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A REVIEW OF THE ROLE OF MEDICINAL PLANTS IN DIABETES MELLITUS MANAGEMENT

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ABSTRACT

Diabetes mellitus (DM), commonly referred to as diabetes, encompasses a group of metabolic disorders characterized by elevated blood sugar levels. This condition arises either due to insufficient insulin production by the body or the inability of cells to respond adequately to insulin. The classic symptoms include polyuria (frequent urination), polydipsia (increased thirst), and polyphagia (increased hunger). Traditionally, diabetes is categorized into three main types: Type 1 DM, also known as insulin-dependent diabetes mellitus (IDDM), where the body fails to produce insulin, necessitating insulin injections or the use of insulin pumps. This type is often referred to as "juvenile diabetes." Type 2 DM, or non-insulin-dependent diabetes mellitus (NIDDM), results from insulin resistance, where cells do not utilize insulin effectively, with or without an absolute insulin deficiency. This type was previously termed "adult-onset diabetes." The third type is gestational diabetes, occurring when women develop high blood glucose levels during pregnancy, which may precede the development of type 2 DM. Current pharmacotherapy options for managing diabetes mellitus include insulin and oral hypoglycemic agents. These medications work by either enhancing insulin secretion from the pancreas or reducing plasma glucose concentrations, thereby increasing glucose uptake and decreasing gluconeogenesis. However, these treatments do not restore normal glucose homeostasis and typically require lifelong administration. Several herbal remedies have shown efficacy due to their beneficial constituents in treating diabetes and its complications. This review discusses the classification of diabetes, management goals, and both synthetic and herbal treatments for diabetes mellitus.

Keywords: Insulinoma, hyperinsulinemia, adiponectin, Momordica charantia.

INTRODUCTION

Diabetes mellitus (DM) is the most prevalent endocrine disorder globally, affecting approximately 100 million people (6% of the population). It arises from inadequate insulin production by the pancreas, leading to fluctuations in blood glucose levels. Diabetes mellitus is associated with damage to multiple biological systems, including blood vessels, eyes, kidneys, heart, and nerves [1].

There are two main types of diabetes mellitus: insulin-dependent diabetes mellitus (IDDM, Type I) and non-insulin-dependent diabetes mellitus (NIDDM, Type II). Type II diabetes is characterized by peripheral insulin resistance and impaired insulin secretion, while Type I diabetes involves an autoimmune response targeting insulin-secreting cells in the pancreas [2].

Diabetes mellitus significantly increases the risk of various complications, including peripheral and cardiovascular diseases, stroke, neuropathy, renal failure, retinopathy, blindness, and limb amputations [3]. Treatment primarily focuses on symptom management and prolonging life expectancy by mitigating risk factors and preventing long-term diabetic complications.

For individuals with Type I diabetes, insulin replacement therapy is essential, whereas Type II diabetes management typically involves dietary adjustments and lifestyle modifications [4]. Additionally, hypoglycemic medications such as biguanides and sulfonylureas are commonly used to treat diabetes. However, these drugs are not without drawbacks, as they may cause harmful side effects and diminish in effectiveness over prolonged use [5].

One significant limitation of current medications is their potential for adverse effects, necessitating continuous administration [6]. Globally, medicinal plants and their bioactive constituents are utilized for diabetes treatment, particularly in regions with limited access to conventional anti-diabetic medications[7].

Table of List:

s.no	Name of the plant	Common name	Family	Used
1.	Pterocarpus santalinus	Red sandalwood	Fabaceae	ameliorates diabetes mellitus via anti-inflammatory pathways and enhancement of insulin function.
2.	Brassica juncea	Chinese mustard	Brassicaceae	mentioned in Ayurveda for treatment of diabetes
3.	Swertia punicea	Ganyancao and Zihong	Gentianaceae	to cure Fever and diabetics Mellitus
4.	Gymnemasylvestre	Gurmar	Asclepiadaceae	in the control of blood glucose in insulin-dependent diabetes mellitus
5.	Ricinus communis	Costor oil plant	Euphorbiaceae	used in traditional medicine such as abdominal disorders, arthritis, backache, muscle aches, bilharziasis, chronic backache and sciatica, chronic headache, constipation,
6.	Combretum micranthum	Kinkeliba	Combretaceae	use Combretum micranthum for high blood pressure, stomach upset, and many other conditions

Classification of Diabetes Mellitus

The classification of diabetes mellitus was initially established by the World Health Organization in 1980 [8], with subsequent updates in 1985 [9]. The focus of this classification is on primary or idiopathic diabetes mellitus, which is the most prevalent and

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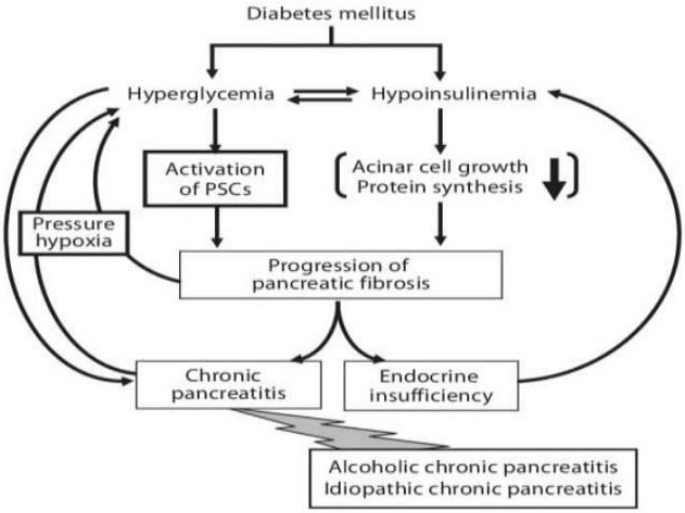
significant type. It distinguishes between primary diabetes mellitus and secondary diabetes mellitus, which includes hyperglycemia resulting from pancreatic islet cell destruction due to various known causes such as inflammatory pancreatic disorders, hemochromatosis, surgery, tumors, and specific acquired or inherited endocrinopathies [10].

This classification system encompasses different forms of hyperglycemia, along with clinical stages and etiological types of diabetes mellitus. The type of diabetes a person has is often determined by the conditions present at the time of diagnosis, although some individuals may present with characteristics that do not neatly fit into a single class. Hyperglycemia is a common feature across a wide range of conditions that collectively constitute primary diabetes mellitus.



Insulin Dependent Diabetes Mellitus (Type 1 IDDM)

Formerly known as juvenile-onset or ketosis-prone diabetes, insulin-dependent diabetes mellitus (IDDM), or type 1 diabetes mellitus, is characterized by autoimmune destruction of pancreatic beta-cells. This type of diabetes is predominantly observed in children and young adults, often presenting abruptly and sometimes fatally [16]. Patients may also exhibit symptoms of other autoimmune disorders like Addison's disease, Hashimoto's thyroiditis, or Graves' disease.

Autoantibodies such as anti-glutamic acid decarboxylase (GAD), islet cell antibodies, or insulin antibodies are typically present in type 1 diabetes, reflecting the autoimmune mechanisms that lead to beta-cell death. The rate of beta-cell destruction varies widely among individuals, with some experiencing rapid loss and others a slower decline. As a consequence of this pancreatic beta-cell loss, insulin secretion is severely diminished or absent, necessitating insulin therapy.

Upon initial diagnosis of fasting diabetic hyperglycemia, 85–90% of individuals with type 1 diabetes exhibit markers of immune destruction, such as islet cell autoantibodies, insulin autoantibodies, and glutamic acid decarboxylase (GAD) autoantibodies. While the exact cause of diabetes mellitus remains uncertain, it is associated with autoantibodies that target and damage beta-cell islets.

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Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) refers to the onset of glucose intolerance during pregnancy, either for the first time or detected during routine screening. It encompasses women who develop type 1 diabetes mellitus during pregnancy and those with previously undiagnosed asymptomatic type 2 diabetes mellitus discovered during pregnancy. This condition, if not clearly identified as diabetes before pregnancy, is termed gestational diabetes mellitus (GDM). Children born to mothers with gestational diabetes mellitus are at increased risk of obesity and type 2 diabetes later in life, which is attributed to intrauterine exposure to hyperglycemia. GDM typically manifests during pregnancy and resolves after childbirth.

Other Specific Types (Monogenic Types)

Monogenic types of diabetes include mutations in hepatocyte nuclear factor (HNF)-1a, a liver-specific transcription factor located on chromosome 12, which is the most common form of monogenic diabetes. These genetic abnormalities, also known as beta cell genetic defects, often lead to early-onset hyperglycemia, typically before the age of 25. They are collectively referred to as maturity-onset diabetes of the young (MODY). Other specific types include maturity-onset diabetes in youth, insulin action defects, exocrine pancreas diseases associated with other endocrinopathies (such as acromegaly), and pancreatic dysfunction resulting from medications, chemicals, or infections.

These specific types collectively account for less than 10% of all diabetes mellitus cases.
The review was conducted by thoroughly searching various research articles and patents from online journals including PubMed, Google Scholar, ScienceDirect, and others. Scientific literature on validated plants with significant antidiabetic properties was collected.

Pterocarpus santalinus (Fabaceae)

Pterocarpus santalinus, commonly known as red sandalwood, is widely distributed across South India. It contains a variety of chemical constituents such as triterpenoids, flavonoids, anthocyanins, saponins, tannins, phenols, and carbohydrates. The primary active compound in the plant is santalin. Additionally, it includes pterocarpol, pterocarptriol, ispterocarpolone, pterocarpo-diolones, cryptomeridol, and β-eudeslol. The plant serves as an astringent tonic, aphrodisiac, antihelmintic, and antidiabetic agent, and is also used to treat ulcers and inflammation traditionally. Several studies have highlighted its antidiabetic properties, with reports that the ethanolic fraction of the plant exhibited hypoglycemic effects at a dose of 0.25 g/kg body weight/day. Halim and Mishra reported that streptozotocin-induced diabetic rats treated with an aqueous extract of the plant at a dose of 250 mg/kg, along with vitamin E, showed significant reduction in blood glucose levels.

Brassica juncea (Brassicaceae)

Brassica juncea, commonly known as Chinese mustard or brown mustard, is widely distributed in Asia, North America, Europe, and Africa. It contains significant chemical elements including triterpenes, saponins, alkaloids, and flavonoids. Pharmacologically, it exhibits properties such as antiscorbutic, diuretic, stimulant, stomachic, antihelmintic, antidysenteric, diaphoretic, and antiarthritic effects. In streptozotocin-induced diabetic male

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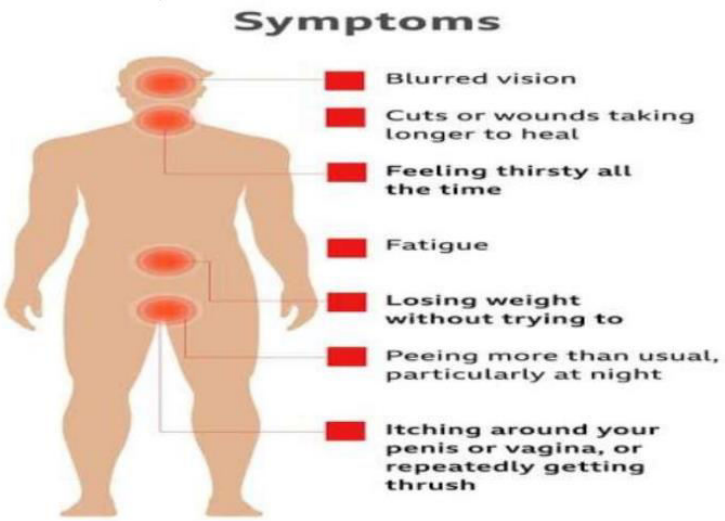
albino rats, the aqueous seed extract of the plant demonstrated potent hypoglycemic activity at doses of 250 mg/kg, 350 mg/kg, and 450 mg/kg, as reported by Thirumalai T et al.

Symptoms and causes of Diabetes

Increased thirst and urination;



Ketones, which result from the breakdown of muscle and fat due to insufficient available insulin, can be detected in the urine.

Pharmacological treatments for diabetes

Sulfonylureas: Sulfonylureas were among the first oral hypoglycemic drugs widely used, as referenced. They work by binding to specific sulfonylurea receptors on pancreatic β-cells, thereby stimulating insulin production. It is recommended to take them 15 to 30 minutes before meals.

Meglitinide analogues: Repaglinide and netaglinide are non-sulfonylurea insulin secretagogues that belong to the meglitinide analogues. Derived from benzoic acid, these compounds enhance insulin secretion by binding to distinct receptor sites on β-cells that are non-sulfonylurea in nature.

Biguanides, such as Metformin, Phenformin, and Buformin, enhance peripheral glucose uptake, particularly in skeletal muscle, and reduce hepatic glucose production. Metformin is the most commonly prescribed medication for type 2 diabetes in children and adolescents.

Alpha-glucosidase inhibitors: Alpha-glucosidase is an enzyme located in the brush border of the small intestine that breaks down oligosaccharides and disaccharides into monosaccharides. Drugs like acarbose competitively inhibit this enzyme. The initial dosage is typically 25–50 mg once daily, which may be increased to 50 mg two or three times daily, to be taken immediately after meals.

Thiazolidinediones (Glitazones): These agents enhance insulin sensitivity in skeletal muscle and adipose tissue while also inhibiting hepatic glucose production. Pioglitazone has partial PPAR-alpha agonist activity and is usually taken once daily at doses ranging from 15 to 45

mg. Rosiglitazone is taken once or twice daily, with doses ranging from 2 to 8 mg. It typically takes 2 to 4 weeks for these medications to become effective.

Causes of Diabetes Mellitus

Diabetes mellitus can arise from various abnormalities and disturbances in β-cell function, leading to inadequate responses to increased glucose levels or relative β-cell insufficiency. This ultimately results in reduced insulin secretion and potential β-cell failure.

1. **Diminished insulin sensitivity:** This can occur due to down-regulation of insulin receptors in peripheral tissues, reducing the number of functional receptors. Despite normal glycemic levels, individuals may exhibit hypersensitivity to insulin and hyperinsulinemia, often associated with dyslipidemia, hyperuricemia, and abdominal adiposity. Relative insulin resistance is particularly evident in the liver, muscle, and fat tissues, potentially contributing to angiopathy.
2. **Excessive glucagon and obesity:** High levels of glucagon, a hormone that increases blood glucose, coupled with obesity, can lead to a relative deficiency of insulin production by β-cells. Anomalies in nitric oxide metabolism have also been implicated, affecting perineural blood flow and contributing to nerve damage.
3. **Genetic factors:** Certain genetic disorders such as maturity-onset diabetes of the young (MODY), other endocrine disorders, history of pancreatectomy, and gestational diabetes mellitus (GDM) can predispose individuals to diabetes mellitus.
4. **Specific receptor imbalances:** Imbalances in specialized receptors such as the glucagon-like peptide-1 (GLP-1) receptor, peroxisome proliferator-activated receptor gamma (PPARγ), beta3 (ß3) adrenergic receptor, and various enzymes like α-glycosidase and dipeptidyl peptidase IV (DPP-IV) enzyme can contribute to the pathogenesis of diabetes mellitus.
5. **Advanced glycation-end products and oxidative stress:** Current research is focused on understanding the role of advanced glycation-end products, protein kinase C, oxidative stress, and the polyol pathway in diabetic neuropathy. These mechanisms highlight the complex interplay of metabolic and biochemical processes involved in diabetes mellitus.

Diagnosis of Diabetes Mellitus

Diagnosing diabetes mellitus requires careful consideration, especially since it has significant lifelong implications for patients. It is crucial not to diagnose diabetes based solely on a single abnormal blood glucose reading in asymptomatic individuals. Various diagnostic tests are available, including blood sugar tests, urine sugar tests, glucose tolerance tests, renal glucose threshold tests, tests for reduced, increased, and renal glycosuria, cortisone-stressed glucose tolerance tests, intravenous glucose tolerance tests, and oral glucose tolerance tests.

Treatment of Diabetes Mellitus

The primary goal of treating diabetes mellitus is to address the underlying causes and manage insulin therapy effectively. Once the condition is stabilized, insulin requirements typically return to normal levels. The management of diabetes mellitus aims to achieve the following objectives:

1. Normalize the disrupted metabolism of the diabetic individual while ensuring their comfort and safety.
2. Prevent or delay the progression of short-term and long-term complications associated with the disease.
3. Empower patients with the knowledge, motivation, and resources necessary for informed self-care.

Types of Therapy Involved in Diabetes Mellitus

1. **Stem cell therapy:** Recent studies suggest that persistent inflammation and insulin resistance in patients with type 2 diabetes mellitus (T2DM) may be primarily attributed to monocytes and macrophages. Stem cell educator therapy is a novel approach aimed at modulating or correcting immunological dysfunctions. This therapy involves a closed-loop system where blood is collected from patients, lymphocytes are purified from the whole blood, adherent cord blood-derived multipotent stem cells (CB-SCs) are co-cultured with purified lymphocytes in vitro, and the educated lymphocytes (not the CB-SCs) are subsequently infused back into the patient's circulation.
2. Antioxidant Therapy

Patients diagnosed with type 2 diabetes often undergo treatment to manage oxidative stress through various antioxidants, including vitamins, plant-derived active ingredients, supplements, and medications with antioxidant properties. Key supplements such as Vitamins C, E, and β-carotene are particularly effective in mitigating oxidative stress and its associated complications. Antioxidants play a critical role in lowering the risk of diabetes and its related health issues.

B. Dietary Management

Appropriate energy intake is essential for both diabetic and non-diabetic individuals, emphasizing adherence to specific dietary guidelines such as:

1. Maintaining a well-balanced diet rich in fats, proteins, and carbohydrates, with careful attention to carbohydrate intake.
2. Striving for consistency to achieve a diet close to normal.
3. Regularly spacing meals evenly throughout the day in terms of portion sizes.
4. Reducing total calorie consumption by moderating both fat and carbohydrate intake.
5. Encouraging patients to maintain consistent dietary habits daily.

C. **Newer Insulin Delivery Devices**

Significant advancements have been made to enhance precise glucose control and simplify insulin delivery. These innovations include pen devices, insulin syringes, implantable insulin pumps, inhaled insulin, and various methods of insulin administration.

D. **Oral Hypoglycemic or Antidiabetic Agents**

The development of clinically effective drugs began in 1957 with the introduction of the biguanide phenformin alongside sulfonylureas. Continuous research has led to newer

strategies such as dipeptidyl peptidase-4 (DPP-4) inhibitors, thiazolidinediones, meglitinide analogues, α-glucosidase inhibitors, and other emerging therapies.

Important Features of Oral Hypoglycemic Agents

Diabetes mellitus is recognized as a prevalent condition with significant impacts on morbidity, mortality, and quality of life. It can also be a complication of Cushing syndrome, resulting from prolonged exposure to glucocorticoids. This condition presents with various clinical symptoms including central obesity, proximal muscle weakness, hirsutism, neurophysiological disturbances, autonomic neuropathy, gastrointestinal problems, and dental issues.

CONCLUSION

Diabetes mellitus encompasses a range of metabolic disorders characterized by elevated blood glucose levels if left untreated. Type 1 diabetes results from the autoimmune destruction of insulin-producing beta cells in the pancreas, leading to insufficient insulin production. In contrast, type 2 diabetes involves autoimmune attacks on the pancreas and/or insulin resistance, where the pancreas may still produce normal or excessive amounts of insulin. The primary objective of diabetes management is to normalize carbohydrate metabolism as much as possible. Individuals with type 1 diabetes require insulin replacement therapy through injections or tablets to manage their absolute insulin deficiency. Type 2 diabetes, which involves insulin resistance, can often be managed with dietary adjustments and exercise. Additional goals of diabetes management include preventing or mitigating complications arising from the disease and its treatment.

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