1. REVIEW OF LITERATURE

Diabetes mellitus is an endocrine disorder with an alteration in the metabolic pathway of carbohydrates, lipids and proteins, which show a characteristic increase in the blood glucose levels. This is mainly due to the decreased secretion of insulin from the islets of Langerhans in pancreas or due to the resistance of insulin receptors.

A medical condition producing excessive thirst, urination and severe weight loss has interested medical authors for over three millennia. It is not a newly born disease, discovered around 230 B.C. Apollonius of Memphis for the first time he coined the term “diabetes” which in Greek means “to pass through” (dia-through, betes- to go). He first described that it is a disease associated with kidney.

At the same time physicians in India observed that the urine from people with diabetes was attracted by ants and flies. They described this as the first clinical test for diabetes. They named this condition as “Madhumeha” or “honey urine”. They also noticed the patient suffers from thirst and foul breath.

The first complete clinical description of diabetes is given by Aulus Cornelius Celsus (30 BC-50 AD) in his work entitled as De medicina. Aretaeus of Cappadoica (2nd century) who practiced in Greek provided a detailed accurate clinical description, between what we now call diabetes mellitus and diabetes insipidus in his work On the causes and indication of Acute and Chronic Disease.

Aretaeus wrote in his book “Diabetes is a dreadful affliction, not very frequent among men, being a melting down of the flesh and limbs into urine. The patient never stops drinking water and the urine flow is incessant, like the opening of the aqueducts. Life is short, unpleasant and painful, thirst unquenchable, drinking excessive and disproportionate to the large quantity of urine, for yet more urine is passed….. If for a while they abstain from drinking, their mouths become parched and their bodies dry; the viscera seem scorched up, the patients are affected by nausea, restlessness and a burning thirst, and within a short time they expire.”
Galen a Roman physician attributed the development of diabetes to weakness of the kidney and gave it as like Apollonius of Memphis. Later in the 5th century AD two physicians, Sushruta and Charaka from India were the first persons who differentiate the two types of diabetes mellitus between the thin and fat individuals.

During 7th century Li Hsuan from China noted that patients with diabetes were suffered with boils and lung infection. He prescribed them avoidance of sex and wine as treatment for diabetes.

Avicenna or Ibn-Sina (980-1037 AD), from Baghdad prepared a complete description of diabetes. Its clinical features, such as sweet urine and increased appetite, and complications like gangrene of diabetes and sexual dysfunction.

The current origin of diabetes is understood during the year of sixteenth and eighteen century in Europe. In the period of 1494-1541, Paracelsus who is a Swiss physician evaporated the urine of diabetic patient. He thought that the residue consisted of salt.

Thomas willis in Oxford noticed the sweet taste of urine in patients with diabetes and Thomas cawely (1788) suggested the link between the pancreas and diabetes when he observed the people with pancreatic injury. Jhon Rollo added the term “mellitus” to diabetes in order to describe difference between diabetes insipidus. In the nineteenth sand the early period of twentieth century there is a tremendous development in the field of modern science, including biochemistry and experimental pharmacology.

Eugene Chevreul (1815) in Paris proved that the sugar in urine of individuals with diabetes was glucose. Von Fehling developed the quantitative test for glucose in urine. There after it became an accepted diagnostic criterion for diabetes.

William Prout was the first person who describes about the diabetic coma and Wilhelm Petters (1857) demonstrated the presence of acetone in the urine of patients with diabetes. Adolf Kussmaul suggests the acetonemia is one of the causes for diabetic coma. Before the discovery of Insulin, treatment for diabetes is mainly done by maintaining the low diet. Frederick Allen an American diabetologist of the time explained that patients with diabetes
will not utilize the food efficiently. Where the dietary treatment in Type 1 patients are not showing any effect but where as in Type 2 diabetes it is shown a good effect.

**Paul Langerhans** (1869), a German pathologist announces in his doctoral thesis that a small group of cells present in the pancreas. In which one set secretes the normal pancreatic juice, the function of the other was unknown. After several years these cells are named as “Islets of Langerhans”

**Steasbourge, Oscar Minkowski and Joseph von Mering** (1889) reported that dogs whose pancreas was removed developed severe thirst, excessive urination, weight loss. They again tested the urine of the dog and found the presence of sugars.

**Edouard Hrdon** (1893) explained that complete removal of pancreas from the dog shows symptoms of diabetes. He also grafted a small piece of pancreas under the skin of dog then there is no evidence of symptoms of diabetes. Then he concluded that internal secretions of pancreas are mainly responsible for the pathogenesis of diabetes.

Later a number of researchers worked to isolate the active components from pancreas. **Jhon Rennie** and **Thomas Fraser** (1902), from Scotland extracted a substance from the endocrine pancreas, but after injecting the extract the dog died immediately.

Then after **Georg Ludwig Zuelzer** (1904) a German physician extracted the compound from pancreas of a dog. And then injected the extract to a dog, which showed a lowered amount of blood glucose and raised blood pH.

**Frederick Madison Allen and Elliot P Joslin** (1910-1920) were two leading diabetes specialists. Allen (1913) published a book on “Studies concerning Glycosuria and Diabetes” which is significant for the revolution in diabetes therapy that developed from it. After three years he studied a 100 case reports of diabetes patients and published a book on “Total Dietary Regulation in the treatment of Diabetes”. Afterwards he became the director of diabetes research at the Rockefeller Institute.
C.K. Watanabe (1918) discovered that certain compounds of Guanidine show a hypoglycaemic effect. Initially it shows a hyperglycaemia followed by hypoglycaemia. By finding this E. Frankl and his team modified guanidine compound and synthesized a different derivatives of mono and biguanidine. But the biguanidine derivative has shown better hypoglycaemic effect. Whereas the first commercial available guanidine was introduced in the year 1928 and marketed as Synthalin (Decamethyl-diguanide). In 1957, Phenylethyl-biguanidine was discovered in US, it is available for the clinical use from 1959 under the name of Phenformin. Later these drugs were removed from the usage due to its toxicity to liver, kidney and an increased in frequency of lactic acidosis. Another biguanide, Metformin has been used in Europe without significant adverse effects and was approved in US.

On October 31, 1920 Dr. Banting got an idea after reading Moses Barron’s paper where he studied the “Relationship between the Islets of Langerhans to Diabetes with special references to cases of Pancreatic lithiasis” in the issue of Surgery, Gyencology and Obstetrics. In summer 1921, he discovered the pancreatic extracts and named it as “Isletin” later it was changed by Macleod to “Insulin”. Later he presented his work at Physiological Journal Club of Toronto on November 14, 1921.

On May 3, 1922, Macleod presented result of Toronto group’s research to the Association of American Physicians. In the year 1923, Nobel Prize was awarded to the Banting and Macleod. They shared their portions of the prize with Best and Collip, respectively.

Mac cracken j (1997) There after it was purified and it is modified into Protamine-zinc insulin which is a long acting insulin in the year 1930. In 1940 Neutral Protamine Hagedron (NPH) was discovered. In the same year diabetic complications came forward. Lente series of insulin was introduced in the year 1950. Later 1982 R-DNA human insulin is approved for marketing. In 1986 Insulin pen delivery system was introduced.

Ken Ebihara, et al (2001) Lipoatrophic diabetes is a disease which is due to deficiency of leptin, it is due to the mutation of lamina A/C. Leptin act on the central nervous system receptor and other sides to reduce food intake. It has been concluded that treatment with
leptin can improve the insulin resistance and diabetes of a mouse model. It is suggesting that a long term treatment of leptin can useful therapeutically for Lipoatrophic diabetes.

**SD Sokeng, et al (2001)** studied the antihyperglycemic effect of *Bridelia ndellensis* ethanol extract and fractions in streptozotocin-induced diabetic rats. The ethanol extract of *B. ndellensis* had no hypoglycemic effect in Type 1 diabetic rats in fasting and postprandial glucose load conditions and in Type 2 diabetic rats in fasting condition. However, the extract and its ethyl acetate and dichloromethane fractions significantly lowered blood glucose levels in Type 2 diabetic rats when fed simultaneously with glucose. Therefore, the active principles responsible for the antihyperglycaemic effect are concentrated in the ethyl acetate and dichloromethane fractions of the extract.

**M.J.Janbon (2002)** discovered that some of the sulfonylurea agents tested for the treatment of typhoid fever. These drugs are having a side effect which included confusion, cramps, and coma to hypoglycemia. Later researchers worked a lot and found out the mechanism of action of these drugs and they found these are ineffective when they are administered to the pancreatectomized animals. In 1956 Tolbutamide became the first commercially available sulfonylurea compound in US. About 20 different agents of this class have been in use since that time.

In 1997, repaginate, the first member of a new class of oral insulin secretagogues called meglitinides was approved for clinical uses; these agents are used as therapy for postprandial hyperglycaemia. Where Thiazolidinediones were introduced as a second major class of insulin sensitizer. In this Troglitazone is the first drug use in US where it is removed from usage due to hepatic toxicity. Other two agents of this class , Rosiglitazones and Pioglitazones are having a very less side effects and are used world widely.

**James R Gavin, et al (2002)** Investicated that the Classification of diabetes mellitus is an important requirement for epidemiological and clinical research. It is also an important for the clinical management of diabetes and also to identify and differentiate its various forms and stages.

The National Diabetes Data group revised its previous classification which is presented in the year 1979, by the recommendation of WHO expert committee. A new classification of
diabetes was published based on pathogenesis, natural history, response to therapy, and prevention. These were similar in phenotypically but differ in etiologies.

Perheentupa (2002) founded the APS-1 (Auto Immune Polyendocrine Syndrome Type-1) and IPEX (Immune Deregulation, Polyendocrinopathy, Enteropathy, X-Linked) are the monogenic autoimmune syndromes which causes a autoimmune diabetes. IPEX syndrome was mainly observed in neonates. About 20% of patients with APS-1 diabetes as children or young adults.

Gangadevi T, et al (2003) studied antidiabetic activity of ethanol extract of Cassia kleinii leaf in streptozotocin-induced diabetic rats and isolation of an active fraction and toxicity evaluation of the extract. 200mg/kg alcohol extract (200 mg/kg) showed significant Antidiabetic property in streptozotocin diabetic rats as judged from body weight, serum glucose, lipids, cholesterol and urea, and liver glycogen levels. However, the extract did not significantly influence the levels of serum insulin in both diabetic and normoglycemic rats.

Vinay Kumar, et al (2004) studied the Pancreatitis is a group of disorders characterized by inflammation of the pancreas, infection, pancreatectomy, and pancreatic carcinoma. It is also caused by mutation in the cationic trypsinogen (PRSS1) and trypsin inhibitor (SPINK1). The cysts are formed in the pancreas which makes the pancreas silent.

Antonie Maassen J, et al (2004) Mitochondria are the major source of cellular energy. Mitochondria have their own DNA. Mitochondrial DNA encodes several genes in oxidative phosphorylation pathway, ribosomal RNAs and 22 transfer RNAs. Mitochondrial diabetes is associated with the mutation of A3243G on the tRNA (Leu, UUR) gene. The molecular mechanism by which the A3243G mutation affects insulin secretion may involve a decrease of cytosolic ADP/ATP levels leading to a blockage of glucose sensor in the β-cells of langerhans. This causes a defective insulin production from the β-cells, such as in MODY-2.

Adisakwattana, et al (2005) The long term hyperglycemia leads to an progression of micro and macro vascular complications, which may in turn leads to neuropathy, nephropathy, muscular dystrophy, cardiovascular and cerebro vascular diseases.
Jacques young et al. (2005) saided that There are unusual causes that defect in the insulin action and insulin resistance. Mutation of the insulin receptor causes hyperinsulinemia and modest hyperglycemia. Mutation of the lamina A (LMNA) gene causes a polycystic ovary syndrome which now it is called as Type A insulin resistance, Rabson-Mendenhall and Leprechaunism are the two syndromes which are mainly seen in the children. The later has a characteristic facial features and low-set ears, prominent eyes, hirsutism and neonatal growth retardation. This metabolic abnormalities leads to severe insulin resistance.

Hye Sun Park (2005) Impaired generation of ROS can also causes some mutation in the insulin gene but there is no scientific evidence up to now.

SD Sokeng, et al (2005) studied antihyperglycemic effect of Bridelia ndellensis ethanol extract and fractions in streptozotocin-induced diabetic rats. The ethanol extract of B. ndellensis had no hypoglycemic effect in Type 1 diabetic rats in fasting and postprandial glucose load conditions and in Type 2 diabetic rats in fasting condition. However, the extract and its ethyl acetate and dichloromethane fractions significantly lowered blood glucose levels in Type 2 diabetic rats when fed simultaneously with glucose. Therefore, the active principles responsible for the antihyperglycaemic effect are concentrated in the ethyl acetate and dichloromethane fractions of the extract.

Vibha Tandon, et al (2005) studied Hypoglycaemic and antidiabetic effect of aqueous extract of leaves of Annona squamosa (L.) in experimental animal. Extract of leaves at a dose 350 mg/kg reduced the fasting blood glucose (FBG) level slightly by 6.5% within 1 h and the peak blood glucose at 1 h during glucose tolerance test (GTT) was reduced by 15% in normal healthy rats. In STZ diabetic rats also, there was 16.5% decrease in FBG, 24 and 67% reduction in blood glucose at 1 h and 2 h during GTT. After ten days of treatment of a group of STZ diabetic rats with 350 mg/kg of the extract, there was 75.5% fall in FBG level and no sugar in fasting urine was observed.
SB Sridhar, et al (2005) performed a preclinical evaluation of antidiabetic activity of *Eugenia jambolana* seeds. Doses of 500 and 1000mg/kg showed an increase in body weight on 20 day in relation to the 5 day. It was also observed there is an decreased fasting blood glucose levels in glucose tolerance test compare with the 20 day and 5 day. He suggested that the seed extracts are complementary therapy for Type 2 and Type 1 diabetes.

Costa M, et al (2005) explained Disease of exocrine pancreas include cystic fibrosis, congenital anomalies, acute and chronic pancreatitis and neoplasm’s. Cystic fibrosis is a genetic defect of the chromosome 7, the characteristic feature is the formation of cyst and fibrosis in the pancreas. As the chromosome 7 encodes a chloride channel protein called cystic fibrosis transmembrane regulatory (CFTR). The absences of CFTR leads to the thick and viscous secretion associated with destruction of the organs.

Geeta Watal, et al (2006), studied the Hypoglycemic and antihyperglycemic activity of *Aegle marmelos* seed extract in normal and diabetic rats by a 250 mg/kg dose of *Aegle marmelos* was found to be most effective dose and it decreases blood glucose level (BGL) by 35.1% in normal healthy rats after 6 hrs of administration. Treatment of severely diabetic rats for 14 days with a dose of 250 mg/kg reduces the fasting blood glucose by 60.84%.

Paul desire dzeufiet djomeni et al (2006) carried out hypoglycaemic and antidiabetic effect of root extracts of *Ceiba pentandra* in normal and diabetic rats. A sequential doses of *C. pentandra* (40, 75,150 and 300 mg/kg) is orally administered to fasted normal and diabetic groups and blood glucose levels were determined. In both groups, 40 and 75 mg/kg of the extract, significantly reduced blood glucose levels 8 h after administration, which was consistent and time-dependent. *C. pentandra* at the lower dose of 40mg/kg produced blood glucose lowering effect of 40.0% and 48.9%, in normal and diabetic rats respectively when compared with control rats. The higher doses of 150 and 300 mg/kg did not affect significantly the blood glucose levels. But the 14 h fasting blood glucose concentration was lowered by 59.8 % and 42.8% at the doses of 40 and 75 mg/kg and the corresponding urine glucose levels reductions were 95.7% and 63.6%, respectively. Therefore, the results indicated that *C. pentandra* possessed hypoglycaemic effect.
Martha Thomson, et al (2007) studied the Anti-diabetic and hypolipidaemic properties of garlic (*Allium sativum*) in streptozotocin-induced diabetic rats. A dose of 500mg/kg extract of raw garlic is administered daily through intraperitoneally route for seven weeks significantly lowered serum glucose, cholesterol and triglyceride levels. Compared to control diabetic rats, garlic-treated rats had 57% less serum glucose, 40% lower serum cholesterol levels and 35% lower triglyceride. In addition, urinary protein levels in garlic-treated diabetic animals were 50% lower compared to the diabetic control.

Pushparaj PN, et al (2007) studied Anti-diabetic effects of *Cichorium intybus* in streptozotocin-induced diabetic rats. 125mg/kg body weight of CIE exhibited the most potent hypoglycemic effect. Moreover, daily administration of CIE (125 mg/kg) for 14 days to diabetic rats attenuated serum glucose by 20%, triglycerides by 91% and total cholesterol by 16%. However, there was no change in serum insulin levels, which ruled out the possibility that CIE induces insulin secretion from pancreatic cells. In addition, hepatic glucose-6-phosphatase activity (Glc-6-Pase) was markedly reduced by CIE when compared to the control group.

Sangameswaran B and Jayakar B (2007) studied on Anti-diabetic and spermatogenic activity of *Cocculus hirsutus* (L) Diels. The effect was more pronounced in diabetic animals in which administration for 15 days after streptozotocin (STZ) induced diabetes, significantly reduced blood glucose levels. After STZ-induced diabetes, it was observed that both standard drug (glibenclamide) and methanolic extract of *C. hirsutus* were significantly superior to control in reducing blood sugar on long treatment (15 days). The data suggested that *C. hirsutus* could be of benefit in diabetes mellitus in controlling blood sugar.

Geeta Watal, et al (2007) studied Assessment of antidiabetic potential of *Cynodon dactylon* extract in streptozotocin diabetic rats. 250, 500 and 1000 mg/kg bw of aqueous extract of *Cynodon dactylon* were evaluated and the dose of 500 mg/kg was identified as the most effective dose. It lowers blood glucose level around 31% after 4 h of administration in normal rats and fall of 23% in blood glucose level within 1 h during glucose tolerance test (GTT) of mild diabetic rats. This dose has almost similar effect as sthat of standard drug tolbutamide (250 mg/kg bw). Severely diabetic rats were also treated daily with 500 mg/kg bw for 14 days and a significant reduction of 59% was observed in fasting blood glucose level.
Mujeeb Mohd, et al (2009), carried out antidiabetic activity of the aqueous extract of *Annona squamosa* in streptozotocin induced hyperglycemic rats. Dose of 250 mg/kg and 500 mg/kg roots extract of *Annona squamosa* was tested for antidiabetic activity in Streptozotocin (STZ) induced hyperglycaemic rats. The blood glucose levels were measured at 0, 2h, 4h and 6h after the treatment. The extract reduced the blood glucose in STZ induced diabetic rats from 285.52 to 208.81 mg/dl, 6h after oral administration of extract.

Nirmala, et al (2009), studied the Hypoglycemic effect of *Basella rubra* in streptozotocin induced diabetic albino rats 400 mg/100 gm body weight of *Basella rubra* is fed to diabetes induced rats. when tested after ingestion the fasting blood glucose levels were remarkably reduced to normal and liver glycogen content was remarkably increased. In pancreatic sections of diabetic rats fed with B. *rubra*, the islets were normal comparable to diabetic controlled rats.

Parthasarathy, et al (2009) studied the antidiabetic activity of bark and leaf extracts of *Thespesia populena* in streptozotocin induced diabetic rats. Ethanolic extract of the bark and leaf extract at a dose of 400mg/kg were administered orally for a period of 15 days. It reduces blood glucose levels in a dose dependent manner. The extract also having an anti-oxidant activity.

M Salahuddin and SS Jalalpure (2010) examined the Evaluation of antidiabetic activity of *Cassia glauca* Lam. leaf in streptozotocin induced diabetic rats in 500mg/kg aqueous extract of *Cassia glauca* leaves oral administration has no significant effect on blood glucose levels in normoglycemic rats. Whereas aqueous extract showed statistically significant effect by reducing the effect of external glucose load. In chronic model of diabetic, 500mg/kg aqueous extract of *Cassia glauca* leaves and 0.25mg/kg glibenclamide were administered for 21 days. At the end of treatment, there was significant increase in the body weight, liver glycogen, serum insulin level and the HDL cholesterol levels. There was a significant decrease in fasting blood glucose, glycated hemoglobin, total cholesterol and serum triglycerides.
K. S. Dangi and S.N. Mishra (2011) studied the Effect of *Capparis aphylla* stem extract treatment in normal and streptozotocin induced diabetic rats infected with *Candida albicans* was carried out by Administration of conventional (300mg/kg), methanolic extract (300mg/kg), glibenclamide (600μg/kg) reduced total blood glucose level by 28.16%, 64.4%, 45.1% on 8 day respectively, While 75% with active fraction (30mg/kg). The methanolic extract as well as active fraction antimicrobial potential in terms of percent growth inhibition was found to be higher than standard drugs.

Sudipta Das, et al (2011) worked on Preclinical Evaluation of Antihyperglycemic Activity of *Clerodendron infortunatum* Leaf Against Streptozotocin-Induced Diabetic Rats. Hyperglycemic rats treated with MECI intraperitoneally at the doses of 250 and 500 mg/kg body weight daily for 15 days is significant (*P*<0.001) and dose-dependently reduced and normalized blood glucose levels as compared to that of the STZ control group. Serum biochemical parameters were significantly (*P*<0.001) restored towards normal levels in MECI treated rats as compared to the STZ control.