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# An overview on pharmacological aspects of anti-diabetic activity

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**Abstract**: Diabetes mellitus is not a single disease but is a group of metabolic disorders affecting a huge number of populations in the world. It is mainly characterized by chronic hyperglycemia, resulting from defects in insulin secretion or insulin action. It is predicated that the number of diabetes person in the world could reach up to 366 million by the year 2030. Even though the cases of diabetes are increasing day by day, except insulin and oral hypoglycemic drugs no other way of treatment has been successfully developed so far. The review also contains brief idea about diabetes mellitus and the experimental screening model with their relevant mechanism and significance mainly used now days. Streptozotocin and alloxan are mainly used for evaluating the ant diabetic activity of a drug. This review contains list of medicinal plants which have been tested for their ant diabetic activity in the streptozotocin induced diabetic rat model. From the available data in the literature, it was found that plant having antidiabetic activity is mainly due to the presence of the secondary metabolite. Thus, the information provided in this review will help the researchers for the development of an alternative methods rather than insulin and oral hypoglycemic agents for the treatment of diabetes mellitus, which will minimize the complication associated with the diabetes and related disorder.

**Key words:** Aldose reductase, Streptozotocin, Antioxidant, Diabetes mellitus, Insulin, Phytoconstituents, Alloxan, Oral hypoglycemic agents.

## Introduction

Diabetes mellitus (DM) is a chronic disease characterized by a deficiency in insulin production and its action or both. That leads to prolonged hyperglycemia with disturbances in most metabolic processes inside the human body [1]. Untreated cases show severe tissue and vascular damage leading to serious complications such as retinopathy [2], neuropathy [3], nephropathy [4], cardiovascular complications [5] and ulceration [6]. Moreover, diabetes has an indirect relation with a many other disease being the most common endocrine disorder. It was estimated that about 200 million people worldwide suffered from DM in 2010, and it is expected to reach 300 million by 2025 [7].

Both insulin and glucagon, pancreatic endocrine hormones, are responsible for controlling blood-glucose level within the body in an adequate level based on the body needs. Normally, insulin is secreted by the β-cells found at the islets of Langerhans in response to high levels of blood sugar. It potentiates the ability of muscle, red blood cells, and fat cells to absorb sugar out of the blood and consume it in other metabolic processes, which restore the sugar levels to the normal level.

On the contrary, glucagon is secreted by α- cells of the pancreas as a result of low blood-glucose level in between meals and during exercise. That

stimulates the liver and other cells in muscles to release glucose out of the stored block in our bodies [8]. Olden Traditional practise of medicine in South Cameroon and some countries use *A. occidentale L.* (Anacardiaceae) as a remedy in treatment of diabetes mellitus [9]. Type 2 diabetes is tested by n-STZ rat model in which insulin level of plasma is decreased [10].

## Epidemiology of diabetes mellitus:

The word 'diabetes' is derived from the Greek word "Diab" (meaning to pass through, referring to the cycle of heavy thirst and frequent urination); 'mellitus' is the Latin word for "sweetened with honey" (refers to the presence of sugar in the urine). Greeks had knowledge of a disease accompanied by polyurea and wasting of body, whereas Aretaeus of Cappadocia mentioned a disease characterized by thirst and polyurea. Subsequently, the knowledge spreaded to Chinese, Iranians and Arabians. From the Middle East, the knowledge of diabetes mellitus had spread to Spain as a disease characterized by polyurea, polydipsia with sugary flavoured urine. With the discovery of sugar in urine and its detection by laboratory test, the knowledge permeated into the 18th century. The estimated burden of diabetes in India was 22 millions in 1990, 28 million in 1995 and 33 millions in 2000. It is the most common metabolic associated disease in the world. NIDDM is the most common

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form of diabetes constituting nearly 90% of the diabetic population in any country with varying numbers in different geographical region.

According to ancient Hindu physicians, 'Madhumeha' is a disease in which a patient passes sweet urine and exhibits sweetness all over the body. They had recorded in their observations that 'if too many ants swarm around a spot of urine, then the person have symptoms of diabetes mellitus' [11]. Mostly in india it is predicted that now at present 19.4 million people are affected by diabetes and it will be reached to 57.2 million by year 2025[12]. According to World Health Organization projection, the diabetes population is likely to increase to 300 million or more by the year 2025 [13]. The occurrence and consequences associated with diabetes are found to be high in countries like India (31.7%), China (20.8%) and United State of America (17.7%) [14]. Globally, diabetes mellitus presents enormous and increasingly important public health issues It is predicted that by 2030, India, China and the United States will have the largest number of people with diabetes [15]. The current studies in India indicate that there is an alarming rise in prevalence of diabetes which has gone beyond epidemic form to a pandemic one [16]. In most western countries, type 1 diabetes accounts for over 90% of childhood and adolescent diabetes although less than half of individuals with type 1 diabetes are diagnosed before the age of 15 years. Type 2 diabetes is becoming more common in youth onset diabetes in certain at risk populations. In addition, there is a distinct slowly progressive form of type 1 diabetes in Japan, which represents approximately one third of cases of type 1 diabetes. Type 1 diabetes is more common in the offspring of diabetic men compared with diabetic women [17].

**Pathophysiology of diabetes mellitus**
Diabetes mellitus has a profound adverse effect on quality of life in terms of social, psychological well-being as well as physical health. Diabetic complications are mainly mediated through oxidative stress such as increased production of ROS or impaired antioxidant defense systems. Enhancement of lipid peroxidation, alteration in antioxidant enzymes and impaired glutathione metabolism are the main factors involved in the development of diabetes [18]. Production of free radicals is also involved in the pathogenesis of various type of disease including diabetes mellitus [19]. Increased formation and accumulation of advanced glycation products

(AGEs) is also involved in the diabetic complications, such as retinopathy, neuropathy, and renal dysfunction through a series of pathological changes [20]. Though several hormones are involved in the regulation of blood glucose level, the most important ones are insulin and glucagon. When imbalanced occurs in the level of hormones in the body, sugar starts accumulating in the blood and when concentration of glucone increased in the blood then finally it will passes in urine along with other minerals [21]. In most cases of diabetes, primarily T-cell mediates pancreatic islet β-cell destruction, and becomes clinically symptomatic when 90% of pancreatic beta cells are destroyed. Serological markers such as islet cell, glutamic acid decarboxylase (GAD), IA-2, IA- 2β, or insulin autoantibodies, are present in 85-90% of individuals when fasting hyperglycemia is detected. Sometimes environmental triggers, such as chemical or viral initiated pancreatic β-cell destruction, which can triger consequences and thereby leads to the cause in diabetes mellitus. From the study it was found that enterovirus infection is also associated with the development of diabetes mellitus [22].

**Causes of diabetes mellitus**
The cause of diabetes depends on the type of diabetes. Type 1 occurs mainly due to β-cell destruction, mediated through either immune mediated or idiopathic, whereas Type 2 diabetes occurs mainly due to insulin resistance or with relative insulin deficiency. Diabetes is also associated with lifestyle factors and genetics [23]. There are various types of other factors that involved in the development of diabetes which are the genetic material such as chromosomal and mitochondrial DNA mutation. Leprechaunism, Rabson-Mendenhall syndrome and lipoatrophic diabetes is associated with the genetic defects in insulin action. In some cases congenital rubella and cytomegalovirus infection also lead to the cause of diabetes mellitus. Sometimes drugs and other chemicals such as pentamidine, nicotinic acid, glucocorticoids, thyroid hormone, β-adrenergic agonists, thiazides, α-interferon can cause diabetes mellitus. Abnormalities in the pancrease such as pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, fibrocalculous pancreatopathy can also develop diabetes. There are other factors related to immune system such as 'Stiff-man' syndrome and anti-insulin receptor antibodies that are involved in the development of the diabetes. Disease associated with pancrease such as aromegaly, Cushing's syndrome, glucagonoma,

phaeochromocytoma, hyperthyroidism and aldosteronoma can also mediate diabete mellitus. There are some other genetic syndromes such as Down syndrome, Klinefelter syndrome, Turner syndrome, Wolfram syndrome, Friedreich's ataxia, Huntington's chorea, Laurence-Moon-Biedl syndrome, Myotonic dystrophy, Prader-Willi syndrome which were also involved in the development of diabetes in some cases.

**Symptoms and Diagnosis Methods for Diabetes:**
diabetes can be identified by based on symptoms, intensity and type of diabetes.in un tretaeted diabates minly charcterizatbon of disease is done by high glucose levels this fluctation leads to blurred vision and in soome cases high glucose level result in coma and sometimes may be to death. Symptoms includes frequent urination and glucose is lost in urine followed by loss of water from body and thirst. Patient also suffers from appetite, increase in food intake and loosing of body weight. Nausea vomiting are common sufferings. Diabeient loose immunity over skin, bladder and vagiinal infecions. Diaetes is diagnosed early in he moring through FPG method where meassuremnt of fasing plasama glucose level is done. According to calculation paient havinh 100mg/dI is normal, having range of 100 to 125mg/dI are noted as pre-diabetic and above the 125mg/dI is diabetic [24].

**Drugs Controlling Diabetes Mellitus and their mechanism of action:**
The common strategy for treatment focused mainly on regulating and decreasing blood sugar to fall within the normal level. The main mechanisms in both traditional and Western medicines involve decrease blood sugar through stimulating pancreatic β-cells; inhibiting other hormones elevating blood sugar; increasing the affinity, and sensitivity of insulin receptor. On the other hand, lowering glycogen release; enhancing glucose utilization within many tissues and organs; clearing free radicals, resisting lipid peroxidation, correction of the lipid and protein metabolic disorders and improving human blood circulation are also involved [25].

The present oral antidiabetics include sulfonyl ureas that decrease blood sugar, mainly by elevating insulin release from islets of Langerhans. They combine with sulfonylurea receptor on β-cells resulting in adenosine triphosphate–dependent potassium channels closure. Medication includes anti-diabetic drugs

ex sulfonyl urea, this receptor binds to β-cells receptor results in closure of adenosine triphosphate-dependent potassium channels finally regulates insulin from islets of langerhans and reduce blood suagr levels. Depolarisation of cell memberane leads to influx of calcium due to insulin secreation by granular cells in presence of insulin. Consequently, the cell membrane depolarizes and the subsequent calcium influx accompanied by secretion of stored insulin from secretory granules within the cells occurs. This mechanism works only in the presence of insulin [26].

The alpha-glucosidase inhibitors "starch blockers" inhibit certain enzymes responsible for the breakdown of carbohydrates in the small intestine. They act mainly by decreasing the rate of carbohydrate absorption in the body. Moreover, acarbose, an important example in this class, reversibly inhibits both pancreatic α-amylase and α-glucosidase enzymes by binding to the carbohydrate-binding region and interfering with their hydrolysis into mono-saccharides. This results in a slower absorption together with a reduction in postprandial blood-sugar levels [28].

Another known drug is the biguanides; they reduce hepatic gluconeogenesis and replenish peripheral tissues' sensitivity to insulin through elevating insulin-stimulated uptake and utilization of sugar. However, biguanides are ineffective in insulin absence. The best example of this class is metformin [27].

The most important class of oral antidiabetic agents is the thiazolidinediones (TZDs). Their main mechanism of action includes muscle improvement and sensitivity of adipose tissue to insulin and to a smaller extent; liver glucose production is reduced. TZDs are potent and selective agonists to the nuclear peroxisome proliferator activated receptor-gamma (PPARγ) present in liver, skeletal muscle and adipose tissue. Receptor stimulations controls the transcription of insulin-responsive genes mainly in the transport regulation, production and utilization of glucose. Moreover, it was shown that TZDs can improve β- cell function by lowering free fatty acids levels that play an ultimate role in β-cell death [29].

Another last class of oral hypoglycemics are commonly available non-sulfonyl ureas secretagogues. Secretion of insulin from active β-cells is increased by this group and mechanism is

similar as sulfonyl ureas, but they bind to different β-cells receptors [30].

## Conclusion

Our intention in present paper is to discuss about the diabetes and its problems, epidemiology, diagnostic methods, suitable therapies and study of plants with anti-diabetic potential screened in the streptozotocin-induced diabetic rat model. There is need of investigating and evaluation of plants with its mechanism for anti diabetic activity because some of them may be toxic in nature when consumed Some of the plants have proven for having hypoglycemic effects and anti-diabetic activity When compared with standard drug. There is deficiency in scientific and clinical data which is important to check its safety and efficacy so the importance of plants in medicine is decreased so, clinical research is conducted for safety side, Like simple bioassays are developed for biological standardization, Evaluation of pharmacological and toxicological, and various animal models are developed for toxicity and safety evaluation are also useful for the scientific validation of herbal drugs. It is also prominent to separate and test the active components from the plant extracts to get better treatment options compared to the traditional methods, which can be used for the treatment of various type of disorder including diabetes mellitus.

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