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DIABETES MELLITUS A SHORT REVIEW

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Abstract

Diabetes mellitus is an epidemic and also life threatening disease affecting over millions of people all over the world. Diabetes is caused due to genetic and epigenetic factors. The broad classification of Diabetes includes type I and type II diabetes. Much research on causes, prevention and treatment of Diabetes mellitus is being performed all over the world. This review details about the types of Diabetes mellitus, their symptoms, pathophysiology, drugs and phytocompounds in the treatment of Diabetes mellitus.

Key words: *Diabetes mellitus, epigenetic, epidemic, genetic factors.*

Introduction

Diabetes mellitus is currently one of the most costly and burden some chronic diseases and is a condition that is increasing in epidemic proportions throughout the world. Diabetes affects about 5% of the global population and the management of diabetes without any side effects is still a challenge to the medical system (Akram Eidi and Maryam Eidi, 2009). It is a chronic disease characterized by high blood glucose levels due to absolute or relative deficiency of circulating insulin levels (Venkatesh *et al.*, 2003). It could also mean a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (Edwin *et al.*, 2007).

Diabetes is defined as a state in which the homeostasis of carbohydrate and lipid metabolism is improperly regulated by the pancreatic hormone, insulin, ultimately resulting in increased blood glucose level. It is the world's largest endocrine disorder and is one of the major killers in recent times (Bhat *et al.*, 2008). According to World Health Organization (WHO), the world wide global population is in the midst of a diabetes epidemic with people in Southeast Asia and Western Pacific being mostly at risk. The number of cases for diabetes which is currently at 171 million is predicted to reach 366 million by the end of 2030 (Christudas Sunila *et al.*, 2011).

In diabetes mellitus oxidative stress is significantly increased through both nonenzymatic and enzymatic mechanisms as a result of prolonged exposure to hyperglycemia. Evidence suggests that markers of oxidative stress exist in diabetic rats, such as overproduced reactive oxygen species (ROS) in pancreatic islets (Amaral *et al.*, 2008). Because the mechanism of diabetes mellitus is quite complex, many currently available synthetic chemical antidiabetic agents have low rates of response and remission and with severe adverse-effects. Accordingly, it is necessary to research and develop more effective hypoglycemic agents with lower adverse-effect (Sun *et al.*, 2008). The use of ethanobotanicals has a long folkloric history for the treatment of blood glucose lowering abnormalities (Sharma *et al.*, 2007). Therefore, the search for more effective and safer antidiabetic/hypoglycaemic agents has continued to be an important area of active research.There are three main types of diabetes namely type I diabetes, type II diabetes and gestational diabetes.

Type I diabetes

Insulin-dependent diabetes mellitus (IDDM) is a disorder caused by progressive destruction of the insulin secreting beta-cells. Type 1 diabetes occurs in a genetically susceptible human population as a result of the loss of the insulin producing pancreatic beta cells.

This accounts for the drastic drop in the insulin level in the diabetic patients (Sezik *et al.*, 2005). It results from a chronic autoimmune response directed against the insulin producing beta-cells in the islets of Langerhans, resulting in beta -cell destruction (Daneman, 2006). The majority of type-I diabetes is immune mediated nature where cell loss is a T-cell mediated autoimmune attack. There is no preventive measure against type-I diabetes (Dorner, 2010). The symptoms include polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), feeling tired or fatigue, weight loss

Hyperglycemic condition causes increased glycosylation leading to biochemical and morphological abnormalities due to altered protein structure which over a period of time develops diabetic complications such as nephropathy, retinopathy, neuropathy and cardiomyopathy (Poonam Shokeen *et al.*, 2008). Currently available therapy for diabetes include insulin (Kameswararao *et al.*, 2003). In recognition of this, the need for therapeutics is crucial and stabilizing blood glucose levels and improving insulin sensitivity should be the primary targets of therapies. Patients suffering from type-1 diabetes mellitus require lifelong insulin therapy for survival as there is no cure for this immune-mediated disease (George *et al.*, 2011).

• Autoimmune diabetes mellitus:

The slowly progressive form of diabetes mellitus occurs in adults and is sometimes referred to as latent autoimmune diabetes in adults (LADA). Few children and adolescents are affected with ketoacidosis during the first manifestation of the disease. The rate of β-cell destruction is quite variable and being rapid in some individuals and this form of diabetes accounts only for 3-10% of those with diabetes. Auto antibodies are present in 85-90% of individuals when fasting hyperglycemia is initially detected (Munday, 2005).

• Idiopathic Diabetes:

There are some forms of insulin dependent diabetes have no known etiologies. Some of these patients have permanent insulinopenia and are prone to keto acidosis, but have no evidence of autoimmunity (Lie-Fen shyur *et al.*, 2005).

Type II diabetes

Non-Insulin Dependent Diabetes Mellitus (NIDDM) is the most common form of diabetes mellitus which accounts for more than 90% of diabetic patients. Current understanding of disease progression in NIDDM is that insulin resistance in peripheral tissues leads to compensatory hyperinsulinemia, followed by beta-cell failure, which leads initially to prandial and later to over fasting hyperglycemia (Kwanghee Kim *et al.*, 2009). It is a term used for individuals who have insulin resistance and attenuated glucose utilization. It is strongly associated with obesity, affects 90-95% of patients with diabetes (George *et al.*, 2011).

People with type II diabetes are asymptomatic for many years or decades, with time an increase in blood sugar levels leads to symptoms. Following signs and symptoms of type II diabetes

- ♦ blurred sight.
- ♦ decreased sensation or numbness in the hands and feet.
- ♦ frequent bladder and vaginal infections.
- ♦ frequent need to urinate.
- ♦ increased thirst and hunger.
- ♦ male impotence (erectile dysfunction).

• **Pathophysiology:**

Dysfunction of β-cell is a major factor across the spectrum of prediabetes to diabetes. A study of obese adolescents confirms what is increasingly being stressed in adults as well: β-cell dysfunction develops early in the pathologic process and does not necessarily follow the stage of insulin resistance (Bacha *et al.*, 2010). Insulin resistance due to high-calorie diet, increased glucagon levels steroid administration, or lack of physical inactivity and increased glucose-dependent insulinotropic polypeptide (GIP) levels accompany glucose intolerance. However, the postprandial glucagonlike peptide-1 (GLP-1) response is unaltered (Hansen *et al.*, 2011).

Metabolic abnormalities in NIDDM contribute to hyperglycemia. To begin at the hepatic level, the note of the liver in the pathogenesis of NIDDM is overproduction of glucose. Increased basal hepatic glucose production is a characteristic feature of essentially all NIDDM patients with fasting hyperglycemia. The etiology of type-II is a combination of insulin resistance with inadequate compensatory insulin-secretory response. Patients with diabetes experience significant morbidity and mortality from microvascular (retinopathy, neuropathy and nephropathy) and macrovascular complications (heart attack, stroke and peripheral vascular disease) (Altan, 2003). α-Glucosidase and α-amylase inhibitors restrict postprandial glucose rise by retarding the process of carbohydrate absorption and hydrolysis. These inhibitors have been found useful in managing type-II diabetes (Gholamhoseiniana *et al.*, 2009).

• **Secondary Diabetes Mellitus:**

Diabetes mellities due to gene defects, trauma or

surgery or the effects of drugs are more appropriately called secondary diabetes mellitus. A type of diabetes called Maturity Onset Diabetes of the Young (MODY) is increasingly seen in adolescence (Umapathy and Mooradian, 2011).

• Gestational Diabetes Mellitus:

Gestational diabetes mellitus (GDM) defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy. It increases the risk of pregnancy complications and subsequent type-II diabetes in the mother and her offspring (Rodrigues *et al.,* 2002). Pregnancy serves as a metabolic stress test and uncovers underlying insulin resistance and β-cell dysfunction (Setji *et al.,* 2005).

Gestational diabetes is pathophysiologically similar to type II diabetes mellitus. Approximately 90% of the persons identified have a deficiency of insulin receptors (prior to pregnancy) or a marked increase in weight that has been placed on the abdominal region. The other 10% have deficient insulin production and will proceed to develop mature onset insulin dependent diabetes. Type-II diabetes mellitus is one of the common diseases in our community so the prevalence of GDM is likely to be high (Zargar *et al*., 2001).

The most common complications of pregnancy is Gestational diabetes mellitus (GDM. Women with gestational diabetes have up to a 45% risk of recurrence with the next pregnancy and up to a 63% risk of developing type II diabetes later in life according to CDC (Center for Disease Control), Insulin sensitivity usually begins in the second trimester and continues to progress through the pregnancy (Luerssen and Winsch, 2005).

The common symptoms include increased thirst, increased urination, weight loss in spite of increased appetite, fatigue, nausea and vomiting, frequent infections including those of the bladder, vagina and skin, blurred vision. The traditional method of screening for GDM is to assess risk factors: age, pre-pregnancy, weight, family history of diabetes in a first-degree relative and previous perinatal loss. Unfortunately, screening based solely on risk factors will only identify approximately 50% of women with GDM (WHO, 2000).

• Medicinal plants vs diabetes mellitus:

Medicinal plants and their extracts have been reported to be effective in the treatment of diabetes. Plants contain natural antioxidants that can preserve β-cell function and prevent diabetes induced ROS formation (Mustafa Aslan *et al.,* 2010). Diet control, exercise and the use of hypoglycemic or lipid-lowering diets and drugs are the treatments for diabetes. However, many oral hypoglycemic agents have a number of serious adverse effects. Management of hyperglycemia or hyperlipidemia with low side effects is still a challenge to the medical system (May *et al.,* 2002).

Many new bioactive principles isolated from plants having anti hyperglycemic effects have shown anti-diabetic activity equal and even more potent than known oral hypoglycemic agents such as daonil, tolbutamide and chlorpropamide. Many plant compounds are not characterized and documented. More investigations and sincere efforts are still sought to evaluate the precise mechanism of action of medicinal plants with anti-diabetic effect at the molecular level (Bnouham *et al.,* 2006).

Though different types of oral hypoglycemic agents are available, there is a growing trend towards using natural products as treatment. China has a long history of using herbs for the treatment of human diseases and several medicinal plants are used for the treatment of diabetes. *Selaginellatamariscina* is one such plant (Hnatyszyn *et al.,* 2002).

Leaves, fruits, stem and roots of *Aeglemarmelos* have been used in ethno medicine for several medicinal properties: astringent, antidiarrheal, antidysenteric, demulcent, antipyretic, antiscourbutic, haemostatic, aphrodisiac and as an antidote to snake venom. It is also known as herbal medicine for the treatment of diabetes mellitus. *Ficus religiosa* has been used in the traditional system of ayurveda to treat diabetes. The leaves of Ficusreligiosa have been studied for anti-hyperglycaemic activity.

In Ayurveda, the unripe fruits of *Carissa carandas* were used as an anthelmintic, astringent, appetizer, anti-pyretic, anti-diabetic, aphrodisiac, in biliary disorders, stomach disorders, rheumatism and diseases of the brains.

Antioxidants and defense mechanism

• Free radicals:

Free radical is commonly produced in all cells as part of normal cellular function and might play a role in many diseases. Antioxidant scavenges free radical induced tissue damage by preventing their formation and increasing their decomposition. As a result of this high reactivity, most radicals have a very short half life (10-6 seconds or less) in biological systems, although some species may survive for much longer (Young and Woodside, 2001). Anti-oxidants help organisms deal with oxidative stress, caused by free radical damage. Free radicals have one or more unpaired electrons making them highly unstable and cause damage to other molecules by extracting electrons from them in order to attain stability. Reactive

oxygen species (ROS) formed *in vivo*, such as superoxide anion, hydroxyl radical and hydrogen peroxide, are highly reactive and potentially damaging transient chemical species. These are continuously produced in the human body, as they are essential for energy supply, detoxification, chemical signaling and immune function.

• Oxidative stress and human health:

In diabetes, oxidative stress has been found to be mainly due to an increased production of oxygen free radicals and a sharp reduction of antioxidant defenses has been observed (Deliorman Orhan *et al.,* 2005). The elevated levels of blood glucose in diabetes are associated with increased lipid peroxidation, which may contribute to long-term tissue damage (Bhor *et al.*, 2004). Since diabetes mellitus is considered as a free radical-mediated disease, increased free radical production as well as reduced antioxidant defense responses may give rise to increased oxidative stress in diabetic condition (Price *et al.,* 2001; Abou-Seif and Youssef, 2004).

• Antioxidant:

Antioxidants have been shown to prevent the destruction of beta-cells by inhibiting the peroxidation chain reaction and thus they may provide protection against the development of diabetes (Montonen, 2005). Disturbances of antioxidants defense system in diabetes involves: enhancement of lipid peroxidation, alteration in antioxidant enzymes and impaired glutathione metabolism (Bagri *et al.,* 2009). Diabetes is usually associated by increased production of the molecules of reactive oxygen species (ROS) and/or impaired antioxidant defense systems, which result oxidative damage leading to ROS mediated diabetic pathogenesis.

Recent reports suggest that cruciferous vegetables act as good source of natural antioxidants due to high levels of carotenoids, tocopherols and ascorbic acid and convincing epidemiological evidence shows these compounds may help to protect the human body against damage by reactive oxygen and nitrogen species. Foremost are their antioxidative effects, manifested by the ability to scavenge free radicals or to prevent oxidation of low-density lipoproteins (Gayatri Nahak and Rajani Kanta Sahu, 2010).

Mammalian cells possess elaborate defence mechanisms for radical detoxification. Antioxidants are agents, which scavenge the free radicals and prevent the damage caused by them. Some of these compounds are of exogenous nature and are obtained from food. Examples include antioxidants like α-tocopherol, β-carotene and ascorbic acid and some micronutrient elements such as zinc and selenium (Chin-Shiu Huang *et al.,* 2011).

α-tocopherol is found in green parts of plants and scavenges lipid peroxide radicals through the concerted action of their antioxidants. It were also known to protect lipids and other membrane components by physically quenching and chemically reacting with O_2 in chloroplasts, thus protecting the structure and function of Photosystem II. Researchers reported a two-fold increase in a α-tocopherol in turf grass under water stress (Mohammed Fazil Ahmed *et al.,* 2010).

Vitamin C (ascorbate) is a most powerful antioxidant which is synthesized in the mitochondria and is transported to other cell components through a protein - electro chemical gradient or by facilitated diffusion. It is one of the most extensively studied antioxidants and has been detected in the majority of plant cell types, organelles and apoplast.

Glutathione is the major source of non-protein thiols in most of the plant cells. It takes part in the control of H_2O_2 levels, by changing the ratio of its reduced form to oxidized form. It is a tripeptide which has been detected virtually in all cell compartments such as chloroplast, cytosol, vacuoles, endoplasmic reticulam and mitochondria. The chemical reactivity of the thiol group of glutathione makes it particularly suitable to serve a broad range of biochemical functions in all organisms (Liere *et al.,* 2005).

• Alloxan - the diabetogenic agent:

Alloxan is a hydrophilic and chemically unstable pyrimidine derivative, which is toxic to pancreatic β-cells because it can generate toxic free oxygen radicals during redox cycling in the presence of reducing agents such as glutathione and cysteine. Alloxan (2, 4, 5, 6-tetra oxy pyrimidine) is an oxygenated pyrimidine derivative and it is present as alloxan hydrate in aqueous solution (Lenzen, 2008). Fig. 1 depicts the structure of Alloxan.

It is a β-cytotoxin, induces "chemical diabetes"

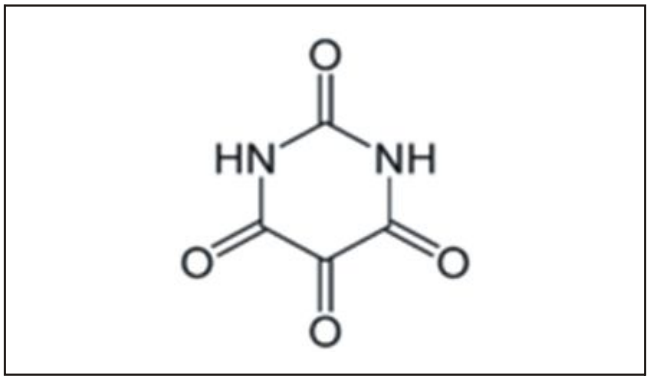

Fig. 1: Structure of Alloxan.

(alloxan diabetes) in a wide variety of animal species by damaging the insulin secreting cells of the pancreas. This damages a large number of β-cells, resulting in decrease in endogenous insulin release, which paves the ways for the decreased utilization of glucose by the tissue (Saravanan and Pari, 2005). In addition hypoglycaemia is induced by sulphonylureas by increasing the secretion of insulin from pancreas and these compounds are active in mild alloxan-induceddiabetes, but they areinactive in intense alloxan diabetes.

Alloxan is a poison and is the most famous spinner up of super oxide free radicals known to science. In rat studies, alloxanspined up enormous amounts of free radicals in pancreatic beta cell leading to diabetes. It is a compound that can indeed destroy cells in the pancreas and cause diabetes in rats (Joe Schwarcz *et al.,* 2003). The possible role in the production of diabetes are two characteristic reactions of alloxan, aminoacid and glutathione oxidation (Gerhard *et al.,* 2003).

The oxidation of essential -SH groups inhibition of β-cell glucokinase, generation of free radicals and disturbances in-intracellularcalcium homeostasis are te-toxic action of Alloxan (Patil *et al.,* 2011). Alloxan exerts its diabetogenic actions when administered intravenously, intraperitoneal or subcutaneously. It has been suggested that this cytotoxic effect involves both a rapid uptake of alloxan and a drug-induced generation of oxygen-containing radicals and peroxide. The action of alloxan in the pancreas is preceded by its rapid uptake by the insulin-secreting cells and also due to autoimmune destruction of the β-cells of the pancreas.

In acute pancreatitis, pain in the upper abdomen is commonly caused due to sudden destruction or inflammation of the pancreatic tissue. The pain is usually moderate to severe. In chronic pancreatitis too, there will be pain. But this pain is more mild to severe, usually in the upper abdomen, radiating to the back and is aggravated by food (Wadkar *et al.,* 2008). An elusive diagnosis is needed for pancreatic diabetes caused by Chronic pancreatitis because it is occasionally painless and often not accompanied by clinical malabsorption until after hyperglycemia occurs (Robert *et al.,* 2006).

References

Abou-Seif, M.A. and A.A. Youssef (2004). Evaluation of some biochemical changes in diabetic patients, *Clinica. Chimica. Acta.*, **346:** 161-170.

Amaral, S., P.J. Oliveira and J. Ramalho-Santos (2008). Diabetes and the impairment of reproductive function: possible role of mitochondria and reactive oxygen species, *Curr. Diabetes Rev*., **4:** 46-54.

Akram Eidi and Maryam Eidi (2009). Antidiabetic effects of sage (*Salvia officinalis* L.) leaves in normal and streptozotocin-induced diabetic rats, Diabetes and Metabolic Syndrome: *Clinical Research and Reviews*, **3:** 40-44.

Altan, V.M. (2003). The pharmacology of diabetic complications, *Current Medicinal Chemistry*, **10:** 1317-1327.

Bacha, F., S. Lee, N. Gungor and S.A. Arslanian (2010). From pre-diabetes to type II diabetes in obese youth: pathophysiological characteristics along the spectrum of glucose dysregulation, *Diabetes Care*, **33(10):** 2225-31.

Bagri, P., M. Ali, V. Aeri, M. Bhowmik and S. Sultana (2009). Antidiabetic effect of *Punicagranatum* flowers: effect on hyperlipidemia, pancreatic cells lipid peroxidation and antioxidant enzymes in experimental diabetes, *Food Chem. Toxicol*., **47:** 50-54.

Bhat, M., S.S. Zingarde, S.Y. Bhargava, A.R. Kumar and B.N. Joshi (2008). Antidiabetic Indian plants: a good source of potent amylase inhibitors, *Evidence Based on Complementary and Alternative Medicine*.

Bhor, V.M., N. Raghuram and S. Sivakami (2004). Oxidative damage and altered antioxidant enzymes activities in the intestine of treptozotocin-induced diabetic rats, *International Journal of Biochemistry Cell Biology*, **36:** 89-97.

Bnouham, M., A. Ziyyat, H. Mekhfi, A. Tahri and A. Legssyer (2006). Medicinal plants with potential antidiabetic activity-A review of ten years of herbal medicine research (1990-2000), *International Journal of Diabetes & Metabolism*, **14:** 1-25.

Chin-Shiu Huang, Mei-Chin Yin and Lan-Chi Chiu (2011). Antihyperglycemic and antioxidative potential of *Psidiumguajava* fruit in streptozotocin-induced diabetic rats, *Food and Chemical Toxicology*, **49:** 2189-2195.

Christudas Sunil, Savarimuthu Ignacimuthua and Agastian Paul (2011). Antidiabetic effect of *Symplocoscochinchinensis* (Lour.) S. Moore. in type II diabetic rats, *Journal of Ethnopharmacology*, **134:** 298-304.

Daneman, D. (2006), Type 1 diabetes, *Lancet*, **367:** 847-858.

Deliorman Orhan, D., M. Aslan, N. Sendogdu, F. Ergun and E. Yesilada (2005). Evaluation of the hypoglycemic effect and antioxidant activity of three *Viscum album* subspecies (European mistletoe) in streptozotocin-diabetic rats, *Journal of Ethnopharmacology*, **98:** 95-102.

Dorner, J.L. (2010). Mechanism of cell injury by activated oxygen, *Environmental Health Perspectives*, **102:** 17-24.

Edwin, E., E. Sheeja, S.P. Dhanabal and B. Suresh (2007). Antihyperglycemic activity of *Passifloramollissima* Bailey, *Indian Journal of Pharmaceutical Sciences*, **64:** 570-571.

Gayatri Nahak and Rajani Kanta Sahu (2010). Free Radical Scavenging activity of multi-vitamin plant (*Sauropusandrogynus* L. Merr.), *Researcher*, **2(11):** 6-14.

George, C., A. Lochner and B. Huisamen (2011). The efficacy of *Prosopisglandulosa* as antidiabetic treatment in rat models of diabetes and insulin resistance, *Journal of Ethnopharmacology*, **137:** 298-304.

Gerhard, A.S., A.S. Gunasekaran, Manickam and M.A. Vijayalakshmi (2003). Antidiabetic activity of *Aloevera* and history of organs in streptozotocin-induced diabetic rats, *Curr. Sci*., **94:** 1070-1076.

Gholamhoseiniana, A., H. Fallaha and F. Sharififar (2009). Inhibitory effect of methanol extract of *Rosa damascena* Mill. flowers on alpha-glucosidase activity and postprandial hyperglycemia in normal and diabetic rats, *Phytomedicine*., **16:** 935-41.

Hansen, KB., T. Vilsboll, J.I. Bagger, J.J. Holst and F.K. Knop (2011). Increased postprandial GIP and glucagon responses, but unaltered GLP-1 response after intervention with steroid hormone, relative physical inactivity and high-calorie diet in healthy subjects, *J. Clin. Endocrinol. Metab*., **96(2):** 447-53.

Hnatyszyn, O., J. Mino, G. Ferraro and C. Acevedo (2002). The hypoglycemic effect of *Phyllanthussellowianus* fractions in streptozotocin-induced diabetic mice, *Phytomedicine*, **9:** 556-559.

Joe Schwarcz, S.O., J.I. Odimegwu and V.N. Enwuru (2003). Evaluation of hypoglycemic and hypolipidemic effects of ethanolic extracts of Treculia African Decne and *Bryophyllumpinnatum* Lam and their mixture on streptozotocin (STZ)- induced diabetic rats, *African Journal of Biotechnology*, **7(15):** 2535-2539.

Kameswararao, B., M.M. Kesavulu and C. Apparao (2003). Evaluation of antidiabetic effect of *Momordicacymbalaria* fruit in alloxan-diabetic rats, *Fitoterapia*, **74:** 7-13.

Kwanghee Kim, Hyunyul Kim, Jeunghak Kwona, Sungwon Leea, Hyunseok Konga, Sun-A Im, Young-Hee Lee, Young-Ran Lee, Sun-Tack Oh, Tae Hyung Jo, Young In Park, Chong-Kil Lee and Kyungjae Kim (2009), Hypoglycemic and hypolipidemic effects of processed *Aloe vera* gel in a mouse model of non-insulin-dependent diabetes mellitus, *Phytomedicine*, **16:** 856-863.

Khane, Thippeswamy, B.S. and V.P. Veerapurg (2012). Antidiabetic, antihyperlipidemic and antioxidant activities of methanolic extract of *Amaranthusviridis* Linn in alloxan Ashok Kumar, B.S., Lakshman, K., Jayaveea, K.N., Sheshadri Shekar, D., Saleemulla induced diabetic rats, *Experimental and Toxicologic Pathology*, **64:** 75-79.

Lenzen, P.Z. (2008). Diabetes epidemiology as a tool to trigger diabetic research and care. *Diabetologia*, **42:** 499-518.

Lie-Fen shyur, J.K., S. Yadav and V. Vats (2005). Medicinal plants of India with anti-diabetic potential, *J. Ethnopharmacol*., **81:** 81-100.

Liere, S., T. Ozben and N. Tuncer (2005). Serum and urine malondialdehyde levels in NIDDM patients with and without hyperlipidemia, *Free Radical Biology and Medicine*, **19:** 893-896.

Luerssen, M.A. and A.L. Winsch (2005). Identifying and treating gestational diabetes mellitus: Advances in screening and current interventions, *American Journal of Nursing*, **105(4):** 65-71.

May, L., J. Lefkowitch, M. Kram and D. Rubin (2002). Mixed hepatocellular cholestatic liver injury after pioglitazone therapy, *Annuals of Internal Medicine*, **136:** 449-452.

Mohammed Fazil Ahmed, Syed Mohammed Kazim, Syed Safiullah Ghori, Syeda Sughra Mehjabeen, Shaik Rasheed Ahmed, Shaik Mehboob Ali and Mohammed Ibrahim (2010). Antidiabetic activity of *Vincarosea* extracts in alloxan-induced diabetic rats, *International Journal of Endocrinology*, 1-6.

Montonen, J. (2005). Plant foods in the prevention of type II diabetes mellitus with emphasis on dietary fiber and antioxidant vitamins - publications of the National Public Health Institute Helsinki, M.S. Thesis, Department of Public Health, University of Helsinki, 18.

Munday, E. (2005). Nutritional benefits of flavonoids, International conference on food factors "Chemistry and Cancer Prevention", Hamamatsu, Japan, C, 6-2.

Mustafa Aslan, Nilüfer Orhan, Didem Deliorman Orhan and Fatma Ergun (2010), Hypoglycemic activity and antioxidant potential of some medicinal plants traditionally used in Turkey for diabetes, *Journal of Ethnopharmacology*, **128:** 384-389.

Narayan Kesari, Rajesh Kumar Gupta, Santosh Kumar Singh, Sandhya Diwakar and GeetaWatal (2006). Hypoglycemic and antihyperglycemic activity of *Aeglemarmelos*seed extract in normal and diabetic rats, *Journal of Ethnopharmacology*, **107:** 374-379.

Patil, R.N., R.Y. Patil, Bharati Ahirwa and Dheeraj Ahirwar (2011). Evaluation of antidiabetic and related actions of some Indian medicinal plants in diabetic rats, *Asian Pacific Journal of Tropical Medicine*, 20-23.

Price, K.D., C.S.C. Price and R.D. Reynolds (2001). Hyperglycemia-induced ascorbic acid deficiency promotes endothelial dysfunction and the development of atherosclerosis. *Atherosclerosis*, **158:** 1-12.

Robert, Fumelli, P., R. Galassi, N. Dousset, M. Taus, G. Ferretti, L. Mazzanti, G. Curatola, M.L. Solera and P. Valdiguie (2006). Increased susceptibility to lipid oxidation of low-density lipoproteins and erythrocyte membranes from diabetic patients, *Metabolism*, **43:** 1470-1474.

Rodrigues, S., E. Robinson and K. Gray-Donald (2002). Prevalence of gestational diabetes mellitus among James Bay Cree women in northern Quebec, *Can. Med. Assoc. J*., **160:** 1293-7.

Shokeen Poonam, Prachi Anand, Y. Krishna Murali and Vibha Tandon (2008). Antidiabetic activity of 50% ethanolic

extract of *Ricinuscommunis* and its purified fractions, *Food and Chemical Toxicology*, **46:** 3458-3466.

Saravanan, R. and L. Pari (2005). Effect of Cogent db, a herbal drug, on serum and tissue lipid metabolism in experimental hyperglycaemic rats, *Diab. Obes. Metabol.*, **5:** 156-62.

Setji, T.L., A.J. Brown and M.N. Feinglos (2005). Gestational diabetes mellitus, *Clinical Diabetes*, **23:** 17-24.

Sezik, E., M. Aslan, E. Yesilada and S. Ito (2005). Hypoglycemic activity of *Gentianaolivieri* and isolation of the active constituent through bioassay-directed fractionation techni- ques, *Life Sci*., **76:** 1223-1238.

Sharma, S., M. Chaturvedi, M. Edwin, S. Shukla and H. Sagrawat (2007). Evaluation of the phytochemicals and anti-diabetic activity of *Ficusbengalensis*, *Int. J. Diabet*., **27(2):** 56-59.

Sun, J.E., Z.H. Ao, Z.M. Lu, H.Y. Xu, X.M. Zhang, W.F. Dou and Z.H. Xu (2008). Antihyperglycemic and anti-lipidperoxidative effects of dry matter of culture broth of *Inonotusobliquus* in submerged culture on normal and alloxan-diabetes mice, *Journal of Ethnopharmacology*, **118:** 7-13.

Umapathy, B. and A.D. Mooradian (2011). Antioxidant vitamins and their influence in diabetes mellitus, *Curr. Diabetes. Rep*., **2:** 448-56.

Venkatesh, S., R.G. Dayanand, R.B. Madhava, M. Ramesh and A.V.N. Apparao (2003). Anti-hyperglycemic activity of *Carallumaattenuta*, *Fitoterapia*, **74:** 274-279.

Wadkar, Vishwakarma and Goyal (2008). Antidiabetic Activity of *Zingiberofficinoleroscoe* in streptozotocin – induced non-insulin dependent diabetic rats, *Indian Journal of Pharmacology Science*, **67:** 553-557.

Young, I.S. and J.V. Woodside (2001). Antioxidants in health and disease, *J. Clin. Pathol*., **54:** 176-186.

Zargar, A.H., A.K. Khan, S.R. Masoodi, B.A. Laway, A.I. Wani, M.I. Bashir and F.A. Dar (2001). Prevalence of type II diabetes mellitus and impaired glucose tolerance in the Kashmir valley of the Indian sub-continent, *Diab. Res. Clin. Prac*., **47:** 135-46.