

## **MEDICINAL PLANTS FOR THE TREATMENT OF DIABETES MELLITUS: A COMPREHENSIVE REVIEW**

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### **Abstract**

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The increasing global prevalence of diabetes, coupled with the limitations and adverse effects associated with conventional antidiabetic therapies, has intensified interest in alternative and complementary treatment approaches. Medicinal plants have been used traditionally across various healthcare systems for the prevention and management of diabetes and its associated complications. This comprehensive review aims to summarize current knowledge regarding medicinal plants with demonstrated antidiabetic potential, their bioactive constituents, mechanisms of action, and supporting preclinical and clinical evidence. A wide range of plant species, have shown promising antihyperglycemic effects through multiple pathways such as enhancement of insulin secretion, improvement of insulin sensitivity, inhibition of carbohydrate-digesting enzymes, modulation of glucose uptake, antioxidant activity, and protection of pancreatic  $\beta$ -cells. Phytochemicals including flavonoids, alkaloids, terpenoids, saponins, phenolic compounds, and glycosides play significant roles in mediating these therapeutic effects. Although numerous experimental studies support the efficacy of medicinal plants, further well-designed clinical trials, standardization of herbal formulations, and comprehensive safety evaluations are necessary to establish their therapeutic potential and facilitate their integration into evidence-based diabetes

management. Medicinal plants represent a valuable source of novel antidiabetic agents and offer promising opportunities for the development of safer, affordable, and effective treatment strategies.

**Keywords:** Diabetes mellitus, medicinal plants, phytochemicals, antidiabetic activity, herbal medicine, hyperglycemia, pancreatic  $\beta$ -cells.

## Introduction

Diabetes mellitus (DM) has become a major worldwide healthcare concern due to its sharp increase in occurrence (Rodriguez, 2023). DM affects people of all ages, socioeconomic backgrounds, and demographic subgroups in nearly every country on the planet. Although DM affects everyone on the earth, both its incidence and death rates are gradually rising. Its incidence is highest in Low to Middle Income Countries (LMICs) (Sidahmed *et al.*, 2023). Ancient peoples recognized illnesses that shared the characteristics of DM. Determining the causes of hyperglycemia through study was made possible by the realization that diabetes was not a single illness (Tattersall and Matthews, 2024).

DM is now recognized as an illness that exhibits the “iceberg” phenomenon, meaning that the number of documented instances represents just a small portion of the enormous number of unidentified cases. It is a chronic illness stemming from either inadequate synthesis of insulin by the pancreas or inefficient utilization of that production by the body (Punthakee *et al.*, 2018). Uncontrolled diabetes frequently results in hyperglycemia, or elevated blood glucose, which over time seriously damages numerous bodily systems, including the blood vessels and neurons (Bishu *et al.*, 2019).

## Classification of Diabetes Mellitus

### A] Insulin dependent diabetes mellitus (Type 1 diabetes mellitus)

Type 1 diabetes mellitus, also known as autoimmune diabetes or previously referred to as juvenile-onset or ketosis-prone diabetes, is a condition where the body's immune system attacks and damages the insulin-producing beta cells in the pancreas. This type of diabetes is commonly diagnosed in children and young adults, with a sudden and potentially life-threatening onset. People with Type 1 diabetes often have other autoimmune disorders, such as Graves' disease, Hashimoto's thyroiditis, and Addison's disease (Jun and Yoon, 2002; Boney *et al.*, 2005). It's characterized by the presence of

specific antibodies like anti-glutamic acid decarboxylase, islet cell, or insulin antibodies, which signify the autoimmune process responsible for the destruction of beta cells (American Diabetes Association, 2014).

The rate of beta-cell destruction can vary from person to person, happening rapidly in some and slowly in others. As a result of this destruction, there is a severe deficiency or absence of insulin secretion, necessitating the use of insulin injections for treatment.

Typically, individuals with Type 1 diabetes have markers of immune destruction, such as islet cell auto-antibodies, auto-antibodies to insulin, and auto-antibodies to glutamic acid decarboxylase (GAD), present when fasting diabetic hyperglycaemia is initially detected, occurring in about 85-90% of cases. Although the exact cause of diabetes mellitus remains uncertain, in most cases, there is evidence of an autoimmune mechanism at play (Alberti and Zimmet, 1998).

### **B] Non-insulin dependent diabetes mellitus (Type 2 Diabetes Mellitus)**

Type 2 diabetes mellitus, which is also called adult-onset diabetes, is a disease where your body has trouble using insulin, a hormone that helps control your blood sugar (American Diabetes Association, 2014). People with this type of diabetes often have a hard time with insulin's job (Jacob, 1987; Blood *et al.*, 1975; Kumar, 1992). Over time, it can lead to problems with blood vessels, kidneys, eyes, and nerves, and these issues can make people sick or even cause them to pass away because of diabetes. There are many reasons why someone might get type 2 diabetes, like being overweight, not getting enough exercise, getting older (especially for middle-aged and older folks), or it could be in their genes (Ross and Wilson 2010). People with this type of diabetes also have a higher chance of having big or small blood vessel problems, which can be really serious (Tripathi, 2013; Dyck *et al.*, 1993).

### **C] Gestational Diabetes Mellitus**

Gestational diabetes mellitus (GDM) is a type of diabetes that can occur for the first time or be diagnosed during pregnancy. It includes women who develop Type 1 diabetes during pregnancy and those with undiagnosed, symptom-free Type 2 diabetes that's found during pregnancy. GDM is a form of diabetes diagnosed during pregnancy, but it might not continue after the baby is born. Over time, children born to mothers with GDM have a higher chance of becoming overweight and developing type 2 diabetes

when they grow up. This increased risk is linked to exposure to high blood sugar levels while they were in the womb (Waugh and Grant, 2010; Harris, 1993).

### **Pathophysiology of diabetes mellitus**

Type 2 diabetes mellitus is characterized by inadequate insulin secretion and insulin resistance from beta cells of pancreas. This cause increase in the breakdown of fat and decrease glucose levels in circulation, liver, muscle cells and fat cells (Duggan and Chen, 2019; Ivana *et al.*, 2022).

#### **A] Type 1 Diabetes**

Type 1 diabetes is characterized by the autoimmune destruction of insulin-producing beta cells in the pancreas. This process begins when a genetic predisposition is triggered by environmental factors, such as viral infections. Immune cells mistakenly recognize beta cells as foreign invaders, launching an autoimmune attack that leads to their destruction. As a result, insulin production decreases or ceases entirely. Without sufficient insulin, glucose cannot enter cells for energy, leading to hyperglycemia. The lack of insulin in type 1 diabetes causes several pathophysiological effects: Hyperglycemia: Elevated blood glucose levels result from the inability to transport glucose into cells. Ketosis: In the absence of insulin, the body breaks down fat for energy, producing ketones, which can lead to diabetic ketoacidosis. Gluconeogenesis: The liver produces excess glucose, further contributing to hyperglycemia (McIntyre *et al.*, 2019).

#### **B] Type 2 Diabetes**

Type 2 diabetes primarily involves insulin resistance and impaired insulin secretion. Genetic factors play a significant role, but environmental factors like obesity and sedentary lifestyles are crucial contributors. Insulin resistance means that body cells do not effectively respond to insulin, requiring the pancreas to produce more insulin to maintain glucose control.

#### **Pathophysiological processes in type 2 diabetes include**

- **Insulin Resistance:** Cells, especially in muscle, liver, and adipose tissue, become resistant to insulin's signaling, making it challenging for glucose to enter cells.

- **Beta Cell Dysfunction:** Over time, the pancreas may not produce enough insulin, or the insulin it produces is less effective.
- **Excess Gluconeogenesis:** The liver continues to produce glucose, contributing to hyperglycemia.
- **Incretin Hormone Dysregulation:** Disruption in hormones like glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) affects insulin secretion and glucose control.
- **Lipotoxicity:** Increased fat deposits in muscle and liver cells lead to impaired insulin action.
- **Chronic Inflammation:** Inflammation, often linked to obesity, further exacerbates insulin resistance. Both types of diabetes can lead to a range of complications, including cardiovascular issues, kidney disease, neuropathy, and retinopathy, all stemming from prolonged hyperglycemia and its effects on blood vessels and various tissues. Understanding the complex pathophysiological processes involved in diabetes is critical for developing effective treatment strategies and preventive measures (Griffiths and Rossini, 1975).

## Epidemiology

Globally, 1 in 11 adults has DM (90% having T2DM). The onset of T1DM gradually increases from birth and peaks at ages 4 to 6 years and then again from 10 to 14 years. Approximately 45% of children present before age ten years. The prevalence in people under age 20 is about 2.3 per 1000 (Felner *et al.*, 2005; Marcovina *et al.*, 2007; Gale and Gillespie, 2001). While most autoimmune diseases are more common in females, there are no apparent gender differences in the incidence of childhood T1DM. In some populations, such as in older males of European origin (over 13 years), they may be more likely to develop T1DM compared to females (3:2 male to female ratio). The incidence of T1DM has been increasing worldwide. In Europe, Australia, and the Middle East, rates are rising by 2% to 5% annually. In the United States, T1DM rates rose in most age and ethnic groups by about 2% yearly, and rates are higher in Hispanic youth. The exact reason for this pattern remains unknown. However, some metrics, such as the United States Military Health System data repository, found plateauing over 2007 to 2012 with a prevalence of 1.5 per 1000 and incidence of 20.7 to 21.3 per 1000 (Mamoulakis *et al.*, 2003; Tuomilehto, 2013; Patterson *et al.*, 2009).

The onset of T2DM is usually later in life, though obesity in adolescents has led to an increase in T2DM in younger populations (Vehik *et al.*, 2007; Rush *et al.*, 2018). T2DM has a prevalence of about 9% in the total population of the United States, but approximately 25% in those over 65 years. The International Diabetes Federation estimates that 1 in 11 adults between 20 and 79 years had DM globally in 2015. Experts expect the prevalence of DM to increase from 415 to 642 million by 2040, with the most significant increase in populations transitioning from low to middle-income levels (Zheng *et al.*, 2018).

T2DM varies among ethnic groups and is 2 to 6 times more prevalent in Blacks, Native Americans, Pima Indians, and Hispanic Americans compared to Whites in the United States (Harris *et al.*, 1998). While ethnicity alone plays a vital role in T2DM, environmental factors also greatly confer risk for the disease. For example, Pima Indians in Mexico are less likely to develop T2DM compared to Pima Indians in the United States (6.9% vs. 38%) (Carter *et al.*, 1996; Schulz *et al.*, 2006).

## Diagnosis

Understanding your blood work results is crucial in monitoring your health. There are various tests that can help diagnose diabetes. The fasting glucose test measures your blood sugar after a period of not eating. If it's equal to or greater than 126mg/dl, it might indicate diabetes, especially if you have other symptoms. (American Diabetes Association). The random glucose test, on the other hand, doesn't require fasting and a result of 200 mg/dl or higher, along with other symptoms, can diagnose diabetes (American Diabetes Association) (Murata *et al.*, 2017).

The two-hour oral glucose tolerance test involves drinking a sugary solution to see how your body handles glucose. In diabetics, either there's not enough insulin or your cells don't respond well to it, leading to high blood sugar levels. This test requires two confirmatory tests. The Haemoglobin A1c test is another important tool, reflecting your average blood sugar levels over three months by measuring glycated haemoglobin. This is because red blood cells live for about three months, and haemoglobin is found in them. This observation suggests that once an individual's A1C level reaches or exceeds 6.5%, or when their FPG and 2-h PG values cross their respective diagnostic threshold indicating the clinical importance of these diagnostic markers in monitoring and

managing diabetes-related Complications (American Diabetes Association) (Ansari and Rasheed, 2010).

Additionally, doctors might also consider checking for specific antibodies like anti-islet cell antibodies, anti-glutamic acid antibodies, and anti-insulin antibodies, especially when assessing your age and risk factors. These antibodies can provide valuable insights into your body's immune response and help in determining the likelihood of developing diabetes. Understanding your blood work and considering antibody tests can be instrumental in managing your health (Poznyak *et al.*, 2020).

## Complications

Microvascular complications such as retinal degeneration, nephropathy, and neuropathy fall under the category of diabetes-related complications, while macrovascular problems such as coronary artery disease (CAD), peripheral vascular disease (PVD), and cerebrovascular events (CVA) fall under the category of diabetes-related complications (Jialal and Singh, 2019).

**I] Retinopathy:** A well-known consequence of both type 1 and type 2 diabetes mellitus is diabetic retinal damage (DR), which has been reported to appear in almost all cases of type 1 and 75% of cases of type 2 diabetes after fifteen years of insulin. DR is divided into proliferative diabetes-related retinopathy (PDR) and non-proliferative diabetic retinopathy (NPDR), also known as background retinopathy. Microaneurysms and retinal hemorrhages are the initial obvious symptoms of NPDR, which is characterized by vascular closure. The development of cotton-wool patches, vein beading, and intraretinal endothelial anomalies are all symptoms of increasing capillary nonperfusion. PDR is characterized by the creation of fresh arteries on the inner retina and posterior surface of the vitreous, this happens with continued retinal ischemic (Kesavadev *et al.*, 2020).

**II] Nephropathy:** Nephritis is the main cause of protracted renal failure. The first symptom is microalbuminuria, which may be identified by calculating the ratio of albumin to creatinine in a random spot sample. Microalbuminuria is more prevalent in type 2 DM patients than in type 1 DM patients. A 24-hour urine collection approach indicates that the unexpected outcome for microalbuminuria is 150–300 mg/day, but the abnormal value for macroalbuminuria is higher than 300 mg/day.

Even though diabetic nephropathy can be divided into stages: both microscopic and macro levels of albumin based on information about albumin from the urine excretion, the risk for developing diabetic nephropathy and cardiovascular disease starts even when the elimination of albumin from values are below the normoalbuminuric assortment (Sarella *et al.*, 2023).

**III] Cardiovascular Diseases:** Cardiovascular illness is to blame for as much as 65 percent of diabetics' mortality.<sup>31</sup> ischemic heart disease and stroke are the main causes of diabetes-related morbidity. As was already noted, patients with diabetes have mortality rates from cardiac disease that are 2 to 4 times higher than those without diabetes. Additionally, diabetics have a two to four times higher chance of getting a stroke than non-diabetics.

Over 70% of people with diabetes have hypertension or use medication to control it. How diabetes patients' hyperglycemia influences cardiovascular issues is unclear. The same factors that put non-diabetics at risk for coronary artery disease apply to diabetics as well, including cigarette smoking, high blood pressure, and raised cholesterol levels (Palermi *et al.*, 2021).

### **Treatment**

Managing diabetes, whether it's Type 1 or Type 2, involves a variety of treatments and precautions to stay healthy. In Type 1 diabetes, the key is insulin. This hormone helps regulate your blood sugar levels, and people with Type 1 diabetes need to take insulin to stay healthy (Colberg *et al.*, 2010).

Type 2 diabetes often starts with making important lifestyle changes. Things like exercise and changes to your diet can help promote weight loss and better blood sugar control. In Type 2 diabetes, often caused by metabolic syndrome, which is linked to obesity and poor diets, various medications can help. Metformin is usually the first choice, but there are other options like GLP-1 agonists, DPP-4 inhibitors, SGLT2 inhibitors, and more. Sometimes, insulin may be needed if multiple medications don't keep blood sugar levels in check (Nasri, 2014).

When you have diabetes, it's crucial to watch out for chronic complications. Neuropathy, which can cause numbness and pain, can be managed with medications like gabapentin and pregabalin, and regular podiatry visits are essential for foot care. Nephropathy,



which affects the kidneys, is treated with medications like ACE inhibitors and ARBs. It's vital to monitor kidney function and check for increased creatinine and blood urea nitrogen in the blood. Regularly checking the amount of albumin in the urine is also important (Tahrani *et al.*, 2016).

For retinopathy, a condition that affects the eyes, medications like VEGF inhibitors can help, and procedures like laser photocoagulation or vitrectomy may be necessary. Regular optometry visits are a must. Atherosclerosis, a condition affecting blood vessels, can be managed with aspirin and monitoring lipid levels. In cases of high atherosclerotic disease risk, a statin may be prescribed to reduce complications (Davari *et al.*, 2020).

Keeping blood sugar levels under control is a top priority. The HbA1c level should be below 7%, and if it's uncontrolled (above 7%), it should be checked every three months. If it's well controlled (7% or less), checking every six months is recommended. Managing diabetes involves a combination of treatments, regular check-ups, and a healthy lifestyle to lead a happy and healthy life (Bakris and Weir, 2002; Davari *et al.*, 2020).

### Herbal medicines used for the treatment of Diabetes Mellitus

The ethnobotanical information reports about 800 plants that may possess antidiabetic potential. Several herbs have shown antidiabetic activity when assessed using presently available experimental techniques.

**Table 1: Medicinal plants having anti-diabetic activity**

| S. No. | Names of plants             | Part used | Mechanism of action | References                        |
|--------|-----------------------------|-----------|---------------------|-----------------------------------|
| 1.     | <i>Alangium lamarckii</i>   | Leaves    | Anti diabetic       | Kumar <i>et al.</i> , (2012)      |
| 2.     | <i>Albizia odoratissima</i> | Bark      | Anti diabetic       | Kumar <i>et al.</i> , (2011)      |
| 3.     | <i>Axonopus compressus</i>  | Leaves    | Anti diabetic       | Ibeh and Ezeaja, (2011)           |
| 4.     | <i>Berberis vulgaris</i>    | Root      | Hypoglycaemic       | Meliani <i>et al.</i> , (2011)    |
| 5.     | <i>Brassica juncea</i>      | Seed      | Hypoglycaemic       | Thirumalai <i>et al.</i> , (2011) |
| 6.     | <i>Caesalpinia digyna</i>   | Root      | Anti diabetic       | Kumar <i>et al.</i> , (2011)      |

|     |                                 |             |                                 |                                     |
|-----|---------------------------------|-------------|---------------------------------|-------------------------------------|
| 7.  | <i>Catharanthus roseus</i>      | Leaf        | Hypoglycaemic                   | Ohadoma and Michael, (2011)         |
| 8.  | <i>Centaurium erythrea</i>      | Leaf        | Anti diabetic                   | Sefi <i>et al.</i> , (2017)         |
| 9.  | <i>Chaenomeles sinensis</i>     | Fruits      | Anti diabetic                   | Sancheti <i>et al.</i> , (2013)     |
| 10. | <i>Cocos nucifera</i>           | Leaf        | Antihyperglycemic               | Naskar <i>et al.</i> , (2012)       |
| 11. | <i>Costus speciosus</i>         | rhizome     | Anti diabetic                   | Eliza <i>et al.</i> , (2009)        |
| 12. | <i>Cyclocarya paliurus</i>      | Bark        | Hypoglycemic                    | Guan <i>et al.</i> , (2011)         |
| 13. | <i>Dillenia indica</i>          | Leaves      | Anti diabetic                   | Kumar <i>et al.</i> , (2011)        |
| 14. | <i>Embelia ribes</i>            | Berries     | Anti diabetic                   | Mahendran <i>et al.</i> , (2006)    |
| 15. | <i>Hybanthus enneaspermus</i>   | Whole plant | Anti diabetic                   | Patel <i>et al.</i> , (2021)        |
| 16. | <i>Lippa nodiflora</i>          | Whole plant | Anti diabetic and Hypolipidemic | Balamurugan and Ignacimuthu, (2011) |
| 17. | <i>Lithocarpus polystachyus</i> | Leaves      | Hypoglycemic                    | Hou <i>et al.</i> , (2011)          |
| 18. | <i>Marrubium vulgare</i>        | Aerial part | Hyperglycemia and dyslipidemia  | Elberry <i>et al.</i> , (2011)      |
| 19. | <i>Ocimum sanctum</i>           | Aerial part | Anti diabetic                   | Patil <i>et al.</i> , (2011)        |
| 20. | <i>Opuntia streptacantha</i>    | Leaves      | Antihyperglycemia               | Cetto and Wiedenfeld, (2011)        |
| 21. | <i>Psidium guajava</i>          | Fruits      | Antihyperglycemia               | Huang <i>et al.</i> , (2011)        |
| 22. | <i>Semecarpus anacardium</i>    | nut         | Anti diabetic                   | Khan <i>et al.</i> , (2012)         |
| 23. | <i>Prosopis glandulosa</i>      | Whole plant | Anti diabetic                   | Georgea <i>et al.</i> , (2011)      |
| 24. | <i>Ophiopogon japonicus</i>     | Root        | Hypoglycemic                    | Chen <i>et al.</i> , (2011)         |
| 25. | <i>Setaria italica</i>          | Seed        | Antihyperglycemic               | Sireesh <i>et al.</i> , (2011)      |
| 26. | <i>Solanum torvum</i>           | Fruits      | Antihyperglycemic               | Gandhi <i>et al.</i> , (2011)       |

## **Conclusion**

Medicinal plants have emerged as promising therapeutic agents for the management of diabetes mellitus owing to their diverse pharmacological activities, wide availability, and long history of traditional use. Numerous plant species possess significant antidiabetic potential through mechanisms such as enhancing insulin secretion, improving insulin sensitivity, inhibiting carbohydrate-hydrolyzing enzymes, promoting glucose uptake, reducing oxidative stress, and protecting pancreatic  $\beta$ -cells. The presence of bioactive phytoconstituents, including flavonoids, alkaloids, phenolic compounds, terpenoids, saponins, and glycosides, contributes substantially to these beneficial effects. Despite encouraging findings from in vitro, in vivo, and limited clinical studies, challenges related to the standardization, quality control, safety assessment, dosage optimization, and validation of herbal preparations remain significant barriers to their widespread clinical application. Therefore, rigorous scientific investigations, well-designed randomized clinical trials, and the development of standardized formulations are essential to establish the efficacy and safety of medicinal plants in diabetes management. In conclusion, medicinal plants represent a valuable reservoir of bioactive compounds with the potential to complement conventional antidiabetic therapies and contribute to the development of novel, cost-effective, and safer treatment options for diabetes mellitus and its associated complications.

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