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Diabetes Mellitus: A Brief Review

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ABSTRACT:

"Diabetes mellitus" is a "disorder of carbohydrate metabolism" which is characterized by high blood glucose levels in the blood. It is caused either by impaired insulin secretion or loss of insulin activity due to the presence of insulin resistance and relative insulin deficiency at the target cells. "Type 1 diabetes mellitus (T1DM)" which makes up only 5 % of the cases is an auto immune disorder. In "type 2 diabetes mellitus (T2DM)" which accounts for more than 95 % of the cases, either the pancreas does not produce enough insulin or the insulin produced is not able to perform its function at the target site due to the presence of insulin resistance. As estimated by "International Diabetes Federation (IDF)" in 2015, the global burden of "diabetes aged between 20 to 79 years was about 415 million" and it was projected to rise to "642 million by 2040". Present therapy for T2DM relies mainly on several approaches intended to reduce the hyperglycemia itself such as "Sulphonylureas, Metformin, α-glucosidase inhibitors", and many more. However, these therapies have limited efficacy, limited tolerability and have significant mechanism-based side effects.

Due to this reason, many traditional plant treatments are widely practiced throughout the world for the treatment of diabetes. These natural products are safe because they are more harmonious with biological systems and have less side effects compared to synthetic drugs. I n the present review we discussed about diabetes and their clinical management.

Key Words: Diabetes, Side effect, Insulin, Traditional medicine

INTRODUCTION:

Diabetes is a condition of glucose metabolism that is brought on by flaws in insulin secretion, action, or both. As a result, different organs such as the heart, kidneys, nerves, eyes, and blood vessels are damaged. It manifests itself through symptoms like thirst, polyuria, blurred eyesight, and weight loss. If untreated, it can potentially result in the development of ketoacidosis or a non-ketotic hyperosmolar condition, which can cause stupor, coma, and death.

The word diabetes is a Greek term which was used for the first time by Apollonius of Memphis around 230 BC which means("Dia") "through" and ("bêtes") means pass, referring to the cycle of heavy thirst and frequent urination (Papaspyros, 1964). Later on, a Latin word "Mellitus" was added as it made the urine sweet. The earliest Egyptian manuscript known as EbersPapyrusdating back to 1500 BC which was excavated in the year 1862 AD from an

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ancient grave in Thebes, Egypt described amedicalcondition of "too great emptying of the urine" referring to diabetes mellitus. In the fifth century AD, the difference between the two types of diabetes was observed by two Indian physicians, Sushruta and Charaka noted that those who were thin had diabetes at younger ages as opposed to those who were heavier, who had a later onset and survived longer after diagnosis. In his enormous eight-volume work DeMedicina, written between 30 and 50 BC, Aulus Cornelius provided the first comprehensive description of diabetes. Avicenna, also known as "Ibn-Sina (980–1037 AD)", was the court physician to the "Caliphs of Baghdad". He compiled the exhaustive "medical text Canon Avicennae", which included a detailed description of diabetes along with its clinical characteristics and complications (Medvei 1993).

CLASSIFICATION OF DIABETES MELLITUS:

According to American Diabetes Association (ADA) in2017, diabetes mellitusis classified into the following categories as mentioned below:

"1. Type 1 diabetesmellitus (T1DM)- It is an auto immune disorder which is an outcome of beta celldestruction by body's own immune system leading to absolute insulin deficiency.

2. Type 2 diabetes mellitus (T2DM)- It is characterized by the presence of insulin resistance progressively leading to beta cell failure.

3. Gestational diabetes mellitus (GDM)- It is a condition of hyperglycemia which occurs during the second or thirdtrimester of pregnancy which is not clearly overt diabetes

4. Other specific types of diabetes such as Maturity Onset of Diabetes of the Young (MODY), Latent Autoimmune Diabetes in Adults (LADA) and Double Diabetes (DD)".

(Standards of Medical Care in Diabetes, 2017).

Type 1 diabetes Mellitus (T1DM)

Juvenile-onset diabetes, which makes up between 5 and 10 percent of all cases of diabetes, is another name for it. The beta cells are killed by cellular-mediated immunity in this auto immunological illness. One or more autoimmune indicators, such as autoantibodies against islet cells, autoantibodies against glutamic acid decarboxylase65 (GAD), and autoantibodies against insulin, are present in the blood of people with type 1 diabetic mellitus (T1DM). Ketoacidosis, which first appears in infants and teenagers, is the disease's initial symptom. High blood glucose levels lead to frequent urination causing dehydration and also leads to weight loss. It also damages various organs of the body such as nerves, blood vessels, heart, kidneys, hardening of arteries leading to heart attacks and strokes. In adults' patients of T1DM, a partial survival of beta cells may occur which may prevent ketoacidosis for some years. After many years, the beta cells secrete little or no insulin as manifested by low plasma C peptide levels, hence, these patients depend on insulin for survival and are at risk for the development of ketoacidosis. These patients arealso prone to various other autoimmune

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disorderssuch as Hashimoto thyroiditis,Gravesdisease, Addison disease, celiacdisease, vitiligo, autoimmune hepatitis,myasthenia gravis, and pernicious anemia (Standards of Medical Care in Diabetes-2017).

Type 2 Diabetes (T2DM)

"It is also known as non-insulindependent diabetes mellitus (NIDDM) or adult-onset diabetes which accounts for approximately 90-95% of all diabetic population. It is a disorder of carbohydrate metabolism which is a combination of relative insulin deficiency and presence of peripheral insulin resistance eventually which leads to beta cell failure (Cantley et. al. 2015). It further causes reduced glucose transport in the liver and peripheral tissues. Due to decline in insulin production, breakdown of fat takes place which leads to dyslipidemia. Alpha cells are also found to be impaired in T2DM leading to increase in glucagon and hepatic glucoselevels in post prandial state, possibly due to low serum insulin levels and prevailing insulin resistance" (Burcelin et. al., 2008).

DOUBLE DIABETES (DD):

This term was first introduced by Libman and Beckerin 1991 during a study which reported that patients of T1DM who had a family history of T2DM were at risk to become overweight and rarely achieve optimal glycemic control (Libman et. al., 2003).This is a condition which is characterized by hallmarks of both T1DM and T2DM. Such a patient of T1DM having auto antibodies against its pancreatic beta cells develops insulin resistance (Pozzilli et. al., 2011).Latent Autoimmune Diabetes in Adulthood(LADA) occurs in adults usually above the age of 35 years diagnosed by the presence of autoantibody and insulin independence followinga diagnosis of hyperglycemia for a period of at least sixmonths (Palmer et. al. 2003).

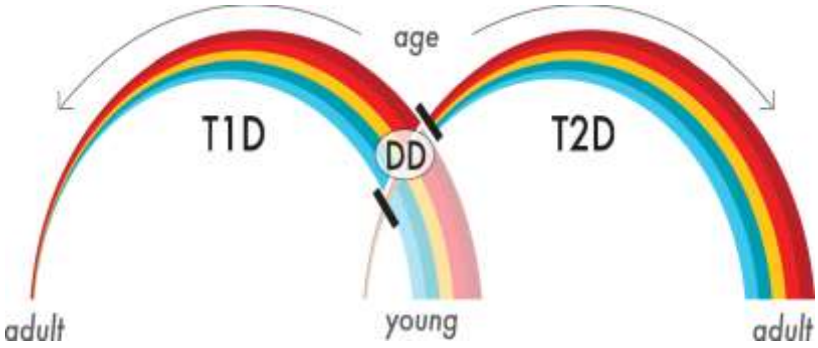

Fig. 1: Showing the occurrence of Double Diabetes (Pozzilli et. al., 2007)

Diagnostic criteria for Diabetes

The diagnosis of diabetes is done by measuring the plasma glucose levels either in overnight fasting plasma glucose (FPG) or the 2 hour plasma glucose (2h PG)after a 75 gram oralglucose tolerance test (OGTT) or the A1C levels.

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According to guidelines issued by ADA in 2017, If the FPG ≥ 126 mg/dl or a 2 hour PG ≥200 mg/dlafter an OGTT or an HbA1c value ≥6.5% or a random blood glucose levels are ≥ 200 mg/dl in subjects with classical symptoms of hyperglycemia then that subject is said to be having diabetes. In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing(Standards of Medical Care in Diabetes, 2017).

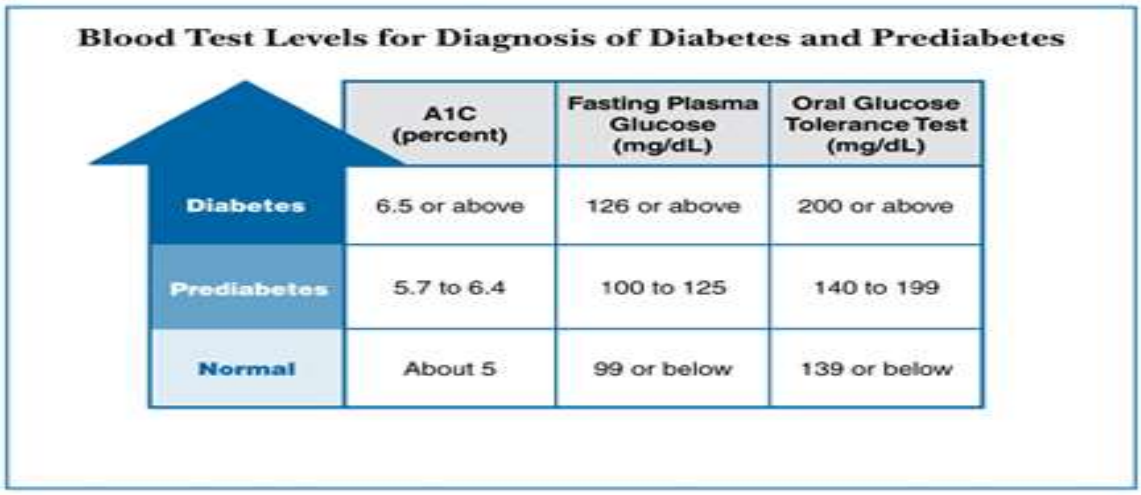

Fig.2: Showing the diagnostic criteria of Diabetes Mellitus(American Diabetes Association, 2012).

Complications of diabetes mellitus

Diabetes gives rise to various complications which under acute condition may cause mortality due to diabetic ketoacidosis resulting from hyperglycemia and coma due to hypoglycemia. These complicationsare wide ranging and are grouped under two broad categories namely micro-vascular and macro-vascular complications.

Micro-vascular complications are associated with the damage to the small blood vessels which include retinopathy, neuropathy and nephropathy whereas macro-vascular complications deals with damage to the arteries which include increased cardiovascular diseaseresulting in myocardial infarction and strokes.

Role of Insulin in diabetes mellitus

Insulin is an anabolic hormone which acts on various organs including the liver, skeletal muscle and adipose tissue (Bogan, 2012). It regulates various metabolic functions including glycogen synthesis, glycogenolysis, gluconeogenesis, and lipogenesis, which is strictly controlled through intracellular signaling mechanisms of downstream of the insulin receptor tyrosine kinase. Additionally, it causes the uptake of circulating glucose, lipids, amino acids and various other metabolites into the target tissues and maintains a healthy glycemic and lipid profile. In healthy individuals, skeletal muscle is the primary site of insulin stimulated glucose disposal compared to adipose tissues (Satoh, 2014).

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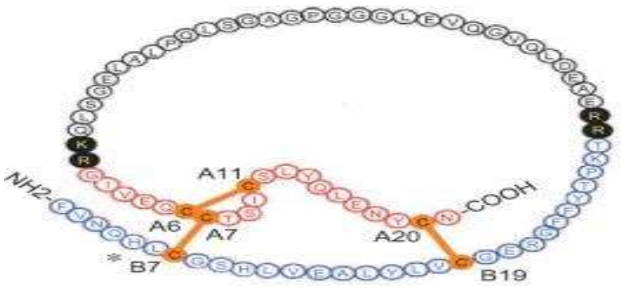

Fig 3: Showing the structure of Insulin (Weiss, 2009).

Role of Glucose transporters in diabetes mellitus

Glucose is an important metabolic substrate which is utilized by mammalian cells for the biosynthesis of glycogen, fat, glycolipids, nucleic acids and various glycoproteins. Some tissues like brain and skeletal muscles require glucose as an energy source in the form of ATP which is generated through the glycolysis and TCA cycle and reducing power in the form of NADPH though the pentose phosphate shunt pathway. In the first step the blood glucose is transported across the plasma membrane by a family of structurally related carrier proteins known as Glucose Transporters. Fourteen members of glucose transporter proteins have been identified in human which are encoded by the SLC2 genes. These are classified into three classes viz. class1, class 2 and class 3 and are expressed in a highly controlled tissue-specific fashion. Under normal physiological conditions, glucose transport occurs primarily by facilitated diffusion, which is an energy independent process (Thorens et. al., 2010).

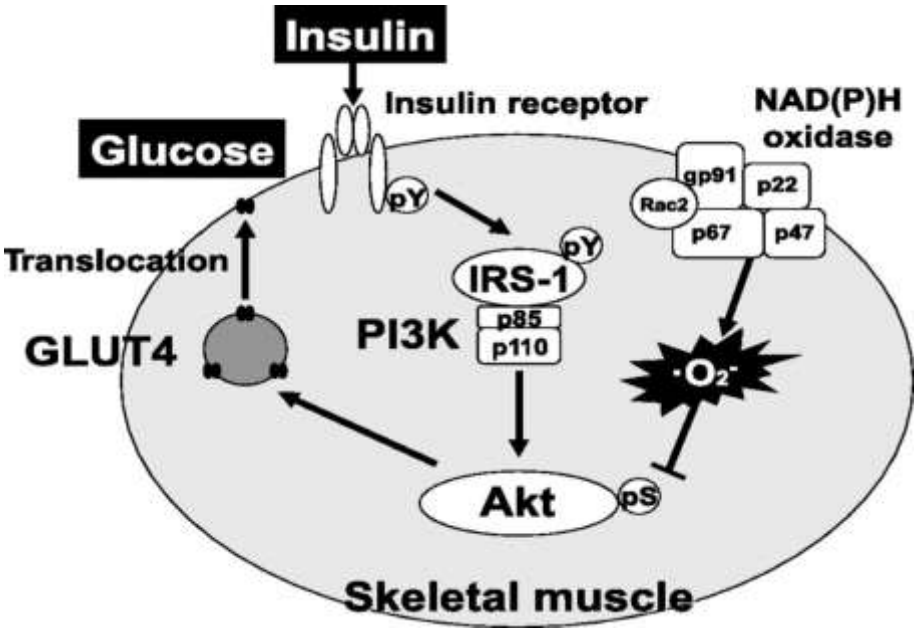

Fig.4: Showing the mechanism of action of Glucose Transporter Molecules (Tsutsui et. al., 2011)

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THERAPEUTIC TARGETS IN DIABETES MELLITUS:

1. Peroxisome Proliferator-Activated Receptors (PPARs)

PPAR-γ has been reported to be expressed in a variety of tissues including adipose, skeletal muscles, liver, immune regulatory cells (e.g., monocytes, macrophages), colon mucosa, and the placenta (Tontonoz et. al., 2008). PPAR-γ gets activated through a variety of endogenous and synthetic ligands. PPAR-γ is target for Thiazolidinedione (TZDs) class of anti-diabetic drugs, which is a synthetic ligand for the same. It activates PPAR-γ which results in improved insulin resistance, dyslipidemia and lowers blood glucose levels in T2DM patients (Monsalve et. al., 2013).

2. Role of incretins& DPP-4 inhibitors in diabetes

Dipeptidyl Peptidase 4 (DPP-4), also known as CD 26, is a 110 kDa trans-membrane protein and was first characterized by HopsuHavu and Glenner (Hopsu-Havu et. al., 1966), which is widely expressed in a wide variety of tissues such as “liver, lung, kidney, intestinal brush-border membranes, lymphocytes and endothelial cells”. Incretin peptides such as “Glucose-dependent Insulinotropic Polypeptide (GIP) and Glucagon Like Peptide (GLP)” which are secreted from “K and L cells” from the gut regulates postprandial blood glucose levels by inducing insulin secretion from pancreatic beta cells via glucose dependent manner (Drucker et. al. 2006).

MANAGEMENT OF DIABETES:

The manifestations of diabetes results in the onset of various micro-vascular and macro-vascular diabetic complications which are the major causes of morbidity and mortality leading to considerable human suffering and enormous economic loss.In spite of the great achievements in the treatment of diabetes, many patientsdo not achieve optimal glycemic goals which result in a decreased lengthand quality of life.Traditionally, the success of patientsto manage their diabetes depends on its ability to adhere to a prescribed therapeutic regimen and life style changes which are mentioned as below:

Insulin

Insulin is an anabolic hormone which acts on various target tissues, such as liver, skeletal muscle and adipose tissues. Various metabolic processes such as “glycogen synthesis, glycogenolysis, gluconeogenesis, and lipogenesis” are strictly regulated through intracellular signaling pathway downstream of insulin receptor (Satoh, 2014). By acting of these target tissues, insulin promotes the uptake of circulating glucose into skeletal and adipose tissues thereby regulates the blood glucose level. It stimulates the uptake of various metabolites such as fatty acids, triglycerides, cholesterol and amino acids into the target tissues and prevents their breakdown (Dimitriadis et. al., 2011). It has been reported in the U.K. Prospective Diabetes Study (UKPDS), that subjects with T2DM on insulin therapy gained an average 4

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kg weight, which leads to 0.9 percent decrease in HbA1C level as compared to subjects on conventional therapy (Petznick, 2011).

Diet

Diet therapy is an important and a key factor for the management of diabetes which promotes healthy eating and is aimed at maintaining optimal glycemic and lipid profile, appropriate energy for optimal growth and development and to prevent the development of diabetes related complications. The traditional approach to diet therapy focuses on modifying the quality and quantity of food and limiting the intake of refined sugars, unhealthy amount of fats and protein. On the other hand, increased intake of grains, legumes, fruits, and vegetables is recommended. "Fruits are an important part of a balanced diet and play a key role in human nutrition by supplying the necessary growth regulating factors essential for the maintenance of normal health. They are an important source of various vitamins (vitamin C and vitamin A) and are good source of various minerals, flavonoids (anti-oxidants), saponins, polyphenols, carotenoids, isothiocyanates and several kinds of dietary fibers" (Sparks et. al., 2005).

Physical activity

Physical activity is a general term that includes all bodily movement via the contraction of skeletal muscle that increases energy consumption which helps in improvement of physical fitness, improved glycemic control, reduced cardiovascular risk factors, contribute to weight loss, and improve well-being (Hamasaki et. al., 2016). Studies have reported that a sedentary lifestyle is a major risk factor of the development of CVD, T2DM and mortality and it has been recommended by the American College of Sports Medicine and the American Diabetes Association that at least 150 min/week of moderate to vigorous physical activity should be performed by T2DM patients (Colberg et. al., 2010), have resulted in beneficial effects on glycemic control and other health-related outcomes for patients with T1DM (Yardley et. al., 2014).

SYNTHETIC ANTI-DIABETIC DRUGS:

Drugs used to treat diabetes by lowering blood glucose levels which are administered orally are called as oral hypoglycemic agents ororal anti-diabetic drugs. There are different classes of anti-diabetic drugs, and their selection depends on the nature of the diabetes, age as well as other factors. Some of them are described as below.

1. α- Glucosidase inhibitors

Alpha Glucosidase Inhibitors (AGIs) are oral hypoglycemic drug which is used for the treatment and management ofdiabetesmellitus(Garber et. al., 2013). Acarboseis a pseudo tetra saccharide, having nitrogen bound betweenthe first and second glucose molecule is the most widely used drug for the management of T2DM for over 20 years(Joshi et. al., 2015).

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2. Biguanides

It is an orally administered, biguanide class of anti-diabetesdrug which is used for the treatment of hyperglycemia in obese and T2DM patients. During the 1950s, threemainbiguanideswere introduced for the treatment of diabetes of which metformin had a superior safety profile and was welltolerated. Phenformin and Buformin were the other two biguinides which were withdrawn during the early 1970s as they posed the increased risk of developing lactic acidosis and increased cardiacmortality.

3. Third generation Sulphonylureas drug

This drug was discovered in 1942 byJanbonand colleagues during an experiment when they observed that some sulfonamides caused hypoglycemia in experimental animals which lead them to the synthesis of carbutamide (1-butyl-3-sulfonylurea) (Sola et. al., 2015). It wasthe first sulfonylurea which was used for the treatment of diabetesbut due to itsadverse effects on bone marrow it was soon withdrawn from the market.

4. Thiazolidinediones

These Thiazolidinediones (TZDs) class of oral anti diabetic drugs acts by enhancing the peripheral insulin sensitivity and reduces the insulin resistance in adipose tissue, muscle and the liverthrough the activation of the peroxisome proliferator activated receptor gamma (PPAR gamma) which consequently improves the metabolic control in T2DM subjects (Rizos et. al., 2016).

5. Dipeptidyl Peptidase-4 (DPP-4)

In another approach for the treatment of diabetes,incretin hormones such as Glucagon Like Peptide 1 (GLP-1) and Glucose dependent Insulinotropic Peptide (GIP) suppresses post prandial glucagon release, delay gastric emptying and increase satiety(Kim et. al. 2008). Animal studies have reported that GLP-1 and its analogs stimulate beta cells proliferation and differentiation which lead to increased insulinsecretion from the pancreatic islets in glucose dependent manner(Tamura et. al., 2015).

MEDICINAL PLANTS WITH ANTI-HYPERGLYCEMIC PROPERTIES:

Since time immemorial various medicinal herbs and plants have been used widely in various traditions and cultures throughout the world as a source of medicine for the treatment of various diseases including diabetes mellitus. Due to the lack of proper health care system in various remote parts of the world, majority of people living in those areas heavily depend on these traditional medicinal plants for treatment which involves the use of plant extracts or their active principles. At present various species of plants are used in the treatment of diabetes mellitus.

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1. Acacia Arabica

It is commonly known as babool and in Indian medicinal system it is used as a home remedy for the treatment of diabetic complications. It has been reported that the extract of this plant acts as secretagouge agent which helps in insulin secretion (Singh, 2011).

2. Aeglemarmelos

It is commonly known as bael, bili, bhel, Bengal quince or golden apple. The leaf extract of this plant is widely used in Indian medicinal system for the treatment of hyperglycemia and diabetes. Studies have reported that after continuous oral induction of the methanolic extract of this plant has been reported to reduce blood glucose in alloxan induced diabetic rats (Ayodhya et. al., 2010).

3. Aloe barbadensis

It is a popular house plant having a long history of multipurpose folk medicine. The plant has two basic products i.e. gel and latex. Aloe veragel is the product of leaf pulp or mucilage and Aloe latex is commonly known as “aloe juice,”. Studies have reported that administration of aloe gum effectively improves hyperglycemia and glucose tolerance in alloxan induced diabetic rats, which is proposed to be mediated through stimulation of insulin secretion from pancreatic beta cells (Singh, 2011).

4.AzadirachtaIndica

It also commonly known as Neem or Indian Lilac and belongs to the family Meliaceae. Studies have reported that hydro-alcoholic extracts of this plant possess anti-hyperglycemic property in streptozotocin induced diabetic rats (Aswathy et. al., 2017). This plant has many properties such as anti-bacterial, antimalarial, antifertility, hepato-protective and antioxidant effect.

5. Buteamonosperma

It is commonly known as flame-of-the-forest, Buteafrondosa, Dhak and Palas and belongs to the family Fabaceae. Studies have reported that the methanolic extract of *B. mono sperma*seeds, demonstrated significant anthelmintic activity, anticonvulsive and hepato-protective activity in vitro. The extracts made from the bark of this plant tested on normal and alloxan induced diabetic mice resulted in significant anti-hyperglycemic activities (Deore et. al., 2008).

6. WithaniaSomnifera

In Sanskrit it is commonly known as Ashwagandha which is a perennial plant and belongs to the family Solanaceae. It has various properties including antioxidant and anti-inflammatory. (Khan et al.,2015). For the assessment of the hypoglycemic and hypolipidemic effects, the root and leaf extract were prepared and investigated in alloxan induced diabetic rats for eight

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weeks. After treatment, blood glucose levels and other serological parameters were found to be restored to their normal level after eight weeks of treatment, suggesting that the root and leaf extracts possess hypoglycemic and hypolipidemic properties against alloxan-induced diabetic rats (Khan et. al. 2015).

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