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Review

The search for new hypoglycemic agents from plants

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Diabetes mellitus is a serious endocrine disorder that causes millions of deaths worldwide. The conventional drugs are associated with a number of adverse effects and limitations. In the search for better alternatives, many medicinal plants have been investigated and a variety of compounds have also been isolated. In the present review, medicinal plants selected from those that have been investigated for their antidiabetic potential between the year 2000 and 2013 are presented. The most common families of plants presented are the Asteraceae, Euphorbiaceae and Gentianaecae. The structures of some previously isolated compounds with antidiabetic potential are presented. Most of the isolated antidiabetic principles are alkaloids, flavonoids, amino acid, steroids and organic acids. It was however discovered that most of the investigations are preliminary in nature. More detailed investigations into the efficacy, mode of action and safety profile of these plants and the isolated compounds in preclinical and clinical studies are recommended.

Key words: Antidiabetic plants, hyperglycemia, hypoglycemia, medicinal plants review.

INTRODUCTION

Diabetes mellitus is a chronic disorder characterized by elevated blood glucose levels and disturbance in carbohydrate, fat and protein metabolism (Aguwa, 2004). Diabetic patients experience various vascular complications such as, atherosclerosis, diabetic nephropathy, retinopathy and neuropathy (Sheetz, 2002). The 2012 report by the International Diabetes Federation (IDF) showed that more than 371 million people (8.3% of the world's population) had diabetes and the number of people with diabetes was increasing in every country, while 4.8 million people died and 471 billion USD were spent due to diabetes in 2012 (IDF, 2012).

The currently available therapy for diabetes includes insulin and various oral anti-diabetic agents such as the sulfonylureas, biguanides, thiazolidinediones and α-glucosidase inhibitors. These drugs are used as monotherapy or in combination to achieve better glycemic control. Each of the oral antidiabetic agents is however, associated with a number of serious adverse effects (Moller, 2001; Nwaegerue et al., 2007). Plant-based drugs have been known to be safe and cheaper. Before the discovery of insulin by Banting and Best (1922), the only options were those based on traditional practices (Ribnicky et al., 2009). Thus the search for safer and easily available antidiabetic agents among medicinal plants continues. According to world ethnobotanical information reports, almost 800 plants possess antidiabetic potential (Alarcon-Aguilara et al., 1998).

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Recently, an ethnobotanical survey of the plants used in the treatment of diabetes mellitus was conducted in some areas of South-Western Nigeria. The survey revealed the use of about 132 different plants species belonging to 56 families in the treatment of diabetes mellitus (Soladoye et al., 2012). Though these plants are claimed to possess hypoglycemic properties, most claims are anecdotal and few have received adequate medical or scientific evaluation (Bailey and Day, 1989). Several reviews on the plants used in the management of diabetes have been reported in the past (Bnouham et al., 2006; Kavishankar et al., 2011; Akah et al., 2002). However, information on the nature and source of the putative hypoglycemic active agents of some of the plants are scattered. Plant products are known to be rich in phenolic compounds, flavonoids, terpenoids, coumarins and other constituents which reduce blood glucose levels (He et al., 2005; Jung et al., 2006). There is need therefore to update the current knowledge as more plants are being investigated and to highlight the molecular structures and nature of some of the isolated hypoglycemic agents from plants. Here we present a list of selected plants which have been investigated for their hypoglycemic potentials between years 2000 to 2013. Also presented are the molecular structures and sources of some of the potential hypoglycemic compounds which have been isolated from medicinal plants.

Some plants investigated for antidiabetic activity

The first part of the present review work was conducted by searching the PubMed, Medline and Google scholar for medicinal plants that have been investigated between 2000 and 2013. Only some of the plants were selected based on their ethno-botanical importance and the depth of research on them. The second part of the work involves the hypoglycemic or antidiabetic plants with their active principles isolated. Unlike the first part of the work, the compounds were not necessarily identified in the period 2000 to 2013. The botanical, family and the common names of the medicinal plants that have been investigated for their antidiabetic potential are presented in Table 1. The most commonly occurring family of plants listed include Asteraceae (6), Euphorbiaceae (5), Gentianeacea (5), Brassicaceae (3), Caesalpiniaceae (3), Lamiaceae (3), Myrtaceae (3), Asclepiadaceae (2), Convolvulaceae (2), Cucurbitaceae (2), Oxalidaceae (2) and Papillionaceae (2). The investigations carried out on the plants have employed several plant extracts (aqueous, other solvents) in various models such as *in vitro* techniques involving enzyme inhibition or isolated cells, *in vivo* techniques involving administration (through oral or parenteral route, in various doses) in normal, chemical (alloxan, streptozotocin)-induced or in genetically modified diabetic animals (mice, rabbits, rats and dogs) and oral glucose tolerance test (OGTT). The experiments in animals were of acute (within 24 h) or chronic (a few days to few months) duration. Few of the studies have been carried out in humans. Toxicity studies and investigations on the mode of action of the plants are limited.

Chemical structures of isolated compounds from antidiabetic plants

The active compounds from the antidiabetic medicinal plants with their sources are shown in Figure 1. Twenty eight (28) compounds from different medicinal plants are shown. They have varied structures but most of them are alkaloids (11) or flavonoids (10) in nature. Others are amino acids (2), steroids and organic acid.

DISCUSSION

In this review, selected plants which have been investigated for antidiabetic potentials between year 2000 and 2013 are presented. The present work and earlier reviews on this subject show that a lot of research work has been performed in recent times in the search for antidiabetic agents from plants. However, not all the listed plants from ethnobotanical surveys are fully explored and most of the investigations have been preliminary studies. More detailed researches are therefore advocated in the search for more efficacious and safer hypoglycemic agents from plants. In addition, their long-term benefits in diabetic complications need to be evaluated in controlled studies.

The variety of phytoconstituent classes and the wide differences in the molecular structure of the isolated compounds suggest the possibility of different mechanisms of action in lowering blood glucose. Some have been shown to inhibit α-amylase with others potentiating the action or enhancing the release of insulin. Alkaloids inhibit α-glucosidase and decrease glucose transport through the intestinal epithelium. Polysaccharides increase the level of serum insulin, reduce the blood glucose level and enhance tolerance to glucose. Flavonoids suppress the glucose level, reduce plasma cholesterol and triglycerides significantly and increase hepatic glucokinase activity probably by enhancing the insulin release from pancreatic islets. Saponins stimulate the release of insulin and block the formation of glucose in the bloodstream (Patel et al., 2012; Bhushan et al., 2010). The detailed investigation into the actual mechanism of action of many of the plants and the isolated compounds is however, lacking. Further investigations to establish the actual mode of action of these plants and the isolated compounds are needed.

Besides efficacy and mode of action, the majority of the plants extracts and isolated compounds have not been subjected to thorough toxicological studies in animal models

Table 1. Medicinal plants with investigated antidiabetic potentials.

S/no.	Botanical name	Family	Significant bioactivity in relation to hypoglyceamia
1	*Abelmoschus moschatus* Medik	Malvaceae	The active principle of this plant, myricelin, improves insulin sensitivity in rats (Liu et al., 2007)
2	*Achiliea santolina L.*	Asteraceae	Exhibits hypoglycemic and antioxidant activities (Yazdanparast et al., 2007)
3	*Achyrocline satureioides* (Lam.) DC	Asteraceae	A new prenylated dibenzofuran, achyrofuran, derived from the plant significantly lowers blood glucose levels when administered orally at 20 mg/kg q.d (Carney et al., 2002)
4	*Ajuga iva* L. Schreberr (Medit)	Lamiaceae	Exhibits strong hypoglycemic effect in diabetic rats (aqueous extract at 10 mg/kg) (El Hilaly and Lyoussi, 2002)
5	*Annona squamosa* L.	Annonaceae	Isolated juercetin-3-O-glucoside from the leaves exhibits anti-hyperglycemic and antioxidant activities in animals (Panda and Kar, 2007)
6	*Anthocleista djalonensis* A. Chev (cabbage tree)	Gentianeacea	Extracts show α-amylase and *in vivo* hypoglycemic activity in rats (Olubomehin *et al*., 2013)
7	*Anthocleista Schweinfurthii*	Gentianeacea	Hypoglycemic (Schweinfurthiin, a new steroid and two known compounds, bauerenone and bauerenol were isolated) (Mbouangouere et al., 2007)
8	*Anthocleista vogelii* Planch	Gentianeacea	Extracts show α-amylase (Olubomehin et al., 2013)
9	*Artemisia dracunculus L.*(dragon herb)	Asteraceae	Hypoglycemic comparable to metformin (Ribnicky et al., 2009)
10	*Averrhoa bilimbi* L	Oxalidaceae	Hypoglycemic (leaf extract, 125 mg/kg, OGTT in normal and streptozotocin (STZ)-induced diabetic rats) (Pushparaj et al., 2001)
11	*Bauhinia candicans* Benth	Leguminosae	hypoglycemic (20 % dried leaf infusion in alloxan-induced diabetic rats but not in normal) (Fuentes et al., 2004)
12	*Biophytum sensitivum* (L) DC.	Oxalidaceae	Hypoglycemic (leaf extract in alloxan-induced diabetic rabbits, OGTT) (Puri, 2001)
13	*Bixa orellana* L.	Bixaceae	Hypoglycemic (normal and STZ-induced diabetic dogs) (Russell et al., 2008)
14	*Boerhaavia diffusa L.*	Nyctaginaceae	Decreases blood glucose level and increases plasma insulin levels, antioxidant (Pari et al., 2004)
15	*Brassica nigra* (L) Koch	Brassicaceae	Hypoglycemic (200 mg/kg aqueous extract to diabetic animals daily once for one month) (Anand et al., 2007)
16	*Butea manosperma* (Lam)	Caesalpiniaceae	Anti-hyperglycemic (Somani et al., 2006)
17	*Capparis spinosa* L.	Capparidaceae	Hypoglycemic (aqueous extract at 20 mg/kg in STZ-diabetic rats, acute and chronic treatments; no effect on normal animals) (Eddouks et al., 2004)
18	*Carum carvi L.*	Apiaceae	Potent anti-hyperglycemic (Eddouks et al., 2004)
19	*Cassia auriculata* L.	Caesalpinaceae	Hypoglycemic and enhances the activity of hepatic hexokinase, phosphofructokinase, suppresses glucose-6-phosphatase and fructose-l,6-bisphosphatase in diabetic animals after 15 day treatment (400 mg/kg) (Gupta et al., 2010)
20	*Cichorium intybus* L.	Asteraceae	Hypoglycemic in acute and chronic studies (125 mg/kg daily for 14 days to diabetic rats attenuates serum glucose by 20%, triglycerides by 91% and total cholesterol by 16% (Pushparaj et al., 2007)
21	*Clausena anisata* (Willd) Benth.	Rutaceae	Hypoglycemic (800 mg/kg, p.o., normal and diabetic rats) (Ojewole, 2002)
22	*Cocos nucifera* Linn. (Coconut palm)	Palmae	Neutral detergent fiber from the plant tested in rats fed 5%, 15% and 30% glucose causes significant lowering in glycaemia and serum insulin (Sindurani and Rajamohan, 2000)
23	*Cogniauxia podoleana*	Cucurbitaceae	Hypoglycemic and anti-hyperglycemic (Diatewa et al., 2004)
24	*Commelina communis* L.	Conimelinaceae	Anti-hyperglycemic, management of non-insulin-dependent diabetes (Youn et al., 2004)
25	*Curcuma longa* L.	Zingiberaceae	Hypoglycemic, plays a role in PPAR-gamma activation (Kuroda et al., 2005)

Table 1. Cont'd.

26	*Cynodon dactylon* Pers. (Bermuda grass)	Poaceae	Anti-hyperglycemic (Jarald et al., 2008)
27	*Eclipta alba* (L) Hassk.	Asteraceae	Leaf suspension (2 and 4 g/kg, p.o.) for 60 days produces hypoglycemia and decreases the activities of glucose-6- phosphatase and fructose-1,6-bisphosphatase, and increase the activity of liver hexokinase (Ananthi et al., 2003)
28	*Enicostemma littorale* Blume	Gentianaceae	Dried plant equivalent extract of 1.5 g/100 g causes hypoglycemia in diabetic rats without toxic effect (Maroo et al., 2003)
29	*Eruka sativa*	Brassicaceae	Hypoglycemic, antioxidant and improved lipid profile (after daily oral admin of oil of the seeds 2 weeks before or after diabetes induction with alloxan) (El-Missiry et al., 2000)
30	*Gentiana olivieri* L.	Gentianaceae	Hypoglycemic, anti-hyperlipidemic (Sezik et al., 2005)
31	*Ginkgo biloba* L.	Ginkgoaceae	Hypoglycemic (OGTT in humans), increases pancreatic beta-cell in NIDDM (Sugiyama et al., 2004; Kudolo et al., 2001)
32	*Glycyrrhiza uralensis* Fish.	Papilionaceae	PPAR-gamma ligand-binding activity, decreases the blood glucose levels (Kuroda et al., 2003)
33	*Gongronema latifolium* Benth.	Asclepiadaceae	Antidiabetic and antioxidant (aqueous and ethanol extract of leaf, p.o.) (Ugochukwu and Babady, 2003; Ugochukwu and Babady, 2002)
34	*Gymnema montanum* Hook	Asclepiadaceae	Anti-peroxidative, antioxidant (Ramkumar et al., 2005)
35	*Helicteres isora* L., As.	Sterculiaceae	Hypoglycemic comparable with insulin and metformin, antioxidant and hypolididemic (Suthar et al., 2009)
36	*Hintonia standleyana*	Rubiaceae	Anti-hyperglycemic (Guerrero-Analco et al., 2005)
37	*Hordeum vulgare* L. (Barley)	Gramineae	Glycemic responses in healthy and Type II diabetic patients show that barley is a suitable cereal for diabetic patients (Shukla et al., 2001)
38	*Ibervillea sonorae* S.	Cucurbitaceae	Hypoglycemia in acute and chronic studies (Alarcon-Aguilar et al., 2005)
39	*Ipomoea aquatic* Forsk.	Convolvulaceae	Boiled whole extract exhibits hypoglycemic effect with optimum dose of 3.4 g/kg and optimum activity observed 2 h after admin (Malalavidhane et al., 2003)
40	*Ipomea batata* Linn (Sweet potato)	Convolvulaceae	Hypoglycemia and reduction in hyperinsulinemia in rats (p.o.) in chronic studies, results comparable to troglitazone (Kusano and Abe, 2000)
41	*Lepidium sativum* L.	Brassicaceae	Aqueous extract (10 mg/kg/h) causes potent hypoglycemia in normal and diabetic rats (Eddouks and Maghrani, 2008)
42	*Loranthus micranthus* Linn	Loranthaceae	Weakly acidic fraction of methanol extract (250 and 500 mg/kg) shows activity in alloxanized rats; (Osadebe et al., 2010).
43	*Morus indica*. L.	Moraceae	Hypoglycemic (Devi and Urooj, 2008)
44	*Musa sapientum* Kuntz (Banana)	Musaceae	Hypoglycemia in OGTT; chloroform extract of the flowers at 1.5, 0.2 and 0.25 g/kg for 30 days (p.o.) causes a decrease in blood glucose and glycosylated haemoglobin level (Pari and Umamaheswari, 2000)
45	*Ocimum sanctum* Linn. *(*Tulasi)	Lamiaceae	Shows antidiabetic, antioxidant and other activities in diabetic rats (Vats et al., 2004)
46	*Origanum vulgare* L.	Lamiaceae	Aqueous extract of exhibits anti hypergly-cemic activity in STZ rats without affecting basal plasma insulin concentrations (Lemhadri et al., 2004)
47	*Phyllanthus amarus* Schum. Thonn	Euphorbiaceae	Oral administration of ethanolic leaf extract (400 mg/kg) for 45 days resulted in a significant ($p<0.05$) decline in blood glucose and significant recovery in body weight of diabetic mice (Shetty et al., 2012)
48	*Phyllanthus niruri* L.	Euphorbiaceae	Methanol extract of aerial parts shows antidiabetic activity in normal and alloxan-induced rats (Okoli et al., 2009)
49	*Phyllanthus sellowianus* Mull. Arg.	Euphorbiaceae	Hypoglycemic (Hnatyszyn et al., 2002)
50	*Piper longum*	Piperacea	The aqueous extract at a dosage of 200 mg/kg is found to possess significant antidiabetic activity (Nabi et al., 2013)

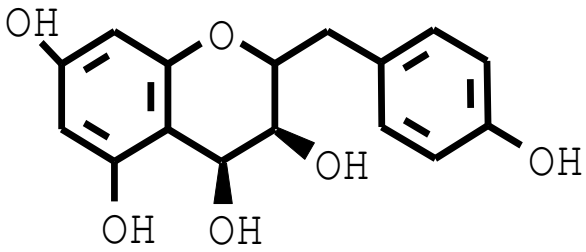
Table 1. Cont'd.

51	*Psidium guajava* L.	Myrtaceae	Leaf extract inhibit the increase of plasma sugar level in alloxan- induced diabetic rats during OGTT; leaf extracts also shows significant inhibitory effect on glucose diffusion in vitro (Mukhtar et al., 2004; Basha and Kumari, 2012)
52	*Punica granatum* L. (pomegranate)	Lythraceae	Hypoglycemia (aqueous-ethanolic extract of flowers in normal and hyperglycaemic rats (400 mg/kg) (Jafri et al., 2000)
53	*Retama raetam (RR)* (Forssk) Webb.	Papilionaceae	Aqueous extract possess significant hypoglycemic effect in normal and STZ rats (Maghrani et al., 2005)
54	*Sambucus nigra* L.	Adoxaceae	Insulin-releasing and insulin-like activity (Gray et al., 2000)
55	*Sanguis draxonis*	Apocynaceae	Increase insulin sensitivity and improve the development of insulin resistance in rats (Hou et al., 2005)
56	*Sclerocarya birea* (A. Rich)	Anacardiaceae	Hypoglycemic (Ojewole, 2003)
57	*Scoparia dulcis* L.	Scrophariaceae	Hypoglycemic, antihyperlipidemic, antidiabetic (Beh et al., 2010)
58	*Spergularia purpurea*	Caryophyllaceae	Hypoglycemic (aqueous extract in normal and diabetic rats at 10 mg/kg) (Jouad et al., 2000; Eddouks et al., 2003)
59	*Suaeda fruticosa (SF)* Euras	Chenopodiaceae	Hypoglycemic (aqueous extract in normal and diabetic rats at 192 mg/kg but no effect on plasma triglycerides in both groups (Benwahhoud et al., 2001)
60	*Syzygium alternifolium* (Wt) Walp	Myrtaceae	Hypoglycemic, antihyperglycemic and antihyperlipidemic (Rao and Rao, 2001)
61	*Tamarindus indica* L.	Caesalpinaceae	Hypoglycemic and hypolipidemia in STZ- diabetic rats (aqueous extract of seed in a chronic study) (Maiti et al., 2005)
62	*Terminalia bellirica* (Gaertn)	Combretaceae	Stimulates insulin secretion. Enhances insulin action andinhibits both protein glycation and starch digestion (Kasabri et al., 2010)
63	*Terminalia chebula* Retz.	Combretaceae	Dose-dependent hypoglycemic, antidiabetic and renoprotective,decreases hepatic and skeletal muscle glycogen content, increases insulin release from the pancreatic islets (Rao and Nammi, 2006)
64	*Tinospora cordifolia* Miers.	Menispermaceae	Hypoglycemic (aqueous root extract orally in alloxan rats, 400 mg/kg equivalent to 1 unit/kg of insulin) (Sengupta et al., 2009)
65	*Urtica pilulifera* L.	Urticaceae	Hypoglycemic (Kavalali et al., 2003)
66	*Vernonia amygdalina* Del.	Astereaceae	Extract improves biochemical and heamatological parameters in diabetic rats; combination of extract with metformin at various ratios shows that the ratio of 1:2 (extract: metformin) causes the most significant ($p<0.05$) reduction in blood sugar (66.07%) compared to control (Akah et al., 2009; Adikwu et al., 2010)
67	*Withania soimifera* (L) Dunal	Solanaceae	Hypoglycemic, antioxidant, diuretic and hypocholesterolemic (Adallus and Radhika, 2000)
68	*Zygophyllum gaetulum* Emb and Maire	Zygophyllaceae	Hypoglycemic, increases plasma insulin levels (Jaouhari et al., 2000)

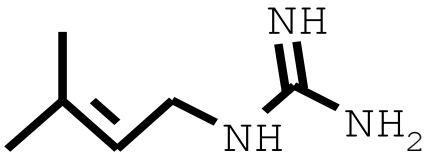
let alone in clinical settings. Isolating the compounds is a necessary step in the search for a new hypoglycemic agent. The safety of the isolated compounds is also of importance as it is possible that the isolated compound could be more toxic than when present in the plant in association with other agents. For instance, *Galega officinals* which is rich in guanidine was traditionally used in the management of diabetes in Europe. However, guanidine proved too toxic to be used in clinical practice. Metformin, a biguanide and the current drug of choice in the management of type 2 diabetes was later developed from the guanidines (Sterne, 1969; Bailey, 1988). Those plants with promising antidiabetic potential as well as the isolated compounds therefore need to be subjected to detailed toxicological evaluation.

Conclusion

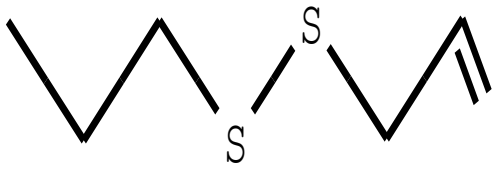
The present review has indicated that there is currently great interest in the search for anti-diabetic agents from plants and many potential compounds have been isolated. However, most of the investigations have been preliminary in nature. There is urgent need therefore to fully explore these promising plants by carrying out further



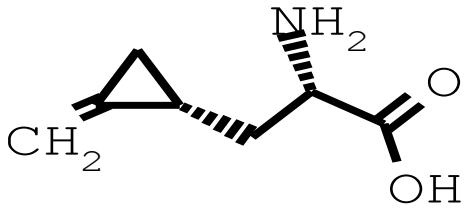
Cis-3,4-Leucopelargonidin
(from *Fiscus bengalensis;* Cherian et al., 1993)



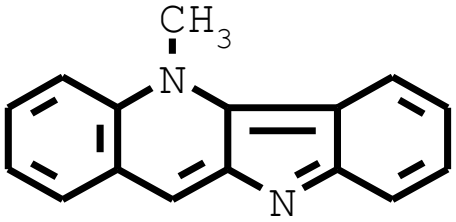
Galegine
(from *Galega officinalis;* Hadden, 2005)



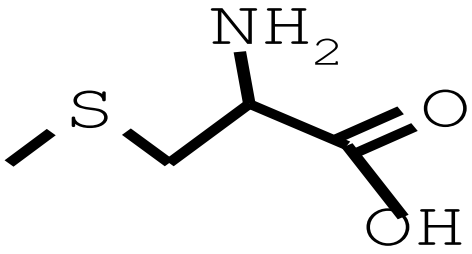
Poly allyl disulphide
(from *Allium cepa*; Romas-Ramos et al., 1995)



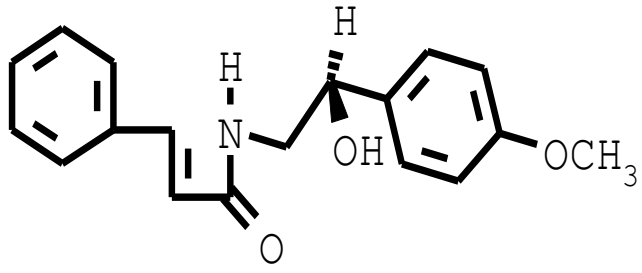
Hypoglycin
(from *Blighia sapadia* Chen et al., 1957)



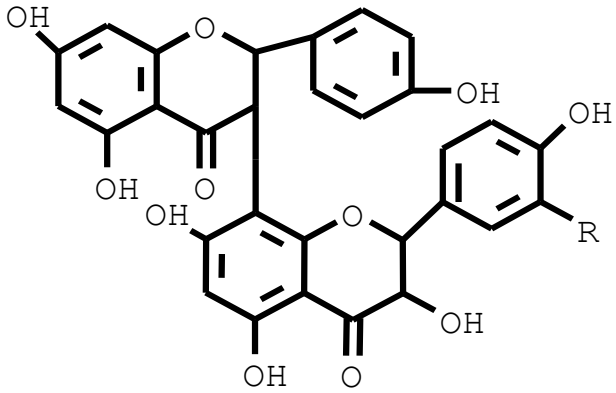
Cryptolepine
(from *Cryptolepis sanquinolenta*; Luo et al., 1998)



Cysteine
(from *Allium cepa*; Kumari et al., 1995)

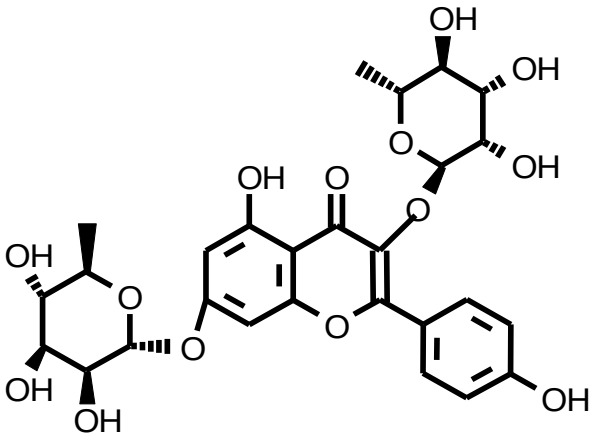


Aegeline
(from *Aegle marmelose;* Narender et al., 2007)

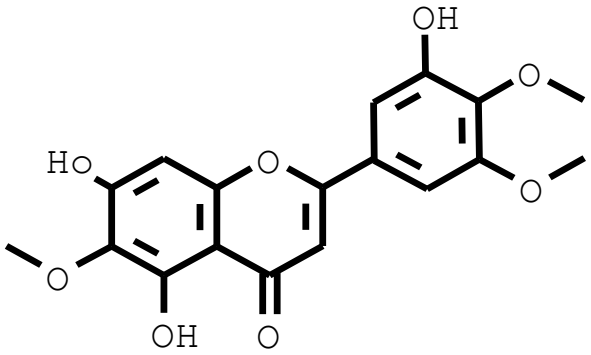


Kolaviron
(from *Garcina kola*; Iwu et al., 1990)

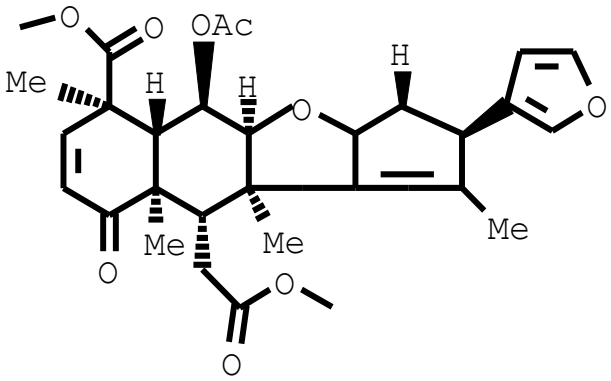
Figure 1. Chemical structures of some antidiabetic principles isolated from plants.



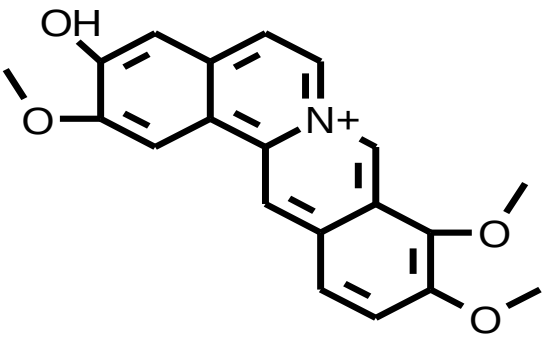
Kaemferitrin
(from *Bauhinia forficate*; De Sousa et al., 2004)



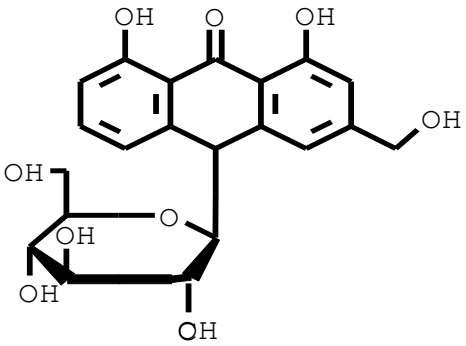
5, 7, 3-Trihydroxy 3, 6, 4-trimethoxyflavone
(from *Brickelia veronicaefolia*; Perez et al., 2000)



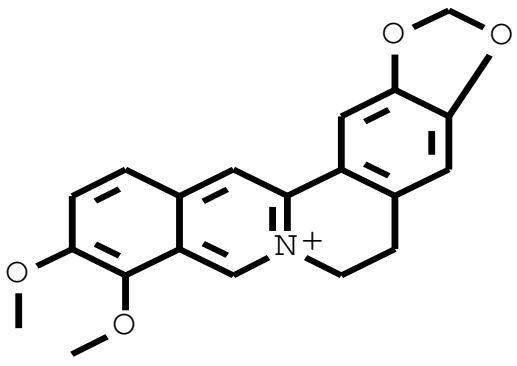
Nimbidin
(from *Azadirachta indica*; Waheed et al., 2006)



Jatrorrhizine
(from *Berberis aristata* Sadiq et al., 2013; Atta-ur-Rahman, 1989)

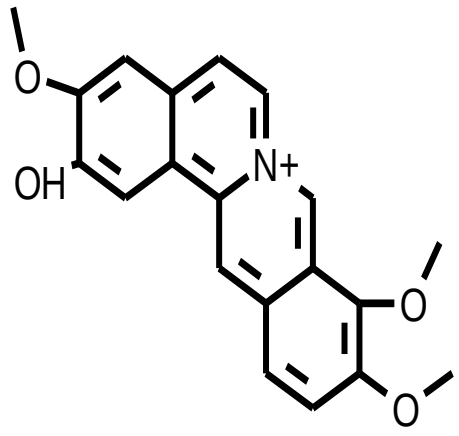


Isobarbaloin
(from *Aloe vera ;* Akira *et al*., 2009)

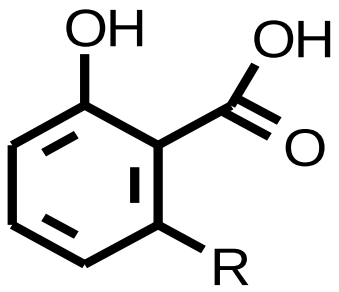


Berberine
(from *Berberis aristata*; Chen et al., 1986; Handa et al., 1989)

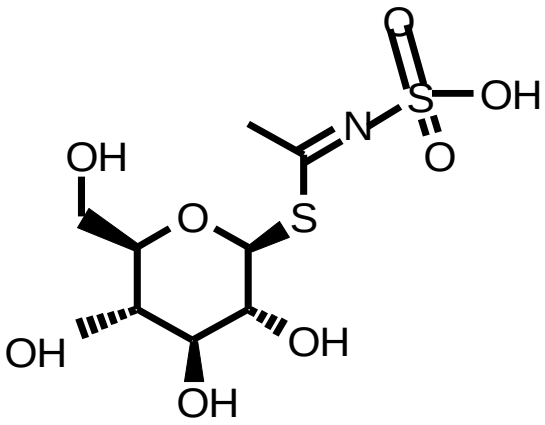
Figure 1. Cont'd.



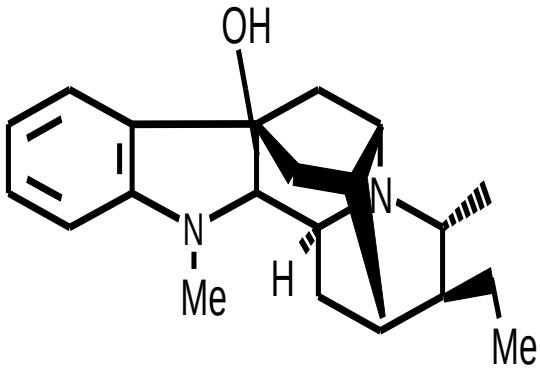
Columbamine
(from *Berberis aristata*; Handa et al., 1989)



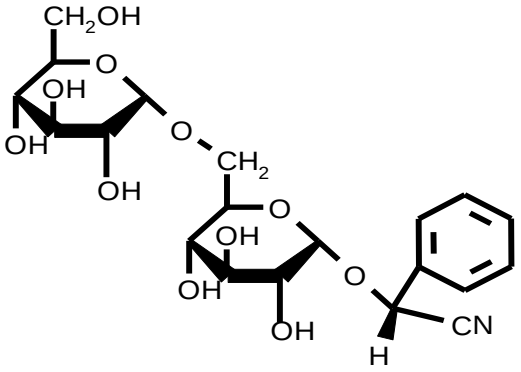
Anacardic acid
(from *Anacardium occidentale*; Tedong et al., 2010)



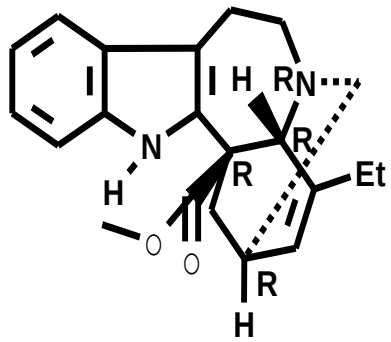
Glucocapparin
(from *Capparis sepiaria*; Juneja et al., 1970)



Ajmaline
(from *Rauwolfia serpentine*; Chatterjee et al., 1960)

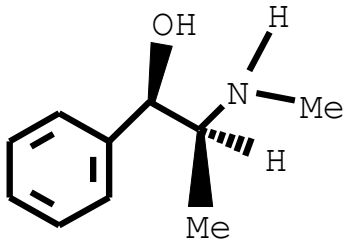


Amygdalin
(from *Prunus persica*; Mirmiranpour *et al*., 2012)

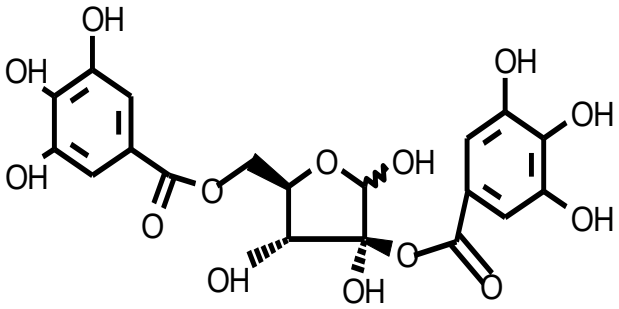


Catharanthine
(*Catharnthus roseus*; Handa et al., 1989; Atta-ur-Rahman, 1989)

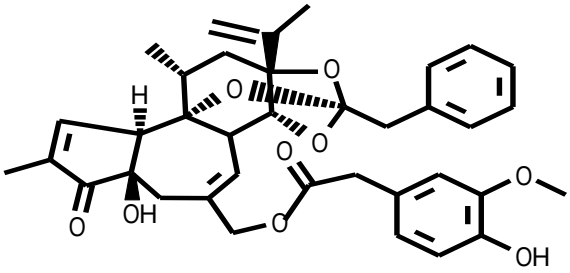
Figure 1. Cont'd.



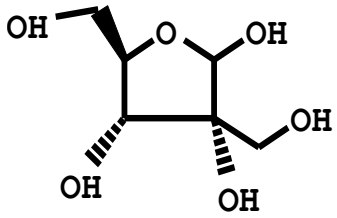
Ephedarn
(from *Ephedra distachya*; Handa et al., 1989)



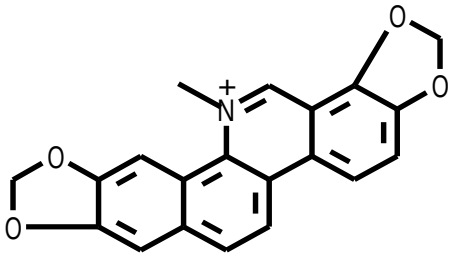
Hamamelitannin
(from *Hamada salicornica*; Ajabnoor et al., 1984)



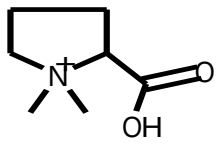
Euphorbol
(from *Euphorbia prostrate*; Alarcon-Aguilara et al., 1998)



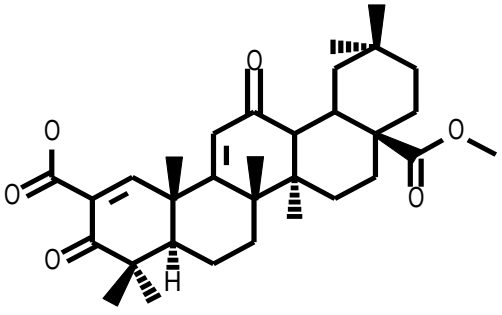
Hamamelose
(from *Hamada salicornica*; Ajabnoor et al., 1984)



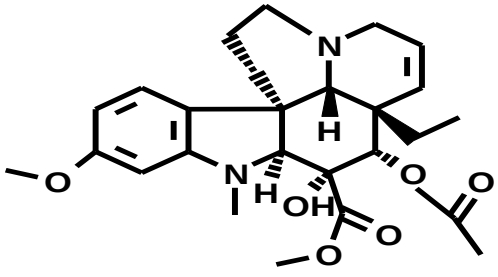
Sanguinarine
(from *Fumaria* parviflora; Hilal et al., 1989)



Stachydrine
(from *Capparis sepiaria*; Juneja et al., 1970)



Tormantic acid
(from *Poterium ancisroides*; Ivorra et al., 1988)



Vindoline
(from *Catharanthus roseus*; De and Saha, 1975)

Figure 1. Cont'd.

research geared towards identifying and exhaustively evaluating the putative phytochemicals with more emphasis on their pharmacological and toxicological profile. The list of plants in this review is not exhaustive of all the plants investigated for hypoglycemic effects. However, it is hoped that the list of medicinal plants presented here

will further broaden the knowledge base on the various medicinal plants available for the management of diabetes mellitus. The studies already performed and highlighted the need for more studies in this direction.

Conflict of Interests

The author(s) have not declared any conflict of interests.

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