Journal of Pharmacognosy and Phytochemistry

Available online at www.phytojournal.com

E-ISSN: 2278-4136
P-ISSN: 2349-8234
JPP 2015; 4(1): 197-202
Received: 15-03-2015
Accepted: 17-04-2015

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GLP-1 secretagogues potential of medicinal plants in management of diabetes

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Abstract
Increase in prevalence of Diabetes Mellitus (DM) is a major public health problem. It is a progressive disorder which commonly requires multiple pharmacotherapy for managing blood glucose and other DM related complications. Use of incretin based therapy is a potential solution for management of Type 2 DM (T2DM). Glucagon Like Peptide (GLP-1) is a incretin hormone which enhances serum insulin after food intake. Insulin resistance and T2DM are associated with impaired postprandial secretion of GLP-1. Recently GLP-1 agonists have shown good therapeutic potential in management of T2DM and reliving T2DM related complications. Owing to high cost of treatment and general toxicity in long term use of GLP-1 agonists, enhancing endogenous GLP-1 secretion is a good alternative. Hence, there is search for GLP-1 receptor agonists which may enhance GLP-1 production. Recently, GLP-1 secretagogues activity of medicinal plants has been reported. Increase in GLP-1 secretion by phytochemicals may help in management of T2DM with lesser side effects and low cost as compared to the GLP-1 agonists of synthetic origin. Present review is a compilation of GLP-1 secretory activity of medicinal plants, the assay system for activity studies and effective dose/concentration. Wherever reported, Phytochemicals with potential GLP-1 secretory activity has also been incorporated in the review. *Mangifera indica, Glycine max, Cinnamomum zeylanicum, Pinus koraiensis, Ilex paraguariensis, Berberis vulgaris* and *Prunus africana* showed promising activity *in vitro* and *in vivo* assay systems.

Keywords: Diabetes, GLP-1, Medicinal Plants

1. Introduction
Diabetes mellitus (DM) is one of the most common metabolic disorder characterized by hyperglycemia and related complications. It is estimated that currently 200 million people are affected by DM [1]. It is estimated that that by 2025, more than 300 people globally will have confirmed DM and other 50 million will be undiagnosed [2, 3].
The disorder is already declared epidemic by WHO. DM is characterized by deficiency in production of insulin by the β-cells in pancreas (Type I), or by the ineffectiveness of the produced insulin (Type II) [4]. The discovery of insulin has revolutionized the diabetes care and this hormone is currently the drug of choice for patients with type I and type II diabetes as well. But insulin therapy suffers disadvantage of painful injections, weight gain, hypoglycemia and its excess dose may lead to coma or death [5]. A number of oral hypoglycemic agents with varied mechanism of action ranging from enhancing insulin production to insulin sensitivity have developed in recent times [6].
The 'incretin effect' is relatively recently discovered phenomenon in management of T2DM. The effect is known as enhanced insulin secretion by intestinal hormones, glucagon-like peptide (GLP)-1and glucose-dependent insulinotropic hormone (GIP) after food intake [7].The incretin effect is very important for maximizing insulin responses which is an important factor in glucose homeostasis by promoting insulin secretion immediately on meal ingestion, thereby making limited postprandial glucose excursions.
It has previously been reported that there is impaired secretion of GLP-1 in T2DM patients [8]. Exogenous introduction of GLP-1 significantly stimulates and may even restore to normal glucose-induced insulin secretion in patients with diabetes and reduction in GLP-1 secretion is likely to result in an impaired insulin secretion [9].
Glucagon-like peptide 1 (GLP-1) is a 30-amino acid peptide hormone produced from the intestinal endocrine epithelial L-cells, that potently stimulates glucose-dependent insulin secretion. GLP-1 rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4), which is an integral membrane glycoprotein consisting of 766 amino acids and is widely distributed throughout the body. The glucose-dependent nature of GLP-1 is an efficient protective

measure against DM. The glucose competence concept describes the mutual interdependence between glucose metabolism and GLP-1 actions on β-cells i.e, glucose is required for GLP-1 secretion, and GLP-1 is required to make β-cells competent to respond to glucose [10]. This improves the ability of β-cells to sense and respond to glucose in subjects with impaired glucose tolerance [11]. In addition to stimulate insulin secretion, GLP-1 also plays important role in transcription of proinsulin gene and insulin biosynthesis [12, 13]. DPP-4 is regarded as a proteolytic enzyme involved in the inactivation of bioactive peptides, particularly in relation to immune-modulation and glucose homeostasis [14, 15] by degradation of GLP-1 by removal of the N-terminal dipeptide. Since the N-terminal end of GLP-1 is required for biological activity [16] these results show that DPP-4 mediates the inactivation of the hormones. The inactivation of GLP-1 by DPP-4 is rapid, which is due to the localization of the enzyme in capillaries close to the intestinal cells where the hormones are produced [17] as well as the high abundance of the enzyme in the vasculature, circulation and liver [14]. DPP-4 inhibitor prolongs and enhances GLP 1 activity that plays an important role in insulin secretion and blood glucose control regulation.

2. GLP-1 in management of diabetes mellitus

Incretin based therapy would be a novel and complementary approach to diabetes management for many reasons. An incretin based medication would be the first antidiabetic agent to stimulate insulin secretion without causing hypoglycemia or weight gain. Current research suggests that GLP-1 is the most important hormone with incretin potential. Their action is terminated by enzymes known as dipeptidyl peptidase-4 (DPP-4). The observation that the incretin response may be diminished in individuals with T2DM has led to advances in the management of this disease. Agents that act as GLP-1 inducres (metformin) or mimetics (exenatide and liraglutide) improve glycated hemoglobin levels either as monotherapy or in combination with other agents. Importantly, these agents either leads to weight loss or are weight neutral and are associated with a low risk of hypoglycemia—properties that further contribute to their clinical utility.

Since half life of GLP-1 is 2-3 minutes, relatively stable GLP-1 agonists may be a drug of choice. Metformin has been used to control hyperglycemia in patients with T2DM, and it is currently recommended as the first-line drug treatment along with lifestyle modification [18]. Metformin is now increasingly being used in combination with new incretin-based therapies: glucagon-like peptide 1 (GLP-1) analogues and dipeptidyl peptidase-4 (DPP-4) inhibitors [19–20], both of which enhance pancreatic beta cell function. Interestingly, there have been a few reports suggesting a direct interaction between metformin and the incretin axis [21–23]. It was also reported that metformin acutely and selectively increased plasma levels of GLP-1 [7–24] amide [7–25] after an oral glucose load [26], while it did not increase plasma levels of the other incretin hormone, glucose-dependent insulinotropic polypeptide (GIP), or peptide YY, a gastrointestinal hormone co-localised with GLP-1 in L cells [27]. Therefore, the action of metformin on the gut endocrine system may be L cell specific and, more precisely, GLP-1-specific. Moreover, it has recently been reported that metformin inhibits the apical sodium-dependent bile acid transporter and thus may increase the concentration of bile acids in the intestine [28], which could stimulate GLP-1 secretion from L cells via the G-protein-coupled receptor TGR5 [29]. Alternatively, DPP-4 activity might be inhibited by metformin, resulting in an increase in GLP-1 levels in the plasma. Indeed, DPP-4 activity in the circulation has been reported to be reduced in rodents or humans treated with metformin [30, 31] which may be due to degradation of DPP-4 or act as a competitive inhibitor against DPP-4 to prevent degradation of GLP-1.

Exenatide is a synthetic version of the naturally occurring peptide exendin-4, a salivary protein found in the Gila monster, having homology with native human GLP-1 but is resistant to the action of DPP-4 [32, 33]. The drug has been approved by the US Food and Drug Administration (FDA) in April 2005, and the European Medicines Evaluation Agency (EMEA) in November 2006 for use as add-on to metformin and/or sulphonylureas for the treatment of T2DM. In December 2006 the FDA permitted to use exenatide with Thiazolidinediones (TZDs) [34, 35] and with or without metformin [35, 36]. Few side effects of exenatide such as nausea and vomiting have been reported. Six cases of haemorrhagic or necrotizing pancreatitis have also been reported [37].

Liraglutide is a synthetic analogue of human GLP-1 with 97% homology but is resistant to the action of the enzyme DPP-4. Liraglutide (Victoza) has been approved by the FDA in 2010 for use as second line therapy or as add-on therapy to oral antidiabetic agents [38], while the EMEA approved its use in June 2009, as add-on therapy to metformin and or sulphonylureas, and TZDs [34]. There was no significant effect of renal or hepatic impairment on the safety or side effect profile of liraglutide [24, 25].

Although the GLP-1 agonists are very recent class of drugs available for management of DM, serious type of side effects such as pancreatitis and renal and hepatic impairments have raised doubt about their safety.

3. Role of medicinal plants in enhancing GLP-1 level

The plant kingdom is a good potential source for the discovery of novel medicines to treat numerous diseases including DM. The literature survey shows the use of about 400 plants and 700 plant based recipes for the management of DM throughout the world [39-41]. Regeneration of β cells and enhancement of insulin secretion form pancreas, increase in glucose uptake by muscles and adipose tissue, decrease in gluconeogenesis and decrease in intestinal α- glucosidase have been proposed as the mechanism of antidiabetic action of medicinal plants [42]. Recently GLP-1 modulatory activity has been reported in medicinal plants [43-46]. The plants exhibiting GLP-1 inducing activity hold the promise of management of DM. Table 1 summarizes the details of medicinal plants possessing GLP-1 inducing activity.

Table 1: Medicinal plants with GLP-1 inducing level

Common Name	Botanical Name	Family	Part used:	Dose/ Concentration	Animal model	Phytochemicals	Mechanism	Author and Year	References
Agave	Agave tequilana Gto.	Agavaceae	Roots	supplementation with 10% fructans	Male C57BL/6J mice	Agave fructan	Agave fructans induced GLP-1 and enhanced concentration of its precursors.	Urías-Silvas *et al.*, 2008	[47]
Barberry	Berberis vulgaris	Berberidaceae	Roots, rhizomes	500mg/kg	Rat	Berberine	Antidiabetic effect of Berberine is produced by increasing insulin secretion and stimulating glycolysis, Berberine also increases glucose transporter-4 (GLUT-4) and GLP-1 levels.	Cicero and Tartagni, 2012	[48]
Bitter melon	Momordica charantia	Cucurbitaceae	Fruit	5000mg/kg	Mice	Karavilagenine E	Higher serum GLP-1, insulin and lower glucose were observed in mice orally administered with a single dose of WES for 30min, indicating that WES stimulated GLP-1 secretion in vivo as well.	Huang *et al.*, 2013	[49]
Cinnamon tree	Cinnamomum zeylanicum	Lauraceae	Bark	3g cinnamon	Humans	cinnamon	Ingestion of 3 g cinnamon reduced postprandial serum insulin and increased GLP-1 concentrations without significantly affecting blood glucose	Hlebowicz *et al.*, 2009	[45]
Gardenia	Gardenia jasminoides	Rubiaceae	Fruit	-	insulin-secreting cell lines (INS-1 cells)	Geniposide (GP)	Geniposide prevents the oxidative stress-induced neuron apoptosis, and improved glucose stimulated insulin secretion by activating glucagon-like peptide 1 receptor (GLP-1R) in INS-1 cells.	Liu *et al.*, 2012	[50]
Korean Pine	Pinus koraiensis	Pinaceae	Seeds	50 µM dose of each FFA.	Human females	Free fatty acids (FFA) and triglycerides (TG)	GLP-1 was higher 60 min after pine nut introduced	Pasman *et al.*, 2008	[51]
Little dragon	Artemisia dracunculus L.	Asteraceae	Leaves	500 mg/kg	KK-A(gamma) mice	Tarralin	The extract was also shown to increase the binding of glucagon-like peptide (GLP-1) to its receptor *in vitro*.	Ribnicky *et al.*, 2006	[52]
Mango	Mangifera indica	Anacardiaceae	Leaves	320µg/ml	*In vitro*		*Mangifera indica* inhibits the DPP-4 and enhance GLP-1 for T2DM.	Yogisha and Raveesha, 2010	[46]
Mate tea	Ilex paraguariensis	Aquifoliaceae	Leaves	50 & 100 mg/kg/d	Male mice	Matesaponin, 3,5-O-dicaffeoyl-D-quinic acid, mate-saponin 2.	Acute administration of major constituents of mate showed significant increases in GLP-1 levels. Compounds (3,5-O-dicaffeoyl-D-quinic acid and matesaponin 2, respectively) and the (a-linolenic acid) showed significant increases in GLP-1 levels.	Hussein *et al.*, 2011	[43]
Pygeum	Prunus africana	Rosaceae	Bark	100, 200 and 400 mg/kg	Wistar rats		It is concluded that this plant increases insulin secretion by lowering DPP-4 activity and hence increasing the half-life of GLP-1.	Suleiman, 2009	[53]
Soybean	Glycine max	Fabaceae	Roots	20 mg/kg	Diabetic mice	Glyceollins	Glyceollins also potentiated GLP-1 secretion to enhance insulinotropic actions in enteroendocrine cells. In conclusion, glyceollins help	Park *et al.*, 2010	[54]
Wheat	Triticum aestivum	Poaceae	Fibers	24g/day	Humans		Increase wheat fibre intake takes many months but eventually results in increased short-chain fatty acids (SCFA) production and glucagon-like peptide-1 (GLP-1) secretion.	Freeland *et al.*, 2010	[44]
Yacon	Smallanthus sonchifolius	Asteracea	Roots	340 or 6800mg FOS/kg bw/ day	Diabetic rats	Fructooligosaccharides	Diabetic rats treated with a diet supplemented with yacon flour the Glucagon like peptide-1 content increases significantly as compared with diabetic control.	Habib *et al.*, 2011	[55]

4. Possible mechanism of glp-1 induction by phytochemicals

The phytochemicals may activate GLP-1 receptor on the enetroendocrine cells of gut, resulting in activation of a series of signal transducers such as G protein α-gustducin, phospholipase C beta 2 (PLCβ2), inositol 1,4,5-trisphosphate receptor type 3 (IP3R3), and transient receptor potential (TRP) channels. These processes eventually results in depolarization of the enetroendocrine cell membrane through elevation of intracellular $Ca2^{+}$ concentration and releases GLP-1. A schematic view of GLP-1 mediated secretion of insulin from beta cells is given in figure 1.

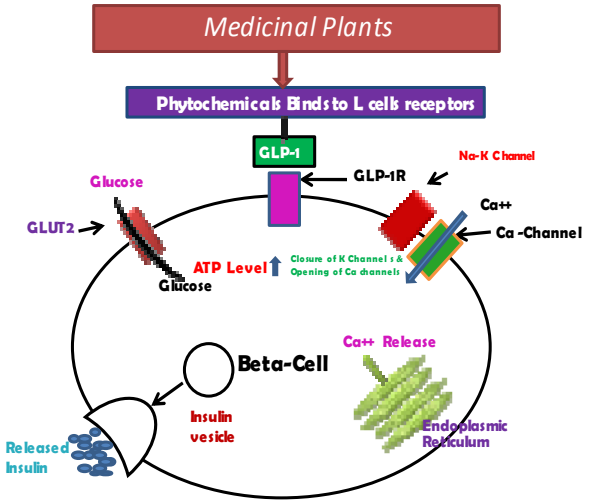

Fig 1: Possible mechanism by which medicinal plants of GLP-1 induction by phytochemicals

5. Conclusions

Long term glucose control is needed to reduce diabetes related complications. Good efficacy, easy in dispensing, low cost of treatment and safety in long term use are the key characteristics of an ideal antidiabetic agent. The drawbacks of the present day antidiabetic drugs necessitated the search for newer drugs with novel mechanism of action. Incretin based antidiabetic therapies are of relatively recent origin and have been used since past few years and improves glycaemic control with good tolerability, beneficial effects on weight and low risk of hypoglycemia. Apart from increase in insulin, GLP-1, preserves human islet morphology and improves beta-cell function. However, the long term safety data for incretin based therapy is not yet as extensive studied as for the traditionally available antidiabetes agents. Gastrointestinal side effects are relatively common with GLP-1 agonists. Nearly 30%-45% of patients experience one or more episodes of nausea, vomiting, or diarrhea.

Medicinal plants inducing GLP-1 activity may help in management of the growing prevalence of T2DM. Phytochemicals not only offers relatively safer alternative but also a low cost solution during long treatment regimen. The present review identifies *Mangifera indica, Glycine max, Cinnamomum zeylanicum, Pinus koraiensis, Triticum aestivum, Ilex paraguariensis, Berberis vulgaris* and *Prunus africana* as the potential source for purification and identification potential drug lead molecules for increasing GLP-1 activity. Good ED/EC50 of *Pinus koraiensis* (50µM), *Mangifera indica* (320µg/ml), *Glycine max* (20 mg/kg) indicated that these plants are potential source of lead drug molecules for increasing GLP-1 level.

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