

Review Article

International Journal of Research and Development in Pharmacy & Life Science

> An International open access peer reviewed journal ISSN (P): 2393-932X, ISSN (E): 2278-0238 Journal homepage: http://ijrdpl.com



Medicinal plants used for Diabetes mellitus: An Overview

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Keywords: Hypoglycemic, insulin, flavonoids, glycosides

Article Information:

Received: May 11, 2018; Revised: June 04, 2018; Accepted: July 01, 2018 Available online on: 15.07.2018@http://ijrdpl.com



http://dx.doi.org/10.21276/IJRDPL.2278-0238.2018.7(4).3022-3029 **ABSTRACT:** Before the advent of insulin, diabetes was treated with plant medicines. Numerous biologically active plants are discovered by evaluation of ethnopharmacological data, and these plants may offer the local population immediately accessible therapeutic products. The earliest known documentation of plant-derived treatments for diabetes is present in the Ebers Papyrus of about 1550 BC. Since then, multitudes of herbs, spices, and other plant materials have been described for the treatment of diabetes throughout the world. Traditional anti-diabetic plants might provide a useful source of new oral hypoglycemic compounds for development as pharmaceutical entities, or as simple dietary adjuncts to existing therapies. Renewed attention to alternative medicines and natural therapies has stimulated a new wave of research interest in traditional practices. Since last 20 years, scientific investigations have confirmed the efficacy of many of these preparations; some of them are remarkably effective. From these researches, it has been well established that present phytoconstituents like alkaloids, flavonoids, glycosides and polysaccharides are responsible for the hypoglycaemic effect.

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INTRODUCTION

Diabetes mellitus is a syndrome of disordered metabolism, usually due to a combination of hereditary and environmental causes, resulting in abnormally high blood sugar levels (hyperglycemia). Blood glucose levels are controlled by a complex interaction of multiple chemicals and hormones in the body, including the hormone insulin made in the β cell of pancreas. Diabetes mellitus refers to the group of diseases that lead to high blood glucose levels due to defect in either insulin secretion or in its action [1].

Diabetes develops due to diminished production of insulin (in Type 1) or resistance to its effects (in type 2 and gestational). Both leads to hyperglycemia, which largely causes the acute signs of diabetes: excessive urine production, resulting compensatory thirst and increased fluid intake, blurred vision, unexplained weight loss, lethargy and changes in energy [1].

Diabetes mellitus is a metabolic disorder initially characterized by a loss of glucose homeostasis with disturbance of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both [2].

Without enough insulin, the cells of body cannot absorb enough glucose from the blood hence blood glucose levels rise, which is termed as hyperglycemia. If the glucose level in the blood remains high over for a longer period, this can result in long term damage to organs, such as the kidney, liver, eyes, nerves, heart and blood vessels. Complication of some of these organs can lead to death also [3].

• The World Health Organization (WHO guideline) criteria define diabetes by fasting plasma glucose (FPG) level of 140mg/dL (7 mmol/L) or greater, or post-prandial 2-h plasma glucose (PG) level of 200mg/dL (11.1 mmol/L) or greater during an oral glucose tolerance test 4.

The National Diabetes Data Group of the National Institutes of Health recommends the following criteria for diagnosing diabetes:

- a) Fasting (overnight) venous plasma glucose concentration greater than or equal to 140 mg/dL on at least two separate occasions.
- b) Venous plasma glucose concentration greater than or equal to 200 mg/dL at 2-h post-ingestion of 75 g of glucose and at least one other sample during the 2-h test.

Classification of diabetes mellitus

The two most common types of diabetes are insulin- dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM). WHO classifications also include malnutrition-related diabetes mellitus and gestational diabetes. Malnutrition-related diabetes was omitted from the new classification because its etiology is uncertain.

1. Type 1 diabetes mellitus (NIDDM)

It results from cellular mediated autoimmune destruction of the insulin secreting β -cells of the pancreas, from resulting in absolute deficiency of insulin from the body. Patients are more prone to ketoacidosis. It occurs in children and young, usually before the age of 40 year, although disease onset can occur at any age. The patient with type I diabetes needs insulin therapy for survival. It may account for 5-10% of all diagnosed cases of diabetes. Autoimmune, genetic and environmental factors are the major risk factor for type I diabetes.

Diabetic ketoacidosis is caused by reduced insulin levels, decreased glucose use and increased gluconeogenesis from elevated counter regulatory hormones, including catecholamines, glucagon and cortisol. Primarily it affects patients with type I diabetes, but also may occurs in patients with type 2. Patients with diabetic ketoacidosis usually present with polyuria, polydypsia, polyphagia and weakness

2. Type II diabetes mellitus (IDDM)

Type II diabetes mellitus is characterised by decreased ability of insulin to stimulate glucose uptake in peripheral tissues, insulin resistance and inability of the pancreatic β -cell to secrete insulin adequately, forming with β -cell failure. The major sites of insulin resistance in type 2 diabetes are liver, skeletal muscle and adipose tissue.

Both defects, insulin resistance and β –cell failure, are caused by a combination of genetic and environmental factors. Environmental factors, such as lifestyle habits (i.e. physical in activity and poor dietary intake), obesity and toxins may act as initiating factors or progression factors for type II diabetes. The genetic factors are still poorly understood.

Type II diabetes is increasingly being diagnosed at any age and it accounts for 90-95% of all diagnosed cases of diabetes. It is associated with old age, obesity, family history of diabetes, impaired glucose metabolism and physical inactivity. The distinguished feature of type-1 &II are represented in table 1.

Type 1 versus Type 2 Diabetes Mellitus (DM)		
	Type I DM	Type II DM
CLINICAL	Onset: Generally, occurs in children and young < 20 year	Onset: Generally, occurs in old age person > 40-45 year
	Normal weight	Obese
	Markedly decreased	Increased blood insulin(early); normal to moderate
	blood insulin level	decreased insulin level (late)
	Anti-islet cell antibodies remain present	No anti-islet cell antibodies are found
	Ketoacidosis is common	Ketoacidosis is rare; non ketotic hyperosmolar coma may be observed
GENETICS	30-70% concordance in twins	50-90% concodance in twins
	Linkage to MHC class II HLA genes	No HLA linkage
		Linkage to candidate
		Diabetogenic genes
		(PPARy, calpain 10)
	Autoimmune destruction of β -cells mediated by	Insulin resistance develop in skeletal muscle, adipose
PATHOGENESIS	T cells and humoral mediators (TNF, IL-1, NO)	tissue and liver
	Absolute insulin deficiency is formed	B-cell dysfunction and relative insulin deficiency
	Insulitis early	No insulitis
ISLET CELLS	Marked atrophy and fibrosis	Focal atrophy and amyloid deposition
	β-cell depletion	Mild β-cell depletion

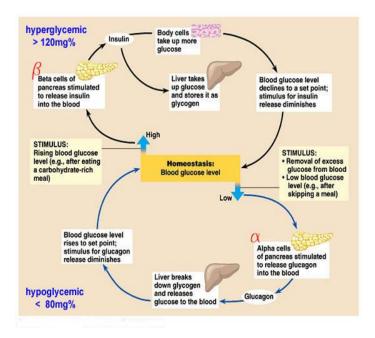
Table 1: Types of Diabetes mellitus

Gestational diabetes mellitus

Gestational diabetes i.e. blood glucose elevation during pregnancy is a significant disorder of carbohydrate metabolism which can lead to elevated blood glucose in genetically predisposed individuals. It is more common among obese women and women with a family history of diabetes. It usually resolves once the baby is born; however, after pregnancy 5-10% of women with gestational diabetes are found to have type II diabetes and 20-25% of women have a chance of developing diabetes in the next 5-10 years.

Pathophysiology of diabetes mellitus

The pancreas plays primary role in the metabolism of glucose by secreting insulin and glucagone. The islets of Langerhans secrete insulin and glucagon directly into the blood. Insulin is a protein that is essential for proper regulation of glucose and maintenance of proper blood glucose levels.



The role -of Pancreas in the body

• Glucagon opposes the action of insulin. It is secreted when blood glucose level falls. It increases blood glucose concentration partly by breaking down, stored glycogen in the liver by a pathway knows as glycogenolysis. Gluconeogenesis is the production of glucose in the liver from non-carbohydrate precursors such as glycogenic amino acids.

Complication of Diabetes mellitus

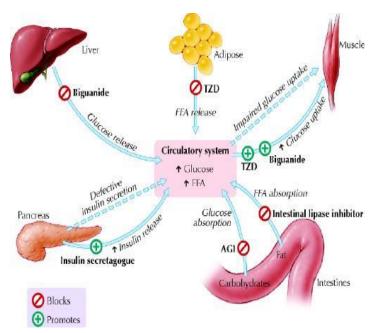
The important morphological changes are related to the many late systemic complication of diabetes. There is extreme variability among patients in the time of onset of these complications, their severity, and the particular organ or organs involved. In individuals with tight control of diabetes, the onset might be delayed. In most patients, however, morphological changes are likely to be found in the arteries (macrovascular disease), basement membranes of small vessels (microangiopathy), Renal (diabetic *nephropathy*), retinal (retinopathy), nervous (neuropathy) and other tissues.

Management of diabetes mellitus

Diet, exercise, modern drug including insulin and oral hypoglycemic drugs such as sulfonylurea and biguanides are being used to manage the pathogenesis of diabetes mellitus. Insulin plays a key role in glucose homeostasis along the side of a counter regulatory hormone, glucagon, which raises serum glucose. Carrier proteins (GLUT 1-5) are essential for glucose uptake into the cells. In individuals with type II diabetes, a

common sequence of therapy stats with diet treatment and exercise followed by oral antihyperglycemic agents is used.

In general, insulin therapy has been considered to be the last therapeutically effective option when diet, exercise and oral antihyperglycemic agent therapies have failed. Oral agents acting as indicated in figure are used in patients with type II D.M. who fails to meet glycemic goals with multiple nutrition therapy and exercise. Traditionally plants are also used for the treatment o diabetes throughout the world [4]. Management of diabetes without any side effect is still a challenge for the medical system. This leads to an increasing search for improved antidiabetic drugs.



TZD= Thiazolidinedione; FFA= Free fatty acid; AGI= α -glucosidase inhibitor

Major target organs and mechanism of actions of orally administered antihyperglycemic agent in type II diabetes mellitus.

Classification of Oral hypoglycaemic drugs

Sulfonylureas:

- First generation Tolbutamide, Chlorpropamide
- Second generation Glipizide, Gliclazide, Glimepiride
 - 1. Biguanides: Phenformin, Metformin
 - 2. Meglitinide analogs: Repaglinide, Nateglinide
 - 3. Thiazolidinediones: Rosiglitazone, Pioglitazone
 - 4. α-Glucosidase inhibitors: Acarbose, Miglitol

PLANTS REPORTED WITH ANTIDIABETIC ACTIVITY

• *Vuyyuru et al, (2012);* evaluated the hydro-alcoholic extract of leaves of *Ananas comosus* L. for antidiabetic potential against streptozotocin induced diabetic rats.

The dose of 200, 400 and 600 mg/kg body weight of hydro-alcoholic extract of leaves of *Ananas comosus* L were administered orally. It was concluded that hydroalcoholic extract of leaves of *Ananas comosus* L. at the dose of 600mg/kg possess significant antidiabetic property [5].

- *Kala et al, (2012);* evaluated the ethanolic extract of leaf of *Eugenia floccosa* Bedd (Family: *Myrtaceae*) for antioxidant, antihyperlipidaemic and antidiabetic potential in Wistar Albino rats against alloxan induced diabetes. The result showed that ethanolic extract of leaf of *Eugenia floccose* at the dose of 150 and 300 mg/kg lowers the blood glucose level and concluded that the ethanolic extract of *Eugenia floccosa* possesses significant antidiabetic, antihyperlipidaemic and antioxidant effects against alloxan induced diabetic rats [6].
- *Macharla et al, (2012);* evaluated the aqueous ethanolic extract of stem of *Bambusa arundinaceae* for anti-diabetic potential against alloxan induced diabetic rats. The results showed that aqueous ethanolic extract significantly reduces the blood glucose level in alloxan induced diabetic rats and concluded that ethanolic extracts of stem of *Bambusa Arundinaceae* possess significant anti-diabetic activity in comparison to the standard glibenclamide [7].
- *Shahin and Ali, (2012);* evaluated the extract of leaves of *Artocarpus heterophyllus* for antidiabetic potential against normal and streptozotocin induced diabetic rats. The result showed that *Artocarpus heterophyllus* extract at the dose of 250 mg/kg body weight lowers the blood glucose level in normoglycemic and streptozotocin induced diabetic rats [8].
- *Kannan et al, (2012);* evaluated the ethanolic extract of fruits of *Terminalia chebula* Retz. for antidiabetic potential in wistar albino rats against alloxan induced diabetes. The result showed that the ethanolic extract of fruits of *Terminalia chebula* Retz. at the dose of 200mg/kg lowers the blood glucose level [9].
- *Kumar et al, (2012);* evaluated the hydro-alcoholic extract of stem bark of *Bauhinia variegata* for antidiabetic potential in rats against alloxan-induced diabetes. The result showed that hydro-alcoholic extract of stem bark of *Bauhinia variegata* at the dose of 200 and 400 mg/kg body weight lowers the blood glucose level [10].
- *Sundarrajan et al, (2011);* evaluated the methanolic extract of *Hibiscus cannabis* for antidiabetic potential in rats against streptozotocin induced diabetes. The result showed that *Hibiscus cannabis* methanolic extract at the dose of 400mg/kg body weight lowers the blood glucose level. It was also concluded from phytochemical investigation that the activity might be due to presence of flavonoid content [11].

- Subrahmanyam et al, (2011); evaluated the antidiabetic activity of Abelmoschus esculentus (ladies finger) fruit extract in rabbits against alloxan induced diabetes and result showed that 1mg/ml fruit extract of Abelmoschus esculentus gradually decrease the blood glucose levels [12].
- *Chaurasia et al, (2011);* evaluated the methanolic and aqueous extracts of *Morus alba* (Moraceae) leaves for antidiabetic potential in rats against streptozotocin induce diabetes and proved that methanolic extract possess significant antidiabetic activity, while the aqueous extract show the moderate antidiabetic activity [13].
- Girija et al, (2011); evaluated the methanolic extract of leaves of Amaranthus caudatus, Amaranthus spinosus and Amaranthus viridis for antidiabetic and antipotential against Cholesterolemic normal and streptozotocin induce diabetic rats and proved that all the three plant at the dose of 400 mg/kg possess significant antidiabetic and anti- Cholesterolemic activity, while at the dose of 200 mg/kg possess moderate antidiabetic and anti- Cholesterolemic activity. They concluded that the methanolic extract of leaves of Amaranthus caudatus, Amaranthus spinosus and Amaranthus viridis showed significant antidiabetic and anti- Cholesterolemic potential [14].
- *Mishra and Garg, (2011);* evaluated the methanolic extract of fruit pulp of *Feronia elephantum* Corr. for hypoglycemic and antidiabetic potential against glucose loaded and alloxan induced diabetic rats. The result showed that the methanolic extract of *Feronia elephantum* Corr. possess significant hypoglycemic and antidiabetic activity in alloxan induced diabetic rats [15].
- **Panchal et al**, (2011); evaluated the methanolic and aqueous extract of root of *Moringa oliefera* for antidiabetic potential in rats against streptozotocin induce diabetes and proved that methanolic and aqueous extract of root of *Moringa oliefera* possess significant antidiabetic activity [16].
- *Velraj et al, (2011);* evaluated the ethyl acetate (EAESOF) and ethanolic (EESOF) extract of fruit of *Scindapsus officinalis* for antidiabetic potential in rats against alloxan induce diabetes. The result showed that ethyl acetate (EAESOF) and ethanolic (EESOF) extract of fruit of *Scindapsus officinalis* at the dose of 200mg/kg body weight possess antidiabetic activity in alloxan induced diabetic rats [17].
- *Siddaiah et al, (2011);* evaluated the Methanolic extract of leaves of *Ximenia Americana* for hypoglycemic potential against normal glucose fed and alloxaninduced diabetic rats, and proved that Oral administration of extract of leaves of *Ximenia Americana* at the dose of 200, 400 and 600mg/kg body weight for seven days showed significant reduction in blood glucose level, and concluded that methanolic

extract of leaves of *Ximenia americana* at the dose of 600mg/kg body weight lowers the blood glucose level more significantly as compare to 200 and 400 mg/kg bodyweight [18].

- Shah et al, (2011); evaluated the ethanolic extract of leaf, flower and seed of *Prunus amygdalus Batsch* for antidiabetic activity against normal and streptozotocin induced diabetic mice. The result showed that the ethanolic extract of leaf, flower and seed of *Prunus amygdalus* Batsch at the dose of 200 and 500 mg/ kg body weight possess significant antidiabetic and hypolipidemic activity [19].
- *Gulfraz et al, (2011);* evaluated the ethanolic extract of leaves and roots of *Justicia adhatoda* Linn for antidiabetic potential in rats against alloxan induce diabetes. The result showed that the oral administration of extract of leaves and roots of *Justicia adhatoda* Linn at the dose of 50 and 100mg/kg body weight lowering the blood glucose level and concluded that ethanolic extracts of leaves of *Justicia adhatoda* Linn at the dose of 100mg/kg possess more significant antidiabetic property as compared to the *ethanolic* extracts of roots of *Justicia adhatoda* Linn. [20].
- **Bhati et al, (2011);** evaluated the petroleum ether, chloroform, alcohol, hydroalcoholic, and aqueous extract of rhizome of *Smilax china* L. for antidiabetic potential against alloxan induce diabetes in rats. The result showed that the hydroalcoholic and aqueous extract of rhizome of Smilax *china* L. possess significant antidiabetic property [21].
- Lanjhiyana et al, (2011); evaluated the ethanolic extract of aerial leave of *Pongamia pinnata* for antidiabetic potential in rats against alloxan induce diabetes. The result showed that the ethanolic extract of aerial leave of *Pongamia pinnata* possess potential hypoglycemic activity in normoglycemic rats and antihyperglycemic activity in alloxan-induced rats [22].
- *Khan et al, (2011);* evaluated an indigenious herbal formulation containing *Methi* (fenugreek), *Sesamum indicum* (black sesame seed), Acacia catechu (Katha safeed), *Azadirachta indica* (Neem leaves), Momordica charantia (karela) for hypoglycaemic activity in adult wister albino rats against normal glycemic, glucose loaded and alloxan induced hypoglycemic rats. The result showed that formulation possess promising results that is comparable to that of the reference standard glibenclamide [23].
- **Ramakrishna et al, (2011);** evaluated the ethanolic extract of *Triumfetta Pilosa Roth* for antidiabetic potential in rats against Streptozotocin induced diabetes. The result showed that the ethanolic extract of *Triumfetta Pilosa Roth* possess significant antidiabetic property [24].
- Choudhury et al, (2011); evaluated the methanolic extracts of leaves of various Ocimum species i.e.

Ocimum gratissimum linn., Ocimum americanum linn., Ocimum sanctum linn. and Ocimum basilicum linn. for antidiabetic potential against alloxan induced diabetic model in wistar rats. The result showed that all extracts at the dose of 0.5 mg/Kg concentration possess antidiabetic activity. But the methanolic extract of Ocimum sanctum Linn. possess better antidiabetic activity in comparison with other species of Ocimum and standard drug [25].

- Aruna, (2011); evaluated the petroleum ether, chloroform, ethyl acetate and ethanolic extract of seeds of *Cassia auriculata* Linn. for antidiabetic potential in rats against alloxan induced diabetes. The result showed that Petroleum ether and ethyl acetate extract of seeds of *Cassia auriculata* Linn. *possess significant anti diabetic activity*. It was also concluded from phytochemical investigation that the activity might be due to presence of flavonoid content [26].
- Ramírez-Espinosa et al, (2011); evaluated the oral antidiabetic activity of four structurally-related triterpenic acids: ursolic (RE-01), oleanolic (RE-02), moronic (RE-03) and morolic (RE-04) acids for antidiabetic potential against STZ-nicotinamide diabetic rats. The result showed that these triterpenes at the dose of 50 mg/kg body weight possess significant antidiabetic activity in comparison with control group. The in vitro inhibitory activity of compounds against protein tyrosine phosphatase 1B (PTP-1B) was also evaluated. At 50 μM, the enzymatic activity was almost completely inhibited [27].
- *Ezike et al, (2010);* evaluated the methanolic extract of leaves of *Cajanus cajan (L.) for* antidiabetic potential against alloxan induced diabetic and oral glucose loaded rats. The result showed that the methanolic extract of leaves of *Cajanus cajan (L.)* at the dose of 400 and 600 mg/kg significantly reduces blood glucose level in alloxan induced diabetic and oral glucose loaded rats in a dose –relate manner [28].
- *Kumar et al, (2010);* evaluated the methanolic and aqueous extracts of leaves of *C. igneus* for hyperglycemic and hyperlipidemic activity in rats against alloxan induced diabetes. The result showed that the methanolic and aqueous extracts of leaves of *C. igneus* at the dose of 200mg/kg body weight possess significant hyperglycemic and hyperlipidemic activity. It was also concluded that the methanolic extracts of leaves of *C. igneus* possess better antidiabetic property as compared to the aqueous extract [29].
- **Bhat et al, (2010);** evaluated the ethanolic extract of leaves of *Costus igneus* for antidiabetic potential in albino rats against alloxan induced diabetes. The result showed that the ethanolic extract of leaves of *Costus igneus* possess significant antidiabetic property [30].
- *Kumar and Kumar (2010);* evaluated the ethanolic extracts of leaf, flower and stem of *Euphorbia hirta* Linn. for antidiabetic activity against normal and

streptozotocin (STZ) induced diabetic mice. The result showed that the ethanolic extracts of all part of *Euphorbia hirta* Linn. at the dose of 250 and 500 mg/kg body weight lowers the blood glucose level [31].

- *Parthasarathy et al, (2009);* evaluated the ethanolic extract of the bark and leaf of *Thespesia populnea* for antidiabetic activity against the streptozotocin (STZ)– induced diabetic rats. The result showed that the ethanolic extract of bark and leaf of *Thespesia populnea* possess anti-diabetic effect against STZ induced diabetic rats and concluded that the extracts showed that the possible mechanism due to inhibition of generation of free radical [32].
- Chittagong et al, (2009); evaluated the hot water extraction of leaves of Lagerstromia speciosa L for antidiabetic potential in rats against streptozotocin induce diabetes. The result showed that the hot water extract of L. speciosa leave attributed its prominent hypoglycemic activity on experimental diabetic rats through suppression of gluconeogenesis and stimulation of glucose oxidation using the pentose phosphate pathway [33].
- *Adeyemi et al, (2009);* evaluated the methanolic extracts of *Annona muricata* (Linn.) for antidiabetic potential in wistar rats against streptozotocin-induced diabetes. The result showed that a significant difference exists between the blood glucose concentrations of treated and untreated hyperglycemic groups of rats and concluded that *A. muricata* possesses antihyperglycemic activities [34].
- *Tenpe & Yeole*, (2009); compared five different marketed polyherbal formulations against alloxan induced diabetic rats for antidiabetic potential. The result showed a significant increase in serum glucose (p<0.001) and improvement in the other biochemical parameters with treatment of polyherbal formulations which altered in diabetic rats as compared to the standard drug [35].
- *Sikarwar et al, (2009);* evaluated the petroleum ether, chloroform, alcohol and aqueous extracts of leaf of *Nerium indicum* for antidiabetic potential against alloxan induced diabetic in albino rats. The result showed that chloroform and ethanolic extract of leaf of *Nerium indicum* possess significant antidiabetic activity while petroleum ether and aqueous extract possess moderate antidiabetic activity [36].
- Jarald et al, (2008); evaluated the antidiabetic activity of various extracts i.e. petroleum ether, chloroform, acetone, ethanol, aqueous and crude aqueous of the flower buds of *Michelia champaca* against glucose overloaded hyperglycemic rats. The result showed that the ethanolic extract of *M. champaca* possess significant antihyperglycemic activity but did not produce hypoglycemia in fasted normal rats. Apart from this extract, the crude aqueous and petroleum ether extracts were found active only at the end of the

first hour and concluded that ethanolic extract of *Michelia champaca* showed significant antidiabetic activity [37].

- *Tailang et al, (2008);* evaluated the ethanolic extract of leaves of *Cinnamomum zeylanicum* for antidiabetic potential in wistar rats against alloxan induce diabetes. The result showed that the oral administration of ethanolic extract of *Cinnamomum zeylanicum* at the doses of 100, 150 & 200 mg/kg body weight significantly reduce the blood glucose level [38].
- Sabu & Kuttan, (2004); evaluated the methanolic extract of Leaves of Aegle marmelos for antidiabetic and antioxidant potential against alloxan induced diabetic rats. The result showed that the methanolic extract of Leaves of Aegle marmelos effectively reduces the oxidative stress induced by alloxan and significantly reduces the blood glucose level [39].
- *Nagappa et al, (2003);* evaluated the petroleum ether, methanol, and aqueous extracts of fruit *Terminalia catappa Linn (combretaceae)* for antidiabetic activity in wistar rats against alloxan induce diabetes. The result showed that all the three extracts of *Terminalia catappa* possess a significant antidiabetic activity [40].
- *Annapurna et al, (2001);* evaluated the antidiabetic activity of a polyherbal preparation (tincture of panchparna) against normal and alloxan induced diabetic rats. The result showed that a polyherbal preparation (tincture of panchparna) at the dose of 1ml/kg body weight possess significant antidiabetic activity in normal and alloxan induced diabetic rats [41].

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How to cite this article:

Chaudhary N and Tyagi N. Medicinal plants used for Diabetes mellitus: An Overview. Int. J. Res. Dev. Pharm. L. Sci. 2018; 7(4): 3022-3029. doi: 10.13040/IJRDPL.2278-0238.7(4).3022-3029.

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