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Review Article

ANTIHYPERGLYCEMIC EFFECT IN THE MANAGEMENT
OF DIABETES MELLITUSShubhangi Ganpat Atole^{1*}, Bhumika santosh Bhagwat², Aishwarya Dnyaneshwar
Takale³, Dr. Vijay Sonawane⁴¹Dattakala College of Pharmacy, Pune - Solapur Rd, Chincholi, Maharashtra 413130² Assistant Professor, Dattakala College of Pharmacy, Pune - Solapur Rd, Chincholi,
Maharashtra 413130**Abstract:**

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin resistance, or a combination of both. The increasing global prevalence of diabetes has created a need for effective, safe, and accessible therapeutic strategies to achieve glycemic control and reduce diabetes-associated complications. This review aims to discuss the antihyperglycemic effects of conventional and emerging therapeutic agents, emphasizing their mechanisms of action, clinical applications, safety profiles, and future perspectives in diabetes management. Relevant scientific literature, clinical studies, review articles, and established clinical guidelines concerning diabetes pathophysiology, glucose-lowering pharmacotherapy, and natural products were considered to develop a narrative overview of current therapeutic approaches. Antihyperglycemic agents reduce blood glucose through several mechanisms, including suppression of hepatic glucose production, stimulation of insulin secretion, improvement of insulin sensitivity, enhancement of incretin activity, inhibition of intestinal carbohydrate digestion, and promotion of urinary glucose excretion. Major drug classes include biguanides, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, and insulin preparations. Emerging approaches, including dual incretin receptor agonists and advanced insulin delivery systems, offer additional therapeutic opportunities. Medicinal plants and naturally derived compounds have also demonstrated potential antihyperglycemic activity; however, their clinical effectiveness and safety require further rigorous evaluation. Treatment selection must consider glycemic efficacy, hypoglycemia risk, body-weight effects, cardiovascular and renal outcomes, adverse reactions, and patient-specific requirements. Individualized antihyperglycemic therapy, combined with lifestyle modification and regular monitoring, is essential for effective diabetes management. Continued research, high-quality clinical trials, and improved access to evidence-based treatments may further enhance therapeutic outcomes and reduce the long-term burden of diabetes mellitus.

Keywords: Diabetes mellitus; antihyperglycemic agents; hyperglycemia; insulin resistance; glycemic control; antidiabetic drugs; medicinal plants; diabetes management.

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INTRODUCTION:

Diabetes mellitus is a chronic, multifactorial metabolic disorder characterized by persistent elevation of blood glucose levels resulting from defects in insulin secretion, insulin action, or both. Insulin is a peptide hormone secreted by pancreatic beta cells that plays a central role in maintaining glucose homeostasis by promoting glucose uptake in insulin-sensitive tissues, regulating hepatic glucose production, and facilitating the storage and utilization of nutrients.¹

The global burden of diabetes has increased considerably because of population ageing, urbanization, sedentary lifestyles, dietary changes, increasing prevalence of obesity, and longer life expectancy. Type 2 diabetes mellitus accounts for the majority of diagnosed diabetes cases, although type 1 diabetes and other forms also contribute significantly to the overall disease burden. The consequences extend beyond individual health to healthcare expenditure, productivity losses, and the long-term demand for medical services. Early diagnosis, sustained glycemic control, prevention of complications, and equitable access to effective treatment are consequently important public health priorities. The World Health Organization and the International Diabetes Federation provide complementary epidemiological data and guidance for understanding the worldwide impact of diabetes mellitus.²

The clinical management of diabetes requires an integrated approach involving lifestyle modification, nutritional management, physical activity, patient education, regular monitoring, and pharmacological intervention when indicated. The selection of treatment depends on the type of diabetes, degree of hyperglycemia, age, body weight, kidney function, cardiovascular risk, comorbidities, treatment affordability, and individual preferences. Although conventional glucose-lowering medicines have substantially improved diabetes management, no single therapeutic approach is suitable for every patient. These considerations have stimulated continued

research into agents that improve insulin secretion and sensitivity, reduce glucose production or absorption, enhance urinary glucose excretion, and provide additional cardiovascular, renal, and metabolic benefits.³

Classification of diabetes mellitus and its therapeutic implications

Diabetes mellitus comprises several clinical conditions that differ in their underlying pathophysiology, progression, and treatment requirements. The principal categories include type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes mellitus, and other specific forms associated with genetic defects, pancreatic diseases, endocrinopathies, or drug-induced disturbances of glucose metabolism. Understanding these categories is essential for selecting appropriate antihyperglycemic interventions because the mechanisms responsible for hyperglycemia vary among individuals and disease types. A therapeutic strategy that is effective for insulin resistance may not be sufficient when endogenous insulin production is severely deficient.⁴

Type 1 diabetes mellitus is primarily associated with autoimmune destruction of pancreatic beta cells, resulting in severe insulin deficiency. Insulin replacement is essential for survival and for preventing acute metabolic complications. In contrast, type 2 diabetes mellitus is characterized by a combination of insulin resistance, progressive beta-cell dysfunction, and dysregulated hepatic glucose production. Its management commonly involves lifestyle interventions and glucose-lowering medications selected according to glycemic requirements, comorbidities, and individual treatment goals. Gestational diabetes mellitus is diagnosed during pregnancy and requires careful management to reduce adverse maternal and fetal outcomes. Other specific forms may require treatment directed toward the underlying genetic, pancreatic, endocrine, or medication-related cause.⁵

Table 1. Classification of Diabetes Mellitus and Its Therapeutic Implications

Type of diabetes mellitus	Major pathophysiological characteristics	Common clinical features	Therapeutic implications
Type 1 diabetes mellitus (T1DM)	Autoimmune destruction of pancreatic beta cells resulting in severe or absolute insulin deficiency	Polyuria, polydipsia, unexplained weight loss, fatigue, and risk of diabetic ketoacidosis	Lifelong insulin therapy is essential. Continuous glucose monitoring, insulin pumps, nutritional management, and patient education may improve glycemic control.
Type 2 diabetes mellitus (T2DM)	Insulin resistance, progressive beta-cell dysfunction, and increased hepatic glucose production	Frequently associated with overweight or obesity, fatigue, increased thirst, and gradual disease	Lifestyle modification and individualized pharmacotherapy, including metformin, SGLT2 inhibitors, GLP-1 receptor agonists, other glucose-lowering

		progression	agents, or insulin when indicated.
Gestational diabetes mellitus (GDM)	Glucose intolerance first recognized during pregnancy that does not meet criteria for overt diabetes outside pregnancy	Often asymptomatic; detected through antenatal screening	Medical nutrition therapy, appropriate physical activity, and glucose monitoring; insulin or other guideline-supported treatment when required.
Monogenic diabetes	Genetic defects affecting beta-cell function or insulin secretion, including maturity-onset diabetes of the young (MODY) and neonatal diabetes	Often early onset; family history may be prominent, depending on the subtype	Genetic evaluation and subtype-specific management. Some forms respond to sulfonylureas, whereas others require insulin or alternative treatment.
Pancreatic or exocrine disease-related diabetes	Damage to pancreatic tissue associated with chronic pancreatitis, pancreatic surgery, cystic fibrosis, or other pancreatic disorders	Features of diabetes accompanied by an underlying pancreatic condition; impaired insulin and sometimes glucagon secretion	Treat the underlying disorder where possible, individualize glucose-lowering therapy, and assess nutritional status and pancreatic exocrine function. Insulin may be required.
Drug- or chemical-induced diabetes	Disturbance of glucose regulation caused by medicines or chemicals, such as glucocorticoids and certain anticancer therapies	Hyperglycemia developing or worsening during exposure to a causative agent	Review the causative medication, monitor glucose, modify treatment where clinically feasible, and introduce individualized glucose-lowering therapy as necessary.
Other specific forms of diabetes	Endocrine disorders, genetic syndromes, or other defined conditions affecting insulin secretion or action	Clinical presentation varies according to the underlying cause	Management directed toward the underlying disease alongside appropriate glucose-lowering treatment.

Concept and significance of antihyperglycemic effects

Antihyperglycemic effects refer to the ability of a therapeutic intervention to reduce elevated blood glucose concentrations toward an individualized target range. These effects may be achieved through different physiological and biochemical pathways, including suppression of excessive hepatic glucose production, stimulation of insulin secretion, improvement of peripheral insulin sensitivity, delayed intestinal carbohydrate digestion, enhancement of incretin activity, and increased renal glucose excretion. The availability of agents acting through distinct mechanisms has expanded the possibilities for individualized treatment and combination therapy in diabetes mellitus.⁶

Epidemiological significance and need for improved treatment strategies

The increasing prevalence of diabetes mellitus highlights the need for effective prevention, early diagnosis, and long-term disease management. According to the International Diabetes Federation's Diabetes Atlas, 11th edition, an estimated 589 million adults aged 20–79 years were living with diabetes worldwide in 2024, equivalent to approximately 11.1% of this age group. The number is projected to reach approximately 853 million by 2050 if current demographic and epidemiological trends continue. The Atlas also estimates that a substantial proportion of affected adults remain undiagnosed, increasing the possibility that the disease will be recognized only after complications have developed.

Table 2. Global burden of diabetes mellitus and projected trends

Epidemiological indicator	Estimate
Adults aged 20–79 years living with diabetes in 2024	589 million
Estimated global prevalence in 2024	11.1%
Adults with diabetes estimated to be undiagnosed	252 million
Projected adults living with diabetes by 2050	853 million
Projected global prevalence by 2050	13.0%

Pathophysiology of Hyperglycemia

Hyperglycemia is the principal metabolic abnormality associated with diabetes mellitus and develops when the mechanisms responsible for maintaining glucose homeostasis become impaired.

Under normal physiological conditions, blood glucose concentrations are regulated through coordinated interactions among the pancreas, liver, skeletal muscle, adipose tissue, gastrointestinal tract, kidneys, and central nervous system.

Following food intake, pancreatic beta cells release insulin, which promotes glucose uptake by skeletal muscle and adipose tissue and suppresses hepatic glucose production.⁷

Insulin resistance in skeletal muscle, liver, and adipose tissue

Insulin resistance refers to a diminished biological response to insulin in target tissues. It is a major

contributor to the development of type 2 diabetes mellitus and is commonly associated with obesity, physical inactivity, ectopic lipid accumulation, and genetic susceptibility. In skeletal muscle, insulin resistance reduces insulin-stimulated glucose uptake and utilization, limiting the disposal of glucose following meals.⁸

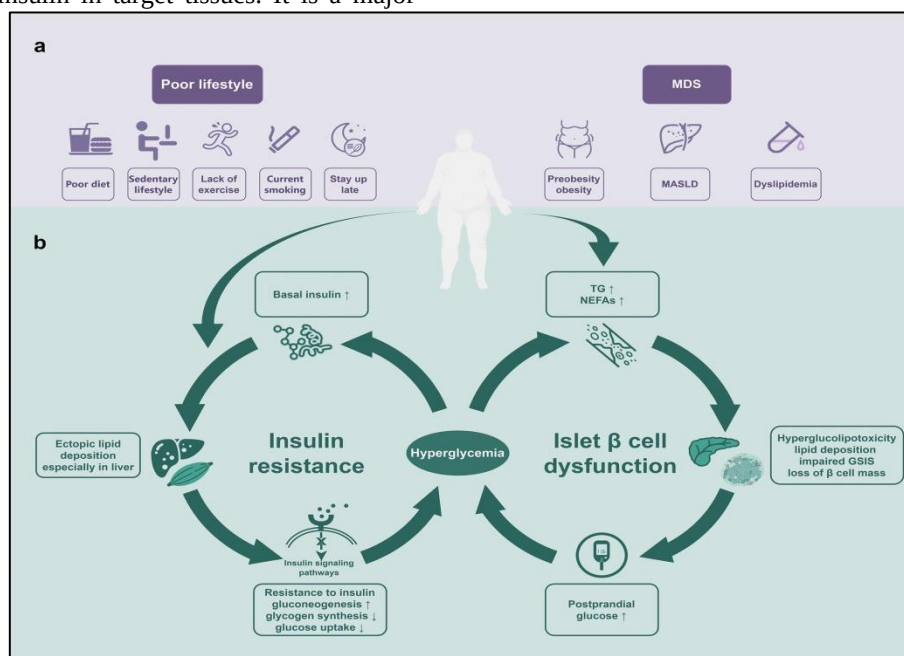


Figure 1. Pathophysiology of diabetes mellitus

Impaired pancreatic beta-cell function

Pancreatic beta cells play a central role in glucose homeostasis by detecting changes in blood glucose and secreting insulin accordingly. During the early stages of insulin resistance, beta cells may compensate by increasing insulin secretion. However, prolonged metabolic stress can impair their ability to maintain adequate insulin production. Contributing factors include chronic exposure to elevated glucose and fatty acid concentrations, oxidative stress, endoplasmic reticulum stress, islet inflammation, and genetic susceptibility.⁹

Increased hepatic glucose production

The liver is a major regulator of circulating glucose, particularly during fasting. It maintains blood glucose through glycogenolysis, the breakdown of stored glycogen, and gluconeogenesis, the formation of glucose from non-carbohydrate precursors such as lactate, glycerol, and amino acids. Insulin normally suppresses these processes after food intake, while glucagon promotes hepatic glucose release when glucose availability decreases.

Abnormal glucagon secretion

Glucagon, secreted by pancreatic alpha cells, acts in opposition to insulin by stimulating hepatic glycogenolysis and gluconeogenesis. Under normal conditions, glucagon secretion increases when blood glucose falls and is suppressed when glucose

concentrations rise after meals. In diabetes mellitus, this regulation may become impaired, leading to inappropriate glucagon secretion during hyperglycemia.

Altered incretin activity

The incretin effect describes the greater insulin response to orally consumed glucose than to an equivalent glucose stimulus administered intravenously. It is mediated mainly by glucagon-like peptide-1 (GLP-1), released from intestinal L cells, and glucose-dependent insulinotropic polypeptide (GIP), released from intestinal K cells. These hormones enhance glucose-dependent insulin secretion after meals. GLP-1 also suppresses glucagon secretion when glucose concentrations are elevated, slows gastric emptying, and influences appetite and satiety.

Increased renal glucose reabsorption

The kidneys contribute to glucose homeostasis by filtering glucose from the blood and reabsorbing most of it through sodium-glucose cotransporters in the proximal renal tubules. SGLT2 is responsible for the majority of renal glucose reabsorption under normal physiological conditions. Although this process prevents excessive glucose loss in urine, it can contribute to persistent hyperglycemia when renal glucose reabsorption remains substantial despite elevated plasma glucose.

Contribution of obesity, inflammation, and oxidative stress

Obesity, particularly excess visceral and ectopic fat accumulation, is closely associated with insulin resistance. Enlarged adipocytes and altered adipose tissue function can promote the release of free fatty acids and inflammatory mediators, including tumor necrosis factor- α and interleukin-6. These signals may interfere with insulin signaling and contribute to metabolic inflammation. In addition, lipid accumulation in the liver and skeletal muscle can disrupt normal cellular responses to insulin.

Antihyperglycemic Effects: Mechanisms and Therapeutic Targets

Antihyperglycemic agents reduce elevated blood glucose concentrations by targeting one or more of the physiological mechanisms involved in glucose regulation. These medicines differ in their molecular targets, onset of action, duration of effect, and effects on body weight and other metabolic outcomes. An understanding of these mechanisms is essential for evaluating therapeutic efficacy, selecting suitable medicines, and designing rational combination regimens. The principal therapeutic strategies include stimulation or replacement of insulin, improvement of insulin sensitivity, suppression of hepatic glucose production, reduction of intestinal carbohydrate digestion, enhancement of incretin signaling, and promotion of urinary glucose excretion.¹⁰⁻¹⁴

Stimulation of insulin secretion

Insulin secretagogues increase insulin release from pancreatic beta cells. Sulfonylureas, such as glimepiride and gliclazide, stimulate insulin secretion by binding to the sulfonylurea receptor 1 (SUR1) component of ATP-sensitive potassium channels. Channel closure causes membrane depolarization, calcium influx, and insulin granule exocytosis. Meglitinides act through related pathways and are used primarily to improve meal-related glucose control. These agents can effectively reduce blood glucose, but their insulin-secretory effects may occur independently of the prevailing glucose concentration, increasing the risk of hypoglycemia. Their effectiveness also depends on the presence of sufficient functional beta-cell capacity. Insulin preparations provide an alternative by replacing or supplementing endogenous insulin when secretion is inadequate.

Improvement of insulin sensitivity

Insulin sensitizers improve the response of peripheral tissues to endogenous insulin. Metformin primarily reduces hepatic glucose production and also improves aspects of peripheral glucose utilization. Its actions involve multiple cellular pathways, and no single mechanism fully explains its overall clinical effect. Thiazolidinediones, such as pioglitazone, activate PPAR- γ , a nuclear receptor involved in the regulation of genes related to lipid metabolism, adipocyte function, and insulin sensitivity. Improved insulin action can increase glucose

utilization and reduce excessive hepatic glucose output. However, treatment selection must account for adverse effects; for example, pioglitazone may cause fluid retention, weight gain, and worsening of heart failure in susceptible patients.

Suppression of hepatic gluconeogenesis

Hepatic gluconeogenesis is an important source of circulating glucose during fasting. Excessive glucose production contributes substantially to fasting hyperglycemia in type 2 diabetes mellitus. Metformin reduces hepatic glucose production through a combination of metabolic and cellular effects, thereby improving fasting glucose and contributing to lower HbA1c. Insulin also suppresses hepatic glucose production, while other treatments can influence this process indirectly through changes in glucagon secretion, insulin sensitivity, and energy balance. Reducing inappropriate hepatic glucose release is therefore a central therapeutic strategy in the management of diabetes.

Reduction of intestinal carbohydrate absorption

Alpha-glucosidase inhibitors, including acarbose and voglibose, inhibit enzymes responsible for the breakdown of complex carbohydrates and disaccharides into absorbable monosaccharides in the small intestine. This action delays carbohydrate digestion and glucose absorption, reducing postprandial glucose excursions. Their effect is most evident following carbohydrate-containing meals. Gastrointestinal adverse effects, including flatulence, abdominal discomfort, and diarrhea, may limit tolerability. Nevertheless, these agents illustrate how modifying nutrient digestion can help control postprandial hyperglycemia without directly stimulating insulin secretion.

Enhancement of glucose-dependent insulin secretion

Incretin-based therapies improve glucose regulation by enhancing the physiological effects of intestinal hormones. GLP-1 receptor agonists, such as semaglutide and liraglutide, activate GLP-1 receptors to increase glucose-dependent insulin secretion, suppress inappropriate glucagon secretion, and influence appetite and gastric emptying. DPP-4 inhibitors, such as sitagliptin and linagliptin, inhibit the enzyme responsible for degrading endogenous incretin hormones, thereby prolonging their activity. Because these treatments enhance insulin secretion in a glucose-dependent manner, the risk of hypoglycemia is generally low when they are used alone, although the risk can increase when combined with insulin or sulfonylureas. Dual GIP/GLP-1 receptor agonists, including tirzepatide, target two incretin pathways and can produce substantial improvements in glycemic control and body weight in appropriate patients.

Promotion of urinary glucose excretion

SGLT2 inhibitors reduce glucose reabsorption in the proximal renal tubules by inhibiting sodium–glucose cotransporter 2. This increases urinary glucose excretion and lowers blood glucose independently of direct insulin stimulation. These agents can also produce modest reductions in body weight and blood pressure. Importantly, selected SGLT2 inhibitors have demonstrated cardiovascular and kidney benefits in specific patient populations, including people with heart failure or chronic kidney disease. However, their use requires consideration of kidney function, volume status, genital infections, and the risk of ketoacidosis, which may occur even without markedly elevated blood glucose.

Regulation of appetite, body weight, and glucose homeostasis

Body weight and energy balance influence insulin sensitivity and long-term glycemic control. Excess adiposity, especially visceral fat accumulation, is associated with insulin resistance, chronic low-grade inflammation, and increased metabolic stress. Lifestyle interventions involving balanced nutrition, physical activity, and weight management are therefore fundamental components of diabetes care. Pharmacological approaches can complement these measures. GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists can reduce appetite and energy intake, while SGLT2 inhibitors may produce modest weight loss through urinary calorie excretion. By contrast, insulin and sulfonylureas can be associated with weight gain. The effects on body weight, hypoglycemia, tolerability, and cardiorenal outcomes should therefore be considered alongside glucose-lowering efficacy when selecting therapy.

Conventional Antihyperglycemic Agents

Antihyperglycemic agents are used to control elevated blood glucose levels in patients with diabetes mellitus. These drugs act through different mechanisms, including reducing hepatic glucose production, stimulating insulin secretion, improving insulin sensitivity, delaying carbohydrate absorption, and increasing urinary glucose excretion. The selection of therapy depends on diabetes type, glycemic control, comorbidities, adverse effects, and patient-specific requirements.¹⁵⁻²⁰

Biguanides

Metformin is the principal biguanide used in type 2 diabetes mellitus. It primarily reduces hepatic glucose production and improves glycemic control. It is generally weight-neutral or associated with modest weight loss and has a low risk of hypoglycemia when used alone. Gastrointestinal disturbances and vitamin B12 deficiency are important considerations.

Sulfonylureas

Sulfonylureas, such as glimepiride and gliclazide, stimulate insulin secretion by closing ATP-

sensitive potassium channels in pancreatic beta cells. They effectively reduce blood glucose but may cause hypoglycemia and weight gain. Their effectiveness depends on residual beta-cell function.

Meglitinides

Repaglinide and nateglinide are short-acting insulin secretagogues that primarily control postprandial hyperglycemia. They are administered in relation to meals but may cause hypoglycemia and weight gain.

Thiazolidinediones

Pioglitazone improves insulin sensitivity through activation of peroxisome proliferator-activated receptor gamma (PPAR- γ). It improves glucose utilization but may cause weight gain, fluid retention, and worsening of heart failure in susceptible patients.

Alpha-glucosidase inhibitors

Acarbose and voglibose delay intestinal carbohydrate digestion by inhibiting alpha-glucosidase enzymes. They reduce postprandial glucose elevations but may cause flatulence, abdominal discomfort, and diarrhea.

DPP-4 inhibitors

Sitagliptin, linagliptin, and vildagliptin inhibit dipeptidyl peptidase-4, prolonging endogenous incretin activity. They improve glucose-dependent insulin secretion, have a low hypoglycemia risk when used alone, and are generally weight-neutral.

SGLT2 inhibitors

Empagliflozin and dapagliflozin inhibit renal glucose reabsorption, increasing urinary glucose excretion. They lower blood glucose and may provide cardiovascular and kidney benefits in appropriate patients. Important risks include genital infections, volume depletion, and diabetic ketoacidosis.

GLP-1 receptor agonists

Semaglutide, liraglutide, and dulaglutide enhance glucose-dependent insulin secretion, suppress inappropriate glucagon secretion, and regulate appetite. They improve glycemic control and can promote weight loss. Gastrointestinal adverse effects are common.

Dual GIP/GLP-1 receptor agonists

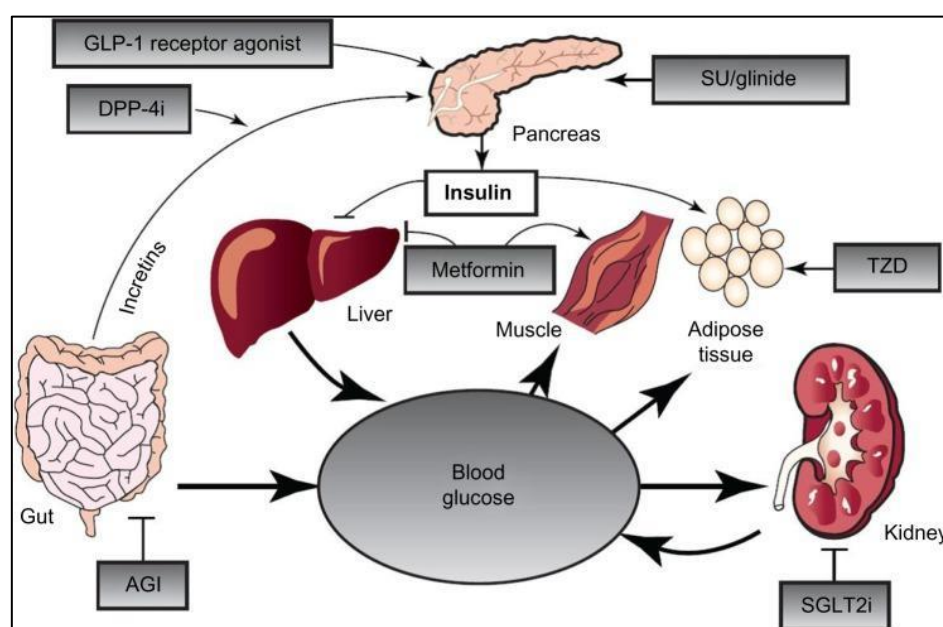
Tirzepatide activates both GIP and GLP-1 receptors, improving glycemic control and reducing body weight. Gastrointestinal adverse effects, cost, and individual clinical considerations may influence its use.

Insulin and insulin analogues

Insulin is essential in type 1 diabetes and is used in type 2 diabetes when clinically indicated. Rapid-acting, short-acting, intermediate-acting, and long-acting formulations support different treatment requirements. Hypoglycemia, weight gain, and administration burden are important limitations.

Table 3. Antihyperglycemic Agents

Drug class	Examples	Main action	Major limitation
Biguanides	Metformin	Reduces hepatic glucose production	Gastrointestinal effects
Sulfonylureas	Glimepiride	Stimulates insulin secretion	Hypoglycemia
Meglitinides	Repaglinide	Controls postprandial glucose	Hypoglycemia
Thiazolidinediones	Pioglitazone	Improves insulin sensitivity	Fluid retention
Alpha-glucosidase inhibitors	Acarbose	Delays carbohydrate digestion	Gastrointestinal effects
DPP-4 inhibitors	Sitagliptin	Enhances incretin activity	Modest glucose-lowering effect
SGLT2 inhibitors	Empagliflozin	Increases urinary glucose excretion	Genital infections; ketoacidosis risk
GLP-1 receptor agonists	Semaglutide	Enhances incretin signaling	Gastrointestinal effects
Dual GIP/GLP-1 agonist	Tirzepatide	Activates two incretin receptors	Gastrointestinal effects
Insulin preparations	Human insulin	Replaces or supplements insulin	Hypoglycemia

**Figure 2. Molecular and physiological targets of antihyperglycemic agents**

Emerging and Novel Antihyperglycemic Therapies

The development of novel antihyperglycemic therapies aims to improve glycemic control, reduce body weight, minimize adverse effects, and address the limitations of existing treatments. Recent advances include dual incretin receptor agonists, new oral and injectable formulations, advanced insulin delivery systems, and investigational approaches targeting pancreatic beta-cell function and glucose regulation. Although some newer therapies are already approved for clinical use, others remain under investigation and require further evidence regarding long-term efficacy and safety.²¹⁻²³

Newer incretin-based therapies

Incretin-based therapies have expanded the treatment options for type 2 diabetes mellitus.

GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists improve glucose-dependent insulin secretion and influence appetite regulation. Tirzepatide, a dual GIP/GLP-1 receptor agonist, has demonstrated substantial improvements in glycemic control and body weight in clinical trials. Newer formulations and dosing approaches aim to improve convenience, adherence, and therapeutic effectiveness. However, gastrointestinal adverse effects, cost, contraindications, and individual treatment requirements remain important considerations.

Oral peptide and non-peptide therapies

Oral formulations of peptide-based medicines represent an important development in drug delivery because peptides are generally susceptible to enzymatic degradation and have limited intestinal permeability. Oral semaglutide provides

an established example of an oral GLP-1 receptor agonist formulation. Research into oral delivery technologies, absorption enhancers, and non-peptide receptor agonists may further expand treatment options. Nevertheless, bioavailability, dosing requirements, stability, and clinical safety must be evaluated for each formulation.

Novel insulin formulations and delivery systems

Advances in insulin therapy include rapid-acting and ultra-long-acting insulin analogues, inhaled insulin, insulin pumps, and automated insulin delivery systems. These approaches aim to better approximate physiological insulin secretion and improve flexibility in daily diabetes management. Continuous glucose monitoring can support dose adjustment and reduce the burden of frequent finger-prick testing. However, device cost, training, accessibility, and the risk of hypoglycemia remain important challenges.

Glucose-responsive insulin technologies

Glucose-responsive insulin is an emerging research approach designed to adjust insulin activity according to changes in blood glucose

concentrations. Potential strategies include glucose-sensitive materials, modified insulin molecules, and delivery systems that respond to glucose-related biochemical signals. The intended objective is to improve glucose control while reducing the risk of hypoglycemia. Most such approaches remain investigational, and substantial research is required to establish reliable glucose responsiveness, safety, and clinical effectiveness.

Emerging molecular targets and beta-cell replacement

Research is exploring additional targets involved in glucose metabolism, insulin sensitivity, inflammation, and pancreatic beta-cell preservation. Cell-based therapies and islet transplantation are also being investigated to restore insulin-producing capacity in selected patients with severe insulin deficiency. These approaches may offer future therapeutic opportunities, but their applicability is limited by issues such as immune rejection, immunosuppression, cell survival, manufacturing complexity, and long-term safety.²⁴⁻²⁵

Table 4. Emerging Antihyperglycemic Therapeutic Strategies

Therapeutic approach	Representative example	Potential benefit	Major limitation
Dual incretin receptor agonism	Tirzepatide	Improved glycemic control and weight reduction	Gastrointestinal effects and cost
Oral peptide delivery	Oral semaglutide	Avoids injection administration	Specific dosing and administration requirements
Advanced insulin delivery	Insulin pumps and automated delivery systems	More flexible insulin administration	Cost, training, and device dependence
Glucose-responsive insulin	Investigational glucose-sensitive insulin systems	Potentially better glucose-responsive insulin action	Clinical validation remains necessary
Beta-cell replacement	Islet transplantation and cell-based approaches	Potential restoration of insulin production	Immune rejection, availability, and long-term safety
Novel molecular targets	Investigational metabolic targets	Potential new mechanisms of glucose regulation	Variable evidence and development status

Medicinal Plants and Natural Products with Antihyperglycemic Potential

Medicinal plants and naturally derived compounds have attracted interest as potential sources of antihyperglycemic agents. Various plant extracts contain bioactive constituents, including polyphenols, flavonoids, alkaloids, saponins, and terpenoids, that may influence glucose metabolism, insulin sensitivity, carbohydrate digestion, and oxidative stress. Although traditional use and preclinical studies provide a basis for further investigation, the clinical effectiveness and safety of natural products vary considerably.²⁶⁻²⁸

Gymnema sylvestre

Gymnema sylvestre is a medicinal plant traditionally used in the management of diabetes. Gymnemic acids are among its principal bioactive constituents and have been investigated for their potential effects on intestinal glucose handling and glucose regulation. Some preliminary studies

suggest possible improvements in glycemic parameters.

Momordica charantia

Momordica charantia, commonly known as bitter melon, contains several potentially bioactive constituents, including cucurbitane-type compounds and other phytochemicals investigated for their metabolic effects. Proposed mechanisms include modulation of glucose uptake, insulin signaling, and carbohydrate metabolism. Experimental findings are promising in some settings, but clinical studies have produced variable results. Differences in preparation, dosage, and study quality prevent firm conclusions about its effectiveness as a diabetes treatment.

Trigonella foenum-graecum

Trigonella foenum-graecum, or fenugreek, contains soluble dietary fiber, including galactomannan, as well as other constituents investigated for their metabolic effects. Its fiber content may delay carbohydrate absorption and reduce postprandial

glucose excursions. Other proposed mechanisms include effects on insulin secretion and insulin sensitivity. Although some clinical studies suggest potential improvements in glycemic parameters, variations in seed preparation and dosage limit direct comparisons. Fenugreek may also affect gastrointestinal tolerance and interact with glucose-lowering medicines.

Berberis species and berberine

Berberine is a naturally occurring alkaloid found in several plant genera, including *Berberis*. It has been investigated for its potential effects on glucose and lipid metabolism, including pathways associated with cellular energy regulation and insulin sensitivity. Some clinical studies have reported improvements in glycemic parameters, but study heterogeneity, formulation differences, and limitations in the quality of available evidence require cautious interpretation. Potential drug interactions and gastrointestinal adverse effects must also be considered. *Berberine* should not be assumed to be equivalent to an approved antidiabetic medicine.

Cinnamon and other polyphenol-rich plants

Table 5. Selected Medicinal Plants and Natural Products with Potential Antihyperglycemic Effects

Medicinal plant or compound	Major constituents	Proposed mechanism	Key evidence limitation
<i>Gymnema sylvestre</i>	Gymnemic acids	Potential effects on glucose absorption and glucose regulation	Limited high-quality clinical evidence
<i>Momordica charantia</i>	Cucurbitane-type compounds and other phytochemicals	Potential modulation of glucose metabolism and insulin signaling	Variable results across clinical studies
<i>Trigonella foenum-graecum</i>	Galactomannan, 4-hydroxyisoleucine	Delayed carbohydrate absorption and possible metabolic effects	Variation in preparation and dosage
<i>Berberis species</i>	Berberine	Modulation of metabolic signaling and glucose regulation	Evidence quality, bioavailability, and interactions
<i>Cinnamon</i>	Polyphenols and other constituents	Proposed effects on insulin sensitivity	Inconsistent clinical findings and product variability

Comparative Evaluation of Antihyperglycemic Agents

Antihyperglycemic agents differ in their glucose-lowering efficacy, effects on body weight, risk of hypoglycemia, safety, and additional cardiovascular or renal benefits. Therefore, treatment selection should be individualized according to the patient's glycemic status, comorbidities, affordability, and treatment preferences.²⁹⁻³¹

Table 6. Comparative Evaluation of Antihyperglycemic Agents

Drug class	Glycemic efficacy	Weight effect	Hypoglycemia risk when used alone
Metformin	High	Neutral or modest loss	Low
Sulfonylureas	High	Gain	High
DPP-4 inhibitors	Modest	Neutral	Low
SGLT2 inhibitors	Moderate to high, depending on renal function and agent	Loss	Low
GLP-1 receptor agonists	High to very high, depending on agent	Loss	Low
Thiazolidinediones	High	Gain	Low

Insulin	High; dose-dependent	Gain	High
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Clinical Management and Individualized Selection of Therapy

Effective diabetes management requires a combination of lifestyle modification, appropriate pharmacological treatment, and regular monitoring. Medical nutrition therapy, physical activity, weight management, and patient education are essential components of care. Pharmacological treatment should be selected according to diabetes type, HbA1c, risk of hypoglycemia, kidney function, cardiovascular disease, heart failure, obesity, and treatment cost. In type 1 diabetes mellitus, insulin replacement is essential. In type 2 diabetes mellitus, treatment may involve one or more glucose-lowering medicines. SGLT2 inhibitors and GLP-1 receptor agonists with demonstrated outcome benefits may be prioritized for suitable patients with specific cardiovascular or kidney conditions, independently of the need for additional glucose lowering. Regular assessment of HbA1c, blood glucose, adverse effects, medication adherence, and treatment response helps determine whether therapy should be continued or adjusted.²¹⁻²⁷

Table 7. Factors Influencing the Selection of Antihyperglycemic Therapy

Clinical factor	Therapeutic consideration
Type 1 diabetes	Insulin replacement is essential
Type 2 diabetes with obesity	Consider agents that support weight reduction
Heart failure	Consider an SGLT2 inhibitor with demonstrated benefit when appropriate
Chronic kidney disease	Select therapy according to renal function and demonstrated kidney benefits
High hypoglycemia risk	Prefer suitable agents with a lower risk of hypoglycemia
Limited affordability	Consider effective, accessible, and appropriate treatment options
Inadequate glycemic control	Reassess adherence and consider treatment intensification

Safety, Adverse Effects, and Drug Interactions

The safety of antihyperglycemic agents is a major consideration in diabetes management. Sulfonylureas and insulin can cause hypoglycemia, while metformin commonly causes gastrointestinal disturbances and may contribute to vitamin B12 deficiency with long-term use. SGLT2 inhibitors are associated with genital infections, volume depletion, and a risk of diabetic ketoacidosis. GLP-1 receptor agonists commonly produce gastrointestinal adverse effects, whereas thiazolidinediones may cause fluid retention and weight gain.²⁵⁻³⁰

Drug interactions, renal and hepatic function, age, nutritional status, and concomitant illnesses can influence treatment safety. Combining insulin or sulfonylureas with other glucose-lowering agents may increase hypoglycemia risk and require dose adjustment. Patients should receive appropriate education regarding medication use, glucose monitoring, warning signs of adverse effects, and circumstances requiring medical assessment. Regular clinical review and pharmacovigilance help improve treatment safety and adherence.

CONCLUSION:

Diabetes mellitus remains a major global health challenge requiring effective and sustained control of blood glucose concentrations. This review highlights the diverse mechanisms through which antihyperglycemic agents regulate glucose homeostasis, including stimulation of insulin secretion, improvement of insulin sensitivity, suppression of hepatic glucose production, modulation of incretin activity, and enhancement of urinary glucose excretion. Conventional medicines remain important in clinical practice, while newer

therapies, particularly SGLT2 inhibitors and incretin-based agents, have expanded treatment options by offering additional benefits for selected patients beyond glycemic control. The potential role of medicinal plants and naturally derived compounds provides further opportunities for drug discovery and therapeutic development. Nevertheless, variability in preparation, limited clinical evidence, safety concerns, and possible drug interactions necessitate careful evaluation before their routine clinical use. Individualized treatment selection based on diabetes type, comorbidities, renal function, body weight, hypoglycemia risk, affordability, and patient preferences is essential for optimizing outcomes. Future research should prioritize long-term safety, comparative effectiveness, standardized natural products, innovative drug delivery systems, and accessible treatment strategies. Integrating evidence-based pharmacotherapy with lifestyle modification, patient education, and regular monitoring remains fundamental to improving glycemic control and reducing diabetes-associated complications.

CONFLICT OF INTEREST:

The Author declares that there is no conflict of interest.

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