Available online on 15.01.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Review Article

Indian medicinal plants with antidiabetic potential

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ABSTRACT

Diabetes Mellitus is a metabolic disorder affecting a large proportion of world's population. It is characterized by the appearance of persistent hyperglycemic conditions in affected individuals due to the incompetency of bodily mechanisms to curb the rising glucose levels in the blood. Medicinal plants are utilized since the ancient times as the source of therapeutic agents for the treatment and cure of a variety of disorders. The use of medicinal plant in the traditional systems of medicines for the management or treatment of diabetes have provided admirable results suggesting a potential role that herbals can play in the management of the disorder. The ease of access, affordability and the ability of herbals to produce minimum side effects on administration has convinced a major portion of population globally to switch to this alternative approach of medicine. Moreover, a number of studies have suggested that the medicinal plants employ the multi target approaches that make them least susceptible to failure during the course of treatment. The present review summarizes the antidiabetic profile of medicinal plants found in the Indian subcontinent that are evaluated for their hypoglycemic activity. Medicinal plants showing prominent anti-diabetic activity during the initial studies should be further explored to identify the active principles present in them that can become the promising drug candidates for the disease treatment in the coming future.

Keywords: Anti-diabetic, Diabetes Mellitus, Insulin, hypoglycemic, anti-hyperglycemic, anti-hyperlipidemic

Article Info: Received 10 Nov 2018; Review Completed 23 Dec 2018; Accepted 28 Dec 2018; Available online 15 Jan 2019

Cite this article as:

Chhipa AS, Sisodia SS, Indian medicinal plants with antidiabetic potential, Journal of Drug Delivery and Therapeutics. 2019; 9(1):257-265 http://dx.doi.org/10.22270/jddt.v9i1.2282

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INTRODUCTION

Diabetes mellitus is the chronic condition of abnormally elevated levels of glucose in the blood. With an elevation in blood glucose level, the release of hormone insulin occurs from the beta cells of pancreas. Insulin is the major metabolic hormone in the body. It stimulates muscle and fat cells to reduce the glucose levels from the blood as well as stimulates the liver for glucose metabolism, thus effectively reducing blood glucose levels by various mechanisms.

Diabetic patients tend to have a chronically high blood glucose levels. Two reasons can be attributed to this. Either there is not enough insulin produced by the Beta cells (Type 1 diabetes) or there may be reduced sensitivity of body cells to insulin (Type 2 diabetes). Type 1diabetes is generally considered as an autoimmune disorder where the body's defense mechanisms fail to recognize the self-pancreatic cells and produce immune mechanisms against them, thus destructing the insulin-producing Beta cells. This type of diabetes is rare and occurs in around 5% diabetic population. Type 1 diabetes is also known as insulin dependent diabetes mellitus or IDDM. Type 2 diabetes affects a majority of diabetic patients. It is also known as Non-insulin dependent diabetes mellitus or NIDDM. [1]

Apart from Type 1 & 2 diabetes, conditional diabetes like situation may also arise. As in case of Gestational diabetes, pregnant mother may be diagnosed diabetic during pregnancy which may or may not subside after childbirth. Diabetes can also be drug-induced, for example: in the case of patients taking glucocorticoids, glucose levels in the blood increases till the treatment is continued. Discontinuation of glucocorticoids brings back the normoglycaemic condition. Another example would be a person treated with thiazides who develops diabetes years later. [2]

Types of Diabetes

In general considerations, all forms of diabetes are categorized under the two major forms of diabetes i.e. Type 1 and Type 2 diabetes:

Type 1 Diabetes

Type 1 diabetes is considered as an autoimmune disorder where the body's defense mechanisms fail to recognize the self-pancreatic cells and produce immune mechanisms against them, thus destructing the insulin-producing Beta cells. The chances of occurrence of this form of diabetes is generally rare when compared with other forms of diabetes and is generally seen in around 5- 10% of diabetic populations. Auto destruction of beta cells in type-1 diabetes

is caused by islet cell autoantibodies, insulin directed antibodies, autoantibodies towards Glutamic Acid Decarboxylase or GAD or antibodies directed towards the tyrosine phosphatases. When diagnosed with Type-1 diabetes, multiple antibodies towards pancreatic cells are detected in the patient's blood. Association with HLA gene is also suspected to act as a predisposing factor for the cause of this type of diabetes.

Destruction of Beta cells in type-1 diabetes may vary from patient to patient. Destruction may be rapid in some individuals as in case of infants and children or slow as in case of adults and elderly. The first sign of type-1 diabetes in children and adolescents is the appearance of ketoacidosis in diagnosis. Moderate hyperglycemia leading to severe hyperglycemia and ketoacidosis in the presence of infections may also occur in some children. Adult patients tend to retain the residual beta cell functions to prevent ketoacidosis for several years by completely depending on external insulin and live at a lower risk of ketoacidosis.

Multiple genetic predispositions are thought to induce autoimmune destruction of β-cells. Patients of Type-1 diabetes also remain at a higher risk of developing other autoimmune disorders that may include Graves' disease, Hashimoto's thyroiditis, Addison's disease, vitiligo, celiac sprue, autoimmune hepatitis, myasthenia gravis, and pernicious anemia.[2]

A small proportion of type-1 patients may have chronic insulinopenia and are much prone to ketoacidosis but show no symptoms of an autoimmune disorder. This form of diabetes is strongly inherited but is not HLA associated. Such patients may also suffer from frequent ketoacidosis with varying degree of insulin levels between episodes of ketoacidosis. The requirement of insulin in the affected individuals with this type of diabetes may vary.[2]

Type 2 Diabetes

Type-2 or adult-onset form of diabetes affects a majority of the population (around 90-95%) and is characterized by insulin resistance and relative insulin deficiency. These patients generally do not need insulin replacement for their survival.

A majority of type-2 diabetes patients suffer from obesity that leads to additional insulin resistance. In non-obese type-2 diabetes patients, body fat distribution occurs predominantly in the abdominal region. Ketoacidosis is a rare condition in type-2 diabetes; although infection or stress factor may lead to ketoacidosis in such patients. Patients with type-2 diabetes are at a higher risk of developing macrovascular and microvascular complications. Insulin levels in such patients appear to be normal, the higher blood glucose levels even in the presence of insulin leads to the conclusion that beta cells are functional and the elevation in glucose levels is due to some other factor. While resistance to insulin can be improved with therapeutic approaches or by lifestyle modifications such as weight reduction, complete restoration of the normoglycemic condition is seldom observed. Age, obesity, hypertension and lack of physical activities may increase the risk of type-2 diabetes. Gestational diabetes (a form of conditional diabetes) may also take the form of permanent type-2 diabetes after childbirth in women if proper measures are not taken. Association of type-2 diabetes with genetic predispositions is strongly believed to exist although clear mechanisms are poorly understood in this case.[2]

Common symptoms of diabetes include frequent urination, excessive thirst, increased appetite, fatigue, blurred vision, slow wound healing, weight loss – regardless of increased appetite (type 1), tingling, pain, or numbness of hands/feet (type 2).[3]

PHYSIOLOGY AND BIOCHEMISTRY OF GLUCOSE REGULATION

Overview of Glucose Metabolism

Glucose is the major fuel to fulfill the cellular energy demands in the body. The glucose in the blood is regulated mainly by insulin and has varying fates in the human body. It generates energy molecules (ATP) by converting into a three carbon molecule, Pyruvate which then enters the tricarboxylic acid (TCA) cycle and oxidative phosphorylation in mitochondria. Excess of glucose in the blood is converted into fat and glycogen that act as long term and short term deposits of energy molecules respectively.

In the presence of an excess of glucose in the blood, Insulin is released to handle the blood glucose levels. Upon release, Insulin exerts the following actions on body cells:

- Activate insulin dependent GLUT-4 transporters in muscle and fat cells to shift glucose from the blood to the adipose tissue.
- Increase peripheral uptake of glucose by cells for its breakdown in the energy-releasing molecules, releasing their energy in the form of ATP (via glycolysis -TCA cycle-Oxidative phosphorylation pathway)
- Stimulates hepatocytes in the liver and muscle cells to store glucose in the form of glycogen that acts as the short term reserve of energy.

Another hormone called Glucagon is released from the alpha cells in islets of Langerhans of pancreas that opposes the actions of insulin. Blood with low levels of glucose when passes through the capillaries in the islets of Langerhans; alpha cells sense the low levels of glucose in blood and release Glucagon to increase the glucose levels in the blood by depleting glucose stores. On contrary to insulin action that stimulates the formation of glycogen from glucose, glucagon reverses insulin action and converts the glycogen into glucose. Glucagon also depletes fats and proteins to generate energy when glucose levels in the body are scarce.[1]

Regulation of Blood Glucose

Blood glucose levels fluctuate as per the body's requirements. These fluctuating levels of glucose in blood should lie in the range 70 to 110 mg/dl of blood to ensure the normal functioning of metabolic machinery of the body. The levels of glucose in the blood raise under three conditions: diet, glycogen breakdown or hepatic synthesis of glucose.

Elevation of glucose levels with diet depends upon the glycemic index (higher in case of carbohydrates intake) and rates of absorption and digestion. Transport of glucose across the biological membranes takes place by the utilization of special transporters called Glucose transporters or GLUTs. Six types of GLUT transporters are known (GLUT 1-5, 7). GLUT 1&3 transporters have a high affinity for glucose. These transporters shift the glucose from the blood to cells down the concentration gradient and are found in high concentration in neurons where a continuous supply of glucose is mandatory. These transporters are not insulin dependent. GLUT-2 transporters are bidirectional and are found in liver and beta cells of the pancreas where the bidirectional movement of glucose in desirable. GLUT-4 is an insulin-sensitive transporter and its expression depends on the insulin concentration in blood. A high

increase in glucose levels in the blood triggers the insulin release that in turn stimulates the expression of GLUT-4 receptors in adipose tissues to store excess glucose as energy stores in the form of fat. GLUT-5 receptors are fructose sensitive transporters. They are found in high concentration in testis, GIT and sperm cells. GLUT-7 receptors are found on smooth endoplasmic reticulum plays a vital role in the process of gluconeogenesis.

The liver acts as the major machinery for the production of glucose. During starvation, it releases glucose from the glycogen and ensures that the levels of glucose in the blood lie in the normal range. Liver also synthesizes glucose from the intermediates of carbohydrate, protein, and fat metabolism. [1]

Insulin

Insulin Synthesis

The insulin gets synthesized in the beta cells of pancreas. Beta cells are found as clumps in the endocrine part of the pancreas called the "islets of Langerhans."

Insulin synthesis begins with the transcription of the insulin gene on chromosome no. 11. The mRNA synthesized during transcription is transported to the cytosol for the subsequent translation of mRNA to form insulin polypeptides. During the process of translation, two introns from mRNA are spliced out that encode 110 amino acids long protein. The primary translation product of insulin consists of an initial segment (24 amino acids long) and is called preproinsulin which is inactive. The initial segment is necessary for crossing the endoplasmic reticulum membrane. Once inside the endoplasmic reticulum, the preproinsulin is converted into proinsulin by the cleavage of the initial segment by protease enzymes. The proinsulin produced consists of three amino acid chains: the A chain, the B chain and the connecting C peptide chain linked together.

The proinsulin inside the endoplasmic reticulum is further exposed to several specific peptidases that cleave the C-peptide chain from the A&B chains thus producing the active insulin. The mature insulin and C-peptide are then transferred to the Golgi apparatus to be packed as secretory granules in the beta cell's cytosol. Entry of glucose stimulates the exocytosis of granules and insulin release. [1]

Insulin Structure

Insulin molecule consists of two amino acid chains named chain A (21 amino acids) and chain B (30 amino acids). The chains A&B are linked together by 2 disulphide bridges. A third disulphide bridge also exists on A-chain that links the 6th and 11th residues of the A chain together.

The design of recombinant insulin is done in such a way that the propensity of insulin molecule to form dimers and hexamers is either prevented or reduced but its binding to insulin receptor is not compromised. This approach has enabled to prepare a wide range of recombinant insulin that varies in their duration of action from short acting to long acting. [1]

Insulin Secretion

As discussed already, the rising levels of glucose in the blood that are detected by the pancreatic beta cells trigger the insulin release. The secretion of insulin release from the beta cells is a multistep process. The sequence of events that occur in beta cells during the insulin release is as follows:

- Type 2 glucose transporters (GLUT2) transport the glucose down the concentration gradient from blood to the cells. Once inside, the glucose is rapidly phosphorylated into glucose-6-phosphate by the enzymes Hexokinase and Glucokinase in some cells where a high concentration of glucose is handled. The enzyme hexokinase acts rapidly even in the presence of a small amount of glucose in cells. Glucokinase, on the other hand, acts slowly and only in the presence of high concentration of glucose in the cells. In scientific terms, hexokinase has less Km and Vmax while glucokinase has high Km and Vmax. Low Km and Vmax are desirable in almost all cells as a high concentration of glucose in normal cells is seldom achieved. Glucokinase is found to be active in liver cells where hepatocytes handle a high concentration of glucose and a high Km and Vmax are necessary.
- Metabolism of glucose occurs through Glycolysis- TCA cycle- oxidative phosphorylation pathway that ultimately generates the energy molecules ATP.
- Elevation in ATP levels inside the cells allows the binding of ATP to ATP sensitive-gated potassium channels in the beta cell membrane. Binding of ATP closes the potassium channels thus preventing the positively charged potassium ions (K^+) from leaving the beta cells.
- Intracellular positivity due to increased concentration of K^+ causes depolarization in the beta cells.
- Voltage-sensitive calcium channels open, allowing calcium ions (Ca^{2+}) to flood inside the cell.
- Intracellular increase in calcium concentration stimulates the secretion of insulin by the process of exocytosis.

In response to the rise in glucose levels, insulin release occurs in two phases. During the first phase, an immediate release of insulin occurs from the secretory granules filled with preformed insulin. This is followed by a brief fall in insulin release. The second phase of insulin release occurs after this short delay is composed of newly synthesized insulin. This biphasic release of insulin gives a biphasic response curve of insulin towards increased glucose levels.

Insulin exerts its action for a short duration after its release in the bloodstream. The presence of enzyme insulinase in liver and kidneys degrades the circulating insulin thus limiting the half-life of insulin to around 6 minutes. [1]

Insulin Receptor

The binding of insulin to the insulin receptor initiates a cascade of phosphorylation and dephosphorylation reactions inside the cells. The action of insulin on the insulin receptor is terminated by dephosphorylation of the receptor. The insulin receptor is a tyrosine kinase receptor found embedded in the plasma membrane and is composed of pairs of alpha and beta subunits. The insulin binding site is located on the extracellular alpha subunit of the receptor. The beta subunit is present inside the cell-bound with tyrosine molecule.

Binding of insulin to alpha subunits induces a conformational change in the receptor that signals the intracellular beta subunit to undergo phosphorylation. Phosphorylation of tyrosine of each beta subunit occurs along with other target proteins resulting in diverse cellular activities that are governed by insulin [1]

Insulin Action

The binding of insulin to insulin receptor results in the expression of a wide range of biological actions that take place during its lifespan. Once released, insulin rapidly

increases the glucose uptake into many tissues that express insulin sensitive GLUT-4 transporters, such as skeletal muscle and fat. Insulin also enhances the transporters activity and number by increasing their recruitment from the cytoplasm to the cell surface. As discussed, not all tissues require insulin for glucose uptake; cells such as hepatocytes, RBCs, GIT cells, nephrons and cells of the neurons use GLUT-1&3 glucose transporters which are independent of insulin action. Depending upon the phosphorylation of enzymes by insulin binding, the activity of these enzymes is altered variably with time. [1]

ANTI-DIABETIC DRUGS

Metformin

Metformin is a hypoglycemic agent that reduces plasma glucose levels by causing the inhibition of hepatic gluconeogenesis. Intestinal absorption of sugars is also reduced or retarded after the administration of metformin. Reduction in LDL and VLDL levels with an increase in HDL level is also seen in patients after 4-6 weeks long treatment with metformin. Secondary actions of Metformin include decreased appetite and reduction in cardiovascular mortality. Adverse effects of metformin may cause severe lactic acidosis especially in patients with congestive heart failure. Hypoglycemia may occur when metformin is combined with other antihyperglycemic agents.

Nateglinide

Nateglinide belongs to meglitinide class of hypoglycemic drugs. It binds to ATP sensitive K+ channels like sulfonylureas but with less affinity. They stimulate insulin synthesis by causing intracellular depolarization, thus, acting in a manner similar to sulfonylurea to promote insulin secretion with shorter onset and duration of action. It is effective in causing prandial and postprandial release of insulin. It produces less hypoglycemia in comparison to sulfonylurea due to their short duration of action. Its duration of action is prolonged by CYP3A4 inhibitors while decreased by CYP3A4 promoters. Combination with gembifrozil and repaglinide causes severe hypoglycemia. [4]

Pioglitazone

Pioglitazone is an activator peroxisome proliferator-activated receptor-γ (PPAR-γ). PPAR-γ agonists regulate the production of adipocytes, fatty acids secretion and metabolism of glucose. Pioglitazone binds to PPAR-γ receptors and increases the sensitivity of insulin to adipocytes, hepatocytes and skeletal muscle cells. An appreciable reduction in hyperglycemia, HbA1c levels and triglycerides levels with the increase in HDL levels after administration occurs. Subcutaneous accumulation of fats is seen in patients taking pioglitazone. Adverse effects include hepatotoxicity that may be fatal. Hepatic functions must be monitored routinely in patients taking pioglitazone. Concomitant administration with oral contraceptives may lead to the failure of contraceptives. [4]

Miglitol

Miglitol is an oligosaccharide derivative that is generally taken before the meal to delay carbohydrate absorption and digestion. Miglitol inhibits glucosidase enzyme present in the intestinal brush borders that mediate the digestion of carbohydrates. Adverse effects include diarrhoea, flatulence and cramps. It is contraindicated in patients with intestinal pathology. [4]

Glimipride

Glimipride is a long-acting sulfonylurea that acts by blocking ATP sensitive K+ channels. It works in a manner similar to meglitinides but has a longer duration of action. It enhances the number and binding of insulin to target cells and reduces glucagon secretion. Adverse effects include weight gain, hyperinsulinemia and hypoglycemia. Accumulation of glimepiride occurs due to hepatic and renal insufficiency leading to the associated risk of hypoglycemia. [4]

IMPORTANCE OF HERBAL MEDICINES

Since ancient times, herbal remedies are used for the treatment of a variety of diseases and disorders. The use of medicinal herbs still continues to be an approach of choice for the treatment of ailments. Herbs are utilized in almost all cultures as the source of active therapeutic constituents. Their ease of access, affordability and lack of side effects make them acceptable approach for disease treatment especially in developing and underdeveloped countries where the modern system of medicine is poorly developed. A variety of active constituents are isolated from medicinal plants that have established themselves as potential candidates for disease treatment. Different species of medicinal plants are explored for their antidiabetic potential and are used in traditional medicinal practices to control diabetes. Before the advent of insulin, traditional plants were used extensively for the treatment of both types of diabetes.

MEDICINAL PLANTS EXPLORED AS ANTI-DIABETIC

Acacia arabica

Acacia arabica (babul) is used in the traditional Indian system of medicine for the treatment and management of diabetes. When powdered seeds extract was administered to rats in varying doses of 2, 3, 4g/kg; hypoglycemia was observed in control rats but not in alloxanised rats. The plant extract was found to be secretagogue and requires functioning beta cells for activity. Plant extract initiates insulin release from beta cells.

Adansonia digitata

Different plant parts of *Adansonia digitata* including leaves, bark and fruits are used in traditional African system of medicine for the management of diabetes. The plant is also consumed as a regular food. For its wide range of medicinal properties, the plant is also referred to as "the small pharmacy or chemist tree." [9]. When methanolic stem bark extract of *Adansonia digitata* was administered to streptozotocin-induced diabetic Wistar rats, an appreciable reduction in glucose levels was observed that was comparable to controlled rats. Progressive increase in dose resulted in varying hypoglycemic action of extract. When a dose of 100mg/kg was administered, a significant reduction in glucose levels was observed after 1, 3, 5 and 7 hours of extract administration. A dose of 200 mg/kg reduced the blood glucose levels significantly after 3, 5 and 7 hours of administration. A dose of 400 mg/kg showed hypoglycemic action after 5 and 7 hours of administration, compared to control normal saline. The results were suggestive of potential hypoglycemic activity of plant extract. [6].

Adhatoda vasica

The methanolic extract of leaves of *Adhatoda vasica* Nees (Acanthaceae) caused inhibition of enzyme sucrase that catalyses the conversion of sucrose into glucose. The possible sucrose inhibitory activity was found due to the presence of compounds vasicine and vasicinol in the

extract. The IC_{50} values were found to be 125µM and 250µM for vasicine and vasicinol respectively. Further evaluation of pharmacokinetics data suggested that the inhibitory activities of the two compounds were due to the inhibition of sucrose hydrolysing activity of α-glucosidase. The compounds bound competitively with K_i values of 82 µM and 183 µM, respectively. These results were suggestive of antidiabetic activity of plant extract containing vasicine and vascinol. Further exploratory studies of the two compounds are required to establish them as potential hypoglycemic candidates. [7]

Aegle marmelos

The leaf extract of *Aegle marmelos* has been used routinely in the traditional Indian system of medicine for the management and treatment of diabetes. When a methanolic extract of plant's leaves was administered to alloxan induced diabetic rats, it showed a significant reduction in glucose levels in the blood. Continuous administration of extract showed hypoglycemic effects after the 6th day. The reduction in glucose levels was found to be around 54% on the 12th day of extract treatment. Apart from excellent antidiabetic activity, results were also suggestive of potential antioxidant activity of plant extract. [8]

Aloe barbadensis

Aloes are used since ages as traditional remedies for the treatment of a variety of diseases. Two fundamental parts isolated from aloes are gel and latex. The *Aloe vera* gel is isolated from the leaf pulp while the Aloe latex is the bitter yellow exudate that is isolated from the pericyclic tubules lying under the leaf's outer skin. Diabetic rats and normal rats showed appreciable improvement in glucose tolerance when extracts of aloe gum were administered. [9] Prolonged treatment with Aloe barbadensis exudates reduced glucose levels in the blood of alloxanised diabetic rats. The possible mechanism of action is thought to be due to secretagogue effects of plant extract on pancreatic beta cells. Bitter principles isolated from the plant also showed hypoglycemic effects in diabetic rats. [9]

Andrographis paniculata

The chloroform extract of *Andrographis paniculata* roots showed excellent antihyperglycemic activity in alloxan-induced diabetic rats. Acute and chronic studies were also performed and a significant reduction in glucose levels was observed in both the studies. Induction of albuminuria, proteinemia and uremia was inhibited by the plant extract. The study supports the traditional usage of plant roots for the management of diabetes and indicates antidiabetic activity of the plant. [10].

Anthocephalus indicus

Anthocephalus indicus is used in Ayurvedic system of medicine since the ancient times for the treatment of diarrhea, pain, detoxification and as aphrodisiac. Ethanolic extract of plant's roots was administered in alloxanized diabetic rats to evaluate the antidiabetic, antioxidant and antihyperlipidemic activities of plant extract. The study was carried out for 21 days with a dose of 500mg/kg. A significant decrease in glucose, triglycerides, total cholesterol, phospholipid and free fatty acids levels was observed. The plant also showed potential antioxidant activity. The root extract when used at the dose range of 100- 400µg/kg, inhibited the generation of superoxide anions and hydroxyl radicals in enzymic and non-enzymic systems, *in-vitro.* The results were indicative of antidiabetic, lipid-lowering and antioxidant activities of the plant. [11]

Artanema sesamoides

Methanolic extract of *Artanema sesamoides* was administered in streptozotocin-induced diabetic rats. Administration of extract resulted in a significant reduction in blood glucose levels with an increase in liver glycogen levels in diabetic rats when compared with control rats. Increased levels of liver SGPT, SGOT, and serum alkaline phosphatase were also suppressed after administration. A potential antioxidant activity of plant was also observed. Study results indicated a potential antidiabetic activity of the plant. Further studies for the isolation and characterization of active constituents are required to identify antidiabetic constituents. [12]

Azadirachta indica

Hydroalcoholic extracts of *Azadirachta indica* showed anti-hyperglycemic activity when administered in streptozotocin-induced diabetic rats. Extract administration resulted in increased uptake of glucose and deposition of glycogen in rat hemi diaphragm. The plant has also shown excellent antioxidant, hepatoprotective, antibacterial, antimalarial and antifertility effects. [13]

Boerhavia diffusa

Commonly known as Punarnava, it is used extensively in Indian system of medicine as a diuretic, hepatoprotective and for the treatment of various other diseases. Aqueous extract of *Boerhavia diffusa* leaves when given in a dose of 200mg/kg for 4 weeks to alloxan-induced diabetic rats showed a significant decrease in blood glucose levels in normal and alloxanized rats. A significant decrease in hepatic enzymes was also observed. Rats treated with extract also showed significant glucose tolerance. The extract showed more antidiabetic activity when compared with standard drug glibenclamide (600µg/kg). [14]

Butea monosperma

Also known as *Butea frondosa*, it is found distributed throughout the geographical regions of India. *in vitro* study of methanol extract of seeds suggested a significant anthelmintic activity, anticonvulsive and hepatoprotective activities of the plant. The plant is also used traditionally for the management of diabetes. Significant reduction in blood glucose levels was observed in normal and alloxan-induced diabetic mice. Results indicate the antidiabetic potential of the plant. [15]

Caesalpinia bonducella

The Plant is found to be widely distributed throughout India and other tropical regions around the globe. Hypoglycemic activity of four different extracts (petroleum ether, ether, ethyl acetate and aqueous) of the seed kernels was tested in normal and alloxan induced diabetic rats. Polar extracts (ethyl acetate and aqueous) showed significant hypoglycemic activity in diabetic rats. The hypoglycemic effect was comparable to standard drug glibenclamide. Diabetes-induced changes in lipid profiles and liver functioning were also restored after the treatment with polar extracts. Non-polar extracts showed insignificant antidiabetic activity. Phytochemical screening of polar extract confirmed the presence of triterpenoids and glycosides. [16]

Cassia auriculata

C. auriculata is found commonly in Asian countries and used and widely used in the Ayurvedic system of medicine. Its extract is used as a tonic, astringent and in the treatment of conjunctivitis, ophthalmia and diabetes in the

traditional system of medicine in India. It is one of the ingredients in the Ayurvedic formulation ''*Avaaraipanchagachooranam"* used for the treatment of diabetes. Aqueous and ethanolic extracts of the plant have shown a significant reduction in blood glucose levels when administered in Alloxan-induced diabetic rats (0.25-0.5g/kg). The plant also showed antihyperlipidemic and antidiabetic activity in streptozotocin-induced diabetic rats. Phytochemical screening of plant extract confirmed the presence of flavonoids and phenolics. Ethanolic extract showed more prominent antidiabetic potential in comparison to aqueous extract. Study doses also resulted in significant hypolipidemia in addition to anti-diabetic activity in the streptozotocin-induced diabetic model [17].

Cocinia Indica

Orally administered extract of leaves of *Cocinia Indica* at a dose of 500 mg/kg resulted in significant hypoglycemia in alloxanized dogs. Glucose tolerance was also increased in normal and diabetic dogs after the treatment with plant extract. [18]

Eugenia jambolana

Eugenia jambolana is used traditionally in India for the management of diabetes. The plant is also added in various herbal formulations for the treatment of diabetes. Alcoholic and aqueous extracts of the plant have shown significant anti-hyperglycaemic effects. Around 75% reduction in glucose levels was observed in cases of mild diabetes (plasma sugar >180 mg/dl). Around 55% and 17% reduction in glucose was observed in cases of moderate (plasma sugar >280 mg/dl) and severe diabetes (plasma sugar >400 mg/dl) respectively. Studies on pulp extract of the plant showed significant hypoglycemic activity in streptozotocin-induced diabetic mice within 30 minutes of administration. Seed extract showed hypoglycemic effects within 24 hours. *in vitro* studies suggest a secretagogue effect of plant extract on isolated islets of Langerhans from normal and diabetic rats. Inhibition of insulinase activity was also observed in liver and kidney cells. [19]

Ficus bengalensis

Also known as a banyan tree, it is found to be widely distributed throughout the Indian subcontinent. The bark of *Ficus bengalensis* is used traditionally in India for the treatment of diabetes. Ethanolic extract of *Ficus bengalensis* showed significant glucose lowering activity were comparatively evaluated for their blood glucose lowering activity. Ethanolic extract of fruit at a dose of 120mg/kg showed more prominent antidiabetic activity when compared with root or bark extract. Hypoglycemic activity of the extract was comparable to that of standard drug glibenclamide. [20]

Ficus racemosa

Methanolic extract of stem bark of *Ficus racemosa* given at the doses of 200mg/kg and 400mg/kg to normal and alloxan-induced diabetic rats showed significant hypoglycemic effects of extract both groups. The effects were comparable to that of standard drug glibenclamide. The study confirmed the traditional claim of the antidiabetic effect of the plant. [21]

Hemidesmus indicus

Hemidesmus indicus has been used traditionally for the treatment of veneral diseases, skin diseases, urinary infections and infertility. Hypoglycemic activity of aqueous plant extract (500mg/kg/day) was evaluated on blood glucose with fed, fasted and glucose-loaded diabetic and nondiabetic rat models. Significant reduction in blood glucose levels with the restoration of serum electrolytes, glycolytic enzymes and hepatic CYP450 was observed due to the reduction in lipid peroxidation products levels at the end of 12 weeks long study. Results were indicative of antidiabetic and antioxidant potential of the plant. [22]

Hibiscus rosa-sinesis

Commonly known as Gudhal, is a flowering tree distributed throughout India. Both acute and subacute models were used for the evaluation of antidiabetic activity of plant extract. Rats were administered with ethanolic extract of flower at doses of 250mg/kg and 500mg/kg. An appreciable reduction in blood glucose levels was observed in both the models. For acute model, reduction in glucose levels was observed after 1, 3, 5 hours of extract treatment. Reduction in glucose levels was observed after 1, 3, 5, 7 days of treatment with extract in case of the sub-acute model. Results suggested the applicability of ethanolic of plant extract in both acute and chronic diabetic complications. [23]

Holarrhena antidysenterica

Also known as kurchi, *Holarrhena antidysenterica* is an indigenous plant distributed throughout in Indian subcontinent. Evaluation of hypoglycemic effects of seeds of the plant was done on albino rats. Study groups were comprised of normal control that received normal saline 1.5 ml/kg, normal rats treated with 350 mg extract/kg, diabetic rats treated with normal saline 1.5ml/kg and diabetic rats treated with 350 mg extract/kg. The standard group received standard drug glibenclamide 0.5mg/kg. Reduction in glucose levels was observed after the 7th day of extract administration. The reduction was significant in both preprandial and postprandial glucose levels. Reduction in glucose levels was also seen in normal rats. Decrease in glucose levels from the 7th day was 142.5±1.82 and 182.5±5.88 in fasting and fed state respectively. No significant antihyperlipidemic effect was observed on normal rats however, improvement in lipid profile was observed in diabetic rats from the day 7. Particularly, antihypercholesterolemic activity was evident from day 14. On the 28th day, lipid levels observed were 63.80±3.35 and 84.27±3.07 mg/100 ml in fasting and fed state respectively. An appreciable reduction in blood urea nitrogen levels on the 28th day was also observed. [24]

Lawsonia inermis

Lawsonia inermis is commonly known as mehndi in India. It has been widely used traditionally for the treatment of diabetes. The validity of traditional claim was confirmed in a study carried out on alloxanized rats. Extract of plant leaves was prepared and administered in normal and diabetic rats at a dose of 800mg/kg body weight. Reduction in glucose levels was observed on the 14th day of the study. Glucose level was reduced from 194mg/dl to normal levels. Significant reduction in lipid profile was also observed. [25]

Lepidium sativum

Aqueous extract of *Lepidium sativum* seeds was evaluated for its hypoglycemic effect. The study included normal and streptozotocin-induced diabetic rats. Both acute and chronic studies were performed and a significant reduction in glucose levels at dose 20mg/kg was observed. Normalization of glucose levels was seen after 2 weeks of extract administration. A significant reduction in glucose levels was observed in normal rats in both acute and chronic studies. Basal plasma insulin levels were found not

affected in both diabetic and normal rats indicating a mechanism of action independent of insulin release. [26]

Momordica Charantia

Momordica charantia or bitter melon is traditionally used as an antidiabetic and antihyperglycemic plant in India and in other Asian countries. Various studies performed on Extracts of fruit pulp, seed, leaves and whole plant have shown an appreciable hypoglycemic effect in animals. A Polypeptide p, isolated from fruit, seeds and tissues of M. charantia when administered subcutaneously in langurs and humans has shown significant hypoglycemic effects. Ethanolic extracts of the plant at a dose of 200 mg/kg when given to normal and streptozotocin-induced diabetic rats showed good anti-hyperglycemic and also hypoglycemic effects. Inhibition of enzymes glucose-6-phosphatase, fructose-1, 6-biphosphatase with stimulation of hepatic glucose-6-phosphate is assumed to be the possible mechanism of action of the plant. [27]

Myristica fragrans

Commonly known as Nutmeg, *Myristica fragrans* is used traditionally for the treatment of diarrhoea, mouth sores and insomnia. Petroleum ether extract of seeds (200mg/kg) was administered to normal, alloxanized (120 mg/kg, *s.c*.) and glucose fed (1.5 g/kg, *p.o*.) rats. Each group consisted of n=5 rats. A significant reduction in glucose levels was observed in normal rats. The reduction was from 56.5±3.19 to 49.75±2.05 mg% in 4 hours, from 145.75±9.65 to 81.5±4.03 mg% in oral glucose tolerance test (OGTT) at ½ h compared to control glucose-fed rats, from 305.8±12.49 to 276.6±6.11 mg% after single dose treatment and from 326.25±7.05 to 268.0±9.6 mg% in alloxan-induced diabetic rats. The treatment with extract was continued daily for two weeks. Body weight was also reduced after treatment with extract. Improvement in lipid profile and haemoglobin content was also noticeable when compared to diabetic control rats. [28]

Ocimum sanctum

Ocimum sanctum is commonly known as tulsi plant. It is employed traditionally for the treatment of a variety of disorders. Earlier studies performed on leaves of the plant have confirmed the glucose lowering activity of the plant in diabetic rats and humans. A study on complete ethanolic extract and different fractions (aqueous, butanol, ethyl acetate) of leaves extract were carried out to determine the mechanism of action and effect on insulin secretion. Stimulation of insulin secretion occurred in isolated islets and in a clonal ratß-cell line in a concentration-dependent manner when complete ethanolic extract and fractions of extracts were administered to diabetic rats.

The stimulatory effects of these extracts were elevated with glucose, isobutylmethylxanthine, tolbutamide and a depolarizing concentration of KCl. Diazoxide and verapamil reduced the secretions of insulin. Two other fractions (chloroform and hexane) showed stimulatory effects by decreased cell viability. The effects were unaltered in the presence of diazoxide and verapamil. Extract was also found to increase intracellular Ca^{2+} in clonal BRIN-BD11 cells and was partially reduced by verapamil. Study results suggested the antidiabetic potential of *Ocimum sanctum* due to its secretagogue effect on islets cells. [29]

Onion (Allium cepa)

Onion is a native of Eurasia subcontinents and is distributed widely throughout the world. The plant is regularly consumed as food in almost all parts of the world. An active phytoconstituent called allyl propyl disulphide (APDS) isolated from the bulb of the plant has shown to inhibit the breakdown of insulin by the liver. A significant increase in insulin production in the pancreas is also observed when the specified amount of APDS was administered in experimental rats thus allowing an overall increase in insulin levels in the blood to exert its antidiabetic potential. [30]

Phyllanthus niruri

Commonly known as Bhuiamla, is a wild plant found to be distributed all over the Indian subcontinent. The plant is used extensively in traditional Indian system of medicine for the treatment of a variety of disorders including diabetes. Antidiabetic potential of the plant was evaluated in normal, insulin-dependent diabetes mellitus (IDDM), and non-insulin-dependent diabetes mellitus (NIDDM) rats. Evaluation of lipid metabolism and antioxidant activity was done after administration of alcoholic plant extract. The hypoglycemic effect was observed in IDDM affected rats. Lipid-lowering and antioxidant activities were observed in all animals. Results suggested the antidiabetic and independent lipid-lowering potential of the plant. [31]

Pterocarpus marsupium

It is a large tree that is found in hilly regions of Indian subcontinent. A number of phytoconstituents are isolated and identified from *Pterocarpus marsupium*. Beta cells degranulation was seen when flavonoid fraction of plant is administered. Marsupin, pterosupin and liquiritigenin isolated from the tree have improved the lipid profile in flavonoid fraction. Another active principle Epicatechin that is isolated from the plant has shown insulinogenic properties *in-vitro*. Epicatechin is found to stimulate the uptake of Oxygen in fat cells and increases the glycogen content in the diaphragm of the rat in a dose-dependent manner. [32]

Rubia cordifolia

Rubia cordifolia is a popular herb in the traditional system of medicine. It is commonly known as majit. Aqueous roots extract of *Rubia cordifolia* when administered in streptozotocin-induced diabetic rats, an appreciable reduction in blood glucose levels with improvement in lipid profile was observed. The root extract also improved the liver functioning by the reduction in serum transaminases levels in the blood. The extract had minimum effects of hypercholesterolemia. The results were suggestive of significant hepatoprotective, antidiabetic and antihyperlipidemic activity of the plant. [33]

Terminalia chebula

Terminalia chebula is commonly known as hard or hartiki in India. It is frequently used in Ayurveda for the management and treatment of diabetes. Antidiabetic activity of *Terminalia* was evaluated in streptozotocin-induced diabetic rats. Ethanolic extract of fruits of the plant at a dose of 200mg/kg was administered to animals for 30 days. Reduction in glucose and glycosylated haemoglobin (Hba1C) was measured and a significant reduction in glucose and Hba1C was seen in diabetic rats. An insulin stimulating effect was confirmed by measuring the plasma insulin levels. Carbohydrate metabolizing enzymes were normalized after extract administration for 30 days. Histopathological studies revealed the normalization of histopathological abnormalities at end of the study. [34]

Tinospora cordifolia

It is a deciduous climbing shrub commonly known as Guduchi and found widely distributed in the Indian subcontinent. 6 weeks long treatment with aqueous extract (400mg/kg) showed a significant reduction in glucose levels in blood and urine in alloxan-induced diabetic rats. Improvement in lipid profiles in serum and tissues was also observed. Falling body weight was normalized after the treatment. The hypoglycemic effect was equivalent to 1 unit/kg of insulin. Continuous administration of extract showed a significant reduction in glucose levels and increased glucose tolerance in rodents. [35]

Trigonellafoenum-graceum

foenum-graecum or fenugreek is consumed as food and spice in the Indian subcontinent. The plant is cultivated worldwide and is used as a herb and as a spice (seeds) around the world. Blood sugar levels of diabetic patients were reduced with the administration of fibre rich fractions of seeds. The plant seeds have also improved the lipid profile of diabetic patients to some extent when a dose of 5-30g of seeds was given to the patients. The seeds also result in mild digestive distress in patients taking seeds. The fibre-rich fraction of fenugreek seeds can lower blood sugar levels in people with diabetes, and to a lesser extent, lowers blood cholesterol. Additionally, the soluble fibre content of fenugreek may play a role in aiding weight control. A typical dose range is 5 to 30 g three times per day with meals. Known side effects of high doses include mild digestive distress. Fenugreek should not be used by pregnant or nursing women [36].

Withania somnifera

Commonly known as Ashwagandha, it is used widely in traditional medicine for the treatment and management of a variety of disorders including tumours. The roots of the plant are found rich in steroidal lactones called withanolides. The leaf and root extracts of *Withania somnifera* have shown excellent hypoglycemic and lipid-lowering effects in alloxan-induced diabetic rats when administered with extracts for eight weeks. The results obtained were comparable with standard drug glibenclamide. Changes in blood glucose and other serological parameters to normal levels were observed at the end of the study. [37]

DISCUSSION

Medicinal plants, since the time immemorial, are utilized for the purpose of maintaining the well beings of humans. Plant-based drugs have gained popularity among the general population due to their capability to treat the cause of diseases with no or least side effects. A number of phytoconstituents isolated from different plants have established themselves as potential drug candidates for the treatment or management of diseases. Apart from their capability of treating a disease with least side effects possible, natural drugs are also gaining affinity due to their affordability, ease of access and acceptability based on the historical claims. The capability of medicinal plants to cure diseases which are otherwise non-curable in the rational or modern system of medicine has further consolidated the faith of humans in natural approaches. Medicinal plants act by multi-target approaches and target more than one biological target at a time. This multi-target capability of plants prevents the failure of a therapy for the disease treatment.

Diabetes is a metabolic disorder. Its treatment therapy includes replacement therapy and administration of hypoglycemic agents for type-1 and type-2 diabetes respectively. The treatment regimen of diabetes includes the approaches for the management of diabetes. No drug has been discovered so far that can treat the cause of diabetes and provide a complete cure from the disease. Traditional systems of medicines have claimed to cure diabetes by using herbal principles. Plants are extensively evaluated to determine their potential in the treatment of diabetes. Majority of plants that are evaluated have shown the excellent capability to reduce the blood sugar levels along with other the improvement in lipid profiles and liver functioning. This approach of medicinal plants to treat multiple causes simultaneously makes them capable to control the disease progression through multiple mechanisms.

If explored appropriately, plants can be the infinite sources of active principles that can cure the diseases and disorders with the occurrence of minimum side effects. Medicinal plants that show prominent antidiabetic activity in the initial studies should be further explored to isolate and characterize active phytoconstituents that can become possible drug candidates in the near future.

REFERENCES

[1] Dean L, McEntyre J. The Genetic Landscape of Diabetes [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004. Chapter 1, Introduction to Diabetes. 2004. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1671/

[2] Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2010;33 Suppl 1(Suppl 1):S62-9

[3] A. Ramchandran, Know the signs and symptoms of diabetes. *Indian J Med Res*. 2014; 140(5):579-81

[4] Shiao-Wei Shen, Rubin Bressle,Oral hypoglycemic agents,Disease-a-Month.1976; 22(5):2-35

[5] Wadood A, Wadood N, Shah SA. "Effects of Acacia arabica and Carallumedulis on blood sugar levels of normal and alloxan diabetic rabbits". *Journal of Pakistan Medical Association,* 1989; 39(8):208-212

[6] Tanko Y, Yerima M, Mahdi MA, Yaro AH, Musa KY, Mohammed A. "Hypoglycemic Activity of Methanolic Stem Bark of Adansonniadigitata Extract on Blood Glucose Levels of Streptozocin-Induced Diabetic Wistar Rats". *International Journal of Applied Research in Natural Products*, 2008; 1(2):32-36

[7] Hong Gao, Yi-Na Huang, Bo Gao, Peng Li, Chika Inagaki and Jun Kawabata. "Inhibitory effect on α-glucosidase by *Adhatoda vasica* Nees." Food Chemistry; 2000; 108(3): 965-972.

[8] Sabu MC, Ramadasan K. "Antidiabetic activity of *Aegle marmelos* and its relationship with its antioxidant properties". Indian Journal of Physiology and Pharmacology,2001; 48(1):81-88.

[9] Ajabnoor MA. "Effect of aloes on blood glucose level in normal and alloxan diabetic mice". Journal of Ethnopharmacology, 1990; 8:215-220.

[10] Nalamolu Koteswara Rao. "Anti-Hyperglycemic and renal protective activities of *Andrographis paniculata* roots chloroform Extract". Iranian Journal of Pharmacology & Therapeutics, 2006; 5:47-50.

[11] Kumar V, Khanna AK, Khan MM, Singh R, Singh S, Chander R et al. "Hypoglycemic, lipid lowering and antioxidant activities in root extract of *Anthocephalus indicus* in alloxan induced diabetic rats". Indian Journal of Clinical Biochemistry, 2009; 24(1):65-69.

[12] Selvan VT, Manikandan L, Kumar GPS, Suresh R, Kakoti BB, Gomathi P et al. "Antidiabetic and antioxidant effect of methanol extract of Artanemasesamoides in Streptozotocin-induced Diabetic rats". International Journal of Applied Research in Natural Products, 2008; 1(1):25-33.

[13] Chattopadhyay RR, Chattopadhyay RN, Nandy AK, Poddar G, Maitra SK. "The effect of fresh leaves of *Azadirachta indica* on glucose uptake and glycogen content in the isolated rat hemi diaphragm". Bulletin of the Calcutta School of Tropical Medicine, 1987; 35:8-12,.

[14] Pari L, Satheesh MA. "Antidiabetic activity of *Boerhaavia diffusa* L. effect on hepatic key enzymes in experimental diabetes". Journal of Ethnopharmacology, 2004; 91(1):109-113.

[15] Deore SL, Khadabadi SS, Daulatkar VD, Deokate UA, Farooqui IU. "Evaluation of hypoglycemic and antidiabetic activity of bark of *Butea monosperma*". Pharmacognosy Magazine; 2008 4(13):134-138.

[16] Parameshwar S, Srinivasan KK, Rao CM. "Oral Antidiabetic Activities of Different Extracts of *Caesalpinia bonducella* Seed Kernels". Pharmaceutical Biology,2002; 40(8):590-595.

[17] Hakki;m FL, Girija S, Kumar RS, Jalaludeen MD. "Effect of aqueous and ethanol extracts of *Cassia auriculata* L. flowers on diabetes using alloxan induced diabetic rats". International Journal of Diabetes & Metabolism, 2007; 15:100-106.

[18] Kamble SM, Kamlakar PL, Vaidya S, Bambole VD. "Influence of *Coccinia indica* on certain enzymes in glycolytic and lipolytic pathway in human." Indian Journal of Medical Science, 1998; 52(4):143-146.

[19] Ravi K, Sivagnanam K, Subramanian S. "Antihyperlipidemic effect of *Eugenia jambolana* seeds kernels on streptozotocin induced diabetes in rats". Journal of Medicinal Food, 2004; 72(2):187-191.

[20] Sharma S, Chaturvedi M, Edwin E, Shukla S, Sagrawat H. "Evaluation of the phytochemicals and antidiabetic activity of *Ficus bengalensis*". International Journal of Diabetes, 2007; 27(2):56-59.

[21] Rao RB, Murugesan T, Sinha S, Saha BP, Pal M, Mandal SC. "Glucose lowering efficacy of *Ficus racemosa* bark extract in normal and alloxan diabetic rats". Phytotherapy Research, 2002; 16(6), 590-592.

[22] Mahalingam G, Krishnan K. "Hypoglycemic activity of *Hemidesmus indicus* R. Br. on streptozotocin-induced diabetic rats". International Journal of Diabetes, 2008; 28(1): 6-10.

[23] Venkatesh S, Thilagavathi J, ShyamSundar D. "Anti-diabetic activity of flowers of *Hibiscus rosasinensis*", Fitoterapia, 2008; 79(2):79-81.

[24] Pankaj NK, Alam M, Roy BK, "Antidiabetic activity of seed powder of *Holarrhena antidysenterica* in rabbits". Journal of Research, Birsa Agricultural University, 2006.

[25] Syamsudin, Inawati, Winarno H. "The effect of inai (*Lawsonia inermis*) leaves extract on blood glucose level: an experimental study". Research Journal of Pharmacology, 2008; 2(2):20-23

[26] Eddouks M, Maghrani M, Zeggwagh NA, Michel JB. "Study of the hypoglycaemic activity of *Lepidium sativum* L. aqueous extract in normal and diabetic rats". Journal of Ethnopharmacology, 2008; 97:391-395.

[27] Cakici I, Hurmoglu C, Tunctan AB, Kanzik NI, Sener B. "Hypoglycemic effects of *Momordica charantia* extract in normoglycaemic or cyproheptadin induced hyperglycaemic mice". Journal of Ethnopharmacology, 1994; 44(2):117-122.

[28] Somani RS, Singhai AK. "Hypoglycaemic and antidiabetic activities of seeds of *Myristica fragrans* in normoglycaemic and alloxan-induced diabetic rats". Asian journal of experimental sciences, 2008; 22(1):95-102.

[29] Hannan JMA, Marenah L, Ali L, Rokeya B, Flatt PR, Wahab YHA. "*Ocimum sanctum* leaf extracts stimulate insulin secretion from perfused pancreas, isolated islets and clonal pancreatic ß-cells". Journal of Endocrinology, 2006; 189:127-136.

[30] Augusti KT. "Studies on the effects of a hypoglycaemic principle from *Allium cepa*". Indian Journal of medicinal research, 1973; 6(7):1066-1071.

[31] Jasmin HB, Narasimhacharya AVRL. "Comparative antidiabetic, hypolipidemic, and antioxidant properties of *Phyllanthus niruri* in normal and diabetic rats". Pharmaceutical Biology 2007; 45(7):569-574.

[32] Indian Council of Medical Research (I.C.M.R), Collaborating Centres. Flexible dose open trial of Vijayasar in cases of newly diagnosed non-insulin dependent diabetes mellitus, New Delhi. Indian Journal of Medical Research, 1998; 108:24-29.

[33] Nilambari D, Shrikant T, Vipinchandra PA. "Comprehensive Review of *Rubia cordifolia* Linn." Pharmacognosy Reviews, 1998 2(3):124-134.

[34] Kumar GPS, Arunselvan P, Kumar DS, Subramanian SP. "Anti-diabetic activity of fruits of *Terminalia chebula* on streptozotocin-induced diabetic rats". Journal of Health Science, 2006; 52(3):283-291.

[35] Stanely P, Prince M, Menon VP. "Hypoglycemic and other related action of *Tinospora cordifolia* roots in alloxan induced diabetic rats". Journal of Ethnopharmacology, 2000; 70(1):9-15.

[36] Zia T, Hasan SN, Hasan SK. "Evaluation of the oral hypoglycaemic effect of *Trigonella foenum-graecum* L. (methi) in normal mice". Journal of Ethnopharmacology, 2001; 75(2-3):191-195.

[37] Kumar RU, Kasturirenghan S, Mariashibu TS, Manoharan R, Vasudevan RA, Sei CK et al. "Hypoglycaemic and hypolipidaemic effects of *Withania somnifera* root and leaf extracts on Alloxan-induced diabetic rats". *Int. J. Mol. Sci*, 2009; 10:2367-2382