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WHAT DO YOU KNOW ABOUT DIABETES MELLITUS?

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ABSTRACT

Modern human lifestyle is one of the major reasons for greater incidences of diabetes mellitus. Understanding the pathological precautions to be taken and results of diabetes is very important for people with diabetes. Diabetes is not just an increase in glucose in serum but also is major reasons for various other complications like cataract and atherosclerosis during the later years of life. Many plants all over the world have been reported for significant antidiabetic activity. In the present paper a complete consolidated profile is reviewed here.

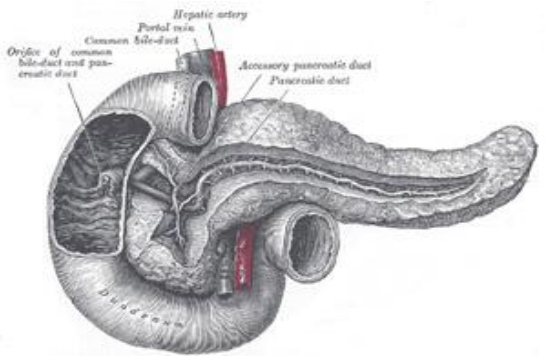
Key words:
Antidiabetic activity, Diabetes mellitus.

INTRODUCTION:

World Health Organization (WHO) definition of diabetes is, "Diabetes is a chronic metabolic disorder of carbohydrate, fat & protein metabolism characterized by high blood sugar levels because the pancreas does not produce enough insulin, or cells do not respond to insulin produced"[4]. Glucose is the main source of fuel for our body. When food is digested it is changed into fats, protein, or carbohydrates. Foods that affect blood sugars are called carbohydrates. Carbohydrates, when digested, change to glucose. Glucose is then transferred to the blood and is used by the cells for energy. In order for glucose to be transferred from blood into the cells, the hormone - insulin - is needed. Insulin is produced by the beta cells in the pancreas (the organ that produces insulin). The clinical diagnosis of diabetes is often indicated by the presence of symptoms such as polyuria, polydipsia, and unexplained weight loss, and is confirmed by measurement of abnormal hyperglycaemia[11]. The World Health Organization (WHO)[11] advises that the range of blood glucose indicative of diabetes mellitus is as follows:

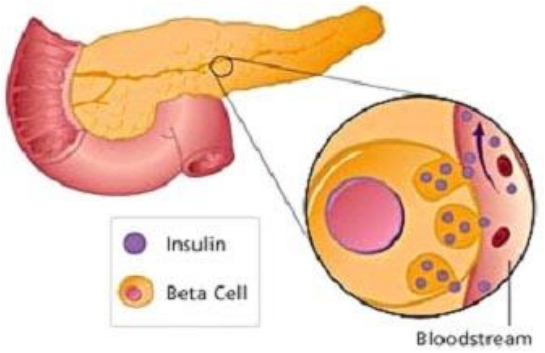
- Fasting venous plasma glucose (FPG) ≥7.0 mmol/l; or
- Venous plasma glucose ≥11.1 mmol/l at two hours after a 75 g oral glucose load (oral glucose tolerance test (OGTT)).

The blood glucose level regulates the secretion of insulin by negative feedback mechanism[3]. Diabetes is classified into two types: type 1 & type 2. Insulin insensitivity is usually evidenced by excess body weight or obesity and exacerbated by overeating and inactivity. It is commonly associated with raised blood pressure, a disturbance of blood lipid levels, and a tendency to thrombosis. This combination is often recognized as the 'metabolic syndrome' and is associated with fatty liver and abdominal adiposity (increased waist circumference). Because of the problems of maintaining good blood glucose control associated with the increasing insulin deficiency, the degree of hyperglycemia occurring in some individuals is sufficient to give rise to a risk of the specific (micro vascular') complications of diabetes. Due to early death caused by cardiovascular disease these are less common than in people with Type 1 diabetes, but include eye damage (sometimes blindness), kidney damage (sometimes requiring dialysis or transplantation), and nerve damage (resulting in amputation, painful symptoms, erectile dysfunction, and other problems).[11]



INSULIN:

Insulin is a poly peptide hormone produced by beta cells. It influences the metabolism of carbohydrates, fats and proteins. It is considered as anabolic hormone, as it promotes the synthesis of glycogen, triglycerides and proteins. Insulin accelerates the transport of glucose from blood into the cell, especially skeletal fiber. The conversion of glucose to glycogen, entry of amino acid into the cell and synthesis of proteins and lipogenesis. Insulin also decreases glycogenolysis & slows gluconeogenesis.



STRUCTURE: Human insulin contains 51 amino acids arranged in two polypeptide chains. Chain A has 21 amino acids& chain B has 30 amino acids. The two chains are held together by two inter chain disulphide bridge connecting A7 to B7 & A20 to B19. There is an intra-chain disulphide link in chain A between amino acid 6 & 11.[1,2]

BIOSYNTESIS: The gene of synthesis of insulin is located at chromosome 11. The synthesis involves two precursors, pre-proinsulin with 108 AA's & mol wt. of 11500 Daltons which directs the nascent polypeptide chain to the rough endoplasmic reticulum (RER). The signal peptide is cleaved as the polypeptide is translocating into the lumen of the RER, forming proinsulin. In the RER the proinsulin folds into the correct conformation and 3 disulfide bonds are formed. Proinsulin is transported to the trans-Golgi network (TGN) where immature granules are formed, with 86 AA's & mol wt. 9000 Daltons. The amino acids are subsequently cleaved to form insulin and C-peptide through the action of cellular endopeptidases known as prohormone convertases (PC1 and PC2), as well as the exoprotease carboxypeptidase E[11]. The endopeptidases cleave at 2 positions, releasing a fragment i.e., the C-peptide, and leaving 2 peptide chains, the B and Achains, linked by 2 disulfide bonds. The cleavage sites are each located after a pair of basic residues (lysine-64 and arginine-65, and arginine-31 and -32), and after cleavage these 2 pairs of basic residues are removed by the carboxypeptidase[12]. Insulin and C-peptide are produced in equal concentrations. C-peptide has no biological activity but it is useful for estimation of the insulin produced. Insulin combines with zinc to form complex in this form it is stored in cytosol of cells & release in response to stimuli by exocytosis.[2,3]

The endogenous production of insulin is regulated in several steps along the synthesis pathway:

- At transcription from the insulin gene
- In mRNA stability
- At the mRNA translation
- In the posttranslational modifications

RELEASE: Beta cells in the islets of Langerhans release insulin in two phases. The first phase release is rapidly triggered in response to increased blood glucose levels. The second phase is a sustained, slow release of newly formed vesicles triggered independently of sugar. In the first phase of release, glucose enters the β-cells through the glucose transporter, GLUT2 and undergoes glycolysis and the respiratory cycle, where multiple, high-energy ATP molecules are produced by oxidation, leading to a rise in the ATP: ADP ratio within the cell. An increased intracellular ATP: ADP ratio closes the ATP-sensitive potassium channel. This prevents potassium ions (K+) from leaving the cell by facilitated diffusion, leading to an increase of potassium ions. As a result, the depolarization of the cell surface membrane. On depolarization, voltage-gated calcium ion (Ca2+) channels open which allows calcium ions to move into the cells by facilitated diffusion. An increased intracellular calcium ion concentration causes the activation of phospholipase C, which cleaves the membrane phospholipid phosphatidyl inositol 4, 5-bisphosphate into inositol 1,4,5-trisphosphate and diacylglycerol. Inositol 1, 4, 5-trisphosphate (IP3) binds to receptor proteins in the plasma membrane of the endoplasmic reticulum (ER). This allows the release of Ca2+ ions from the ER via IP3-gated channels and further raises the intracellular concentration of calcium ions. Significant increase in amounts of calcium ions in the cells causes the release of previously synthesized insulin, which has been stored in secretory vesicles.This is the primary mechanism for release of insulin. Few substances stimulate insulin release, for example amino acids, acetylcholine, sulfonylurea, cholecystokinin and gastrointestinal juices.[3]

The blood content of insulin can be measured in international units, such as μIU/mL or in molar concentration, such as pmol/L. A typical blood level between meals is 8–11 μIU/mL.[2]

DISTRIBUTION & DEGREDATION:

Insulin circulates in the body like a monomer[3]. Under fasting condition, the pancreas secrete about 40μg of insulin/hr into portal vein. Once an insulin molecule is attached to the receptor and elicits its action, it is released back into the extracellular matrix or may be degraded by the cell. The two primary sites for insulin clearance are the liver and the kidney. The liver clears most insulin during first-pass metabolism; the kidney clears most of the insulin in systemic circulation. Degradation normally involves endocytosis of the insulin-receptor complex, followed by the action of insulin-degrading enzyme[2, 3].

MOLECULAR MECHANISM OF INSULIN:

Insulin affects a wide range of physiological processes, although it is best known for its important regulatory role in glucose homeostasis.

The insulin signaling pathway: The diverse effects of insulin are mediated through a multicomponent signaling complex that is strongly conserved across a wide range of species[14]. Binding insulin to its receptor triggers a cascade of signaling events that ultimately leads to modifications in a number of biological processes.

Receptors: Insulin initiates it action by binding to cell surface receptor. Such receptors are present in mammalian cells, including not only the classic target for insulin action. The number of receptors varies from as few as 40 per cell on erythrocytes to 300000 per cell on adipose and hepatocytes[2]. The insulin receptor is a large trans membrane glycoprotein composed of two 35,000 Daltons extracellular α-subunits containing the insulin binding sites and two 95,000daltons membrane-spanning β-subunits with intrinsic tyrosine protein kinase activity. The subunits are linked by disulphide bonds to form a β-α-α-β heterotetramer, both subunits are derived from a single precursor molecule that contain entire sequence of α and β subunit separated by processing site consisting of 4 basic amino acid residues. The insulin like growth factor-1 (IGF-1) receptor is structurally related to the insulin receptor, with more than 80% amino acid sequence homology in the kinase domains[14]. As such, insulin and IGF-1 share common signal transduction mechanisms. There is little homology between the extracellular domains of the insulin and IGF-1 receptors, consistent with the differing ligand preferences of these two receptors.[2.3]

PATHOPHYSIOLOGY:

Diabetes mellitus is a chronic metabolic disorder of carbohydrate, protein and fat metabolism. A defective or deficient insulin secretory response, which translates into impaired carbohydrate use, is characteristic feature if diabetes mellitus resulting in hyperglycemia.[5]

CLASSIFICATION AND INCIDENCE:

Diabetes represents a heterogeneous group of disorders that have hyperglycemia as a common feature. It may occasionally arise secondary from a disease-causing extensive destruction of beta cells. Diabetes is classified as:

1. **Type 1 diabetes mellitus:** It is a form of diabetes mellitus that results from autoimmune destruction of insulin-producing beta cells of the pancreas ant known as insulin dependent diabetes mellitus. The classical symptoms are polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), and weight loss[17]. The etiology is based on:
   - **a.** Genetic susceptibility
   - **b.** Autoimmunity
   - **c.** Environmental factors
2. Type II diabetes mellitus: it is also known as noninsulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes. The two metabolic defects that characterize type II diabetes are:
   - **a.** Deranged beta cell secretion of insulin
   - **b.** Insulin resistance
   - **c.** Obesity

COMPLICATIONS

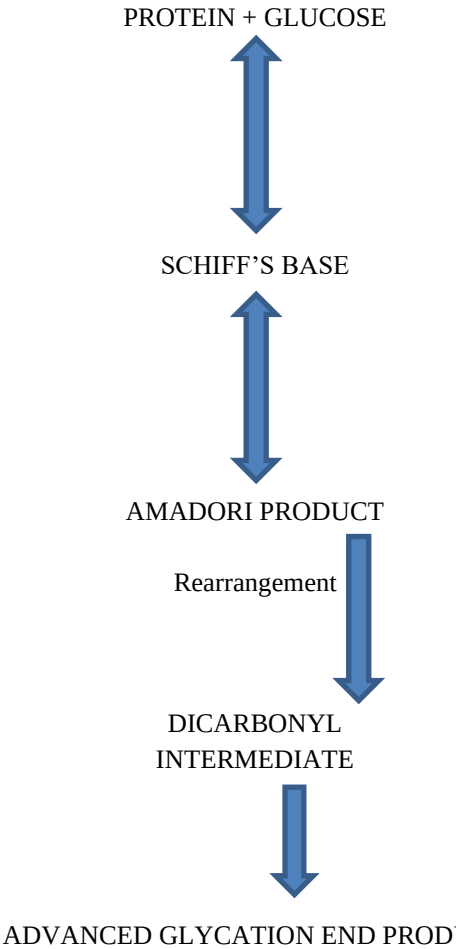
As a consequence of hyperglycemia, every tissue and organ of the body undergoes biochemical and structural alteration which account for major complications of diabetes. These complications are related to the severity of hyperglycemia. Therefor control of blood glucose is associated with minimizing the development of complications. Role of oxidative stress is well defined in many studies.[90]

PATHOGENISIS OF COPLICATIONS: The two metabolic events are responsible for the complications. They are:

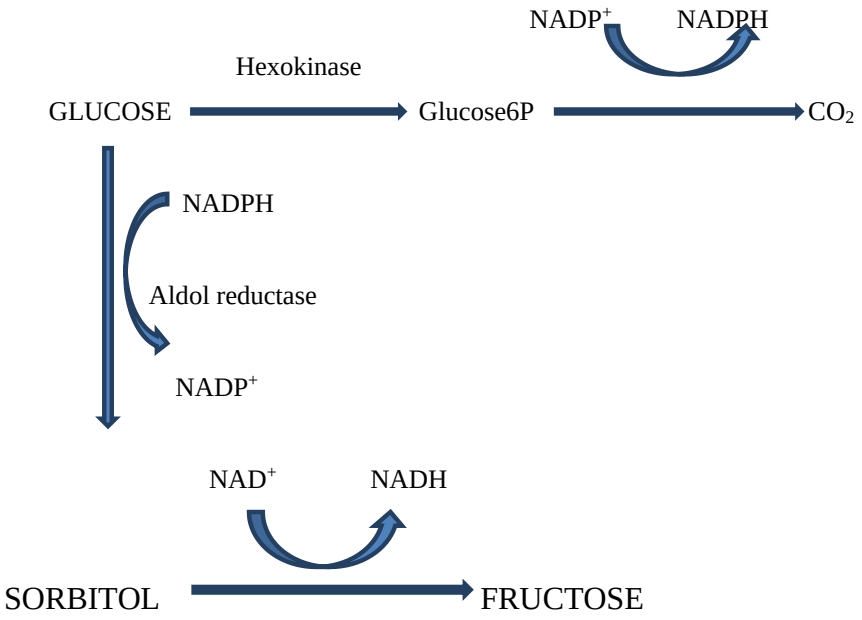
1. **Non-enzymatic glycosylation:** Glycation or non-enzymatic glycosylation is the result of typically covalent bonding of a protein or lipid molecule with a sugar molecule, such as fructose or glucose, without the controlling action of an enzyme. The process of glycations mainly occurs in the bloodstream to a small proportion of the absorbed simple sugars:

glucose, fructose, and galactose. Glycation is the first step in the evolution of these molecules through a complex series of very slow reactions in the body known as Amadori reactions, Schiff base reactions, and Maillard reactions; which led to advanced glycation end products (AGEs). Sustained hyperglycemia leads to glycation of the proteins, preferably at amino group of lysine residue, which adversely affects their function. Reducing sugars, such as glucose, react non-enzymatically with the free amino groups of proteins to initiate advanced glycation, resulting in formation of a diverse group of moieties. This reaction initiates the formation of reversible Schiff bases, which by intermolecular rearrangement are converted into stable, covalently-bonded Amadori products.

When large amounts of Amadori products are accumulated, they undergo further rearrangement and cross-linkage to form a heterogeneous group of protein-bound moieties called 'advanced glycated end products (AGEs). Rates of these reactions are quite slow and only the proteins with long half-lives and containing lysine residues, such as collagen under high sugar concentrations undergo this glycation. AGEs play an important role in the structural and functional alterations of proteins, which occur during aging and diabetes. Glycation is an unavoidable process of metabolism in physiological states. In hyperglycemic conditions, rate of glycation is increased, renal clearance of AGEs is decreased and/or the expression of AGEs receptors is increased, leading to the AGE-mediated cell activation and amyloidosis[23]. In the pathogenesis of diabetes-related AGE formation, hyperglycemia results in higher cellular glucose levels in those cells unable to reduce glucose intake (e.g., endothelial cells). This results in increased levels of nicotinamide adenine dinucleotide (NADH) and FADH, increasing the proton gradient beyond a particular threshold at which the complex III prevents further increase by stopping the electron transport chain[24]. This results in mitochondrial production of reactive oxygen species, activating PARP1 by damaging DNA. PARP1, in turn, induces ADP-ribosylation of GAPDH, a protein involved in glucose metabolism, leading to its inactivation and an accumulation of metabolites earlier in the metabolism pathway. These metabolites activate multiple pathogenic mechanisms, one of which includes increased production of AGEs[25].



2. **Polyol pathway:** It is also called the sorbitol-aldose reductase pathway; the polyol pathway appears to be implicated in diabetic complications, especially in microvascular damage to the retina, kidney and nerves. Most cells require the action of insulin for glucose to gain entry into the cell, the cells of the retina, kidney, and nervous tissues are insulin-independent, and so glucose moves freely across the cell membrane, regardless of the action of insulin. The cells utilize glucose for energy as normal, and extra glucose not used for energy will enter the polyol pathway. When blood glucose is normal (about 100 mg/dl or 5.5 mmol/l), this interchange causes no problems, as aldose reductase has a low affinity for glucose at normal concentrations. In a hyperglycemic state, the affinity of aldose reductase for glucose rises, causing much sorbitol to accumulate, and using much more NADPH, leaving less NADPH for other processes of cellular metabolism. This reaction oxidizes NADPH to $NADP^+$. Sorbitol dehydrogenase can then oxidize sorbitol to fructose, which produces NADH from NAD^+. The amount of sorbitol that accumulates, however, may not be sufficient to cause osmotic influx of water. The NADPH acts to promote nitric oxide and glutathione production, and its deficiency will cause glutathione deficiency as well. A glutathione deficiency, congenital or acquired, can lead to hemolysis caused by oxidative stress. Nitric oxide is one of the important vasodilators in blood vessels. Therefore, NADPH prevents reactive oxygen species from accumulating and damaging cells[25]. Excessive activation of the polyol pathway increases intracellular and extracellular sorbitol concentrations, increased concentrations of reactive oxygen species, and decreased concentrations of nitric oxide and glutathione. Each of these imbalances can damage cells.[8,9]



Diabetes mellitus may develop complications which are broadly classified into two major groups

1. **Acute metabolic complications:** Diabetic ketoacidosis, hyper-osmolar non ketotic coma and hypoglycemia are acute complications associated with diabetes.
    - **Diabetic ketoacidosis:** It happens predominantly in those with type 1 diabetes, but it can occur in those with type 2 diabetes under certain circumstances. DKA results from a shortage of insulin in response to the body switches to burning fatty acids and producing acidic ketone bodies that cause most of the symptoms and complications. Diabetic ketoacidosis arises because of a lack of insulin in the body. The lack of insulin and corresponding elevation of glucagon leads to increased release of glucose by the liver from glycogen and through gluconeogenesis. High glucose levels spill in urine, take water and solutes (such as sodium and potassium) along with it in a process known as osmotic diuresis. This leads to polyuria, dehydration, and polydipsia. The absence of insulin also leads to the release of free fatty acids from adipose tissues which are converted, again in the liver,

into ketone bodies (acetoacetate and β-hydroxybutyrate). The ketone bodies, however, have a low pKa and therefore turn the blood acidic (metabolic acidosis). If the urinary excretion of ketone bodies is prevented due to dehydration leads to systemic metabolic ketoacidosis.[8]

- **Hypoglycemia:** Hypoglycemia, or abnormally low blood glucose, is an acute complication of several diabetes treatments. Hypoglycemia is harmful as it produces permanent brain damage, may result in worsening diabetic control & rebound hyperglycemia so called SOMOGG's effect.[9]
- **Hyper-osmolar nonketotic coma:** it is cause by severe dehydration resulting from sustained hyperglycemic diuresis. The loss of glucose in urine is so intense that the patient is unable to drink sufficient water to maintain urinary loss of fluids. The usual features of ketoacidosis are absent but prominent central nervous signs are present. Blood sugar level is extremely high and plasma osmolality is also high. The increasing hemoconcentration and volume depletion may result in:
  - Disordered mental functioning.
  - Neurologic signs including focal signs such as sensory or motor impairments or focal seizures or motor abnormalities, including flaccidity, depressed reflexes, tremors or fasciculation's.
  - Hyper viscosity and increased risk of thrombosis
  - Ultimately, if untreated, will lead to death

2. **Late complications:** Chronic elevation of blood glucose level leads to damage of blood vessels (angiopathy). The endothelial cells lining the blood vessels take in more glucose than normal, since they do not depend on insulin. They then form more surface glycoproteins than normal and cause the basement membrane to grow thicker and weaker. In diabetes, the resulting problems are grouped under "microvascular disease" and "macro vascular disease". The examples of late complication are:
   - **Atherosclerosis:** Diabetes accelerates the development of atherosclerosis, so that consequent atherosclerotic lesions appear earlier in diabetic patents than normal individuals. These are more often associated with plaques, ulceration, calcification and thrombosis. The cause for this accelerated atherosclerotic process is not clearly known but contributory factors are hyperlipidemia, reduced HDL level, no enzymatic glycosylation, increased platelet adhesiveness, obesity and hypertension.

NO serves to relax the smooth muscles in the walls of the vessels and prevent cells from sticking to the walls. A disruption of this mechanism is thought to be at the heart of the increased formation of plaques in diabetes. High blood sugar, elevated fatty acids and triglycerides lead to stickier walls, encouraging the attachment of cells that produce local tissue reaction. The local tissue reaction traps floating particles and different blood cells, hardening the vessel walls. Insulin stimulates the production of NO by the cells lining the blood vessels. In type II diabetes the actions of insulin and stimulatory effect is lost, resulting in increased tendencies towards plaque formation.

In the presence of raised blood sugar and resistance to insulin, the lining cells of the blood vessels not only reduce production of NO, but they also increase the production of substances that constrict the blood vessel encouraging plaque formation. The smooth muscles of the blood vessels are also hyperactive in diabetes.

Platelets and clotting factors are also affected by the high blood sugar, fatty acids and free radicals in diabetes. The blood cells are much stickier and the factors that inhibit clots do not work well under the peculiar circumstances of diabetes.

- **Microangiopathy:** It is characterized by basement membrane thickening of small blood vessels and capillaries of different organs and tissue such as skin, muscle, eye and kidney. The pathogenesis is due to recurrent hyperglycemia that causes increased glycosylation of hemoglobin and other proteins.
- **Diabetic nephropathy:** renal involvement is a common complication and a leading cause for death in diabetes. The earliest detectable change in the course of diabetic nephropathy is a thickening in the glomerulus. At this stage, the kidney may leak more serum albumin (plasma protein) than normal in the urine (albuminuria) and this can be detected by sensitive medical tests for albumin. This stage is called "micro albuminuria". As diabetic nephropathy progresses, increasing numbers of glomeruli are destroyed by progressive nodular glomerulosclerosis.
- **Diabetic retinopathy:** Diabetic retinopathy is the result of microvascular retinal changes. Hyperglycemia-induced intramural pericyte death and thickening of the basement membrane lead to

incompetence of the vascular walls. These damages change the formation of the blood-retinal barrier and also make the retinal blood vessels become more permeable[26]. The pericyte death is caused when "hyperglycemia persistently activates protein kinase C-δ (PKC-δ, encoded by Prkcd) and p38 mitogen-activated protein kinase (MAPK) to increase the expression of a previously unknown target of PKC-δ signaling, Src homology-2 domain–containing phosphatase-1 (SHP-1), a protein tyrosine phosphatase. This signaling cascade leads to PDGF receptor- dephosphorylation and a reduction in downstream signaling from this receptor, resulting in pericyte apoptosis[27]. Small blood vessels such as those in the eye are especially vulnerable to poor blood sugar (blood glucose) control. An over accumulation of glucose and/or fructose damages the tiny blood vessels in the retina. During the initial stage, called non proliferative diabetic retinopathy (NPDR), most people do not notice any change in their vision. Early changes that are reversible and do not threaten central vision are sometimes termed simplex retinopathy or background retinopathy[28].

- **Proliferative diabetic retinopathy:** As the disease progresses, severe nonproliferative diabetic retinopathy enters an advanced, or proliferative (PDR), stage when blood vessels proliferate. The lack of oxygen in the retina causes fragile, new blood vessels to grow along the retina and in the clear, gel-like vitreous humour that fills the inside of the eye. Without treatment, these new blood vessels can bleed, cloud vision, and destroy the retina. Fibro vascular proliferation can also cause fractional retinal detachment. The new blood vessels can also grow into the angle of the anterior chamber of the eye and cause neovascular glaucoma.

HYPOGLYCEMIC AGENTS:

Insulin therapy: human insulin, bovine insulin and procaine insulin

Oral hypoglycemic's

1. Sulfonylureas:
   a. 1st generation: Chlorpropamide, Tolbutamide, Tolazamide
   b. 2nd generation: Glipizide, Gliclazide, Glibenclamide
2. Biguanides: Metformin, Phenformin.
3. Meglitinide: Repaglinede, Nateglinide.
4. Thiazolidinedione: Rosiglitazone, Pioglitazone, Troglitazone.
5. Alpha glucosidase inhibitor: Acarbose.

Table I: Plants With Antidiabetic Activity

S. No.	Plant name	Part	Family	Model	Extract	Animal species	Dose	'p' value	Mechanism of action	Reference
1	Calligonium comosum	Whole plant	Pollygonaceae	Alloxan induced	Aqueous extract	Albino rats	200mg/kg	-	Release insulin & glucose utilization	T. S Khdiej et, al[29]. (1990)
2	Azadirachta indica	leaf		Alloxan induced	Aqueous extract	Albino rats	200-300mg/kg	<0.05	-	T.S Kholije[30] (1990)
3	Eryngium creticum	Areal parts	Umbelliferae	STZ induced	Aqueous decoction	Fisher rats		<0.05		J. Maaji et. Al[31]. (1991)
4	Catharanthus roseus	fresh leaves	Apocyanaceae	Alloxon induced	Fresh juice	Albino rats				Srinivas N et al[32]. (2003)
5	Cissus sicyodes	Leaves	Vitaceae	Alloxan induced	Alcoholic extract	Albino rats	100 – 200mg/kg			Glauce SB Viana et al[33]. (2004)
6	Chemalia sinensis	Leaves	Theaceae	STZ induced	Aqueous extract	Albino mice	30, 150, 300mg/kg			Hiroshi Tsuneki et al[34]. (2004)
7	Allium sativum	Bulbs	Liliaceae	STZ induced	Ethanolic extract	Wistar rats	0.1. 0.25, 0.5g/kg	<0.05		A. Eidi et al[35].(2005)
8	Acacia catechu	Hard wood	Leguminosae	Alloxan induced	Ethyl acetate extract	Albino rats	500mg/kg	<0.05		D. Ray et al[36]. (2006)
9	Cocculus hirsutus	leaves	Menispermaceae	Alloxan induced	Aqueous extract	Swiss mice	250, 300mg/kg	<0.01		S. Bodhankar et al[37]. (2006)
10	Terminalia chebulia	seeds	Combeteraceae	STZ induced	Methanolic extract	Sprague Dawley	100mg/kg	<0.05		N. K. Rao et al[38]. (2006)
11	Pongamia pinnata	Flowers	Fabaceae	Alloxan induced	Aqueous extract		300mg/kg	<0.05		R. Punitha et al[39]. (2006)
12	Momordica dioica	Fruit	Cucurbitaceae	Alloxan induced	Ethyl acetae,	Wistar rats	200mg/kg	<0.05		M Ramesh et al[40] (2006)

					alcoholic extract					
13	Copttis chinesis	Inflorescence	Rananculaceae	Alloxan induced	powder	Wistar rats	0.25-0.5mg/kg	<0.05		L. Yuan et al[41]. (2006)
14	Momordica charanta	Fruit	cucurbitaceae	Alloxan induced		Wister rats	150 & 300mg/kg	<0.05		N.Fernandes et al[42]. (2007)
15	Diospyros peregrina	Fruits	Ebenaceae	Alloxan induced		Wistar rats	150-300mg/kg			S.Deewanjee et al[43]. (2007)
16	Curcuma longa	Rhizome	Zingiberaceae	STZ, nicotinamide		Wistar rats	80mg/kg	<0.05		L. Pari et al[44] (2007)
17	Cantratherum antihelmenthicum	Seeds	Asteraceae		Aqueous extract	Albino rats		<0.05		Naidu et al[45] (2007)
18	Berberis aristata	Roots	Berberidaceae	Alloxan induced		Wistar rats		<0.05		B. C. Semwal et al[46]. (2008)
19	Swietenia macrophylla	Seeds	Meliaceae	STZ & nicotinamide	Methanolic extract	Wistar rats	300mg/kg	<0.01		A. Maiti et al[47]. (2008)
20	Vernonia antihelmenthicu	Seeds	Asteraceae	Alloxan induced	Metanolic extract	Albino rats	500, 1000mg/kg	<0.01		A. Karthikian et al[48]. (2008)
21	Ichinocarpus fruitences	Roots	Apocynaceae	STZ induced	Aqueous extract	Wistar rats	250, 500mg/kg	<0.05		R. Barik et al[49]. (2008)
22	Michelia champaca	Flower buds	magnoliaceae	Alloxan induced	Ethanol, aqueous extract	Albino rats	200, 400mg/kg	<0.05		E. Jaraid et al[50] (2008)
23	Morus alba	Leaf	Moraceae	STZ induced	Ethanolic extract	Wistar rats	400, 600mg/kg	0.05		P. R Nail et al[51]. (2008)

24	Partthenium hystophorus	Flower	Compositae	Alloxan induced	Aqueous extract	Wistar rats	100mg/kg	<0.01		S. V. Patel et al[52] (2008)
25	Salvadora oleoides	Stem & leaves	Salvandoriaceae	Alloxan induced	Ethanol extract	Albino rats		<0.01		J. P .Yama et al[53] (2008)
26	Angelica gigas		Apiaceae	STZ induced	Ethanol extract	mice	30mg/kg			S. B Han et al[54]. (2008)
27	Ecklonia stolonifera	Algal leaf			Aqueous extract	KK A4 rats		<0.05	Inhibit alpha glucosidase	K. Iwai et al[55] (2008)
28	Tridax procumbens	Whole plant	Asteraceae	Alloxan induced	Alcoholic extract	Wistar rats	200 – 250mg/kg	<0.05		Hemant Pareek et al[56]. (2009)
29	Hemidesmus indicus	Roots	Apocynaceae	STZ induced		Albino rats		<0.05		K. Kannabiran et al[57]. (2009)
30	Cassia glacula	Leaf	Cassalpiniaceae	STZ induced	pet.Ether, chloroform	Wistar rats	100mg/kg	<0.01		M. Farawan et al[58]. (2009)
31	Cirsium japonicum	Areal parts	Asteraceae	STZ induced	Ethanol extract	Sprague dawely		<0.01		Z. Liao et al[59] (2009)
32	Carni fructus		Corniaceae			Db/db mice		<0.01		V. C Kim et al[60] (2009)
33	Morus alba	leaves	Moraceae	STZ induced	ethanolic extract	Sprague-Dawley rats	0.25, 0.5 and 1.0 g/kg/day	<0.05	stimulation of insulin release & glucosidase inhibitory activity	P. Pannangpetch[61] (2009)
34	Flacourtia jangomas	Leaves & stem	Flacourtiaceae	STZ induced	Methanol extract	Wistar rats	400mg/kg	<0.01		K. A Singh et al[62] (2010)

35	Nelumbo nucifera	seeds	Nelumbonaceae	STZ induced	Seeds ash	Wistar rats	200mg/kg	<0.05	insulin secretary/ mimetic activity	S. S. Pillai[63] (2010)
36	Cassia occidentalis	Whole plant	Caesalpiniaceae	Alloxan induced	Pet. Ether, chloroform. Aq	Wistar rats	200mg/kg	<0.05		L. Verma et al[64] (2010)
37	Barleria prionitis	Leaf & roots	Acanthaceae	Alloxan induced	Pet. Ether, alcohol.	Albino rats	200mg/kg	<0.05		D. Reema et al[65]. (2010)
38	Cassia grandis	Stem	leguminosae	Alloxan induced	Aqueous & ethanol	Albino rats	150mg/kg	<0.05		S. R Lodha et al[66] (2010)
39	Crateva nurvala	Bark	Capparidaceae	Alloxan induced	Pet. Ethre chloroform	Wistar rats		<0.05		B. M Patil et al[67] (2010)
40	Stevia rebaudiana	Leaves	Asteraceae	Alloxan induced	Aqueous extract	Wistar rats				B. K Roy et al[68]. (2010)
41	Abutilon indicum	Leaves, twigs, roots	Malvaceae	STZ induced		Wistar rats	0.25. 0.5g/kg	<0.05	PPAR gama activation	JJ Black et al[69] (2010)
42	Byrsonima crarsifolia	Fruit & seed	Malpigliaceae	STZ induced	Methanol, hexane	Wistar rats		<0.05		Gomez et al[70]. (2010)
43	Chaenomeles senensis	Fruit	Rosaceae	STZ induced	Methyl alcohol	Wistar rats		<0.05	Inhibition of alpha glucosidase	S. V Seo et al[71] (2010)
44	Clerodendron infortunaton	Leaf	Verbenaceae	STZ induced	Methanol extract	Wistar rats	200, 500mg/kg	<0.01		S Das et al[72]. (2010)
45	Calitropis gigantia	Whole plant	Aselepidaceae	Alloxan induced		Wistar rats			Alpha amylase inhibitor	N. K Caudhery al[73]. (2011)

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