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Article

Antidiabetic activities of alkaloids isolated from medicinal plants

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Diabetes mellitus is a metabolic disorder affecting a great part of population around the world. It is the fifth leading death causing disease in the world and its cases are increasing day by day. Traditional medicine is thought to have promising future in the treatment of diabetes mellitus. In contrast to synthetic drugs phytochemicals are considered to be free from side effects. As one of the main class of natural products, alkaloids and their derivatives have been widely used as sources of pharmacological agents against a variety of medical problems. Many studies confirmed the role of alkaloids in the management of diabetes and numerous alkaloids isolated from different medicinal plants were found active against diabetes. Like other natural products, alkaloids regulate glucose metabolism either by inhibiting or inducing multiple candidate proteins including AMP-activated protein kinase, glucose transporters, glycogen synthase kinase-3, sterol regulatory element-binding proteins 1, glucokinase, glucose-6-phosphatase, acetyl-CoA carboxylase among the others. A comprehensive review of alkaloids reported in the literature with anti-diabetic activities and their target enzymes is conducted, with the aim to help in exploring the use of alkaloids as anti-diabetic agents. Future work should focus on rigorous clinical studies of the alkaloids, their development and relevant drug targets.

Keywords: Phytotherapy. Alkaloids. Diabetes.Anti-diabetic agents.

DIABETES MELLITUS

Diabetes mellitus (DM) is a combination of two Greek words, diabetes means flow and mellitus means honey, a condition in which extreme flow of urine occurs (Perez *et al.*, 1998). It is a metabolic disorder in which glucose level increases in blood because of defects in action and secretion of insulin (Kumar *et al.*, 2011). Diabetes is characterized by hyperglycemia and metabolic changes in lipids, proteins, and carbohydrates (Kameswara Rao *et al.* 2003). It causes many complications like blindness in adults, failure of kidneys, local death of soft tissues, neuropathy, heart problems and mortality (Marles, Farnsworth, 1995). World Health Organization (WHO) projections indicate that the diabetic population prevalence will be 300 million or more in the coming decades (Smith, Adanlawo, 2012). Currently it is the fifth leading death-causing disease in the world (Ibrahim *et al.*, 2010).

Types of Diabetes mellitus

There are two main types of DM known as type I and II (Holt, 2004). Type I DM is due to the effect of cellular mediated autoimmune decimation of the pancreatic insulin-producing β-cells, as a result insulin is reduced in the body for metabolism. Diabetic patients become more susceptible to ketoacidosis. It occurs in early stage, usually before 40 years of age, however the onset of disease can occur at any age. Type I diabetic patient totally depend

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on hypoglycemic medication for survival (Prakash *et al*., 2015). Type I diabetes shows about 5–10% of all the diabetic cases and its incidence are increasing world-wide (Daneman, 2006). Type II DM is the most common type of diabetes (Kumar *et al*., 2011). This type is caused due to impaired insulin secretion by the β-cells of pancreas (Butler *et al*., 2003). Inheritance of Type II occurs through the human leukocyte antigen (HLA) complex.

In comparison to synthetic drugs, phytochemicals are considered to be free of side effects (Amin *et al*., 2013). Despite the availability of many oral hypoglycemic drugs and insulin; interest in the use of herbal medicine is increasing due to its cost and lower toxicity than synthetic drugs (Kameswara Rao *et al*., 2003). According to WHO reports about 80% of the world population use herbal medicines for curing different diseases. Among the estimated 400,000 plants, only 6% have been studied and 15% were analyzed for the phytochemical studies. A planned activity guide is needed for the evaluation of phytopharmacology of herbal medicines (Smith, Adanlawo, 2012). Kingdom Plantae encourages an infinite active source of elements helpful for the treatment in different stubborn disorders (Parekh, Jadeja, Chanda, 2005). Numerous natural compounds like alkaloids, terpenoids, flavonoids, glycosides, polysaccharides, and saponins isolated from different medicinal plants were found active against diabetes (Dineshkumar, Mitra, Mahadevappa, 2010).

In 2012, 39 new drugs, including 33 organic molecules and 6 biological drugs were approved by the US Food and Drug Administration (FDA) (Mullard, 2013). Of the 33 small organic molecules, at least 16 were either alkaloids or related to their structures, which reinforce the alkaloids structural characteristics in drug discovery. While the synthetic alkaloids produced from medicinal chemistry via lead optimization and rational drug design, those isolated from biological sources provide novel leads with diverse drug targets. Keeping in view the potential of alkaloids and structures as therapeutic agents, in this review we focused on the alkaloids reported for having anti-diabetic activities.

ALKALOIDS

Alkaloid means "alkali like" and this name was given because most of them are basic in nature and form salts with acids (Robinson, 1968). Alkaloids are nitrogen containing heterocyclic organic compounds of plant origin with different pharmacological activities (Sato *et al*., 2001; Buckingham *et al*., 2010). Alkaloids are classified based on their carbon-nitrogen skeleton. Most alkaloids are colorless, crystalline solid slightly soluble in neutral or alkaline aqueous solution but readily soluble in different organic solvents. The principal bioactive constituents of different alkaloids have been shown to present different activities such as sedative, analgesic, antipyretic, anti-inflammatory, anti-tumor, inhibition of linoleic acid peroxidation, 2,2-diphenyl-picrylhydrazyl (DPPH) radical scavenging, antibacterial, antifungal, antiviral activities and notably the anti-diabetic activity (Benabdesselam *et al*., 2007; Kucukboyaci *et al*., 2010).

Alkaloids as anti-diabetic agents

Among other pharmacologically active compounds, plant leaves contain about 150 useful alkaloids (Verma, 2016). *Catharanthus roseus* leaves and stems are the sources of alkaloids and have been reported to have hypoglycaemic activity in streptozotocin induced diabetic rats (Ahmed *et al*., 2010). Conophylline is an alkaloid obtained from *Ervatamia microphylla* plant (Zhang *et al*., 2013) is responsible for changing pancreatic originator cells to insulin producing cells. Orally administered Conophylline resulted in increased insulin level of normal and streptozotocin-induced diabetic Sprague-Dawley rats. Treatment of induced diabetic rats with alkaloids for 15 days resulted in decrease in glucose level while increased plasma insulin level. Extract from leaves of *Ervatamia microphylla* containing conophylline is considered to be helpful in the treatment of type II DM (Fujii, Takei, Umezawa, 2009).

A carbazole alkaloid called mahanimbine present in leaves, stem bark and root of *Murraya koenigii* (Jain, Momin, Laddha, 2012), is found to be active as anti-diabetic against diabetes associated with abnormalities in lipid profiles. Tiruchenduramine, a new carboline guanidine derivative isolated from the Indian ascidian *Synoicum macroglossum,* demonstrated hypoglycemic activity by inhibiting alpha-glucosidase from mild to moderate level (Nandy *et al*., 2014). Mahanimbine were shown to possess activity against lipidemia and hyperglycemia. They are effective in the treatment of diabetes-related with irregular lipid profile and cardiac disease (Dineshkumar *et al*., 2010).

Different countries are using *Catharanthus roseus* (L.) G. Don, a herbal plant, for the treatment of diabetes (Tiong *et al*., 2013). A variety of alkaloids such as

vindoline, vindolidine, vindolicine and vindolinine were extracted and identified from dichloromethane leave extract of *Catharanthus roseus*. At the dose of 25.0 µg/mL leave extract and the compounds vindoline and vindolicine didn't show any toxic effect on pancreatic β-TC6 cells. In pancreatic β-TC6 or myoblast C2C12 cells, vindolicine showed the highest activity. Against type II diabetes mellitus, compounds vindolidine and vindolinine showed good inhibition activity against tyrosine phosphatase-1B. In ORAC and DPPH assays vindolicine showed the maximum antioxidant potential and in β-TC6 cells at a concentration of 12.5 and 25.0 µg/mL, showed elevated H_2O_2-induced oxidative damage (Tiong *et al*., 2013). Among the 100 known species of *Ziziphus* (*Rhamnaceae*) six are native to Pakistan (Kaleem *et al*. 2014). From *Ziziphus* oxyphylla Edge alkaloids such as nummularin-C, nummularine-R and hemsine-A are locally used against diabetes. These alkaloids show potent inhibition of α-glucosidase, reasonable anti-glycation potential and no activity against chymotrypsin. To PC-3 cell line all the three compounds were non-toxic and represented the ability to control the hyperglycemia (Choudhary *et al*., 2011).

The high amount of berberine produced by the roots of *Berberis lyceum Royle* is used as antidiabetic agent. Oral administration of berberine to diabetes induced rats at concentration of 50 mg/kg resulted in a substantial decrease of blood glucose level. A high effect was observed on glycosylated hemoglobin, lipid profile, glucose tolerance and body weight of the laboratory animals (Gulfraz *et al*., 2008).

Crude extract and alkaloid fraction from *Coptidis Rhizoma* showed high inhibitory activity against Rat Lens Aldose Reductase (RLAR) (Jung *et al*., 2008). In this study different bioactive compounds such as berberine, coptisine, palmatine, jateorrhizine, epiberberine, groenlanedicine and magnoflorine were purified from the active n-butanol fraction and their chemical structures were elucidated using different techniques. Oxidized form of the dioxymethylene group in the A and D ring of the berberine, coptisine, palmatine, jateorrhizine, epiberberine, groenlandicine was found to be responsible for the aldose reductase (AR) inhibition.

Methanolic extract of *Coptis japonica* contains different alkaloids like berberine chloride, palmatine iodide, isoquinoline (Lee, 2002). Despite its tremendous therapeutic potential little attention is given to analyze the AR inhibitory activity of *Coptis japonica*. The inhibitory response of isoquinoline, berberine, and palmatine varied with chemical and concentration. Palmatine iodide and berberine chloride showed the IC_{50} values as 13.45 nM and 13.98 nM, respectively. Berberines and palmatines are useful for AR inhibition as new agents and lead compounds.

Extracts of *Berberis. brevissima* and *Berberis. parkeriana* roots with methanol were analyzed for antidiabetic and pathogenic activity (Ali *et al*., 2013). Active components of these species contain columbamine, dehydrocheilanthifoline, berberine, jatrorrhizine, 8-oxo-berberine, and glutamic acid. The most active compound against diabetes was noted to be 8-oxo berberine with 29% of the positive control. In mexico *Tecoma stans* is traditionally used for the treatment of diabetes (Costantino *et al*., 2003). The alkaloid isolated for the hypoglycemic action from this plant includes tecomine which was tested *in vivo*.

Three norditerpenoid alkaloids i.e. nigelladines A-C and one pyrroloquinoline from *Nigella glanduliferat* were extracted with chloroform. These alkaloids lack any toxic effect against the A431 cell line at concentration of 100 µM however, showing a potential protein tyrosine phosphatase 1B (PTP1B) inhibitory effect (Chen *et al.,* 2014). PTP1B has been implicated as a negative regulator of the insulin signaling pathway *in vitro*. Regulation of insulin signal transduction by PTP1B has been observed in cell lines derived from both liver and muscle, in which it was shown to inhibit insulin-stimulated glycogen synthesis (Johnson, Ermolieff, Jirousek, 2002).

Brassica oleracea var. capitata is used in different countries for the treatment of DM. Chemical analysis of *B. oleracea* var. capitata seed through GC-MS identified twenty-four different compounds including one alkaloid (2,3-Dicyano-5,6-diphenylpyrazine) with antidiabetic activity (Mohammed *et al*., 2014).

The alkaloids present in Tinospora cordifolia were found to prevent the hyperalgesia in experimental diabetic neuropathy (Nadig *et al*., 2012). It has an AR inhibitory activity *in vitro* which may contribute to its beneficial effects. Insulin mimicking and releasing effect of an alkaloid rich fraction containing jatrorrhizine, magnoflorine, palmatine and isoquinoline was assessed *in vivo* and *in vitro*. It considerably reduced glucose formation in the rat liver like tolbutamide, in which it stimulates the secretion of insulin by the pancreas, increases the release of insulin in RINm5F cells. Testing *in vitro* for 30 minutes, palmatine, magnoflorine and jatrorrhizine stimulate release of insulin from RINm5F cell line. Oral administration of palmatine, jatrorrhizine,

and magnoflorine considerably reduced serum glucose during fasting and reduced blood glucose level. Further *in vivo* examination demonstrated the insulin releasing potential by increasing the insulin level of serum in glucose nourished rats. These results indicated that alkaloids found in *Tinospora cordifolia* (TC) have anti-hyperglycemic potential. Hypoglycemic potential of isoquinoline alkaloid rich fraction (AFTC) derived from stem of TC may be due to mechanism of releasing insulin and mimicking-insulin activity to improve hyperglycemia (Patel, Mishra, 2011).

Anti-diabetic Mechanism of Alkaloids

Anti-diabetic alkaloids play an efficient role against hyperglycemia by promoting glucose consumption and glycogen synthesis (Tang *et al*., 2017). Phyto-drugs regulates the metabolism either by inhibiting or inducing multiple molecules including AMP-activated protein kinase (AMPK), Glucose transporter 4(GLUT4), glycogen synthase kinase-3 (GSK3), sterol regulatory element-binding proteins 1 (SREBP1), glucokinase (GK), glucose-6-phosphatase (G6Pase), acetyl-CoA carboxylase (ACC), peroxisome proliferator-activated receptor (PPAR) and protein of tyrosine phosphatase 1B (PTP1B) expression in the stimulation of insulin (Gupta *et al*., 2016).

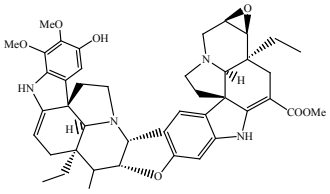
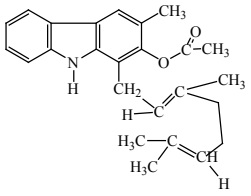
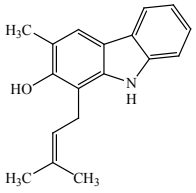
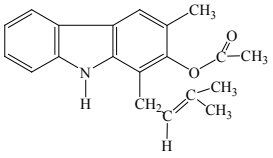
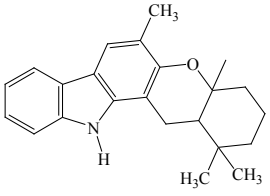
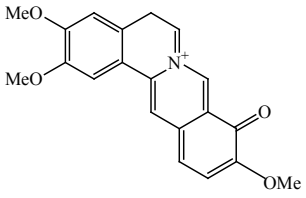
So far, few studies have reported the structure-activity relationship of the alkaloids with antidiabetic properties. Derivatives of tetrahydropalmatine with nitrogen and different hydroxyl groups were prepared and their inhibitory activity against the maltase-glucoamylase (MGAM) enzyme was reported (Shang *et al*., 2013). This study suggested the permanent positive charge and hydroxyl groups as the key features for alkaloids with MGAM inhibitory activity. Another study (Jung *et al*., 2008) showed that in protoberberine-type alkaloids (berberine, palmatine, jateorrhizine, epiberberine, coptisine, and groenlandicine) the presence of dioxymethylene group in their structure were at least partly attributed to the rat lens aldose reductase (RLAR) and human recombinant aldose reductase (HRAR) inhibitory activities. But, the presence of dioxymethylene group in the D ring seems to play a much more crucial role in the aldose reductase inhibitory activity.

According to Sharma *et al*. (2010), alkaloid rich extract from *Capparis decidua* produced a significant change in the activity of hepatic hexokinase i.e. glucokinase and glucose-6-phosphatase of treated animals ($p < 0.05$) and were nearly similar to that of the control. This effect was in agreement with the changed expression levels of hepatic hexokinase type IV, glucose-6-phosphatase and phosphoenol pyruvate carboxykinase, the enzymes linked to the glucose maintenance and glycogen production. This change in the enzymes activities and expression patterns may be attributed to the effect of the alkaloids that plays prominent role in ameliorating carbohydrate metabolism.

Zhou *et al*. (2007) investigated that Berberine alkaloids stimulate glucose uptake in 3T3-L1 adipocytes in different doses at various time intervals with the maximum effect at 12 hours. These alkaloids may induce glucose transport by enhancing the Glucose transporter 1 (GLUT1) activity. Additionally, they also increase phosphorylation of adenosine monophosphate–activated protein kinase and acetyl-coenzyme A carboxylase. Berberine favor glucose uptake using a mechanism distinct from insulin by activating AMP–activated protein kinase. Tang *et al*. (2017) reported three alkaloids (Nigelladines A, B, and C) of *N. glandulifera* that improve insulin-dependent glucose consumption and promote glycogen synthesis in L6 myotubes. Hexokinase involves in glycolysis and glucose conversion and catalyzes the first step in glucose metabolism. The compounds Nigelladines A, B and C enhanced the lactic acid production and hexokinase activity in an insulin-dependent manner, resulting in the increase of glucose consumption in L6 myotubes. Results show that the increase in glucose consumption induced by Nigelladines A, B and C is related with activation of glycolysis pathway.

In summary, alkaloids use a complex mechanism by altering activities of different enzymes related directly or indirectly to the carbohydrates metabolism to control glucose level in the body. Some important anti-diabetic alkaloids are summarized in Table I.

TABLE I – Alkaloids with anti-diabetic activity

Plant	Part used	Solvent	Isolated Alkaloids	Structure	Experiment	Activity	Reference
Ervatamia microphylla	Leaves	Ethanol	Conophylline		*In Vivo* oral administration	Stimulate iPMSCs proliferation	(Fujii *et al*., 2009)
Murraya koenigii	Leaves	Petroleum ether And Mathanolic	Mahanimbilyl acetate		*In Vivo* oral administration	Hypoglycemic Activity	(Adebajo *et al*., 2006)
			Girinimbine				
			Girinimbilylacetat				
			Bicyclomahanimbiline				
Tinospora cordifolia	Stem	Petroleum ether	Palmatine		*In Vitro*	Anti-hyperglycemic potential	(Sangeetha, Priya, Vasanthi, 2013)

(continuing)

TABLE I – Alkaloids with anti-diabetic activity

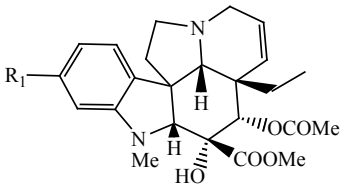
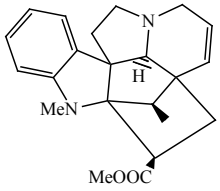
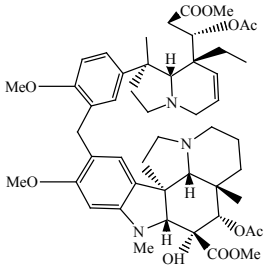
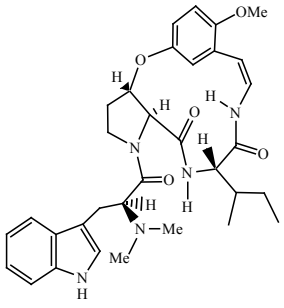
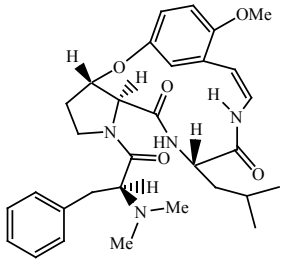
Plant	Part used	Solvent	Isolated Alkaloids	Structure	Experiment	Activity	Reference
Catharanthus roseus	Leaves	Dichloromethane	Vindoline Vindolidine		*In Vitro*		(Tiong *et al*., 2013)
			Vindolicine				
			Vindolinine				
Ziziphus oxyphylla	Whole plant		Nummularine-R		*In Vitro*	Control the postprandial hyperglycemia	(Choudhary *et al*., 2011)
			Nummularin-C				

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TABLE I – Alkaloids with anti-diabetic activity

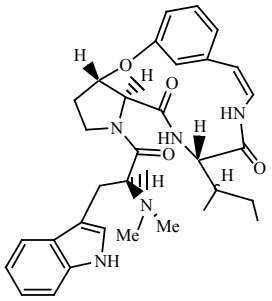
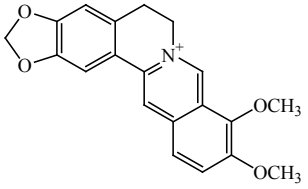
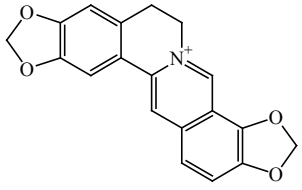
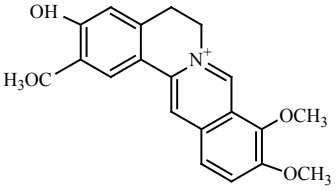
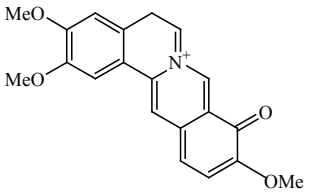
Plant	Part used	Solvent	Isolated Alkaloids	Structure	Experiment	Activity	Reference
Ziziphus oxyphylla	Whole plant		Hemsine-A		*In Vitro*	Control the postprandial hyperglycemia	(Choudhary *et al*., 2011)
Berberis lyceum	Root	Methanol	Berberine		*In Vivo* intravenous injection	Hypoglycemic Activity	(Gulfraz *et al*., 2008)
Coptis chinensis	Rhizome	Methanol	Coptisine		*In Vitro*	Anti-diabetic	(Lee, 2002; Jung *et al*., 2008; Ali *et al*., 2013)
			Jateorrhizine				
			Palmatine				

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TABLE I – Alkaloids with anti-diabetic activity

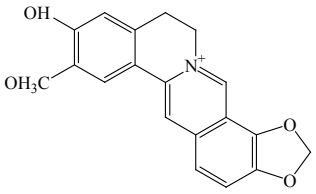
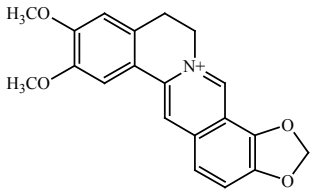
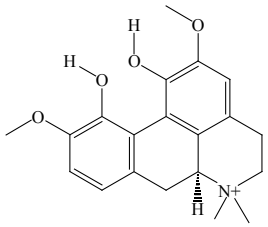
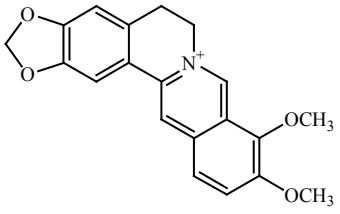
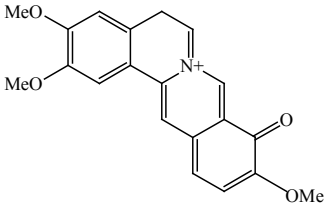
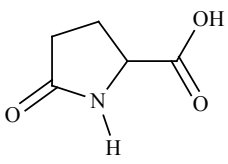
Plant	Part used	Solvent	Isolated Alkaloids	Structure	Experiment	Activity	Reference
Coptis chinensis	Rhizome	Methanol	Groenlandicine		*In Vitro*	Anti-diabetic	(Chem, 2002; Jung *et al*., 2008; Ali *et al*., 2013)
			Epiberberine				
			Magnoflorine				
			Berberine				
			Palmatine				
			Glutamic acid				

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TABLE I – Alkaloids with anti-diabetic activity

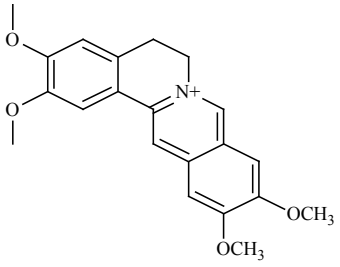
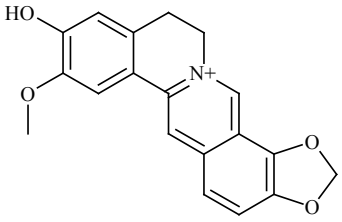
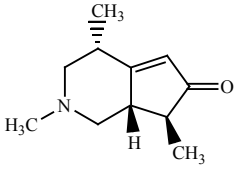
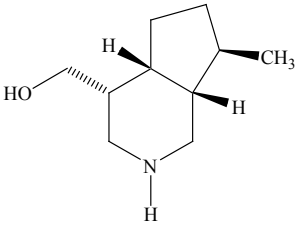
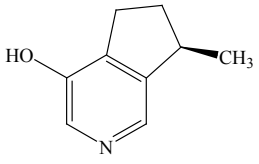
Plant	Part used	Solvent	Isolated Alkaloids	Structure	Experiment	Activity	Reference
Coptis chinensis	Rhizome	Methanol	Columbamine		*In Vitro*	Anti-diabetic	(Chem, 2002; Jung *et al*., 2008; Ali *et al*., 2013)
			Dehydrocheil -anthifoline				
Tecoma stans	Leaves	Et2O/NH3	Tecomine		*In Vivo*, *In Vitro*	Potent stimulating effect on the basal glucose uptake rate	(Costantino *et al*., 2003)
			Tecostanine				
			Boschnlakine				

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TABLE I – Alkaloids with anti-diabetic activity

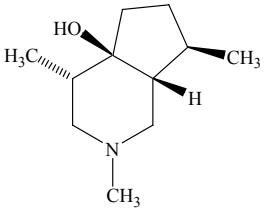
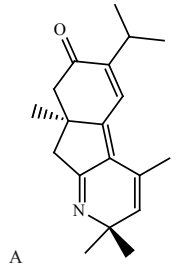
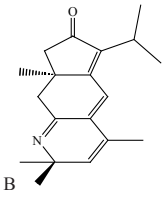
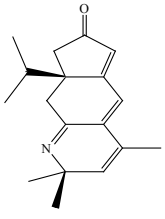
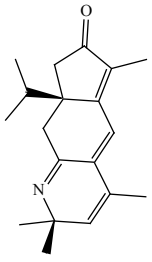
Plant	Part used	Solvent	Isolated Alkaloids	Structure	Experiment	Activity	Reference
Tecoma stans	Leaves	Et2O/NH3	5β-Hydroxyskita-nthine		*In Vivo*, *In Vitro*	Potent stimulating effect on the basal glucose uptake rate	(Costantino *et al*., 2003)
Nigella glandulifera.	Seed	Petroleum ether	Nigelladine A, B and C	 A  B  C	*In Vitro*	PTP1B inhibitory activity	(Chen *et al*., 2014)
			Pyrroloquinoline alkaloid				

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TABLE I – Alkaloids with anti-diabetic activity

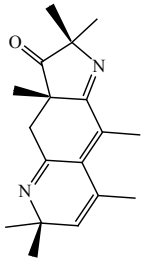
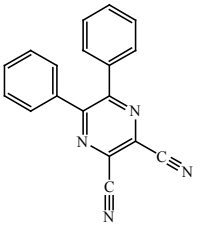
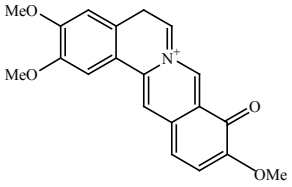
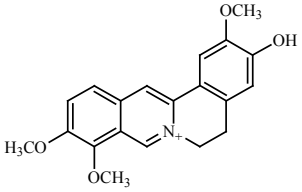
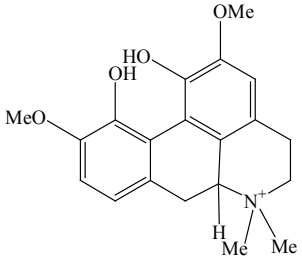
Plant	Part used	Solvent	Isolated Alkaloids	Structure	Experiment	Activity	Reference
Nigella glandulifera.	Seed	Petroleum ether	Nigellaquinomine		*In Vitro*	PTP1B inhibitory activity	(Chen *et al*., 2014)
Brassica oleracea var. capitata	Seed	Ethanolic Acetic Acid	2,3-Dicyano-5,6-diphenylpyrazine		*In Vivo*	Antidiabetic activity	(Mohammed *et al*., 2014)
Tinospora cordifolia	Stem	Methanol And CHCl3	Palmatine,		*In Vitro*, *In Vivo*	Antidiabetic Activity	(Patel, Mishra, 2011)
			Jatrorrhizine				
			Magnoflorine				

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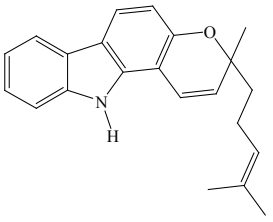
TABLE I – Alkaloids with anti-diabetic activity

Plant	Part used	Solvent	Isolated Alkaloids	Structure	Experiment	Activity	Reference
Murraya koenigii	Leaves	Petroleum ether	Mahanimbin-e		*In Vivo* Intra-peritoneal injection and *In Vitro* alpha amylase and alpha glucosidase activity	Anti-hyperglycemic and Anti-lipidemic effects.	(Dineshkumar *et al*., 2010)

CONCLUSION

Among the phytochemicals alkaloids is one of the most studied and widely distributed class of secondary metabolites. Besides many other pharmacological activities, different alkaloids were found to have anti-diabetic activities; however, more attention is needed to exploit their use in the treatment of diabetes. Here we provided a review of different alkaloids reported in the literature with anti-diabetic activities in order to strengthen research in treatment of this important metabolic disorder.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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