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Review Article

Incretins mimetic effects of Herbal drugs for management of Diabetes Mellitus: A research based approach

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ABSTRACT

Insulin is a life saving hormone which is secreted from beta cell of Pancreas. It helps to reduce high blood sugar in the blood by trapping the glucose molecule and enter into cell. Now a day, insulin resistance diabetes mellitus (IRDM) becomes a serious public health problem in the world and also a great headache to the scientific communities. That's why, world scientist are enormously seeking the alternative of insulin or insulin like effective drugs. It has been proved that nature is having all remedies to combat disease related morbidity and mortality. We have to search, we have to know, we have to identify and we have to apply appropriate technology to evaluate new molecules, new metabolites or active compounds for reducing the devastating effects of diabetes as well as insulin resistance diabetes mellitus. Evidence based studies showed that berbery, bitter melon, cinnamom tree, gardenia, korean pine, little dragon, mango, pygeum, fenugreek and lychee composed of incretins mimetic compounds. But isolation of active metabolomics and the multicentre base clinical trials are needed to propagate the herbal medicine in the world. It is an attempt to amalgamate, to congregate, to concise some incretins mimetic medicinal plants which will help to get new generic compound and also give new clue for further research on DM.

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INTRODUCTION:

In 1932, La Barre used the word "incretin" to refer an extract from upper gut mucosa that produce hypoglycemia (1). Incretins are a group of metabolic hormones which are having mimetic effect of insulin. It helps to increase the amount of secretion of insulin from the pancreatic cells of Islets of Langerhan's after meal. It also play vital role for reducing the rate of absorption of nutrients from gut into blood by reducing food intake, inhibit glucagon release from the alpha cells of pancreas (2). Two types of incretin hormones have been identified in ruminants and human, such as glucose dependent insulinotropic polypeptide (GIP) and glucagon like peptide-1(GLP-1). More than 200 species (1200) of medicinal plants have been claimed to have antidiabetic properties (3). Out of them, around 33% have been scientifically studied and documented. The study revealed that these drugs are having ability to modulate one or more pathways and regulate insulin resistance, beta cell function & GLP-1 homeostasis (1). Evidence based studies showed that Berbery, bitter melon, cinnamom tree, gardenia, Korean pine, little dragon, mango, pygeum, fenugreek and lychee composed of incretins compounds (1). But isolation of active metabolomics and the multicentre base clinical trials are needed to propagate the herbal medicine in the world.

Evidence based approaches of Incretins mimetic (GIP &GLP-1): GIP is the first incretin hormone which is composed of 42-Amino Acids peptide from the post translational processing of 153-Amino Acids precursors encoded by gip gene and structurally related with secretin, glucagon and vaso-active intestinal peptide (VIP) (4). The insulinotropic effect of incretins may achieve by binding with receptor of GIPR which is positively coupled to increase in intracellular cAMP and Ca+2 levels in the beta cells. It also has significant effects on fatty acid metabolism through stimulation of lipoprotein lipase activity in adipocytes and bone remodeling (5). Secretin is initially synthesized as a 120-AAs precursor protein known as prosecretin. This precursor is contained an N-terminal signal peptide, spacer, secretin itself and a 72 AAs C-terminal peptide. The mature secretin peptide is a linear peptide hormone which is composed of 27 –AAs and has a molecular weight of 3055. The AAs sequences of secretin have similarity with glucagon, VIP and gastric inhibitory peptide. Secretin helps to regulate the P^H of the duodenum by inhibiting the secretion of gastric acid from parietal cells of the stomach, stimulating the production of bicarbonate from the centroacinar cells and intercalated ducts of the pancreas and bile production (6).

GLP-1 is playing a dominant role for modulating beta cell function, increase insulin secretion, insulin sensitivity & beta cell mass; reduce glucagon secretion, attenuate gastric emptying and decrease appetite or weight gain. It has a short half life (<2 minute) due to its fast cleavage by dipeptidyl peptidase-4 (DPP-4). Evidence based study showed that an oral dose of glucose can trigger higher peak in plasma insulin concentration compare to an intravenous dose. Obese patients with gastric bypass showed remarkable metabolic adaptation and frequent diabetes remission in one year later. It usually deduced during cloning and characterized by proglucagon gene which is a post translational cleavage product. It has also been shown to stimulate β-cells from apoptosis and to stimulate β-cells proliferation by up regulation of the beta cell transcription factor. One study showed that people with type-2 DM do not have enough incretins which could exacerbate the problem of high blood glucose (7) .

Incretins mimetic effect of Herbal drugs: GLP-1 secretagogue activity of medicinal plants has less side-effects and low cost as compared to GLP-1 agonists of synthetic origin. *Berberis vulgaris, Magniferaindica, Glycine max, Cinnamomumzeylanicum, Pinus koraiensis*and *Prunus Africana* have showed potential GLP-1 secretory activity in vitro and in-vivo assay system (1)

Barbery: Root and rhizome (500mg/kg) of the *Berberis vulgaris (Berberine) have shown significant effect on insulin secretion, stimulate glycolysis, increase glucose transporter-4 (GLUT-4) and GLP-1 in rat model (8)*

Bitter melon*:* Fruit (5000mg/kg) of the*Momordicachirantia (Karavilagenin E)* orally administered as single dose for 30 minutes and showed higher serum GLP-1 and lower glucose level in WES mice model (9)

Cinnamom Tree*: Bark (3gm) of the Cinnamomumzeylanicum (Cinnamon)*-have shown reducepost prandial serum insulin and increased GLP-1 concentration without significantly affecting blood glucose in human (10)

Korean Pine: Seeds (50 microgram /dose of each FFA) of *Pinus koraiensis* in human female subjects showed that GLP-1 was higher after 60 minutes of administration (11)

Little dragon: Leave extracts (500 mg/kg) of *Artemisia dracunculus* (Torralin) was shown to increase the binding of glucagon like peptide -1 to its receptors in KKA mice model (12)

Mango: Leaves (320 microgram/ml) of *Magniferaindica* inhibits the DPP-4 and enhance GLP-1 for T2DM (13).

Pygeum- Bark (100,200 & 400 mg/kg) of *Prunus africana* in Wistar rat model showed that the extract increases insulin secretion by lowering DPP-4 activity and increasing the half life of GLP-1(14).

Soybean: Root (20 mg/kg) of *Glycine max* (Glyceollins) has shown potential effects on GLP-1 secretion to enhance insulinotropic action in enteroendocrine cells of diabetic mice (15).

Wheat: Fibers (24 gm/day) of *Triticumaestivum* have shown increased short chain Fatty acid production and glucagon like peptide-1 secretion in human model for many days (16).

Gardenia: Fruit of the *Gardenia jesminoides (geniposide)* prevents the oxidative stress induced neuron apoptosis and improved glucose stimulated insulin secretion by activating glucagon like peptide 1 receptor in INS-1cell (17)

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-gustducin, phospholipase C beta 2 (PLC2), 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 Ca^{2+} concentration and releases GLP-1(1).

The most active plants for management of Diabetes Mellitus are *Allium sativum, Gymnemasylvestre, Citrulluscolocynthis, Trigonellafoenumgreacum*, and *Ficusbengalensis*. The review describes some new bioactive drugs and isolated compounds from plants such as roseoside, epigallocatechin gallate, beta-pyrazol-1-ylalanine, cinchonainIb, leucocyandin 3-O-beta-d-galactosyl cellobioside, leucopelargonidin-3- O-alpha-L rhamnoside, glycyrrhetinic acid, dehydrotrametenolic acid, strictinin, isostrictinin, pedunculagin, epicatechin and christinin-A showing significant insulinomimetic and antidiabetic activity with more efficacy than conventional hypoglycaemic agents. Antidiabetic activity of medicinal plants is attributed to the presence of polyphenols, flavonoids, terpenoids, coumarins and other constituents which show reduction in blood glucose levels (18).

Conclusion:

Incretins (GIP and GLP-1) are very effective drug for management of DM. Some of the medicinal plants are rich in incretin mimetic compound. Extensive researches on medicinal plants or herbal drugs are needed to combat the modern disease of civilization.

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