

Insulinotropic Effect of Herbal Drugs for Management of Diabetes Mellitus: A Congregational Approach

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Abstract

Insulin is a lifesaving 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 entering 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 catastrophic effects of diabetes as well as insulin resistance diabetes mellitus. Evidence based studies showed that berbery, bitter melon, cinnamon tree, gardenia, Korean pine, little dragon, mango, pygeum, fenugreek and lychee composed of insulinotropic 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 insulinotropic medicinal plants which will help to get new generic compound and also give new clue for further research on DM.

Keywords: Insulinotropic; Herbal drugs; Insulin resistance Diabetes mellitus

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 decreasing 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 and GLP-1 homeostasis [1]. Research based studies showed that berbery, bitter melon, cinnamon tree, gardenia, Korean pine, little dragon, mango, pygeum, fenugreek and lychee composed of insulinotropic 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 Insulinotropic Compound (GIP and 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 vasoactive 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-AA precursor protein known as prosecretin. This precursor is contained an N-terminal signal peptide, spacer, secretin itself and a 72

AA C-terminal peptide. The mature secretin peptide is a linear peptide hormone which is composed of 27-AAAs and has a molecular weight of 3055. The AAAs 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 and 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 and 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). DPP-4 inhibitors reduce glucagon and blood glucose levels. The mechanism of DPP-4 inhibitors is to increase incretin levels (GLP-1 and GIP), which inhibit glucagon release, increases insulin secretion, decreases gastric emptying, and decreases blood glucose levels. Data 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].

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Insulinotropic 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*, *Magnifera indica*, *Glycine max*, *Cinnamomum zeylanicum*, *Pinus koraiensis* and *Prunus Africana* have showed potential GLP-1 secretory activity *in vitro* and *in vivo* assay system [1].

Barbery

Root and rhizome (500 mg/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]. Berberine also inhibits dipeptidyl peptidase-4, which usually enhance antihyperglycemic activity.

Bitter melon

Fruit (5000 mg/kg) of the *Momordica chirantia* (*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 (3 gm) of the *Cinnamomum zeylanicum* (*Cinnamon*)-have shown reduce post prandial serum insulin and increased GLP-1 concentration without significantly affecting blood glucose in human [10].

Korean pine

Seeds (50 mg/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

Leaf extracts (500 mg/kg) of *Artemisia dracunculus* (*Torrain*) was shown to increase the binding of glucagon like peptide 1 to its receptors in KKA mice model [12].

Mango

Leaves (320 mg/ml) of *Magnifera indica* inhibits the DPP-4 and enhance GLP-1 for T2DM [13].

Pygeum

Bark (100, 200 and 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 *Triticum aestivum* 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].

Turmeric

Bark of turmeric (*Berberis aristata*) has the ability to inhibit dipeptidyl peptidase IV activity (*in vitro*). The crude bark extract had shown IC50 value of 14.4µg/ml and the standard diprotin-A displayed 1.5 µg/ml.

Possible Mechanism of GLP-1 Induction by Phytochemicals

The phytochemicals may activate GLP-1 receptor on the enteroendocrine 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 enteroendocrine cell membrane through elevation of intracellular Ca²⁺ concentration and releases GLP-1 [1]. The most active plants are *Allium sativum*, *Gymnema sylvestre*, *Citrullus colocynthis*, *Trigonella foenum greacum*, and *Ficus bengalensis*. The review describes some new bioactive drugs and isolated compounds from plants such as roseoside, epigallocatechin gallate, beta-pyrazol-1-ylalanine, cinchonain Ib, leucocyanidin 3-O-beta-d-galactosyl cellobioside, leucopelargonidin-3- O-alpha-L rhamnoside, glycyrrhetic acid, dehydrotrametenolic acid, strictinin, isostrictinin, pedunculagin, epicatechin and christinin-A showing significant insulinomimetic and antidiabetic activity with more efficacy than conventional hypoglycaemic agents. Thus, from the review majorly, the 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]

Conceptual Amalgamation of Insulinotropic Drugs and Ancient Unani/Ayurvedic/Herbal Treatment

Ancient Greco-Arabian philosophers were described the medicinal use of animal for different health ailments. Al-Dimiri (1344-1405) was described hundreds of animal in his book and stated that ten of which were used for health disorders. Avicena, Al-Kindi and Al-Antaki also prescribed many animal based remedies and stated that Lizard is very effective in Diabetes like symptoms. Exenatide is derived from saliva of Lizard (*Heloderma suspectum*), which is a glucagon-like peptide-1 agonist (GLP-1 agonist) belonging to the group of incretin mimetics, approved by FDA in 2010 for the treatment of diabetes mellitus type 2. It can be administered as a subcutaneous injection (under the skin) of the abdomen, thigh, or arm within the 60 minutes before the first and last meal of the day [19-24]. So, it is indicated that ancient philosopher's concept and modern concept are having positive correlation with management of diseases. More and more clinical trials are needed to prove their empirical concept and give a new horizon for treatment of incurable diseases.

Conclusion

Incretions (GIP and GLP-1) and DPP-4 inhibitors are very effective drugs for management of DM. Different *in vivo* and *invitro* studies showed that some of the medicinal plants are rich in insulinotropic compound. Identification, isolation of active metabolites, and multi center for establishing the safety profile of these herbal drugs and extensive researches on medicinal plants or herbal drugs are needed to combat the modern diseases of civilization likes DM. It is an initiative to turn attention on therapeutic efficacy of herbal drugs for management of DM to the scientific communities.

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