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A Comprehensive Review Of Neomarica Gracilis: Phytochemistry, Antidiabetic Activity, And Therapeutic Prospects

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Abstract

A chronic metabolic disorder called diabetes mellitus is characterised by persistent hyperglycemia brought on by decreased insulin production, insulin resistance, or both. The global prevalence of diabetes continues to increase, necessitating the development of safer and more effective therapeutic agents. Medicinal plants have gained significant attention due to their diverse bioactive compounds and minimal adverse effects compared to synthetic drugs. Neomarica gracilis, an ornamental perennial herb belonging to the Iridaceae family, has recently emerged as a promising medicinal plant because of its "rich phytochemical composition, including flavonoids, phenolic acids, alkaloids, tannins, saponins, and terpenoids". These secondary metabolites have anti-inflammatory, glucose-lowering, and antioxidant properties that may be useful for managing diabetes. Streptozotocin (STZ)-induced diabetic rats represent one of the most widely accepted experimental models for evaluating antidiabetic agents because STZ selectively destroys pancreatic β-cells, mimicking diabetic pathology. This review discusses the pharmacological significance of Neomarica gracilis, the pathophysiology of diabetes mellitus, the mechanism of STZ-induced diabetes, phytochemical constituents responsible for antidiabetic activity, experimental approaches for evaluating antidiabetic efficacy, and possible molecular mechanisms underlying glucose regulation. The review also highlights current research gaps, future perspectives, and the potential of Neomarica gracilis as a natural source for developing novel antidiabetic therapeutics.

Keywords; Neomarica gracilis, Diabetes mellitus, Streptozotocin, Antidiabetic activity, Medicinal plants, Oxidative stress, Phytochemicals, Insulin, Herbal medicine.

INTRODUCTION

Diabetes mellitus (DM) is a severe, long-term, multifactorial metabolic disorder with significant acute and long-term effects. People in both industrialised and developing nations are affected by diabetes mellitus (DM) and its sequelae, which provide a significant socioeconomic problem. This illness is said to afflict 25% of the world's population. Diabetes is largely influenced by both genetic and environmental factors. When diabetes develops, the body's cells are unable to adequately metabolise sugar because insulin (a peptide hormone that controls blood glucose) is either insufficient or insensitive to target tissues (Abel et al., 2024). When the pancreas either generates insufficient amounts of insulin or the body is unable to utilise the insulin it does produce efficiently, insulin's inability to metabolise sugar results. This causes the body to break down its own fat, protein, and glycogen to make sugar, which raises blood sugar levels and causes the liver to generate excess byproducts called ketones. Diabetes is characterised by persistent hyperglycemia and abnormalities in the metabolism of macromolecules due to deficiencies in insulin action, secretion, or both. Diabetes results in long-term harm, malfunction, and failure of many organ systems, including the heart, blood vessels, eyes, kidneys, and nerves, which can cause disability and early death. The length of time the illness has existed and how successfully it has been managed may have an impact on the degree of harm hyperglycemia causes to the corresponding organ systems. Diabetes is also accompanied by a number of symptoms, including thirst, polyuria, blurred eyesight, and weight loss (Powers et al., 2022).

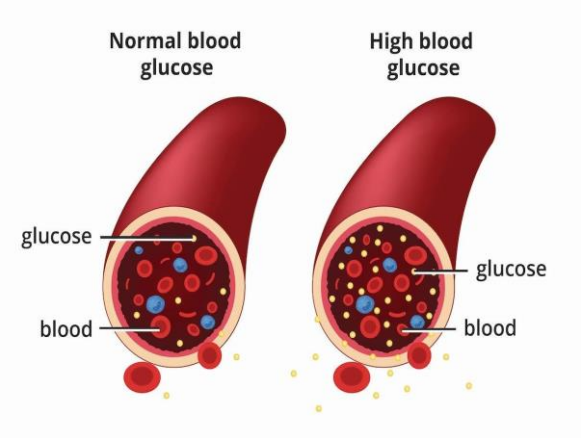

Figure 1: Diabetes mellitus (DM)

Natural antioxidants found in plants, such as tannins, flavonoids, vitamins C and E, help protect ß-cell function and stop the production of ROS brought on by diabetes. An attempt was made in this review paper to enumerate the herbal plants that have antidiabetic action through various methods. The prevalence and fatality rates of diabetes mellitus are steadily rising, making it a severe health issue. Diabetes mellitus is characterised by high plasma glucose levels brought on by either inadequate insulin or insulin resistance, or both, resulting in anomalies in the metabolism of proteins, lipids, or carbohydrates. It may potentially result in acute or long-term consequences that include microangiopathy, ketoacidosis, and other associated illnesses if it is not treated or managed **(Balaji *et al.*, 2019).** Two categories can be used to group various forms of reported diabetes mellitus:

Type 1 diabetes mellitus (IDDM) is characterised by the body's inability to produce insulin. Young adults and kids are most frequently affected. Five to ten percent of all diabetes cases are type 1.

Ninety to ninety-five percent of cases of diabetes are type 2, or noninsulin-dependent diabetic mellitus (NIDDM), in which the body either does not make enough insulin or uses produced insulin improperly. Due to a rise in the number of senior individuals, obesity, and sedentary lifestyles, type 2 diabetes is approaching pandemic proportions **(Zheng *et al.*, 2018).**

ETIOLOGY

Insulin-producing beta cells and glucagon-secreting alpha cells are the two primary subtypes of endocrine cells found in the pancreatic islets of Langerhans. The amount of hormones secreted by beta and alpha cells is constantly altered by the glucose environment.

Inappropriately skewed glucose levels result from an imbalance between insulin and glucagon. Hyperglycemia results from either insufficient or impaired insulin activity (insulin resistance) in the case of diabetes mellitus. Beta cell death in the pancreas, usually as a result of an autoimmune disease, is the hallmark of type 1 diabetes. Insulin is either nonexistent or very low as a result of the complete loss of beta cells **(Katsarou *et al.*, 2017).**

An imbalance between insulin levels and insulin sensitivity results in a functional deficit of insulin in type 2 diabetes, which has a more subtle beginning. But obesity and ageing are the most prevalent causes of insulin resistance, which is multifactorial. One important risk factor for both kinds is the genetic background. As more research is done on the human genome, several loci that increase the risk of diabetes mellitus are discovered. Human leukocyte antigen (HLA) and major histocompatibility complex (MHC) polymorphisms have been shown to affect the likelihood of type 1 diabetes. A more intricate interaction between genetics and lifestyle is involved in type 2 diabetes. There is convincing evidence that T2DM has a more stronger genetic profile than T1DM. Most individuals with the condition have at least one parent who has type 2 diabetes **(Sirdah and Reading, 2020).**

When one twin in a pair of monozygotic twins has T2DM, the other twin has a 90% chance of getting the disease at some point in their lives. To date, approximately 50 polymorphisms have been identified as potentially contributing to the risk or protection of T2DM. These genes encode proteins that are involved in a number of processes that contribute to diabetes mellitus, such as "the formation of the pancreas, the synthesis, secretion, and development of insulin, amyloid deposition in beta cells, insulin resistance, and defective control of gluconeogenesis". Genetic loci for "the transcription factor 7-like 2 gene (TCF7L2)", which raises the risk of type 2 diabetes, were discovered by a genome-wide association study (GWAS) **(del Bosque-Plata *et al.*, 2021).** NOTCH2, JAZF1, KCNQ1, and WFS1 are other loci that may be involved in the development of type 2 diabetes. Non-insulin-dependent diabetes diagnosed at a young age (typically under 25 years) is the hallmark of MODY, a heterogeneous disorder. Unlike T1DM, it does not require autoantibodies and has an autosomal dominant transmission. Hepatocyte nuclear factor-1-alpha (HNF1A) and glucokinase (GCK) gene mutations, which occur in 52 to 65 and 15 to 32 percent of MODY patients, respectively,

are two genes that have consequences in this illness. Since some people have mutations but never develop the disease, while others will exhibit clinical signs of MODY but lack a detectable mutation, the genetics of this condition are yet unknown **(Antal, 2021).**

In essence, gestational diabetes is diabetes that develops during pregnancy. The exact cause of its development remains unknown; however, some conjecture that HLA antigens, particularly HLA DR2, 3, and 4, may be involved. Proinsulin overproduction is also believed to contribute to gestational diabetes, and proinsulin may cause beta-cell stress, according to some. Others contend that the function of beta cells and peripheral insulin sensitivity may be influenced by the presence of high concentrations of hormones, including "cortisol, prolactin, human placental lactogen, and oestrogen" **(Sapra *et al.,* 2021).** Due to the glucogenic action of the endogenous hormones that are oversecreted in these conditions, a number of endocrinopathies, such as "acromegaly, Cushing syndrome, glucagonoma, hyperthyroidism, hyperaldosteronism, and somatostatinomas", have been linked to glucose intolerance and diabetes mellitus. Diabetes mellitus is linked to conditions like idiopathic hemochromatosis because of the pancreas's excessive iron accumulation and beta cell death **(Popoviciu *et al.,* 2023).**

EPIDEMIOLOGY

DM affects 1 in 11 adults worldwide (90% have T2DM). T1DM progressively worsens from birth, peaking between the ages of 4 and 6 and then again between the ages of 10 and 14. Before the age of 10, about 45% of children are present. In those under 20, the frequency is around 2.3 per 1000. There are no obvious gender differences in the prevalence of children T1DM, despite the fact that most autoimmune diseases are more prevalent in females. Certain groups, particularly older boys of European descent (over 13 years old), may have a higher risk of developing type 1 diabetes than females (3:2 male to female ratio) **(Stene and Lernmark, 2023).** Globally, the prevalence of T1DM has been rising. Rates are increasing by 2% to 5% a year across Australia, Europe, and the Middle East. The majority of age and ethnic groups in the US had an annual increase in T1DM rates of around 2%, with Hispanic youngsters seeing higher rates. The precise cause of this pattern is yet unclear. However, certain measurements, like "the United States Military Health System data repository", showed plateauing between 2007 and 2012 with an incidence of 20.7 to 21.3 per 1000 and a prevalence of 1.5 per 1000 **(Lado and Lipman, 2016).**

However, obesity in adolescents has resulted in a rise in T2DM in younger populations, despite the fact that the onset of T2DM typically occurs later in life. In the US, the prevalence of type 2 diabetes is around 9% overall, but it is roughly 25% among people over 65. According to estimates from the International Diabetes Federation, 1 in 11 adults worldwide between the ages of 20 and 79 had diabetes in 2015. By 2040, experts predict that the number of people with DM will rise from 415 to 642 million, with the largest increase occurring in populations moving from low to middle-income levels. In the United States, the prevalence of T2DM varies among ethnic groups, with "Blacks, Native Americans, Pima Indians, and Hispanic Americans" each having a 2 to 6 times higher prevalence than Whites. Although ethnicity is a major contributing factor to type 2 diabetes, environmental variables can significantly increase the risk of the condition. For instance, Pima Indians in Mexico had a lower risk of developing type 2 diabetes than Pima Indians in the US (6.9% vs. 38%) **(Golden *et al.,* 2019).**

PATHOPHYSIOLOGY

Hyperglycemia is a possibility for a patient with diabetes. Since several causes can frequently contribute to the condition, the pathophysiology of diabetes mellitus might be ambiguous. Insulin secretion can be hampered by hyperglycemia alone, which can also affect pancreatic beta-cell activity. As a result, hyperglycemia creates a vicious loop that impairs metabolic function. In this setting, blood glucose levels exceeding 180 mg/dL are frequently regarded as hyperglycaemic; nevertheless, there is no precise cutoff point due to the multiplicity of processes. Because the glucose transporters in the nephron become saturated at increasing blood glucose levels, patients suffer from osmotic diuresis. Serum glucose levels over 250 mg/dL are likely to result in polyuria and polydipsia symptoms, while the impact varies **(Rabbani and Thornalley, 2024).**

Excess fatty acids and proinflammatory cytokines cause insulin resistance by impairing glucose transport and increasing fat breakdown. The body reacts to insufficient insulin synthesis by improperly raising glucagon, which exacerbates hyperglycemia. Although insulin resistance is a part of type 2 diabetes, the patient's inability to produce enough insulin to offset their insulin resistance is what causes the condition to reach its full severity **(Rachdaoui, 2020).**

Additionally, nonenzymatic glycation of proteins and lipids is brought on by chronic hyperglycemia. The

glycation haemoglobin (HbA1c) test is used to quantify the degree of this. Small blood arteries in the kidney, retina, and peripheral nerves are harmed by glycation. The process is accelerated by higher glucose levels. In addition to the avoidable consequences of blindness, dialysis, and amputation, this damage causes the usual diabetes sequelae of diabetic retinopathy, nephropathy, and neuropathy **(Kafle, 2022).**

SIGN AND SYMPTOMS:

Blood sugar levels have an impact on diabetes symptoms. There may be no symptoms at all in some people, particularly those with type 2 diabetes, gestational diabetes, or prediabetes. The symptoms of type 1 diabetes are usually more severe and appear more quickly.

Common signs seen in insulin-dependent and noninsulin-dependent diabetes:

- Excessive thirst
- Frequent passage of urine
- Unexpected loss of body weight
- Presence of ketone bodies in urine (due to insufficient insulin)
- Fatigue and weakness
- Irritability or variations in emotional behavior
- Reduced clarity of vision
- Delayed wound healing
- Recurring infections **(Mohanty *et al.*, 2025).**

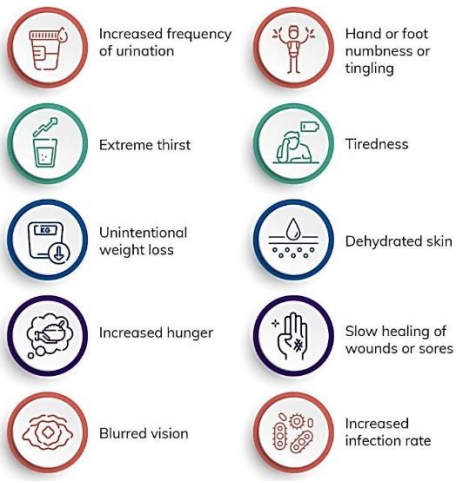

Figure 2: Sign and Symptoms

CAUSES OF DIABETES MELLITUS

Diabetes may develop due to several factors including:

- Genetic predisposition
- Autoimmune destruction of pancreatic β-cells
- Obesity and sedentary lifestyle
- Poor dietary habits
- Age-related metabolic changes **(Martemucci *et al.*, 2023).**

TREATMENT AND MANAGEMENT

For effective disease management, a variety of therapies are needed due to the complexity of diabetes' physiology and treatment. Patient involvement and diabetic education are essential to management. Patients who are able to control their diet (restricting carbohydrates and total calories), exercise often (greater than 150 minutes per week), and independently check their blood sugar levels will fare better. In order to avoid unintended effects, lifelong treatment is sometimes required. Ideally, HbA1c should be kept below 7% and glucose levels between 90 and 130 mg/dL. Although glucose control is essential, hypoglycemia may result from overly aggressive management, which can have fatal or adverse consequences **(Chatterjee *et al.*, 2018).**

The majority of treatment for type 1 diabetes is insulin administration by daily injections, an insulin pump, or both, as the disease is largely caused by insufficient insulin production. Diet and exercise may be sufficient therapies for type 2 diabetes, particularly in the early stages. Other treatments can focus on insulin sensitivity or boost the pancreas' production of insulin. "Biguanides (metformin), sulfonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones, glucagonlike-peptide-1 agonists, dipeptidyl peptidase IV inhibitors (DPP-4), selective amylinomimetics, and sodium-glucose transporter-2 (SGLT-2)" inhibitors are among the specific drug subclasses. The first line of treatment for diabetes is metformin, which lowers both basal and postprandial plasma glucose. Patients with type 2 diabetes may also require insulin administration, particularly those with poor glucose management in the latter stages of the disease. Bariatric surgery is a potential way to restore normal glucose levels in severely obese people. It is advised for those with serious comorbidities who have not responded to previous therapies **(Khan, 2024).** Better cardiovascular outcomes are correlated with the GLP-1 agonists semaglutide and liraglutide. Along with possible renoprotection and heart failure prevention, "the SGLT-2 inhibitors empagliflozin and canagliflozin" have also been demonstrated to enhance cardiovascular outcomes **(Preda *et al.*, 2024).**

Since microvascular problems are a feared consequence of diabetes, routine tests are essential. To check for diabetic retinopathy, routine diabetic retinal exams should be carried

out by competent medical personnel. Patients with neuropathy who are at risk for amputation can be found by neurologic examination and monofilament testing. In order to find foot lesions that can go undetected because to neuropathy, clinicians may also advise patients to examine their feet every day. Neuropathic pain in diabetics may require the use of topical capsaicin, duloxetine, anticonvulsants, low-dose tricyclic antidepressants, and painkillers. In addition to the estimated GFR, urine microalbumin testing can detect early renal abnormalities from diabetes with albuminuria more than 30 mg/g creatinine. In patients with both Type 1 and Type 2 diabetes mellitus, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are the recommended medications to postpone the transition from microalbuminuria to macroalbuminuria due to their antiproteinuric impact **(Banerjee *et al.,* 2022).**

Additionally, the American Diabetes Association advises diabetics to undergo routine blood pressure checks, with a target systolic blood pressure of 130 mmHg and a diastolic blood pressure of 85 mmHg. "Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, beta-blockers, and/or calcium channel blockers" are commonly used in pharmacologic treatment for hypertensive diabetes. Low-density lipoprotein cholesterol (LDL-C) should be less than 100 mg/dL in the absence of cardiovascular disease (CVD) and less than 70 mg/dl in the presence of atherosclerotic cardiovascular disease (ASCVD), according to the American Diabetes Association. For the management of diabetics' dyslipidaemia, statins are the first-line treatment. Although the impact of aspirin in lowering cardiovascular events in patients with diabetes is still unknown, the American Diabetes Association advises that low-dose aspirin may potentially be helpful for diabetic patients who are at high risk for cardiovascular events **(De Boer *et al.,* 2017).**

THE STREPTOZOTOCIN (STZ) MODEL: A CORNERSTONE OF PRECLINICAL RESEARCH

To transition a traditional herbal remedy into a scientifically validated medicine, rigorous preclinical evaluation is mandatory. The streptozotocin (STZ)-induced diabetic rat model has long been established as the gold standard for this purpose. STZ, a naturally derived compound, induces a state of diabetes that reliably mimics many key features of the human condition, particularly the hyperglycemia and oxidative stress characteristic of Type 1 diabetes, or aspects of Type 2 diabetes under specific protocols. Its reliability and reproducibility have made it an indispensable tool for screening and mechanistically investigating new antidiabetic agents **(Furman, 2021).**

The Chemistry and Selectivity of STZ

STZ's remarkable selectivity for pancreatic β-cells is the key to its utility. As a glucosamine-nitrosourea compound, its glucose moiety is recognized by the Glucose Transporter 2 (GLUT2), which is abundantly expressed on the surface of rodent β-cells but has low expression in most other tissues. This ensures that STZ is preferentially taken up by its target cells (**Rais *et al.,* 2022).**

Molecular Cascade of β-Cell Toxicity

- **DNA Alkylation:** Once inside the cell, STZ acts as a potent DNA alkylating agent, transferring a methyl group to the DNA bases, which causes DNA fragmentation and strand breaks **(Zhu, 2022).**
- **PARP Hyperactivation and Energy Depletion:** The cell's primary DNA repair enzyme, Poly(ADP-ribose) polymerase-1 (PARP-1), detects the DNA damage and becomes hyperactivated. In its attempt to repair the extensive damage, PARP-1 consumes its substrate, NAD+, at an enormous rate. This leads to a rapid and catastrophic depletion of intracellular NAD+ pools **(Pandey andBlack, 2021).**
- **ATP Depletion:** NAD+ is an essential coenzyme for glycolysis and oxidative phosphorylation. Its depletion brings ATP production to a halt, plunging the cell into an energy crisis **(Xiao *et al.,* 2018).**

Dosing Paradigms and Model Variations

The experimental outcome can be tailored by adjusting the STZ dose:

High-Dose Model (e.g., 50-65 mg/kg, single i.p. injection): This causes rapid and near-total destruction of β-cells, leading to severe insulin deficiency and hyperglycemia. This model is an excellent analogue for Type 1 Diabetes.

Low-Dose/Multiple-Dose Model (e.g., 20-40 mg/kg for several consecutive days): This induces partial β-cell destruction and a milder diabetic state.

When combined with a high-fat diet (HFD) prior to STZ administration, it can be used to model Type 2 Diabetes, where insulin resistance (from HFD) is coupled with impaired insulin secretion (from STZ) **(Nath *et al.,* 2017).**

Table 1: Plant extracts with antidiabetic potential.

Species	Extract	Part of the Plant	Induction of Diabetes
Acacia arabica	chloroform	bark	streptozotocin
Albizzia lebbeck	methanol	stem bark	streptozotocin
Aloe vera	Aqueous/ ethanolic	leaves	streptozotocin
Anacardium occidentale	Aqueous/ methanol	leaves	streptozotocin
Caesalpinia ferrea	aqueous	stem bark	streptozotocin
Camellia sinensis	crude tea	leaves	streptozotocin
Casearia esculenta Roxb	aqueous	root	streptozotocin
Catharanthus roseus	ethanolic	leaves	streptozotocin
Cinnamomum cassia	ethanolic	bark	streptozotocin
Coscinium fenestratum	ethanolic	stem	streptozotocin
Gymnema sylvestre	ethanolic	leaves	streptozotocin
Moringa oleifera	methanolic	leaves	streptozotocin
Opuntia ficus-indica	petroleum ether	stems	streptozotocin
Passiflora nitida	hydro-ethanolic	leaves	streptozotocin
Persea americana	aqueous	leaves	streptozotocin
Sonchus oleraceus	hydro-alcoholic	whole plant	streptozotocin
Terminalia chebula	chloroform	seed	streptozotocin
Piper longum	aqueous	root	streptozotocin

NEOMARICA GRACILIS

Figure 3: Neomarica gracillis

Taxonomica

Kingdom: Plantae
Division: Magnoliophyta
Class: Liliopsida
Order: Asparagales
Family: Iridaceae
Genus: Neomarica
Species: Neomarica gracilis
Common Name: Walking Iris, Apostle Plan Plant
Type: Perennial herb

Neomarica gracilis is a perennial herbaceous plant belonging to the family Iridaceae, a family well known for its ornamental and medicinal plant species. The genus *Neomarica* comprises several species distributed mainly in the tropical and subtropical regions of Central and South America. Among them, *Neomarica gracilis* has attracted increasing scientific interest because of its rich phytochemical composition and potential pharmacological properties. Although the plant is primarily cultivated as an ornamental species due to its attractive flowers and elegant foliage, recent phytochemical and pharmacological investigations suggest that it may also possess significant medicinal value. *Neomarica gracilis* thrives in warm, humid climates and is widely distributed throughout tropical and subtropical regions, particularly in Brazil and other parts of South America. It has also been introduced into several countries in Asia, Africa, and North America as an ornamental garden plant. The species grows well under partial shade or filtered sunlight in fertile, well-drained soils rich in organic matter. It is highly adaptable to a range of environmental conditions and exhibits good tolerance to moderate drought once established, making it suitable for both ornamental landscaping and potential cultivation for medicinal purposes **(Mussa, 2024).**

Importance in Antidiabetic Research

The increasing prevalence of diabetes mellitus has intensified the search for safer and more effective plant-derived therapeutic agents. *Neomarica gracilis* has emerged as a promising candidate because its phytochemicals may target multiple mechanisms involved in diabetes pathogenesis. The leaf extract is believed to reduce oxidative stress, suppress inflammatory responses, improve insulin secretion, enhance peripheral glucose uptake through GLUT4 translocation, activate AMPK and PI3K/Akt signaling pathways, stimulate PPAR-γ activity, and inhibit carbohydrate-digesting enzymes such as α-amylase and α-glucosidase. Through these complementary mechanisms, *Neomarica gracilis* may help improve glycemic control,

regulate lipid metabolism, protect pancreatic β-cells, and reduce the risk of diabetes-related complications. Although these findings are promising, comprehensive phytochemical characterization, mechanistic studies, toxicological evaluations, and well-designed preclinical and clinical investigations are still required to fully establish its therapeutic efficacy and safety **(Ansari *et al.*, 2024).**

Classification of Bioactive Compounds with Antidiabetic Properties

a. Polyphenols

Polyphenols constitute a vast and varied category of chemicals distinguished by the presence of several phenolic units. They are plentiful in many fruits, vegetables, tea, coffee, and red wine. Polyphenols are recognized for their powerful antioxidant properties, which are essential in mitigating oxidative stress, a condition that contributes to the onset of diabetes and its consequences (Muscolo *et al.,* 2024).

Antidiabetic Mechanisms:

Antioxidant Activity: By scavenging free radicals and lowering oxidative stress, polyphenols enhance insulin production and save pancreatic beta cells from harm

Insulin Sensitization: By improving glucose absorption in tissues, polyphenols increase insulin sensitivity by activating signalling pathways including the AMP-activated protein kinase (AMPK) pathway.

Glucose Metabolism: Inhibiting carbohydratedigesting enzymes like alpha-amylase and alphaglucosidase, polyphenols lower blood glucose levels after a meal **(Sun *et al.*, 2020).**

b. Flavonoids

Among the many polyphenols found in plants, flavonoids are among the most abundant. They are known to have antioxidant, anti-inflammatory, and antidiabetic properties, and they also provide vibrant colours to many fruits and vegetables. Citrus fruits, berries, tea, and chocolate are some of the foods that are rich in flavonoids **(Khoo *et al.*, 2017).**

Antidiabetic Mechanisms:

Antioxidant Activity: Like polyphenols, flavonoids protect against oxidative stress by neutralizing free radicals, which helps preserve the function of insulinproducing beta cells.

Anti-inflammatory Effects: Flavonoids inhibit the production of pro-inflammatory cytokines, which are involved in the development of insulin resistance. Regulation of Glucose Transport: Flavonoids enhance the expression and activity of glucose transporters, such as GLUT4, which facilitates glucose uptake into muscle and adipose tissues.

Enzyme Inhibition: Flavonoids can inhibit key enzymes involved in glucose metabolism, such as alphaglucosidase and dipeptidyl peptidase-4 (DPP-4), leading to better glycemic control **(Martín and Ramos, 2021).**

c. Alkaloids

Alkaloids are nitrogen-containing compounds that are primarily found in plants. They are known for their wide range of biological activities, including antidiabetic effects. Alkaloids are present in foods like coffee, tea, and certain vegetables, as well as in medicinal plants **(Rajput *et al.*, 2022).**

Antidiabetic Mechanisms:

- Insulin Secretion: Certain alkaloids have the ability to enhance blood glucose homeostasis by stimulating the release of insulin from pancreatic beta cells.
- Enzyme Inhibition: alkaloids may reduce carbohydrate digestion and postprandial blood glucose levels by inhibiting enzymes like alpha-amylase and alpha-glucosidase.
- Anti-inflammatory Activity: Alkaloids' antiinflammatory properties make them useful for lowering insulin resistance and enhancing glucose metabolism **(Christodoulou *et al.*, 2019).**

d. Terpenoids

Terpenoids, or isoprenoids, constitute a vast and varied category of chemical molecules synthesized by numerous plant species. They are recognized for their fragrant characteristics and are frequently included in essential oils. Terpenoids have been investigated for their possible medicinal effects, including antidiabetic characteristics **(Al Kury *et al.*, 2021).**

Antidiabetic Mechanisms:

- **Insulin Sensitization:** Terpenoids can enhance insulin sensitivity by modulating the activity of key

signaling pathways involved in glucose metabolism.

- **Anti-inflammatory and Antioxidant Effects:** Terpenoids lower inflammation and oxidative stress, two important processes in the development of diabetes and insulin resistance.
- **Modulation of Lipid Metabolism:** Terpenoids have been shown to improve lipid profiles, which is beneficial for managing diabetes-related cardiovascular risks **(Feng *et al.*, 2024).**

POSSIBLE MOLECULAR MECHANISMS OF ANTIDIABETIC ACTION

Activation of AMP-Activated Protein Kinase (AMPK)

A vital cellular energy sensor, "AMP-activated protein kinase (AMPK)" controls the metabolism of fats and carbohydrates, which is essential for preserving energy balance. AMPK is activated under conditions of energy deficiency, characterized by a decrease in intracellular adenosine triphosphate (ATP) levels and a corresponding increase in adenosine monophosphate (AMP) levels. Once activated, AMPK initiates a series of metabolic adaptations aimed at restoring cellular energy balance. By encouraging "the translocation of glucose transporter type 4 (GLUT4) to the cell membrane", it improves the absorption of glucose in skeletal muscle and facilitates the effective use of circulating glucose **(López *et al.*, 2016).** In addition, AMPK enhances lipid metabolism by promoting fatty acid oxidation and inhibiting "fatty acid and cholesterol synthesis". It also inhibits hepatic gluconeogenesis, thereby reducing endogenous glucose production and contributing to lower fasting blood glucose levels. Furthermore, activation of AMPK improves insulin sensitivity in peripheral tissues, enhances mitochondrial biogenesis and function, and promotes overall metabolic health. The phytochemicals present in *Neomarica gracilis*, particularly flavonoids and phenolic compounds, are believed to activate the AMPK signaling pathway, resulting in enhanced glucose utilization, reduced oxidative stress, improved energy metabolism, and better glycemic control. Consequently, AMPK activation represents one of the key molecular mechanisms through which *Neomarica gracilis* may exert its potential antidiabetic effects **(Smitha Grace *et al.*, 2019).**

PI3K/Akt Signaling Pathway

The phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway is one of the principal intracellular insulin signaling cascades that regulates glucose homeostasis, glycogen synthesis, and cellular survival. Activation of this pathway begins when insulin binds to its receptor, leading to the phosphorylation of insulin receptor substrates (IRS) and subsequent activation of PI3K. Activated PI3K generates phosphatidylinositol-3,4,5-trisphosphate (PIP3), which in turn activates Akt. Once activated, Akt increases glucose absorption and lowers blood glucose levels by promoting "the translocation of glucose transporter type 4 (GLUT4) from intracellular vesicles to the plasma membrane of skeletal muscle and adipose tissues" **(Świderska *et al.*, 2020).** By inhibiting "glycogen synthase kinase-3 (GSK-3)", Akt also promotes glycogen synthesis, which leads to an increase in the storage of glucose as glycogen in the skeletal muscles and liver. Additionally, by activating downstream signalling molecules like "the mammalian target of rapamycin (mTOR)", the PI3K/Akt pathway controls metabolism, cellular proliferation, and protein synthesis. Another important function of Akt is the promotion of cell survival by suppressing apoptotic signaling pathways and protecting pancreatic β-cells from oxidative stress-induced apoptosis, thereby preserving insulin secretion and pancreatic function. Impaired PI3K/Akt signalling in diabetes is linked to β-cell dysfunction, reduced glucose absorption, and insulin resistance. The phytochemicals present in *Neomarica gracilis*, particularly flavonoids, phenolic compounds, and terpenoids, are believed to enhance PI3K/Akt signaling by improving insulin receptor sensitivity and reducing oxidative stress and inflammation. Consequently, activation of this pathway may increase GLUT4 translocation, enhance glucose transport, promote glycogen and protein synthesis, improve insulin sensitivity, preserve pancreatic β-cell viability, and restore glucose homeostasis, thereby contributing significantly to the antihyperglycemic effects of *Neomarica gracilis* leaf extract **(Sayem *et al.*, 2018).**

GLUT4 Translocation

“Glucose transporter type 4 (GLUT4)” is the primary insulin-responsive glucose transporter predominantly expressed in skeletal muscle, cardiac muscle, and adipose tissue. It plays a critical role in maintaining glucose homeostasis by facilitating the uptake of glucose from the bloodstream into peripheral tissues. Under normal physiological conditions, GLUT4 is stored within intracellular vesicles and translocates to “the plasma membrane” in response to insulin stimulation. Binding of insulin to its receptor activates the insulin signaling cascade, particularly the phosphoinositide 3-kinase (PI3K)/Akt pathway, which triggers the movement of GLUT4-containing vesicles to the cell surface. Once inserted into “the plasma membrane”, GLUT4 enables rapid glucose transport into cells, where glucose is utilized for energy production or stored as glycogen **(van Gerwen *et al.*, 2023).**

In diabetic conditions, especially type 2 diabetes mellitus, impaired insulin signaling reduces GLUT4 translocation, leading to decreased glucose uptake by skeletal muscle and adipose tissue, persistent hyperglycemia, and insulin resistance. By increasing insulin receptor sensitivity and triggering important signalling pathways including PI3K/Akt and AMP-activated protein kinase (AMPK), the phytochemicals found in Neomarica gracilis, such as flavonoids, phenolic compounds, and terpenoids, are thought to improve GLUT4 translocation. These bioactive substances may make it easier for GLUT4 vesicles to reach the plasma membrane, which would improve peripheral glucose utilisation, increase glucose entry into muscle and fat cells, and reduce blood glucose levels. Additionally, improved GLUT4 expression and translocation contribute to better glycogen synthesis, enhanced energy metabolism, and restoration of insulin sensitivity. By promoting efficient glucose uptake and utilization in peripheral tissues, *Neomarica gracilis* leaf extract may play a significant role in improving glycemic control and reducing insulin resistance, making GLUT4 translocation one of the important molecular mechanisms underlying its potential antidiabetic activity **(Gogoi, 2016).**

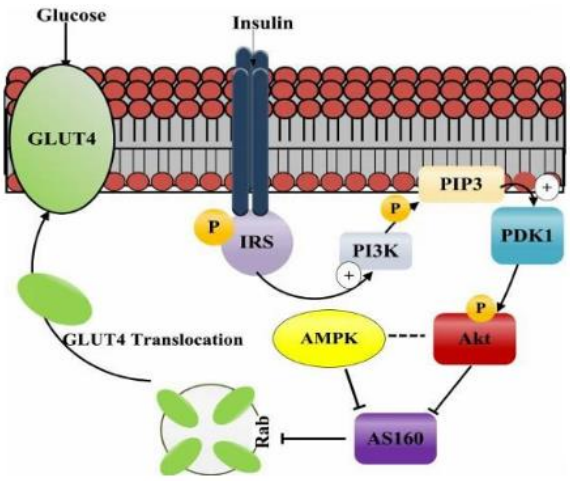

Figure 4: Molecular Mechanisms of Antidiabetic Action

Inhibition of α-Glucosidase

α-Glucosidase is a key digestive enzyme located in the brush border membrane of the small intestine, where it catalyzes the final step in carbohydrate digestion by hydrolyzing oligosaccharides and disaccharides into absorbable glucose molecules. This enzymatic process facilitates the rapid absorption of glucose into the bloodstream following a carbohydrate-rich meal, leading to a postprandial rise in blood glucose levels. Excessive postprandial hyperglycemia is a major factor in the development of long-term diabetic complications, oxidative stress, and poor glycaemic control in people with diabetes mellitus. Therefore, inhibition of α-glucosidase has become an important therapeutic strategy for managing diabetes by delaying carbohydrate digestion and reducing glucose absorption **(Kashtoh and Baek, 2022).** The phytochemicals present in *Neomarica gracilis*, particularly phenolic compounds, flavonoids, tannins, and other polyphenolic constituents, are believed to possess natural α-glucosidase inhibitory activity. These bioactive compounds may bind to the active site of the enzyme or alter its catalytic activity, thereby slowing the hydrolysis of complex carbohydrates into glucose. As a result, the digestion and absorption of dietary carbohydrates are delayed, leading to a gradual release of glucose into the circulation rather than a rapid spike in blood sugar levels. This mechanism helps reduce postprandial hyperglycemia, improve overall glycemic control, decrease the demand for insulin secretion, and minimize fluctuations in blood glucose concentrations. Furthermore, by lowering postprandial glucose excursions, α-glucosidase inhibition may reduce glucose-induced oxidative stress and inflammation, thereby protecting pancreatic β-cells and preventing the development of diabetes-associated complications. Natural inhibitors produced from medicinal plants are typically thought to have a better safety profile than some "synthetic α-glucosidase inhibitors', which may induce gastrointestinal side effects such flatulence, abdominal pain, and diarrhoea. Therefore, “the α-glucosidase inhibitory activity” of *Neomarica gracilis* leaf extract represents an important molecular mechanism contributing to its potential antihyperglycemic and antidiabetic effects **(Xiao *et al.*, 2026).**

FUTURE PROSPECTIVE

Neomarica gracilis leaf extract's medicinal potential presents a number of encouraging avenues for further investigation. To identify and quantify the active components responsible for its antidiabetic effect, a thorough phytochemical profile employing sophisticated analytical methods as "HPLC, LC–MS/MS, GC–MS, and NMR spectroscopy is necessary". Standardization of extraction procedures and quality control measures will improve reproducibility and facilitate the development of consistent herbal formulations.

Future investigations should focus on elucidating the molecular mechanisms of action through studies involving insulin signaling pathways, glucose transporter regulation, inflammatory mediators, oxidative stress biomarkers, and gene expression analyses. To determine the extract's safety

profile, long-term toxicological, pharmacokinetic, and pharmacodynamic investigations are also crucial. Development of "novel drug delivery systems", including nanoparticles, phytosomes, liposomes, or nanoemulsions, may enhance the bioavailability and therapeutic efficacy of the active phytochemicals. Furthermore, well-designed preclinical and multicenter clinical trials are needed to validate its efficacy in humans and support its translation into evidence-based herbal medicine. Such studies could position *Neomarica gracilis* as a valuable natural source for future antidiabetic drug discovery.

CONCLUSION

Diabetes mellitus continues to be a major global health concern, necessitating the creation of safer and more effective treatment approaches. Medicinal plants continue to represent an important source of bioactive compounds with multitarget pharmacological activities. *Neomarica gracilis* leaf extract possesses promising phytochemical constituents, including flavonoids, phenolics, alkaloids, tannins, saponins, and terpenoids, which are known to "exhibit antioxidant, anti-inflammatory, and antihyperglycemic properties". These compounds may protect pancreatic β-cells, enhance insulin secretion, improve glucose utilization, reduce oxidative stress, and attenuate diabetic complications. Experimental evaluation using streptozotocin-induced diabetic rat models provides a reliable platform for assessing its therapeutic potential. Although preliminary evidence supports the potential antidiabetic effects of *Neomarica gracilis*, further studies are required to isolate the active compounds, clarify their molecular mechanisms, standardize formulations, and establish long-term safety and clinical efficacy. With continued research, *Neomarica gracilis* may emerge as a promising candidate for the development of novel plant-based antidiabetic therapies.

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