Chapter 2

Literature Review
2. LITERATURE REVIEW

2.1 Diabetes: Classification, Prevention, Complication’s and Treatments

2.2 Experimental Models of Diabetes

2.3 Different Herbs and their Combinations Used in Treatment of NIDDM

2.4 Herbal Formulations

2.5 *Eugenia jambolana*
   - A. Classification
   - B. Synonyms
   - C. Part used
   - D. Botanical description
   - E. Traditional uses
   - F. Phytochemistry
   - G. Pharmacology
   - H. Various combination studies of *Eugenia jambolana*.

2.6 *Momordica charantia*
   - A. Classification
   - B. Synonyms
   - C. Parts Used
   - D. Botanical description
   - E. Traditional uses
   - F. Phytochemistry
   - G. Pharmacology
   - H. Various combination studies of *Momordica charantia*.

2.7 *Gmelina arborea*
   - A. Classification
   - B. Botanical synonym
   - C. Part used
   - D. Botanical description
   - E. Traditional uses
   - F. Phytochemistry
   - G. Pharmacology
2.1 Diabetes

2.1.1 Different Types:

DM is classified on the basis of the pathogenic process that leads to hyperglycemia, as opposed to earlier criteria such as age of onset or type of therapy (Fig. 2.1). The spectrum from normal glucose tolerance to diabetes in type 1 DM, type 2 DM, other specific types of diabetes, and gestational DM is shown from left to right. Arrows indicate that changes in glucose tolerance may be bi-directional in some types of diabetes.

The two broad categories of DM are designated type 1 and type 2. Type 1A DM results from autoimmune beta cell destruction, which leads to insulin deficiency. Individuals with type 1B DM lack immunologic markers indicative of an autoimmune destructive process of the beta cells. However, they develop insulin deficiency by unknown mechanisms and are ketosis prone. Relatively few patients with type 1 DM are in the type 1B idiopathic category; many of these individuals are either African-American or Asian in heritage. Type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production. Distinct genetic and metabolic defects in insulin action and/or secretion give rise to the common phenotype of hyperglycemia in type 2 DM. Distinct pathogenic processes in type 2 DM have important potential therapeutic implications, as pharmacologic agents that target specific metabolic derangements of pancreatic islets (~80%) are destroyed. Hormones that antagonize the action of insulin can lead to DM. Viral infections have been implicated in pancreatic islet destruction, but are an extremely rare cause of DM. Congenital rubella greatly increases the risk for DM; however,
most of these individuals also have immunologic markers indicative of autoimmune beta cell destruction.

**Gestational Diabetes Mellitus (GDM)**

Glucose intolerance may develop during pregnancy. Insulin resistance related to the metabolic changes of late pregnancy increases insulin requirements and may lead to IGT. GDM occurs in approximately 4% of pregnancies in the United States; most women revert to normal glucose tolerance post-partum but have a substantial risk (30 to 60%) of developing DM later in life.

**Etiologic Classification of Diabetes Mellitus:**

**I. Type 1 diabetes** (β-cell destruction, usually leading to absolute Insulin deficiency)
   - A. Immune-mediated
   - B. Idiopathic

**II. Type 2 diabetes** (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)

**2.1.2: Type 1 Diabetes Mellitus:**

Type 1 diabetes mellitus accounts for 10% of all diabetes cases. It involves the autoimmune destruction of insulin-producing pancreatic beta-cells via auto-aggressive T-cells and pancreatic macrophage infiltration.

**Pathogenesis:**

Type 1A DM develops as a result of the synergistic effects of genetic, environmental, and immunologic factors that ultimately destroy the pancreatic beta cells. The temporal development of type 1A DM is shown schematically as a function of beta cell mass in figure 2.2. Individuals with a genetic susceptibility have normal beta cell mass at birth but begin to lose beta cells secondary to autoimmune destruction that occurs over months to years. This autoimmune process is thought to be triggered by an infectious or environmental stimulus and to be sustained by a beta cell–specific molecule. In the majority of individuals, immunologic markers appear after the triggering event but before diabetes becomes clinically overt. Beta
cell mass then begins to decline, and insulin secretion becomes progressively impaired, although normal glucose tolerance is maintained. The rate of decline in beta cell mass varies widely among individuals, with some patients progressing rapidly to clinical diabetes and others evolving more slowly. Features of diabetes do not become evident until a majority of beta cells are destroyed (~80%). At this point, residual functional beta cells still exist but are insufficient in number to maintain glucose tolerance. The events that trigger the transition from glucose intolerance to frank diabetes are often associated with increased insulin requirements, as might occur during infections or puberty. After the initial clinical presentation of type 1A DM, a phase may ensue during which time glycemic control is achieved with modest doses of insulin or, rarely, insulin is not needed. However, this fleeting phase of endogenous insulin production from residual beta cells disappears as the autoimmune process destroys the remaining beta cells, and the individual becomes completely insulin deficient.

Figure 2.2: Temporal model for development of type 1 diabetes
Preventive strategies (Reimann et al. 2009)

Primary prevention — identification of risk groups and induction of immune tolerance:
Screening for susceptibility genes in the general population may play a major role in primary
type 1 diabetes prevention, since ~90% of Type 1 diabetes patients do not have a family
history of diabetes. Primary prevention (Fig. 2.3) may consist of measures to eradicate
environmental risk factors; however, this method will be difficult without clear evidence and
definitions for suitable targets. Nevertheless, screening in newborns may be the most efficient
way of preventing future autoimmune disease, as the immune system matures mainly during
the postnatal period through breastfeeding, and is partly modified by nutritive factors. In
particular, the timing of exposure to certain food components in the first year of life seems to
be critical in the onset of islet autoimmunity for young children.

Figure 2.3: Potential concepts for prevention and therapeutic intervention of type 1 diabetes,
as they relate to the timing of loss of β-cell mass
Secondary prevention: modulation of immune response:
A wealth of evidence indicates that the autoimmune process which leads to beta-cell destruction remains sub-clinical for many years in most patients. Greater than 80% of beta-cells have already been destroyed by the time that the first clinical symptoms become apparent, most notable are those associated with hyperglycemia. Importantly, autoantibodies to beta cell antigens are present long before the onset of type 1 diabetes, and can be detected as early as 5 years of age in most cases of future diabetes. The main autoantigens associated with Type 1 diabetes are insulin, glutamic acid decarboxylase 65 (GAD65), islet-associated antigen 2/ICA512 (IA-2/ICA512), and the cation efflux transporter (ZnT8). Autoantibodies against at least one of these four antigens can be detected in 90% of those with recent-onset type 1 diabetes. The presence of multiple antiislet autoantibodies in serum is highly predictive of future type 1 diabetes, and is associated with a progressive loss of insulin secretion during the preclinical stage. Therefore, antibody screening may be a viable approach for detecting individuals at preclinical stages, and is recommended with follow-up testing for risk stratification.

Tertiary prevention: preservation and expansion of beta-cell mass Transplantation.
Tertiary prevention is usually initiated after the onset of type 1 diabetes for the preservation and expansion of residual beta cell mass and function (Fig. 2.2). Accordingly, insulin independence rates of almost 100% have been achieved using at least two donor pancreata or an average of 11,000 islet equivalents per kilogram bodyweight. However, the limited availability of donor organs, the difficulty in isolating large numbers of islet cells from a single pancreatic gland, the fragility of purified β-cells, and alloimmunity as well as the recurrence of autoimmunity are still major barriers to pancreatic allotransplantation. Concomitant application of glucocorticoid-free immunosuppressive regimens after transplantation, which consist of a combination of systemic immunosuppressive agents (rapamycin, tacrolimus, and daclizumab), may be crucial for beta-cell survival. Immunosuppression to avoid expansion of autoaggressive T-cells was also successfully achieved by application of a combination of rapamycin and cytostaticmycophenolate mofetil in islet recipients.
Regeneration and proliferation of beta-cells:
Novel approaches targeting beta-cell regeneration or neogenesis are currently underway to circumvent the limited availability of donor organs. Pluripotent embryonic stem cells from pancreatic and non-pancreatic tissues have been proposed as an alternative to provide an unlimited source of insulin-secreting cells.

2.1.3 Type 2 Diabetes Mellitus:
Type 2 diabetes mellitus has become an epidemic, and virtually no physician is without patients who have the disease. Whereas insulin insensitivity is an early phenomenon partly related to obesity, pancreas β-cell function declines gradually over time already before the onset of clinical hyperglycaemia. Insulin resistance and abnormal insulin secretion are central to the development of type 2 DM. Although controversy remains regarding the primary defect, most studies support the view that insulin resistance precedes insulin secretory defects and that diabetes develops only if insulin secretion becomes inadequate

Pathophysiology:
Insulin is the key hormone for regulation of blood glucose and, generally, normoglycaemia is maintained by the balanced interplay between insulin action and insulin secretion. Importantly, the normal pancreatic β cell can adapt to changes in insulin action- ie, a decrease in insulin action is accompanied by upregulation of insulin secretion (and vice versa). Figure 3.4 illustrates the curvilinear relation between normal β –cell function and insulin sensitivity (Bergman, 1989). Deviation from this hyperbola, such as in the patients with impaired glucose tolerance and type 2 diabetes in figure 3.4, occurs when β cell function is inadequately low for a specific degree of insulin sensitivity. Thus, β –cell dysfunction is a critical component in the pathogenesis of type 2 diabetes. However, not only deviation from but also progression along the hyperbola affects glycaemia. When insulin action decreases (as with increasing obesity) the system usually compensates by increasing β-cell function. However, at the same time, concentrations of blood glucose at fasting and 2 h after glucose load will increase mildly (Stumvoll et al., 2003)

Insulin resistance:
Insulin resistance is said to be present when the biological effects of insulin are less than expected for both glucose disposal in skeletal muscle and suppression of endogenous glucose
production primarily in the liver (Dinneen et al., 1992). In the fasting state, however, muscle
accounts for only a small proportion of glucose disposal (less than 20%) whereas endogenous
glucose production is responsible for all the glucose entering the plasma. Endogenous glucose
production is accelerated in patients with type 2 diabetes or impaired fasting glucose (Weyer
1999; Meyer et al., 1998). Because this increase occurs in the presence of hyperinsulinaemia,
at least in the early and intermediate disease stages, hepatic insulin resistance is the driving
force of hyperglycaemia of type 2 diabetes (Fig. 2.4).

**Figure: 2.4** Hyperbolic relation between β-cell function and insulin sensitivity

**Obesity**
Insulin resistance is strongly associated with obesity and physical inactivity, and several
mechanisms mediating this interaction have been identified. A number of circulating
hormones, cytokines, and metabolic fuels, such as non-esterified (free) fatty acids (NEFA)
originate in the adipocyte and modulate insulin action. An increased mass of stored
triglyceride, especially in visceral or deep subcutaneous adipose depots, leads to large
adipocytes that are themselves resistant to the ability of insulin to suppress lipolysis. This results in increased release and circulating levels of NEFA and glycerol, both of which aggravate insulin resistance in skeletal muscle and liver (Fig. 2.5) (Boden G, 1997) Excessive fat storage not only in adipocytes but “ectopically” in non-adipose cells also has an important role. For example, increased intramyocellular lipids are associated with skeletal muscle insulin resistance under some circumstances.

**Figure: 2.5:** Pathophysiology of hyperglycaemia and increased circulating fatty acids in type 2 diabetes

**Preventive strategies** (Reimann et al. 2009):

**Detection of relevant target groups and risk factor reduction:**

Owing to the irreversible nature of type 2 DM, early intervention during development is crucial to prevent the disease or delay disease onset (Fig. 2.8). At preclinical stages, the self-regenerating capacity of β-cells may still be well-preserved, such that reversing organ damage should be possible. Although universal population screening is not yet recommended,
targeting high-risk subjects seems to be a viable alternative. According to the American Diabetes Association (ADA), a test to detect preclinical stages should be safe, acceptable, and predictive. Measuring fasting plasma glucose (FPG) and 2 h oral glucose tolerance test (OGTT) values satisfy the ADA criteria, with positive values predicting the development of diabetes in either test.

**Lifestyle modification:**
Reduction of the individual number of modifiable risk factors is considered a prime target in type 2 DM prevention. In particular, lifestyle interventions aimed at reducing obesity by modifications in eating behavior and physical activity directly address risk factors for diabetes and cardiovascular disease. Results of recent well-designed large clinical trials in individuals with IGT support this strategy.

**Pharmacological strategies:**
Pharmacological intervention trials with glucose-lowering agents also proved successful in reducing cumulative diabetes incidence rates in individuals. Other promising novel therapeutic agents are currently under investigation; these target insulin sensitization (11beta-HSD-1 inhibitors and antagonists of glucocorticoids receptor), hepatic glucose output (antagonists of glucagon receptor, inhibitors of glycogen phosphorylase and fructose-1,6-biphosphatase), and urinary elimination of excess glucose (SGLT inhibitors). Glucokinase activators capable of enhancing insulin secretion and improving hepatic glucose metabolism have also received much focus with IGT.

**Secondary prevention: optimizing glycemic control and beta-cell function**
Several studies, such as the United Kingdom Prospective Diabetes Study (UKPDS), ADVANCE (Action in Diabetes and Vascular Disease: PreterAx and DiamicroN Controlled Evaluation), and ADOPT (A Diabetes Outcome Progression Trial), have clearly illustrated that tight glycemic control achieved with traditional medications (insulin, sulfonylureas, glitinides, acarbose, metformin, and thiazolidinediones) can result in significant reductions in the development of diabetes associated secondary complications. Consequently, there are intense efforts to develop therapeutic agents that preserve or restore functional beta-cell mass. In particular, mimetics of incretin have received a great deal of attention in recent years due to
GLP-1-potentiating effects. Released by gastrointestinal L-cells, GLP-1 stimulates insulin release, suppresses glucagon secretion, and slows gastric emptying, thus promoting effects that contribute to improved glycemic control.

Figure 2.6: Potential concepts for prevention and therapeutic intervention of type 2 diabetes.

**Tertiary prevention: Conventional approach.**

In the conventional sense, tertiary prevention refers to any measures aimed at avoiding or delaying long-term microvascular and macrovascular complications involved in diabetes. The current strategies are based on i) tight glycemic control to optimize glucose (HbA1c) levels, and ii) minimization of cardiovascular risk factors. In previous years, post-challenge hyperglycemia has been especially linked to diabetic vascular complications, and in this regard, has become a prime target for pharmacotherapy. A number of agents, such as exenatide, α-glucosidase inhibitors, rapid acting insulin secretagogues, short-acting insulin analogs, and pramlintide (an analog of the beta-cell peptide hormone amylin), have been
proven to be particularly beneficial in targeting postprandial glucose levels. Additionally, multidrug regimens have been applied to achieve optimal lipid and blood pressure values and reduce the risk of thrombus formation in diabetic patients.

**Incretin mimetics and beta-cell regeneration.**

Since loss of functional beta-cell mass also occurs in type 2 DM, regenerative medicine has become an emerging field in tertiary prevention. Embryonic stem-cell transdifferentiation and beta-cell replication and neogenesis are two potential ways of replenishing beta-cell mass. There is some evidence that mature beta-cells retain their proliferative capacity, even in advanced years. Incretin mimetics and DPP-4 inhibitors have been especially suggested as a therapeutic option, due to proliferative, neogenic, and antiapoptotic actions, but their long-term effects on beta-cell mass in patients with diabetes remains to be firmly established.

### 2.1.3 Complications:

**Acute Complications of DM;**

Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are acute complications of diabetes. DKA was formerly considered a hallmark of type 1 DM, but it also occurs in individuals who lack immunologic features of type 1A DM and who can subsequently be treated with oral glucose-lowering agents (these individuals with type 2 DM are often of Hispanic or African-American descent). HHS is primarily seen in individuals with type 2 DM. Both disorders are associated with absolute or relative insulin deficiency, volume depletion, and acid-base abnormalities. DKA and HHS exist along a continuum of hyperglycemia, with or without ketosis. Both disorders are associated with potentially serious complications if not promptly diagnosed and treated.

**Chronic Complications of DM**

The chronic complications of DM affect many organ systems and are responsible for the majority of morbidity and mortality associated with the disease. Chronic complications can be divided into vascular and nonvascular complications. The risk of chronic complications increases as a function of the duration of hyperglycemia; they usually become apparent in the
second decade of hyperglycemia. Since type 2 DM often has a long asymptomatic period of hyperglycemia, many individuals with type 2 DM have complications at the time of diagnosis.

I. Microvascular Complications of DM
   a. Eye disease
      i. Retinopathy (nonproliferative/proliferative)
      ii. Macular edema
   b. Neuropathy
      i. Sensory and motor (mono- and polyneuropathy)
      ii. Autonomic
   c. Nephropathy

II. Macrovascular Complications of DM
   a. Coronary artery disease
   b. Peripheral vascular disease
   c. Cerebrovascular disease

III. Other
   a. Gastrointestinal (gastroparesis, diarrhea)
   b. Genitourinary (uropathy/sexual dysfunction)
   c. Dermatologic
   d. Infectious
   e. Cataracts
   f. Glaucoma
   b. Infections
   c. Skin changes

Diabetic Retinopathy:
Diabetic retinopathy is increasingly becoming a major cause of blindness throughout the world in the age group of 20-60 years (Thylefors et al., 1995; WHO, 1997). Diabetic retinopathy is the cause of blindness in approximately 2.5 million of the estimated 50 million blind people in the world. However, diabetic retinopathy, as a cause of blindness, is less common in India according to population-based studies (Dandona et al., 1999; Narendran V, 2002). Diabetic retinopathy is classified into two stages:
I. Nonproliferative Diabetic Retinopathy

II. Proliferative Diabetic Retinopathy

**Diabetic Neuropathy**

Peripheral diabetic neuropathy (PDN) affects up to 60% to 70% of diabetic patients, and is the leading cause of foot amputation (Boulton, 2001). The prevalence of neuropathy is estimated to be about 8% in newly diagnosed patients and greater than 50% in patients with long-standing disease (Boulton et al., 2005). It may manifest as polyneuropathy, mononeuropathy, and/or autonomic neuropathy. As with other complications of DM, the development of neuropathy correlates with the duration of diabetes and glycemic control; both myelinated and unmyelinated nerve fibers are lost. The syndromes may be grouped under two general headings: diffuse and focal neuropathies. The diffuse neuropathies, i.e., distal symmetrical sensorimotor polyneuropathy (DPN) and diabetic autonomic neuropathy (DAN) are common, usually chronic, and often progressive. The focal neuropathies are less common, usually acute in onset, and often self-limited.

**Diabetic nephropathy** (Kasper, 2005)

Diabetic nephropathy is the leading cause of end stage renal disease worldwide and is associated with increased cardiovascular risk. The classical definition of diabetic nephropathy is of a progressive rise in urine albumin excretion, coupled with increasing blood pressure, leading to declining glomerular filtration and eventually end stage renal failure. The natural history of diabetic nephropathy is characterized by a fairly predictable sequence of events that was initially defined for individuals with type 1 DM but appears to be similar in type 2 DM. Glomerular hyperperfusion and renal hypertrophy occur in the first years after the onset of DM and cause an increase of the glomerular filtration rate (GFR). During the first 5 years of DM, thickening of the glomerular basement membrane, glomerular hypertrophy, and mesangial volume expansion occur as the GFR returns to normal. After 5 to 10 years of type 1 DM, ~40% of individuals begin to excrete small amounts of albumin in the urine.

*Microalbuminuria* is defined as 30 to 300 mg/d in a 24-h collection or 30 to 300 μg/mg creatinine in a spot collection (preferred method). The appearance of microalbuminuria (incipient nephropathy) in type 1 DM is an important predictor of progression to overt proteinuria (>300 mg/d) or overt nephropathy. Blood pressure may rise slightly at this point.
but usually remains in the normal range. Once overt proteinuria is present, there is a steady decline in GFR, and ~50% of individuals reach ESRD in 7 to 10 years. The early pathologic changes and albumin excretion abnormalities are reversible with normalization of plasma glucose. However, once overt nephropathy develops, the pathologic changes are likely irreversible. The nephropathy that develops in type 2 DM differs from that of type 1 DM in the following respects: (1) microalbuminuria or overt nephropathy may be present when type 2 DM is diagnosed, reflecting its long asymptomatic period; (2) hypertension more commonly accompanies microalbuminuria or overt nephropathy in type 2 DM; and (3) microalbuminuria may be less predictive of diabetic nephropathy and progression to overt nephropathy in type 2 DM. Finally, it should be noted that albuminuria in type 2 DM may be secondary to factors unrelated to DM, such as hypertension, congestive heart failure, prostate disease, or infection.

2.1.4 Treatments/Management:

WHO suggested the evaluation of the potential of plants as effective therapeutic agents, for the chronic metabolic disorders like diabetes, hypertension etc, especially in areas where we lack safe modern drug (WHO, 1994). In case of diabetes, though the presently available oral hypoglycemic are effective in controlling acute metabolic abnormalities, they are associated with side effects. Countering the metabolic abnormalities of diabetes prevents its long-term complications i.e. nephropathy, neuropathy. Even Though insulin is widely accepted as an ideal choice for treatment of diabetes mellitus, the difficulty of repeated administration led to the search for oral hypoglycemic agents. Some of the drugs such as Sulfonylureas and biguanidines are being used for this purpose. A variety of plant preparations have been mentioned in Ayurveda and other indigenous systems of medicine, which are claimed to be useful in diabetes mellitus and their complications.

The interacting defects in multiple organs muscle, liver, adipose tissue and pancreas generate the pathogenic milieu that results in diabetes. Various classes of oral hypoglycemic agents are now available that target the different pathophysiologic factors contributing to diabetes

- α-glucosidase inhibitors to delay intestinal carbohydrate absorption,
- Biguanides to target hepatic insulin resistance,
- Insulin secretagogues to increase pancreatic insulin secretion,
- Insulin sensitizers or thiazolidinediones to target adipocyte and muscle insulin resistance,
Intestinal lipase inhibitor or orlistat to inhibit fat absorption and promote weight loss in obese patient

In case of obese individuals, the body tries to maintain glycemia by increasing the levels of endogenous insulin secretion resulting in hyperinsulinaemia. Nevertheless, the increase in body mass contributes to insulin resistance with glucose intolerance or noninsulin dependent DM. Therefore, obesity remains an important modifiable component of the metabolic disturbance. Also postulated on basis of scientific evidence, among all the constituents of the food, the dietary fat composition may have greater effect on insulin sensitivity (Storlien et al, 1996). It has been shown that sufficient exercise both in terms of intensity and duration exerts beneficial effects on subjects with Non-insulin dependent diabetes (Perseghin et al, 1996). However, at the same time these patients are likely to be old and obese, which reduces compliance and are unable to participate in exercise programs. Treatment with insulin is essential for type I diabetes patients. The administration is carried out apart from insulin resistance; insulin therapy may lead to other complications like blurred vision and hypoglycemia. Insulin has yet been found in the treatment of type I diabetes. When the pancreatic extract was tried in human beings an initial hyperglycemic action was observed and further investigations led to the discovery of the hormone glucagons secreted from cells of the pancreas. Insulin, a protein hormone has a wide range of metabolic action especially on carbohydrate metabolism. Once the b cells of the islets of Langerhans are destroyed by viral action, drug etc, the synthesis of insulin decreases or stops depending on the extent of the damage. The biochemical characteristics of the disease are an increased blood glucose concentration resulting in glycosuria and ketonuria. If the disease remains untreated, ketoacidc sets in with polyuria, coma and finally death. Since in hypertension, the choice of anti-hypertensive agents depends on the range of side effects, the same is true for diabetes. For instance, treatment with Metformin may lead to better effects on both dyslipidemia and insulinemia than treatment with Sulfonylureas. It is clear that the treatment of insulin resistance has great therapeutic potential for the amelioration of type II diabetes. Although currently available clinical / pharmacological modalities are not directed to the treatment of impaired insulin action, recent efforts have focused on the development of insulin sensitizing agents. Major breakthrough in this area occurred in 1982 with discovery of Rosiglitazone, a thiazolidinedione derivative, which was followed by a number of other compounds, such as pioglitazone, troglitazone, enlilagezone, and others. It was found to be
effective in reducing plasma glucose, insulin, non-esterified fatty acids, triglycerides concentrations in genetically insulin resistant animals, including the kka, ob/ob, and db/db mouse and the zfr (Fujita et al, 1983; Fujiwara et al, 1988; Stevenson et al, 1990) as well as in fructose fed and high fat - adapted rats (Lee et al, 1990). Similar effects were seen in human studies of diabetic patients (Nolan et al, 1994; Kumar et al, 1996). Apart from diabetes, insulin resistance is also an essential feature of several other disease states such as obesity, hypertension, impaired glucose tolerance, and polycystic ovarian syndrome. Initial studies with troglitazone have been conducted in some of these conditions and the results have been promising (Nolan et al, 1994). Troglitazone has beneficial effects on blood pressure in obese subjects; the data requires confirmation from other sources. Troglitazone appears to be equal in efficacy to Sulfonylurea or Metformin in reducing glycosylated hemoglobin and also reduces triglyceride levels. Biguanidines on the other hand are effective in increasing insulin sensitivity. However, the effect of biguanides on long term complications has not been studied. The major therapeutic goal in-patients with NIDDM is to reduced blood glucose level along with reduction in obesity and to normalize lipid disturbances and blood pressure, in order to improve the well being of the patients and reduce the risk of development of late diabetic complications.

2.2 Experimental models of diabetes mellitus:

Animal models have been used extensively in diabetes research. Early studies used pancreatectomised dogs to confirm the central role of the pancreas in glucose homeostasis, culminating in the discovery and purification of insulin. Today, animal experimentation is contentious and subject to legal and ethical restrictions that vary throughout the world. Most experiments are carried out on rodents, although some studies are still performed on larger animals. Several toxins, including streptozotocin and alloxan, induce hyperglycaemia in rats and mice. Selective inbreeding has produced several strains of animal that are considered reasonable models of type 1 diabetes, type 2 diabetes and related phenotypes such as obesity and insulin resistance. Apart from their use in studying the pathogenesis of the disease and its complications, all new treatments for diabetes, including islet cell transplantation and preventative strategies, are initially investigated in animals. In recent years, molecular biological techniques have produced a large number of new animal models for the study of diabetes, including knock-in, generalized knock-out and tissue-specific knockout mice.
2.2.1 Animal Models of Type 1 Diabetes Mellitus

Alloxan induced diabetes (Frode and Medeiros, 2008)

Mechanism of Induction of Diabetes:

The mechanism by which alloxan results in diabetes in susceptible species has not been entirely clarified. It has been shown that alloxan has several effects on the β-cells of the pancreas, and it is likely that some combination of these effects results in destruction of β-cells by alloxan. Reviews by Malaisse and Lenzen and Panten present two different proposals to explain the mechanism. Alloxan is highly reactive molecule that is readily reduced to dialuric acid, which is then auto-oxidized back to alloxan resulting in the production of H$_2$O$_2$, O$_2$, and hydroxyl radicals. Alloxan has been shown to reduce DNA strand breaks in isolated islets and in islets following in vivo administration of alloxan. More recent works has shown that the DNA fragmentation is mediated by H$_2$O$_2$. The induction of DNA strand breaks activates nuclear poly (ADP-ribose) synthetase resulting in depletion of cellular NAD levels. Two factors appear to make the islets especially sensitive to the effects of alloxan; the first factor is that alloxan is rapidly taken up into islet cells, and the second factor is sensitivity of islets to peroxides.

A second mechanism proposed for the diabetogenic effects of alloxan concerns its ability to react with protein sulphydryl (SH) groups. The proposed mechanism involves reaction of alloxan with the SH groups on glucokinase, a signal recognition enzyme in the pancreatic β-cells, which couples change in blood glucose concentration to the rate of insulin secretion. By this mechanism, inhibition of glucokinase and other SH-containing membrane proteins on the β-cells would eventually result in cell necrosis. One of the effects of alloxan on the β-cells is the inhibition of glucose-stimulated insulin release, and this is likely related to the inhibition of glucokinase. As yet, however, there is no convincing evidence that the reaction of alloxan with protein SH groups would result in the cellular and nuclear necrosis that occur within minutes when alloxan induces diabetes in rabbits and other animals.

A study of the effects of alloxan on glucose oxidation and viability of islets from humans, rats, and mice showed that there were major species differences in response to alloxan. The range of the diabetogenic dose of alloxan is quite narrow and even light overdosing may be generally toxic and may cause the loss of many animals. This loss is likely to stem from kidney tubular cell necrotic toxicity, in particular when too high doses of alloxan are administered. The most frequently used intravenous dose of alloxan in rats is 65 mg/kg, but
when it is administered intraperitonealy (i.p.) or subcutaneously its effective dose must be higher. For instance, an intraperitoneal dose below 150 mg/kg may be insufficient for inducing diabetes in this animal species. In mice, doses vary among 100 to 200 mg/kg by intravenous route (i.v.).

**Streptozotocin (STZ) induced diabetes (McNeill JH, 1999)**

Streptozotocin (2-deoxy-2-(3-methyl-3-nitrosourea) 1-D-glucopyranose) is a broad spectrum antibiotic which is produced from *Streptomyces achromogenes*. The diabetogenis response to STZ was first detected by Upjohn Laboratories during testing of potential antibiotics from this organism. However Rakieten et al. were the first to describe that β-cell necrosis and the ensuing diabetic state could be produced after a single intravenous dose of STZ in rats and dogs.

**Mechanism of the diabetogenic action of STZ**

The chemical structure of STZ comprises a glucose molecule with a highly reactive nitrosourea side chain that is thought to initiate its cytotoxic action. The glucose moiety directs this agent to the pancreatic β-cell, where it binds to a membrane receptor to generate structural damage. A decrease in diabetes induction efficacy after substitution of glucose by other sugars supports the presence of stereospecific membrane receptor or recognition site on the plasma membrane of the β-cell, identified as probably being the glucose transporter GLUT2. However as no plasma membrane labeling was recorded with radioactive 14C-STZ, another explanation for β-cell plasma membrane damage is that it occurs secondary to other indirect actions of STZ. At the intracellular level, three major phenomenon are currently held responsible for β-cell death: [1] Process of methylation, [2] free radical generation and [3] nitric oxide (NO) production.

Methylation: The deleterious effect of STZ results from the generation of highly reactive carbonium ions (CH$_3$ +), formed from decomposition of the nitroso moiety. The CH$_3$+ ions cause DNA breaks by alkylating DNA bases at various positions, resulting in activation of the nuclear enzyme poly(ADP-ribose) synthetase as part of the cell repair mechanism. As cellular pyridine nucleotide, particularly NAD+ are utilized as substrates for the nuclear enzyme, a profound decline in NAD+ occurs within 20 min. In effect, an abrupt and irreversible NAD+ exhaustion leads to cessation of NAD+-dependant energy and protein metabolism, ultimately
leading to cell death. Inhibition of poly (ADP-ribose) synthetase by agents like 3-aminobenzamide and nicotinamide are known to protect β-cells from NAD+ depletion and cell death after STZ exposure.

Free radicals: free radical involvement in STZ effects have also been investigated. Hydrogen peroxide has been shown to be produced in pancreatic islets upon STZ exposure in vivo and in vitro. Moreover, because superoxide dismutase, a free radical scavenger was demonstrated to provide some protection against the diabetogenic properties of STZ, it was concluded that oxidative stress could play a role in determining STZ toxicity.

Nitric oxide: Involvement of NO has also been proposed as possible mechanism for mediating the diabetogenic effects of STZ. The precise metabolic processes leading to NO generation from STZ is unclear, but may involve the metabolism or spontaneous decay of STZ. Whatever the mechanism, STZ-generated NO seems to be significantly involved in cytotoxicity toward β-cells. This agent can also be used to induce diabetes with multiple low doses. After multiple low dose injection of STZ, islet degeneration due to direct STZ toxicity has been suggested to initiate an inflammatory response whereby mononuclear cells migrate form bloodstream to the tissue, where they differentiate into macrophages. These cells phagocytose the pancreatic β-cells, thereby releasing cytochemical mediators. Subsequently, lymphatic infiltration occurs.

Several mechanisms have been postulated to explain why the fatal events described above occur selectively in β-cells. These include: [1] a high affinity of STZ for the β-cells membrane, [2] unique SH groups that render the β-cells membrane especially sensitive to oxidative interactions, [3] a low capacity of β-cells to scavenge free radicals and [4] a low NAD+/DNA ratio in islets compared with other tissues. In adult rats, 60 mg/kg is the most common dose of STZ to induce insulin dependent diabetes (Patel et al., 2006), but higher doses are also used. STZ is also efficacious after intraperitoneal administration of a similar or higher dose, but single doses below 40 mg/kg may be ineffective (Katsumata et al. 1992). In general, rats are considered diabetic if tail blood glucose concentrations in fed animals are greater than 200-300 mg/dl, two days after STZ injection.

**Spontaneous animal models of Type 1 diabetes**

The non-obese diabetic (NOD) mouse and bio breeding (BB) rat are the two most commonly used animals that spontaneously develop diseases with similarities to human Type 1 diabetes (Table 3.3). These animals have been inbred in laboratories for many generations, by selecting...
for hyperglycaemia. As a result of this process, many genes and phenotypes will have been enriched, but not all will be relevant to the pathophysiology of diabetes, either in rodents or in humans.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>NOD (non-obese diabetic) mouse</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BB (bio breeding) rat</td>
</tr>
<tr>
<td>2</td>
<td>LETL (Long Evans Tokushima lean) rat</td>
</tr>
<tr>
<td>3</td>
<td>New Zealand white rabbit</td>
</tr>
<tr>
<td>4</td>
<td>Keeshond dog</td>
</tr>
<tr>
<td>5</td>
<td>Chinese hamster</td>
</tr>
<tr>
<td>6</td>
<td>Celebes black ape (Macaca nigraka)</td>
</tr>
</tbody>
</table>

2.2.2 Animal Models of Type 2 Diabetes Mellitus:
Animals exhibiting a syndrome of insulin resistance and type 2 diabetes, with characteristics similar to humans, comprise a wide range of species with genetic, experimental or nutritional causation. Some animals with inherent diabetes have pancreas with ‘sturdy’ beta cells capable of maintaining robust, life long insulin secreting capacity characterized by severe hyperinsulinaemia with only mild to moderate hyperglycaemia throughout the life e.g., Zucker fatty rats (ZFR), ob/ob (obese), KK mouse and (corpulent) cp rat group. At the other end of spectrum, some species possess ‘brittle or labile’ pancreatic beta cells allowing only for transient insulin hypersecretion with shortterm obesity. Subsequently, as a result of genetic predisposition and affluent nutrition/other environmental causes, it induces secretion pressure on beta cell which ultimately leads to degranulation, apoptosis and overt hyperglycaemic state. At this point, the animals rapidly lose their previously accumulated adipose tissue, become ketotic and require insulin to survive. e.g., db/db (diabetic) mouse, Zucker diabetic fatty (ZDF) rat, sand rat (Psammomys obesus) and obese rhesus monkeys. The animals with ‘brittle’ pancreas closely simulate the disease evolution from insulin resistance to progressive beta cell failure/frank hyperglycaemia as in human type 2 diabetes, than the animals with sturdy pancreas. Some of these animals with related phenotype of obesity and insulin resistance such as ZFR, ZDF rats and ob/ob, db/db, KK and KK-Ay mice would be greatly helpful in identifying factors involved in obesityinduced diabetes (diabesity). Nevertheless, certain non obese diabetic models are also used in the investigation of type 2 diabetes in
humans that occur in the absence of obesity which allows the dissociation of confounding obesity factors such as leptin deficiency and/or leptin resistance and other associated hypothalamic factors from diabetes genes and factors [e.g., GK (Goto-Kakizaki) rats, Akita mouse].

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Model category</th>
<th>Type II diabetic models</th>
</tr>
</thead>
</table>
| 1      | Spontaneous or genetically derived diabetic animals | *ob/ob* mouse  
*db/db* mouse  
KK mouse  
KK/Ay mouse  
NZO mouse  
NONcNZO10 mouse  
TSOD mouse  
M16 mouse  
Zucker fatty rat  
ZDF rat  
SHR/N-cp rat  
JCR/LA-cp rat  
OLETF rat  
Obese rhesus monkey |
| 2      | Diet/nutrition induced diabetic animals | Sand rat  
C57/BL 6J mouse  
Spiny mouse |
| 3      | Chemically induced diabetic animals | GTG treated obese mice  
Low dose ALX or STZ adult rats, mice. Neonatal STZ rat |
| 4      | Surgical diabetic | VMH lesioned dietary obese diabetic rat  
Partial pancreatectomized animals *e.g.* dog, primate, pig & |
Transgenic or knock out mice involving genes of insulin and insulin receptor and its components of downstream insulin signaling e.g. IRS-1, IRS-2, GLUT-4, PTP-1B and others. PPAR-γ tissue knockout mouse Glucokinase or GLUT 2 gene knockout mice Human islet amyloid polypeptide overexpressed rat (HIP rat)

Spontaneous type 2 diabetic models

Spontaneously diabetic animals of type 2 diabetes may be obtained from the animals with one or several genetic mutations transmitted from generation to generation (e.g., ob/ob, db/db mice) or by selected from non-diabetic outbred animals by repeated breeding over several generation [e.g., (GK) rat, Tsumara Suzuki Obese Diabetes (TSOD) mouse]. These animals generally inherited diabetes either as single or multigene defects. The metabolic peculiarities result from single gene defect (monogenic) which may be due to dominant gene (e.g., Yellow obese or KK/Ay mouse) or recessive gene (diabetic or db/db mouse, Zucker fatty rat) or it can be of polygenic origin [e.g., Kuo Kondo (KK) mouse, New Zealand obese (NZO) mouse].
Type 2 diabetes occurring in majority of human being is a result of interaction between environmental and multiple gene defects though certain subtype of diabetes do also exist with well defined cause \[i.e., \] maturity onset diabetes of youth (MODY) due to defect in glucokinase gene and this single gene defects may cause type 2 diabetes only in few cases. Therefore, polygenic animals represent the human condition more closely when compared to monogenic animals.

**Experimentally-induced diabetes models** (Arulmozhi et al., 2004)

Experimental Type 2 diabetes mellitus can be induced by:

1. Chemical destruction or surgical removal of part of the $\beta$-cell mass
   - a. STZ induced type 2 diabetes
   - b. STZ-Nicotinamide induced type 2 diabetes

2. Lesioning the ventromedial hypothalamus

3. Feeding with high-fat and high-sugar diets

4. Malnutrition *in utero*

5. High doses of counter regulating hormones, particularly glucocorticoids

6. Prolonged cell exposure to hyperinsulinemia

### 2.3 Different Herbs and Their Combinations Used in Treatment of Diabetes:

Various plants and plant derived compounds have been used in the treatment of diabetes to control the blood sugar of the patients. The use of herbs in the management of diabetes mellitus has been prevalent in Indian society from a long time. Several medicinal plants have reported to possess potential hypoglycemic activity in Indian system of medicines. Several reviews have been published on the hypoglycemic medical plants (Ivorra et al., 1989; Bailey CJ, 1989; Rahman and Zaman, 1989; Gori M, 1998; Chitwood M, 1999; Berman BM, 1999; Morelli V, 2000; Shane-McWhorter, 2001; Eisenberg D M, 2003; Srinivasan, 2005; Bnouham et al., 2006;), more particularly use of Indian herbs for hypoglycemic activity (Grover et. al., 2002; Saxena and Vikram, 2004; Chhetri D.R., 2005; Mukherjee PK et al., 2006; Modak M, 2007; Kaushik G et al., 2008). Market survey of herbal antidiabetic prepartain reveled that there are severe preparation available in the Indian market which are claimed reduce blood sugar level but none of them is approved by regulatory authoprity. Diabecon manufactured by ‘Himalaya’ is reported to increase peripheral utilization of glucose, increase hepatic and
muscle glucagon contents, promote B cells repair and regeneration and increase c peptide level. It has antioxidant properties and protects B cells from oxidative stress. It exerts an insulin like action by reducing the glycated haemoglobin levels, normalizing the microalbuminurea and modulating the lipid profile. It minimizes long term diabetic complications. Epinsulin marketed by Swastik formulations, contains epicatechin, a benzopyran, as an active principle. Epicatechin increases the cAMP content of the islet, which is associated with increased insulin release. It plays a role in the conversion of proinsulin to insulin by increasing cathepsin activity. Additionally it has an insulin-mimetic effect on osmotic fragility of human erythrocytes and it inhibits Na/K ATPase activity from patient’s erythrocytes. It corrects the neuropathy, retinopathy and disturbed metabolism of glucose and lipids. It maintains the integrity of all organ systems affected by the disease. It is reported to be a curative for diabetes, Non Insulin Dependent Diabetes Mellitus (NIDDM) and a good adjuvant for Insulin Dependent Diabetes Mellitus (IDDM), in order to reduce the amount of needed insulin. It is advised along with existing oral hypoglycemic drugs and is known to prevent diabetic complication. It has gentle hypoglycemic activity and hence induces no risk of being hypoglycemic. Pancreatic Tonic (ayurvedic herbal supplement): Pancreas Tonic is a botanical mixture of traditional Indian Ayurvedic herbs currently available as a dietary supplement Bitter gourd powder marketed by Garry and Sun, it lowers blood & urine sugar levels. It increases body’s resistance against infections and purifies blood. Bitter gourd has excellent medicinal virtues. It is antidotal, antipyretic tonic, appetizing, stomachic, antibilious and laxative.

The bitter Gourd is also used in native medicines of Asia and Africa. The Bitter gourd is specifically used as a folk medicine for diabetes. It contains compounds like bitter glycosides, saponins, alkaloids, reducing sugars, phenolics, oils, free acids, polypeptides, sterols, 17-amino acids including methionine and a crystalline product named p-insulin. It is reported to have hypoglycemic activity in addition to being antihaemorrhoidal, astringent, stomachic, emmenagogue, hepatic stimulant, anthelmintic and blood purifier. Dia-Care manufactured by Admark Herbals Ltd. is claimed to be effective for both Type 1, Type 2 diabetes within 90 days of treatment and cures within 18 months. Persons taking insulin will eventually be liberated from the dependence on it. The whole treatment completes in 6 phases, each phase being of 90 days. Approx. 5 grams (1 tea spoon) powder is mixed with 1/2 glass of water, stirred properly and kept overnight. Only the water and not the
sediment must be taken in the morning on empty stomach. To the remaining medicine fresh water is added and kept for the whole day and is consumed half an hour before dinner. The taste of the drug is very bitter. It is a pure herbal formula without any side effects.

Diabetes-Daily Care manufactured by Nature’s Health Supply is a Unique, Natural Formula, which effectively and safely Improves Sugar Metabolism. Diabetes Daily Care TM was formulated for type 2 diabetics and contains all natural ingredients listed in Table 3.2 in the proportion optimal for the body’s use.

Gurmar powder manufactured by Garry and Sun is an anti-diabetic drug, which suppresses the intestinal absorption of sacharides, which prevents blood sugar fluctuations. It also correlates the metabolic activities of liver, kidney and muscles. Gurmar stimulates insulin secretion and has blood sugar reducing properties. It blocks sweet taste receptors when applied to tongue in diabetes to remove glycosuria. It deadens taste of sweets and bitter things like quinine (effects lasts for 1 to 2 hours). Besides having these properties, it is a cardiac stimulant and diuretic and corrects metabolic activities of liver, kidney and muscles.

DIABETA, a formulation of Ayurvedic Cure, available in the capsule form is an antidiabetic with combination of proven anti-diabetic fortified with potent immunomodulators, antihyperlipidemics, anti-stress and hepatoprotective of plant origin. The formulation of Diabeta is based on ancient ayurvedic references, further corroborated through modern research and clinical trials. Diabeta acts on different sites in differing ways to effectively control factors and pathways leading to diabetes mellitus. It attacks the various factors, which precipitate the diabetic condition, and corrects the degenerative complications, which result because of diabetes. Diabeta is safe and effective in managing Diabetes Mellitus as a single agent supplement to synthetic anti-diabetic drugs. Diabeta helps overcome resistance to oral hypoglycemic drugs when used as adjuvant to cases of uncontrolled diabetes. Diabeta confers a sense of well-being in patients and promotes symptomatic relief of complaints like weakness giddiness, pain in legs, body ache, polyuria and pruritis.

Syndrex manufactured by Plethico Laboratory contains extracts of germinated fenugreek seed. Fenugreek is used as an ingredient of traditional formulations over 1000 years. We are currently studying the mechanism of this antidiabetic drug using animal model on one hand and cultured islet cells on the other. Thus many different plants have been used individually or in formulations for treatment of diabetes and its complications. One of the major problems with this herbal formulation is that the active ingredients are not well defined. It is important
to know the active component and their molecular interaction, which will help to analyze therapeutic efficacy of the product and also to standardize the product. Efforts are now being made to investigate mechanism of action of some of these plants using model systems.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabecon</td>
<td>Himalaya</td>
<td>Gymnema sylvestre, Pterocarpus marsupium, Glycyrrhiza glabra, Casearia esculenta, Syzygium cumini, Asparagus racemosus, Boerhavia diffusa, Sphaeranthus indicus, Tinospora cordifolia, Swertia chirata, Tribulus terrestris, Phyllanthus amarus, Gmelina arborea, Gossypium herbaceum, Berberis aristata, Aloe vera, Triphala, Commiphora wightii, shilajeet, Momordica charantia, Piper nigrum, Ocimum sanctum, Abutilon indicum, Curcuma longa, Rumex maritimus</td>
</tr>
<tr>
<td>Diasulin</td>
<td></td>
<td>Cassia auriculata, Coccinia indica, Curcuma longa, Emblica officinalis, Gymnema sylvestre, Momordica charantia, Scoparia dulcis, Syzygium cumini, Tinospora cordifolia, Trigonella.</td>
</tr>
<tr>
<td>Pancreatic tonic</td>
<td>Ayurvedic herbal Supplement</td>
<td>Pterocarpus marsupium, Gymnema sylvestre, Momordica charantia, Syzygium cumini, Trigonella foenum graceum, Azadirachta indica, Ficus racemosa, Aegle marmelos, Cinnamomum tamala</td>
</tr>
<tr>
<td>Ayurveda</td>
<td>Chakrapani</td>
<td>Gurmar (Gymnema sylvestre) Karela (Momordica charantia) Pushkarmool (Inula racemosa) Jamun</td>
</tr>
<tr>
<td>alternative herbal formula:</td>
<td>Ayurveda</td>
<td>Gutli (<em>Syzygium cumini</em>) Neem (<em>Azadirachta indica</em>) Methika (<em>Trigonella foenum gracecum</em>) Guduchi (<em>Tinospora cordifolia</em>)</td>
</tr>
<tr>
<td>---------------------------</td>
<td>----------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Bitter gourd</td>
<td>Garry and Sun</td>
<td>Bitter gourd (<em>Momordica charantia</em>)</td>
</tr>
<tr>
<td>Dia-care</td>
<td>Admark Herbals Limited</td>
<td>Sanjeevan Mool; Himej, Jambu beej, Kadu, Namejav, Neem chal.</td>
</tr>
<tr>
<td>Diabetes-Daily Care</td>
<td>Nature’s Health Supply</td>
<td>Alpha Lipoic Acid, Cinnamon 4% Extract, Chromax, Vanadium, Fenugreek 50% extract, <em>Gymnema sylvestre</em> 25% extract Momordica 7% extract, Licorice Root 20% extract</td>
</tr>
<tr>
<td>Gurmar</td>
<td>Garry and Sun</td>
<td>Gurmar (<em>Gymnema sylvestre</em>)</td>
</tr>
<tr>
<td>Epinsulin</td>
<td>Swastik Formulations</td>
<td>vijaysar (<em>Pterocarpus marsupium</em>)</td>
</tr>
<tr>
<td>Diabecure</td>
<td>Nature beaute Santé</td>
<td><em>Juglans regia</em>, <em>Berberis vulgaris</em>, <em>Erythrea centaurium</em>, <em>Millefolium</em>, <em>Taraxacum</em></td>
</tr>
<tr>
<td>Diabeta</td>
<td>Ayurvedic cure Ayurvedic Herbal Health Products</td>
<td><em>Gymnema sylvestre</em>, <em>Vinca rosea</em> (Periwinkle), <em>Curcuma longa</em> (Turmeric), <em>Azadirachta indica</em> (Neem), <em>Pterocarpus marsupium</em> (Kino Tree), <em>Momordica charantia</em> (Bitter Gourd), <em>Syzygium cumini</em> (Black Plum), <em>Acacia arabica</em> (Black Babhul), <em>Tinospora cordifolia</em>, <em>Zingiber officinale</em> (Ginger)</td>
</tr>
<tr>
<td>Syndrex</td>
<td>Plethico Laboretaries</td>
<td>Germinated Fenugreek seed extract</td>
</tr>
</tbody>
</table>
## Table 2.4 Medicinal plants with antidiabetic and related properties

<table>
<thead>
<tr>
<th>Plant Name</th>
<th>Ayurvedic/ common name/ herbal formulation</th>
<th>Antidiabetic and Other Beneficial Effects In Traditional Therapy</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Annona squamosa</em></td>
<td>Sugar apple</td>
<td>Hypoglycemic and antihyperglycemic activities of ethanolic leaf-extract, Increased plasma insulin level</td>
<td>Kaleem et al., 2006; Gupta et al., 2005</td>
</tr>
<tr>
<td><em>Artemisia pallens</em></td>
<td>Davana</td>
<td>Hypoglycemic, increases peripheral glucose utilization or inhibits glucose reabsorption</td>
<td>Subramonium et al., 1996</td>
</tr>
<tr>
<td><em>Areca catechu</em></td>
<td>Supari</td>
<td>Hypoglycemic</td>
<td>Chempakam et al., 1993</td>
</tr>
<tr>
<td><em>Beta vulgaris</em></td>
<td>Chukkander</td>
<td>Increases glucose tolerance in OGTT</td>
<td>Yoshikawa et al., 1996</td>
</tr>
<tr>
<td><em>Boerhavia diffusa</em></td>
<td>Punarnava</td>
<td>Increase in hexokinase activity, decrease in glucose-6- phosphatase and fructose bis-phosphatase activity, increase</td>
<td>Pari et al. 2004; 2004 (a) Satheesh et al., 2004</td>
</tr>
<tr>
<td>Plant Name</td>
<td>Common Name</td>
<td>Activity/Effect</td>
<td>Reference(s)</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>--------------</td>
<td>------------------------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Bombax ceiba</td>
<td>Semul</td>
<td>Hypoglycemic</td>
<td>Saleem et al., 1999</td>
</tr>
<tr>
<td>Butea monosperma</td>
<td>Palasa</td>
<td>Antihyperglycemic</td>
<td>Somani et al., 2006</td>
</tr>
<tr>
<td>Camellia sinensis</td>
<td>Tea</td>
<td>Anti-hyperglycemic activity, antioxidant</td>
<td>Devasagayam et al., 1996;</td>
</tr>
<tr>
<td>Capparis deciduas</td>
<td>Karir or Pinju</td>
<td>Hypoglycemic, antioxidant, hypolipidaemic</td>
<td>Agarwal &amp; Chauhan, 1988</td>
</tr>
<tr>
<td>Caesalpinia</td>
<td>Sagarghota, Fevernut</td>
<td>Hypoglycemic, insulin secretagogue, hypolipidemic</td>
<td>Chakrabarti, et al., 2003,</td>
</tr>
<tr>
<td>Coccinia indica</td>
<td>Bimb or Kanturi</td>
<td>Hypoglycemic</td>
<td>Kamble et al., 1998</td>
</tr>
<tr>
<td>Emblica officinalis</td>
<td>Amla,</td>
<td>Decreases lipid peroxidation, antioxidant, hypoglycemic</td>
<td>Bhattacharya et al., 1999;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Kumar et al., 1999</td>
</tr>
<tr>
<td>Eugenia uniflora</td>
<td>Pitanga</td>
<td>Hypoglycemic, inhibits lipase activity</td>
<td>Arai et al., 1999</td>
</tr>
<tr>
<td>Enicostema littorale</td>
<td>Krimihrita</td>
<td>Increase hexokinase activity, Decrease glucose 6-phosphatase and fructose 1,6 bisphosphatase activity. Dose dependent hypoglycemic activity</td>
<td>Maroo et al., 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vijayvargia et al., 2000</td>
</tr>
<tr>
<td>Species</td>
<td>Common Name</td>
<td>Effect</td>
<td>Reference</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------</td>
<td>---------------------------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td><em>Ficus bengalenesis</em></td>
<td>Bur</td>
<td>Hypoglycemic, antioxidant</td>
<td>Augusti et al., 1994</td>
</tr>
<tr>
<td><em>Gymnema sylvestre</em></td>
<td>Gudmar or Merasingi</td>
<td>Anti-hyperglycemic effect, hypolipidemic</td>
<td>Chattopadhyay, 1999, Preuss et al., 1998</td>
</tr>
<tr>
<td><em>Hemidesmus indicus</em></td>
<td>Anantamul</td>
<td>Anti snake venom activity, anti-inflammatory</td>
<td>Alam &amp; Gomes, 1998</td>
</tr>
<tr>
<td><em>Hibiscus ros-sinesis</em></td>
<td>Gudhal or Jassone</td>
<td>Initiates insulin release from pancreatic beta cells</td>
<td>Sachadeva et al., 1999</td>
</tr>
<tr>
<td><em>Ipomoea batatas</em></td>
<td>Sakkargand</td>
<td>Reduces insulin resistance</td>
<td>Kusano et al., 2000</td>
</tr>
<tr>
<td><em>M.. cymbalaria</em></td>
<td>Kadavanchi</td>
<td>Hypoglycemic, hypolipidemic</td>
<td>Rao et al., 1999</td>
</tr>
<tr>
<td><em>Murraya koenigii</em></td>
<td>Curry patta</td>
<td>Hypoglycemic, increases glycogenesis and decreases gluconeogenesis and glycogenolysis</td>
<td>Khan et al., 1995</td>
</tr>
<tr>
<td><em>Musa sapientum</em></td>
<td>Banana</td>
<td>Antihyperglycemic, antioxidant</td>
<td>Dhanabal et al., 2005</td>
</tr>
<tr>
<td><em>Phaseolus vulgaris</em></td>
<td>Hulga, white kidney, Bean</td>
<td>Hypoglycemic, hypolipidemic, inhibit alpha amylase activity, antioxidant. Altered level of insulin receptor</td>
<td>Tormo et al., 2004, Pari et al., 2004</td>
</tr>
<tr>
<td>Plant Name</td>
<td>Common Name</td>
<td>Activity Description</td>
<td>Reference</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-----------------</td>
<td>--------------------------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Punica granatum</td>
<td>Anar</td>
<td>Antioxidant, anti-hyperglycemic effect</td>
<td>Jafri et al., 2000</td>
</tr>
<tr>
<td>Salacia reticulate</td>
<td>Vairi</td>
<td>Inhibitory activity against sucrase, α-glucosidase inhibitor</td>
<td>Yoshikawa et al., 1989</td>
</tr>
<tr>
<td>Scoparia dulcis</td>
<td>Sweet broom weed</td>
<td>Insulin-secretagogue activity, anti-hyperlipidemic, hypoglycemic, antioxidant</td>
<td>Pari et al., 2005, 2006</td>
</tr>
<tr>
<td>Swertia chirayita</td>
<td>Chirata</td>
<td>Stimulates insulin release from islets</td>
<td>Saxena et al., 1993</td>
</tr>
<tr>
<td>Syzygium Alternifolium</td>
<td>Shahajire</td>
<td>Hypoglycemic and antihyperglycemic</td>
<td>Rao et al., 2001</td>
</tr>
<tr>
<td>Terminalia belerica</td>
<td>Behada,</td>
<td>Antibacterial, hypoglycaemic</td>
<td>Sabu et al., 2002</td>
</tr>
<tr>
<td>Terminalia chebula</td>
<td>Hirda</td>
<td>Antibacterial, hypoglycaemic</td>
<td>Sabu et al., 2002</td>
</tr>
<tr>
<td>Tinospora crispa</td>
<td>Guduchi</td>
<td>Anti-hyperglycemic, stimulates insulin release from islets</td>
<td>Noor et al., 1998</td>
</tr>
<tr>
<td>Vinca rosea</td>
<td>Sadabahar</td>
<td>Anti-hyperglycemic</td>
<td>Chattopadhyay et al., 1991</td>
</tr>
<tr>
<td>Withania somnifera</td>
<td>Ashvagandha</td>
<td>Hypoglycemic, diuretic and hypocholesterolemic</td>
<td>Adallu et al., 2000</td>
</tr>
</tbody>
</table>