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HERBAL MEDICINE USED IN DIABETES: AN OVERVIEW

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ABSTRACT
Traditional Medicines derived from medicinal plants are used by about 60% of the world's population. This review focuses on Indian Herbal drugs and plants used in the treatment of diabetes, especially in India. Diabetes is an important human ailment afflicting many from various walks of life in different countries. In India it is proving to be a major health problem, especially in the urban areas. Though there are various approaches to reduce the ill effects of diabetes and its secondary complications, herbal formulations are preferred due to lesser side effects and low cost. A list of medicinal plants with proven antidiabetic and related beneficial effects and of herbal drugs used in treatment of diabetes is compiled. One of the etiologic factors implicated in the development of diabetes and its complications is the damage induced by free radicals and hence an antidiabetic compound with antioxidant properties would be more beneficial.

(KEYWORDS: Diabetes mellitus, Incretins, Herbal plants, Antioxidant)

INTRODUCTION
Diabetes mellitus, one of the most common endocrine metabolic disorders has caused significant morbidity and mortality due to microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (heart attack, stroke and peripheral vascular disease) complications. Human bodies possess enzymatic and non-enzymatic antioxidative mechanisms which minimize the generation of reactive oxygen species, responsible for many degenerative diseases including diabetes. The disease is rapidly increasing worldwide and affecting all parts of the world. Due to deficiency of the insulin people suffering from diabetes**.** Type 2 diabetes mellitus (T2DM) is a predominant form of diabetes worldwide and is one of most common health problems facing mankind. T2DM accounts for >90% of cases globally. Most of the therapeutic agents for T2DM targeting different pathways shown undesirable side effects, such as hypoglycaemia, obesity, edema and decreased sensitivity to insulin. However, therapies targeting incretins hormones recently emerged as potential safe target for the treatment of T2DM.

Incretin pathway regulate the daily blood glucose level in the human body. It accounts for 50%-70% of the total beta cells derived insulin secretion in response to ora; glucose ingestion.

Blood glucose levels fluctuate based on daily glucose consumption. modulation of blood glucose majorly depends on two incretins pathway hormones i.e. GIP and GLP-1. when the glucose level upsurge in blood, GIP and GLP-1 are secreted by the L cell located at GIT.

Recently, some medicinal plants have been reported to be useful in diabetes worldwide and have been used empirically in antidiabetic and antihyperglycemic remedies. Antihyperglycemic activity of the plants is mainly due to their ability to restore the function of pancreatic tissues by causing an increase in insulin output or inhibit the intestinal absorption of glucose or to the facilitation of metabolites in insulin dependent processes.

What is diabetes?
Diabetes is the condition in which the body does not properly process food for use as energy. Most of the food we eat is turned into glucose, or sugar, for our bodies to use for energy. The pancreas, an organ that lies near the stomach, makes a hormone called insulin to help glucose get into the cells of our bodies. When you have diabetes, your body either doesn't make enough insulin or can't use its own insulin as well as it should. This causes sugars to build up in your blood. This is why many people refer to diabetes as "sugar." Diabetes can cause serious health

complications including heart disease, blindness, kidney failure, and lower-extremity amputations. Diabetes is the seventh leading cause of death in the United States**.**

What are the types of diabetes?

Type 1

Type 1 diabetes, previously called insulin-dependent diabetes mellitus (IDDM) or juvenile- onset diabetes, may account for 5 percent to 10 percent of all diagnosed cases of diabetes. Risk factors are less well defined for Type 1 diabetes than for Type 2 diabetes, but autoimmune, genetic, and environmental factors are involved in the development of this type of diabetes.

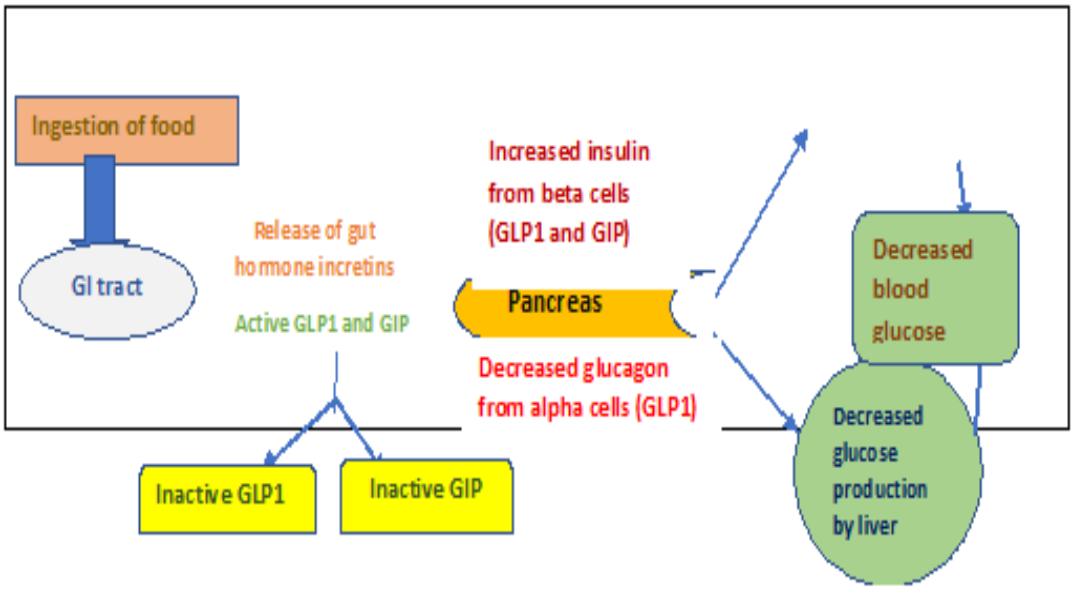
Type 2

Type 2 diabetes was previously called non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes. Type 2 diabetes may account for about 90 percent to 95 percent of all diagnosed cases of diabetes. Risk factors for Type 2 diabetes include older age, obesity, family history of diabetes, prior history of gestational diabetes, impaired glucose tolerance, physical inactivity, and race/ethnicity. African Americans, Hispanic/Latino Americans, American Indians, and some Asian Americans and Pacific Islanders are at particularly high risk for type 2 diabetes.Gestational diabetes develops in 2 percent to 5 percent of all pregnancies but usually disappears when a pregnancy is over. Gestational diabetes occurs more frequently in African Americans, Hispanic/Latino Americans, American Indians, and people with a family history of diabetes than in other groups. Obesity is also associated with higher risk. Women who have had gestational diabetes are at increased risk for later developing Type 2 diabetes. In some studies, nearly 40 percent of women with a history of gestational diabetes developed diabetes in the future.

What are incretins?

Incretins refer an extract from upper gut mucosa that produce hypoglycaemia. Incretins are 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 Langerhans after meal. It also plays vital role for reducing the rate of absorption of nutrients from gut into blood by reducing food intake, inhibit glucagon release from alpha cells of pancreas.

Mechanism of action of Incretins mimetic



What is GIP and GLP-1?

Two types of incretins hormones have been identified in humans and in ruminants, such as Glucose dependent insulinotropic polypeptide(GIP) and glucagon like peptide-1 GIP is 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's, glucagon and vaso active intestinal peptide.

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 level in the beta cells.

Secretins help to regulate the pH of the duodenum by inhibiting the secretion of gastric acid from parietal cells of the stomach, stimulating the production of bicarbonate from the pancreas and bile production.

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 short half life (<2 min) due to its fast cleavage by dipeptidyl peptidase-4 (DPP-4).

Medicinal plants used to treat diabetes

Plants have always been a very good source of drugs and many of the currently available drugs have been derived directly or indirectly from them. The ethnobotanical information suggests that about 800 plants may possess anti-diabetic potential, among all of them Momordica charantia to be beneficial for treatment of type 2 diabetes. Several such herbs have shown anti-diabetic activity when evaluated using different type of experimental techniques. Wide arrays of plant derived active principles representing different type of biological activity, among these alkaloids, glycosides, galactomannan gun, polysaccharides, peptidoglycans, hypoglycans, guanidine, steroids, carbohydrates, glycopeptides, terpenoids, amino acids and inorganic ions have demonstrated activity including treatment of diabetes.

Incretin mimetic effect of herbal plants

(1) Berberis

Biological source: Root and rhizome of **Berberis vulgeris.**

Mechanism of action: Berberis shown significant effect on insulin secretion, stimulate glycolysis, increase glucose transporter-4 (GLUT-4) and GLP-1 In rat model. Berberine promoted glucose-stimulated insulin secretion rather than basal insulin secretion in dose-dependent manner in rat's pancreatic islets. Berberine can enhance glucose-stimulated insulin secretion in rat via islets, and probably exerts the insulinotropic effect a pathway involving hepatic nuclear factor 4 alpha (HNF4) alpha and glucokinase, which is distinct from sulphonylureas. Significant insulin sensitizing activity was observed in 3T3-L1 adipocytes which were given 50 M berberine plus 0. 2 nM insulin to reach a glucose uptake level increased b 10 nM of insulin alone. This was associated with increased glucose transporter- 4 translocation into the plasma membrane via enhancing insulin signalling pathways and the insulin receptor substrate- 1-phosphoinositide 3 KinaseAkt. Berberine also increased glucose-stimulated via insulin secretion and proliferation in Min6 cells an enhanced insulin/insulin-like growth factor- 1 signalling cascade. Data suggested that berberine can act as an effective insulin sensitizing and insulinotropic agent.

2) Momordica charantia

Biological source: Fruit of the **Momordicachirantia (Karavilagenin E).**

Orally administered as single dose for 30 min and showed higher serum GLP-1 and lower glucose level in WES mice model.

Momordica charantia (Cucurbitaceae) Significant reduction of blood glucose level and increased concentration of plasma insulin have been observed in diabetic rats that were treated with fruit juice of Momordica charantia. The observed effect was due to an increase in the number of beta cells in treated animals compared to untreated one. The phytochemical momordicin, charantin, and a few compounds such as galactose-binding lectin and insulin-like protein isolated from various parts of this plant have been shown to have insulin mimetic activity. Aqueous extract of unripe fruits of Momordica charantia has also been shown to partially stimulate insulin release from isolated beta-cell of obese-hyperglycaemic mice suggesting that the insulin-releasing action is the result of perturbations of membrane functions. Momordica charantia increases the renewal of partial cells in the pancreas or may permit the recovery of partially destroyed cells and stimulates pancreatic insulin secretion.

3) Wheat plant

Biological source: Fibres of **Triticumaestivum.**

It shown increased short chain fatty acid production and glucagon like peptide-1 secretions in human model for many days.

4) Soya bean Root

Biological source: Root of **Glycine max.**

It has shown potential effect on GLP-1 secretion to enhance insulinotropic action in enteroendocrine cells of diabetic mice.

In North America, soybean is called soya bean. It is widely grown for its edible bean that has several benefits. Of any plant, soy contains the greatest concentration of the potent antioxidants; isoflavones which are a class of phytoestrogens 14. Glycine max isoflavones include genistein, daidzein, and glycitein. Moreover, the dried bean contains vegetable protein (40%), complex carbohydrates (35%), fat (18-22%), dietary fibre, oligosaccharides, minerals and other phytochemicals like saponines12. Its low glycemic index is attributed to its complex carbohydrates and dietary fiber.

Glycine max reduced weight loss in diabetics. The ability of germinated Glycine max to restore the body weight to some extent may be related to its ability to reduce hyperglycaemia due to increase in isoflavones concentration compared to the non- germinated Glycine max. Also, it may be due to controlling muscle wasting which means the reversal of gluconeogenesis contents, thus it can be beneficial for diabetic individuals. ingestion of Glycine max diet improved the glycemic control in streptozotocin induced diabetic rats. Many mechanisms have been postulated for the mode of action of Glycine max as anti-hyperglycaemic agent, some of which were proved experimentally. It is possible that Glycine max fibers, which contains pectin's, galactomannans and arabinogalactans with high viscosity, delay gastric emptying and glucose absorption. Also, Glycine max was reported by Adedayo et al. (2013)52 to have inhibitory effects against amylase and glucosidase which are enzymes on the brush borders of the small intestine that catalyse the conversion of carbohydrates into glucose and facilitate the glucose absorption from intestinal lumen. This in turn may help to reduce postprandial hyperglycaemia by inhibiting the enzymatic hydrolysis of carbohydrates, and hence may delay the absorption of glucose. Moreover, the Glycine max isoflavones; genistein and daidzein, which are phytoestrogens having estradiol effects, were reported to bind to estrogen receptor α that is a key molecule involved in the metabolism of lipid and glucose. This estrogen receptor is found in pancreatic β cells that regulates the biosynthesis and secretion of insulin from pancreas, also it helps in survival of β-cells. Thus, Glycine max isoflavones stimulate insulin synthesis and secretion**.**

5) Mango leaves

mango leaves

Leaves (320 mg/ml) of Magnifera Indica inhibit the DPP-4 and enhance GLP-1 for T2DM.

Methanolic extract of Magnifera Indica leaves were tested in vitro for DPP-4 inhibitory activity. The extract showed potent activity with an IC 50 values of 182.7ug/ml.

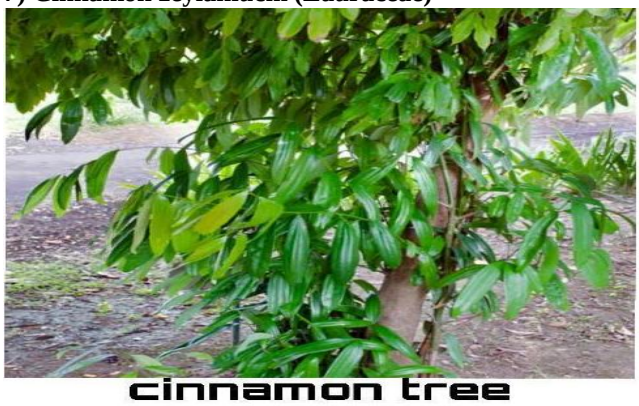
Inhibitory effect of magnifera Indica on DPP-4 and the potential to be novel, efficient and tolerable approach for diabetes.(Yogisha S, Raveesha KA)

6) Gardenia Fruit

gardenia fruit

Fruit of the Gardenia jesminoides (Geniposide) prevent the oxidative stress induced neuron apoptosis and improved glucose stimulated insulin secretion by activating glucagon like peptide-1receptor inINS-1 cell.

7) Cinnamon zeylaniucm (Lauraceae)



In vitro incubation of pancreatic islets with cinnamaldehyde isolated from Cinnamon zeylaniucm resulted in enhanced insulin release. The insulinotropic effect of cinnamaldehyde was due to increase in the glucose uptake through glucose transporter (GLUT4) translocation in tissues.(HlebowiczJ, Hlebowicz A)

8) Trigonella foenum-graecum (Leguminosae)

4-Hydroxyleucine, a novel amino acid from fenugreek seeds increased glucose stimulated insulin release by isolated islet cells in rats, mice and humans. Trigonella foenum-graecum has been observed to cause glucose-induced insulin release in vitro and in vivo. A specific amino acid, hydroxy isoleucine, which represents 80% of the free amino acids in Trigonella foenum-graecum seeds, may possess insulin-stimulating properties. The Trigonella foenum-graecum seeds may help to improve insulin sensitivity, which is presumed to be due to the effects of fiber, which slows carbohydrate metabolism resulting in reduced insulin levels and lowered blood glucose. Anti-hyperglycaemic effect of the extracts, powder and gum of Trigonella foenum-graecum seeds and leaves have been linked to delayed gastric emptying caused by the high fiber content, inhibition of carbohydrate digestive enzymes and stimulation of insulin secretion.

9) 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.

10) 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.

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.

Other plants which having insulin mimetic or insulin secretory activity:

Sr.no	Plant botanical name	Common name	Family	Mechanism of action
1	Abies pindrow	Morinda	Pinaceae	Insulin secretagogue activity
2	Acacia arabica	Babool	Leguminosae	Release insulin from Pancreas
3	Agrimony eupatoria	Rosaceae	Leaves	Insulin realising and insulin like activity
4	Aloe Barbadensis	Gheequar	Liliaceae	Stimulating synthesis and release of insulin
5	Annona squamosa	Sharifa	Annonaceae	Increased plasma insulin level
6	Bixa Orellana	Annotta	Bixaceae	Increase plasma insulin concentration and increase insulin binding on insulin receptor
7	Camella sinesis	Green tea	Theaceae	Increase insulin secretion
8	Capsicum frutescens	Mirch	Solanaceae	Increase insulin secretion and reduction of insulin binding on the insulin receptor
9	Eucalyptus globulus	Eucalyptus	Myrtaceae	Increase insulin secretion from clonal pancreatic beta line
10	Ficus religiosa	Peepal	moraceae	Initiating release of insulin
11	Hibiscus Rosa	Gudhal	Malvaceae	Stimulate insulin secretion from beta cells
12	Vinca rosea	Sadabahar	Apocynaceae	Beta cell rejuvenation, regeneration and stimulation.
13	Zingiber officinale	Adrak	Zingiberaceae	Increase insulin level and decrease fasting glucose level
14	Olea europia	Olive	Oleaceae	Increase insulin release and increase peripheral uptake of glucose.
15	Scoparia dulcis	Mithi Patti	Scrophulariaceae	Insulin secretagogue activity

Plant name	Ayurvedic/common name/herbal formulation	Antidiabetic and other beneficial effects in traditional medicine
Annona squamosa	Sugar apple	Hypoglycemic and antihyperglycemic activities of ethanolic leaf extract, increased plasma insulin level
Artemisia pallens	Davana	Hypoglycemic, increases peripheral glucose utilization or inhibit glucose absorption
Areca catechu	Supari	Hypoglycemic
Beta vulgaris	Chukkandar	Increase glucose tolerance in OGTT
Boerhavia diffusa	Punarnava	Increase in hexokinase activity ,decrease in glucose 6 phosphate and fructose bis-phosphate activity, increase plasma insulin level, antioxidant
Bombax ceiba	Semul	Hypoglycemic
Butea Monosperma	Palasa	Antihyperglycemic
Camella sinesis	Tea	Antihyperglycemic activity, antioxidant
Capparis decidua	Karir or pinju	Hypoglycemic , antioxidant, hypolipidemic
Caesalpinia bonducella	Sagarghota,fevernut	Hypoglycemic , insulin secreatogogue,hypolipidemic
Coccinia indica	Bimb or kanturi	Hypoglycemic
Embilica officinalis	Amla, Dhatriphala, a constituent of herbal formulation Triphala churna	Decrease lipid peroxidation,antioxidant,hypoglycemic
Eugenia uniflora	Pitanga	Hypoglycemic ,inhibit lipase activity
Enicostema littorale	Krimihrita	Increase hexokinase activity,Decrease glucose 6 phosphatase and fructose 1,6 bisphosphatase activity, dose dependant hypoglycemic effect
Ficus bengalenesis	Bur	Hypoglycemic antioxidant
Gymnema sylvestre	Gudmar or Merasingi	Antihyperglycemic effect ,Hypolipidemic
Hemidesmus indicus	Anantamul	Anti snake venum activity,Anti inflammatory
Hibiscus rosa sinesis	Gudhal or Jasson	Initiate insulin releasefrom pancreatic beta cell
Ipomoea batatas	Sakkargand	Reduces insulin resistance
Momordica cymbalaria	Kadavanchi	Hypoglycemic,hypolipidemic
Murraya Koenigii	Curry patta	Hypoglycemic, increase glycogenesis and decrease gluconeogenesis and glycogenolysis
Musa sapientum	Banana	Antihyperglycemic, antioxidant

Phaseolus vulgaris	Hulga, white kidney bean	Hypoglycemic, hypolipidemic,inhibit alpha amylase activity,antioxidant, altered level of insulin receptor and GLUT-4 mRNA in skeletal muscle
Prunica granatum	Anar	Antioxidant ,antihyperglycemic effect
Salacia reticulata	Vairi	Inhibitory activity against sucrase , alpha -glucosidase inhibitor
Scoparia dulcis	Sweet broomweed	Inculin secreatogogue activity,antihyperlipidemic,Hypoglycemic, antioxidant
Swertia Chirayita	Chirata	Stimulate insulin release from islets
Vinca rosea	Sadabahar	Antihyperglycemic
Withania somnifera	Ashwagandha, Winter cherry	Hypoglycemic ,diuretic,and hypocholesterolemics

Formulated herbal drugs with antidiabetic activity

Drug	company	Ingredients
Diabecon	Himalaya	Gymnema sylvestre, Pterocarpus marsupium, Glycyrrhiza glabra, Casearia esculenta, Syzygium cumini, Asparagus racemosus, Boerhavia diffusa, Sphaeranthus indicus, Tinospora cordifolia, Swertia chirata, Tribulus terrestris, Phyllanthus amarus, Gmelina arborea, Gossypium herbaceum, Berberis aristata, Aloe vera, Triphala, Commiphora wightii, shilajeet, Momordica charantia, Piper nigrum, Ocimum sanctum, Abutilon indicum, Curcuma longa, Rumex maritimus
Diasulin		Cassia auriculata, Coccinia indica, Curcuma longa, Emblica officinalis, Gymnema sylvestre, Momordica charantia, Scoparia dulcis, Syzygium cumini, Tinospora cordifolia, Trigonella foenum graecum
Pancreatic tonic 180 cp	ayurvedic herbal supplement	Pterocarpus marsupium, Gymnema sylvestre, Momordica charantia, Syzygium cumini, Trigonella foenum graceum, Azadirachta indica, Ficus racemosa, Aegle marmelos, Cinnamomum tamala
Ayurveda alternative herbal formula to Diabetes:	Chakrapani Ayurveda	Gurmar (Gymnema sylvestre) Karela (Momordica charantia) Pushkarmool (Inula racemosa) Jamun Gutli (Syzygium cumini) Neem (Azadirachta indica) Methika (Trigonella foenum gracecum) Guduchi (Tinospora cordifolia)
Bitter gourd Powder	Garry and Sun natural Remedies	Bitter gourd (Momordica charantia)
Dia-care	Admark Herbals Limited	Sanjeevan Mool; Himej, Jambu beej, Kadu, Namejav, Neem chal.
Diabetes-DailyCare	Nature's Health Supply	Alpha Lipoic Acid, Cinnamon 4% Extract, Chromax, Vanadium, Fenugreek 50% extract, Gymnema sylvestre 25% extract Momordica 7% extract, Licorice Root 20% extract
Gurmar powder	Garry and Sun natural Remedies	Gurmar (Gymnema sylvestre)
Epinsulin	Swastik Formulations	vijaysar (Pterocarpus marsupium)
Diabecure	Nature beaute sante	Juglans regia, Berberis vulgaris, Erytherea centaurium, Millefolium, Taraxacum
Diabeta	Ayurvedic cure Ayurvedic Herbal Health Products	Gymnema sylvestre, Vinca rosea (Periwinkle), Curcuma longa (Turmeric), Azadirachta indica (Neem), Pterocarpus marsupium (Kino Tree), Momordica charantia (Bitter Gourd), Syzygium cumini (Black Plum), Acacia arabica (Black Babhul), Tinospora cordifolia , Zingiber officinale (Ginger)
Syndrex	Plethico Laboretaries	Germinated Fenugreek seed extract

CONCLUSION

In conclusion, this review has presented a list of antidiabetic plants used in the treatment of diabetes mellitus. It showed that these plants have hypoglycaemic effects and can be used to treat various type of secondary complications of diabetes mellitus. Plants have been a good source of medicine for the treatment of various type of disease, still many plants and active compounds obtained from plants have not been well characterized. More investigations must be carried out to evaluate the exact mechanism of action of medicinal plants with antidiabetic and insulinomimetic activity.

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