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Progress of Indole Alkaloids for Potential Application in Type 2 Diabetes Mellitus-An Updated Review

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Abstract: The underlying pathology of type 2 diabetes mellitus (T2DM) includes compromised insulin production and resistance by various organs or the mutual occurrence of both, which are the most frequent reasons. This leads to a complete loss of pancreatic beta cells' secretory function. Hence, defined measures and correct parameters must be considered to minimize the disease risk. Herbal medicines and plants are becoming increasingly popular due to their multiple benefits, including low toxicity, safety, and efficacy. The structural variety and therapeutic potential of indole alkaloids (IAs) make them an important class of naturally occurring compounds. This critical review was undertaken to identify and draw attention to the indole-containing plant alkaloids helpful in preventing T2DM. Both preclinical and clinical findings, as well as safety and toxicity, were highlighted in the study. Based on the current scientific literature, it is reasonable to assume that these IAs have great potential as therapeutics, either alone or in conjunction with existing treatments, leading to the development of safer and more effective profiles.

Keywords: type 2 diabetes; indole alkaloids; preclinical and clinical studies; safety and toxicity.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic condition characterized by increased blood glucose levels due to inadequate insulin secretion or insulin resistance. Statistics show approximately 100 million individuals are in contact with this disorder [1–3]. It might result

from decreased insulin production, resistance to insulin's peripheral effects, or perhaps from both [4,5]. Diabetes has a high risk of consequences if it is neglected. Acute outcomes include diabetic ketoacidosis and nonketotic hyperosmolar coma. Strokes, foot ulcers, heart disease, eye damage, and renal insufficiency are chronic effects [6–8] (Figure 1). In 2014, approximately 8.5% of individuals and elders aged 18 and elders had diabetes, and a total of 1.5 million deaths occurred in 2019. Those under the age of 70 accounted for 48% of all fatalities. Diabetes contributed to an additional 4,60,000 cases of renal diseases and 20% of cardiovascular fatalities [9–11].

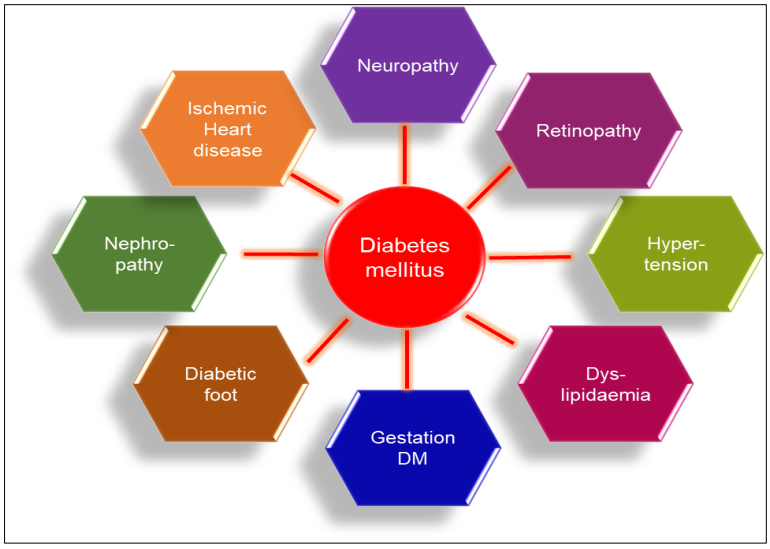

Figure 1. Diabetes-related complications.

International Diabetes Federation data shows that 537 million people (20–79 years old) suffer from DM, which is assumed to rise to 643 million by 2030 and 783 million by 2045 globally. Nearly 240 million people with DM are undiagnosed, resulting in 6.7 million fatalities [12,13]. Death rates are higher than those with acquired immune deficiency syndrome (AIDS), tuberculosis (TB), and hypertension. Around 541 million individuals are prone to T2DM. Greater than 1.2 million infants and adolescents (0–19 years) have type 1 DM [12,14]. Approximately 90% of deaths are caused due to T2DM. More than 400 million people have been diagnosed, which will increase to more than 640 million by 2040 [15,16]. Therefore, the treatment approaches have gained much consideration, from the already available drugs and potential drug candidates to natural compounds. The secondary metabolites extracted, alkaloids (ALK), are generally found in 14–20% of plant species [17]. The ALK originates from tryptophan, which contains amino acids. The clinical application includes all anti-therapeutic properties in inflammation, cancer, hypertension, microbial and mycobacterial infection [18], malaria, analgesics, diarrhea, leishmania, and lipid-lowering [19]. This comprehensive study was conducted to locate and bring to light the indole-containing plant alkaloids that are beneficial in reducing the risk of developing T2DM. The results of the preclinical and clinical stages, as well as those of safety and toxicity, were emphasized in the study.

2. Type 2 Diabetes Mellitus (T2DM)

Adult-onset or non-insulin-dependent diabetes mellitus (NIDDM) is featured as hyperglycemia [4]. Hyperglycaemia causes damage to the kidneys, vasculature, pancreas, heart, nerves, and liver. Around 90% of cases of T2DM occur due to malfunctioning of islet β-cells of the pancreas [6].

2.1. Risk factors.

The appearance of T2DM includes genomic, improper metabolism, and environmental aspects. Even though the risk variables for T2DM that cannot be changed are ethnicity and family history/genetic predisposition, epidemiological research has addressed the three main preventive actions: overweight, sedentary life, and unhealthy consumption [20]. Ethnicity and family history/genetic predisposition: people in Spain, Japan, and the United States show a comparatively elevated risk for T2DM than people in other countries, followed by race and topography [21]. Observation shows Indians are at a greater extent than Americans or Britons, whereas Black people are dominating among all [22]. The primary factor in developing T2DM is inherited predisposition. Multiple genome-centric studies of this diseased state over the earlier decade have shown the complex polygenic phenotype associated with the primary endpoint as a restriction in insulin production and the minority acting by delaying insulin action [23].

Obesity, physical inactivity, and poor diet: Central fat distribution and body mass index [BMI]≥30 kg/m^2 signifies obesity. It is an indicator of NIDDM, including men and women [24]. Increased glycerol levels, hormones, cytokines, proinflammatory markers, and other moieties responsible for developing insulin resistance are usually seen in obese people [25,26]. Unhealthy food consumption linked with the prevalence of NIDDM includes alcohol, saturated fat, and inappropriate/unhealthy consumption [24]. Due to physical inactivity, protein transcription and translation slow down, which imbalances the normal homeostatic functioning of glucose. An inappropriate habit of living influences whole physiology and lowers the efficiency of insulin production. Its underlying mechanism includes mitochondrial dysfunction, inflammation, and endoplasmic and oxidative stress, leading to apoptosis and beta cell necrosis [27].

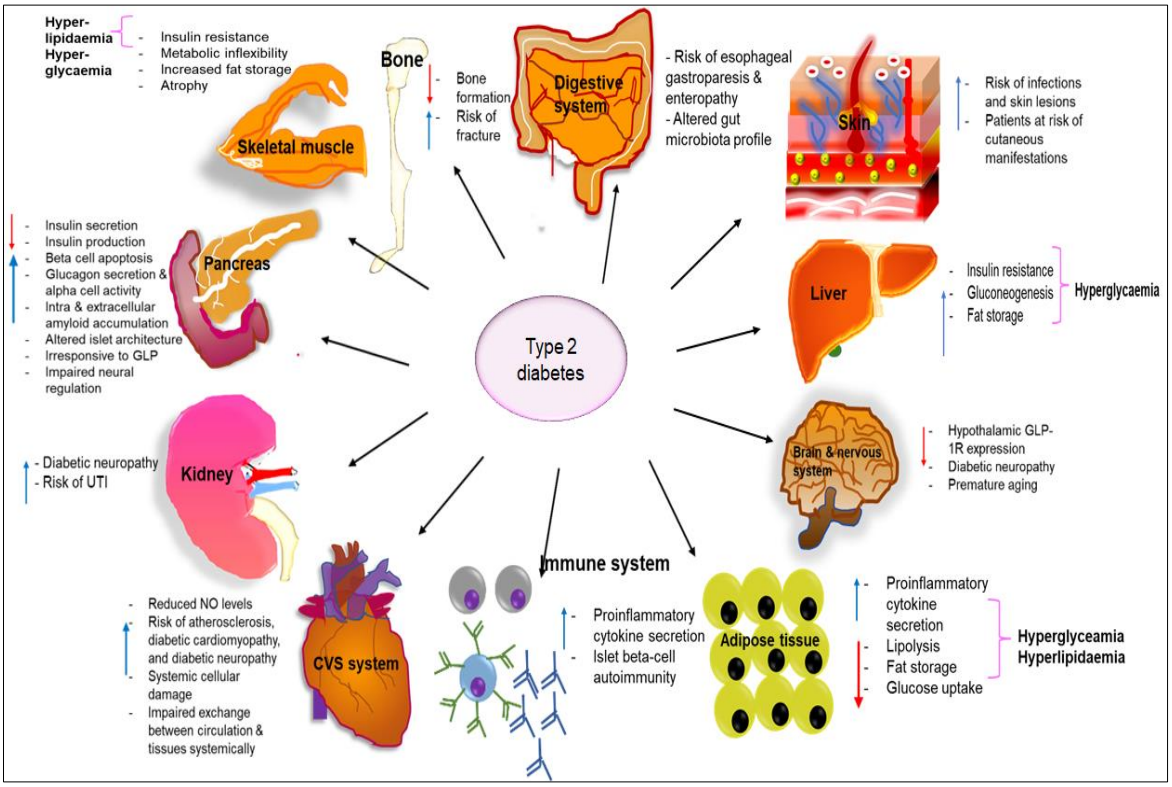

Figure 2. Pathological impacts of T2DM on several systems and organs. The descriptions of the figures are taken from different studies.

Thus, proper intake, a healthy lifestyle, and regular workouts can prevent chances of T2DM. Frequent urination, increased thirst, tiredness, and weight loss are indications of T2DM. The pathological effects are shown in Figure 2, which affect several systems and organs in the body. Few are linked with the disease condition dyslipidemia/hyperlipidemia [28].

2.2. Pathophysiology of T2DM.

Inadequate insulin secretion and resistance cordially develop the pathophysiological conditions of the disorder. The various factors mentioned in Figure 3 depict the pathogenesis of T2DM responsible for insulin secretion and resistance to fatty acid catabolism. If the mentioned mechanism functions abnormally, it can lead to a decrease in pancreatic β-cell mass accompanied by glucotoxicity and lipotoxicity. The continuation of the same dramatically affects the long-term control of blood glucose[29].

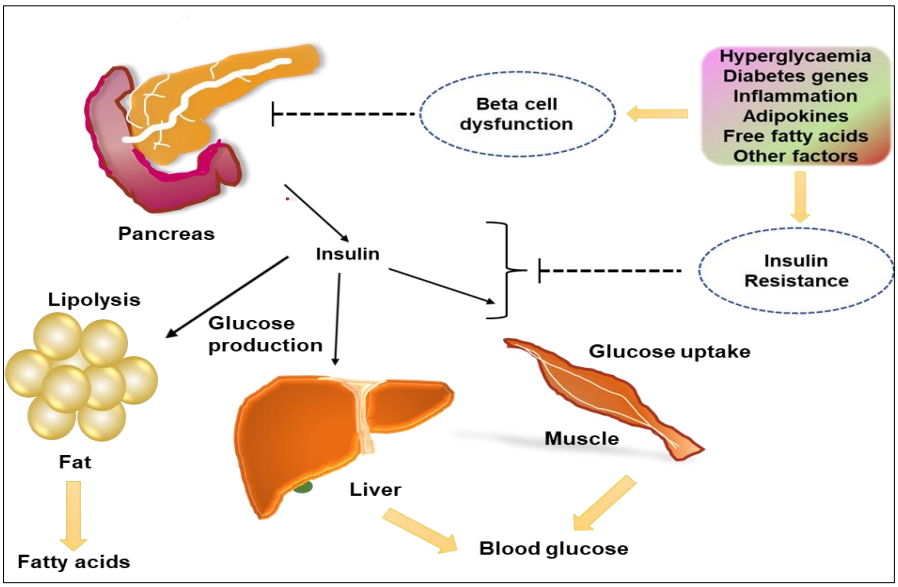

Figure 3. Pathogenesis of hyperglycemia and rise in circulating fatty acids in type 2 diabetes mellitus.

Insulin resistance is a phenomenon where the pancreas generates less insulin than required for both the regulation of endogenous glucose synthesis in hepatocytes and the deposition of glucose in skeletal muscle [30]. Insulin fails to resist lipolysis due to the deposition of macro adipocytes, subsequently in visceral or deep subcutaneous adipose depots. Elevated amounts of non-esterified fatty acids and glycerol in systemic circulation aggravate insulin resistance in the hepatocytes and myofibril [31]. Insulin resistance affects major pathways of normal physiological functions of the body, contributing to a high percentage of circulating fatty acids and hyperglycemia, which results in elevated glucose levels and fatty acids in the systemic circulation, which will worsen both insulin production and resistance[32].

2.3. Treatment.

To normalize blood glucose levels or further avoid the diseased condition, patients receive conventional treatment, which includes α-glucosidase inhibitors, sulfonylureas, metformin, thiazolidinediones (TZDs), and insulin injections [33]. Thus, the various treatment strategies for T2D are described in Table 1, along with a mechanism of action (MOA) [34]. Biguanide shows GI side effects and insufficiency of Vit B12. They are contraindicated if creatinine clearance/glomerular filtration rate<30 mL/min or liver dysfunction [35]. Incretin

displayed rare cases of pancreatitis and arthritis. Also, they can be administered by subcutaneous route only. They are contraindicated with saxagliptin in congestive failure. Acute gallstone disease is a rare occurrence when it is given for a long-term duration. Liraglutide slows the progression of nephropathy. They are contraindicated if there is a family history of thyroid type 2 multiple endocrine neoplasias [36].

Table 1. Antidiabetic drugs use in type 2 diabetes mellitus.

Class and MOA	Drug	References
First Line		
Biguanide: Elevated insulin sensitivity in the liver by AMP-activated protein kinase.	Metformin Metformin extended-release	[35]
Second Line		
Incretin: Enhances glucose-dependent insulin release, lowers gastric emptying, and inhibits glucagon release.	DPP-4 inhibitors: Alogliptin, Linagliptin GLP-1 receptor agonists *Short-acting*: Lixisenatide, Exenatide *Longer-acting*: Exenatide, Dulaglutide *extended-release*: Liraglutide	[36]
SGLT-2 inhibitors: Inhibit glucose uptake by restricting protein transport in renal cells.	Dapagliflozin	[37]
Alpha-glucosidase inhibitor: suppresses an intestinal α-glucosidase and pancreatic α-amylase.	Acarbose	[43]
Insulin: Affiliates insulin receptors to potentiate the metabolism of macronutrients	Bolus Insulins *Rapid-acting*: Aspart (faster-acting), Glulisine, Lispro, U-100,200 *Short-acting*: Regular Basal Insulins *Intermediate-acting*: NPH *Long-acting*: Degludec, U-100,200, Detemir, Glargine, U-100,300, and biosimilar Premixed Insulins: Premixed regular-NPH, Biphasic insulin aspart, Lispro/lispro protamine suspension	[34]
Insulin secretagogue: Triggers sulfonylurea (SU) receptor present on β-cell to trigger the release of insulin.	Sulfonylureas, Gliclazide modified-release, Meglitinides	[39]
Thiazolidinedione: Activates peroxisome proliferator-activated receptors-gamma.	Pioglitazone, Rosiglitazone	[40]
Mass-reducing agent: Inhibits the action of lipase.	Orlistat	[42]

Canagliflozin and empagliflozin are utilized for myocardial infarction and prevent the progression of nephropathy. Treatment with SGLT-2 inhibitors ought to be avoided before severe illness or with major surgery or infections. Dapagliflozin use is restricted in bladder malignancy. Evidence of acute renal failure with dapagliflozin and canagliflozin was seen [37]. Treatment with alpha-glucosidase inhibitors is associated with GI side effects and requires frequent dosing [38]. Insulin shows potent A1C reduction with minimum dose. Its several formulations and administration methods allow it for adaptability in dosage [34]. Gliclazide is preferred over glyburide due to the negligible risk of hypoglycemia and CV mortality. It demonstrates a quick BG reduction response. Meglitinides lower postprandial glycemia and require three doses each day. Repaglinide should not be used in conjunction with clopidogrel and gemfibrozil [39]. Treatment with thiazolidinediones may cause edema, congestive heart failure, rare macular edema, and a greater risk of fractures. Rosiglitazone and Pioglitazone should not be used in MI and bladder cancer, respectively [40]. Treatment with mass-reducing agents promotes weight loss, and it can cause diarrhea and adverse GI events. It needs 3 times daily dose [41,42].

3. Novel IAs Therapies for T2D

Unwanted aftereffects, including weight gain, low blood sugar, acid indigestion, lactic acidosis, edema, and anemia [33] had limited use of conventional medications in the treatment of T2DM (Table 1); the immune system shows resistance to prolonged use, and some drugs are administered till the condition is associated [44]. Therefore, medicinal plants and their bioactive components can be utilized worldwide to treat diabetes mellitus, especially where access to traditional anti-DM medications is limited [45]. Intensive research has examined many pharmacological effects of active chemical constituents in herbal remedies, such as alkaloids. Therefore, creating novel antidiabetic medications from IAs found in nature is a feasible alternative [46]. IAs are nitrogen-containing heterocyclic structures (Figure 4) involved in the metabolism of tryptophan and largely present in bacteria, animals, and plants [47]. The combined mechanism of an antidiabetic effect of IAs includes suppression of α-glucosidase, DPP-IV deactivation, protein tyrosine phosphatase 1B blockage, increasing insulin sensitivity, and altering oxidative stress to manage metabolic sickness are shown in Figure 5. IAs are derived from the different genera. Extracts of *Rauwolfia serpentina* were proven to be more potent in treating diabetes [48]. The basic structure of various IAs is given in Figure 6.

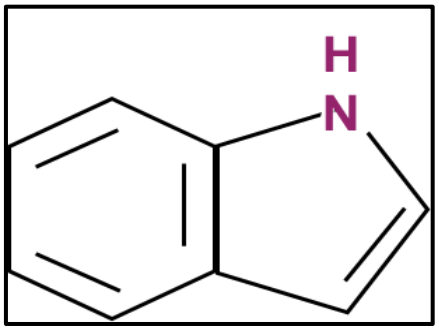

Figure 4. The basic structure of indole.

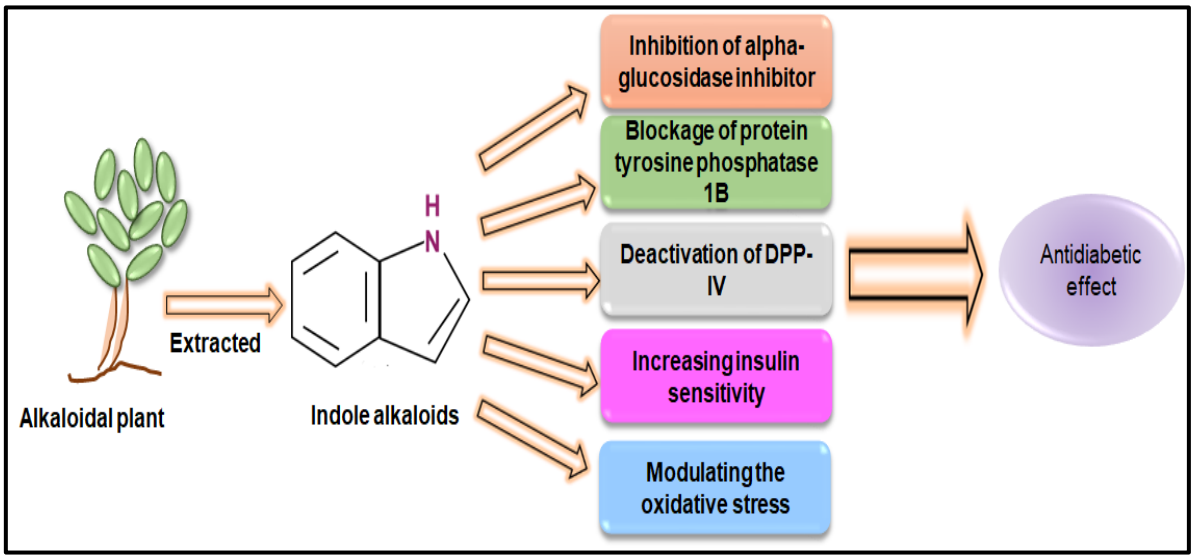

Figure 5. Complex mechanism of action of antidiabetic IAs.

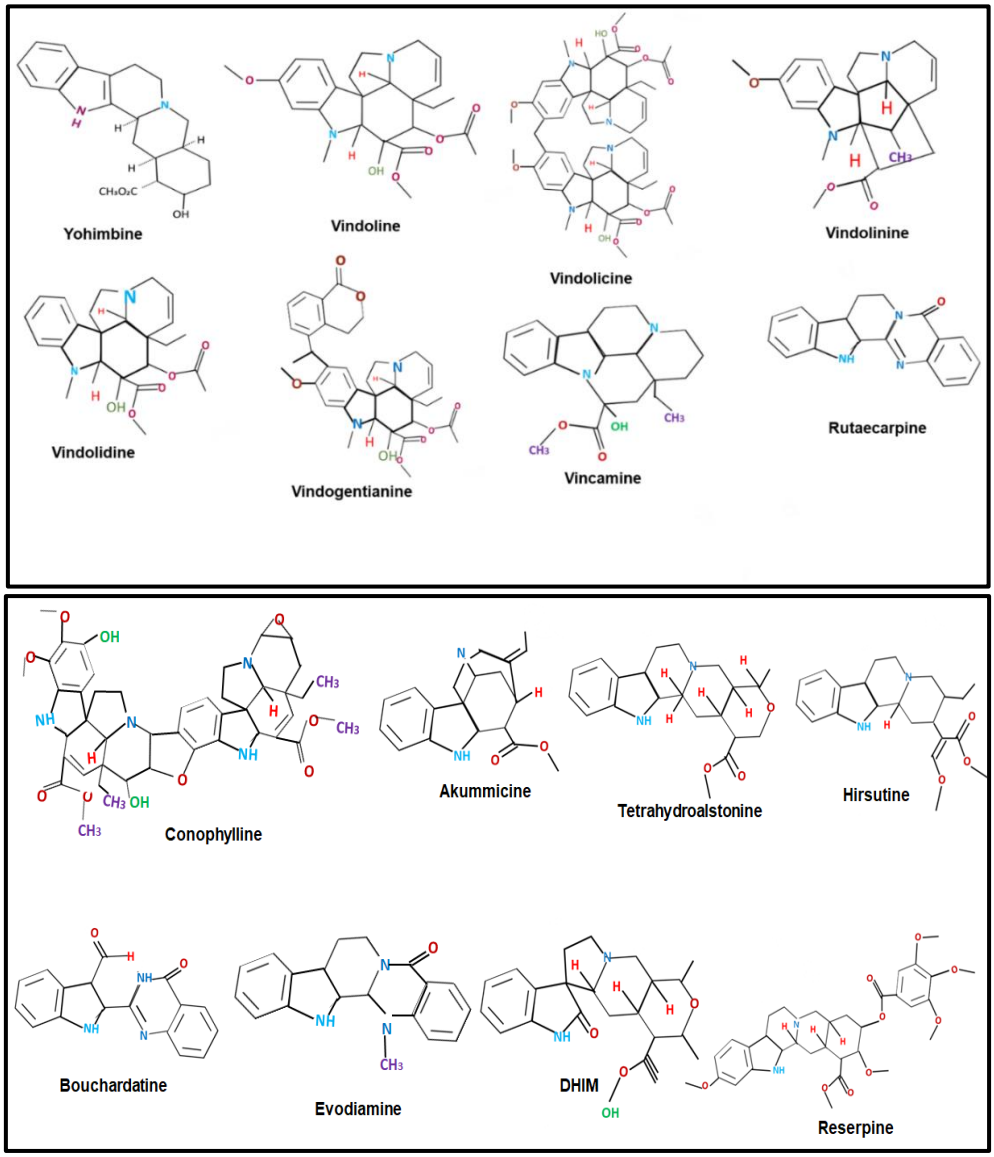

Figure 6. The basic structure of IAs used for T2D.

Yohimbine is derived from the bark of the Pausinystalia yohimbe tree, which is also present in the root of Rauwolfia [49], according to research conducted by Dhiraviam *et al*. Yohimbine resonates with DPP-IV and blocks its release. The DPP-IV enzyme is crucial for controlling glucose metabolism. Thus, they concluded that the yohimbine molecule functions as a new DPP-IV inhibitor for T2DM treatment [50].

Another alkaloid obtained from *Catharanthus roseus (C.roseus)* was prescribed to treat DM. In this research conducted by Gobaza *et al*., *C. roseus* and vindoline (VD) extracts were examined for antioxidant, alpha-glucosidase, and amylase inhibitory properties. They discovered that VD showed considerable antioxidant activity with improved insulin secretion compared to ascorbic acid [51]. The research found that derivatives like VD, vindolidine (VLD), vindolicine (VDC), and vindolinine (VDN) increase glucose uptake in pancreatic β-TC6 and skeletal C2C12 cells by suppression of protein tyrosine phosphatase- 1B (PTP-1B) [52]. The VDC was the most effective and may act as an insulin sensitizer by inhibiting PTP-1B. The VD and VDN on molecular docking show α-glucosidase inhibitory action [53].

The monoterpenoid vincamine (VCA), obtained from the *Madagascar periwinkle*, is therapeutically utilized to treat CVS and cerebral problems. It is also considered to have

nootropic properties as a dietary supplement. VCA has efficacy in β-cell amelioration in T2DM in addition to neuronal protection [54].

Shukla *et al*. studied isomitraphylline alkaloid 16,17-Dihydro-17b-hydroxy (DHIM) collected from *Mitragyna parvifolia* and was addressed as a DPP-IV inhibitor. They administered streptozotocin (STZ) (100 mg/kg) to induce diabetes in rats and then administered DHIM 100 mg/kg orally up to 2 months to diabetic rats. The DHIM increased GLP-1 level, optimized glucose tolerability and hyperglycemia, elevated β-cell proliferation, and lowered pancreatic cell apoptosis. Subsequently, body weight does not show any significant change [55].

The indolomonoterpenoid alkaloid containing 5-fused ring corynanthean skeleton [56] compound tetrahydroalstonine (THA) was obtained from seeds of *Amsoniu elliptica*, leaves and stems of *Uncaria bernagsia*. It was first reported to produce a quick hypoglycemic triphasic response induced with alloxan in diabetic rats. It indicated the recovery time from 2-12 hours post-treatment, after which the continued hypoglycemic effect lasted more than 48 hours post-treatment, as stated by Marles *et al*. [57]. Reserpine has a similar basic structure as yohimbine obtained from *Rauwolfia serpentina* roots, which were supposed to decrease blood pressure [58]. Reserpine inhibits the uptake of dopamine, histamine, and serotonin into storage vesicles, resulting in the depletion of the central and peripheral axons. A robust promoter was discovered to enhance the development of pluripotent stem cells into useful cells and help diabetic mice recover hyperglycemia. This study revealed a novel method for upcoming cell replacement therapy and showed the new function of VMAT2, as explained by Sakano *et al*. [59].

One of the current research highlights that Hirsutine (HR) isolated from herbs of *Uncaria rhynchophylla* can normalize diabetic peripheral neuropathy, lipid panel, and insulin resistance, ameliorating liver steatosis and myocardial hyperplasia in the HFD-induced diabetic model. It also improves glucose intake in insulin-resistant HepG2 and H9c2 cell models by activating the PI3K/Akt signaling cascade. In addition, HR resists the mechanism of gluconeogenesis and potentiates glycogen synthesis in the hepatocytes under insulin-resistant conditions [47].

Akuammicine (AKM) is an IA extracted from *Picralima nitida* seeds. The bioactivity was evaluated in chloroform extract for 6 IAs (AKM, 10- deoxyakuammine, akuammine, akuammidine, burnamine, picraline) and a blend of 4 5- hydroxy tryptamine amides. Reports suggest that, on incubation with chloroform for 24h, AKM revitalizes glucose uptake when examined in completely differentiated 3T3-L1 oleaginous cells. It was concluded that *P. nitida* seeds can be used to treat T2DM [60]. An indolopyridoquinazoline derivative RC, an *Evodia rutaecarpa* (Wu-Zhu-Yu) fruit extract, has potent pharmacological action on obesity, oxidation, cancer, and lipid-lowering effects [61]. Rutaecarpine (RC) C acts as an appetite suppressant in HFD mice, as stated by Kim *et al*. [62].

Another research study disclosed that the conophylline (CNP) (bisindole alkaloid) extracted from *Ervatamia microphylla* leaves [63] has the ability to minimize diabetes complications. CNP causes morphological change/ differentiation and improves insulin production in pancreatic acinar carcinoma AR42J cells via p38 MAPK activation [64]. In Goto-Kakizaki (GK) rats, CNP decreased pancreatic islet fibrosis [65]. Additionally, oral administration of CNP in the GK, neonatal, and adult STZ-induced diabetic rats model reversed the hyperglycemia and noticeably potentiated glucose tolerance, β-cell mass, and insulin content [66].

Evodiamine (Evo), a quinazoline alkaloid obtained from fructus *Evodia rutaecarpa Bentham*. It was first tested for its ability to combat obesity by significantly reducing body weight, serum FFA, epididymal fat mass, and hepatic TG in SD rats given in HFD. The defined cycle for triggering the action might be shown through improving lipolysis, BAT) and heat dissipation [67]. Further research revealed that Evo may inhibit diet-induced obesity by independently activating a pathway uncoupling protein-1 (UCP-1). They also activated extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK) signaling and negatively regulated insulin-induced Akt signaling pathway [68]. Bouchardatine is an IAs identified and extracted from the herb *Bouchardatia neurococca*, which can be extracted from RC. The Bou's ability to decrease lipid deposition by operating the AMPK pathway also hinders major adipogenesis regulators. The rate-limited metabolic enzymes of fatty acid production were initially investigated in the 3T3-L1 cell line, revealing its potential to affect obesity and associated metabolic effects negatively [69].

4. Preclinical and Clinical Evidence on IAs

4.1. Preclinical study.

The data for preclinical evaluation is depicted in Table 2. The study (PS-1) was conducted with the main purpose of enhancing the homeostasis of glucose using the HFD/STZ-induced T2D mice model. The intraperitoneal injection was given to male 6-week-old mice, and a single dose of 100mg/kg STZ was given following a 4-week HFD diet. For 5–6 weeks, a daily i.p. injection of the (physiological saline) and 15–30 mg/kg vincamine HCl (as VCA) was given. Weight and diet were kept track of during the trial. All mice had their fasting blood glucose levels checked once a week following a 6-hour fast. After an overnight fast, a 4-week oral glucose tolerance test (OGTT) (1.0g/kg glucose) was performed. Blood samples were collected from tail veins to estimate glucose and insulin levels [54]. The experiment (PS-2) focused on DHIM's potential to inhibit DPP-IV. The investigation employed 2-day-old Wistar albino rats as test subjects. To induce diabetes, intraperitoneally injected streptozotocin (STZ) (90 mg/kg in 10 mmol/l of citrate buffer, pH 4.5). The citrate buffer injection was given to control animals. Blood glucose concentration was checked and measured 24 hours after the injection every three days. The 3 groups of animals: control, diabetic, and diabetic treated—were separated, and 100 mg/kg of injection was given at 24 hours. Later monitored every 3 days [55]. In PS-3, by using six- to eight-week-old male C57BL/6J, leptin-deficient (ob/ob), leptin receptor-mutated (db/db), the research on animal experiments was conducted. The mice were orally gavaged with D-glucose at a rate of 2 g/kg body weight for a week during the OGTT[70]. For PS-4, male SD rats (250-260 g) were taken. Each group's subjects received low and high dosages of 100 and 200 mg/kg, respectively. At 0 (pre-dose), 0.08, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, and 48 h after oral administration, plasma samples were taken from the orbital venous plexus. The obtained samples were gathered, refrigerated at -80°C until analysis, and were immediately centrifuged at 3000 x g for 15 min [71]. In PS-5, nine groups of experimental mice (six per group) were used: a fructose-administered T2D diabetic group (distilled water 1 ml/kg), a negative control group (0.05% DMSO 1 ml/kg), a positive control group (Pioglitazone 15 mg/kg), and six test groups (MREt 10, 30, and 60 mg/kg and AqMREt 50, 100, and 150 mg/kg). The normal control group (1 ml/kg distilled water) was the eighth group. Mice that were overnight fasted (12–14 hours) were placed into 10 groups of six at random. Each treatment was administered orally once daily for a total of 14 days. Mice were

sacrificed when the animal experiment was finished. Liver, whole blood, and serum were collected to detect a hematological antioxidant level [48]. In PS-6, male C57BL/6 J mice of six weeks old were kept in a room with a 12-hour light/12-hour dark cycle, a constant environment of 25 °C, and 50% relative humidity with ad libitum. After the development of T2DM, the HR administration lasted for 8 weeks. The diabetic model group and the diabetic mice receiving HR treatment were kept alive with HFD feeding, whereas the healthy control group received a regular diet [47]. In PS-7, after 1 week of acclimatization, the animals were grouped into 2: the normal control (fed with standard chow diet ad libitum) and the HFD group (fed with HFD ad libitum). On completion of week 10, the HFD group was treated with STZ (35 mg kg−1 b.w., i.p.) prepared in citrate buffer (pH 4) of 0.1 M for four consecutive days, whereas the control HFD group received an equal amount of vehicle. The fasting blood glucose level of the HFD group was determined on week 11, using blood samples collected from the tail ends by applying blood onto a glucose analyzer. The mice that had blood glucose levels more than 280 mg/dl were deemed diabetic (HFD-db) and were chosen to receive therapy for three weeks with either RC (10 and 20 mg kg1day1 b.w.). On week 14, the animals were slaughtered, and blood samples were collected. The wet weight was calculated after removing the visceral fat [72].

Table 2. Preclinical evaluation of IAs.

Study title	Ethical committee	Outcome	Ref.
VCA as a GPR40 agonist maintain glucose homeostasis in T2DM mice (PS-1)	Institutional Animal Care and Use Committee, Shanghai Institute of Materia Medica, Chinese Academy of Sciences	VCA increases insulin production and provides cell protection & GSIS in INS-832/13 cells. In addition, giving VCA to rats with T2D HFD/STZ or *db/db* improved glucose homeostasis.	[54]
16,17-Dihydro-17b-hydroxy isomitraphylline alkaloid as an inhibitor of DPP-IV and its effect on incretin hormone and b-cell proliferation in the diabetic rat (PS-2)	The Institutional Animal Ethical Committee of DIPSAR approved the experimental protocol numbered DIPSAR/IAEC/2007/23	In response to glucose loading, DHIM significantly decreased plasma glucose concentration and enhanced glucose tolerance. As a result, treated diabetic rats had considerably higher levels of GLP-1 and IL-10. Despite this, there was no apparent change in body mass.	[55]
Evodia alkaloids resist gluconeogenesis and lipogenesis by stimulating the constitutive androstane receptor (PS-3)	The preclinical study followed the Guide for the Care and Use of Laboratory Animals at Zhejiang University.	Frequent reduction in blood glucose level intervals and a smaller area under the curve demonstrated increased glucose tolerance in mice compared to control animals.	[70]
Simultaneous determination of five alkaloids from *R. vomitoria* in rat plasma by LC-MS/MS: Application to a comparative pharmacokinetic study in normal and type 2 diabetic rats (PS-4)	University Ethics Committee approved the experiment protocol and confirmed to the "Principles of Laboratory Animal Care" (NIH publication no. 85-23, revised 1985)	The findings showed that DM considerably changed the pharmacokinetic properties of YOH, AJM, and AJE upon oral treatment of rats. The difference in pharmacokinetic characteristics between normal and T2DM model rats after oral treatment of *R. vomitoria* extract was also reported in this research.	[71]
Antioxidant and haematinic effects of methanolic and aqueous methanolic roots extracts of *R. serpentina* Benth in type 2 diabetic mice (PS-5)	Experimental design and animal handling procedures were approved by the Institutional Ethical Review Board (IERB) of Dow University of Health Sciences (DUHS), Karachi, Pakistan (Reference Letter Number: IRB186/DUHS-10).	According to the findings, fructose-induced T2D mice treated with MREt and AqMREt of *R. serpentina* were able to inhibit the production of ROS and retain their haematinic potential.	[48]
HR ameliorates hepatic and cardiac insulin resistance in high-fat diet-induced diabetic mice and *in vitro* Models (PS-6)	Experimental protocols were approved by the Animal Care Committee of Fudan University and conformed to the Animal Management Rules of the Ministry of Health of the People's Republic of China.	The findings revealed that HR administration increased blood glucose tolerability and insulin sensitivity, as measured by OGTT and ITT tests.	[47]

Study title	Ethical committee	Outcome	Ref.
Rutacarpine (RC) exhibits anti-diabetic potential in the high-fat diet–multiple low-dose streptozotocin-induced T2D mice and *in vitro* by modulating hepatic glucose homeostasis (PS-7).	The protocol was approved by the Institutional Animal Ethics Committee, RIMS, Manipur, India, vide letter no. 1596/GO/a/12/CPCSEA.	It was shown that HFD-db animals treated with RC had considerably lower blood glucose levels and an epididymal fat pad than HFD-db control mice.	[72]

4.2. Clinical study.

The data for clinical evaluation is depicted in Table 3. CS-1 was a dose-escalation, double-blind, placebo-controlled research. An OGTT and fasting blood samples were taken from patients during a screening visit. Blood was taken at 0, 30, and 120 minutes. The profiles of glucose, glucagon, insulin, noradrenaline, FFAs, and metabolites were examined at each time point. In CS-2, 90 postmenopausal women between the ages of 45 and 60 were chosen, and all were separated into 3 groups: I, II, and III, 30 of each. For a period of three months, individuals in groups II and III received daily dietary supplements of 7 g of drumstick leaf powder (DLP) and 9 g of amaranth leaf powder (ALP), respectively. Group I individuals did not get any supplements. The effects of supplementation on blood levels of retinol, ascorbic acid, glutathione peroxidase, superoxide dismutase, and malondialdehyde were examined. The individuals' fasting blood sugar and hemoglobin levels were also discussed.

Table 3. Clinical evaluation of IAs.

Study title	Ethical committee	Outcome	Ref.
VCA as a GPR40 agonist maintain glucose homeostasis in T2DM mice (PS-1)	Institutional Animal Care and Use Committee, Shanghai Institute of Materia Medica, Chinese Academy of Sciences	VCA increases insulin production and provides cell protection and GSIS in INS-832/13 cells. In addition, giving VCA to rats with T2D HFD/STZ or *db/db* improved glucose homeostasis.	[54]
16,17-Dihydro-17b-hydroxy isomitraphylline alkaloid as an inhibitor of DPP-IV and its effect on incretin hormone and b-cell proliferation in the diabetic rat (PS-2)	The Institutional Animal Ethical Committee of DIPSAR approved the experimental protocol numbered DIPSAR/IAEC/2007/23	In response to glucose loading, DHIM significantly decreased plasma glucose concentration and enhanced glucose tolerance. As a result, treated diabetic rats had considerably higher levels of GLP-1 and IL-10. Despite this, there was no apparent change in body mass.	[55]
Evodia alkaloids resist gluconeogenesis and lipogenesis by stimulating the constitutive androstane receptor (PS-3)	The preclinical study followed the Guide for the Care and Use of Laboratory Animals at Zhejiang University.	Frequent reduction in blood glucose level intervals and a smaller area under the curve demonstrated increased glucose tolerance in mice compared to control animals.	[70]
Simultaneous determination of five alkaloids from *R. vomitoria* in rat plasma by LC-MS/MS: Application to a comparative pharmacokinetic study in normal and type 2 diabetic rats (PS-4)	University Ethics Committee approved the experiment protocol and confirmed to the "Principles of Laboratory Animal Care" (NIH publication no. 85-23, revised 1985)	The findings showed that DM considerably changed the pharmacokinetic properties of YOH, AJM, and AJE upon oral treatment of rats. The difference in pharmacokinetic characteristics between normal and T2DM model rats after oral treatment of *R. vomitoria* extract was also the first time reported in this research.	[71]
Antioxidant and haematinic effects of methanolic and aqueous methanolic roots extracts of *R. serpentina* Benth in type 2 diabetic mice (PS-5)	Experimental design and animal handling procedures were approved by the Institutional Ethical Review Board (IERB) of Dow University of Health Sciences (DUHS), Karachi, Pakistan (Reference Letter Number: IRB186/DUHS-10).	According to the findings, fructose-induced T2D mice treated with MREt and AqMREt of *R. serpentina* were able to inhibit the production of ROS and retain their haematinic potential.	[48]
HR ameliorates hepatic and cardiac insulin resistance in high-fat diet-induced diabetic mice and *in vitro*	Experimental protocols were approved by the Animal Care Committee of Fudan University and conformed to the Animal	The findings revealed that HR administration increased blood glucose tolerability and insulin sensitivity, as measured by OGTT and ITT tests.	[47]

Study title	Ethical committee	Outcome	Ref.
Models (PS-6)	Management Rules of the Ministry of Health of the People's Republic of China.		
Rutacarpine (RC) exhibits anti-diabetic potential in the high-fat diet–multiple low-dose streptozotocin-induced T2D mice and *in vitro* by modulating hepatic glucose homeostasis (PS-7).	The protocol was approved by the Institutional Animal Ethics Committee, RIMS, Manipur, India, vide letter no. 1596/GO/a/12/CPCSEA.	It was shown that HFD-db animals treated with RC had considerably lower blood glucose levels and an epididymal fat pad than HFD-db control mice.	[72]

5. Safety and Toxicity of IAs

Because of the structural versatility of IAs and their inherent antidiabetic activities, they have attracted more attention in recent years. However, some of them exhibit toxic effects [46]. Previous research revealed that IAs given beyond the effective dose can lead to toxicity. A leaf outlet was selected to prepare methanolic extract to estimate hepatic and renal functions in Dawley rats. Amount of 0.1, 0.5, and 1.0 g/kg was selected. A dose of 1.0 g/kg causes diarrhea, whereas a dose of 0.1 g/kg is safe without affecting hepatocyte or nephron functions, as stated by Kumar *et al*. [75]. Negligible toxicity is observed in acute toxicity studies of the extracts [76]. A single dose of *C. roseus* 250 mg kg^{-1} was administered in rats, which showed good tolerability properties. On administering a high dose, the extract did not show any aftereffects, and mortality was not observed among rats for 15 days [77]. The adverse events of yohimbine include indigestion, high blood pressure, increased heart rate, bronchial spasm, pulsation, insomnia/ anxiety, cold, sweating, flushing, and headaches, which contribute to its central sympatholytic activity[46]. Vindogentianine (VDG) was incubated for 24 h to estimate its cytotoxic effect in C_2C_{12} mouse myoblast and β-TC6 mouse pancreatic cells (IC_{50} N 50 μg/mL). It was also monitored for real-time cell proliferation, which shows negligible effect on high doses (200 μg/mL). On evaluation, it was observed that VDG exhibited potential hypoglycaemic activity by upregulating glucose uptake in cells and consequently inactivates PTP-1B in vitro studies by Tiong *et al*. [78]. The DHIM, as a deactivator of DPP-IV, consumes a longer duration to decrease postprandial blood glucose, and the clinical investigational data suggest clinical efficacy with the long-acting DPP-IV inhibitor. Drugs of natural origin are referred to as safer than synthetic drugs in terms of toxicity and side effects [55]. Kushwaha *et al*. studied the antioxidant properties of amaranth leaf powder on ninety postmenopausal women. They found reduced blood glucose level antioxidant properties without any adverse event in participating subjects [74]. The IAs, which are plant-derived and synthetic, would be a potential resource for treating diabetes. Aftereffects of IAs can be reduced by adopting parameters like improving potency optimization of pharmacokinetics and reducing toxicity, which will produce safe and reliable agents. The synthetic derivatives can be generated from natural origin with additional optimization for potential anti-diabetic effects [79].

6. Future Perspectives

To minimize side effects, maximize therapeutic effects, and determine clinical effectiveness, IAs should be studied in depth. To find promising lead compounds for further research, it is also important to thoroughly explore the mechanistic activities at the respective binding sites and conduct toxicity studies. Previous studies do not provide sufficient data on the potential applications of IAs; therefore, it became necessary to perform newer trials using novel formulations and techniques to discover new applications. Additionally, because of the

complexity of DM, current experiments will likely concentrate on creating and determining many target medications to improve the quality of life for diabetic patients and successfully halt the progression of resistant illnesses. Thus, clinical investigation on physiological, genetic, and pharmacogenetic interventions may help define mechanisms for diabetes and its prevention that could differ between or among ethnic groups.

7. Concluding Remarks

Diabetes is a major disorder that impacts many lives. In that sense, T2DM is a popular disease that affects humans worldwide. The T2DM progresses in order of complication, i.e., from pre-diabetic to overt diabetes. Conventional therapies lead to side effects and complications; therefore, herbal plants are always a safe and sophisticated therapy for treating diabetes. It remains a good source when extracted from natural or biological origins. Varied beneficial pharmacological indications make IAs popular. They have been recognized in many plant families, including Dogbane, Bedstraw, Davidiaceae, Spigeliaceae, and others. Although plant, semisynthetic, and aquatic sources of IAs are considered. The present review is entitled Current Statistics and Death Rate of Diabetes and Types of Diabetes." The review also highlighted IAs originating from plant sources and their significant application in T2D. Previous animal studies and human clinical trials indicate that indole compounds are promising candidates for treating T2D. The paper also addressed the safety and toxicity of IAs, which will interest researchers in the future.

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Conflicts of Interest

The authors declare no conflict of interest.

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