

## Review Article

# Roles of Alkaloids from Medicinal Plants in the Management of Diabetes Mellitus

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Received 5 August 2021; Accepted 17 October 2021; Published 31 October 2021

Academic Editor: Andrea Mastinu

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Medicinal plants play a fundamental part in health sectors via the management of different infectious diseases because of their wide plenitude wellspring of bioactive phytochemicals. Research activities on them have got attention throughout the world in the present days in search of low-cost and safe compounds for the management of diabetes. This is the literature-based analysis of alkaloids from medicinal plants in preventive or treatment approaches to diabetes. The most abundant and diversified group of secondary metabolites, i.e., alkaloids, show antidiabetic activity through the inhibition of enzymes ( $\alpha$ -amylase,  $\alpha$ -glucosidase, aldose reductase, dipeptidyl peptidase-IV, and protein tyrosine phosphatase-1B); inhibition of advanced glycation end products; increment of insulin secretion and its sensitivity; enhancement of glucose uptake; and their antioxidant ability. The study is useful for the examination of dynamic alkaloids for the advancement of a new medication for mankind.

## 1. Introduction

Diabetes mellitus (DM) is an endocrine disorder characterized by hyperglycemia characterized with fasting blood glucose level  $\geq 7.0$  mM (126 mg/dL) [1–3] caused mainly due to insulin deficiency or insensitivity or inefficiency of disturbing the metabolism of ingested foods, i.e., carbohydrates, fats, and proteins. It is a major public health concern among people, and its prevalence rate is anticipated to be 4.4% in 2030 [4]. Blood glucose level is increased by the action of digestive enzymes on ingested food [5]. If hyperglycemia is not treated, it leads to major complications such as cardiovascular diseases, nerve damage, retinopathy, and nephropathy [6]. According to the ninth edition of the International Diabetes Federation (IDF) report, 463 million adults (20–79 years) of the world lived with diabetes in 2019 and this frequency is estimated to reach 578 million by 2023 and 700 million by 2045 [7].

Among the several types of DM, type 2 accounts for the majority (about 90%) of diabetes cases. Type 2 DM is characterized by impaired insulin secretion and insulin

resistance [8] due to impaired function of  $\beta$ -cells of the islet of Langerhans involving the loss of pulsatility, biphasic nature of insulin secretion, decrease in sensitivity to glucose, and decrease in cell masses. In 2017, 657.2 thousand adults were with diabetes and 11,693 died with diabetes-related complications in Nepal [9] which reached 696.9 thousand with a national prevalence of 4% in 2019 [7]. IDF showed about 12% of global health expenditure was spent on diabetes management, which is a huge loss on the economy [10], and the burden is expected to skyrocket in near future.

Various strategies such as diets, medications, and exercises have been carried out to control blood glucose levels and minimize the life-threatening complications of diabetes [11] depending on numerous factors such as the rate of nutrient uptake, action of digestive enzymes on nutrients food items, activity of insulin, and responses of tissues to insulin [12].  $\alpha$ -Glucosidase inhibitors (acarbose, miglitol, and voglibose), biguanides (metformin), insulin secretagogue sulfonylureas (gliclazide, glimepiride, and glyburide), insulin secretagogue nonsulfonylureas (repaglinide and nateglinide), dipeptidyl peptidase-IV (DPP-IV) inhibitor

(sitagliptin and saxagliptin) insulin sensitizers or thiazolidinediones (rosiglitazone and pioglitazone), and intestinal lipase inhibitor (orlistat) have been used as orally administered antihyperglycemic agents (Figure 1) for the treatment of DM [13, 14].

Commercial  $\alpha$ -glucosidase inhibitors were reported to have several problems such as abdominal distention, meteorism, bloating, and diarrhea [13]. In addition to these, sulfonyleureas: hypoglycemia, mild headaches, increased food intake, weight gain, and increased risk of cardiovascular diseases [12]; biguanides: gastrointestinal issues, metallic taste, impairment of vitamin B12 and B9 absorption, lactic acidosis, and hypoglycemia in combination therapy [15–17]; thiazolidinediones: anemia, insomnia, headache, dizziness, weight gain, visual disturbances, impotence, fatigue, hepatotoxicity, weight gain, fluid retention, congestive heart failure, and bone fractures [15, 18]; incretin mimetics: nausea, vomiting, and diarrhea; incretin-enhancing DPP-IV inhibitors: increased risk of infection and headache; and sodium-glucose cotransporter protein (SGLT-2) inhibitors: increased risk of urinary tract infections and ketoacidosis have the side effects [15].

DM can be managed by different mechanisms of actions such as stimulating  $\beta$ -cells to release insulin, increasing the appetency and sensitivity of insulin receptor site, resisting the digestive enzymes involved in the digestion of carbohydrates, enhancing the glucose uptake in the tissues and organs, clearing away free radicals, resisting lipid peroxidation, and limiting the metabolic disorder of lipids and proteins [19]. About four billion people from the world depend on herbal products directly and indirectly [20] for healthcare with a 15% annual increase [21] in the global economy. A possible synergistic work of different phytochemicals present in plant extract attracts public interest in herbal medicines [20]. More than 1200 plant species are reported as antidiabetic potent [15] and are the promising reservoirs of structurally diverse bioactive compounds. Here, medicinal plant-based alkaloids with potential antidiabetic activities were discussed.

## 2. Methods

This is a literature-based analysis of alkaloids with antidiabetic activities. A systematic literature survey of articles was carried out by searching them in Google Scholar, PubMed, ScienceDirect, Scopus, and Springer link using keywords such as diabetes, antidiabetic, medicinal plants, natural products, hypoglycemic, mechanism of action, and alkaloids.

## 3. Alkaloids with Antidiabetic Activities along with the Mechanism of Action

Alkaloids are nitrogen (in the form of a primary, a secondary, or a tertiary amine)-containing, low-molecular-weight, diverse, basic chemical compounds found in bacteria, fungi, plants, and animals; however, their conveyance inside each kingdom is very restricted [22]. Alkaloids can occur as monomers, dimers, trimers, or tetramers which

may be either homo-oligomers or hetero-oligomers. They are classified based on the chemical structure (heterocyclic/nonheterocyclic) and biological or natural origin (specific sources). Roughly 20% of plant species [23] are the source of these secondary metabolites with significant bioactivities that fill in as a rich supply for drug disclosure. Around 12,000 alkaloids have been assessed from plants with various pharmaceutical importance [23]. Figure 2 shows the overall mechanism of the antidiabetic activity of alkaloids from medicinal plants.

**3.1. Inhibition of Digestive Enzymes.** Hydrolysis of dietary polysaccharides by digestive enzymes is responsible for increasing blood glucose levels.  $\alpha$ -Amylase is a hydrolase enzyme prominent in the pancreatic juice and saliva which catalyzes the hydrolysis of  $\alpha$ -1,4-glycosidic linkages of starch, glycogen, and various oligosaccharides [24].  $\alpha$ -Glucosidase, an enzyme belonging to class hydrolases, secreted by cells lining in the brush borders of epithelial cells of the small intestine catalyzes the hydrolytic breakdown of oligosaccharides into absorbable monosaccharides and causes postprandial hyperglycemia. Inhibition of these digestive enzymes by secondary metabolites from plants is one of the popular strategies for lowering the postprandial blood glucose level [25]. Alkaloids could bind to the competitive or noncompetitive sites of enzymes involved in digestion, and hence, enzyme-substrate complex is not formed, which ultimately reduces the enzyme activity.

Carbazole alkaloids from *Murraya koenigii* L. Spreng, namely, bisgerayafoline D, bismahanimbiniol, bispyrayafoline, O-methyl mahanine, O-methyl mukonal, and mahanine (Figure 3), show  $\alpha$ -glucosidase inhibition ( $IC_{50} = 38.7 \pm 0.4$ ,  $51.3 \pm 0.3$ ,  $29.1 \pm 0.2$ ,  $46.1 \pm 0.3$ ,  $77.5 \pm 0.5$ , and  $21.4 \pm 0.4 \mu\text{M}$ ) using p-nitrophenyl glucopyranoside as a substrate [26]. Additionally, mahanimbine showed noticeable  $\alpha$ -amylase and  $\alpha$ -glucosidase inhibitory properties with an  $IC_{50}$  value of  $83.72 \pm 1.4 \mu\text{g/mL}$  and  $99.89 \pm 1.2 \mu\text{g/mL}$ , respectively [27]. Similarly, quinazoline alkaloids, vasicine, and vasicinol (Figure 3) from *Adhatoda vasica* Nees leaf extract inhibit the sucrose-hydrolyzing activity of rat intestinal  $\alpha$ -glucosidase competitively,  $K_i$  ( $82 \mu\text{M}$  and  $183 \mu\text{M}$ ) with  $IC_{50}$  ( $125 \mu\text{M}$  and  $250 \mu\text{M}$ ), respectively [28].

A protoberberine alkaloid, palmatine, inhibits  $\alpha$ -amylase and  $\alpha$ -glucosidase activities with an  $IC_{50}$  of  $1.31 \pm 0.27$  and  $9.39 \pm 0.27 \mu\text{M}$ , respectively [29]. Oriciacridone C, 1,3,5-trihydroxy-4-( $\gamma,\gamma$ -dimethylallyl)-acridone, and oriciacridone F (Figure 3) from the stem bark of *Oriciopsis glaberrima* showed an  $\alpha$ -glucosidase inhibitory activity ( $56 \pm 5.4$ ,  $17 \pm 1.0$ , and  $34.05 \pm 17 \text{ mM}$ ) [30]. Additionally, piperumbellactam A, B, and C (Figure 3) of *Piper umbellatum* show the  $\alpha$ -glucosidase inhibitory activity of  $98.07 \pm 0.44$ ,  $43.80 \pm 0.56$ , and  $29.64 \pm 0.46 \mu\text{M}$ , respectively [31]. Vindogentianine from *Catharanthus roseus* (L.) G. Don shows the inhibition of  $\alpha$ -amylase ( $IC_{50} = 74.43 \pm 9.38 \mu\text{g/mL}$ ) and  $\alpha$ -glucosidase ( $IC_{50} = 269.72 \pm 15.44 \mu\text{g/mL}$ ) by using dinitrosalicylic acid and p-nitrophenyl- $\alpha$ -D glucopyranoside, respectively [32].

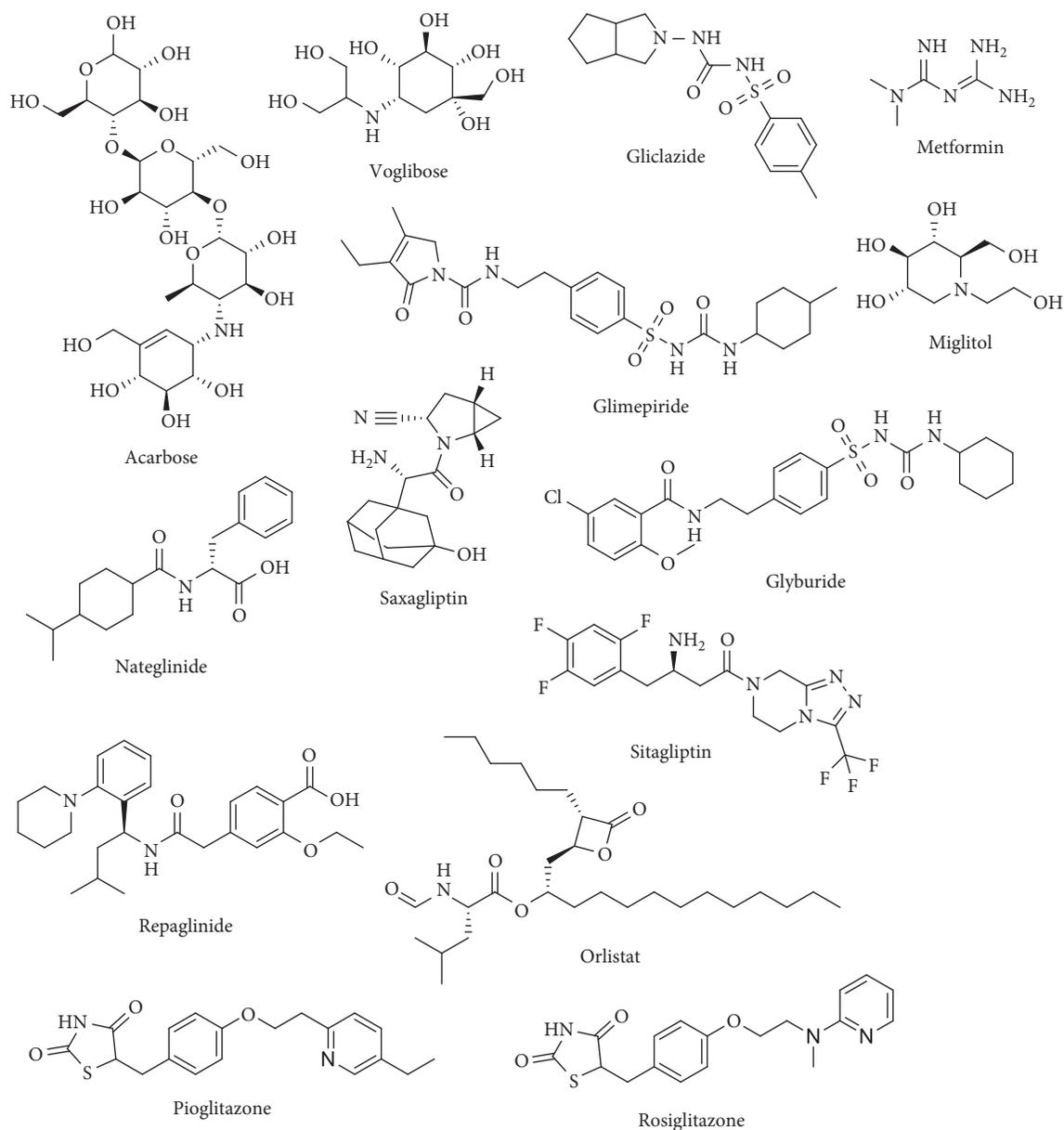


FIGURE 1: Orally administered antihyperglycemic agents for the treatment of diabetes mellitus.

The steroidal alkaloids, namely, holaphylline and sarcovagine D (Figure 3), from *Sarcococa saligna* also showed hypoglycemic effects and controlled diabetes-related complications in diabetic rats induced by streptozotocin (STZ) [33]. O-methylmurrayamine A and koenidine (Figure 3) reduce the blood glucose level by approximately 24.6% ( $p < 0.05$ ) and 22.5% ( $p < 0.01$ ), respectively, during 0–300 minutes in the STZ-induced diabetic rat model comparable to metformin (25.9%,  $p < 0.01$ ) [34]. Echinulin and aristriectin B (Figure 3) from the root of *Combretum dolichopetalum* exhibited substantial antidiabetic activity comparable to glibenclamide on *in vivo* assays [35].

**3.2. Inhibition of Aldose Reductase and Protein Tyrosine Phosphatase-1B.** Aldose reductase (AR), a key enzyme in the polyol pathway, catalyzes glucose reduction to sorbitol,

leading to the overproduction of reactive oxygen species (ROS) [36]. AR transforms cytosolic glucose into sorbitol, a molecule that poorly penetrates cell membranes and is sometimes slowly metabolized. Hyperglycemia can cause intracellular accumulation of sorbitol and its metabolite, fructose, which can create osmotic swelling and cell dysfunction [37]. Under the normal glycemic condition, it plays a role in detoxifying harmful aldehyde in extrahepatic tissue, production of fructose for sperm, osmoregulatory balance in the kidney, and reduction of steroids and catecholamines [38]. In hyperglycemic conditions, various complications appear because of excessive polyol metabolism, which leads to elevating the sorbitol level and osmotic stress prominent to cataractogenesis [39–41]. Additionally, it causes glycation stress, and binding with the receptors increases ROS [4, 5]. Prevention or delay of such complications has been suggested using AR inhibitors [42]. In recent years, compounds

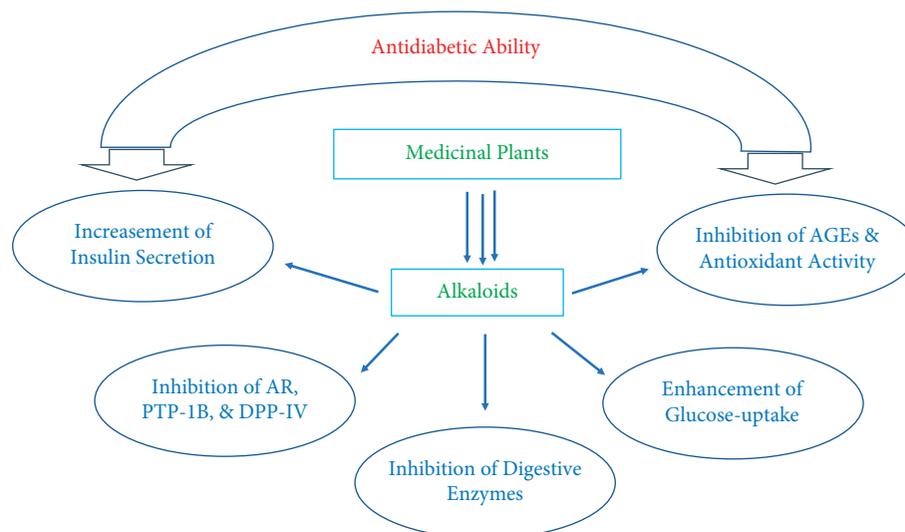


FIGURE 2: Mechanism of the antidiabetic activity of alkaloids from medicinal plants.

with both antioxidant and AR inhibitory activities in diabetes have drawn the attention of scientific communities in managing diabetes [43].

Epiberberine, coptisine, and groenlandicine (Figure 4) isolated from the rhizome of *Coptis chinensis* Franch showed the antidiabetic activity with the  $IC_{50}$  of  $100.07 \pm 0.63$ ,  $118.36 \pm 0.78$ , and  $140.13 \pm 6.50 \mu\text{M}$  for rat lens AR and  $168.10 \pm 05.51$ ,  $187.27 \pm 10.03$ , and  $154.19 \pm 07.17 \mu\text{M}$  for human recombinant AR [44]. The dioxymethylene group and its oxidized form in the D and A ring of protoberberine-type alkaloids are responsible for the AR inhibitory activities [44].

Nonetheless, *Coptis japonica* root-derived alkaloids, i.e., berberine chloride, berberine sulfate, berberine iodide, palmatine sulfate, and palmatine iodide, showed an inhibitory activity towards AR with an  $IC_{50}$  of 13.98, 13.45, 32.84, 51.78, and 51.78 nM, respectively [45]. Jatrorrhizine, palmatine, and magnoflorine (Figure 4) are isoquinoline alkaloids from *Tinospora cordifolia* stem which inhibited the male Wistar rats lens AR with an  $IC_{50}$  of 3.23, 3.45, and  $1.25 \mu\text{g/mL}$ , respectively [46].

The protein tyrosine phosphatase-1B (PTP-1B) is involved in multiple signal transduction pathways as it is present in multiple tissues including the skeletal muscle, liver, adipose tissue, and brain [47]. It acts as a negative regulator of insulin as well as leptin signaling, and hence, inhibition of its activity helps in the treatment of diabetes and related complications. Inhibition of PTP-1B results in the enhancement of insulin receptor and insulin receptor substrates 1 and 2 phosphorylation which causes an increase in glucose uptake [15].

Canthinone alkaloids such as picrasidine L, 3,4-dimethyl-canthin-5,6-dione, 4-ethyl-3-methyl-canthin-5,6-dione, eurycomine E, 5-methoxy-canthin-6-one, and 5-acethoxy-canthin-6-one (Figure 4) inhibit the activity of PTP-1B with an  $IC_{50}$  of  $19.80 \pm 0.62$ ,  $24.72 \pm 0.26$ ,  $27.83 \pm 0.68$ ,  $19.18 \pm 0.76$ ,  $20.30 \pm 0.24$ , and  $28.89 \pm 0.52 \mu\text{M}$ , respectively, by using p-nitrophenyl phosphate as the substrate [48]. Picrasidine L showed a competitive mode of

inhibition of PTP-1B, while the rest showed a noncompetitive mode [48]. Vindogentianine from *Catharanthus roseus* (L.) G. Don shows PTP-1B inhibition with an  $IC_{50}$  of  $15.28 \pm 2.59 \mu\text{g/mL}$  through the substrate-based method [32].

A protoberberine alkaloids berberine, coptisine, and epiberberine (Figure 4) and an aporphine alkaloid magnoflorine (Figure 4) isolated from *Coptis chinensis* Franch exhibited a notable inhibitory activity towards PTP-1B with the  $IC_{50}$  values of 16.43, 51.04, 24.19, and  $28.14 \mu\text{M}$ , respectively [49]. Berberine and epiberberine showed a mixed-type of inhibition while magnoflorine and coptisine showed a noncompetitively type against PTP-1B through the Lineweaver-Burk and Dixon plots [49]. Norditerpenoid alkaloids, namely, nigelladine A, B, and C (Figure 4), from the *Nigella glandulifera* Freyn seeds inhibit the PTP1B activity [50].

**3.3. Increase of Insulin Secretion.** The  $\alpha$ -cells and  $\beta$ -cells of pancreatic islets of Langerhans secrete glucagon and insulin, respectively, that exert antagonistic effects on peripheral organs to control blood glucose levels. Insulin lowers the glucose levels by stimulating glucose uptake in skeletal muscle via inhibiting hepatic glucose production and by dulling lipolysis. In contrast, glucagon increases blood glucose levels by increasing gluconeogenesis and lipolysis [51].

The two incretin hormones, namely, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulin tropic polypeptide (GIP), stimulate insulin release in healthy individuals in response to ingested meals [52]. GLP-1 produced by the *proglucagon* gene in L-cells of the small intestine stimulates insulin biosynthesis and secretion reduces glucagon levels reduces appetite, decreases glucagon release, decelerates gastric emptying, and regeneration and differentiation of the pancreatic islet  $\beta$ -cells in response to meals [53, 54]. The GIP secreted from K cells (*gip* gene) of the upper small intestine is broadly engaged with glucose digestion by enhancing the insulin discharge [52, 55].

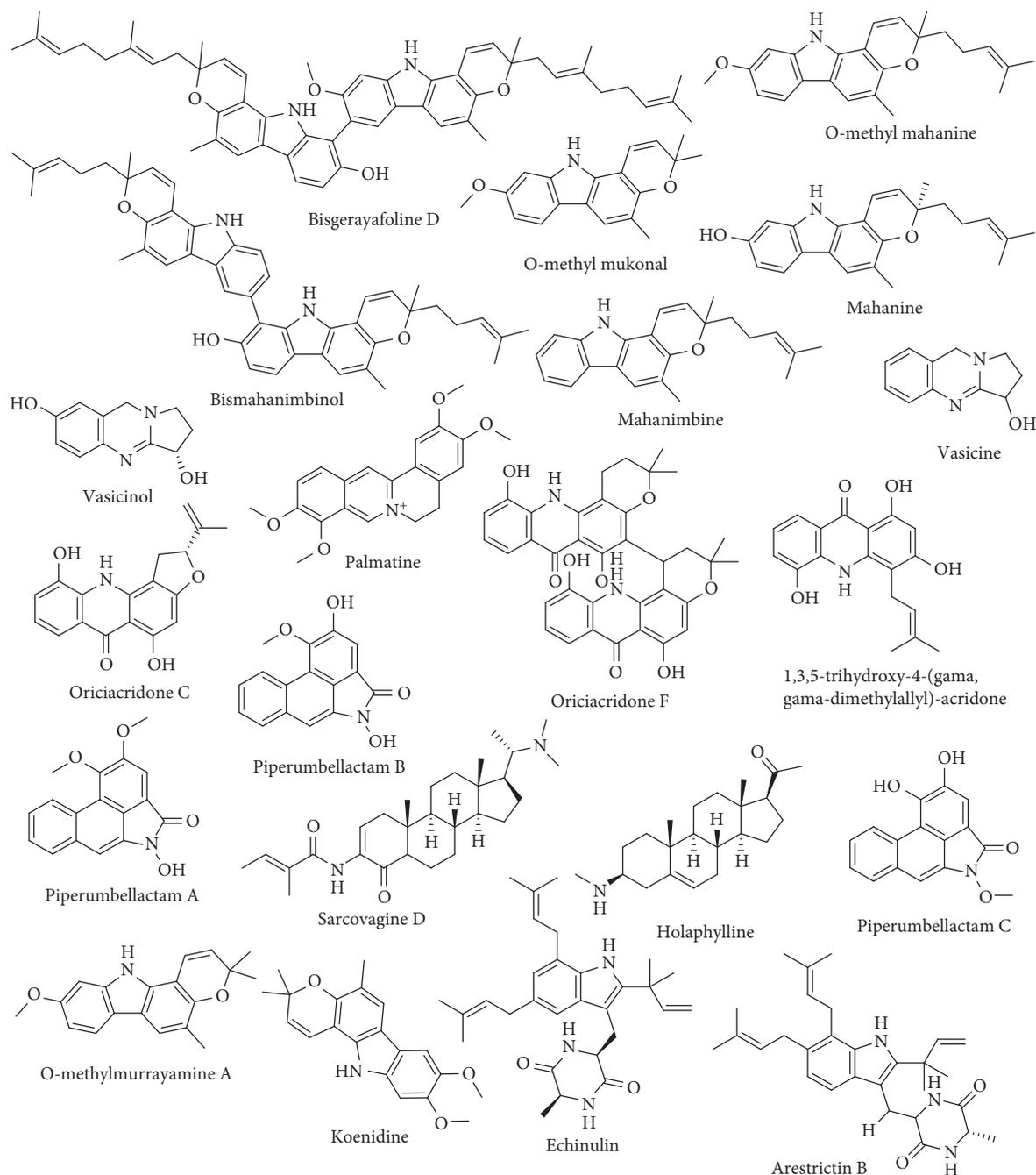


FIGURE 3: Alkaloids with  $\alpha$ -amylase and  $\alpha$ -glucosidase inhibitory activities.

Additionally, it is involved in the metabolism of fats in adipocytes, stimulates lipoprotein lipase activity, controls fatty acid synthesis, and promotes  $\beta$ -cell proliferation and cell survival [56, 57]. Due to the action of DPP-IV, GLP-1 and GIP have extremely short half-lives, i.e., 1-2 min for GLP-1 and 4 min for GIP. Inhibiting DPP-IV improves glucose homeostasis due to delays in the activity of GLP-1 and GIP [54]. Various investigations have uncovered that DPP-IV inhibition helps in the increment of  $\beta$ -cell capacity, physiology, and mass through incretin release which influences a constant arrival of insulin after ingestion of food to bring down glucose levels [56, 58].

Lupanine, 13-hydroxy-lupanine, and 17-oxo-lupanine (Figure 4) are the quinolizidine alkaloids from *Lupinus* species that are capable of animating insulin secretion in a glucose-dependent manner [59]. Through the inhibition of ATP-sensitive potassium channel current and enhancement of the expression of insulin-secreting genes, lupanine improves insulin secretion [59, 60]. Trigonelline from *Trigonella foenum graecum* and *Mirabilis jalapa* L. exhibits antidiabetic activity via incensement of insulin sensitivity [61, 62]. Additionally, palmatine and berberine (Figure 4) showed the antidiabetic activity with the inhibition of DPP-IV with an  $IC_{50}$  of  $8.7 \pm 1.82 \mu\text{M}$  [29] and  $13.3 \mu\text{M}$  [63] respectively.

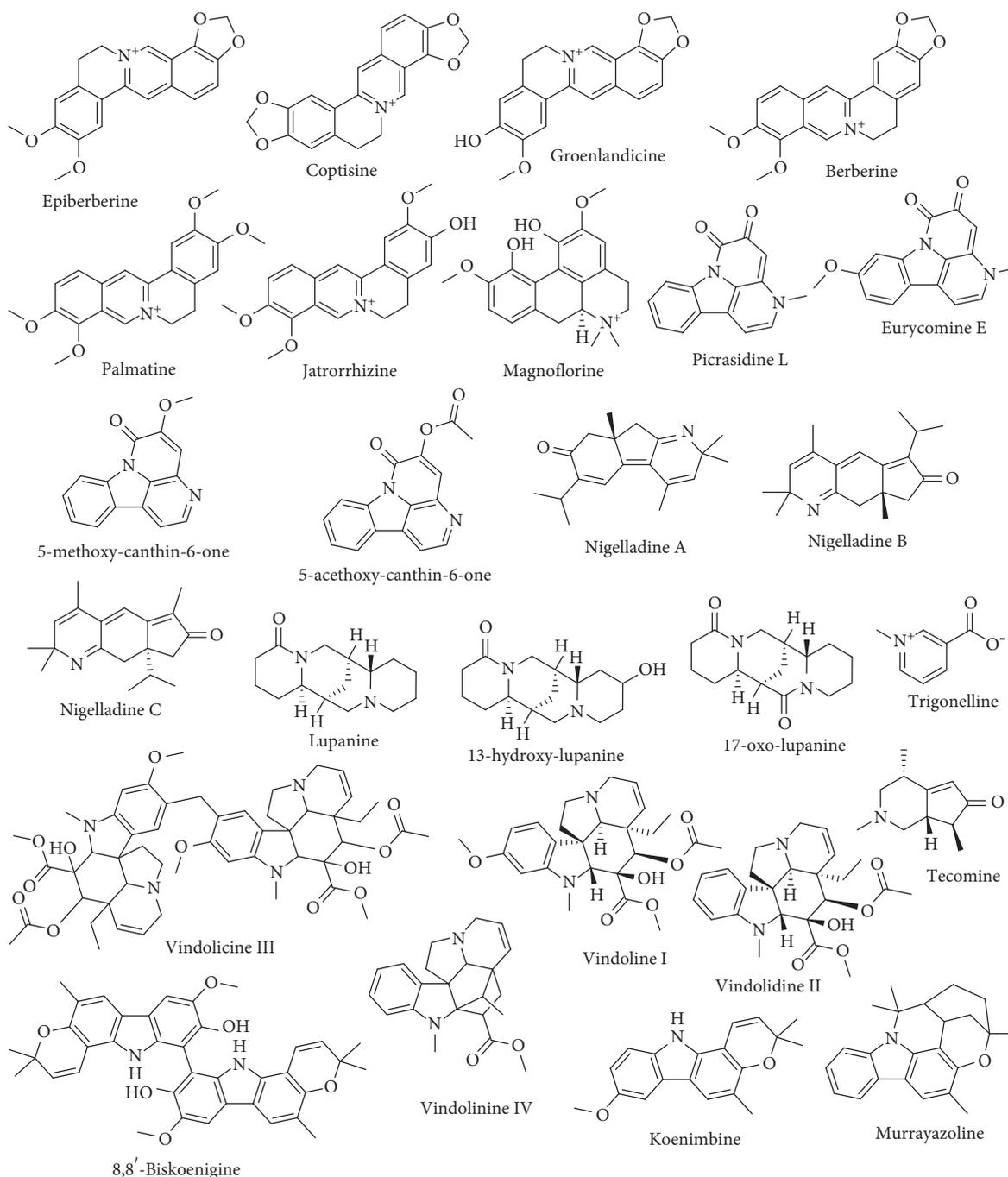


FIGURE 4: Alkaloids with antidiabetic activity.

**3.4. Inhibition of Advanced Glycation End Products.** The reaction between carbonyl groups of reducing sugars and amino groups of proteins, nucleic acids, and lipids results in the accumulation of advanced glycation end products (AGEs) [64]. AGEs are responsible for cellular malfunction resulting in complications in diabetes (retinopathy, nephropathy, neuropathy, and cardiomyopathy) and also to atherosclerosis and aging via altering expression of genes, intracellular signals, release of proinflammatory molecules, and ROS [64–67]. Four benzyloisoquinoline alkaloids, namely, 6,7-dihydroxy-1-(4'-hydroxybenzyl)-2,2-N, N-dimethyl-1,2,3,4-tetrahydroiso

quinoline, 7-hydroxy-1-(4'-hydroxybenzyl)-6-methoxy-2,2-N,N-dimethyl-1,2,3,4-tetrahydroisoquinoline, magnocurarine, and N-methylhigenamine were isolated from *Ocotea paranapiacabensis* and showed the inhibition of AGEs by 62.9%, 83.3%, 26.1%, and 98.2%, respectively, at 150  $\mu\text{M}$  through *in vitro* bovine serum albumin (BSA)/methylglyoxal reagent (MGO) assay [64]. The activity of these benzyloisoquinoline alkaloids is due to the catechol group and a pair of electrons at nitrogen. Berberine (main constituent in *Rhizoma coptidis*) was also shown to have the ability of inhibiting glycosylation and with antioxidant activities [68]. Similarly, a

natural alkaloid, leonurine, from *Herba leonuri* was shown to have significant AGEs inhibition [69]. Liu et al. showed the abilities of matrine-type alkaloids in the management of DM and its complications [70]. As concluding remarks, natural products inhibit the AGEs through different mechanisms such as degradation of products, protecting amino groups, removal or reduction of active carbonyl groups, and balancing ROS [68].

**3.5. Antioxidant Activity.** Hyperglycemia results in oxidative stress and, hence, causes micro- and macrovascular complications [71]. Antioxidant therapy in diabetes helps to lower the complications of diabetes [71, 72]. Antioxidants respond to reactive radicals by accepting or donating electron(s) or by declining the formation of free radicals through the hindrance of activities or expressions of free radical-generating enzymes or by upgrading the activities and expressions of enzymes responsible for the production of antioxidants [73].

In addition to  $\alpha$ -glucosidase inhibitory activity, alkaloids such as oriciacridone C, 1,3,5-trihydroxy-4-( $\gamma,\gamma$ -dimethylallyl)-acridone, and oriciacridone F (Figure 3) showed antioxidant activities with an  $IC_{50}$  of  $60.79 \pm 1.23$ ,  $118.70 \pm 4.24$ , and  $482 \pm 1.8$  mM [30]. Similarly, piperumbellactam A, B, and C were reported with an antioxidant activity of  $13.1 \pm 0.7$ ,  $67.8 \pm 0.5$ , and  $86.4 \pm 0.9$   $\mu$ M, respectively [31]. Bisgerayafoline D, bismahanimbino, bispyrayafoline, O-methyl mahanine, O-methyl mukonal, and mahanine (Figure 3) show the antioxidant ability with  $IC_{50}$  ranging from  $6.3 \pm 2.4$  to  $400 \pm 0.2$   $\mu$ M [26].

**3.6. Enhancement of Glucose Uptake.** Excessive exercise helps in the management of diabetes by translocation of glucose transporter 4 (GLUT-4) [74]. Different alkaloids from medicinal plants are reported with the ability to increase glucose uptake. Vindolicine III (Figure 4) from *Catharanthus roseus* (L.) G. Don was reported to be involved in glucose uptake in  $\beta$ -TC6 and C2C12 cells as well by the antioxidant activity compared to vindoline I, vindolidine II, and vindolinine IV (Figure 4) proving to be useful in the management of hyperglycemia [75]. Similarly, vindogentianine from the same plant induces the significant glucose uptake in  $\beta$ -TC6 pancreatic and C2C12 muscle cells [32].

Carbazole alkaloids, namely, 8,8''-biskoeningine, koenimbine, O-methylmurrayamine A, koenidine, mahanimbine, and murrayazoline (Figure 4), isolated from *Murraya koenigii* (L.) Spreng showed the ability of glucose uptake in L6-GLUT4myc myotubes by  $1.41 \pm 0.04$ ,  $1.34 \pm 0.13$ ,  $1.42 \pm 0.04$ , and  $1.26 \pm 0.02$  fold, respectively, at a concentration of 25  $\mu$ M [34]. Tecomine (Figure 4) from *Tecoma stans* promotes the glucose uptake rate in rat adipocytes ( $EC_{50}$  value of  $6.79 \times 10^{-9}$  M) [76].

In addition to antidiabetic activity, alkaloids were shown to play a great role in the management of neurodegenerative disorders [77], inflammatory bowel diseases [78], viral diseases [79, 80], microbial infections [22, 81], cancers [82], and many more. In recent years, many research studies have

been carried out in medicinal plants to explore bioactive compounds [83–91].

## 4. Conclusions

Nowadays, plant-based natural products are broadly utilized in the management of different infections for the improvement of the life span. Natural products contain different metabolites, especially alkaloids that act differently against infectious diseases and accomplished the medical services decreasing the side effects. Although numerous *in vitro* and *in vivo* assays have shown alkaloids are good candidates, very few or none of the bioactive compounds have reached the clinical trials. The bioactivity of pure compounds alone and in combination resulting in synergistic effects needs to be properly evaluated. Alkaloids with diverse roles in the management of diabetes need to be further assayed to develop them as ultimate drug candidates or food supplements.

## Abbreviations

AGEs:	Advanced glycation end products
AR:	Aldose reductase
DM:	Diabetes mellitus
DPP-IV:	Dipeptidyl peptidase-IV
$EC_{50}$ :	Half maximal effective concentration
GIP:	Glucose-dependent insulin tropic polypeptide
GLP-1:	Glucagon-like peptide-1
GLUT-4:	Glucose transporter-4
$IC_{50}$ :	Half maximal inhibitory concentration
IDF:	International Diabetes Federation
PTP-1B:	Protein tyrosine phosphatase-1B
ROS:	Reactive oxygen species
STZ:	Streptozotocin.

## Data Availability

The data are available upon request.

## Conflicts of Interest

The author declares no potential conflicts of interest.

## Authors' Contributions

B.A designed the concept, performed the literature surveys, prepared the draft, and revised the manuscript.

## Acknowledgments

This research was supported by grants from the University Grants Commission (UGC), Sanothimi, Bhaktapur, Nepal, to Bikash Adhikari with grant ID MRS-76/77-S&T-16.

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