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A REVIEW & STUDY ON ANTIDIABETIC MEDICINALPLANTS HAVING INSULIN MIMETIC PROPERTY

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ABSTRACT
Since long back herbal medicines have been the highly esteemed source of medicine therefore, they have become a growing part of modern, high-tech medicine. In view of the above aspects the present review provides profiles of plants (65 species) with hypoglycaemic properties, available through literature source from various database with proper categorization according to the parts used, mode of reduction in blood glucose (insulinomimetic or insulin secretagogues activity) and active phytoconstituents having insulin mimetics activity. From the review it was suggested that, plant showing hypoglycemic potential mainly belongs to the family Leguminoseae, Lamiaceae, Liliaceae, Cucurbitaceae, Asteraceae, Moraceae, Rosaceae and Araliaceae. The most active plants are Allium sativum, Gymnema sylvestre, Citrullus colocynthis, Trigonella foenum greacum, Momordica charantia 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, 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. 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.

KEYWORDS: Diabetes, Insulin Secretagogues, Insulin Mimetics, Blood glucose, Insulin, Beta cell, Diabetes Mellitus.

1. INTRODUCTION
Diabetes mellitus (DM) is not a single disease but it is a group of met- abolic disorders affecting a huge number of populations in the world. It is mainly characterized by hyperglycemia, hyper aminoacidemia, hyperlipedemia, and hypoinsulinaemia. It leads to decrease in both insulin secretion and insulin action. It is frequently associated with the development of micro and macro vascular diseases which include neuropathy, nephropathy, cardiovascular and cerebrovas- cular diseases. The worldwide prevalence of DM for all age groups was estimat- ed to be 2.8% in 2000 and it is projected to be 5.4% in 2025. At pres- ent available therapies for the treatment of DM comprise insulin and various oral antihyperglycemic agents such as sulfonylurea's, biguanides and glinides. In developing countries as products are expensive and not easily accessible. Currently, there is growing in- terest in herbal formulations due to its fewer side effects. So the tra- ditional herbal medicines are mainly used which are obtained from plants, it plays important role in the management of DM. Recently, some medicinal plants have been reported to be useful in diabetes worldwide and have been used empirically in antidiabetic and antihyperlipidemic 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. More than 400 plant species having hypoglycemic activity have been available in literature, however, searching for new antidiabetic drugs from natural plants is still attractive because they contain substances which demonstrate alternative and safe effects on diabetes mellitus. Most of plants contain glycosides, alkaloids, terpenoids, flavonoids, carotenoids, etc., that are frequently implicated as having antidiabeticeffect.

2. Diabetes Mellitus

Diabetes Mellitus is a heterogeneous complex metabolic disorder characterized by elevated blood glucose concentrations due to either resistance to the action of insulin, insufficient insulin secretion, or both. In a nerve shell it is a disorder in which the body does not produce enough or respond normally to insulin, causing blood sugar (glucose) levels to be abnormally high. Urination and thirst are increased, and people may lose weight even if they are not trying to. Diabetes damages the nerves and causes problems with sensation. Diabetes damages blood vessels and increases the risk of heart attack, stroke, chronic kidney disease, and vision loss. Doctors diagnose diabetes by measuring blood sugar levels. People with diabetes need to follow a healthy diet that is low in refined carbohydrates (including sugar), saturated fat, and processed foods. They also need to exercise and usually take drugs to lower blood sugar levels. Diabetes mellitus is a disorder in which the amount of sugar in the blood is elevated. Doctors often use the full name diabetes mellitus, rather than diabetes alone, to distinguish this disorder from diabetes insipidus. Diabetes insipidus is a relatively rare disorder that does not affect blood glucose levels but, just like diabetes mellitus, also causes increased urination. The major clinical manifestation of the diabetic state is hyperglycemia. However, insulin deficiency and/or insulin resistance also are associated with abnormalities in lipid and protein metabolism, and with mineral and electrolyte disturbances. The vast majority of diabetic patients are classified into one of two broad categories: type 1 diabetes mellitus, which is caused by an absolute or near absolute deficiency of insulin, or type 2 diabetes mellitus, which is characterized by the presence of insulin resistance with an inadequate compensatory increase in insulin secretion. In addition, women who develop diabetes during their pregnancy are classified as having gestational diabetes. Finally, there are a variety of uncommon and diverse types of diabetes, which are caused by infections, drugs, endocrinopathies, pancreatic destruction, and genetic defects. These unrelated forms of diabetes are included in the "Other Specific Types" and classified separately.

TYPE 1 DIABETES MELLITUS

Type 1 diabetes results from autoimmune destruction of the pancreatic beta-cells. Markers of immune destruction of the beta-cell are present at the time of diagnosis in 90% of individuals and include antibodies to the islet cell (ICAs), to glutamic acid decarboxylase (GAD65), tyrosine phosphatases IA-2 and IA-2b, ZnT8, and insulin auto-antibodies (IAAs). Individuals may convert to negative if only one marker is positive, but individual risk of developing type 1 DM increases with the number of positive markers. Two positive antibodies are associated with a 75% chance of developing diabetes in the next 10 years. Diagnostic staging is now available for individuals with autoimmunity, even prior to diagnosis of type 1 DM. While this form of diabetes usually occurs in children and adolescents, it can occur at any age. Younger individuals typically have a rapid rate of beta-cell destruction and present with ketoacidosis, while adults often maintain sufficient insulin secretion to prevent ketoacidosis for many years. The more indolent adult-onset variety has been referred to as latent autoimmune diabetes in adults (LADA). There is still controversy whether adult type 1 DM and LADA are the same clinical entity, but LADA patients are antibody positive and often require insulin therapy within years of diagnosis. Idiopathic forms of type 1 DM often are of African or Asian descent. An intermittent risk of diabetic ketoacidosis, based on their varying insulinopenia, is present. Eventually, all type 1 diabetic patients will require insulin therapy to maintain normoglycemia. For additional information see the chapters that discuss in detail the pathogenesis of type 1 diabetes.

TYPE 2 DIABETES MELLLITUS

Type 2 diabetes is characterized by insulin resistance and, at least initially, a relative deficiency of insulin secretion. In absolute terms, the plasma insulin concentration (both fasting and meal-stimulated) usually is increased, although "relative" to the severity of insulin resistance, the plasma insulin concentration is insufficient to maintain normal glucose homeostasis. With time, however, there is progressive beta cell failure and worsening insulin deficiency ensues. Recently, more sophisticated analyses of the beta-cell response and regulation revealed that most subjects at risk for developing type 2 diabetes, i,e, those with combined impaired fasting glucose and impaired glucose tolerance already have a significant loss, close to 80% of the total insulin secretory capacity of the pancreas. In a minority of type 2 diabetic individuals, severe insulinopenia is present at the time of diagnosis and insulin sensitivity is normal or near normal. Most individuals with type 2 diabetes exhibit intra-abdominal (visceral) obesity, which is part of the "ectopic fat" deposition pattern closely related to the presence of insulin resistance. In addition, hypertension, dyslipidemia (high triglyceride and low HDL- cholesterol levels; postprandial hyperlipemia), vascular endothelial dysfunction and elevated PAI-1 levels often are present in these individuals. This clustering of abnormalities is referred to as the "insulin resistance syndrome" or the "metabolic syndrome". Because of these abnormalities, patients with type 2 diabetes are at increased risk of developing atherosclerotic cardiovascular disease (ASCVD) with macrovascular complications (myocardial infarction and stroke). Type 2 iabetes has a strong genetic predisposition and is more common in minority ethnic groups, e.g. Mexican- Americans, Latinos, African Americans, American Indians, Pacific Islanders, than in individuals of European ancestry. The genetic cause(s) of the common variety of type 2 diabetes is (are) not well defined. A large number of genes have been associated with type 2 DM, but they explain a low percentage of the disease heritability. For additional information see the chapter that discusses in detail the

pathogenesis of type 2 diabetes.

GESTATIONAL DIABETES MELLITUS (GDM)

Gestational diabetes mellitus (GDM) is defined as glucose intolerance which is first recognized during pregnancy. In most women who develop GDM, the disorder has its onset in the third trimester of pregnancy. At least 6 weeks after the pregnancy ends, the woman should receive an oral glucose tolerance test and be reclassified as having diabetes, normal glucose tolerance, impaired glucose tolerance, or impaired fasting glucose. Gestational diabetes complicates about 8-9% of all pregnancies, though the rates may double in populations at high-risk for type 2 diabetes. Clinical detection is important, since therapy will reduce perinatal morbidity and mortality. Dysglycemia risk in GDM is a continuum, and risk assessment for GDM should occur at the first prenatal visit. Two groups, the International Association of Diabetesand Pregnancy Study Groups (IADPSG) and the National Institutes of Health (NIH) Consensus Group recommend different testing methods for the diagnosis of GDM. A large-scale (~25,000 pregnant women) multinational epidemiologic study demonstrated that risk of adverse maternal and neonatal outcomes continuously ncreased as a function of maternal glycemia at 24-28 weeks,even within ranges previously considered normal for pregnancy. These observations led to a revision in the diagnostic criteria recommended by IADPSG for GDM using a "one-step" 75- gram OGTT. A NIH Consensus Development Conference, using the same data,continues to recommend the "two-step" approach to diagnosis. The stated reason was the lack of interventional trials to prove the new criteria could decrease pooroutcomes, as it was observational. The two criteria for diagnoses of GDM aresummarized in Table 3. The Carpenter Coustan values are lower because they arecorrected to account for assays currently in use. All women not known to havediabetes should undergo glucose test screening between weeks 24 and 28 using the"one step" 75 grams of glucose load in the morning after an overnight fasting period of at least 8 hours or the "two-step" method which starts with a non-fasting 50 gramglucose load test (GLT). A fasting 100-gram glucose tolerance test is only performed if the screening 50 gram GLT 1-hour plasma glucose value is ≥140mg/dl (7.8mmol/L). For additional information see the chapter on Diabetes in Pregnancy.

SPECIFIC TYPES OF DIABETES

Genetic Defects

Maturity Onset Diabetes of the Young (MODY) is characterized by impaired insulin secretion with minimal or no insulin resistance. MODY can be subtyped into neonatal and MODY-like. Neonatal diabetes usually has an onset in the first 6months of life and can be transient or permanent. MODY may affect genes important for beta-cell glucose sensing, development, function, and regulation.Genetic inability to convert proinsulin to insulin results in mild hyperglycemia. Similarly, the production of mutant insulin molecules has been identified in a fewfamilies and results in mild glucose intolerance. MODY5 is most often associatedwith renal cysts and was not listed on the most recent ADA classification of diabetes, but can rarely cause diabetes. The natural history of MODY is highly dependent onthe underlying genetic defect and most typically exhibit mild hyperglycemia at anearly age. The disease is inherited in an autosomal dominant pattern. Several genetic mutations have been described in the insulin receptor and are associated with insulin resistance. Type A insulin resistance refers to the clinical syndrome of acanthosis nigricans, virilization in women, polycystic ovaries, and hyperinsulinemia. Leprechaunism is a pediatric syndrome with specific facial features and severe insulin resistance that results from a defect in the insulin receptor. Lipoatrophic diabetes results from postreceptor defects in insulin signaling.

A variety of genetic syndromes have been described in which diabetes mellitus occurs with increased frequency. The etiology of the disturbance in glucose homeostasis in these diverse and seemingly unrelated syndromes remains undefined.

Diseases of the Exocrine Pancreas

Damage of the pancreas must be extensive for diabetes to occur. The most common causes are pancreatitis, trauma, and carcinoma. Chronic pancreatitis can cause general inflammatory/fibrotic changes in the pancreas which can cause diabetes. Cystic fibrosis causes a well-recognized pancreatic exocrine function insufficiency, but the same thick, viscous secretions cause inflammation, obstruction,and destruction of small ducts in the pancreas, which can lead to insulin deficiency. Hemochromatosis has also been associated with impaired insulin secretion and diabetes.

Endocrinopathies

Since growth hormone, cortisol, glucagon, and epinephrine increase hepatic glucose production and induce insulin resistance in peripheral (muscle) tissues, excess production of these hormones can cause or exacerbate underlying diabetes. Although the primary mechanism of action of these counter regulatory hormones is the induction of insulin resistance in muscle and liver, overt diabetes mellitus does not develop in the absence of beta cell failure.

Infections

A variety of infections have been etiologically related to the development ofdiabetes mellitus. Of these, the most clearly established is congenital rubella. Approximately 20% of infants who are infected with the rubella virus at birth develop autoimmune type 1 diabetes later in life. These individuals have the typical type 1 susceptibility genotype, DR3/DR4.

Drugs

A large number of commonly used drugs have been

shown to induce insulinresistance and/or impair beta cell function and can lead to the development of diabetes mellitus in susceptible individuals. An extensive review of these drugs and their mechanism of action has been published. Drug classes which have been extensively associated with elevating glucose levels include: beta-blockers, thiazide diuretics, fluoroquinolones, atypical or second generation anti-psychotics, calcineurin inhibitors, protease inhibitors, nicotinic acid, and corticosteroids. In addition, HMG-CoA reductase inhibitors (statins) have been shown to cause a small increase in the risk of diabetes, though the exact mechanisms of how it may increase the risk of diabetes are not completely understood.

For additional information on these unusual etiologies of diabetes see the chapter on Atypical Forms of Diabetes and Diabetes Mellitus After Solid Organ Transplantation.

3. Insulin

Definition of insulin: a protein pancreatic hormone secreted by the beta cells of the islets of Langerhans that is essential especially for the metabolism of carbohydrates and the regulation of glucose levels in the blood and that when insufficiently produced results in diabetes mellitus.

The role of insulin in the body

It may be easier to understand the importance of insulin therapy if you understand how this naturally occurring hormone usually works in the body and what happens if you have diabetes.

If you don't have diabetes, insulin helps

- Regulate blood sugar levels. After you eat, carbohydrates break down into glucose, a sugar that is the body's primary source of energy. Glucose then enters the bloodstream. The pancreas responds by producing insulin, which allows glucose to enter the body's cells to provide energy.
- Store excess glucose for energy. After you eat — when insulin levels are high — excess glucose is stored in the liver in the form of glycogen. Between meals — when insulin levels are low — the liver releases glycogen into the bloodstream in the form of glucose. This keeps blood sugar levels within a narrow range.

If you have diabetes

Your glucose levels will continue to rise after you eat because there's not enough insulin to move the glucose into your body's cells. People with type 2 diabetes don't use insulin efficiently (insulin resistance) and don't produce enough insulin (insulin deficiency). People with type 1 diabetes make little or no insulin.

Untreated, high blood glucose can eventually lead to complications such as blindness, nerve damage and kidney damage.

4. Insulin Mimetic

What is insulin mimetic?

Insulin-mimetics are agents that have been shown to mimic the actions of insulin including promoting the entry of glucose into tissues, activating signal proteins, influencing the expression of genes and regulating metabolic processes.

Insulin or agents that can mimic its action (insulin-mimetics) are necessary to promote the entry of glucose into tissues where the glucose can either be converted into energy or stored for later use. In recent years, selenium has been shown to mediate a number of insulin-like actions both in vivo and in vitro. These insulin-like actions include stimulating glucose uptake and regulating metabolic processes such as glycolysis, gluconeogenesis, fatty acid synthesis and the pentose phosphate pathway. The mechanism by which selenium is capable of mimicking insulin is not clear; however, reports indicate that selenium does activate key proteins involved in the insulin-signal cascade. Various proteins in the insulin-signal cascade have been shown to be necessary for different insulin-regulated events, and presumably data will be forthcoming soon that illustrate this similarly for selenium. This review compares the action of selenium to that of insulin and discusses the available evidence in support of selenium as an insulin-mimetic. Sulfonylureas increase insulin secretion by pancreatic beta cells by binding to membrane channels.

5. Plant materials tested for their insulinomimetic or secretogogues activity in the different in vivo or in vitro model system

Acacia arabica (Leguminosae)

About 94% seed diet of Acacia arabica showed hypoglycemic effect in rats through release of insulin. However, powdered seeds of Acacia arabica at 2, 3 and 4 g/kg, p.o. exerted a significant hypoglycemic effect in normal rabbits by initiating the release of insulin from pancreatic beta cells.

Aegle marmelos (Rutaceae)

Aqueous leaf extract of Aegle marmelos showed antihyperglycemic activity in streptozotocin induced diabetic rats after 14 days treatment either by increasing utilization of glucose or by direct stimulation of glucose uptake through increased insulin secretion.

Agrimony eupatoria (Rosaceae)

Aqueous extract of Agrimony eupatoria evoked stimulation of insulin secretion from the BRIN-BD11 pancreatic beta cell line in vitro. The effect of extract was found to be glucose- independent.

Alangium salvifolium (Alangiaceae)

Methanolic extract of Alangium salvifolium leaves possesses antihyperglycemic and antihyperlipidemic effects in dexamethasone induced insulin resistance in rats, which may be due to the antioxidant and

insulinotropic effect of extract.

Annona squamosa (Annonaceae)
Annona squamosa commonly called custard apple plant possesses antidiabetic activity. It acts by promoting insulin release from the pancreatic islets, increasing utilization of glucose in muscle and inhibiting the glucose output from liver.

Asparagus racemosus (Liliaceae)
The ethanol extract, hexane, chloroform and ethyl acetate fractions of Asparagus racemosus root were shown to have dose-dependent insulin secretion in isolated perfused rat pancreas, isolated rat islet cells and clonal beta -cells. These findings reveal that constituents of Asparagus racemosus root extracts have insulinotropic 14 activity.

Boerhaavia diffusa (Nyctaginaceae)
Chloroform extracts of leaves of Boerhaavia diffusa showed antidiabetic activity in streptozotocin induced diabetic rats which mainly act by reducing blood glucose level and increasing insulin sensitivity. Hypoglycemic and antihyperglycemic activity of aqueous leaf extract at 200 mg/ kg p.o. for 4 weeks in normal and alloxan induced diabetic rats showed to increase plasma insulin levels and improve glucose tolerance.

Bougainvillea spectabilis (Nyctaginaceae)
The blood glucose lowering potential of ethanolic leaf extract of Bougainvillea spectabilis in streptozotocin-induced type I diabetic albino rats was probably due to increased glucose uptake by enhanced glycogenesis in the liver and also due to increased insulin sensitivity.

Brassica nigra (Cruciferae)
Oral administration of aqueous extract of Brassica nigra for two months decreased serum glucose level, which was due to the release of insulin from pancreas.

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 peripheral tissues.

Caesalpinia bonducella (Cesalpinaceae)
Hypoglycemic activity of aqueous and ethanolic extracts of Caesalpinia bonducella in chronic type II diabetic model, showed an increase secretion of insulin in isolated islets.

Caffeine
Treatment with 0.01% caffeine solution in 90% pancreatectomized diabetic rats for 12-week reduced body weight, fats, and decreased insulin resistance. At the same time caffeine also enhanced glucose-stimulated first- and second-phase insulin secretion and beta-cell hyperplasia.

Enicostemma littorale (Gentianaceae)
Aqueous extract of Enicostemma littorale induced serum insulin levels in alloxan- induced diabetic rats at 8 h was associated with potentiation of glucose-induced insulin release through K+-ATP channel dependent pathway.

Ephedra distachya (Ephedraceae)
The alkaloids of Ephedra distachya herbs and l-ephedrine have shown antihyperglycemic effect in diabetic mice due to regeneration and restoration of atrophied pancreatic islets that induces the secretion of insulin.

Eriobotrya japonica (Rosaceae)
Aqueous extract of Eriobotrya japonica and the compounds cinchonain Ib, procyanidin B-2, chlorogenic acid and epicatechin, were tested for insulin secretory activity in INS-1 cells, showed significantl increase of insulin secretion from INS-1 cells in dose-dependent manner.

Ginkgo biloba (Ginkgoaceae)
Effect of Ginkgo biloba extract in humans and healthy rats shows that Ginkgo biloba significantly increased the insulin concentration.

Radix glycyrrhizae (Fabaceae)
Radix glycyrrhizae and glycyrrhetinic acid enhanced glucose-stimulated insulin secretion in isolated islets. In addition, they induced mRNA levels of insulin receptor substrate-2, pancreas duodenum homeobox-1, and glucokinase in the islets, which contributed to improve beta-cell viability.

Helicteres isora (Sterculiaceae)
Antihyperglycemic activity of butanol extracts of root of Helicteres isora at 250 mg/kg, p.o. in glucose loaded rats acts through insulin-sensitizing activity.

Hibiscus rosa sinensis (Malvaceae)
Oral administration of ethanol extract of Hibiscus rosa sinesis at 250 mg/kg, p.o. showed mild but significant hypoglycemia which was mainly due to insulin release by stimulation of pancreatic beta cells.

Hordeum vulgare (Gramineae)
The germinant fruits of Hordeum vulgare showed hypoglycemic and hyperinsulinemic effects in NIDDM subjects, due to mobilization of insulin in NIDDM, which makes it a suitable cereal for diabetes mellitus.

Lepechinia caulescens (Lamiaceae)
Lepechinia caulescens significantly decreased glucose tolerance suggesting that Lepechinia caulescens has insulinomimetic activity.

Mucuna pruriens (Leguminosae)
Blood glucose lowering activity of powdered seeds of

Mucuna pruriens was observed at 0.5, 1 and 2 g/kg, p.o. in normal rabbits as well as 1 and 2 g/kg, p.o. in alloxan-diabetic rabbits. It possibly acts through stimulation of the release of insulin or by a direct insulin-like action due to the presence of trace elements like manganese, zinc, etc.

Nigella sativa oil (Ranunculaceae)
Significant decreases in blood glucose level, and increase in serum insulin level were observed on treatment with Nigella sativa oil for 4 weeks. Immunohistochemical staining of pancreas from Nigella sativa oil-treated group showed large areas with positive immunoreactivity for the presence of insulin.

Panax ginseng (Araliaceae)
Ginseng polypeptides isolated from the root of Panax ginseng, when injected subcutaneously at daily doses of 50 and 100 mg/kg for 7 successive days in mice resulted in decreased blood glucose, increased liver glycogen level and stimulated insulin secretion. The aqueous ethanolic extract of Korean red ginseng significantly evoked a insulin release in a glucose-independent manner.

Pandanus odorus (Pandanaceae)
4-Hydroxybenzoic acid from Pandanus odorus at 5 mg/kg increased serum insulin levels and liver glycogen content in healthy rats.

Parinari excelsa (Chrysobalanaceae)
Flavonoid of Parinari excelsa showed hypoglycemic effect due to the ability of insulin secretory activity in the diabetic animal models.

Radix rehmanniae (Scrophulariaceae)
The pectin type polysaccharide, obtained from the rhizome of Radix rehmanniae exhibited hypoglycemic activity in normal and streptozotocins induced diabetic mice by stimulating the secretion of insulin and reducing the glycogen content in the mice.

Rehmania glutinosa (Scrophulariacea)
Intraperitoneal administration of the ethanol precipitate fraction obtained from the hot water extract from the rhizome of Rehmania glutinosa stimulated the secretion of insulin and reduced the glycogen content in the livers of healthy mice.

Ricinus communis (Euphorbiaceae)
Administration of ethanolic extract of Ricinus communis to the diabetic rats at 500 mg/kg, p.o. for 20 days, significantly increased the insulin levels and caused improvement in lipid profile and body weight of the diabetic animals.

Syzygium cumini (Rutaceae)
Oral administration of pulp extract of the fruit of Syzygium cumini to normoglycemic and STZ induced diabetic rats showed hypoglycemic activity in 30 min possibly mediated by insulin secretion and inhibited insulinase activit.

Salvia lavandifolia (Lamiacea)
Hypoglycaemic effect of Salvia lavandifolia may be due to potentiation of insulin release induced by glucose and hyperplasia of the pancreatic islet beta cells along with some other mechanisms. The antidiabetic activity of the extract of Salvia lavandifolia at 10 mg/kg induced an increase in the size and number of cells in the islets of Langerhans with increase in pancreatic insulin content.

Teucrium polium (Lamiaceae)
Aqueous extract of Teucrium polium crude extract is able to enhance insulin secretion through enhancing insulin secretion by the pancreas. The insulinotropic properties of Teucrium polium extracts can be attributed to the presence of apigenin existing only in methanol fraction but not in aqueoue fractions. Crude extract of Teucrium polium is capable of enhancing insulin secretion at high glucose concentration and plant extract seems to be capable of regenerating the islets of Langerhans in the treated diabetic rats compared to the untreated diabetic rats.

Tinospora crispa (Menispermaceae)
Antihyperglycaemic effect of Tinospora crispa extract is probably due to the stimulation of insulin release via modulationofbeta-cellCa2+ concentration.

Tribuluks terrestris (Zygophyllaceae)
The extract of Tribuluks terrestris significantly decreases blood glucose level in normal and alloxan-induced diabetic mice, mainly due to the increased serum insulin level.

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, hydroxyisoleucine, 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- hyperglycemic 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.

Zizyphus spina-christi (Rhamnaceae)
The effect of the butanol extract of Zizyphus spina-christi leaves and its major saponin glycoside, christinin-A, on the serum glucose and insulin levels showed that

christinin-A potentiated glucose-induced insulin release in non-diabetic control rats. Serum insulin and pancreatic cAMP levels showed significant increase in diabetic rats treated for a period of 4 weeks with the butanol extract of Zizyphus spina-christi.

6. Table of Important anti-diabetic potential herbal plants sourceand their active principles

Table 1: Important anti-diabetic potential herbal plants source and their active principles.

Scientific Name (Family)	PartsUsed	Extraction solvent	Diabetic inducedby	Active Ingredient's	Probable Mecha-nism of action
Vernonia amygdalina (asteraceae)	Leaves	Hydroalcoholic, methanol, acetone and N-hexane	Alloxan	Anthraquinone, tannins, flavonoids, akaloids, saponins, glycosides, terpenoids	Hypoglycemic activityby enhancing insulin secretion and insulin activity, lipid metabolism and antioxidant.
Aegle marmelos (Rutaceae)	Leaves, juice	Methanol	Alloxan Alloxan	Citral, cineole, citro-nellal, skimmianine, aegilin	Stimulates insulin secretion from betacells inhibits insulin degradative process.
Euonyrnus alatus (Celastraceae)	Leaves	Ethanol	STZ	Rutin, β-sitosterol and quercetin	Hypoglycemic ac- tivityby β-sitosterol, Stimulates insulin secretion from β cells inhibits insulin degradative process.
Fructus Coini (Cornaceae)	Leaves, Seeds	Ether, benzene and chloroform	STZ	Bornyl acetate, camphor, borneol, beta-sitosterol, van- illic acid, stearic acid and palmitic acid	Increases gluconeo- genesis and decreases Glycogenolysis.
Tephrosia villosa (Leguminosae)	Whole plant	Alcohol/water	STZ	Flavones, flavanones, prenylated flavo- noids, chalcones and rotenoids	Hypoglycemic, hypolipidemic and antioxidant property decreased influx of glucose in polyol pathway, increasing NADPH/NADP ratio and increased activity of glucose peroxidase.
Zaleya decandra (Aizoaceae)	Whole plant	Methanol	STZ	Terpenes and triter-penoids, sterols and steroids, phenolics, flavonoids, gums, resins, quinones, anthocy-anidine, saponins, antioxidantsand fatty acids	Stimulates insulin secretion from beta cells inhibits insulin degradative process.
Vernonia amygdalina (Asteraceae)	Leaves, flowers & Seed	Hydroalcoholic, methanol, acetone and N-hexane	STZ	Anthraquinones, tannins, flavonoids, alkaloids, saponins, glycosides, cyano- genic glycosides, terpenoids, tannins	Hypoglycemic activityby inhibiting oxidativeStress.
Heinsia crinata (Rubiaceae)	Root, cortex	Methanol,hexane	Alloxan	Flavonoids, hy- droxy-anthraqui- nones, saponins, steroids, tannins and glycoside	Hypoglycemic activ- ityby lowering blood glucose and stim-ulating peripheral utilization of glucose.
Barleria prionitis (Acanthaceae)	Rhyzomes	N-Hexane, ethyl acetate,methanol andwater	Alloxan	Glycosides, methyl ester, 6-o-trans- p-coumaroyl-8-o-acetylshanzhiside methyl ester, barlerin, acetylbarlerin, 7-me-thoxydiderroside and lupulinoside	Increase in glucose uptake and glycogen deposition, inhibits activity of epineph-rine on glucose metabolism result- ing in utilization of peripheral glucose. does not alter cortisol concentration.

Acacia Arabica (Leguminosae)	Seeds, leaves	Eyhanol, methanol	STZ	Kaempferol, querce- tin, 3,4',7-trihydrox- yl-3', 5-dimethoxy- flavone,	Hypoglycemic effect in rat, through release of insulin.
				catechin, epicatechin, afzele-chin, epiafzelechin, mesquitol, ophioglo- nin, aromadendrin and phenol	
Nymphaea Pubescens (Nymphaeaceae)	Flower, leaves	Ethanolicextract	Alloxan	Alkaloids, carbohy- drates, glycosides, sterols, phenolic com- pounds and tannins, amino acids, proteins and flavonoids	Increase the insulinsecretion or inhibit the intestinal absorp- tion of glucose.
Paspalum scrobicu- latum (Poaceae)	Stem juice, rhizomes, roots	Aqueous and ethano- lic extract	Alloxan	Steroids, lipids, amino acids and carbohydrates	Reduce the bloodglucose and lipid parameters.
Adina cordifolia (Rubiaceae)	Leaves	Hydro-alcoholic	Alloxan	Tannins, saponins and flavonoids.	Increase the insulinsecretion or inhibit the intestinal absorp- tion of glucose.
Afzelia africana (Fabaceae)	Stem bark	Aqueous	STZ	Flavonoids, proanthocyanidins, tannins, phenols and Flavonols.	Potentiating of insu-lin from β cells or byincreasing peripheral glucose uptake.
Acanthopanaxsenticosus (Araliaceae)	Whole plant	Hydroalcoholic	Alloxan	Polysaccharide.	Potent antioxidantactivity leads to antidiabetic activity.
Aralia elata (Araliaceae)	Root cortex	Ethanol	STZ	β-sitosterol, oleanolic acid, daucosterol, oleanolic aci- do-28-o-β-d-gluco- pyranoside, araloside a and sucrose. Except oleanolic acid	The hypoglycemic activity of A. elata ismainly mediated through inhibition ofaldose reductase activity.
Grewia Asiatica(Mal- vaceae)	Fruit, Stem bark and leaves	Ethanol	Aloxan	Anthocyanin, cyan- idin 3- glycoside 9, vitamin C	reduction in serumglucose level of allox- an induced diabetic rabbits. This anti-hyperglycemic may
					be mediated by its antioxidant and radical scavengingactivity rather thanby stimulating the release of insulin.
Gymnema sylvestre (Asclepiadaceae)	Leaves	Ethanool	STZ	Gymnemic acid, gurmarin, and saponins	Causinga prominent suppression in blood-glucose, glycosylatedhemo- globin and glycosylat- ed plasmaproteins together with restor- ing blood glucose homeostasis in type 2 diabetic patients.
Lawsonia inermis (Lythraceae)	Whole plant	Ethanol as wellas 95% methanol	Alloxan	Carbohydrates, flavonoids, proteins, phenolic compounds, tannins, terpenoids, alkaloids, quinones, xanthones, coumarins	Extracts of the whole plant exhibited potent hypoglycemic and hypolipidaemic activities in alloxan induced diabetic micecausing significant reduction in serum glucose, cholesterol and triglycerides levelexceeding the effect of glibenclamide.

Panax ginseng (Araliaceae)	Root and leaves	Methanol	STZ	Triterpene glycosides, ginseno- side, peptides, fatty acids and polyacety- lene alcohol	aqueous extract showed a remarkablehypoglycemic activity,increasing insulin production, reducing pancreatic β-cells death and resistance to insulin, thus improving post- prandial glycemia in diabetic patients.

7. DISCUSSION

Diabetes is a disorder of carbohydrate, fat and protein metabolism caused due to insufficient production of insulin or its inhibitory action, which can be considered as a major source of high economic loss which can in turn obstruct the development of nations. Before there were drugs from drug companies, natural cures were used and they can still be used today. There are many herbs with strong antidiabetic proper- ties. Herbal treatments for diabetes have been used in patients with insulin dependent and noninsulin dependent diabetes, diabetic reti- nopathy, diabetic neuropathy etc. The families of plants with the most potent hypoglycaemic effects include Leguminoseae, Lamiaceae, Liliaceae, Cucurbitaceae, Asteraceae, Moraceae, Rosaceae, Euphor- biaceae and Araliaceae. The most commonly studied species are: Opuntia streptacantha, Trigonella foenum graecum, Momordica cha- rantia, Ficus bengalensis, Polygala senega and Gymnema sylvestre. In the experiments, oral glucose tolerance test, streptozotocin and alloxan induced diabetic mouse or rat were most commonly used model forthe screening of antidiabetic drugs. Numerous mechanisms of actions have been proposed for plant extracts. Some hypothesis relates to their effects on the activity of pancreatic beta cells, increase in the inhibitory effect against insulinase enzyme, increase of the insulin sensitivity or the insulin-like activity of the plant extracts. Other mechanisms may also be involved such as increase of peripheral utilization of glucose, increase of synthesis of hepatic glycogen or decrease of glycogenolysis, inhibition of intestinal glucose absorption, reduction of glycaemic index of carbohydrates and reduction of the effect of glutathione. In this review, natural products classified into terpenoids, alkaloids, flavonoids, phenolics, and some other categories have shown antidiabetic potential through the insulinomimetic activity of the plant extract. Roseoside, epigallocatechin gallate, beta-pyrazol-1-ylalanine, cinchonain, leuco- cyandin 3-O-beta-d-galactosyl cellobioside, leucopelargonidin-3-O-al- pha-L rhamnoside, glycyrrhetinic acid, dehydrotrametenolic acid, strictinin, isostrictinin and pedunculagin, epicatechin and christinin-A isolated from the plant material have shown significant insulinomimetic activity along with significant antidiabetic potential. Additionally, some flavonoids and polyphenols, as well as sugar derivatives, are found to be effective due to some other extrapancreatic mechanisms. In this review 20 plants are included which have shown antidiabetic action through relese of insulin and some extra pancreatic mechanisms.

8. CONCLUSION

Present study has described a list of 20 antidiabetic plants used in the treatment of diabetes mellitus. Majority of plants are containing phy- toconstituents such as flavonoids, terpenoids, coumarins and polyphe- nols. Among of them flavonoids including flavan-3-ols, flavanones, flavonols, anthocyanidins, flavones and isoflavones. Terpenoids in- cluding Monoterpenoids, Diterpenoids, Triterpenoids and Polyter- penoids. Furthermore, phenolic compounds such as eugenol, eugenol acetate and gallic acid are present. These are capable to produce insu- linomimetic action and also show that these plants have hypoglyce- mic effects and can be used to treat various types of secondary com- plications of diabetes mellitus.

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