", "studies in human", "clinical study" as the query words, and filtered for ten years of publication period. Eighteen plants showed inhibition against DPP-IV as proven by in silico, in vitro, and in vivo studies; however, only ten plants were reported for efficacy in clinical studies. Several plant-based DPP-IV inhibitors, eg, *Allium sativum, Morus Alba, Curcuma longa, Pterocarpus marsupium*, and *Taraxacum officinale*, have established their functional role in inhibiting DPP-IV and have proven their effectiveness through studies in humans earning them a prominent place in therapeutic discovery.

Keywords: antidiabetics, antioxidants, diabetes mellitus, incretin hormone, medicinal plants

Introduction

As the world information society has grown, so has the number of the population with sedentary behavior. This term refers to any activity that requires a minimal amount of energy to maintain when a person is awake. This can include sitting, leaning, or lying down. Previous works have demonstrated that this less-active behavior is inextricably linked to all-cause mortality, eg, due to heart and blood vessel dysfunction, and type 2 diabetes mellitus (T2DM).[1,2] The prevalence of T2DM in young people and adolescents is rising dramatically. The most predisposing causes of T2DM in elderly patients are being overweight with a lineage of DM, and a sedentary lifestyle.[3] Adult-onset diabetes or non-insulin-dependent diabetes is a polygenic syndrome in which genetic and environmental health risks combine, leading to insulin resistance in the liver and muscles, and reducing the number of pancreatic β-cells. Most patients who suffer from T2DM are overweight, and the disease may go undetected for a long time as the patients move through the asymptomatic "pre-diabetes" stage.[4] Chronic complications of DM lead to the impairment and malfunction of the organ.[5] Therefore, achieving close to normal glucose levels is considered the main objective of DM management, which can be accomplished by the administration of oral hypoglycemic drugs.

Medications for DM fall into one of five categories, each with its unique mechanism of action: those that increase insulin secretion (eg, sulfonylureas and glinides), those that decrease the absorption of glucose in the intestine (eg,

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acarbose), drugs belonging thiazolidinediones and biguanides classes, drugs that decrease the reabsorption of glucose in the urine (eg, gliflozin), and drugs that target the incretin system (eg, DPP-IV inhibitors and GLP-1 analogs). Side effects of anti-DM medications include urinary tract infections (UTI), ketoacidosis, hypoglycemia, and weight gain. In addition to posing insurmountable obstacles to establishing effective dosing regimens in a clinical context, patients with DM may experience a decline in quality of life (QoL) due to side effects from their medication.[6] Therefore, discovering plant-derived DPP-IV inhibitors is always challenging.

In this article, we discuss plants with DPP-IV inhibitory activity through in silico modeling, in vitro enzymatic, in vivo animal experiments, and studies in humans. The mechanism by which DPP-IV inhibitors affect glucagon-like peptide-1 (GLP-1) levels and their effect on insulin were also described.

Glucagon-Like Peptide-1 (GLP-1): The Incretin Hormone Secretion

The rationale behind the increased production of insulin in response to meals when glucose is consumed orally, as opposed to intravenous administration, despite similar plasma glucose levels, can be attributed to the insulinotropic actions of incretin hormones. The enteroendocrine cells (EECs) in the digestive tract release incretin, which is crucial to the signalling process. EECs are part of the intestinal lining, which also includes mucus-secreting cells and absorptive epithelial cells. The EECs secrete hormones that function in food ingestion, abdominal peristaltic, stomach emptying, glucose balance, and regulation of hunger, among other functions. These hormones are released in response to nutrients and non-nutritional chemicals that either act on sensory transporters and receptors or on cellular metabolism. The primary secretions of EECs have allowed for their classification. GLP-1 is the incretin hormone that elevates insulin levels. GLP-1 and peptide YY (PYY) are secreted by L-cells, cholecystokinin (CCK) by I-cells, secretin by S-cells, glucose-dependent insulinotropic polypeptide (GIP) by K-cells, and gastrin by G-cells. I-cells and K-cells are duodenal EEC cells, L-cells are located in the ileum and colon.[7] Intestinal and pancreatic GLP-1 receptors on vagal afferent neurons have revealed a pathway of communication between the intestines, the pancreas, and the brain. Similar to the GLP-1 EECs, the brain is capable of synthesizing GLP-1. The amazing scope of action of GLP-1 is highlighted by the fact that it influences eating behavior by communicating across the stomach, the brain, and the pancreas. Because of these roles, GLP-1 has been successful in the pharmacological control of T2DM.[8,9] It has been extensively studied that the carbohydrates, proteins, and lipids of a meal may promote GLP-1 production from GLP-1 EECs.[10]

Moreover, the glucose uptake across cell membranes are affected by mediators, among those is sodium-coupled glucose transporters (SGLT), that play a crucial role in arbitrating glucose's influence on GLP-1 release from EECs. Depolarization of the membrane, brought on by the influx of Na^+ ions, activates the voltage dependent calcium channels (VDCC) and the exocytosis of GLP-1-containing vesicles.[11] Amino acids affect the secretion of GLP-1 by a similar mechanism mediated by Na^+ ions.[12] G protein-coupled receptors (GPCRs) as GPR142 and CASR are activated by oligopeptides.[13,14] Long-chain fatty acids are recognized by GPR40 and GPR120, whereas shorter fatty acids are recognized by other GPCRs.[15] In pharmaceutical treatments for diabetes and obesity, one of the primary objectives is to increase the amount of GLP-1 that is secreted, and as a result, a lot of work has been put into figuring out the molecular processes that cause GLP-1 to be secreted. The decrease of stomach capacity and increase of stomach pressure in gastric bypass and other weight-loss surgeries are caused by GLP-1 secretion and stomach emptying (Figure 1).[16,17]

Most of GLP-1 in the lower brain stem occurs in the nucleus tractus solitarius (NTS), where it is produced by GLP-1 producing pre-proglucagon (PPG) neurons[18] in respond to the release of GLP-1 in the peripheral. The vagal nerve is stimulated when the gastrointestinal GLP-1 binds to its receptor (GLP-1r), and eventually triggers the NTS PPG neurons to release GLP-1.[19] Hence, there is a positive correlation between the secretion of GLP-1 in the periphery and the secretion of GLP-1 in the brain. As a whole, it shows that NTS PPG neurons and EECs respond differently to the same stimuli for GLP-1 release. Hormonal cues and vagal activity activate PPG neurons in the NTS, while dietary intake is the major activator for GLP-1 release from EECs. NTS PPG neurons integrate various inputs via excitatory, inhibitory, and neuro-modulatory influences before sending the signal to other central nodes. To further understand the mechanism on how GLP-1 work, the intracellular GLP-1 signaling pathway on insulin secretion is provided in the next section.

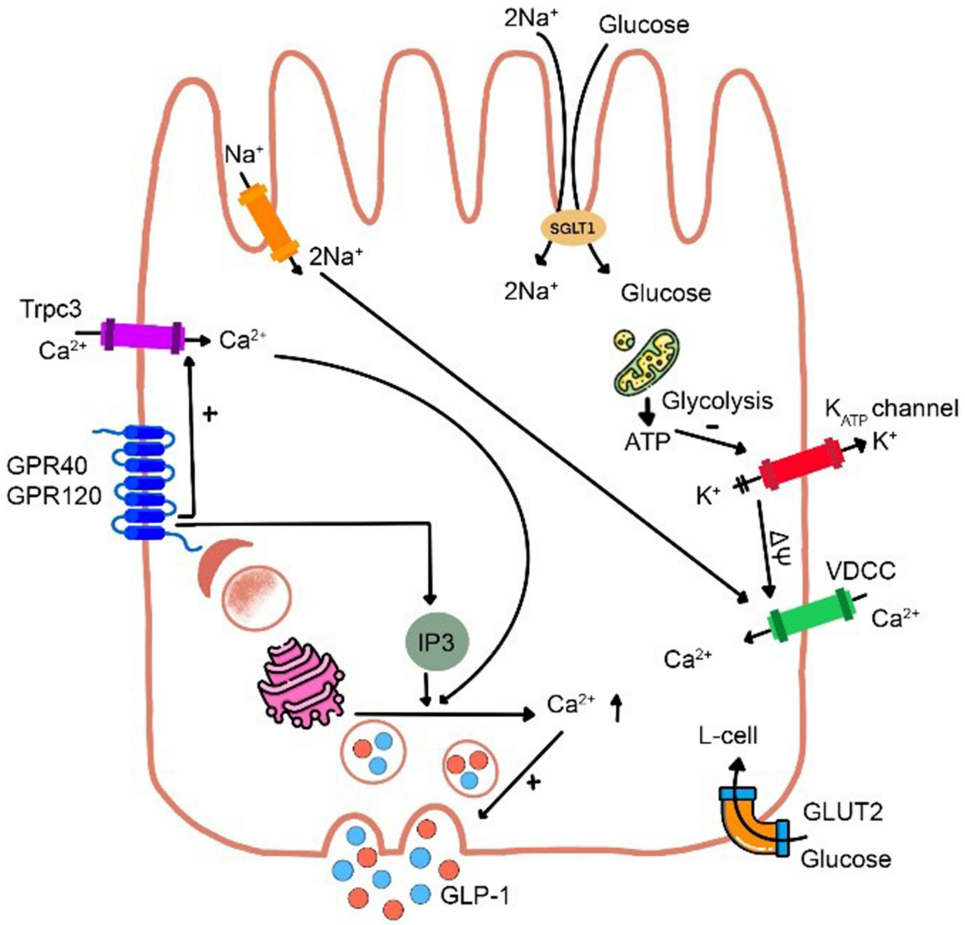

Figure 1 Schematic on GLP-1 secretion in the L-cell. Glucose arising from carbohydrate metabolism is transported at the luminal face of the L-cell via sodium-glucose cotransporter-1 (SGLT-1), which is coupled with Na^+ influx, depolarizing the cell membrane ($\Delta\Psi$), opening VDCC, increasing intracellular Ca^{2+} levels, and triggering exocytosis of GLP-1 containing granules at the L-cell's basolateral face. Increased intracellular ATP from glucose metabolism closes K_{ATP} channels, potentiating GLP-1 release. Long-chain fatty acids interact with G protein-coupled receptors (GPR40 and GPR120), triggering intracellular Ca^{2+} release to prompt GLP-1 release. Amino acids affect the secretion of GLP-1 by a similar mechanism mediated by Na^+ ions.

Abbreviations: GLUT2, glucose transporter 2; GLP-1, glucagon-like peptide-1; GLP-2, glucagon-like peptide-2; Trpc3, transient receptor potential channel 3, VDCC, voltage-dependent calcium channel; SGLT1, sodium/glucose co-transporter 1.

Pancreatic Insulin Secretion and the GLP-1 Signaling Pathway

Larger amounts of cyclic adenosine monophosphate (cAMP) are resulted from the stimulation of adenylate cyclase by GLP-1r via the activation of GPCRs (Gs).[20] Accumulation of cAMP has been connected to intracellular signaling through protein kinase A (PKA) and other cAMP dependent pathways (eg, EPAC). GLP-1 may trigger a series of processes within the cell, including insulin synthesis, when it activates these pathways.[21–23] Inhibition of ATP-regulated K^+ channels, enhancement of L-type VDCC activity, and activating the non-specific cation channels via PKA and EPAC, are all effects of GLP-1 that have been well-established.[24] These procedures activate the secretion of insulin in response to calcium and increase calcium influx. In instance, preventing the depolarization of the glucose-affected membrane by inhibiting ATP-regulated K^+ channels increase a cell's sensitivity to glucose. Stimulation of phospholipase C (PLC) and protein kinase C (PKC) is associated with heterotrimeric G protein subunit (Gq), which may be triggered by the GLP-1r. Strong evidence for a function for PLC/PKC in promoting insulin secretion can be obtained by imaging cytosolic/submembranous diacylglycerol (DAG), a PKC activator.[25]

It is confirmed that in patients with T2DM, the activity of pancreatic β-cells declines with time, thus, increasing this activity is essential to restore normal insulin secretion. GLP-1 can stimulate β-cells development from human precursor cells in rats, as well as stimulate their proliferation and inhibit their death.[26,27] By activating the transcription and expression of insulin genes via both PKA-dependent and -independent signaling pathways, GLP-1 restores insulin storage and reduces β-cell depletion. Several kinases involved in cell signaling are activated in β-cells as a feedback to

GLP-1 secretion. PKA activation in β-cells controls the insulin gene transcription factor of pancreatic and duodenal homeobox 1 (Pdx-1) by speeding its migration to the nucleus and subsequent uniting to the gene promoter in the nucleus. The GLP-1r activates the PKA pathway, which in turn upregulates the expression of the genes for cyclin D1 and insulin. T-cell factor-like 2 (TCFL2) and β-catenin are essential for this pathway.[28] GLP-1-induced PKA activity controls NFAT transcription factor activation via a calcium/calcineurin mechanism.[29] PKA is a nuclear enzyme that activates cAMP-response element binding protein (CREB), a transcription factor essential for the survival and growth of β-cells. GLP-1 also boosts the growth of β-cells via the CREB-mediated synthesis of insulin receptor substrate-2 (IRS-2), which in turn stimulates the PI3-kinase/Akt/PKB signaling pathway and cyclin D1 expression via cAMP and CREB.[30,31] Moreover, the secretion of betacellulin via non-receptor cytoplasmic tyrosine kinase (Src) stimulates the epidermal growth factor (EGF) receptor, resulting in increased PI3-kinase and Akt/PKB activity and the proliferation of β-cells.[32]

Thus far we are aware that despite food, stimulation of nerve activity, and other hormones can modulate the release of GLP-1. The hormone somatostatin decreases the production of GLP- 1. GLP-1 is rapidly degraded by an enzyme, namely dipeptidyl peptidase-IV (DPP-IV).

Structure and the Active Site of DPP-IV

DPP-IV (Figure 2a) is a transmembrane glycoprotein serine dipeptidyl dipeptidase. This enzyme catalyzes the breakdown of GLP-1 to generate GLP-1 amide and the N-terminal histidine–alanine dipeptide. The primary structure of this enzyme reveals a short amine-terminal cytoplasmic domain of 6 amino acid residues, a longer transmembrane domain of 22 amino acid residues, and a larger portion of 738 amino acid residues. The catalytic domain (amino acid residues 506–766), a short flexible stalk (amino acid residues 29–39), and areas rich in glycosylation (amino acid residues 101–350) and cysteine (amino acid residues 55–100, 351–497) make up the extracellular domain.[33] DPP-IV consists of a β-propeller and a catalytic α/β hydrolase, consists of the catalytic triad Ser630, Asp708, and His740, in its extracellular domains. The β-propeller is composed of highly glycosylated (where adenosine deaminase attached to) and cysteine-rich sections. Most of the DPP-IV activity in plasma comes from membrane-free DPP-IV protein, which can be cleaved by metalloproteases (MMPs).[33,34]

The active site of DPP-IV comprises of S2, S1, S'1, S'2 subsites and the S2 extended subsite (depicted in Figure 2b). S2 extensive subsite composed of Val207, Ser209, Phe357, and Arg358. S2 subsite composed of Arg125, Phe357, Arg358 as well as Glu205, Glu206, and Arg669. S1 subsite composed of Val711, Trp659, Tyr662, Ser630, Val656 Tyr666, and Asn710. S'1 subsite composed of Pro550, Ser630, Phe357, Tyr547, Tyr631, and Tyr666. S'2 subsite composed of Trp629, Tyr547, His740, and Ser630.

Because of these subsites, DPP-IV inhibitors were classified into: (1) class I inhibitors which establish interactions with the core S1 and S2 subsites and form a covalent bond with Ser630 in the catalytic triad; (2) class II inhibitors which occupy the S1' and/or S2' subsites in addition to the S2 subsite; and (3) class III inhibitors which build interactions with the S1, S2, and S2 extensive subsites. By creating salt bridges, DPP-IV inhibitors have a profound effect on the S2 subsite amino acids Glu206 and Glu205. Glu206 and Glu205 are the residues with which sitagliptin, an established DPP-IV inhibitor, forms the strongest bonds, through the amine group in the drug. In the S1 subsite, Tyr662 and Tyr666 interact weakly with the trifluorophenyl ring of sitagliptin. Interaction between the triazolopyrazine moiety of sitagliptin and Phe357 is strong due to the presence of π-π stacks interaction. There is also moderate interaction between the CF3 group of sitagliptin and Arg358.[35–37]

Adverse events (AEs) linked with DPP-IV inhibitors (sitagliptin, saxagliptin, linagliptin, vildagliptin, and alogliptin) extracted from the FDA Adverse Event Reporting System (FAERS) from 2004 to 2019 were defined as gastrointestinal nonspecific inflammation and dysfunctional conditions, hypersensitivity, severe cutaneous adverse reactions, and noninfectious diarrhoea.[38] The reported adverse events of DPP-IV inhibitors have led to the perspective of finding effective and safe add-on medicinal plants.

Plant-Based DPP-IV Inhibitor with Antioxidant Properties

DM and its complications, including insulin resistance and insufficiency, have been linked to oxidative stress (OS), thus, this disease may be related to decreased levels of antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px). Lack of these enzymes may give rise to the production of reactive oxygen

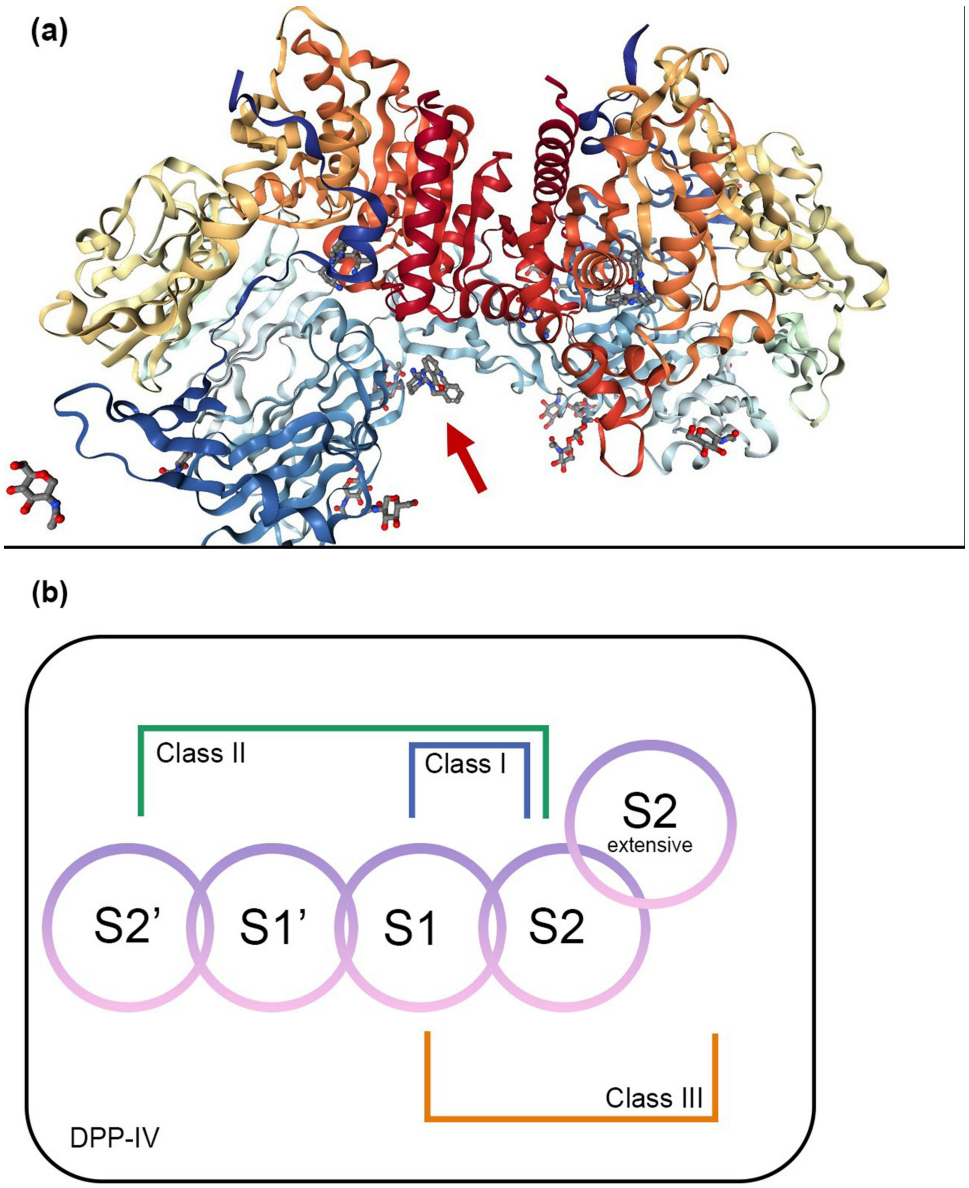

Figure 2 (**a**) 3D structure of human dipeptidyl peptidase-IV in complex with a potent selective inhibitor, alogliptin (indicated by red arrow) (PDB ID 2ONC; PDB DOI https://doi.org/10.2210/pdb2ONC/pdb; Resolution 2.55 Å; deposited by Feng et al, 2007. Total structure weight: 346.99 kDa); (**b**) DPP-IV binding subsites for the inhibitors which are numbered from the cleavage point to the S2, S1, S1', S2', and S2 extensive subsites. Class I inhibitors bind to S1 and S2 subsites; Class II inhibitors to S2', S1', and S2 subsites; Class III inhibitors to S1, S2, and S2 extensive subsites. Adapted from *Biochem Biophys Res Commun*, 434(2), Nabeno M, Akahoshi F, Kishida H, et al. A comparative study of the binding modes of recently launched dipeptidyl peptidase IV inhibitors in the active site. 191–196, Copyright (2013), with permission from Elsevier.[35]

species (ROS) and eventually, the development of diabetes complications via the increase of the susceptibility of tissues to oxidative stress.[39] In patients with DM, glucose and free fatty acids are excessively oxidized to ROS, leading to the intrinsic apoptosis of β-cells. Cytochrome C is then liberated into the cytoplasm followed by the translocation of pro-apoptotic proteins, Bax and Bak, across the mitochondrial outer membrane. Apoptosis is triggered when caspase-9 is activated by cytochrome C, which also activates caspases 3 and 7.[40,41]

Plant-based antioxidants such as kinsenosides and flavonoids have demonstrated antidiabetic activity, and these compounds also help to maintain the health and function of pancreatic β-cells in animal models.[40,41] The expression of pro-apoptotic genes increases in diabetics, while anti-apoptotic gene expression decreases. Flavonoids were reported to protect the growth of β-cells by reducing the expression of these genes.[40] Antioxidants from plants that also inhibit DPP-IV, are thought to be the best way to maintain the function of β-cells thus treating DM.[42]

Plant-Derived DDP-IV Inhibitors from in silico, in vitro, in vivo, to Studies in Humans

Phytoconstituents with health benefits are generally utilized to treat potentially life-threatening diseases. Indigenous plants have been used to treat diabetes long before insulin and other synthetic anti-DM drugs were introduced, and they still become the focus of interest of anti-DM researches.[43] Comprehensive studies of plants with inhibitory activity against DPP-IV are listed in Tables 1–4, respectively.

Allium sativum

Three isolates of *A. sativum* (garlic) tubers, namely caffeic acid 3-glucoside, malonyl genistein, and calenduloside E (oleanolic acid 3-O--d-glucosiduronic acid), were computationally studied to examine their binding mode to DPP-IV. Of the three isolates, caffeic acid 3-glucoside revealed the weakest affinity with a docking score of −7.436 kcal/mol,

Table 1 In silico Study

Plant	Compound Name	Binding Energy (kcal/mol)	Amino Acid Residues Involved in the Interaction (Hydrogen Bond)	Amino Acid Residues Involved in the Interaction (Hydrophobic Bond)	Reference
Liliaceae family					
Allium sativum	Caffeic acid 3-glucoside	−7.436	Asn711, Ser631, Glu203, Tyr548, Glu203, Tyr663, Arg123, His124, Tyr667	N/A	[44]
	Malonylgenistin	−7.438	Val207, Arg358, Ser630, Ser209, Phe357, Tyr662	Tyr662, His740, Tyr666, Val711	
	Calenduloside E	−10.172	Glu204, Ile205, Trp630, Arg123, Tyr548	Phe355, Tyr548, Tyr667	
Malvaceae family					
Urena lobata	β-Sitosterol	−6.59	N/A	N/A	[45]
	Gossypetin	−5.20	N/A	N/A	[45]
	Chrysoeriol	−4.66	N/A	N/A	[45]
	Mangiferin	−7.66	N/A	N/A	[45]
	Stigmasterol	−7.42	N/A	N/A	[45]
Moringaceae family					
Moringa oleifera	Urethane	−84.99	Asn710, Glu205, Glu206	Val656, His704	[46]
	Isothiocyanate	−81.10	His740, Arg125, Ser630, Asn710, Tyr662, Tyr547, Ser630	N/A	[46]
	Dipeptide	−47.36	Tyr547	N/A	[46]
Zingiberaceae family					
Curcuma longa	Calebin A	−98.721	Glu206, Tyr662, Ser552, Cys551, Tyr585	N/A	[47]
	Curcumin	−66.765	N/A	N/A	[48]

(*Continued*)

Table 1 (Continued).

Plant	Compound Name	Binding Energy (kcal/mol)	Amino Acid Residues Involved in the Interaction (Hydrogen Bond)	Amino Acid Residues Involved in the Interaction (Hydrophobic Bond)	Reference
Solanaceae family					
Withania coagulans	Withasomnine	−6.6	N/A	N/A	[49]
	Withanolide E	−7.6	N/A	N/A	[49]
	Withanone	−7.9	N/A	N/A	[49]
	Withaferine A	−8.1	N/A	N/A	[49]
	Withangulatin A	−8.8	N/A	N/A	[49]
	Withacoagulin H	−8.9	N/A	N/A	[49]
	Withanolide D	−9.2	N/A	N/A	[49]
	Withanolide B	−9.5	N/A	N/A	[49]
	Sitoindoside IX	−9.8	N/A	N/A	[49]
Hypoxidaceae family					
Curculigo latifolia	Phlorizin	−10.9	Arg125, Asp545, Asp454, Gln553, Lys554, Trp629	Tyr547	[50]
	Scandenin	−9.3	N/A	Trp629	[50]
	Pomiferin	−9.6	Asp556, Asp560	Trp629	[50]
	Berberine	−8.9	Gln553, Ser630	Tyr547	[50]
	Monobenzone	−7.4	Ser630	N/A	[50]
	Mundulone	−9.3	Ser630, His740	Trp629	[50]
	Dimethycaffeic acid	−7.1	Gln553, Ser630	Tyr547	[50]
Rutaceae family					
Melicope latifolia	Methyl p-coumarate	−5.7	N/A	N/A	[51]
Melicope glabra	Trans-decursidinol	−7.7	Glu206, Arg125, Ser630, Glu205	Glu205, Tyr666	[52]
	Swermirin	−5.4	Lys122, Asp739	His740, Arg125	[52]
	Methyl 3,4,5-trimethoxycinnamate	−5.6	Arg125, Tyr547, Arg669, Val 207, Tyr662	Tyr666, Glu205	[52]
	Renifolin	−7.8	Glu206, Glu205, Asn710, Arg125, Ser630	Tyr547, Phe357	[52]
	4',5,6,7-tetramethoxyflavone	−7.7	Arg125, Ser630, His740, Asn710, Tyr547, Val207	Glu205, Phe357	[52]

(*Continued*)

Table 1 (Continued).

Plant	Compound Name	Binding Energy (kcal/mol)	Amino Acid Residues Involved in the Interaction (Hydrogen Bond)	Amino Acid Residues Involved in the Interaction (Hydrophobic Bond)	Reference
	Isorhamnetin	−7.8	Glu206, Arg358, Tyr547	Phe357, Tyr666	[52]
	Quercetagetin-3,4'-dimethyl ether	−7.9	Ser209, Arg125, Tyr631	Glu205, Glu206, Tyr666, Phe662	[52]
	5,3',4'-trihydroxy -6,7-dimethoxyflavone	−8.1	Glu206, Arg125, Asn710, His740, Ser630	Glu205	[52]
	2-methoxy-5-acetoxyfruranogermacr-1(10)-en-6-one	−6.3	His126, Arg125	Glu205, Tyr666, Phe357	[52]
Apiaceae family					
Angelica keiskei	4-hydroxyderricin	−7.42	Glu206	Phe357	[53]
	Xanthoangelol	−7.81	Glu205, Glu206	Phe357	[37]
Fabaceae family					
Glycyrrhiza uralensis	Licochalcone A	−6.16	Glu203	N/A	[54]
	Licochalcone B	−6.29	Arg123, Ser631, Arg670, His741	N/A	[54]

Abbreviation: N/A, Not applicable.

Table 2 In vitro Study Using Human DPP-IV Inhibitory Screening Kit

Plant (Family)	Plant Part Used/ Compound Used	Solvent	IC_{50} in µg/mL or % Inhibitory	Reference
Allium sativum	Tubers	Methanol	70.88 µg/mL	[44]
Urena lobata	Roots and leaves	Ethanol	1.65 mg/mL	[45]
Momordica charantia	Fruits	Water	28.15%	[55]
Moringa oleifera	Isothiocyanate	N/A	157.694 µM	[46]
Camellia sinensis	Leaves	Water	59%	[56]
Curcuma longa	Calebin A	N/A	55.9%	[47]
	Curcumin	N/A	50%	[48]
Morus alba	Leaves	Water	480 µg/mL	[57]
Withania coagulans	Fruits	Ethanol	63.2%	[49]
Curculigo latifolia	Roots	Water	66.15%	[50]
	Fruits	Water	42.79%	[50]
Eugenia jambolana	Fruits	N/A	278.94 µg/mL	[58]
Gymnema sylvestre	Leaves	N/A	773.22 µg/mL	[58]

(*Continued*)

Table 2 (Continued).

Plant (Family)	Plant Part Used/ Compound Used	Solvent	IC_{50} in µg/mL or % Inhibitory	Reference
Pterocarpus marsupium	Bark	N/A	273.73 µg/mL	[58]
Glycyrrhiza uralensis	Licochalcone A	N/A	347.93	[54]
	Licochalcone B	N/A	797.84	[54]
Melicope latifolia	Bark	Chloroform	37.16 µg/mL	[51]
	Methyl p-coumarate	N/A	911.44 µM	[51]
Melicope glabra	Leaves	Chloroform	169.40 µg/mL	[52]
	Bark	Chloroform	332.31 µg/mL	[52]
Taraxacum officinale	Whole plant	Acetone	44.85%	[55]
	Whole plant	Ethanol	43.69%	[55]
Coptis chinensis	Berberine	N/A	13.3 µM	[59]
Angelica keiskei	Yellow sap	Ethanol	5.94 µg/mL	[37]
	Yellow sap	Ethyl acetate	34.03 µg/mL	[37]
	Xanthoangelol	N/A	10.49 µM	[37]
	4-hydroxyderricin	N/A	81.44 µM	[53]

Table 3 In vivo Study

Plant	Model Category	Dose	Duration of Treatment (Days)	Result	Reference
Liliaceae family					
Allium sativum	STZ-induced SD rats	500 mg/kg BW	56	↓Blood glucose, ↑ insulin serum, ↓ HbA1C	[60]
Malvaceae family					
Urena lobata	High fructose diet-induced Sprague-Dawley rats	1000 mg/kg	28	↑GLP-1 bioavailability, ↓blood glucose, ↑insulin serum	[61]
Cucurbitaceae family					
Momordica charantia	STZ-induced Wistar rats	10%	84	↓Fasting blood glucose, ↑insulin-positive pancreatic beta cells	[62]
Moringaceae family					
Moringa oleifera	Alloxan-induced Sprague-Dawley rats	50 mg/day	56	↓Blood glucose	[63]
Theaceae family					
Camellia sinensis	High fat diet Sprague-Dawley rats	250 mg/5 mL per kg	9	↑Oral glucose tolerance, ↑insulin serum, ↑β-cell mass	[56]

(*Continued*)

Table 3 (Continued).

Plant	Model Category	Dose	Duration of Treatment (Days)	Result	Reference
Moraceae family					
Morus alba	STZ-induced Wistar rats	0.5 g/kg/day	28	↓Blood glucose, ↑insulin serum	[64]
Solanaceae family					
Withania coagulans	High sucrose-induced Wistar rats	400 mg/kg	28	↑β-cell mass, ↓blood glucose, ↑insulin serum, ↑% insulin sensitivity	[49]
Hypoxidaceae family					
Curculigo latifolia	High fat diet and STZ-induced Sprague-Dawley rats	200 mg/kg	28	↑Insulin serum, ↓plasma glucose	[61]
Myrtaceae family					
Eugenia jambolana	STZ-induced Wistar albino rats	15 mg/kg	56	↓Fasting blood glucose	[58]
Apocynaceae family					
Gymnema sylvestre	STZ-induced Wistar rats	120 mg/kg	21	↑Insulin serum, ↓blood glucose	[65]
Fabaceae family					
Pterocarpus marsupium	STZ-induced Wistar rats	1%	60	↑Insulin serum, ↓blood glucose	[66]
Asteraceae family					
Taraxacum officinale	STZ and nicotinamide-induced Wistar rat	1000 mg/kg polyherbal with Momordica charantia extract	28	↓Blood glucose	[55]
Ranunculaceae family					
Coptis chinensis	STZ and high glucose-induced Wistar rats	180 mg/kg	168	↓Fasting blood glucose, ↓glycosylated hemoglobin	[67]
Apiaceae family					
Angelica keiskei	STZ-induced mice	800 mg/kg	28	↓Fasting blood glucose	[68]

Notes: ↓ = Decrease; ↑ = Increase.
Abbreviation: STZ, Streptozotocin.

compared to that of malonyl genistein and calenduloside E which was −7.438 kcal/mol and −10.172 kcal/mol, respectively. Moreover, the in vitro testing of the tuber extract revealed an inhibition towards DPP-IV (IC_{50} of 70.9 g/mL).[44] In addition in vivo study in streptozotocin-induced rats showed a significant elevation of blood insulin and a reduction in blood glucose and HbA1c levels at week-8 post fresh garlic extract intervention.[60] Randomized controlled trials involving sixty T2DM patients revealed a significant decrease of fasting plasma glucose (FPG), total cholesterol, LDL-C, triglycerides in 6 weeks after garlic powder tablets administration.[69]

Table 4 Studies in Human

Plant	Dosage Form	Sample Size (Patients)	Gender Male (%)	Clinical Conditions	Standard Drug	Design of the Study	Length of Therapy (Days)	Efficacy or Clinical Outcomes	Adverse Effect	Reference
Liliaceae family										
Allium sativum	Garlic tablets	60	55%	T2DM with fasting blood sugar level between 100 to 130 mg/dL.	Metformin	Single-blind and placebo-controlled study. **Intervention group** (n=30) garlic tablet 300 mg three times daily and metformin 500 mg twice daily. **Control group** (n=30) placebo and metformin 500 mg twice daily	168	Reduction in fasting blood sugar, total cholesterol, LDL-C, triglycerides.	No AE and SAE was observed	[69]
Cucurbitaceae family										
Momordica charantia	Bitter melon capsules	90	55.6%	T2DM diabetes, a glycosylated hemoglobin (HbA1c) level no greater than 7.5%	N/A	Single-center, randomized, double blind, placebo-controlled study. **Intervention group** (n=62) bitter melon capsules 2380 mg/day. **Control group** (n=28) placebo	84	Reduction in fasting blood sugar	Gastrointestinal symptoms, including anorexia, nausea, abdominal discomfort, and soreness; foamy urine; and skin rashes. No clinically SAE was observed	[70]
Moringaceae family										
Moringa oleifera	Leaf powder	27	N/A	T2DM for at least 1 year	N/A	**Intervention group** (n=14) meal supplemented with 20 g of *Moringa oleifera* leaf. **Control group** (n=13) placebo	180	Reduction in blood glucose level	N/A	[71]

(*Continued*)

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Table 4 (Continued).

Plant	Dosage Form	Sample Size (Patients)	Gender Male (%)	Clinical Conditions	Standard Drug	Design of the Study	Length of Therapy (Days)	Efficacy or Clinical Outcomes	Adverse Effect	Reference
Moraceae family										
Morus Alba	1-deoxynojirimycin (DNJ) in mulberry leaves powder	85	20%	Obese persons (BMI ≥ 25 kg/m2) aged 20–65 years, who had FPG of 100–140 mg/dL and/or 2-h PPG following a 75 g oral glucose tolerance test (OGTT) of 140–199 mg/dL	N/A	Randomized controlled clinical study. **Intervention group** (n=64) 3 groups, single dose of 50 g sucrose solution (150 mL), mixed with mulberry leaf powder at weights 2.3; 4.6; 6.9 g. **Control group** (n=21) 1 group of placebo.	84	Reduction in fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c)	Gastrointestinal symptoms including bloating, flatulence, and loose stools, did not cause alteration in hepatic and renal function, no SAE was observed.	[72]
Myrtaceae family										
Eugenia jambolana	Fruits tablet (GlycaCare-II® polyherbal supplement)	69	47.8%	Prediabetes and newly diagnosed T2DM. Prediabetes was classified as per American diabetes association criteria HbA1c 5.7–6.4% and FBS between 100 mg/ dL to 125 mg/dL. Newly diagnosed T2DM patients had an HbA1c value of 6.5–7.5% and FBS>125 mg/dL	Metformin	Randomized, double-blind, active-controlled clinical trial. **Intervention group** prediabetic (n= 17) GlycaCare-II 522.5 mg twice daily, newly diagnosed T2DM (n= 24) GlycaCare-II 522.5 mg twice daily. **Control group** prediabetic (n=17) metformin 500 mg a day, newly diagnosed T2DM (n=16) metformin 500 mg a day	120	Reduction in Fasting blood glucose, HbA1C, and Postprandial blood glucose	No AE and SAE was observed	[73]

Fabaceae family										
Pterocarpus marsupium	Bark tablet (GlycaCare-II® polyherbal supplement)	69	47.8%	Prediabetes and newly diagnosed T2DM. Prediabetes was classified as per American diabetes association criteria HbA1c 5.7–6.4% and FBS between 100 mg/ dL to 125 mg/dL. Newly diagnosed T2DM patients had an HbA1c value of 6.5–7.5% and FBS>125 mg/dL	Metformin	Randomized, double-blind, active-controlled clinical trial. **Intervention group** prediabetic (n= 17) GlycaCare-II 522.5 mg twice daily, newly diagnosed T2DM (n= 24) GlycaCare-II 522.5 mg twice daily. **Control group** prediabetic (n=17) metformin 500 mg a day, newly diagnosed T2DM (n=16) metformin 500 mg a day	120	Reduction in Fasting blood glucose, HbA1C, and Postprandial blood glucose	No AE and SAE was observed	[73]
Apocynaceae family										
Gymnema sylvestre	Leaves capsules	16	N/A	T2DM with fasting blood sugar level was 125 mg/dL or above	N/A	**Intervention group** (n=8) 1 g/day dosage (in two divided doses 12 hourly). **Control group** (n=8) placebo	30	Reduction in fasting blood glucose	No AE and SAE was observed	[74]
Asteraceae family										
Taraxacum officinale	Root capsules (SR2004 polyherbal supplement)	119	58.2%	T2DM and any combination of oral hypoglycemics and/ or insulin with a HbA1c 7.1–10% in the last 6 months, body mass index (BMI) < 45 kg/m^2	N/A	Single center, unblinded, prospective interventional study. **Intervention group** (n=119) 10% Taraxacum, 2 capsules three times a day, 30 minutes before meals taken with water.	84	Reduction in blood glucose and HbA1C	Minor abdominal symptoms reported in sixteen patients (16%), no SAE was observed.	

(*Continued*)

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Table 4 (Continued).

Plant	Dosage Form	Sample Size (Patients)	Gender Male (%)	Clinical Conditions	Standard Drug	Design of the Study	Length of Therapy (Days)	Efficacy or Clinical Outcomes	Adverse Effect	Reference
Zingiberaceae family										
Curcuma longa	Curcumin capsules	53	39.6%	T2DM, noninsulin dependent diabetic, aged between 40 and 70 years old and BMI 18.5–35 kg/ m^2 with a diagnose of 1 to 10 years	N/A	Randomized, double-blind, placebo-controlled trial. **Intervention group** (n=25) three capsules of 500 mg curcumin. **Control group** (n=28) placebo	70	Reduction in fasting blood glucose	No AE and SAE was observed	[75]
Ranunculaceae family										
Coptis chinensis	Berberine pills	201	61.7%	Newly diagnosed T2DM	N/A	Randomized, double-blind, placebo-controlled trial. **Intervention group** (n=98) Berberine 0.6 g per 6 pills, twice daily before meal. **Control group** (n=103) placebo	336	Reduction in fasting blood glucose and HbA1C	Gastrointestinal symptoms, no SAE was observed	[76]

Abbreviations: AE, Adverse effect; N/A, Not applicable; SAE, Serious adverse effect; T2DMm, Type 2 diabetes mellitus.

Momordica charantia

The unripe fruit of *M. charantia* L. (Cucurbitaceae), generally known as bitter melon, is used as a vegetable in the tropics and subtropics countries. The aqueous extract of *M. charantia* fruits inhibited 28.15% of DPP-IV by in vitro assay.[55] The number of pancreatic β-cells was reported to increase after oral doses of *M. charantia* in streptozotocin-induced diabetic Wistar rats. There was also a significant reduction in FPG.[62] A randomized, placebo-controlled study involving 66 T2DM patients showed a reduction of FPG after 12 weeks of *M. charantia* supplements.[70]

Moringa oleifera

M. oleifera is abundant in both macronutrients and micronutrients, in addition to other bioactive constituents, all of which are essential for maintaining the body's normal functioning and warding off certain diseases. In silico study of isothiocyanate which was found in the seed and leaf of *M. oleifera* indicated the formation of hydrogen bonds with His740 in S'2 subsite, Arg125 in S2 subsite, and Ser630, Asn710, and Tyr662 in S1 subsite of DPP-IV. The benzene ring of isothiocyanate builds a pi–pi interaction at with Phe357 in the S'1 subsite with binding energy of −81.10 kcal/mol. Isothiocyanate also inhibited DPP-IV with IC_{50} values of 157.694 μM.[46] Furthermore, an in vivo study in alloxan-induced Sprague-Dawley rats exhibited diminished blood glucose levels after treatments with *M. oleifera* leaves.[63] The hypoglycemic effect of *M. oleifera* leaves in seventeen T2DM patients has confirmed a reduction of blood glucose level.[71]

Morus alba

The IC_{50} of aqueous extract of *M. alba* leaves for DPP-IV inhibitory activity assay was 480 g/mL.[57] Significant hypoglycemic effects, as measured by lower blood glucose and increased insulin concentration, were also reported in streptozotocin-induced Wistar rats.[64] Obese people (BMI 25 kg/m^2) with FPG between 100–140 mg/dL and/or 2 hours postprandial glucose between 140–199 mg/dL fared well in human study. FPG and HbA1c were shown to be lowered by consuming *M. alba* leaves.[72]

Eugenia jambolana

E. jambolana Lam., or black plum, has been proven for its inhibitory activity against DPP-IV enzyme by in vitro, having an IC_{50} value of 278.94 g/mL.[58] In streptozotocin-induced diabetic rats a substantial decrease in FPG was announced after a treatment with α-hydroxy succinamic acid, an active component isolated from the fruit-pulp of *E. jambolana*.[77] *E. jambolana* fruits extract in the form of polyherbal tablets (GlycaCare-II®) was shown to reduce HbA1c, postprandial blood glucose, and FPG by a statistically significant result in prediabetic and newly diagnosed diabetic patients for 120 days.[73]

Pterocarpus marsupium

The heartwood of the *P. marsupium* plant was reported for its DPP-IV inhibitory activity with an IC_{50} value of 273.73 g/mL.[58] Supplementation with *P. marsupium* bark extracts significantly elevated insulin serum and reduced blood glucose in streptozotocin-induced Wistar rats.[66] *P. marsupium* bark extract in the form of polyherbal tablets (GlycaCare-II®) was shown to significantly lower HbA1c, FPG, and postprandial blood glucose in both prediabetic and newly diagnosed diabetic patients when administered twice daily for 120 days.[73]

Gymnema sylvestre

G. sylvestre, which grows wild in many countries of Asia, Africa, and Australia, is still consumed as a nutritional supplement because of the numerous health benefits. It is widely used in both conventional medicine and alternative like Ayurveda to lower blood sugar levels.[78] In vitro results of *G. sylvestre* leaves extracts confirmed a potential DPP-IV inhibitor with an IC_{50} value of 773.22 μg/mL.[58] Tthe aqueous fraction of *G. sylvestre* ethanol extract significantly dropped the serum glucose and lipids in streptozotocin-induced, high-fat-induced obesity rats.[65] As a supplement, *G. sylvestre* reduced glucose by 37%, cholesterol by 13%, transglutaminase by 5%, and low-density lipoproteins (LDL) by 19%, according to a human study including 32 adult patients with T2DM.[74]

Taraxacum officinale

In many countries, *T. officinale* is consumed as food, while in others, it is utilized in medicinal applications for the management and treatment of T2DM.[79] The acetone extract of *T. officinale* showed the strongest inhibitory activity against DPP-IV followed by the ethanol extract by in vitro study. In streptozotocin-nicotinamide-induced diabetic rats, a polyherbal combination of *T. officinale* and *M. charantia* ethanol extracts was successful in decreasing plasma glucose comparable to glibenclamide and metformin.[69] A single-center, unblinded, prospective interventional study conducted on 119 patients with T2DM treated with SR2004, containing the root extract of *T. officinale* in combination with other plants for 12 weeks, confirmed a reduction of HbA1c, blood glucose, total cholesterol, and serum triglycerides.[80]

Curcuma longa

The rhizomes of *C. longa* L. have been utilized in India and China as an effective treatment for diabetes. Curcumin, the major component in turmeric, exhibits strong anti-oxidative, anti-inflammatory, and anticancer properties.[81] Docking scores of curcumin, which is targeted to DPP-IV for the purpose of lowering blood glucose, resulted a value of −66.765 kcal/mol indicating that the binding site for curcumin is most stable in S1, whereas S2 and S3 require stronger connections.[48] Calebin A, another constituent of *C. longa*, interacts with the active site residues of DPP-IV, with the side-chain carboxylate oxygen and backbone carbonyl group of Glu206 in S2 subsite, Ser552, Cys551, and Tyr585 (docking score of −98.72 kcal/mol).[47] An in vitro study towards the DPP-IV showed that curcumin had a higher inhibitory rate than that of P32/98 and resveratrol.[48] The inhibitory rate of calebin A showed a maximum % inhibition of 55.9% at 26.3 mM.[47] Moreover, a study in fifty-three T2DM patients treated with either 1500 mg of curcumin or a placebo capsule 3x/day for 10 weeks resulted in a considerably reduced mean values for BMI, abdominal circumference, and FPG in curcumin-treated patients. Homeostatic Model Assessment of Insulin Resistance or Pancreatic B Cell Function (HOMA-IR or HOMA-B) demonstrated no difference, as were HbA1c, insulin, malondialdehyde, total antioxidant capacity, or pancreatic β-cell function.[75]

Coptis chinensis

C. chinensis has been traditionally used to lower blood sugar in China. Berberine is its main active component.[82] Berberine was reported could inhibit human recombinant DPP-IV (IC_{50} of 13.3 M).[59] *C. chinensis* (80, 120, and 180 mg/kg) showed significant decrease in HbA1c, free fatty acid, total cholesterol, apolipoprotein B, and triglyceride of diabetic-induced animal models.[67] Treatment with berberine 2x/day for 12 weeks resulted in a significant decrease in FPG and HbA1c in 98 T2DM patients.[76]

Conclusion

To prevent the breakdown of GLP-1 and maintain blood glucose levels, *Allium sativum, Momordica charantia, Moringa oleifera, Morus alba, Eugenia jambolana, Pterocarpus marsupium, Gymnema sylvestre, Taraxacum officinale, Curcuma longa, and Coptis chinensis* have established their functional role at molecular level, by in vitro, and in vivo studies. Moreover, these plants have proven their effectiveness through studies in humans. Based on our findings *Allium sativum* (caffeic acid 3-glucoside, malonylgenistin, calenduloside E as the active constituents), *Morus Alba, Curcuma longa* (calebin A and curcumin), *Pterocarpus marsupium*, and *Taraxacum officinale* have confirmed the best potential earning them a prominent place in DPP-IV inhibitor discovery. Regeneration of pancreatic β-cell mass and their mechanism to prevent oxidative stress in T2DM are additional benefits.

Abbreviations

A *sativum, Allium sativum*; ADA, adenosine deaminase; AE, Adverse effect; *C. chinensis, Coptis chinensis. C. longa, Curcuma longa*; cAMP, cyclic adenosine monophosphate; CAT, catalase; CCK, cholecystokinin; CREB, cAMP-response element binding protein; DAG, diacylglycerol; DM, diabetes mellitus; DPP-IV, dipeptidyl peptidase-IV; *E. jambolana, Eugenia jambolana*; EECs, enteroendocrine cells; EGF, epidermal growth factor; EPAC, exchange protein directly activated by cAMP; *G. sylvestre, Gymnema sylvestre*; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, Glucagon-like peptide 1; GSH-Px, glutathione peroxidase; HbA1c, glycated hemoglobin; *M. oleifera, Moringa oleifera;*

M.alba, Morus alba; M.charantia, Momordica charantia; MMPs, metalloproteases; N/A, not applicable; NTS, nucleus tractus solitarii; OS, oxidative stress; Pdx-1, pancreatic and duodenal homeobox 1; *P. marsupium, Pterocarpus marsupium*; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; PYY, peptide YY; RNS, reactive nitrogen species; ROS, reactive oxygen species; SAE, serious adverse effect; SGLT, sodium-coupled glucose transporters; SOD, superoxide dismutase; STZ, streptozotocin; *T. officinale, Taraxacum officinale*; T2DM, type 2 diabetes mellitus; TCFL2, T-cell factor-like 2; VDCC, voltage dependent calcium channels; Wnt, wingless/integrated; βTC, betacellulin.

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Disclosure

The authors state that they have no conflicts of interest.

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