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Review Article

Recent Advances in Diagnostic and Therapeutic Strategies for Diabetes Mellitus: A Comprehensive Review

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ABSTRACT

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Its global burden continues to escalate, affecting over 540 million individuals as of 2024. This comprehensive review highlights recent developments in the diagnosis and management of diabetes, focusing on both conventional and emerging approaches. Diagnostic innovations include continuous glucose monitoring systems, lab-on-a-chip devices, wearable biosensors, and novel biomarkers such as microRNAs and adipokines, which offer enhanced sensitivity and real-time glycemic profiling. Therapeutically, advancements extend beyond traditional pharmacological interventions—such as insulin, metformin, and sulfonylureas—to include incretin-based therapies, SGLT2 inhibitors, and cardio-renal protective agents. In parallel, plant-based interventions and phytochemicals derived from Momordica charantia, Gymnema sylvestre, Tinospora cordifolia, and others have shown significant antidiabetic activity via multifaceted mechanisms including β-cell preservation, insulin mimetic action, and antioxidative stress modulation. The incorporation of nanotechnology, gene therapy, and stem cell approaches represents a transformative frontier in diabetes care, aiming at disease modification rather than symptomatic control. Despite these promising strides, challenges remain in the form of affordability, health system integration, regulatory oversight, and the need for robust clinical validation, particularly for herbal and nanomedicine-based strategies. This review underscores the importance of a multidisciplinary, patient-centered approach to diabetes management, integrating evidence-based innovations with public health strategies to curb the global impact of the disease.

INTRODUCTION

Diabetes mellitus (DM) is a chronic, progressive metabolic disorder characterized by persistent

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hyperglycemia, resulting from either absolute insulin deficiency, impaired insulin action, or both. The disease manifests in several forms, primarily type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM), and rare monogenic diabetes syndromes. Among these, T2DM accounts for more than 90% of global diabetes cases and is frequently associated with obesity, physical inactivity, and insulin resistance [American Diabetes Association, 2023].

As of 2024, the International Diabetes Federation (IDF) reports that approximately 540 million people are living with diabetes globally, a number projected to exceed 640 million by 2030 and 783 million by 2045, with the most rapid growth occurring in low- and middle-income countries (IDF, 2024). This epidemiological trend has significant implications, not only for healthcare systems but also for socioeconomic development due to the increased burden of diabetes-related morbidity and mortality. Diabetes is a leading cause of cardiovascular disease (CVD), chronic kidney disease, retinopathy, peripheral neuropathy, and lower limb amputations [Zheng et al., 2018].

The pathophysiology of diabetes is complex and multifactorial. In T1DM, autoimmune destruction of pancreatic β-cells results in absolute insulin deficiency. In contrast, T2DM involves a combination of insulin resistance and progressive β-cell dysfunction. GDM, affecting approximately 15% of pregnancies worldwide, arises from insulin resistance induced by placental hormones during gestation and is associated with an increased risk of developing T2DM later in life [McIntyre et al., 2019]. Furthermore, oxidative stress, chronic inflammation, lipotoxicity, and glucotoxicity are known to exacerbate β-cell apoptosis and disrupt glucose homeostasis.

Despite decades of research, diabetes management remains suboptimal for many patients due to delayed diagnosis, inadequate monitoring, therapeutic inertia, and poor adherence. Traditional diagnostic tools, such as fasting plasma glucose (FPG), oral glucose tolerance test (OGTT), and glycated hemoglobin (HbA1c), though widely used, often fail to detect prediabetes or early-stage T2DM, especially in resource-limited settings. Moreover, these tools do not offer real-time monitoring or reflect acute glycemic variability, which is increasingly recognized as an independent risk factor for diabetic complications.

In response, the field of diabetes diagnostics has seen remarkable innovation. Novel biomarkers, including adiponectin, C-peptide, microRNAs, and inflammatory cytokines, are being investigated for their predictive and diagnostic utility [Al-Salam & Ahmad, 2021]. Concurrently, technological advances have led to the development of continuous glucose monitoring systems (CGMs), non-invasive biosensors, lab-on-a-chip platforms, and wearable devices that enable real-time glycemic surveillance and individualized patient management. These innovations promise to shift the diagnostic paradigm toward precision medicine.

Therapeutically, a parallel transformation is underway. While insulin therapy and oral antidiabetic drugs (OADs) such as metformin, sulfonylureas, and thiazolidinediones remain standard treatment modalities, recent decades have witnessed the emergence of targeted therapies. These include dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and sodium-glucose co-transporter-2 (SGLT2) inhibitors, which have demonstrated not only glycemic benefits but also cardiovascular and renal protective effects in

clinical trials [Marso et al., 2016; Zinman et al., 2015].

In addition, complementary and alternative therapies are gaining renewed interest, particularly in the realm of plant-based interventions. Phytochemicals from herbs such as Momordica charantia (bitter melon), Gymnema sylvestre, Ocimum sanctum (holy basil), and Cinnamomum verum (cinnamon) have demonstrated antidiabetic properties via mechanisms such as insulin mimetic activity, enhancement of insulin sensitivity, inhibition of carbohydrate-digesting enzymes, and antioxidant effects [Patel et al., 2012; Khan et al., 2003]. Furthermore, the integration of nanotechnology, gene editing tools (e.g., CRISPR-Cas9), and stem cell therapy represents a futuristic avenue in diabetes care, offering potential for disease modification and even cure.

Given this evolving landscape, it is imperative to provide a comprehensive overview of the most recent advances in both the diagnostic and therapeutic domains of diabetes mellitus. This review aims to synthesize current knowledge on the pathophysiology, emerging diagnostic tools, novel pharmacological and herbal treatment modalities, and the future outlook in diabetes care. In doing so, it underscores the importance of early detection, patient-centered interventions, and translational research to address the global diabetes epidemic.

2. Pathophysiology of Diabetes Mellitus

Diabetes mellitus is not a singular disease but a heterogeneous group of metabolic disorders characterized by hyperglycemia. The underlying mechanisms differ across its various types, each with distinct pathophysiological features, clinical manifestations, and therapeutic approaches.

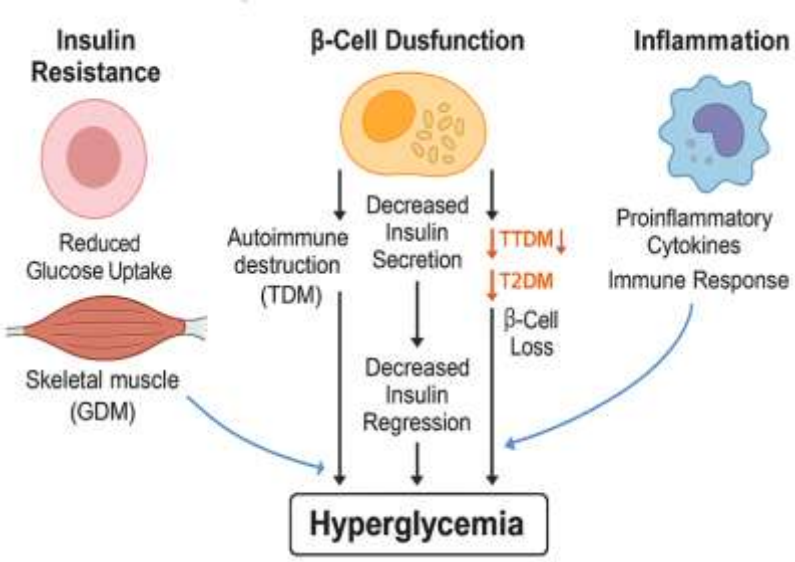


Figure 01: Pathogenesis of Diabetes Mellitus

2.1. Type 1 Diabetes Mellitus (T1DM)

T1DM is an autoimmune disorder resulting from the destruction of insulin-producing β-cells in the pancreatic islets of Langerhans. This process is mediated by autoreactive T lymphocytes, particularly $CD4^+$ and $CD8^+$ cells, and is often associated with the presence of islet-specific autoantibodies such as anti-GAD65, insulin autoantibodies (IAA), and anti-IA-2 (Atkinson et al., 2014). The destruction of β-cells leads to absolute insulin deficiency, necessitating lifelong

exogenous insulin therapy. T1DM typically manifests in childhood or adolescence but may also appear in adults (latent autoimmune diabetes of adults—LADA). Genetic susceptibility (e.g., HLA-DR3/DR4 haplotypes), viral infections, and environmental triggers are implicated in its pathogenesis.

2.2. Type 2 Diabetes Mellitus (T2DM)

T2DM is the most prevalent form of diabetes, characterized by insulin resistance in peripheral tissues—primarily muscle, liver, and adipose tissue—combined with an inadequate compensatory insulin secretory response from pancreatic β-cells (DeFronzo, 2009). Chronic overnutrition, sedentary behavior, obesity, particularly visceral adiposity, and lipotoxicity are key contributors to insulin resistance. Additionally, impaired incretin effect, increased hepatic glucose production, adipokine dysregulation, and low-grade inflammation exacerbate glucose dysregulation.

Importantly, β-cell dysfunction in T2DM is progressive. Initially, β-cells increase insulin output to compensate for resistance, but over time, exhaustion and apoptosis ensue, leading to relative insulin deficiency. The disease course is insidious and may remain asymptomatic for years, contributing to delayed diagnosis.

2.3. Gestational Diabetes Mellitus (GDM)

GDM is defined as glucose intolerance with onset or first recognition during pregnancy. It affects approximately 10–15% of pregnancies worldwide and poses risks to both mother and fetus. The physiological insulin resistance of pregnancy, driven by placental hormones such as human placental lactogen, is normally compensated by β-cell hyperplasia and increased insulin secretion. In women predisposed to β-cell dysfunction, this adaptation is inadequate, resulting in hyperglycemia (McIntyre et al., 2019). GDM increases the lifetime risk of developing T2DM in both the mother and offspring.

2.4. Monogenic and Secondary Forms

Monogenic diabetes, including maturity-onset diabetes of the young (MODY), results from mutations in single genes affecting β-cell development or function (e.g., HNF1A, GCK). These forms are rare, accounting for 1–2% of all diabetes cases, but are important to identify as they often respond to specific oral agents rather than insulin (Fajans et al., 2001). Secondary diabetes can result from other endocrinopathies (e.g., Cushing's syndrome, acromegaly), pancreatic disease, or drug-induced hyperglycemia (e.g., corticosteroids, antipsychotics).

Table 1: Classification and Pathophysiology of Diabetes Mellitus

Type	Etiology	Pathophysiology	Clinical Features
Type 1 DM (T1DM)	Autoimmune destruction of β-cells	Absolute insulin deficiency; presence of autoantibodies	Polyuria, weight loss, ketoacidosis
Type 2 DM (T2DM)	Insulin resistance + β-cell dysfunction	Impaired insulin action and secretion	Obesity, hyperinsulinemia, metabolic syndrome
Gestational DM (GDM)	Pregnancy-induced insulin resistance	Placental hormones cause reduced insulin sensitivity	Hyperglycemia during pregnancy
Monogenic DM	Genetic mutations (e.g., MODY)	Defect in insulin gene or β-cell function	Early-onset DM, non-obese, familial pattern
Secondary DM	Drug- or disease induced (e.g., pancreatitis)	Underlying condition affects glucose metabolism	Varies with underlying cause

2.5. Molecular and Cellular Mechanisms

Hyperglycemia and insulin resistance initiate a cascade of deleterious effects:

- **Glucotoxicity:** Chronic hyperglycemia impairs β-cell function and increases oxidative stress.
- **Lipotoxicity:** Accumulation of free fatty acids in tissues disrupts insulin signaling.
- **Oxidative stress:** Overproduction of reactive oxygen species (ROS) damages cellular components and promotes inflammation.
- **Inflammation:** Activation of proinflammatory cytokines (TNF-α, IL-6) and macrophage infiltration into adipose tissue worsen insulin resistance.
- **Endoplasmic Reticulum (ER) Stress and Apoptosis:** Cellular stress responses contribute to β-cell death and insulin production failure (Back & Kaufman, 2012).

2.6. Complications of Diabetes

Poor glycemic control over time leads to vascular complications:

- **Microvascular complications:** Diabetic retinopathy, nephropathy, and neuropathy result from capillary damage.
- **Macrovascular complications:** Atherosclerosis increases the risk of coronary artery disease, stroke, and peripheral artery disease.

The interplay between hyperglycemia, dyslipidemia, oxidative stress, and inflammation underpins the development of these complications.

3. Recent Diagnostic Approaches in Diabetes Mellitus

Early detection and accurate diagnosis of diabetes are critical for preventing long-term complications and optimizing therapeutic outcomes. Traditional diagnostic methods remain widely used; however, recent innovations have introduced more precise, real-time, and personalized tools for glycemic monitoring and diabetes risk stratification. This section outlines both established and emerging diagnostic strategies for diabetes mellitus.

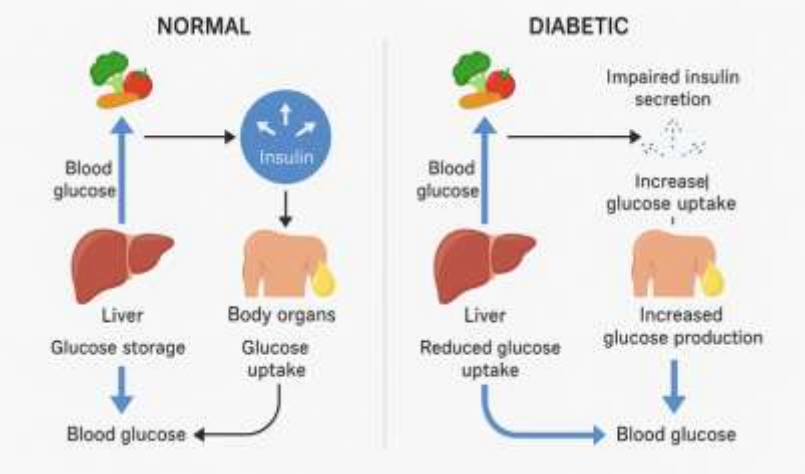


Figure 02: Schematic of Glucose Homeostasis and Dysregulation in Diabetes

3.1. Conventional Diagnostic Criteria

The conventional diagnosis of diabetes mellitus is primarily based on plasma glucose concentrations and HbA1c levels as outlined by the American

Diabetes Association (ADA) and the World Health Organization (WHO). The key diagnostic criteria include:

- **Fasting Plasma Glucose (FPG):** ≥126 mg/dL (7.0 mmol/L)
- **Oral Glucose Tolerance Test (OGTT):** 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) after a 75-g glucose load
- **Random Plasma Glucose:** ≥200 mg/dL in the presence of classic hyperglycemia symptoms
- **Glycated Hemoglobin (HbA1c):** ≥6.5%

While these tests are well-standardized and accessible, they do not reflect acute glycemic variability, and HbA1c can be influenced by hemoglobinopathies, anaemia, and renal disease (Sacks et al., 2011).

Table 2: Key Diagnostic Biomarkers for Diabetes Mellitus

Biomarker	Normal Range	Diagnostic Threshold	Clinical Significance
Fasting Plasma Glucose (FPG)	70–99 mg/dL	≥126 mg/dL on two occasions	Primary diagnostic marker for diabetes; elevated in impaired fasting glucose and diabetes.
Oral Glucose Tolerance Test (OGTT)	<140 mg/dL (2 hours post-glucose)	≥200 mg/dL (2 hours after 75g glucose load)	Indicates impaired glucose tolerance or diabetes.
Glycated Hemoglobin (HbA1c)	<5.7%	≥6.5%	Reflects average plasma glucose over previous 2–3 months. Diagnostic and monitoring marker.
Random Plasma Glucose	Varies	≥200 mg/dL with classic symptoms of hyperglycemia	Used when symptoms are present; helps confirm diagnosis.
C-Peptide	0.5–2.0 ng/mL	Low in Type 1; Normal/High in Type 2	Differentiates between Type 1 and Type 2 diabetes based on endogenous insulin production.
Serum Insulin	2–25 µIU/mL (fasting)	Low in Type 1; Elevated or normal in early Type 2	Indicates insulin secretion levels; helps assess insulin resistance or deficiency.
Autoantibodies (e.g., GAD65, ICA, IAA)	Absent in healthy individuals	Positive in Type 1 Diabetes	Used for autoimmune diabetes screening and diagnosis.
HOMA-IR (Insulin Resistance Index)	<2	>2.5 indicates insulin resistance	Calculated from fasting insulin and glucose; assesses insulin sensitivity.

3.2. Novel Biomarkers for Diabetes Detection and Progression

In the quest for earlier and more precise diabetes detection, several novel biomarkers are being investigated for their diagnostic and prognostic potential:

- **C-peptide:** Reflects endogenous insulin secretion and helps distinguish between T1DM and T2DM.
- **Adiponectin:** An adipokine inversely correlated with insulin resistance; lower levels predict T2DM.
- **Inflammatory markers:** C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) are elevated in insulin-resistant states.
- **MicroRNAs (miRNAs):** Circulating miRNAs (e.g., miR-375, miR-146a) show

promise in early T2DM detection and β-cell dysfunction.

- **Advanced Glycation End Products (AGEs):** Biomarkers of prolonged hyperglycemia that contribute to vascular complications.

These markers can enhance risk stratification, disease staging, and therapeutic monitoring when combined with traditional parameters (Al-Salam & Ahmad, 2021).

3.3. Continuous Glucose Monitoring (CGM) Systems

CGMs are wearable sensors that measure interstitial glucose levels at 1–5-minute intervals, offering a dynamic profile of glucose trends. Devices such as the Dexcom G6, FreeStyle Libre, and Medtronic Guardian allow patients and clinicians to monitor time-in-range (TIR), detect nocturnal hypoglycemia, and assess postprandial excursions.

CGMs improve glycemic control in both T1DM and T2DM, reduce HbA1c levels, and enhance patient adherence (Beck et al., 2017). Their integration with insulin pumps (closed-loop or "artificial pancreas" systems) marks a major leap in personalized diabetes care.

3.4. Biosensors and Non-Invasive Glucose Monitoring

The recent development of non-invasive and minimally invasive glucose monitoring techniques represents a significant advance in diabetes diagnostics. These include:

- **Optical Sensors:** Use near-infrared or Raman spectroscopy to detect glucose through the skin.
- **Electrochemical Biosensors:** Detect glucose based on enzymatic oxidation reactions on wearable devices.
- **Saliva, sweat, and tear-based sensors:** These exploit the presence of glucose in alternative biofluids, reducing the need for finger-prick sampling.

For instance, tear-based glucose sensors incorporated into smart contact lenses, and sweat biosensors integrated into fitness bands, have shown promising early results (Wang et al., 2018).

Table 03: Comparison of Diagnostic Biosensors in Diabetes Mellitus

Biosensor Type	Detection Method	Sample Type	Sensitivity (LOD)	Advantages	Limitations
Enzymatic Glucose Strip	Glucose oxidase (electrochemical)	Capillary blood	~0.5–1.0 mM	Low cost, widely available	Invasive, short-term use
Continuous Glucose Monitor (CGM)	Fluorescent or enzyme-based	Interstitial fluid	~0.1–0.2 mM	Real-time monitoring, trend data	Calibration, sensor lag
Sweat-Based Sensor	Colorimetric, electrochemical	Sweat	~0.2–0.5 mM	Non-invasive, wearable	Low volume & variability in sweat
Tear-Based Sensor (smart lens)	Enzymatic (GOx)	Tear fluid	~0.01 mM	High sensitivity, minimally invasive	Still in early development
Raman Spectroscopy	Optical (non-invasive)	Skin (tissue glucose)	~0.1 mM	Painless, reusable	Expensive, requires calibration

3.5. Lab-on-a-Chip and Point-of-Care Devices

Miniaturized diagnostic platforms known as lab-on-a-chip (LOC) systems combine microfluidics, sensors, and electronics to enable rapid, portable glucose and biomarker testing. These systems offer high sensitivity, low sample volume, and multiplexing capabilities, making them ideal for remote and low-resource settings.

Examples include paper-based electrochemical devices, smartphone-integrated diagnostics, and wearable microfluidic patches. LOC devices are under active development for point-of-care HbA1c, insulin, and C-peptide testing.

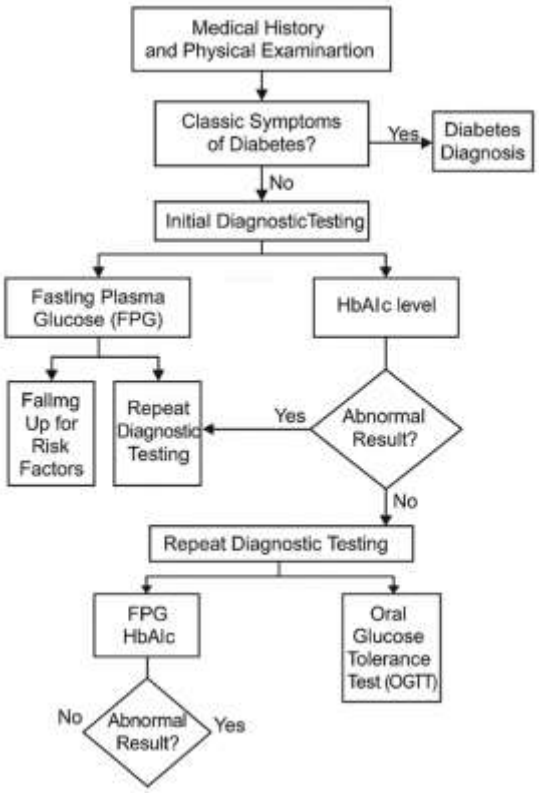


Figure 03: Diagnostic Workflow for Diabetes Mellitus

3.6. Imaging and Molecular Diagnostics

While rarely used for routine diagnosis, advanced imaging techniques and molecular diagnostics can be valuable in research and specialized clinical settings. Techniques include:

- **Positron Emission Tomography (PET):** For β-cell imaging using radiolabeled tracers.
- **MRI and CT Imaging:** To assess pancreatic volume and fat infiltration in T2DM.
- **Genomic and Proteomic Profiling:** To identify individual risk factors and gene variants associated with MODY or gestational diabetes.

These technologies contribute to precision medicine by enabling individualized risk prediction and therapy selection.

4. Therapeutic Strategies for Diabetes Mellitus

Effective management of diabetes mellitus aims to achieve optimal glycemic control, prevent complications, and improve overall quality of life. Treatment modalities have evolved significantly over the past few decades, transitioning from

conventional glucose-lowering agents to innovative therapies targeting multiple pathogenic pathways. This section highlights both established and emerging strategies, including pharmacological agents, plant-derived compounds, nanotechnology, and experimental interventions.

4.1. Conventional Pharmacological Therapies

The mainstays of diabetes management include insulin therapy and various classes of oral antidiabetic drugs (OADs). Each class acts on different physiological mechanisms to regulate blood glucose levels.

4.1.1. Insulin Therapy

Insulin remains essential for patients with T1DM and is often required in advanced T2DM. Types of insulin include:

- **Rapid-acting (e.g., insulin lispro, aspart)**
- **Short-acting (regular insulin)**
- **Intermediate-acting (NPH)**
- **Long-acting (glargine, detemir, degludec)**

Modern insulin delivery methods such as insulin pens and pumps (CSII) improve precision and convenience. Newer formulations like ultra-rapid acting insulin (URLi) and inhaled insulin (Afrezza) offer additional options.

4.1.2. Oral Antidiabetic Drugs (OADs)

Key OAD classes include:

- **Biguanides (Metformin):** First-line therapy that decreases hepatic glucose production and improves insulin sensitivity.
- **Sulfonylureas (e.g., glibenclamide, glipizide):** Stimulate pancreatic insulin secretion.
- **Thiazolidinediones (e.g., pioglitazone):** Improve insulin sensitivity via PPAR-γ activation.
- **Alpha-glucosidase inhibitors (e.g., acarbose):** Delay intestinal carbohydrate absorption.

While effective, many of these drugs have limitations, including hypoglycemia risk, weight gain, and declining efficacy over time.

4.2. Emerging Antidiabetic Agents

Recent therapeutic innovations offer additional benefits beyond glucose lowering, such as cardioprotection, renal protection, and weight loss.

Table 4: Pharmacological Therapies in Diabetes Management

Drug Class	Example Drugs	Mechanism of Action	Therapeutic Role
Biguanides	Metformin	Reduces hepatic gluconeogenesis; increases insulin sensitivity	First-line therapy for type 2 diabetes
Sulfonylureas	Glipizide, Glimepiride	Stimulate insulin secretion from pancreatic β-cells	Effective in early type 2 diabetes with preserved β-cell function
Meglitinides	Repaglinide, Nateglinide	Short-acting insulin secretagogues	Controls postprandial glucose spikes
Thiazolidinediones (TZDs)	Pioglitazone, Rosiglitazone	Activate PPAR-γ → improve insulin sensitivity in muscle and adipose tissue	Used in insulin-resistant type 2 diabetes

DPP-4 Inhibitors	Sitagliptin, Vildagliptin, Linagliptin	Inhibit DPP-4 enzyme → prolong incretin (GLP-1, GIP) action	Modest HbA1c reduction with low risk of hypoglycemia
GLP-1 Receptor Agonists	Exenatide, Liraglutide, Semaglutide	Mimic GLP-1 → enhance insulin secretion, inhibit glucagon, slow gastric emptying	Promotes weight loss and cardiovascular protection
SGLT2 Inhibitors	Dapagliflozin, Empagliflozin, Canagliflozin	Inhibit glucose reabsorption in proximal renal tubules → glucosuria	Weight loss, BP reduction, CV and renal protection
α-Glucosidase Inhibitors	Acarbose, Miglitol	Delay carbohydrate digestion and glucose absorption in intestine	Reduces postprandial hyperglycemia
Insulin Therapy	Regular, NPH, Lispro, Glargine	Replaces or supplements endogenous insulin	Essential for type 1 diabetes; adjunct in type 2 diabetes
Amylin Analogs	Pramlintide	Slows gastric emptying, suppresses glucagon secretion	Used in insulin-treated patients to improve postprandial control

4.2.1. DPP-4 Inhibitors

These agents (e.g., sitagliptin, linagliptin) prolong the action of incretin hormones, enhancing insulin secretion and inhibiting glucagon. They are weight-neutral and have a low risk of hypoglycemia.

4.2.2. GLP-1 Receptor Agonists

GLP-1 RAs (e.g., liraglutide, semaglutide) mimic endogenous incretin hormones, promoting insulin secretion, slowing gastric emptying, and reducing appetite. Clinical trials have shown reductions in cardiovascular events and mortality (Marso et al., 2016).

4.2.3. SGLT2 Inhibitors

SGLT2 inhibitors (e.g., empagliflozin, dapagliflozin) promote urinary glucose excretion, leading to improved glycemic control, weight loss, and cardiovascular and renal benefits (Zinman et al., 2015). These agents have shifted treatment paradigms for T2DM with comorbid heart failure or CKD.

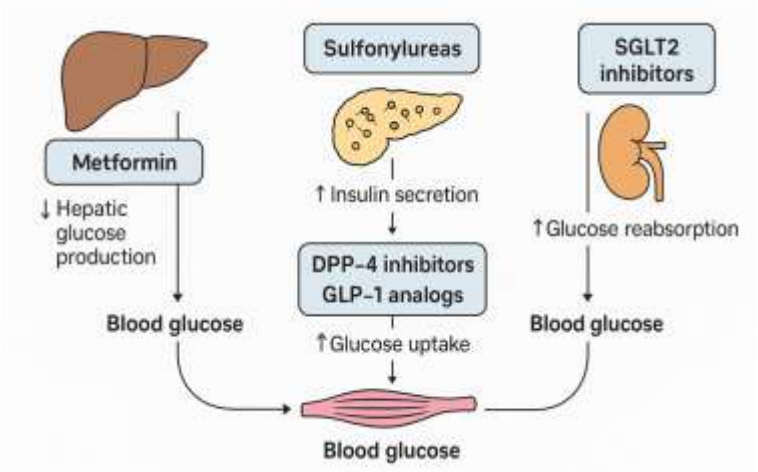


Figure 04: Mechanism of Action of Key Antidiabetic Drug Classes

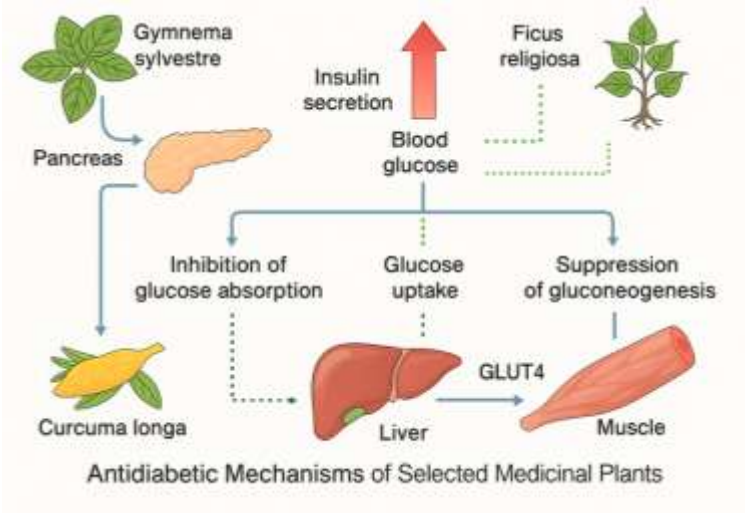


Figure 05: Antidiabetic Mechanisms of Selected Medicinal Plants

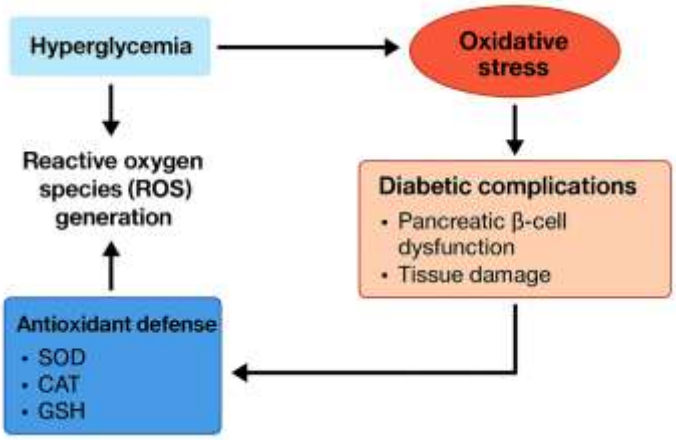


Figure 06: Role of Oxidative Stress and Antioxidants in Diabetes

4.3. Plant-Based and Herbal Therapies

Herbal medicine remains widely used in diabetes management, particularly in traditional systems like Ayurveda, Traditional Chinese Medicine (TCM), and Unani. Numerous plant-derived bioactive compounds demonstrate antihyperglycemic activity through various mechanisms:

4.3.1. Selected Plants and Mechanisms

These plants (Table 5) have demonstrated significant reductions in fasting glucose, HbA1c, and oxidative stress markers in both preclinical and clinical studies (Patel et al., 2012; Khan et al., 2003).

4.3.2 Experimental Evidence from Animal Models

1. Aegle marmelos (Bael): Aegle marmelos (L.) Corrêa, commonly referred to as Bael, is a well-known medicinal plant extensively utilized in Ayurvedic medicine for its antidiabetic, antioxidant, and anti-inflammatory activities. Various parts of the plant, particularly the leaves and fruits, have demonstrated potent hypoglycemic effects, making it a valuable therapeutic agent in the management of diabetes mellitus (Palanivel & Rajkapoor, 2009; Upadhya et al., 2010). Experimental studies in streptozotocin (STZ)-induced diabetic rat models have shown that oral administration of A.

marmelos leaf extract, typically in doses ranging from 100 to 500 mg/kg, significantly lowers fasting blood glucose levels, improves glucose tolerance, and restores body weight (Palanivel & Rajkapoor, 2009). The extract is enriched with bioactive constituents such as aegeline, marmelosin, rutin, and flavonoids, which collectively contribute to its pharmacological efficacy (Mandal et al., 2013). The antidiabetic effects of A. marmelos are primarily mediated through stimulation of residual pancreatic β-cells, enhancement of insulin secretion, and improvement in insulin sensitivity. It also promotes peripheral glucose uptake and inhibits hepatic gluconeogenesis (Upadhya et al., 2010). The plant's antioxidant potential is evident in its ability to elevate endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH), thereby mitigating oxidative damage to pancreatic tissues (Arumugam et al., 2008). Histopathological evaluations further support the protective and regenerative effects of A. marmelos on pancreatic islet architecture, revealing substantial recovery in tissue morphology in treated diabetic animals (Palanivel & Rajkapoor, 2009). Additionally, the anti-inflammatory action, mediated through the downregulation of pro-inflammatory cytokines like TNF-α and IL-6, contributes to the attenuation of diabetic complications and the overall amelioration of metabolic disturbances associated with diabetes (Mandal et al., 2013).

2. Allium sativum (Garlic): Allium sativum, commonly known as garlic, has been widely studied for its antidiabetic, antioxidant, and cardioprotective properties. The therapeutic potential of garlic is attributed to sulfur-containing compounds such as allicin, ajoene, and S-allyl cysteine, which exert insulin-mimetic effects, enhance glucose metabolism, and reduce oxidative stress (Banerjee & Maulik, 2002). In streptozotocin (STZ)-induced diabetic rats, oral administration of garlic extract at doses ranging from 100–300 mg/kg for 2–4 weeks significantly reduced fasting blood glucose levels, elevated plasma insulin, and increased hepatic glycogen content (Sheela & Augusti, 1992). Garlic has also been shown to modulate key hepatic enzymes involved in carbohydrate metabolism, such as glucose-6-phosphatase and hexokinase, contributing to improved glycemic control (Swanston-Flatt et al., 1990). Additionally, garlic exerts antioxidant effects by decreasing lipid peroxidation and enhancing endogenous antioxidant defenses, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) (El-Soud et al., 2010). Clinical trials support these preclinical findings. A double-blind, placebo-controlled study reported that supplementation with aged garlic extract (aged for 20 months to increase bioavailability of S-allyl cysteine) improved fasting blood glucose and HbA1c in patients with type 2 diabetes over a 12-week period (Ashraf et al., 2005). These findings indicate that A. sativum may serve as a valuable adjunct in the management of type 2 diabetes, particularly for patients with concurrent cardiovascular risk factors.

3. Andrographis paniculata (Kalmegh): Andrographis paniculata (Burm.f.) Nees, commonly known as Kalmegh, is a traditional medicinal herb extensively used in Ayurvedic and Traditional Chinese Medicine for its notable antidiabetic, anti-inflammatory, and hepatoprotective properties. Its principal bioactive compound, andrographolide—a bitter diterpenoid lactone—is primarily responsible for its therapeutic potential in diabetes management (Akbar, 2011; Niranjan et al., 2010). Preclinical studies utilizing streptozotocin (STZ)-induced diabetic rat models have shown that oral administration of A. paniculata extract, at doses

ranging from 100 to 400 mg/kg body weight, leads to a significant reduction in fasting blood glucose levels, improvement in insulin sensitivity, and enhancement of glucose tolerance (Zhang & Tan, 2000; Subramanian et al., 2008). In many cases, these effects were comparable to those achieved with standard antidiabetic agents such as metformin or glibenclamide (Saha et al., 2011). The underlying mechanisms involve stimulation of insulin secretion from pancreatic β-cells, inhibition of hepatic gluconeogenesis, and promotion of peripheral glucose uptake. Andrographolide is known to exert its effects by activating AMP-activated protein kinase (AMPK) signaling pathways and enhancing insulin receptor signaling, thereby facilitating glucose metabolism (Lee et al., 2006; Xia et al., 2017). Furthermore, A. paniculata possesses robust antioxidant properties, evidenced by reductions in oxidative stress and lipid peroxidation. These effects are mediated through the upregulation of antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH) (Dandu & Inamdar, 2009). Histopathological analyses have confirmed the protective effects of A. paniculata on pancreatic tissue, showing preservation and partial regeneration of islet architecture (Chandrasekaran et al., 2010). In addition, the plant's immunomodulatory and anti-inflammatory activities—specifically the downregulation of pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6)—contribute to its efficacy in mitigating diabetes-associated complications (Sheeja et al., 2006; Chen et al., 2009).

4. Azadirachta indica (Neem): Azadirachta indica, or neem, is renowned in Ayurvedic medicine for its diverse therapeutic roles, including antidiabetic, anti-inflammatory, and antioxidant properties. It contains active constituents like azadirachtin, nimbidin, and flavonoids (Chattopadhyay, 1996). In alloxan- and STZ-induced diabetic animal models, neem leaf or seed extracts (200–400 mg/kg) significantly reduced fasting blood glucose, preserved pancreatic β-cell function, and improved glucose tolerance (Khosla et al., 2000). Neem also upregulated antioxidant enzyme activity, such as superoxide dismutase (SOD) and catalase, thereby mitigating oxidative damage in pancreatic tissue (Chattopadhyay, 1996). While clinical evidence remains limited, traditional use and preclinical studies justify its continued investigation as a potential adjunct in diabetes therapy.

5. Camellia sinensis (Green Tea): Camellia sinensis, commonly known as green tea, is a widely consumed beverage derived from the unoxidized leaves of the tea plant. It is rich in polyphenolic compounds, particularly catechins such as epigallocatechin gallate (EGCG), epicatechin (EC), and epicatechin gallate (ECG), which have been extensively studied for their antidiabetic, antioxidant, anti-inflammatory, and lipid-lowering properties (Haque et al., 2021; Yang & Zhang, 2020). In experimental studies, green tea extract administered orally in diabetic animal models—typically at doses of 100–300 mg/kg/day—has demonstrated significant reductions in blood glucose levels, improved glucose tolerance, and enhanced insulin secretion and sensitivity (Rains et al., 2011; Huxley et al., 2009). These effects are partially attributed to green tea's modulation of carbohydrate-metabolizing enzymes such as α-glucosidase, α-amylase, and glucose-6-phosphatase (Ghorbani et al., 2017). EGCG also enhances insulin receptor signaling and GLUT-4 translocation, facilitating improved peripheral glucose uptake (Babu et al., 2006). Green tea exhibits strong antioxidant activity, reducing oxidative stress by increasing the activity of endogenous enzymes like superoxide dismutase (SOD), glutathione

peroxidase (GPx), and catalase (CAT) (Singh et al., 2016). Furthermore, it mitigates diabetic complications by suppressing pro-inflammatory markers such as TNF-α and IL-6 and by inhibiting the formation of advanced glycation end-products (AGEs) (Zhao et al., 2020). Histopathological evaluations in diabetic models have shown preservation of pancreatic islets, reduction in hepatic steatosis, and protection against renal and cardiovascular damage in green tea-treated groups (Deka & Vita, 2011; Ghorbani et al., 2017). Collectively, these findings indicate that Camellia sinensis may serve as a valuable adjunct in the management of diabetes mellitus and its related complications.

6. Cinnamomum verum (Ceylon Cinnamon): Cinnamomum verum, commonly known as Ceylon cinnamon, is a medicinal spice rich in bioactive constituents such as cinnamaldehyde, cinnamic acid, and proanthocyanidins. These compounds exhibit notable antidiabetic, antioxidant, and anti-inflammatory properties. Preclinical and clinical studies have demonstrated that cinnamon supplementation enhances insulin sensitivity, facilitates glucose uptake, and significantly reduces fasting blood glucose, HbA1c, and serum lipid levels (Khan et al., 2003; Qin et al., 2010). In diabetic animal models, administration of cinnamon extract at doses ranging from 50 to 200 mg/kg resulted in substantial glycemic improvement, primarily through modulation of the PI3K/Akt and AMPK signaling pathways (Subash-Babu et al., 2014; Ranasinghe et al., 2012). Moreover, cinnamon has been shown to suppress the expression of glucose-6-phosphatase and upregulate GLUT4, thereby promoting glycogen synthesis and improving overall glycemic control (Anderson et al., 2004; Sheng et al., 2008).

7. Curcuma longa (Turmeric): Curcuma longa L., commonly known as turmeric, is a perennial rhizomatous herb of the Zingiberaceae family, traditionally utilized in Ayurvedic and other indigenous medical systems for its broad pharmacological effects, particularly anti-inflammatory, antioxidant, and antidiabetic activities. The primary bioactive constituent of turmeric is curcumin, a polyphenolic compound known to modulate multiple molecular targets implicated in metabolic disorders (Aggarwal & Harikumar, 2009; Gupta et al., 2013). In various preclinical studies involving streptozotocin- or alloxan-induced diabetic rodent models, oral administration of curcumin in doses ranging from 80 to 300 mg/kg/day has demonstrated significant reductions in fasting blood glucose and HbA1c levels, along with improvements in glucose tolerance and insulin sensitivity (El-Moselhy et al., 2011; Jain et al., 2006). These effects are attributed to enhanced pancreatic β-cell function, upregulation of insulin receptor expression, and improved insulin signaling (Rahimi et al., 2016). Mechanistically, curcumin exerts its antidiabetic effects by inhibiting oxidative stress, downregulating pro-inflammatory cytokines such as TNF-α and IL-6, promoting GLUT4 translocation, and modulating AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor gamma (PPAR-γ) pathways (Weisberg et al., 2008; Kang et al., 2010). Additionally, curcumin has been shown to inhibit the formation of advanced glycation end-products (AGEs), which are key contributors to diabetic complications (Soetikno et al., 2013). Histopathological evaluations of diabetic animals treated with curcumin reveal structural regeneration of pancreatic islets, attenuation of hepatic steatosis, and preservation of renal glomerular architecture, underscoring its protective role against diabetes-induced tissue

damage (Hasanein & Shahidi, 2012; Sharma et al., 2006).

8. Ficus religiosa (Sacred Fig / Peepal Tree): Ficus religiosa L., commonly known as the Peepal tree or Sacred Fig, holds significant reverence in traditional medicine systems such as Ayurveda and Unani, where it has been employed for its antidiabetic, antioxidant, and anti-inflammatory properties. The plant is rich in bioactive constituents, including flavonoids, tannins, saponins, and phenolic compounds, which contribute to its pharmacological activity (Grover et al., 2002). Experimental studies utilizing streptozotocin (STZ) and alloxan-induced diabetic rat models have demonstrated that administration of aqueous and ethanolic extracts from the leaves, bark, and fruits of F. religiosa leads to significant reductions in fasting blood glucose levels. In particular, oral administration of aqueous leaf extract at doses ranging from 100 to 400 mg/kg body weight over a period of several weeks resulted in improved oral glucose tolerance and enhanced hepatic glycogen storage (Grover et al., 2002). The antidiabetic activity of F. religiosa appears to involve both insulin secretagogue effects and improved peripheral glucose utilization. Additionally, treatment with F. religiosa extracts has been shown to positively modulate lipid profiles by reducing serum total cholesterol and triglycerides while elevating high-density lipoprotein (HDL) levels. Histopathological evaluations have provided evidence of partial regeneration of pancreatic β-cells and restoration of islet architecture following treatment. Antioxidant defense systems, including superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH), were significantly elevated in the liver and pancreas of diabetic rats treated with F. religiosa, suggesting protection against oxidative stress–induced cellular injury. Although clinical applications of F. religiosa are supported in Ayurvedic practices, comprehensive human trials are limited, and further investigation is warranted to validate its efficacy and safety in diabetic populations.

9. Gymnema sylvestre: Gymnema sylvestre R. Br., traditionally called "Gurmar," is a climbing plant valued in Ayurveda for its sugar-suppressing properties. Its bioactive constituents include gymnemic acids, gymnemasaponins, and gurmarin, which modulate glucose metabolism and insulin pathways (Sahu et al., 2010).

In STZ- or alloxan-induced diabetic rats, G. sylvestre extract significantly reduced blood glucose levels, enhanced insulin secretion, and promoted β-cell regeneration. Oral doses of 200–400 mg/kg body weight improved oral glucose tolerance, lipid profiles, and islet cell architecture over 2–4 weeks (Shanmugasundaram et al., 1990). Gymnemic acids, structurally similar to glucose, block intestinal glucose absorption and enhance insulin release (Persaud et al., 1999). Clinically, G. sylvestre has shown promise in type 2 diabetes. A long-term clinical trial (18–20 months) with 400 mg/day of leaf extract led to significant improvements in fasting glucose, HbA1c, and reductions in dependency on hypoglycemic agents (Baskaran et al., 1990). The extract was well tolerated, further validating its therapeutic utility.

10. Mangifera indica (Mango Tree): Mangifera indica L., commonly known as the mango tree, is not only valued for its fruit but also for its medicinal properties, particularly in traditional systems of medicine. Various parts of the plant, including the leaves, bark, and seeds, have shown antidiabetic, antioxidant, and anti-inflammatory activities. Experimental studies using diabetic rat models, such as streptozotocin (STZ)-induced and alloxan-induced models, have demonstrated significant antihyperglycemic effects of mango leaf extract. Oral administration of the aqueous or

ethanolic leaf extract (typically 200–400 mg/kg body weight) significantly reduced fasting blood glucose levels, improved glucose tolerance, and enhanced insulin sensitivity in diabetic rats (Ojewole, 2005; Patel et al., 2020). The active constituents, including mangiferin (a xanthonoid), quercetin, gallic acid, and other phenolic compounds, are believed to contribute to the antidiabetic activity. These compounds exhibit insulin-mimetic activity, improve pancreatic β-cell regeneration, and enhance peripheral glucose uptake. Mangiferin, in particular, is a potent antioxidant that also reduces oxidative stress markers and lipid peroxidation in diabetic tissues. In addition to its glucose-lowering effects, Mangifera indica has shown improvement in serum lipid profiles by reducing total cholesterol, triglycerides, and LDL-C, while increasing HDL-C in treated diabetic rats. Histological examinations reveal partial recovery of pancreatic islets and reduced hepatic steatosis following extract treatment. Antioxidant markers such as SOD, CAT, and GSH were also significantly elevated in treated groups, suggesting protection against diabetes-induced oxidative tissue injury (Ojewole, 2005; Gupta & Gupta, 2021). Although most studies are preclinical, the results support the potential of M. indica as an adjunctive therapy in diabetes management.

11. Momordica charantia (Bitter Melon): Momordica charantia L., commonly known as bitter melon or "karela," is a widely used medicinal plant in traditional systems like Ayurveda, Unani, and Traditional Chinese Medicine for the management of diabetes mellitus (Grover & Yadav, 2004). The plant's fruits, seeds, and leaves contain bioactive compounds such as charantin, vicine, polypeptide-p, and cucurbitane-type triterpenoids, which contribute to its antidiabetic and insulin-mimetic effects (Patel et al., 2012). Preclinical studies have demonstrated that M. charantia exhibits strong hypoglycemic activity in diabetic animal models. In streptozotocin (STZ)-induced diabetic rats, oral administration of aqueous or ethanolic fruit extracts (150–300 mg/kg/day) significantly lowered fasting blood glucose, improved glucose tolerance, and increased plasma insulin levels (Ahmad et al., 1999). Notably, polypeptide-p, an insulin-like compound isolated from the seeds, mimicked insulin's action by promoting glucose uptake in muscle and adipose tissues (Keller et al., 1985). Additionally, the extract reduced oxidative stress markers and enhanced antioxidant defenses by increasing SOD and catalase activity (Grover & Yadav, 2004). Clinical trials have provided supportive evidence for its efficacy in humans. A randomized controlled trial involving type 2 diabetic patients receiving 2000 mg/day of M. charantia fruit extract for 4 weeks showed a significant reduction in fasting blood glucose and HbA1c levels compared to placebo (Dans et al., 2007). Another study observed that daily consumption of fresh bitter melon juice improved glycemic control and lipid profiles without adverse effects (Srivastava et al., 1993).

Mechanistically, M. charantia exerts antidiabetic effects through multiple pathways: stimulation of insulin secretion, increased peripheral glucose utilization, suppression of hepatic gluconeogenesis, and modulation of carbohydrate-digesting enzymes (Patel et al., 2012). Its antioxidant and anti-inflammatory properties further support its use in managing diabetic complications.

12. Ocimum gratissimum (Clove Basil or Ram Tulsi): Ocimum gratissimum L., commonly known as Clove Basil or Ram Tulsi, is a medicinal herb widely recognized for its hypoglycemic, antioxidant, and anti-inflammatory activities, particularly in traditional medicine systems

(Ezekwesili et al., 2014; Ezeokeke & Obidoa, 2011). Rich in essential oils, flavonoids, and phenolic constituents such as eugenol, thymol, and rosmarinic acid, it exhibits considerable potential in the management of diabetes mellitus (Chattopadhyay, 1999; Aguiyi et al., 2000). Preclinical studies using alloxan- or streptozotocin-induced diabetic rat models have demonstrated that oral administration of O. gratissimum leaf extract (200–500 mg/kg) significantly reduces fasting blood glucose levels, enhances glucose tolerance, and preserves pancreatic β-cell function (Owolabi et al., 2010; Ugochukwu et al., 2003). The antidiabetic mechanisms of O. gratissimum are multifaceted, including insulin-mimetic activity, upregulation of insulin secretion and sensitivity, and inhibition of α-amylase and α-glucosidase enzymes, resulting in delayed glucose absorption and improved glycemic control (Oboh et al., 2010; Eseyin et al., 2014). Additionally, the plant's bioactives modulate carbohydrate metabolism by enhancing peripheral glucose uptake and regulating key metabolic enzymes (Akinmoladun et al., 2007). Histopathological analyses in treated diabetic animals reveal improved pancreatic islet architecture and reduced hepatic and cellular degeneration (Effraim et al., 2002). Its antioxidant effects, mediated through increased levels of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), contribute to the attenuation of oxidative stress and offer protection against diabetic complications (Ezeigbo et al., 2013; Akinmoladun et al., 2007).

13. Ocimum sanctum (Holy Basil): Ocimum sanctum Linn., commonly known as Holy Basil or Tulsi, holds a prominent place in traditional Indian medicine for its diverse therapeutic properties, notably its antidiabetic, antioxidant, and adaptogenic effects. The plant is rich in bioactive constituents such as eugenol, ursolic acid, rosmarinic acid, carvacrol, and flavonoids, all of which contribute to its hypoglycemic activity. Experimental studies involving streptozotocin (STZ) and alloxan-induced diabetic rat models have demonstrated that O. sanctum leaf extracts significantly reduce blood glucose levels, improve insulin secretion, and normalize lipid profiles. Treatment with aqueous or alcoholic extracts at doses ranging from 100 to 200 mg/kg body weight over 2–4 weeks resulted in marked reductions in fasting and postprandial glucose, enhanced glucose tolerance, and restoration of hepatic and muscular glycogen stores (Chattopadhyay, 1993). The antidiabetic effects of O. sanctum are mediated through several mechanisms, including stimulation of pancreatic β-cell insulin secretion, enhancement of peripheral glucose utilization, and inhibition of hepatic gluconeogenesis. Its potent antioxidant activity also helps alleviate oxidative stress—a key factor in β-cell dysfunction and insulin resistance. Clinical data support these findings. In a randomized controlled trial, type 2 diabetic patients who received 2.5 g of fresh O. sanctum leaf powder daily for four weeks exhibited significant reductions in both fasting and postprandial blood glucose levels, with mild improvements in lipid profiles and no major adverse effects (Agrawal et al., 1996). Given its accessibility, safety profile, and multi-targeted pharmacological actions, Ocimum sanctum serves as a promising adjunct in the management of diabetes, particularly in the early stages or in prediabetic individuals.

14. Phyllanthus amarus: Phyllanthus amarus, a small tropical herb from the Euphorbiaceae family, is traditionally employed in Ayurvedic and folk medicine for managing diabetes mellitus, jaundice, and renal ailments. Its pharmacological properties are attributed to bioactive constituents such as lignans (phyllanthin, hypophyllanthin), flavonoids, alkaloids, and tannins, which

contribute to its antidiabetic, hepatoprotective, and antioxidant effects (Patel et al., 2011; Harish & Shivananda, 2010). Experimental studies using streptozotocin (STZ)-induced diabetic rat models have demonstrated that oral administration of Phyllanthus amarus extract (100–400 mg/kg) significantly lowers fasting blood glucose, restores serum insulin levels, and improves glucose tolerance (Chaudhary et al., 2012). The extract has been shown to stimulate pancreatic β-cell regeneration and enhance peripheral glucose uptake by modulating insulin signaling and reducing insulin resistance (Sumanth & Mustafa, 2007). Additionally, P. amarus possesses strong antioxidant activity, increasing the levels of superoxide dismutase (SOD), catalase, and glutathione (GSH), thereby mitigating oxidative stress and lipid peroxidation—key contributors to diabetic tissue damage (Jayanthi & Subash, 2010). Histopathological analyses have revealed decreased necrosis and inflammation in the liver, pancreas, and kidneys of treated diabetic animals (Rai et al., 2013). Furthermore, Phyllanthus amarus exhibits hypolipidemic properties by normalizing elevated triglycerides, total cholesterol, and LDL-C levels, which are commonly associated with diabetic dyslipidemia (Bhattacharjee et al., 2013). These experimental findings suggest its potential as an adjunctive therapy for diabetes and its associated metabolic complications.

15. Pterocarpus marsupium (Indian Kino Tree): Pterocarpus marsupium Roxb., commonly referred to as the Indian Kino Tree or Vijayasar, is a well-documented antidiabetic herb in Ayurvedic medicine. Its heartwood contains several bioactive compounds, including pterostilbene, marsupsin, epicatechin, and liquiritigenin, which collectively contribute to its potent antihyperglycemic activity. Experimental studies using alloxan- and streptozotocin (STZ)-induced diabetic rat models have shown that oral administration of aqueous or ethanolic heartwood extracts at doses ranging from 50 to 200 mg/kg body weight for 2–6 weeks significantly reduced fasting blood glucose levels, improved oral glucose tolerance, and restored liver glycogen content. Among its phytoconstituents, pterostilbene has demonstrated the ability to regenerate pancreatic β-cells and enhance insulin secretion (Manickam et al., 1997). Additionally, P. marsupium possesses antioxidant and anti-inflammatory properties, which protect islet cells from oxidative damage and improve the activities of carbohydrate metabolism enzymes, including hexokinase and glucose-6-phosphatase. Histopathological analyses have supported the regenerative effects of P. marsupium, revealing partial to complete restoration of islet cell architecture, indicating its potential to reverse β-cell damage rather than solely suppress hyperglycemia. Traditional usage also lends support to its efficacy. Aqueous decoctions prepared by soaking tumblers carved from the heartwood in water overnight have demonstrated moderate glucose-lowering effects in type 2 diabetic patients when used as adjunctive therapy (Kumar et al., 2009).

16. Punica granatum (Pomegranate): Punica granatum L., commonly known as pomegranate, is a deciduous fruit-bearing shrub of the Lythraceae family, traditionally employed in Ayurvedic and Unani medicine for managing various metabolic disorders. Its rich phytochemical profile includes ellagic acid, punicalagins, anthocyanins, and flavonoids, which are credited with potent antidiabetic, antioxidant, and anti-inflammatory properties (Viuda-Martos et al., 2010; Jurenka, 2008). Experimental studies in alloxan- and streptozotocin-induced diabetic rat models have demonstrated that oral administration of pomegranate juice or seed extract, typically in doses ranging from 100 to 500 mg/kg/day,

significantly reduces fasting blood glucose, improves serum lipid profiles, and enhances insulin levels (Kaur et al., 2006; Huang et al., 2005). Pomegranate has also been shown to protect pancreatic β-cells and enhance the activity of endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT), thereby attenuating oxidative stress (Lei et al., 2007; Elfalleh et al., 2012). Mechanistically, P. granatum exerts its antidiabetic effects through inhibition of carbohydrate-digesting enzymes, specifically α-glucosidase and α-amylase, as well as suppression of pro-inflammatory cytokines such as IL-6 and TNF-α (Zhang et al., 2011; Sudheesh & Vijayalakshmi, 2005). Moreover, it modulates key signaling pathways including PI3K/Akt and AMPK, which are essential for promoting glucose uptake and improving insulin sensitivity (Shukla et al., 2008; Lansky & Newman, 2007). Histopathological analyses in diabetic animal models have revealed preservation of pancreatic islet architecture, reduced hepatocellular degeneration, and attenuation of glomerular and tubular damage in the kidneys, indicating that P. granatum confers systemic protective effects against diabetes-associated organ damage (Kaur et al., 2006; Huang et al., 2005).

17. Syzygium cumini (Jamun / Java Plum): Syzygium cumini, commonly known as jamun, is widely recognized for its antidiabetic, antioxidant, and anti-inflammatory benefits. The seeds contain jamboline, quercetin, ellagic acid, and anthocyanins, which contribute to its hypoglycemic effects (Ayyanar & Subash-Babu, 2012). Studies in diabetic rats treated with seed powder or aqueous extract (100–500 mg/kg) demonstrated significant reductions in fasting blood glucose, improved insulin levels, restored hepatic glycogen, and normalized lipid profiles (Achrekar et al., 1991). The extract also helped preserve pancreatic islet architecture and β-cell function. Though human trials are fewer, traditional usage and promising animal data support S. cumini's role as a natural antidiabetic agent.

18. Tinospora cordifolia (Willd.): Tinospora cordifolia (Willd.) Miers, commonly known as Guduchi or Giloy, is a vital medicinal herb in Ayurveda, recognized for its potent antidiabetic, immunomodulatory, antioxidant, and hepatoprotective properties (Singh et al., 2003; Sangeetha & Krishnakumari, 2010). The stems and roots of T. cordifolia are frequently employed in traditional formulations for managing metabolic disorders, particularly diabetes mellitus. Preclinical studies using alloxan- and streptozotocin (STZ)-induced diabetic rat models have consistently demonstrated that oral administration of T. cordifolia extract (typically in the range of 100–400 mg/kg body weight) significantly reduces fasting blood glucose levels, improves glucose tolerance, and enhances endogenous insulin secretion (Gupta et al., 2012; Stanely et al., 2000). These outcomes have been shown to be comparable to standard hypoglycemic agents such as glibenclamide and metformin in some models (Prince et al., 2004). The hypoglycemic effect is largely attributed to bioactive compounds like tinosporaside, berberine, magnoflorine, cordifolioside A, and palmatine, which contribute to enhanced insulin release, suppression of gluconeogenesis, and improved glucose uptake in peripheral tissues (Rajalakshmi & Eliza, 2004; Saha & Ghosh, 2012). Furthermore, T. cordifolia exerts powerful antioxidant effects by boosting key enzymatic antioxidants including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), thereby mitigating oxidative stress and protecting pancreatic β-cells from degeneration (Jagetia & Rao, 2006).

Histopathological investigations confirm islet regeneration and amelioration of diabetic complications such as nephropathy and hepatic damage in treated groups (Rao et al., 2008). Additionally, the herb's immunomodulatory activity may contribute to reducing chronic low-grade inflammation, a hallmark of type 2 diabetes, thus further supporting its therapeutic potential as an adjunct in diabetes management (Singh et al., 2003).

19. Trigonella foenum-graecum (Fenugreek): Trigonella foenum-graecum L., commonly known as fenugreek, is a leguminous herb traditionally used for culinary and medicinal purposes. Its seeds contain bioactive compounds such as 4-hydroxyisoleucine, trigonelline, diosgenin, and galactomannan, which are known for their antidiabetic potential (Basch et al., 2003). Experimental studies in diabetic animal models have demonstrated significant hypoglycemic and antihyperlipidemic effects. In alloxan- or STZ-induced diabetic rats, oral administration of fenugreek seed powder (25–50 g/kg of diet) or seed extract (100–300 mg/kg) significantly reduced fasting blood glucose, improved glucose tolerance, and enhanced insulin sensitivity (Raghuram et al., 1994). 4-Hydroxyisoleucine, a unique amino acid found in fenugreek, has been shown to stimulate insulin secretion in isolated islet cells and in vivo (Broca et al., 2000). Moreover, fenugreek polysaccharides delay gastric emptying and carbohydrate absorption, contributing to postprandial glucose regulation (Madar et al., 1988). Clinical trials have shown encouraging results. A placebo-controlled study in type 2 diabetic patients demonstrated that 10–25 grams/day of fenugreek seed powder over 4–6 weeks led to significant reductions in fasting blood glucose, postprandial glucose, and serum triglycerides (Sharma et al., 1990). Other trials have reported improvements in insulin resistance and lipid profiles with minimal adverse effects (Gupta et al., 2001).

20. Zingiber officinale (Ginger): Zingiber officinale Roscoe, commonly known as ginger, is a well-known medicinal plant from the Zingiberaceae family, traditionally used to treat various ailments, including metabolic disorders like diabetes mellitus. Its rhizomes contain a wide range of bioactive compounds, including gingerols, shogaols, paradols, and zingerone, which are responsible for its antidiabetic, antioxidant, and anti-inflammatory properties (Ali et al., 2008; Mashhadi et al., 2013). Experimental studies on diabetic animal models, particularly those induced with streptozotocin or alloxan, have demonstrated that ginger extract at doses of 100–500 mg/kg significantly lowers fasting blood glucose levels, enhances oral glucose tolerance, and restores serum insulin levels (Tzeng et al., 2013; Ebrahimzadeh Attari et al., 2017). The antidiabetic effects of Z. officinale are attributed to its ability to enhance glucose uptake in peripheral tissues, inhibit α-glucosidase and α-amylase activities, and modulate insulin signaling via peroxisome proliferator-activated receptor gamma (PPAR-γ) pathways (Gao et al., 2012). Ginger also exhibits anti-inflammatory properties by reducing levels of pro-inflammatory cytokines such as TNF-α and IL-6, and contributes to improved lipid metabolism by decreasing serum triglycerides and LDL cholesterol (Al-Amin et al., 2006; Nammi et al., 2009). Histopathological evaluations in treated diabetic rats have shown preserved pancreatic islet integrity, reduced hepatic steatosis, and improved renal tissue structure, indicating ginger's protective effects on diabetes-related organ complications (Akhani et al., 2004; Saghir et al., 2021).

4.3.2. Challenges and Considerations

Despite promising results, herbal therapies often lack rigorous standardization, regulatory approval, and long-term safety data. Interactions with conventional drugs must also be carefully considered.

4.4. Nanotechnology-Based Approaches

Nanomedicine is emerging as a transformative tool in diabetes care. Applications include:

- **Nanoparticle drug delivery:** Enhances bioavailability and targeted delivery of insulin, metformin, and phytochemicals.
- **Nano-encapsulation of herbal extracts:** Improves stability and controlled release of plant-based compounds.
- **Glucose-responsive nanogels and microneedles:** Enable closed-loop insulin delivery systems.

These technologies offer improved pharmacokinetics, reduced dosing frequency, and better patient compliance (Yin et al., 2019).

4.5. Gene Therapy and Regenerative Medicine

Gene-editing tools such as CRISPR-Cas9 offer the potential to correct genetic defects in monogenic diabetes or modulate insulin pathways. Stem cell therapy aims to regenerate insulin-producing β-cells using induced pluripotent stem cells (iPSCs). While these interventions are still experimental, they offer a potential cure rather than just symptomatic control.

Table 5. Herbal and Natural Antidiabetic Agents

Sr. No	Plant Name (Botanical)	Common Name	Major Phytoconstituents	Mechanism Highlights	Animal Model & Induction	Dose & Route	Reference
1	Aegle marmelos	Bael	Marmelosin, skimmianine	↓ glucose, ↑ insulin, ↓ gluconeogenesis ,↑ body weight, improved antioxidant enzymes	STZ-induced diabetic rats	100–500 mg/kg orally	Sathish sekar & Subramanian, 2005
2	*Allium sativum*	Garlic	Allicin, S-allyl cysteine	K^+ channel modulation, SUR activation, antioxidant, herb–drug synergy	STZ-rats; normal controls	100–500 mg/kg, 14 days	Banerjee & Maulik, 2002
3	Andrographis paniculata	Creat	Andrographolide	↓ glucose, ↑ insulin sensitivity, improved liver enzymes, β-cell regeneration, AMPK activation, ↑ insulin secretion, ↓ gluconeogenesis, antioxidant	STZ-induced diabetic rats	100–400 mg/kg orally	Zhang & Tan, 2000
4	*Azadirachta indica*	Neem	Azadirachtin, nimbin, quercetin	Antioxidant; β-cell protection; α-glucosidase	STZ/ alloxan diabetic rats	50–400 mg/kg, 6–30 d	Subramanian & Padmanaban, 1999

				inhibition; insulin support			
5	Camellia sinensis	Green tea	Catechins (EGCG)	↓ glucose, ↑ insulin sensitivity, ↑ antioxidant enzymes, ↓ liver/kidney damage, ↑ GLUT4, ↓ α-amylase, ↓ cytokines, antioxidant	STZ-induced diabetic rats	100–300 mg/kg/day orally	Wolfram, 2007
6	*Cinnamomum verum*	Cinnamon	Cinnamaldehyde, eugenol	AMPK/GLUT4/ insulin signaling; α-glucosidase inhibition; anti-inflammatory	STZ, alloxan rats; db/db mice	30–1200 mg/kg, 3–6 wks	Khan et al., 2003
7	Curcuma longa	Turmeric	Curcumin	↓ glucose, HbA1c, ↑ insulin, improved liver and kidney histology, AMPK/PPARγ activation, GLUT4 translocation, antioxidant, anti-inflammatory	STZ/ alloxan diabetic rats	80–300 mg/kg/day orally	Aggarwal & Harikumar, 2009
8	*Ficus religiosa*	Sacred fig	β-sitosterol, flavonoids	Antioxidant, anti-inflammatory, β-cell protection, immunomodulatory	Neonatal HFD + STZ rats	100–400 mg/kg, 4 wk	Grover et al., 2000
9	*Gymnema sylvestre*	Gymnema	Gymnemic acids, saponins	Normoglycemia, improved lipid profile; histopathology and gene expression modulation, suppresses intestinal glucose uptake; enhances β-cell function	Alloxan-induced Wistar rats	250 mg/kg & 500 mg/kg in diet (oral)	Shanmugasundaram et al., 1990
10	*Mangifera indica*	Mango	Mangiferin, catechins, gallic acid	α-glucosidase inhibition, antioxidation, AMPK activation,	STZ-induced Wistar rats	100–400 mg/kg/day, 21–28 days	Ojewole, 2005

				GLUT4 translocation			
11	*Momordica charantia*	Bitter melon	Charantin, vicine, polypeptide-p	↓ blood glucose, ↑ insulin, enhanced glucose uptake, improved pancreas histology ↑ insulin secretion; ↓ intestinal glucose absorption; antioxidant	STZ-diabetic Wistar rats	10 mL/kg juice orally	Grover & Yadav, 2004
12	Ocimum gratissimum	Clove basil	Eugenol, flavonoids, tannins	↓ glucose, ↑ insulin, restored β-cell histology, improved lipids, α-glucosidase inhibition, antioxidant,	Alloxan/STZ diabetic rats	200–500 mg/kg orally	Eseyin et al., 2010
13	*Ocimum sanctum*	Holy basil	Eugenol, ursolic acid, rosmarinic acid	Antioxidant, anti-inflammatory, insulin signaling enhancement, β-cell protection	HFD + STZ diabetic rats	200–400 mg/kg, 28 days	Agrawal et al., 2006
14	Phyllanthus amarus	Bhumi Amla	Lignans, flavonoids, phyllanthin	↓ glucose, ↑ insulin, ↓ lipids, restored organ histology, Insulin signaling, antioxidant, β-cell regeneration, hypolipidemic	STZ-induced diabetic rats	100–400 mg/kg orally	Pari & Amarnath Satheesh, 2004
15	*Pterocarpus marsupium*	Indian kino tree	Pterostilbene, marsupsin	β-cell regeneration, enzyme inhibition, antioxidant, PPARγ activation	STZ rats (55 mg/kg)	125–500 mg/kg, 30 d	Grover et al., 2001
16	Punica granatum	Pomegranate	Punicalagin, ellagic acid	↓ glucose, ↑ insulin, ↓ lipid peroxidation, restored pancreas & kidneys, PI3K/Akt, AMPK modulation, α-glucosidase inhibition, antioxidant	STZ/alloxan diabetic rats	100–500 mg/kg/day orally	Huang et al., 2005

17	*Syzygium cumini*	Jamun	Jamboline, ellagic acid, anthocyanins	Insulin secretion, α-glucosidase inhibition, antioxidant, anti-inflammatory protection	STZ–diabetic Wistar rats	100–200 mg/kg, 30 days	Sharma et al., 2003
18	*Tinospora cordifolia*	Guduchi	Tinosporin, berberine, cordifolioside	Insulin sensitization, antioxidant, anti-inflammatory, hepatoprotection	STZ (45–60 mg/kg) ± HFD-fed rats	100–200 mg/kg, 30 d	Stanely & Menon, 2001
19	*Trigonella foenum-graecum*	Fenugreek	4-hydroxyisoleucine, diosgenin	↓ glucose, HbA_1c, lipids; ↑ GLP-1, GIP; better rheology and organ weights, Enhances incretin axis; antioxidant; enzyme modulation	Alloxan/STZ-diabetic albino/SD rats	0.44–1.74 g/kg; 200–400 mg/kg orally	Basch et al., 2003
20	Zingiber officinale	Ginger	Gingerol, shogaol	↓ glucose, ↓ HbA1c, ↑ insulin, restored pancreas, ↓ TG & LDL, ↑ GLUT4 expression, ↑ PPARγ, ↓ inflammatory cytokines	STZ/alloxan diabetic rats	100–500 mg/kg orally	Al-Amin et al., 2006

4.6. Integrated and Personalized Medicine

4.6. Integrated and Personalized Medicine

The future of diabetes therapy lies in personalized medicine, integrating genetic, metabolic, and lifestyle data to tailor treatment. Tools like continuous glucose monitoring, pharmacogenomics, and AI-driven decision support systems will facilitate individualized care plans and improved outcomes.

5. Future Perspectives and Challenges

Despite remarkable progress in diabetes diagnostics and therapeutics, several critical challenges hinder the widespread implementation and effectiveness of current and emerging strategies. Moving forward, a multidisciplinary, patient-centered, and globally coordinated approach will be essential to address the growing burden of diabetes mellitus.

5.1. Affordability and Accessibility

One of the foremost challenges in diabetes care is the **economic burden** of long-term management. Advanced diagnostic tools (e.g., CGMs, biosensors) and novel pharmacotherapies (e.g., GLP-1 receptor agonists, SGLT2 inhibitors) often remain inaccessible to populations in low- and

middle-income countries due to high costs and lack of healthcare infrastructure. The **cost of insulin** continues to be a significant barrier, particularly for T1DM patients, despite it being on the World Health Organization's list of essential medicines. Affordability also extends to continuous monitoring devices, point-of-care diagnostics, and personalized therapies, which are not yet universally available. Public-private partnerships and policy reforms are needed to ensure equitable access to life-saving technologies.

5.2. Health System Integration

The integration of advanced technologies into routine clinical practice requires **digital literacy**, training of healthcare personnel, and robust health information systems. Many healthcare settings still rely on paper-based records or lack interoperability across platforms, limiting the utility of data-driven care models. Furthermore, the successful implementation of precision diagnostics and therapeutics demands interdisciplinary collaboration among endocrinologists, pharmacologists, data scientists, and primary care providers. Models of integrated care, telemedicine, and AI-assisted platforms must be tailored for scalability across diverse populations.

5.3. Safety and Regulatory Oversight

With the introduction of biosensors, herbal medicines, and nanotherapeutics, **regulatory frameworks** must evolve to ensure safety, efficacy, and quality control. Herbal therapies, in particular, are often under-regulated, leading to variable bioactivity and potential drug–herb interactions. Similarly, **nanomedicines and gene-editing tools** face regulatory uncertainties, especially regarding long-term safety and ethical implications. Accelerated approval pathways and post-marketing surveillance will be crucial for integrating these technologies responsibly into mainstream care.

5.4. Data Privacy and Ethical Considerations

The use of wearable technologies and real-time health tracking raises concerns about **data privacy and security**. Patients must be assured of ethical data usage, consent, and protection from misuse, particularly in low-governance environments. Policies must be developed that balance innovation with privacy and digital rights.

5.5. Behavioral and Psychosocial Barriers

Diabetes is a **self-managed disease**, and patient behavior significantly influences treatment success. However, many patients face psychological barriers such as **diabetes distress**, stigma, fear of hypoglycemia, and poor health literacy, leading to non-adherence and poor outcomes.

Future models of care must address these behavioral dimensions through **motivational interviewing**, patient education, culturally appropriate counseling, and peer-support programs.

Table 6: Comparative Outcomes of Conventional vs. Novel Therapies in Diabetes Management

Therapy Type	Examples	Clinical Efficacy	Common Side Effects	Safety Profile	References
Conventional Therapy	Metformin, Insulin, Sulfonylureas	Effective in lowering fasting blood glucose and HbA1c;	GI upset (metformin), weight gain, hypoglycemia (sulfonylureas)	Long-term safety established; monitoring required	ADA, 2023; UKPDS Study

		cornerstone of T2DM treatment			
Incretin-based Therapy	GLP-1 receptor agonists (e.g., liraglutide), DPP-4 inhibitors	Moderate to high efficacy; improves insulin secretion and weight control	Nausea, pancreatitis risk (rare)	Favorable safety with cardiovascular benefits (GLP-1 RA)	Marso et al., 2016; Nauck et al., 2017
SGLT2 Inhibitors	Empagliflozin, Dapagliflozin	Reduces blood glucose and cardiovascular/renal events	Genital infections, dehydration	Generally safe; caution in elderly and renal impairment	Zinman et al., 2015; Wiviott et al., 2019
Herbal Therapies	*Momordica charantia*, *Tinospora cordifolia*	Comparable reduction in glucose levels in preclinical studies	Minimal; mostly GI discomfort or allergic reactions	Promising in short-term; human trial data limited	Patel et al., 2012; Sumanth & Mustafa, 2007
Nanomedicine-based Delivery	Insulin nanoparticles, herbal nanoformulations	Enhanced bioavailability and targeted delivery in preclinical models	Not fully evaluated in humans	High potential; needs long-term human safety assessment	Zhang et al., 2020; Sahana et al., 2019
Stem Cell Therapy	Pancreatic islet transplantation, MSCs	Experimental; shows β-cell regeneration and insulin independence in early trials	Procedure-related risks, immunogenicity	Under investigation; requires immunosuppression	Voltarelli et al., 2007; Bhansali et al., 2014

5.6. Research and Innovation Gaps

Despite numerous emerging therapies and diagnostics, the **translation of preclinical research** into clinical use remains slow. Herbal and natural products, while widely studied in vitro and in animal models, lack robust human trial data. Similarly, technologies like smart insulin patches, glucose-responsive nanoparticles, and CRISPR-based interventions remain largely investigational.

To bridge these gaps, greater emphasis must be placed on:

- Long-term clinical trials with diverse populations
- Standardization of herbal extracts
- Open-access research platforms
- Collaboration between academia, industry, and government

5.7. Global Collaboration and Policy Support

Diabetes mellitus is a **global pandemic** requiring coordinated efforts across nations. Sustainable Development Goal (SDG) 3.4 calls for reducing premature mortality from non-communicable diseases by one-third by 2030. Achieving this target will require:

- National diabetes registries
- Subsidies for essential diagnostics and drugs
- Investment in public health campaigns
- Inclusion of diabetes care in universal health coverage schemes

By aligning innovation with health policy and universal access, a more equitable future in diabetes care can be envisioned.

CONCLUSION

Diabetes mellitus is a rapidly escalating global health crisis with profound medical, economic, and social implications. Its complex etiology, diverse clinical manifestations, and long-term complications necessitate a multidimensional and integrated approach to diagnosis and therapy. Recent advances in diagnostic technologies—such as wearable biosensors, molecular biomarkers, lab-on-a-chip systems, and continuous glucose monitors—are revolutionizing early detection and real-time disease management. Simultaneously, the therapeutic landscape has expanded beyond traditional insulin and oral antidiabetic agents to include incretin-based drugs, sodium-glucose co-transporter inhibitors, and cardio-renal protective agents. Herbal and plant-based therapies rooted in traditional medicine systems offer additional avenues, particularly in resource-limited settings, although challenges related to standardization, regulation, and evidence-based validation remain. Innovations in nanomedicine, gene editing, and personalized healthcare continue to push the frontiers of diabetes management, moving the field toward disease modification and possibly cure.

However, significant barriers persist—ranging from affordability and access to regulatory oversight and health system integration. Addressing these challenges will require global collaboration, policy reforms, investment in research and education, and equitable distribution of healthcare innovations. The future of diabetes care lies in a synergistic model that combines modern biomedical technology, individualized patient care, and community-based support systems. With sustained efforts, interdisciplinary research, and a patient-centered vision, it is possible to transform the trajectory of this pandemic and significantly reduce its global burden.

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