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Review Article

Alkaloids: Bridging Natural Products in Antidiabetic Therapy

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ABSTRACT

This review thoroughly assesses the antidiabetic properties of natural alkaloids, addressing their modes of action and treatment prospects for diabetes mellitus. Following PRISMA 2020 guidelines, literature from databases like PubMed/MEDLINE, Scopus, and Science Direct, published from 2000 to May 2025, was analyzed. The review highlights several promising alkaloids, including berberine, vindoline, harmine, trigonelline, oxymatrine, and solanine. These compounds have various antidiabetic actions via improving insulin sensitivity, increasing insulin secretion, blocking digestive enzymes, modifying gut microbiota, and reducing oxidative stress and inflammation. For instance, berberine demonstrates efficacy comparable to standard hypoglycemics, partly through gut microbiota modulation. Harmine uniquely promotes pancreatic β-cell regeneration. Despite their therapeutic promise, significant challenges persist, including issues of bioavailability, varying toxicity profiles, and a notable scarcity of robust clinical trials. Standardization of plant sources and extraction methods also remains a critical challenge. Future research must prioritize rigorous clinical validation, advanced formulation development to enhance efficacy and safety, and strengthened regulatory frameworks. Alkaloids represent a promising frontier for developing novel, effective, and safe antidiabetic therapies.

Introduction

Diabetes mellitus is a chronic metabolic disorder marked by persistent hyperglycemia resulting from insufficient insulin production, impaired insulin action, or both. This condition increases the risk of cardiovascular disease, neuropathy, kidney failure, and vision loss.[1] Globally, about 529 million people live with diabetes, and this number is projected to reach 1.31 billion by 2050.[2] The disease, largely genetic in nature, arises from β-cell dysfunction and elevated blood glucose, ranking as the 8th leading cause of mortality and disability worldwide in 2019, affecting nearly 460 million people.[3]

Types of Diabetes Mellitus

Diabetes mellitus (DM) is classified into three forms: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes mellitus (GDM). Among these, T2DM is the most prevalent, representing over 90% of global cases, including in Africa, where data remain limited.[4]

Type 1 Diabetes Mellitus

This autoimmune condition destroys pancreatic β-cells, causing insulin deficiency and hyperglycemia. It accounts for 5 to 10% of cases and is associated with autoantibodies such as GAD65, insulin, IA-2, IA-2b, and ZnT8.[5,6]

Type 2 Diabetes Mellitus

Accounting for 90 to 95% of cases, T2DM involves insulin resistance and relative insulin deficiency. Most patients are overweight or obese, with excess abdominal fat contributing to insulin resistance and metabolic dysfunction, including MASLD.[5]

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Gestational Diabetes Mellitus

GDM arises during pregnancy and may progress to T1DM or undiagnosed T2DM, though it often resolves after delivery. Children of GDM mothers are at higher risk of obesity and T2DM later in life.[6]

Role of Medicinal Plants in the Management of Diabetes Mellitus

Despite advances in antidiabetic drugs, side effects like hypoglycemia, organ toxicity, and weight gain remain concerns. WHO supports medicinal plants, as 4 billion people in developing regions rely on them for metabolic disorders. Plants such as *Berberis vulgaris*, *Trigonella foenum-graecum*, and *Coptis chinensis* show hypoglycemic effects by improving insulin sensitivity and secretion.[7] Drugs like metformin and sulfonylureas are effective but may cause diarrhea, obesity, hypothyroidism, liver failure, and cardiovascular issues. Many modern drugs are plant-derived, emphasizing the value of botanicals.[8] Secondary metabolites (flavonoids, saponins, terpenes, alkaloids, tannins, coumarins, phenols, anthocyanins) show strong antidiabetic potential by targeting key proteins and enzymes in glucose regulation.[9]

METHODOLOGY

Literature Search Strategy and Methodology

This review followed PRISMA 2020 guidelines, with literature (2000–May 2025) searched across Science Direct, PubMed/MEDLINE, EMBASE, Scopus, Web of Science, MDPI, Springer, Google Scholar, and Taylor & Francis. Botanical names were validated via World Flora Online. Search terms included alkaloids, antidiabetic, diabetes mellitus, medicinal plants, insulin sensitivity, hypoglycemic, and specific alkaloids (berberine, vindoline, and trigonelline).

Inclusion criteria

- Peer-reviewed articles in English
- Studies on natural plant-derived alkaloids with antidiabetic activity
- Conducting in vitro, in vivo, and clinical research.
- Botanical names verified using World Flora Online.

Exclusion criteria

- Synthetic alkaloids without natural analogs
- Non-English publications
- Reviews without new data

Two impartial reviewers screened the entire texts, abstracts, and titles as part of the selection process. Disputes were settled through agreements.

ALKALOIDS

Alkaloids are low-molecular-weight nitrogen-containing compounds, often derived from amino acids and forming complex ring structures. Endophytic fungi produce hundreds with diverse bioactivities.[10] Their biosynthesis and pharmacological actions are well studied, and many are exploited in drug development.[11] Alkaloids are classified into three groups: True alkaloids (heterocyclic), protoalkaloids (non-heterocyclic), and pseudoalkaloids (Table 1).

Types of Alkaloids

True alkaloids

These are complex, physiologically active compounds derived from cyclic amino acids, containing intracyclic nitrogen. They commonly exist as salts of organic acids such as oxalic, lactic, malic, tartaric, acetic, and citric acids.[12] Notable examples include pyrrolidine, pyrrolizidine, pyridine, piperidine, tropane, quinolone, isoquinoline, aporphine, quinolizidine, indole, indolizidine, and imidazole alkaloids.[13]

Protoalkaloids

Protoalkaloids originate from amino acids or biogenic amines but have nitrogen outside the ring system, integrated into the side chain rather than the heterocycle.[12] Well-known examples include vinblastine and vincristine, dimeric alkaloids with potent anticancer activity.[13]

Pseudoalkaloids

Unlike true alkaloids, these are not directly derived from amino acids. Instead, their carbon skeletons arise through amination or transamination of amino acid precursors or intermediates. They may also originate from compounds like acetate, pyruvic acid, adenine/guanine, or geraniol.[14] Common pseudoalkaloids include ephedrine, caffeine, and capsaicin.[13]

Specific Alkaloids with Their Antidiabetic Activity

Alkaloids exert antidiabetic effects by stimulating insulin secretion, inhibiting gastrointestinal enzymes, preventing AGEs, and enhancing glucose uptake.[15] They also suppress α-glucosidase and α-amylase, reducing postprandial hyperglycemia. Alkaloids from *B. vulgaris*, *T. foenum-graecum*, *C. chinensis*, and *E. microphylla* lower insulin resistance, enhance secretion, and modulate gut microbiota.[16]

BERBERINE (Isoquinoline)

Berberine, a quaternary benzylisoquinoline alkaloid from *B. vulgaris*, *B. aristata*, and *C. chinensis*, has long been used

Table 1: Examples of Types of Alkaloids

True alkaloids	*Protoalkaloids*	*Pseudoalkaloids*
Pyrrolidine, pyrrolizidine, pyridine, piperidine, tropane, quinolone, isoquinoline, aporphine, quinolizidine, indole, indolizidine, imidazole	Vinblastine, vincristine	Capsaicin, caffeine, ephedrine

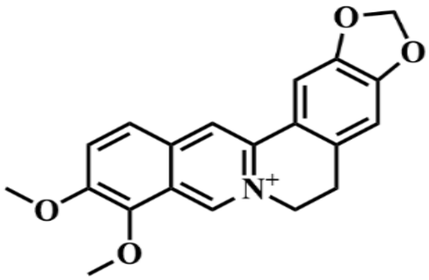

Fig 1: Structure of Berberine.[23]

for infections, wounds, indigestion, and gynecological disorders. Modern studies show anti-inflammatory, hepatoprotective, anti-obesity, hypoglycemic, and hypolipidemic effects.[17] Clinical trials confirmed its ability to reduce HbA1c and fasting glucose, comparable to standard antidiabetics, partly *via* gut microbiota modulation.[18] Nano-formulations improve bioavailability and glucose-lowering efficacy, supporting their role in metabolic and cardiometabolic health [19,20] (Fig. 1). Contemporary issues include variable standardization, extraction inconsistencies, and potential long-term safety and drug interaction concerns.[21,22]

Mechanisms of Action

Summarized in Table 2.

Structural Activity Relationship

Summarized in Fig. 2.

Toxicity

Berberine shows significant toxicity in zebrafish embryos, affecting cardiovascular development and raising concerns for use in sensitive groups such as pregnant women. Its toxicity also impacts gastrointestinal, hepatic, and immune functions, necessitating caution in dosage and administration.[53] Though promising in therapies like cancer treatment, careful supervision and further studies are essential to clarify its clinical safety profile.[54]

VINDOLINE (Indole)

Vindoline, a monoterpene indole alkaloid from *Catharanthus roseus*, is a precursor of vinblastine and vincristine. Traditionally, *C. roseus* has been used to treat diabetes, cancer, hypertension, and infections.[55,61] Vindoline demonstrates antidiabetic activity by enhancing insulin sensitivity, lowering oxidative stress, and reducing hepatotoxicity and hyperlipidemia in diabetic rats.[56,57] Advances in CRISPR-based metabolic engineering have improved vindoline yields.[58] The structure of vindoline is shown in Fig. 3.

Contemporary Issues

Limited clinical validation and lack of toxicity data.[56,58]

Mechanism of action

Summarized in Table 3.

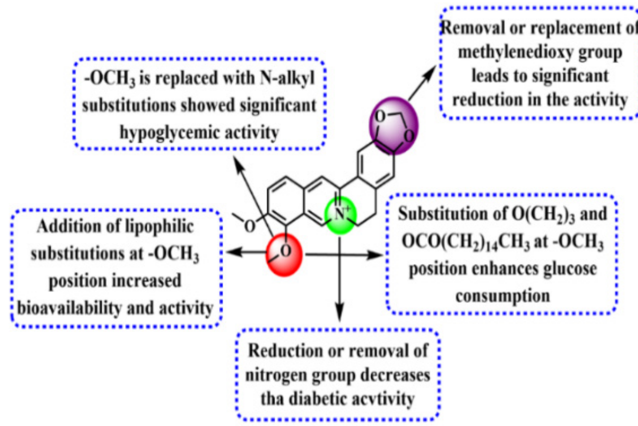

Fig 2: SAR of Berberine[50-52]

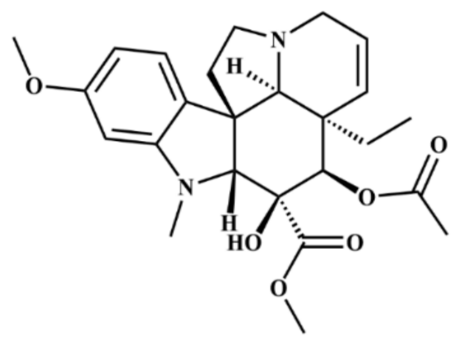

Fig 3: Structure of Vindoline.[67]

Structural activity relationship

Summarized in Fig. 4.

Toxicity

In-silico studies indicate vindoline from *C. roseus* has low acute toxicity and carcinogenic risk, with potential benefits in diabetes by reducing oxidative stress. However, reported effects like neurotoxicity, myelosuppression, and risks with skin exposure demand cautious monitoring, making its therapeutic use in diabetic complications promising but requiring strict safety evaluation.[65,66,75]

4.3 HARMINE (Indole)

Harmine, isolated from *Peganum harmala* L., is known for its anti-inflammatory, anticancer, and neuroactive properties.[76] Importantly, harmine stimulates β-cell regeneration and enhances insulin secretion by inhibiting DYRK1A kinase, making it a unique candidate for diabetes therapy.[77,78] Nano-delivery systems and harmine analogs are being developed to enhance efficacy and reduce toxicity.[79,80] The structure of harmine is shown in Fig. 5.

Contemporary Issues

Neurotoxicity and MAO inhibition, along with a lack of clinical data, limit its application.[78,80]

Mechanism of action

Summarized in Table 4.

Table 2: Mechanism of action of berberine

Mechanism	*Key actions*	*Primary effects*	*References*
Activation of AMPK	• Stimulates AMPK activity (including lysosomal AMPK via reduced UHRF1) • Enhances glucose uptake and lipid metabolism • Inhibits gluconeogenesis and modulates mTOR to improve liver function and reduce fat.	Enhances insulin sensitivity, improves glucose absorption and helps maintain cellular energy balance by lowering blood sugar levels.	[23,24,25,26,27,28]
Activation of PPARγ	• Activates peroxisome proliferator-activated receptor gamma. • Elevates expression of adipogenic markers such as PPARγ and C/EBPβ, enhancing insulin signaling.	Improves insulin sensitivity and regulates glucose and lipid metabolism.	[23,29,30,31]
Inhibition of gluconeogenesis	• Inhibits key hepatic gluconeogenesis enzymes • Elevates FGF21 and GLUT2 levels • Increases insulin and leptin; reduces NEFA and MDA • Enhances hepatic glycolysis via hexokinase and pyruvate kinase • Modulates glycolysis indirectly through FXR inhibition	Lowers hepatic glucose production and fasting blood glucose levels, contributing to overall glycemic control.	[32,23,29,33,34, 35,26,36]
Improved lipid metabolism	• Activates AMPK in fat, liver, and kidney tissues • Promotes ACC phosphorylation, inhibiting lipid synthesis • Reduces HMGCR, limiting cholesterol and triglyceride production	Lowers triglyceride and cholesterol levels, reduces fat accumulation, and improves overall lipid metabolism.	[29,23,37,24,30]
Regulation of gut microbiota	• Modulates gut flora by increasing beneficial bacteria (Bacteroidaceae, Akkermansiaceae) and reducing harmful ones (Lachnospiraceae). • Reduces abundance and activity of TMA-producing bacteria	Enhances insulin sensitivity and improves metabolic balance through beneficial modulation of the gut microbiome.	[38,39,40,34,33,41]
Oxidative stress reduction	• Acts as an antioxidant by scavenging free radicals. • Reduces oxidative damage in cells, including wound repair and neuronal tissues. • Lowers liver oxidative stress while increasing hepatic glycogen.	Protects cells against oxidative damage, which is critical for reducing complications in cardiovascular diseases and diabetes.	[23,25,32,42,43, 44,33,45]
Anti-inflammatory properties	• Lowers pro-inflammatory cytokines (TNF-α, IL-6) • Modulates cAMP/PKA/CREB and NLRP3 inflammasome pathways. • Inhibits apoptosis and extracellular matrix remodelling • Activates Sirt1 to regulate inflammation	Reduces chronic inflammation associated with insulin resistance and diabetes, supporting improved metabolic health and tissue repair.	[23,32,46,42,31,43,44,35,47,48,49]

Structural activity relationship

Summarized in Fig. 6.

Toxicity

Harmine shows strong toxicity, inducing neurological and cardiovascular effects even at low doses through acetylcholinesterase inhibition and MAO inhibition. It also acts as a natural insecticide against *Aedes albopictus* larvae, but its therapeutic and environmental use requires caution and further study to balance efficacy with safety.[92-94]

TRIGONELLINE (Pyridine)

Trigonelline, an alkaloid in fenugreek, shows antioxidant, anti-aging, and antidiabetic effects. Fenugreek seed extract lowers glucose and improves lipid profiles in human and animal models. Derived from vitamin B6, trigonelline enhances insulin sensitivity, reduces nephropathy, protects endothelial function, and supports muscle health via its role as an NAD+ precursor. Despite benefits, challenges in standardizing trigonelline-rich formulations remain[95-97] (Fig. 7).

Contemporary Issues

Evidence is mostly limited to preclinical and in vitro studies, with inconsistent protocols for herbal standardization.[96,98]

Mechanism of action

Summarized in Table 5.

Structural activity relationship

Summarized in Fig. 8.

Table 3: Mechanism of action of vindoline

Mechanism	*Key actions*	*Primary effects*	*References*
Interaction with α-amylase and α-glucosidase	• Vindoline modulates the immune system and inflammation. • It inhibits α-amylase/α-glucosidase, with strong docking affinity for α-glucosidase (−13.2250 vs. acarbose −14.7983).	Supports recovery in diabetic rats by reducing carbohydrate digestion rates and modulating inflammation.	[60,61] (docking details also in [60])
Improvement of glucose uptake	• Enhances basal glucose consumption in insulin-resistant rats. • Upregulates GLUT-4 and insulin receptor substrate-1 (IRS-1) expression in adipocytes and myoblasts.	Boosts insulin sensitivity and increases glucose uptake, aiding in blood sugar management and resolution of insulin resistance.	[62,63,61]
Lipid metabolism modulation	• Exhibits hepatoprotective effects by reducing liver enzyme levels associated with hepatotoxicity. • Lowers serum lipid levels.	Improves the lipid profile in diabetic rats and reduces cardiovascular risks related to hyperlipidemia.	[64,65]
Oxidative stress mitigation	• Functions as a natural antioxidant by scavenging free radicals. • Boosts antioxidant defense through enzyme activity and ferric reducing antioxidant power.	Decreases oxidative stress in diabetic tissues, protecting liver cells and renal tissues, and supporting overall metabolic health.	[64,66,61, 65,62,67,68]
Inflammatory pathway inhibition	• Lowers pro-inflammatory cytokine levels in diabetic rats, including IL-6 and TNF-α.	Mitigates chronic inflammation, thereby enhancing insulin sensitivity and protecting against tissue damage.	[64,69]

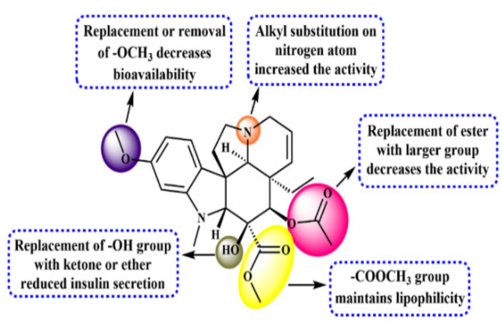

Fig 4: SAR of Vindoline[70-74]

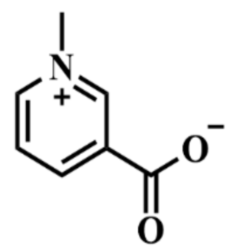

Fig 7: Structure of Trigonelline.[100]

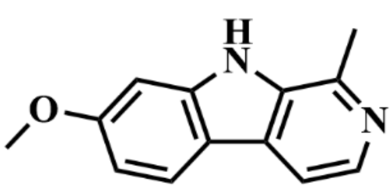

Fig 5: Structure of Harmine.[82]

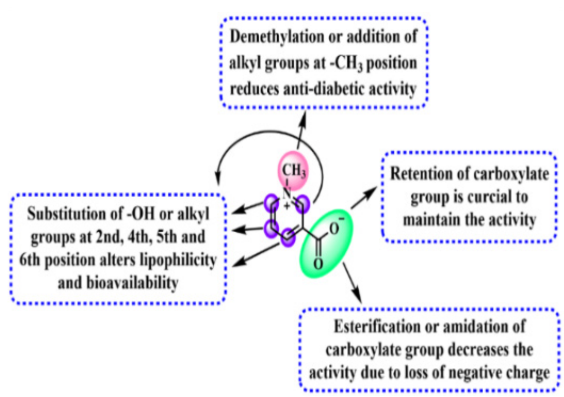

Fig 8: SAR of Trigonelline [109-111]

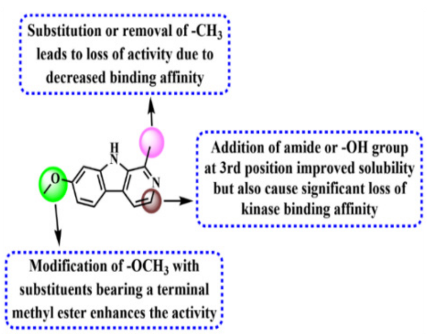

Fig 6: SAR of Harmine[89-91]

Toxicity

Trigonelline is safe for human use and shows benefits in allergic asthma and age-related muscle loss. Toxicity reports indicate low risk at therapeutic doses, and its role as an NAD+ precursor supports muscle function in older adults, highlighting its therapeutic potential with minimal safety concerns.[112-114]

Table 4: Mechanism of action of harmine

Mechanism	*Key actions*	*Primary effects*	*References*
Promotion of β-cell proliferation	• Significantly stimulates proliferation of beta and non-beta cells in human islet microtissues at moderate doses. • Suppresses DYRK1A to enhance pancreatic beta-cell replication.	Increases the number and function of insulin-producing cells, thereby improving insulin secretion and aiding in glucose homeostasis.	[81,82,83]
Regeneration of pancreatic islets	• Regenerates beta cells, including conversion from other cell types. • Restores or preserves pancreatic function in type 1 diabetes	Offers promise as a regenerative therapy for diabetes by re-establishing beta-cell mass and restoring insulin production.	[84,81,83]
Antioxidant activity	• Acts as a potent antioxidant by scavenging free radicals. • Enhances the body's antioxidant capacity to reduce cellular damage.	Lowers oxidative stress levels in diabetic models, which is critical for reducing insulin resistance and protecting pancreatic beta cells.	[84,85]
DYRK1A inhibition	• Blocks dual specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A), a crucial modulator of insulin release and beta-cell proliferation.	Stimulates the replication of pancreatic beta cells, leading to improved insulin levels and better glycemic control.	[82–84, 86-88]
Enhancement of Insulin secretion	• Enhances basal and stimulated insulin secretion from beta cells. • Improves insulin production via DYRK1A suppression.	Improves glycemic control by ensuring sufficient insulin availability to regulate blood glucose levels.	[81,84,83,6, 82,88]
Anti-inflammatory effects	• Blocks inflammatory signaling pathways such as NF-κB. • Reduces levels of pro-inflammatory cytokines.	Mitigates chronic inflammation associated with insulin resistance, thereby enhancing insulin sensitivity and overall metabolic health.	[83,84,85,86]

Table 5: Mechanism of action of trigonelline

Mechanism	*Key actions*	*Primary effects*	*References*
Wnt/β- catenin pathway regulation	• Modulates Wnt/β-catenin signaling involved in cell growth, differentiation, and apoptosis. • Prevents glucose-induced overactivation, reducing excessive proliferation and fibrosis.	Prevents the downstream effects that lead to renal impairment by averting abnormal cell proliferation and fibrosis.	[99]
Modulation of glucose transporters	• Enhances the expression of GLUT-4 by modulating glucose metabolism enzymes in adipocytes.	Improves glucose absorption and uptake in adipocytes, contributing to better blood sugar regulation.	[100]
Activation of the IRS1-GLUT2 pathway	• Stimulates the insulin receptor substrate 1 (IRS1) pathway, which triggers the translocation of GLUT2 to the cell membrane in liver cells.	Enhances glucose metabolism and lowers blood sugar levels by increasing glucose uptake in liver cells.	[101]
AMPK activation	• Promotes autophagy and cell survival by stimulating the AMPK pathway under high-glucose stress conditions.	Improves metabolic activity and energy balance, thereby reducing the harmful consequences of high glucose levels.	[99,102]
Antioxidant activity	• Suppresses ROS formation via PI3K-Akt-Nrf2 pathway activation. • Strengthens antioxidant defense by boosting enzymes, lowering MDA, and increasing total antioxidant capacity.	Reduces oxidative stress and protects cellular components—including pancreatic β-cells—from hyperglycemia-induced oxidative damage.	[100,103,104,105, 102,106,107,108]
Anti-inflammatory effects	• Reduces levels of pro-inflammatory cytokines (e.g., TNF-α, IL-6). • Modulates inflammatory pathways that are typically upregulated in diabetes.	Mitigates chronic inflammation, which improves insulin sensitivity and minimizes diabetes-related complications (including effects on bone and tissue degeneration).	[106,100, 105,108]

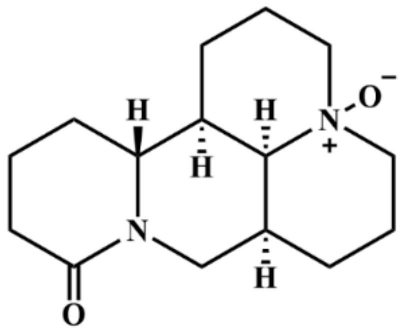

Fig 9: Structure of Oxymatrine.[120]

OXYMATRINE (Quinazolidine)

Oxymatrine, a quinolizidine alkaloid from *Sophora flavescens* roots, shows immune-modulating, antioxidant, anti-inflammatory, antiviral, and cardioprotective effects.[115] Traditionally used for myocardial ischemia, it also regulates metabolism, improves lipid and glucose handling, and protects against obesity and metabolic disorders.[116-117] Studies highlight its antidiabetic potential in kidney disease and diabetes-induced cardiomyopathy by mitigating oxidative stress, inflammation, and apoptosis[118-120] (Fig. 9).

Contemporary Issues

Hepatotoxicity concerns; limited clinical data.[119,120]

Mechanism of action

Summarized in Table 6.

Structural activity relationship

Summarized in Fig. 10.

Toxicity

Oxymatrine shows cytotoxicity by reducing human liver cell viability and inducing programmed cell death, warranting cautious monitoring in clinical use. Further studies are required to clarify its mechanisms and establish safety standards.[133,134]

SOLANINE (Steroidal)

Solanine, a bitter glycoalkaloid ($C_{45}H_{73}NO_{15}$) from nightshade plants (*S. lycopersicum*, *S. tuberosum*, *S. erianthum*), has traditional uses against infections, gastrointestinal issues, fever, gout, dermatitis, and liver disorders. In Nigeria, its leaves are used for cancer and malaria remedies.[135,136] Beyond its role as a plant defense compound, solanine enhances insulin sensitivity, lowers postprandial hyperglycemia in diabetic mice, and modulates mitochondrial function via PPARγ activation [137-139] (Fig. 11).

Contemporary Issues

Strong neurotoxicity narrows its therapeutic window, requiring further safety studies.[138,139]

Mechanism of action

Summarized in Table 7.

Structural activity relationship

Summarized in Fig. 12.

Toxicity

α-Solanine damages mitochondrial membranes, overstimulates the nervous system, leading to neurological symptoms due to cell lysis and blockage of acetylcholinesterase activity.[146-148]

Recent Advances in Alkaloid-based Antidiabetic Therapy

Berberine

Recent studies show berberine lowers blood glucose in T2DM, with efficacy comparable to metformin. Nano-formulations enhance their bioavailability and hypoglycemic effects. Its mechanisms include

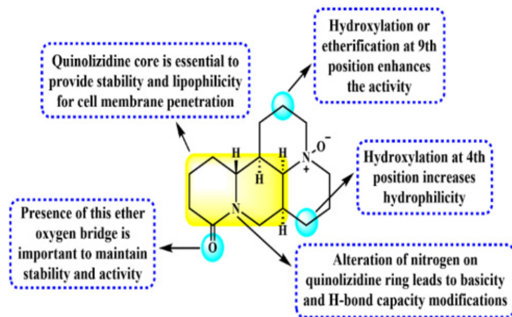

Fig 10: SAR of Oxymatrine[128-132]

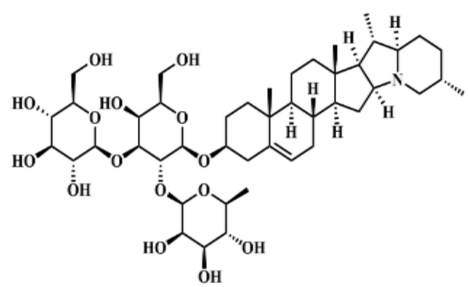

Fig 11: Structure of Solanine.[140]

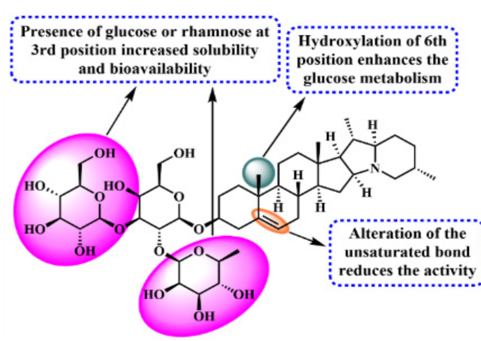

Fig 12: SAR of Solanine [143-145]

Table 6: Mechanism of action of oxymatrine

Mechanism	*Key actions*	*Primary effects*	*References*
Regulation of oxidative stress	• Lowers ROS and MDA while increasing SOD activity. • Activates SIRT1 to boost antioxidant enzyme production in cardiomyocytes.	Lowers oxidative damage in brain, heart, and other tissues; improves cellular stress tolerance and metabolic regulation.	[120–122, 115,123,124]
Anti-Inflammatory effects	• Suppresses expression of pro-inflammatory cytokines (e.g., TNF-α, IL-1β). • Lowers inflammatory markers in the cerebellar cortex.	Reduces liver damage, fibrosis, and neuroinflammation associated with diabetes, thereby alleviating cognitive decline and neurological impairments.	[120,121]
Regulation of gluconeogenesis	• Modulates key enzymes (e.g., PEPCK, G6Pase) involved in hepatic glucose synthesis.	Decreases excessive hepatic glucose production, improves insulin sensitivity, and lowers hyperglycemia.	[120,125]
AKT phosphorylation	• Promotes AKT phosphorylation via the PI3K/Akt signaling pathway. • Enhances cell survival by blocking pro-apoptotic proteins and promoting anti-apoptotic processes.	Improves glucose absorption and utilization in liver cells, counteracting insulin resistance, and protecting hepatocytes from hyperglycemia-induced apoptosis.	[125,122,126]
Inhibition of apoptosis	• Reduces diabetes-induced caspase-3 expression and activity. • Blocks Toll-like receptor 4 (TLR4) activation to mitigate downstream inflammatory signals.	Protects neuronal and liver cells from apoptosis, thereby reducing cell death and tissue damage associated with diabetes.	[115,121,123, 124,126, 127,122]

Table 7: Mechanism of action of solanine

Mechanism	*Key actions*	*Primary effects*	*References*
antihyperglycemic properties	• Stimulates adrenal glands to enhance hepatic glucose synthesis and release. • Induces dose-dependent hyperglycemia in rats, with smaller doses normalizing faster	Increases blood sugar levels by promoting hepatic glucose production.	[140]
Inhibition of Digestive enzymes	• Inhibits α-amylase and α-glucosidase. • Slows starch breakdown and glucose absorption	Reduces postprandial blood sugar spikes by delaying glucose absorption.	[135,141]
Antioxidant properties	• Exhibits antioxidant activity that reduces oxidative stress. • Disrupts mitochondrial membranes by opening potassium channels, altering membrane potential and cytosolic Ca^{2+}, thereby inducing apoptosis.	Lowers oxidative stress linked to insulin resistance and β-cell damage and Induces apoptosis, aiding cancer prevention.	[135,142]
Modulation of signaling pathway (Akt/mTOR)	• Inhibits the Akt/mTOR pathway, which is critical for cell growth, survival, and insulin signaling. • Although more established in cancer models, this modulation might enhance insulin sensitivity or alter glucose metabolism.	Potentially influences glucose uptake and metabolism by promoting autophagy and apoptosis, though this connection in diabetes remains speculative and requires further characterization.	[142]

gut microbiota modulation and anti-inflammatory activity.[18-20]

Vindoline

Vindoline from *C. roseus* improves insulin sensitivity and reduces oxidative stress in diabetic models. CRISPR-based engineering has improved yields, supporting future large-scale production. [56,58]

Harmine

Harmine stimulates insulin secretion and β-cell regeneration by inhibiting DYRK1A. Nanoparticle-based delivery has been developed to enhance efficacy and reduce neurotoxicity. [78,80]

Trigonelline

Trigonelline from fenugreek improves insulin sensitivity, protects against nephropathy, and supports NAD+ synthesis, aiding muscle health in diabetes and aging. [96,97]

Oxymatrine

Oxymatrine reduces inflammation in diabetic nephropathy and protects against cardiomyopathy through Nrf2/HO-1 and JAK/STAT signaling pathways. [117,118]

Solanine

Solanine enhances insulin sensitivity and reduces hyperglycemia in diabetic mice. It modulates mitochondrial function and PPARγ signaling. [138,139]

Review Merits, Limitations, and Future Directions

Berberine

- *Merits*

Most extensively studied alkaloid; lowers glucose and improves insulin sensitivity via AMPK activation and anti-inflammatory effects.[18,19]

- *Limitations*

Poor oral bioavailability and variable extract standardization.[19,21]

- *Future directions*

Development of nano-formulations and derivatives to enhance absorption and efficacy.[19]

Vindoline

- *Merits*

Shows strong antidiabetic potential in preclinical studies; metabolic engineering has increased yields.[56,58]

- *Limitations*

Evidence is largely preclinical; lack of human trials.[56]

- *Future directions*

Clinical validation, improved delivery systems, and safety studies are required.[56,58]

Harmine

- *Merits*

Promotes pancreatic β-cell regeneration, offering unique therapeutic potential.[78]

- *Limitations*

Neurotoxicity and absence of clinical studies.[80]

- *Future directions*

Development of safer analogs and targeted delivery systems.[80]

Trigonelline

- *Merits*

Improves insulin sensitivity and reduces nephropathy in preclinical models.[96]

- *Limitations*

Most findings are from animal studies; lack of human validation.[96,97]

- *Future directions*

Standardized formulations and clinical trials are needed to confirm benefits.[96,97]

Oxymatrine

- *Merits*

Exhibits multiple antidiabetic mechanisms and protects against diabetic complications.[118,119]

- *Limitations*

Hepatotoxicity and insufficient clinical data.[118,119]

- *Future directions*

Dose optimization and long-term safety studies are essential.[118,119]

Solanine

- *Merits*

Demonstrates antidiabetic effects by improving insulin sensitivity in preclinical models.[138]

- *Limitations*

High neurotoxicity and narrow therapeutic index.[139]

- *Future directions*

Research on structural modifications and safe dosing strategies.[138,139]

General Review Merits, Limitations, and Future Directions

General merits of the review

- Comprehensive coverage of recent findings (upto 2025) on key antidiabetic alkaloids.
- Balanced discussion of therapeutic potential and challenges.
- Identification of research gaps, including safety and standardization.

General limitations

- Evidence for many alkaloids is limited to preclinical studies.
- Variability in extraction and formulation affects reproducibility.
- Long-term and population-specific safety data are lacking.

Future directions

- Development of standardized clinical protocols.
- Exploration of patient-specific (personalized) responses.
- Stronger regulatory and ethical frameworks for herbal therapies.
- Use of nanotechnology and metabolic engineering to improve efficacy and safety.

Conclusion

Natural alkaloids like berberine, vindoline, harmine, trigonelline, oxymatrine, and solanine show promise in diabetes management by enhancing insulin sensitivity, secretion, gut microbiota modulation, and reducing oxidative stress and inflammation. Berberine has strong clinical evidence, while harmine offers potential for β-cell regeneration. Others demonstrate encouraging preclinical effects, but challenges remain, including poor bioavailability, toxicity risks, lack of standardized extraction, and limited large-scale trials. Future progress requires optimized dosing, safety evaluation, and advanced delivery systems, with collaborative research to translate these compounds into effective therapies.

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Author Contributions

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