Transworld Research Network
37/661 (2), Fort P.O.
Trivandrum-695 023
Kerala, India

Plants in Traditional and Modern Medicine: Chemistry and Activity, 2010: 69-175
ISBN: 978-81-7895-432-5 Editor: Eugene Kokkalou

2. Medicinal plants used for the treatment of diabetes and its long-term complications

Polyxeni Alexiou and Vassilis J. Demopoulos
Department of Pharmaceutical Chemistry, School of Pharmacy
Aristotle University of Thessaloniki, Greece

Diabetes mellitus is a complex metabolic disorder that affects between 6 to 20% of the population in Western industrialized societies, with an estimated worldwide prevalence of 150 million people in 2000, a number that is expected to increase to 220 million people in 2010 (Zimmet et al., 2001; Fracchiolla et al., 2007). Furthermore, taking into account its present rate of increase, within few decades it will be one of the world's commonest diseases and one of the biggest public-health problems with an estimated minimum of half-a-billion cases (Diamond, 2003).

The word "diabetes" (a Greek word that means "to pass through") was first used by Aretaeous of Capadocia in the 2nd century AD to describe a condition that is characterized by excess of sugar in blood and urine, hunger and thirst (MacFrlance et al., 1997) and the adjective "mellitus" (a latin-greek word that means "honey") was introduced by the English physician John Rollo so as to distinguish the conditions from other polyuric diseases, in which glycosuria does not occur (Rollo 1797). People suffering from diabetes are not able to produce or properly use insulin in the body

Correspondence/Reprint request: Dr. Polyxeni Alexiou, Department of Pharmaceutical Chemistry, School of Pharmacy, Aristotle University of Thessaloniki, Greece. E-mail: ksenia@pharm.auth.gr

and therefore chronic hyperglycemia occurs. In addition, the diabetic individual is prone to late onset complications (Fujisawa et al., 2004), such as retinopathy, neuropathy and vascular diseases, that are largely responsible for the morbidity and mortality observed in diabetic patients.

There are two main types of diabetes, namely type I and type II (World Health Organization. Definition, Diagnosis and Classification of Diabetes mellitus and its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus (Department of Noncommunicable Disease Surveillance, Geneva, 1999)). Type I diabetes, that is called insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes develops when the body's immune system destroys pancreatic β-cells, the only cells in the body that produce the hormone insulin that regulates blood glucose. This type of diabetes usually strikes children and adults and the need for insulin administration is determinant for survival. Type I diabetes accounts for 5% to 10% of all diagnosed cases of diabetes and the risk factors may be autoimmune, genetic, or environmental.

On the other hand, type II diabetes, also called non–insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes, accounts for about 90% to 95% of all diagnosed cases of diabetes. It usually begins as insulin resistance, a disorder in which the cells do not use insulin properly and as the need for insulin rises; the pancreas gradually loses its ability to produce it. This type of diabetes is associated with older age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose metabolism, physical inactivity, and race/ethnicity. It must be noted thought that in the last decay type II diabetes in children and adolescents is being diagnosed more frequently (Fagot-Gampagna & Narayan 2001). In the case of the IDDM, insulin is of crucial importance for the survival of the patients. On the other hand, in the case of NIDDM the treatment includes medicines, diets and physical training.

Up to now, many kinds of antidiabetic medicines have been developed for the patients and most of them are chemical or biochemical agents aiming at controlling or/and lowering blood glucose to a normal level. Despite the impressive advances in health sciences and medical care, there are many patients who are using alternative therapies alone or complementary to the prescribed medication. Traditional plant remedies or herbal formulations exist from ancient times and are still widely used, despite all the controversy concerning their efficacy and safety (Huxtable 1990; Fugh-Berman 2000), to treat hypoglycemic and hyperglycemic conditions all over the world. It must be noted that many ethno-botanical surveys on medicinal plants used by the local population have been performed in different parts of the world and there is a considerable number of plants described as antidiabetic. In addition a variety of compounds have been isolated (alkaloids, glycosides, terpenes, flovonoids, etc) but further studies need to be done so as these ‘leads’ to develop into clinically useful medicines. To date, metformin (a biguanide) is the only drug approved for treatment of type II diabetes mellitus. It is a derivative of an active

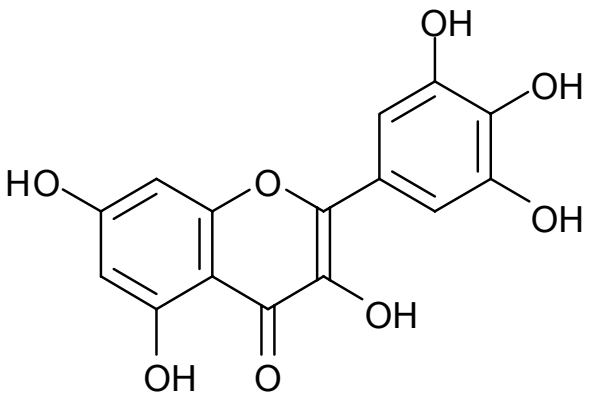
natural product, galegine, isolated from the plant Galega officinalis L. (Witters 2001).

The data presented below are based on a diabetes literature database of antidiabetic medicinal plants (Babu et al., 2006) (DiaMedBase: http://www.progenebio.in/DMP/Turnera.htm). Also, the presented list of antidiabetic plants is enriched by data from review papers (Bnouham et al., 2006; Li et al., 2004; Andrade-Cetto & Heinrich 2005; Pulok et al., 2006).

It must be also noted that there are few references to the Ayurveda and Siddha systems (http://indianmedicine.nic.in/html/). Ayurveda originated in India long back in pre-vedic period. Ayurved texts were documented about 1000 years B.C. The term Ayurveda means 'Science of Life'. It deals with measures for healthful living during the life and it has developed a wide range of therapeutic measures to combat illness. These principles of positive health and therapeutic measures relate to physical, mental, social and spiritual welfare of human beings. Thus, Ayurveda is considered as one of the oldest systems of health care dealing with both the preventive and curative aspects of life in a most comprehensive way and presents a close similarity to the WHO's concept of health propounded in the modern era. Siddha system is one of the oldest systems of medicine in India. The term Siddha means achievements and Siddhars were saintly persons who achieved results in medicine. This system is largely therapeutic in nature.

Abelmoschus moschatus (Malvaceae)

The hypoglycemic action of myricetin, purified from the aerial part of Abelmoschus moschatus, was investigated in STZ-diabetic rats (Liu et al., 2005). I.v. injection of myricetin decreased the plasma glucose concentrations in a dose-dependent manner in STZ-diabetic rats and all the obtained results suggested that myricetin has an ability to enhance glucose utilization to lower plasma glucose in diabetic rats with deficient insulin levels.



myricetin

Acacia arabica (Leguminoseae)

Acacia arabica is a moderate sized, almost evergreen tree found throughout the drier parts of India. The bark of this plant has various traditional uses including that of an antidiabetic remedy.

A significant hypoglycemic effect of powdered seeds in normal rabbits, administered per os (Wadood et al., 1989), was postulated that it is based on the release of insulin from pancreatic β cells.

Azadirachta indica (Meliaceae) and Abroma augusta (Sterculiaceae)

Combination of water extract of dried powder of root and leaves of Abroma augusta and Azadirachta indica respectively was administered per os to alloxan diabetic rats, and this treatment caused significant lowering of blood sugar and reduction in serum lipids. Aqueous extract also decreased the formation of lipid peroxides and increased antioxidant enzymes (SOD, CAT, glutathione peroxidase and GST) in erythrocytes. It also prevented the decrease of body weight. Abroma augusta roots and Azadirachta indica leaves when given together as a water extract have hypoglycemic action and have better effect than given alone (Halim 2003).

Acer ginnala (Aceraceae), Illicium religiosum (Illiciaceae) and Cornus macrophylla (Cornaceae)

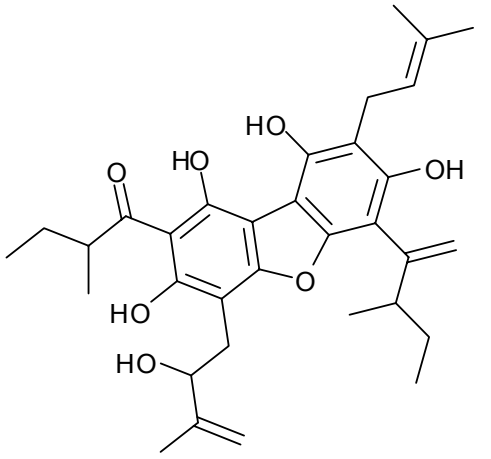
Naturally occurring substances which can prevent and treat diabetic complications were sought by examining ethanolic extracts, prepared from Korean forest plants, for their inhibitory effects on rat lenses ALR2 activity in vitro. Among the plants examined in a reported study, Acer ginnala, Illicium religiosum and Cornus macrophylla exerted the strongest inhibitory activity on ALR2 (Kim & Oh 1999).

Achyranthes aspera L. (Amaranthaceae)

Blood glucose levels of normal and alloxan-induced diabetic rabbits were determined after per os administration of various doses of Achyranthes aspera powdered whole plant and certain aqueous and methanolic extracts (Muhammad et al., 1991). A significant dose-related hypoglycemic effect in normal as well as in diabetic rabbits was observed. It is possible that the plant could act by providing certain necessary trace elements (like calcium, zinc, magnesium, manganese and copper) to the β cells.

Achyrocline satureioides (Asteraceae)

A new dibenzofuran, achyrofuran, was isolated from an extract of Achyrocline satureioides and it significantly lowered blood glucose levels in experimental animals when it was administered per os (Camey et al., 2002).



achyrophuran

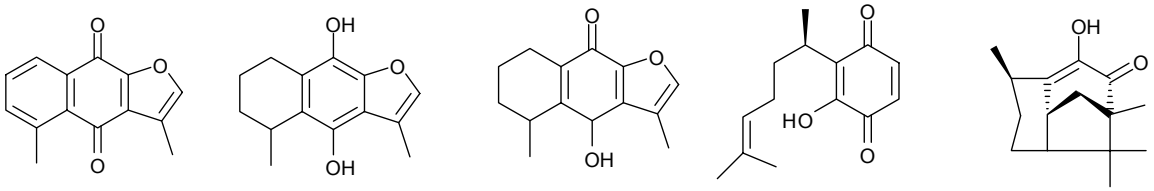
Acosmium panamense (Fabaceae)

This species is widely used, especially in the southern lowland of Mexico, for treating fever, malaria and in recent decades diabetes. The hypoglycemic effects of water and butanolic extracts. prepared from the bark of Acosmium panamense, were studied in STZ-diabetic rats after per os administration. The studied extracts lowered the plasma glucose levels in STZ-diabetic rats (Andrade-Cetto & Wiedenfeld 2004).

Psacalium decompositum, Psacalium peltatum and Acourtia thurberi (Asteraceae)

The effects of Psacalium decompositum, Psacalium peltatum and Acourtia thurberi on blood glucose levels were investigated in fasting mice and temporally hyperglycemic rabbits (Alarcon-Aguilar et al., 1997). The root decoction of Psacalium decompositum reduced the blood glucose of normal mice after i.p. administration and significantly lowered the hyperglycemic peak in rabbits with hyperglycemia. Psacalium peltatum and Acourtia thurberi decoctions also diminished fasting glycemia in mice and hyperglycemia in rabbits, but these effects were minor. The water decoctions of the three roots contained alkaloids and sugars. Psacalium decompositum and Psacalium peltatum showed the presence of maturine. However, other

sesquiterpenoid constituents, such as cacalol and cacalone, were only present in Psacalium decompositum. Acourtia thurberi root water decoction showed the presence of the benzoquinone perezone, and its derivative pipitzol.



Artemisia roxburghiana (Asteraceae), Salvia coccinia (Lamiaceae), Monstera deliciosa (Araceae), Abies pindrow (Pinaceae), Centaurea iberica (Asteraceae), Euphorbia helioscopia (Euphorbiaceae), Bauhinia variegate (Leguminosae), Bergenia himalacia (Saxifragaceae), Taraxacum officinale (Asteraceae), Viburnum foetens (Caprifoliaceae).

In vitro testing of the extracts of medicinal plants collected from Islamabad area and the Murree region on insulin secretagogue activity was carried out using INS-1 cells (insulinoma cell line) (Hussain et al., 2004). Dried ethanol extracts of all plants were tested at various concentrations for insulin release. Promising insulin secretagogue activity was found. It should be pointed out that in some cases, a decrease in insulin secretion was observed. However, the overall results suggest that medicinal plants of Islamabad area and the Murree region of Pakistan may be potential natural resources for antidiabetic compounds.

Aegle marmelose (Rutaceae)

Alloxan induced diabetic animal model was used to evaluate the potential antidiabetic effect of Aegle marmelose leaf extract (Ponnachat et al., 1993). The diabetic animals were given insulin injection and another group Aegle marmelose leaf extract orally. The results indicated that the Aegle marmelose leaf extract has similar hypoglycemic activity to that of insulin treatment.

According to another study (Das et al., 1996) the leaf extract of Aegle marmelose reversed the altered parameters of STZ-diabetic rats to almost normal after per os administration. Treatment with the leaf extract showed improved functional state of pancreatic β cells. The results indicate the potential hypoglycemic effect of the leaf extract, possibly involved in processes for the regeneration of damaged pancreas.

The functional basis of diabetes to a certain extent can be elucidated by studying diabetes-induced changes in metabolic enzymes. MDH is an enzyme directly involved in glucose metabolism. The kinetic parameters of MDH and its purified cytosolic isozyme, S-MDH, have been studied in the liver of STZ-diabetic rats and also the potential of the leaf extract of Agle marmelose as an anti-diabetic agent was investigated (Seema et al., 1996). Insulin as well as the leaf extracts' treatment of the diabetic rats brought about a reversal of Km values at the diabetic rats to almost normal. Since MDH is an important enzyme in glucose metabolism, the variation in its quantitative and qualitative nature may contribute to the pathological status of diabetes. The fact that leaf extract of Aegle marmelose was found to be as effective as insulin in the restoration of blood glucose and body weight to normal levels, its use as potential hypoglycemic agent is suggested.

The antidiabetic effect of an aqueous extract of Aegle marmelos fruits in diabetes was studied (Kamalakkanan et al., 2003). Blood glucose, plasma insulin, glycosylated hemoglobin, liver glycogen, and change in body weight were determined in STZ-diabetic rats. The results showed that glucose levels and glycosylated hemoglobin were increased and plasma insulin and liver glycogen were decreased in the STZ-diabetic rats, and that per os treatment with the aqueous extract of Aegle marmelos fruits reversed the effects of diabetes on these biochemical parameters to almost normal levels. Also, the depressed activities of SOD, CAT and glutathione peroxidase as well as the lowered GSH content in the heart and pancreas of diabetic rats was found to be increased after treatment with the aqueous extract of Aegle marmelos fruits.

Per os administration of Aegle marmelos fruit extract led to a significant lowering of lipids in STZ-diabetic rats (Kamalakkannan et al., 2004). The results of this study demonstrated that an aqueous Aegle marmelos fruit extract exhibits an antihyperlipidemic effect in STZ-diabetic rats.

It is known that certain inorganic elements such as V, Zn, Cr, Cu, Fe, Na, K, and Ni play an important role in the maintenance of normoglycemia by activating the β cells of the pancreas. In a reported study (Nerendhirakannan et al., 2005), the elemental composition in the leaves of Aegle marmelos widely used in the treatment of diabetes-related metabolic disorders has been studied using atomic absorption spectroscopy. The levels of Cu, Ni, Zn, K, Na Fe, Cr, and V were found to be in trace amounts.

Agaricus bisporus (Agaricaceae)

Agaricus bisporus (the cultivated mushroom) that is used for the traditional treatment of diabetes mellitus in northern Europe was studied,

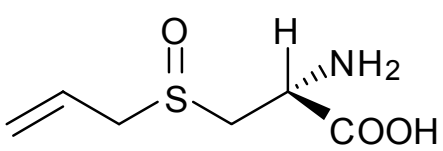
using normal and STZ-diabetic mice, in order to evaluate its effects on glucose homeostasis (Swanston-Flatt et al., 1989). The plant was administered in the diet and/or as decoction or infusion in place of drinking water, to coincide with the traditional method of preparation. It retarded the development of hyperglycemia and reduced the hyperphagia, polydipsia, body weight loss, and glycated haemoglobin. Mushroom also countered the initial reduction in plasma insulin and the reduction in pancreatic insulin concentration, and improved the hypoglycemic effect of exogenous insulin. These studies suggest the presence of potentially useful antidiabetic agents in these mushrooms.

Agrimonia eupatoria (Rosaceae)

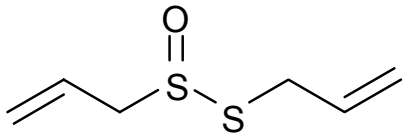
Agrimonia eupatoria (agrimony) has been documented as a traditional treatment of diabetes. The effects of dietary administration of agrimony to STZ-diabetic mice, on in vitro glucose uptake and glucose metabolism, and on insulin secretion were investigated (Gray & Flatt 1998) and the obtained results demonstrated the presence of antihyperglycemic, insulin-releasing and insulin-like activity in Agrimony eupatoria. In addition, treatment with agrimony, supplied in the diet, reduced the level of hyperglycemia in STZ-diabetic mice and this was associated with reduced polydipsia (Swanston-Flatt et al., 1990).

Allium sativum L. (Liliaceae)

Allium sativum (garlic) has been used in cooking for thousands of years and S-allyl cysteine sulphoxide (SACS), a sulphur containing amino acid of which is the precursor of allicin, has been found to show significant antidiabetic effects in alloxan diabetic rats (Sheela & Augusti 1992).



SACS



allicine

Per os administration of it significantly decreased the concentration of serum lipids, blood glucose and activities of serum enzymes like alkaline phosphatase, acid phosphatase and lactate dehydrogenase and liver G6Pase. It also increased liver and intestinal HMGR activity and liver HK activity.

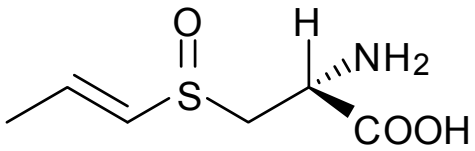
Garlic and garlic preparations are also reported as agents used for the prevention and treatment of atherosclerosis and atherosclerosis-related diseases (Orekhov & Reddy 1997). Garlic indirectly effects atherosclerosis by reduction of hyperlipidemia, hypertension, and probably diabetes mellitus and prevents thrombus formation. In addition, in animal models, garlic causes direct antiatherogenic (preventive) and antiatherosclerotic (causing regression) effects at the level of artery wall. Garlic's direct effect on atherosclerosis may be explained by its capacity to reduce lipid content in arterial cells and to prevent intracellular lipid accumulation.

Based on another study concerning the therapeutic potential of the ethanol extract of garlic, it was found that when it was ingested it was responsible for anti-hyperglycemic and anti-nociceptive effects in alloxan-induced diabetic mice (Kumar & Reddy 1999).

The effect of aged garlic extract administered per os on stress induced hyperglycemia was also investigated using the immobilization stress model in mice (Kasuga et al., 1999). From the obtained results, it was suggested that it may prevent stress-induced hyperglycemia which is the risk of suffering from diabetes mellitus and its progression.

Allium cepa L. (Liliaceae)

Allium cepa (onion) is a common vegetable. Antidiabetic and antioxidant effects of S-methyl cysteine sulfoxide (SMCS) isolated from Allium cepa (onion) were studied in alloxan diabetic rats after using it for treatment for two months (Kumari & Augusti 2002). SMCS ameliorated the diabetic condition significantly and lowered the levels of malondialdehyde, hydroperoxide and conjugated dienes in tissues exhibiting antioxidant effect on lipid peroxidation in experimental diabetes. The probable mechanism of action of SMCS may be partly dependent on the stimulation of insulin secretions and partly due to its antioxidant activity.



SMCS

Onion was found to increase the fasting serum high-density lipoprotein levels, and demonstrated alleviation of hyperglycemia in STZ-diabetic rats (Campos et al., 2003). The hypoglycemic and hypolipidaemic actions of

Allium cepa were associated with antioxidant activity, since onion decreased SOD activities while no increased lipid hydroperoxide and lipoperoxide concentrations were observed in diabetic rats treated with Allium cepa.

Allium cepa L. and Allium sativum L. (Liliaceae)

After per os administration of Allium cepa L. and Allium sativum L. (onion and garlic respectively) sulfoxide amino acids (S-methylcysteine sulfoxide and S-allylcysteine sulfoxide) to alloxan-diabetic rats, their diabetic condition (being characterized by glucose intolerance, weight loss and depletion of liver glycogen), was ameliorated and it was comparable to rats treated with glibenclamide and insulin (Sheela et al., 1995).

Aloe vera (Liliaceae)

Aloe is a desert plant with a cactus like appearance and has been used since prehistoric times for burns and wound healing. The positive influence of Aloe vera on the healing of full-thickness wounds in diabetic rats is reported. The results of this study indicated that Aloe vera treatment of wounds in diabetic rats may enhance the process of wound healing by influencing phases such as inflammation, fibroplasia, collagen synthesis and maturation, and wound contraction. These effects may be due to the reported hypoglycemic effects of the aloe gel (Chithra et al., 1998).

The dried sap of the aloe plant (aloes) is one of several traditional remedies used for diabetes in the Arabian peninsula. Its ability to lower the blood glucose levels, when administered per os, was studied in 5 patients with type II diabetes and in Swiss albino mice made diabetic using alloxan. It was concluded that aloes contain a hypoglycemic agent which lowers the blood glucose levels (Ghannam et al., 1986).

Separate experiments on three main groups of rats, namely, non-diabetic, type I and type II diabetic rats were carried out (Okyar et al., 2001). The plant extracts were administered per os. Aloe vera leaf pulp and gel extracts were ineffective on lowering the blood sugar level of non-diabetic rats. Aloe vera leaf pulp extract showed hypoglycemic activity on type I and II diabetic rats and, the effectiveness being enhanced for type II diabetes in comparison with glibenclamide. On the contrary, Aloe vera leaf gel extract showed hyperglycemic activity on type II diabetic rats. It may therefore be concluded that the pulps of Aloe vera leaves devoid of the gel could be useful in the treatment of type II diabetes mellitus.

The evaluation of the presence of hypoglycemic activity in the alcoholic extract of Aloe vera gel demonstrated that Aloe vera extract maintained the

glucose homeostasis by controlling the carbohydrate metabolizing enzymes (Rajasekaran et al., 2004).

Diabetes mellitus impairs the memory function in experimental animals. Since the mammalian hippocampus and cerebral cortex play a pivotal role in a diverse set of cognitive functions, such as novelty detection and memory, the vulnerability of cortex and hippocampus regions of the brain to oxidative damage in STZ-diabetic mice was examined (Parihar et al., 2004) under the effect of extracts of Aloe vera on prevention of hippocampus and cortical cell degenerations after i.p. injection. It was concluded that impairments in the hippocampus and cortex in STZ-diabetic mice are associated with an increased free radical mediated oxidative damage and that the supplementation of aloe extracts showed preventive effects in attenuating oxidative damage in both brain regions possibly via antioxidative mechanisms.

Aloe barbadensis (Liliaceae)

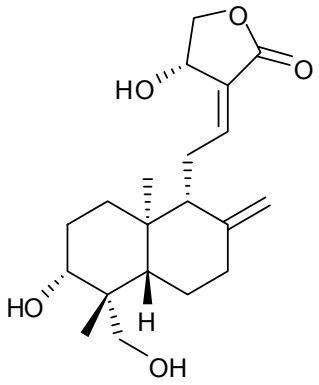
The acute and chronic effects of the extract of Aloe barbadensis leaves and its bitter principle were studied on plasma glucose levels of alloxan-diabetic mice (Ajabnoor 1990). Aloe barbadensis leaf extract was administered per os and the bitter principle was administered i.p. The hypoglycemic effect of a single per os dose on serum glucose level was insignificant whereas that of the bitter principle was very highly significant and extended over a period of 24 h. The hypoglycemic effect of the bitter principle may be mediated through stimulating synthesis and/or release of insulin from the β cells of Langerhans.

Andrographis paniculata (Burm. f.) Nees (Acanthaceae)

Andrographis paniculata is an annual herb commonly known as Kalmegh or ‘King of Bitters’, found throughout India and cultivated in many states of India. The anti-diabetic effect of a crude ethanolic extract of Andrographis paniculata in normal and STZ-diabetic rats was investigated (Zhang & Tan 2000). After per os administration it was found that it possesses antidiabetic property and that this antidiabetic effect may be attributed, at least in part, to increased glucose metabolism. Its hypotriglyceridemic effect is also beneficial in the diabetic state.

The antihyperglycemic action of andrographolide, an active principle in the leaves of Andrographis paniculata, was investigated in STZ-diabetic rats (Yu et al., 2003). Treatment of andrographolide decreased the plasma glucose concentrations of STZ-diabetic rats in a dose-dependent manner. Similar treatment with andrographolide also decreased the plasma glucose in normal rats and the maximum effect was more marked than that in STZ-diabetic rats.

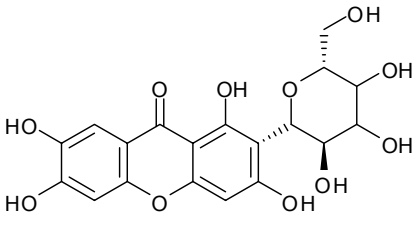
Andrographolide at the effective dose (1.5 mg/kg) significantly attenuated the increase of plasma glucose induced by an intravenous glucose challenge test in normal rats. In the isolated soleus muscle of STZ-diabetic rats, andrographolide enhanced the uptake of radioactive glucose in a concentration-dependent manner. Moreover, the mRNA and protein levels of GLUT4 in soleus muscle were increased after repeated i.v. administration of andrographolide in STZ-diabetic rats. These results suggested that andrographolide can increase the glucose utilization to lower plasma glucose in diabetic rats lacking insulin.



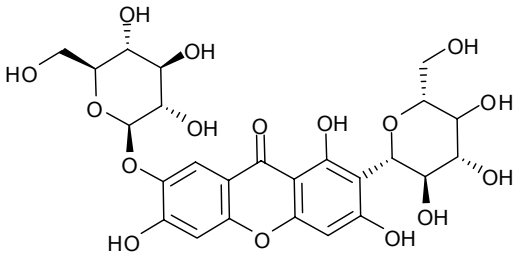
andrographolide

Anemarrhena asphodeloides (Liliaceae)

The rhizome of Anemarrhena asphodeloides has been used as a traditional Oriental medicine for diabetes (polyuria and polydipsia) and antidiabetic activity has been observed. The antidiabetic activity of the rhizome of Anemarrhena asphodeloides was investigated in KK-Ay mice, an animal model of genetic type II diabetes. (Miura et al., 2001). The water extract of the rhizome reduced blood glucose levels after per os administration and also tended to reduce serum insulin levels in the diabetic mice. Additionally, the treated diabetic mice had significantly reduced blood glucose levels in an insulin tolerance test. Based on these results, the antidiabetic mechanism of Anemarrhena asphodeloides water extract may be due to decreased insulin resistance. In addition, its active components were confirmed to be mangiferin and its glycoside.



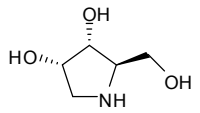
mangiferin



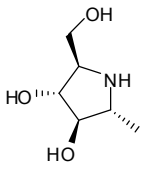
mangiferin-7-O-betaglucoside

Angylocalyx pynaertii (Leguminosae)

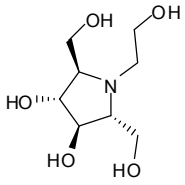
From the pod extract of Angylocalyx pynaertii 13 sugar-mimic alkaloids were isolated and the structures of the new alkaloids were found to be very specific inhibitors of alpha-L-fucosidase with no significant inhibitory activity towards other glycosidases (Yasuda et al., 2002). 1,4-dideoxy-1,4-imino-D-ribitol was found to be a better inhibitor of lysosomal beta-mannosidase than 2,5-imino-1,2,5-trideoxy-D-mannitol. N-Hydroxyethyl-1-deoxynojirimycin (miglitol), which is commercially available for the treatment of diabetes, retained its inhibitory potential towards rat intestinal maltase and sucrase, whereas N-hydroxyphenyl-1,4-dideoxy-1,4-imino-D-arabinitol and the synthetic N-hydroxyethyl derivative of 2,5-dideoxy-2,5-imino-D-mannitol had markedly lower inhibition towards all enzymes tested.



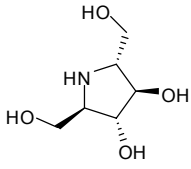
1,4-dideoxy-1,4-imino-D-ribitol



2,5-imino-1,2,5-trideoxy-D-mannitol



N-hydroxyethyl-1,4-dideoxy-1,4-imino-D-arabinitol



2,5-dideoxy-2,5-imino-D-mannitol

Annona squamosa L. (Annonaceae)

The claim by some tribal populations in parts of Northern India that the young leaves of the custard apple tree, Annona squamosa, has antidiabetic properties was investigated (Shirwaikar et al., 2004). Diabetes mellitus was induced with STZ-nicotinamide and graded doses of the aqueous leaf extracts were then administered in drinking water to normal and experimental diabetic rats. The findings of the study supported the antidiabetic claims of Annona squamosa. In addition, the leaf alcohol extract of the plant Annona squamosa was investigated for its antidiabetic activity in the same experimental model. The findings showed the significant antidiabetic potential of the extract in ameliorating the diabetic conditions in diabetic rats. No significant effects were found in the normal rats.

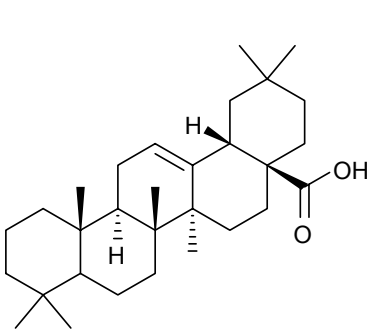
Apocynum venetum L. (Apocynaceae)

Luobuma tea, prepared from the leaves of Apocynum venetum, is a popular beverage in China. In a reported study (Yokozawa & Nakagawa 2004), the activity of Luobuma leaf extract and its components against the formation of AGEs, which are largely involved in the pathogenesis of

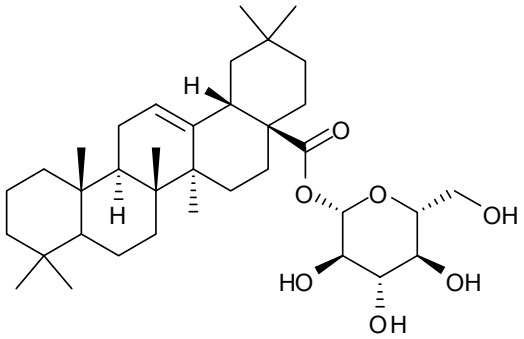
diabetic vascular complications, was examined. Strong in vitro inhibitory activity against the formation of AGEs was shown by Luobuma aqueous extract. Following further fractionation of this extract, polyphenolic compounds were isolated and these purified compounds also exerted inhibitory activities and were more potent than the positive control, aminoguanidine.

Aralia dasyphylla Miq (Araliaceae)

The structures of a triterpenoid and its glycoside were isolated from Aralia dasyphylla. Pharmacological experiments showed that the total saponins exerted preventative effect on CCl_4-induced liver injury of male mice and hypoglycemic effect on a model of alloxan-induced diabetic rats (Yi et al., 1997). Their structures have been identified to be oleanoic acid and oleanoic acid-28-O-beta-D-glucopyranoside.



oleanoic acid



oleanoic acid-28-O-beta-D-glucopyranoside

Phellodendron amurense Rupr (Rutaceae) and Aralia cortex (Araiaceae)

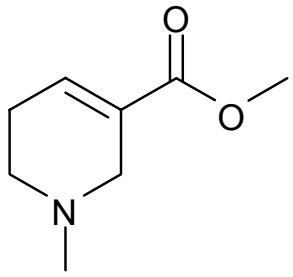
Enhanced activities of the polyol pathway and oxidative damage have been implicated in the pathogenesis of diabetic cataract. It was investigated whether these changes in diabetic lenses could be prevented by the water extract of Phellodendron cortex and Aralia cortex (P55A) (Lee et al., 1999). ALR2 activity was inhibited significantly by the treatment with P55A. Consequently, it caused a reduction in the high sorbitol contents observed in the lenses of diabetic rats. In addition, the greatly elevated content of thiobarbituric acid reactive substances and carbonylated protein in diabetic rats were reduced by P55A treatment. These results suggested that P55A extract exerts an antioxidant effect by reducing lipid peroxidation and protein carbonylation as well as having an inhibitory action against ALR2 in the lenses of diabetic rats.

Arctostaphylos uva-ursi (Ericaceae), Hydrastis canadensis (Ranunculaceae), Viscum album (Viscaceae), Artemisia dracunculus (Asteraceae)

Bearberry (Arctostaphylos uva-ursi), golden seal (Hydrastis canadensis), mistletoe (Viscum album), tarragon (Artemisia dracunculus) and an herbal mixture used for traditional treatment of diabetes were studied in STZ diabetic mice (Swanston-Flatt et al., 1989). These studies suggested that bearberry, golden seal, mistletoe and tarragon may counter some of the symptoms of STZ diabetes without, however, affecting glycemic control.

Areca catechu L. (Palmae)

The nut contains a large quantity of tannin, gallic acid, fixed oil gum, volatile oil, lignin and alkaloids like arecoline, arecain, guracine, etc. Arecoline was investigated and reported to have hypoglycemic activity in an animal model of diabetes upon s.c. administration (Chempakam 1993).



arecolin

Artemisia herba alba (Asteraceae)

Artemisia herba alba has been widely used in Iraqi folk medicine for the treatment of diabetes mellitus. Per os administration of an aqueous extract of the aerial parts of this plant to normoglycemic and to alloxan-diabetic rabbits produced significant hypoglycemic activity, which was consistent and time-dependent (Twaij & Al-Bahr 1988).

In another study, feeding diabetic rats and rabbits with the aqueous extract of the aerial parts of the plant led to a significant reduction in blood glucose levels, prevented the elevation of the glycosylated haemoglobin levels and possessed a hypoliposis (presence of an abnormally small amount of fat in the tissues) effect, in addition to the protection against body weight loss of diabetic animals (Al-Shamaony et al., 1994).

Artemisia pallens wall (Asteraceae)

It is a shrub used in the treatment of diabetes mellitus in the southern part of India. Per os administration of the methanol extract of the aerial parts of Artemisia pallens led to significant blood glucose lowering effect in glucose-fed hyperglycemic and alloxan-induced diabetic rats (Subramoniam et al., 1996). This effect of the extract was dose dependent. In fasted normal rats the extract caused a moderate hypoglycemic effect at a significant higher dose.

Artocarpus heterophyllus (Moraceae) and Asteracanthus longifolia (Amaranthaceae)

Investigations were carried out to evaluate the effects of hot-water extracts of Artocarpus heterophyllus leaves and Asteracanthus longifolia whole plant material on the glucose tolerance of normal human subjects and type II diabetic patients (Fernando et al., 1991). The extracts of both Artocarpus heterophyllus and Asteracanthus longifolia significantly improved glucose tolerance in the normal subjects and the diabetic patients.

Astragalus membranaceus (Leguminosae)

Astragalus membranaceus is a constituent of almost every herbal recipe used in China. A study was conducted so as to examine the effects of Astragalus polysaccharide, a component of an aqueous extract of Astragalus membranaceus roots, on PTP1B, a negative regulator of insulin-receptor signal transduction, and its potential role in the amelioration of insulin resistance (Yong et al., 2005). Astragalus polysaccharide enabled insulin-sensitizing and hypoglycemic activity at least in part by decreasing the elevated expression and activity of PTP1B in the skeletal muscles of type II diabetic rats.

Averrhoa bilimbi L. (Oxalidaceae)

A reported study was conducted in order to investigate the hypoglycemic and hypolipidemic activities of an ethanolic extract of Averrhoa bilimbi leaves in STZ-diabetic rats (Pushparaj et al., 2000). The derived data showed that Averrhoa bilimbi ethanolic extract has hypoglycemic, hypotriglyceridemic, anti-lipid peroxidative and anti-atherogenic properties in STZ-diabetic rats.

The possible mechanism of the hypoglycemic action of the semi-purified fractions of an ethanolic extract of Averrhoa bilimbi leaves in STZ-diabetic male Sprague-Dawley rats was examined (Purshparaj et al., 2001). The results

indicated that the extract is potent in the amelioration of hyperglycemia in STZ-diabetic rats and is a potential source for the isolation of new per os active agent(s) for anti-diabetic therapy.

Azardirachta indica (Meliaceae), Cassia auriculata (Fabaceae) and Momordica charantia (Curcurbiceae)

Diamed is an herbal formulation composed of the aqueous extracts of three medicinal plants (Azardirachta indica, Cassia auriculata and Momordica charantia). Diamed was investigated for its possible antihyperglycemic action in rats with alloxan-induced experimental diabetes (Ramakrishnan & Venkateswaran 2001). The results showed that per os administration of Diamed had antihyperglycemic action in experimental diabetes in rats.

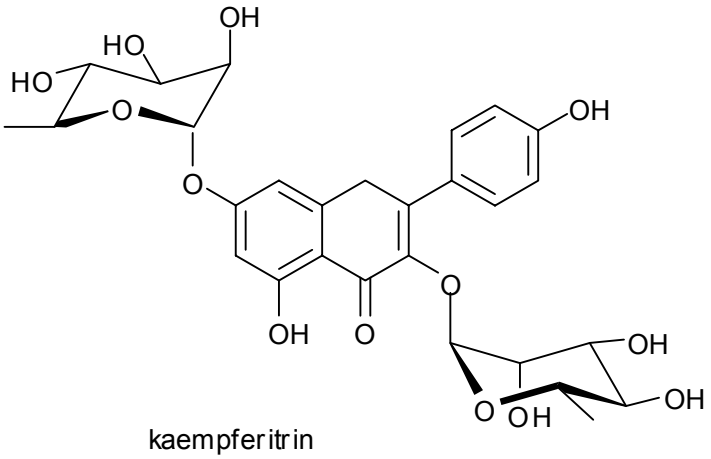
Bauhinia forficata L. (Leguminosae)

Bauhinia forficata, commonly known as 'paw-of-cow', is widely used in Brazil folk medicine for the treatment of diabetes mellitus. Numerous experiments have shown that a decoction of Bauhinia forficata leaves reduces the changes in carbohydrate and protein metabolism that occur in rats with STZ-induced diabetes. In one investigation, the serum activities of enzymes, known to be reliable toxicity markers, were monitored in normal and STZ-diabetic rats so as to discover whether the use of Bauhinia forficata decoction had toxic effects on liver, muscle or pancreas tissue or on renal system. It was found that per os administration of an aqueous decoction of Bauhinia forficata is a potential treatment for diabetes and did not produce toxic effects measurable with the enzyme markers used in the conducted study (Pepato et al., 2004).

Experimental diabetes was used to study the acute effect of the n-butanol fraction of Bauhinia forficata leaves on the serum glucose levels of rats (Silva et al., 2002). Per os administration of n-BuOH fraction led to a significant blood glucose-lowering effect in normal and diabetic rats. Treatment of normal and alloxan-induced diabetic rats decreased glucose levels, while this fraction was devoid of hypoglycemic effect in glucose-fed hyperglycemic normal rats.

Later, in vivo and in vitro treatments were carried out to investigate the effects of kaempferitrin, kaempferol-3,7-O-(alpha)-dirhamnoside, a major flavonoid compound of the n-butanol fraction from Bauhinia forficata leaves, on serum glucose levels, as well as its antioxidant potential (De Sousa et al., 2004). The hypoglycemic effect of kaempferitrin in STZ-diabetic rats was evident at all doses tested. The compound also showed high reactivity with the free radical 1,1-diphenyl-2-picryl hydrazyl (DPPH), inhibited

myeloperoxidase activity and decreased lipid peroxidation, induced by ascorbyl radical either in microsomes or in asolectin and phosphatidylcholine liposomes.



kaempferitrin

Bauhinia candicans Benth. (Leguminosae), Rubus ulmifolius Schott. (Rosaceae), Galega officinalis L. (Leguminosae) and Morus alba L. (Moraceae)

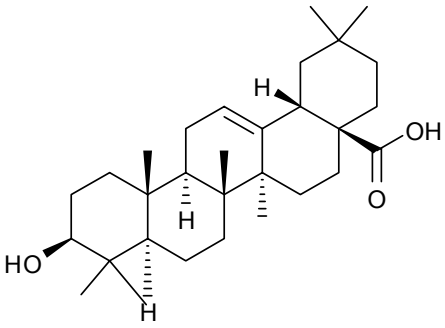
The hypoglycemic activity of a 20% dried leaf infusion of Bauhinia candicans, Galega officinalis, Morus alba and Rubus ulmifolius, used for diabetes in Chilean popular medicine, was evaluated in alloxan and STZ induced hyperglycemic rats (Lemus et al., 1999). Activity-guided fractionation of Rubus ulmifolius showed that petroleum ether extracts elicited a moderate hypoglycemic effect (35%) in the STZ induced model.

Beta vulgaris L. var. cicla (Chenopodiaceae)

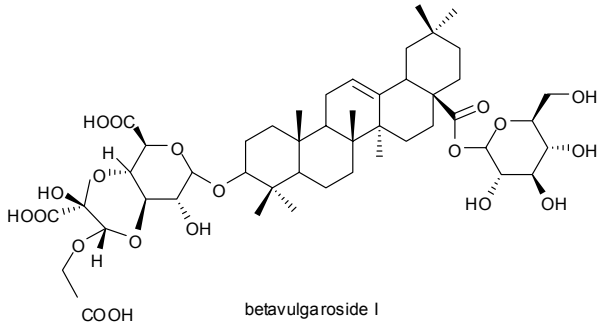
Beta vulgaris (Chard) is one of the plants used as hypoglycemic agent by diabetics in Turkey. The results from the studies indicate that the use of chard may be effective in preventing or at least retarding the development of some diabetic complications (Tunali et al., 1998).

Morphological and biochemical studies demonstrated that the extract of this plant when administered by gavage in experimental animals may reduce blood glucose levels by the regeneration of the β cells (Bolkent et al., 2000).

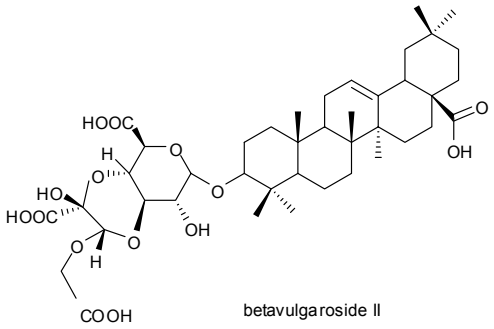
Betavulgarosides I, II, III, IV and oleanolic acid oligoglycosides were isolated from the roots of Beta vulgaris. Betavulgarosides II, III and IV produced hypoglycemic effects that was demonstrated by a per os glucose tolerance test in rats after their per os administration (Yoshikawa et al., 1996).



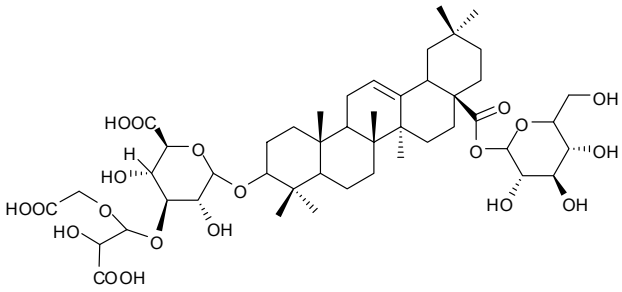
oleanolic acid



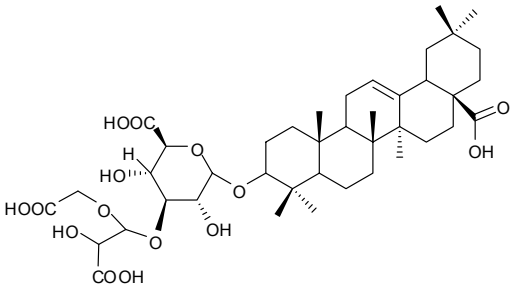
betavulgaroside I



betavulgaroside II



betavulgaroside III

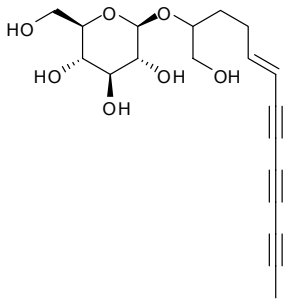


betavulgaroside IV

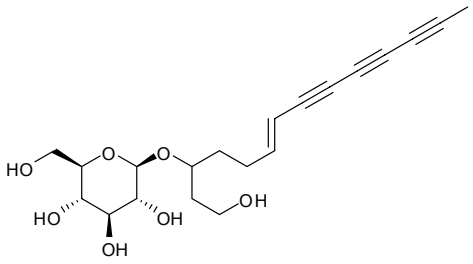
Bidens pilosa (Asteraceae)

Compelling evidence suggests that infiltrating CD4 type I helper T (Th1) cells in the pancreatic islets play a pivotal role in the progression of diabetes in non-obese diabetic mice. Treatment with a butanol fraction of Bidens pilosa suppressed the development of diabetes, helped to maintain levels of blood glucose and insulin in non-obese diabetic mice in a dose-dependent manner and elevated the serum IgE levels regulated by Th2 cytokines (Chang et al., 2004). Moreover, the butanol fraction inhibited the differentiation of naive helper T cells (Th0) into Th1 cells but enhanced their transition into type II helper T (Th2) cells using an in vitro T cell differentiation assay. Two polyacetylenic compounds identified from the butanol fraction also prevented the onset of diabetes, in a similar way with the butanol fraction. The latter compounds showed a stronger activity for T cell differentiation than the

former. In summary, the butanol fraction of Biderns pilosa and its polyacetylenes can prevent diabetes possibly via suppressing the differentiation of Th0 cells into Th1 cells and promoting that of Th0 cells into Th2 cells.



2-beta-D-glucopyranosyloxy-1-hydroxy-5(E)-tridecene-7,9,11-triyne



3-beta-D-glucopyranosyloxy-1-hydroxy-6(E)-tetradecene-8,10,12-triyne

Biophytum sensitivum (Oxalidaceae)

Biophytum sensitivum is an annual herb found throughout tropical India and used in traditional folk medicine for the treatment of hyperglycemic patients. The effect of the leaf extract of Biophytum sensitivum, after per os administration, was studied on glucose homeostasis in rabbits (Puri 2001). The observations suggest that the hypoglycemic response of Biophytum sensitivum may be mediated through stimulating the synthesis/release of insulin from the β cells of Langerhans.

Bixa orellana (Bixaceae)

Various plants are used in Caribbean folklore for the treatment of a variety of illnesses including diabetes mellitus. Preliminary investigations of several crude plant extracts (Russel et al., 2005) have indicated that Bixa orellana (annatto), among others, does actually exhibit hypoglycemic properties.

Boerhavia diffusa (Nyctaginaceae)

Boerhavia diffusa is a common plant that grows widely in the tropics in both dry and rainy seasons in India. A study was designed to investigate the antihyperlipidemic activity of an aqueous extract of Boerhavia diffusa leaves in alloxan diabetic rats (Pari & Satheesh 2004). Hyperlipidemia is an associated complication of diabetes mellitus. Per os administration of Boerhavia diffusa leaf extract resulted in significant reduction in serum and tissue cholesterol, free fatty acids, phospholipids, and triglycerides. Moreover, its

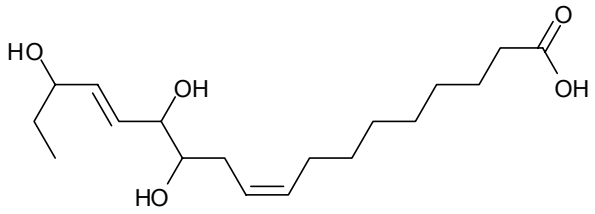
supplementation was found to be more effective than glibenclamide in the treatment of diabetic rats.

Brassica juncea (Brassicaceae)

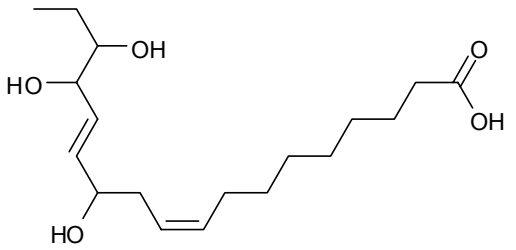
Brassica juncea seeds are consumed in India as a spice (Leaf Moustard) in various food items. Studies showed a hypoglycemic effect of this plant, when added in the diet, in diabetic rats (Grover et al., 2002).

Bryonia alba L. (Curcubiaceae)

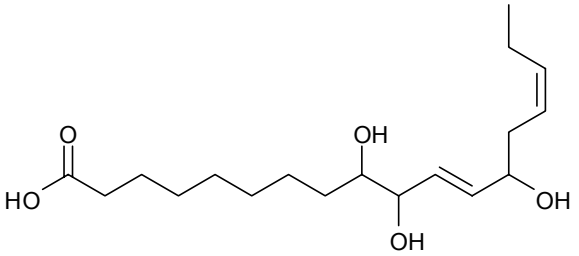
Bryonia alba is a native Armenian medicinal plant. The i.m. administration of trihydroxyoctadecadienoic acid and its derivatives obtained from the roots of the native Armenian plant Bryonia alba was found to restore the disordered lipid metabolism of alloxan-diabetic rats (Karageuzyan et al., 1998). These derivatives of trihydroxyoctadecadienoic acid can correct major metabolic abnormalities typical of severe diabetes mellitus they can influence the profile of the formation of stable prostaglandins by actions such as downstream of prostaglandin endoperoxides.



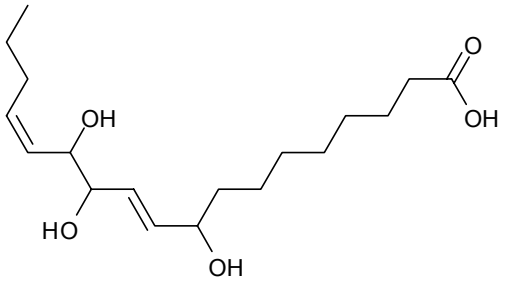
12,13,16-trihydroxy-9Z,14E-octadecadienoic acid



12,15,16-trihydroxy-9Z,13E-octadecadienoic acid



9,10, 13-trihydroxy-11E,15Z-octadecadienoic acid

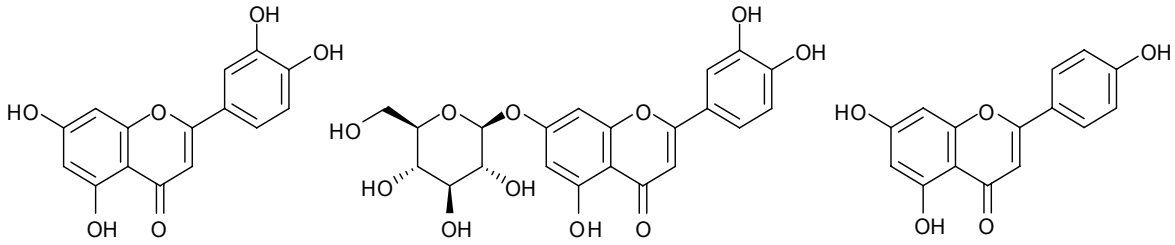


9,12,13-trihydroxy-10E,14Z-octadecadienoic acid

Buddleja officinalis (Loganiaceae)

The inhibitory effects of nine crude extracts were tested on unpurified rat lenses ALR2, an enzyme involved in the complications of diabetes (Matsuda et al., 1995). Among the crude extracts, a 70% methanolic extract of Buddlejae

Flos (flower of Buddleja officinalis) exhibited the highest inhibition. Luteolin, luteolin-7-O-beta-D-glucopyranoside, and apigenin isolated from Buddlejae Flos showed inhibitory activity.

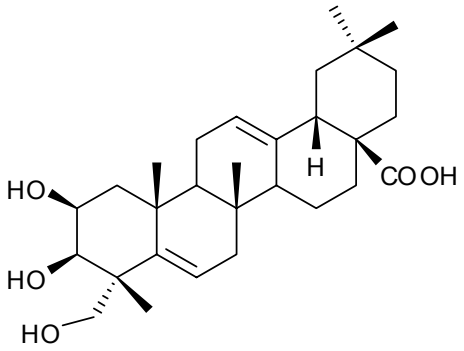


It was suggested that the inhibitory effect of Buddlejae Flos on ALR2 is partially attributable to these flavonols or their glycosides.

Bumelia sartorum (Sapotaceae)

Bumelia sartorum has been mentioned in Brazilian folklore for its reputed use in the treatment of diabetes mellitus and inflammatory disorders. An ethanol extract of root bark elicited a hypoglycemic effect in normal and alloxan-induced diabetic rats (Almeida et al., 1985). In addition, the extract altered glucose tolerance in alloxan-induced diabetic rats, enhanced glucose uptake in skeletal muscle and significantly inhibited glycogenolysis in the liver. These results indicated that the hypoglycemic effect may be similar to chlorpropamide and possibly due to an enhanced secretion of insulin from the islets of Langerhans or an increased utilization of glucose by peripheral tissues. Besides hypoglycemic activity, the ethanol extract also elicited significant anti-inflammatory activity, but did not show any significant effects on blood pressure, respiration or on the various isolated tissue preparations studied.

Bassic acid, an unsaturated triterpene acid isolated from an ethanol extract of Bumelia sartorum root bark, elicited significant hypoglycemic activity in alloxan-diabetic rats and altered the pattern of glucose tolerance in these animals when administered per os (Naik et al., 1991). In addition, bassic acid treatment increased significantly the glucose uptake process and glycogen synthesis in isolated rat diaphragm. Bassic acid treatment increased plasma insulin levels significantly in alloxan-diabetic rats. It was therefore suggested that the hypoglycemia activity of bassic acid may be mediated through enhanced secretion of insulin from the pancreatic β cells.



bassic acid

Caesalpinia bonducella fleming (Leguminosae)

Caesalpinia bonducella is a shrub widely distributed throughout the coastal region of India. The tribal people of India use it for controlling the levels of blood glucose. Hypoglycemic, antihyperglycemic and hypolipidemic activities of the aqueous and 50% ethanolic extracts of Caesalpinia bonducella Fleming (Leguminosae) seeds were studied in normal and STZ-diabetic rats after per os administration (Sharma et al., 1997). The results suggested that Caesalpinia bonducella seeds possess an antidiabetic principle and can be useful for the treatment of diabetes.

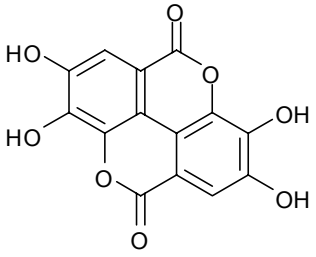
Its seed kernels are used in the management of diabetes mellitus, in the folklore medicine of India as well as the Caribbean Islands. The seed kernel powder was reported to have hypoglycemic activity in experimental animals (Parameshwar et al., 2002). Four extracts (petroleum ether, ether, ethyl acetate and aqueous) of the seed kernels were prepared and tested for their hypoglycemic potentials in normal as well as in alloxan induced diabetic rats. The extracts were administered per os to the experimental animals. In normal rats, only ethyl acetate and aqueous extracts showed hypoglycemic effect, compared to that of glibenclamide. In diabetic rats, both the polar extracts (ethyl acetate and aqueous) as well as glibenclamide, showed significant hypoglycemic effect, besides, reversing the diabetes induced changes in lipid and liver glycogen levels. As far as the non-polar extracts were concerned, the ether extract showed a marginal antidiabetic activity, while the petroleum ether extract failed to show any. Since both the polar extracts were found to contain triterpenoidal glycosides, it was presumed that they might be the active principles contributing to the antidiabetic actions.

A detail study with the aqueous and ethanolic extracts of the seeds of this plant was undertaken in both type I and II diabetes mellitus in rats (Chakrabarti et al., 2003). Significant blood sugar lowering effect of

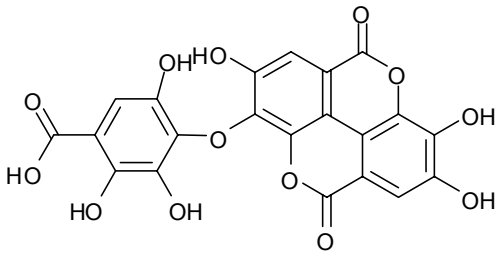
Caesalpinia bonducella was observed in type II diabetic model. Special emphasis was given on the mechanistic study by the gut absorption of glucose and the levels of liver glycogen.

Caesalpinia ferrea Mart (Leguminosae)

Caesalpinia ferrea, called as "Juca", is one of the medicinal plants in Brazil used for the treatment of diabetes. From the fruits of this plant, ellagic acid and 2'-(2,3,6-trihydroxy-4-carboxyphenyl)ellagic acid have been isolated as ALR2 inhibitors (Ueda et al., 2004). Ellagic acid is distributed in fruits and vegetables, so it is suggested that taking them might contribute to the relief of the long-term diabetic complications.



ellagic acid



2'-(2,3,6-trihydroxy-4-carboxyphenyl)ellagic acid

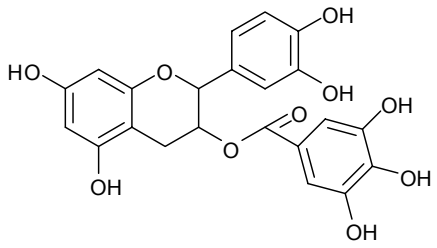
Calamintha officinalis Moench (Lamiaceae)

The results of a reported study clearly demonstrated the hypoglycemic effect of this plant extract in both normal and STZ-diabetic rats (Lemhadri et al., 2004). In addition, no changes were observed in basal plasma insulin concentrations after per os treatment with this plant in normal or STZ diabetic rats, indicating that the underlying mechanism of the plant's pharmacological action seems to be independent of insulin secretion. It was concluded that the aqueous Calamintha officinalis extract exhibited a significant hypoglycemic effect in normal and STZ-diabetic rats without affecting basal plasma insulin concentrations, and supported, therefore, its traditional use by the Moroccan population.

Camellia sinensis (Theaceae)

Camellia sinensis, commonly known as tea, is a small evergreen tree. Native to Southeast Asia, from Sri Lanka and India to Nepal and China, tea has been planted widely in tropical and subtropical areas. The blood glucose lowering activity of Camellia sinensis was studied by many workers. It has recently been

reported that the major green tea polyphenolic constituent, epigallocatechin 3-gallate, mimics the cellular effects of insulin including the reductive effect on the gene expression of rate-limiting gluconeogenic enzymes in a cell culture system (Koyama et al., 2004). Per os administration of green tea that contains this polyphenolic constituent caused a reduction in the levels of mRNAs for gluconeogenic enzymes, PEPCK and G6Pase in the mouse liver. Epigallocatechin 3-gallate alone was also found to down-regulate the gene expression of these enzymes in vitro. The results of this study support the idea that green tea intake may be beneficial in the prevention of diabetes mellitus.



epigallocatechin-3-O-gallate

Carum carvi (Umbelliferae) and Capparis spinosa L. (Capparidaceae)

The hypoglycemic effect of aqueous extracts of Carum carvi and Capparis spinosa L. fruits were investigated in normal and STZ-diabetic rats (Lemhadri et al., 2004). It was concluded that the aqueous extracts after per os administration of both plants exhibit a potent anti-hyperglycemic activity in STZ-diabetic rats without affecting basal plasma insulin concentrations.

Acacia Arabica (Minocaceae) and Caralluma edulis (Apocynaceae)

From a reported study it was concluded that the powdered seeds of Acacia Arabica and Caralluma edulis, when administered per os to normal and alloxan diabetic rabbits, acted by initiating the release of insulin from pancreatic β cells (Wadood et al., 1989).

Luffa aegyptiaca (Cucurbitaceae) and Carissa edulis (Appocynaceae)

The effect of the per os administration of the ethanolic extracts of Luffa aegyptiaca (seeds) and Carissa edulis (leaves) was investigated on blood

glucose levels both in normal and STZ-diabetic rats (El-Fiky et al., 1996). Treatment with both extracts significantly reduced the blood glucose level in STZ-diabetic rats during the first three hours of treatment. Luffa aegyptiaca extract decreased blood glucose level with a potency similar to that of the biguanide and metformin.

Cassia tora (Fabaceae)

Cassia tora fiber supplement consisting of soluble fiber extracted from Cassia semen, a-tocopherol, ascorbic acid and maltodextrin was formulated in a pack, and given to 15 type II diabetic subjects with certain treatment instructions. According to the obtained results, Cassia tora supplements can help to improve serum lipid levels in type II diabetic subjects without serious adverse effects (Sung-Hee et al. 1988).

Cassia alata (Fabaceae)

The per os effectiveness of Cassia alata leaf extract on STZ-induced hyperglycemia in rats has been studied and the results were compared with glybenclamide (Palanichamy et al., 1988). While the extract has no effect on glucose levels in normoglycemic animals, it reduced the blood sugar value in STZ-induced hyperglycemic animals.

Cassia auriculata (Fabaceae)

In experimental diabetes, enzymes of glucose and fatty acid metabolism are markedly altered. Persistent hyperglycemia is a major contributor to such metabolic alterations, which lead to the pathogenesis of diabetic complications. The reported study was designed to study the effect of Cassia auriculata flower extract on hepatic glycolytic and gluconeogenic enzymes and STZ-diabetic rats were given the plant's extract per os for 30 days. (Latha & Pari 2003). In conclusion, the observations showed that the aqueous extract possessed an antihyperglycemic effect and suggested that enhanced gluconeogenesis during diabetes is shifted towards normal and that the extract enhanced the utilization of glucose through increased glycolysis. The effect of the extract was more prominent than that of glibenclamide.

Catharanthus roseus L. (Apocynaceae)

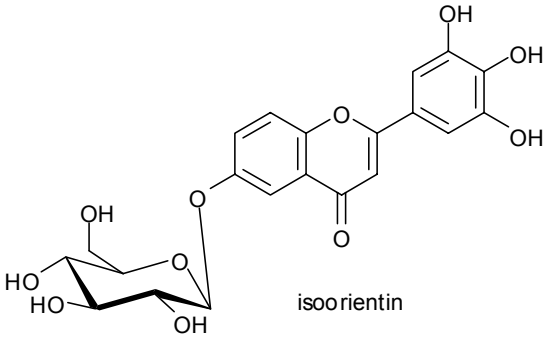
The leaf juice or water decoction of Catharanthus roseus is used as a folk medicine for the treatment of diabetes all over the world. Therefore the leaf

juice of Catharanthus roseus has been evaluated for its hypoglycemic activity in normal and alloxan-induced diabetic rabbits when administered i.v. (Nammi et al., 2003; Satyanarayana et al., 2003). The results indicated a prolonged action in reduction of blood glucose and the mode of action of the active compound(s) of Catharanthus roseus is probably mediated through enhance secretion of insulin from the β cells of Langerhans or through an extrapancreatic mechanism. The reported study clearly indicated a significant antidiabetic activity with the leaf juice of Catharanthus roseus and supported the traditional usage of the fresh leaves by Ayurvedic physicians for the control of diabetes.

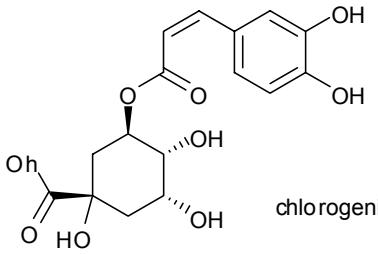
Hypoglycemic activity was detected in dichloromethane:methanol extract (1:1) of leaves and twigs of Catharanthus roseus using STZ-diabetic rat model when administered per os (Singh et al., 2001). The results indicated an increased rate of glucose metabolism in treated rats. Increased levels of lipid peroxidation measured as 2-thiobarbituric acid reactive substances indicative of oxidative stress in STZ-diabetic rats were also normalized by treatment with the extract.

Cecropia obtusifolia Bertol. (Cecropiaceae)

Cecropia obtusifolia has been widely used in Mexican traditional medicine for the control of type II diabetes. The hypoglycemic effects of a single oral dose of water and butanolic extracts prepared from leaves of Cecropia obtusifolia were examined in STZ-diabetic rats (Andrade-Cetto & Wiedenfeld 2001). A hypoglycemic effect to the tested extracts was found. The flavones, isoorientin and 3-caffeoylquinic acid (chlorogenic acid), were isolated as the important constituents of the plant and were identified as the main constituents in both extracts, too.



isoorientin



chlorogenic acid

Based on the European type II diabetes criteria, only patients with poor response to the conventional treatment were selected for the reported study (Herrera-Arellonoa et al., 2004). All patients maintained their medical

treatment and also received a prepared infusion of the dry leaves of the plant for 21 days treatment. The obtained results showed that the infusion prepared with the leaves of Cecropia obtusifolia produced beneficial effects on carbohydrate and lipid metabolisms when it was administered as an adjunct on patients with type II diabetes with poor response to conventional medical treatment.

Cecropia obtusifolia and Cetropia peltata.(Cecropiaceae)

The hypoglycemic effect of methanol leaf extracts from Cecropia obtusifolia and Cecropia peltata was evaluated in healthy mice after per os administration (Nicasio et al., 2005). The results suggested that Cetropia peltata is a better hypoglycemic agent than Cetropia obtusifolia, and it could be considered for developing a phytomedicinal product to carry out clinical trials.

Chamaemelum nobile (Compositae)

Per os administration of the aqueous extract of Chamaemelum nobile exhibited a significant hypoglycemic effect in normal and STZ-diabetic rats without affecting plasma insulin concentrations and support, therefore, its traditional use by the Moroccan population (Lemhadri et al., 2005).

Cinnamomum cassia, Cinnamomum zeylanicum (Lauraceae)

Rats were treated per os with Cinnamomum cassia bark or extracts from Cinnamomum cassia and zeylanicum in order blood glucose and plasma insulin levels to be evaluated (Verspohl et al., 2005). The cassia extract was superior to the zeylanicum extract. The cassia extract was slightly more efficacious than the equivalent amount of Cassia bark. A decrease in blood glucose levels was observed in a glucose tolerance test, whereas it was not observed in rats that were not challenged by a glucose load. The elevation in plasma insulin was direct since a stimulatory in vitro effect of insulin release from INS-1 cells (an insulin secreting cell line) was observed. Thus the cassia extract could have a direct antidiabetic potential.

Cinnamomun zeylanicum (Lauraceae) and Olea europaea (Oleaceae)

The effects of cinnamon bark and olive leaf extracts have been investigated on STZ-induced tissue injury, as well as some biochemical and haematological changes in rats (Onderoglu et al., 1999). The effects on

glycemia were also evaluated. The data indicated that long-term use of olive leaf and cinnamon bark may provide beneficial effects against diabetic conditions. Determination of the underlying mechanism(s) of these beneficial effects, toxicity to other systems and clinical assessments of related plant materials are major topics requiring further studies.

Cissus sicyoides (Vitaceae)

Leaf decoctions of Cissus sicyoides (princess vine) are used widely as a popular remedy for diabetes mellitus in Brazil, where its common name is "vegetal insulin, cipo-puca, anil-trepador, cortina, and insulina". Therefore it was determined whether it has anti-diabetic effects to normal and STZ-diabetic rats, and the effects of this treatment were investigated on the physiological and metabolic parameters that are altered in diabetic animals (Pepato et al., 2003). The decoction treatment significantly reduced the intake of both food and fluids and the volume of urine excreted, as well as the levels of blood glucose, urinary glucose and urinary urea, in comparison with controls. Lipid metabolism was not affected by the treatment; nor was the levels of hepatic glycogen in diabetic animals, which indicated that the mechanism implicated in the improvement in carbohydrate metabolism, observed in animals treated with the decoction, could not involve inhibition of glycogenolysis and/or stimulation of glycogenesis. The fact that normal animals treated with Cissus sicyoides exhibited no changes in any of the measured parameters suggested that its mode of action in diabetic animals does not resemble those of sulphonylurea or insulin. It may, however, act in a similar way to biguanide, via inhibition of gluconeogenesis.

In another study, the hypoglycemic and anti-lipemic effects of the per os administered aqueous extract prepared from fresh leaves of the plant was studied. Additionally, hepatic enzyme levels were also determined (Viana et al., 2004). The results justified the popular use of Cissus sicyoides, pointing out to the potential benefit of the plant aqueous extract in alternative medicine, in the treatment of type II diabetes mellitus.

Citrullus colocynthis (Cucurbitaceae)

The effects of the aqueous, glycosidic, alkaloidal and saponin extracts of the rind of Citrullus colocynthis on the plasma glucose levels were investigated in normal rabbits, while the effects of saponin extracts on the fasting plasma glucose levels were studied in alloxan induced diabetic rabbits (Abdel-Hassan et al., 2000). The results suggested that per os administration of the aqueous extract of the rind of Citrullus colocynthis possessed a

hypoglycemic effect and its hypoglycemic action could be attributed mainly to the presence of saponin, in addition to the presence of glycosidic components.

Loranthus begwensis (Loranthaceae), Citrus limon (Rutaceae), Vernonia amygdalina (Compositae)

The effect of an aqueous extract of African mistletoe (Loranthus begwensis) from two host plants (Citrus limon or Vernonia amygdalina) was studied in male Wistar rats treated per os (Obatomi et al., 1998). Mistletoe extract, irrespective of the host plant, appears to lower the blood sugar levels offering the potential for clinical use of ingredients of its extracts.

Clausena anisata Hook (Rutaceae)

A study was designed to examine the hypoglycemic effect of Clausena anisata root methanolic extract in normal (normoglycemic) and in STZ-diabetic rats (Ojewole 2002). While it is possible that the hypoglycemic effect of the plant extract may be due, at least in part, to its terpenoid and coumarin contents, the mechanism of its hypoglycemic action remaines largely speculative, and is unlikely to be due to the stimulation of pancreatic β cells and subsequent secretion of insulin. Although Clausena anisata root methanolic extract was less potent than insulin as an antidiabetic agent, the results of this experimental animal study indicated that the herb possessed hypoglycemic activity; and thus lend credence to the suggested folkloric use of Clausena anisata root in the management and/or control of type II diabetes mellitus in some communities of South Africa.

Cleome droserifolia (Capparidaceae)

The mechanism of the hypoglycemic effect of the plant Cleome droserifolia was studied in a group of albino rats rendered glucose intolerant by tetracycline induced fatty liver, and compared with normal control rats (Nicola et al., 1996). This plant might prove to have a promising therapeutic value in the treatment of diabetes mellitus because not only possessed a postprandial hypoglycemic effect but also suppressed the hepatic glucose release in the fasting state in a comparable way to this of insulin. The plant also possessed a hypocholesterolemic effect, most pronounced on the LDL cholesterol.

Cnidium officinale Makino (Apiaceae) and Tabanus fulvus Meigan (Tabanidae)

This study described a potent activity of Cnidium officinale Makino (Cnidii rhizome) and Tabanus fulvus Meigan (Tabanus) as an inhibitor of high glucose-induced proliferation of glomerular mesangial cells (GMCs) (Jeong et al., 2005). The results indicated that Cnidii rhizome and Tabanus inhibited the high glucose-induced proliferation of GMCs partially through TGF-beta1 production, suggesting that these natural products may be promising agents for treating the development and progression of diabetic glomerulopathy.

Coccinia indica (Cucurbitaceae)

Administration of Coccinia indica leaf extract, an indigenous plant used in Ayurvedic medicine in India, to normal and STZ-diabetic animals exhibited significant hypoglycemic and antihyperglycemic effect and reversed the associated with diabetes biochemical alterations (Venkateswaran & Pari 2002). The results indicated that the per os administration of Coccinia indica leaf extract to diabetic animals normalized blood glucose and caused marked improvement of altered carbohydrate metabolizing enzymes during diabetes.

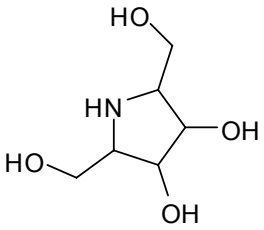
The antioxidant effects of an ethanolic extract of Coccinia indica leaves was studied in STZ-diabetic rats (Venkateswaran & Pari 2003). Per os administration of Coccinia indica leaf extract resulted in a significant reduction in thiobarbituric acid reactive substances and hydroperoxides and a significant increase in reduced GSH, SOD, CAT, glutathione peroxidase and glutathione-S-transferase in liver and kidney of STZ-diabetic rats, which clearly showed the extract's antioxidant property.

Cogniauxia podoleana Baillon (Cucurbitaceae)

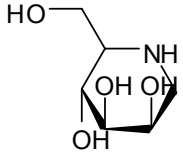
Cogniauxia podoleana leaves are used in Congolese traditional medicine for the treatment of diabetes mellitus. Based on an increasing number of reports on blood glucose level reduction associated with some saponins and flavonoids isolated from medicinal plants, the hypoglycemic and antihyperglycemic effects of flavonoid and saponin fractions of the plant administered per os were investigated on normal and alloxan-induced diabetic rats (Diatewa et al., 2004). The obtained data confirm the antidiabetic activity of the leaves of Cogniauxia podoleana for diabetes mellitus treatment. However, it was important to note that the antihyperglycemic action could not be attributed to the presence of flavonoids because contamination was detected (amino acids, carbohydrates and other compounds) in the diethyl ether fraction containing flavonoids.

Commelina communis (Commeliaceae)

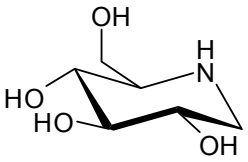
A methanolic extract of Commelina communis showed potent inhibitory activity against alpha-glucosidase (Kim et al., 1999). One pyrrolidine alkaloid, 2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine and four piperidine alkaloids, 1-deoxymannojirimycin, 1-deoxynojirimycin, alpha-homonojirimycin and 7-O-beta-D-glucopyranosyl alpha-homonojirimycin were isolated. These compounds have been identified for the first time from Commelina communis, supporting the pharmacological basis of this plant that has been used as a traditional herbal medicine for the treatment of diabetes.



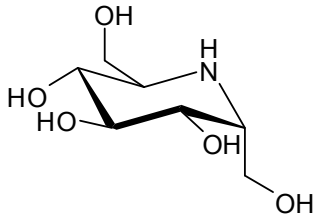
2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine



1-deoxymannojirimycin



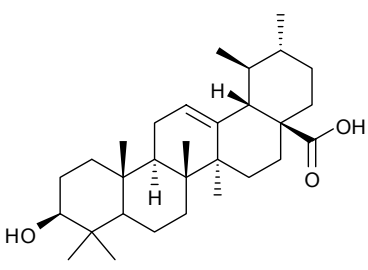
1-deoxynojirimycin



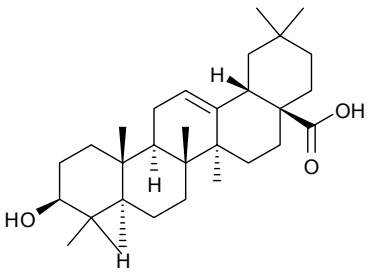
alpha-homonojirimycin

Cornus officinalis Sieb (Cornaceae)

The pulps of Cornus officinalis are a traditional tonic with medicinal positive action on the liver and kidney. According to a reported study fructus had potent anti-diabetic activity towards STZ-diabetic rats when given per os (Yamahara et al., 1981). Ursolic acid and oleanolic acid, found in the extract, were proposed as the main chemical entities responsible for the activity.



Ursolic acid



oleanolic acid

It was also demonstrated, in another study. that an alcoholic extract of Cornus officinalis could increase GLUT4 mRNA and its protein expression in diabetic rats through promoting proliferation of β cells and increasing postprandial secretion of insulin, and therefore accelerating glucose transport (Qian et al., 2001).

Coscinium fenestratum Colebr (Menispermaceae)

The antidiabetic potential of the alcoholic stem extract of Coscinium fenestratum, a medicinal plant widely used in the traditional Ayurveda and Siddha systems of medicine for the treatment of diabetes mellitus was evaluated in the STZ-diabetic model (Shirwaikar et al., 2005). Significant results were observed in the measured parameters, thereby justifying the use of the plant as a pharmacotherapeutic remedy.

Coscinium fenestratum (Menispermaceae)

Alcoholic extracts of the stems of Coscinium fenestratum, a medicinal plant indigenous in India and Sri Lanka used in ayurveda and siddha medicine for treating diabetes, was studied for its carbohydrate metabolism effect and antioxidant status in STZ-diabetic rats (Punitha et al., 2005). Per os administration of Coscinium fenestratum stem alchoholic extracts in gradually increased doses caused a significant increase in antioxidant enzymes such as CAT, SOD, glutathione synthetase, peroxidase, and glutathione peroxidase. It also increased the levels of nonenzymatic antioxidant compounds such as ascorbic acid, ceruloplasmin and tocopherol. Effects of the alcoholic extracts on glycolytic enzymes such as glucose-6-phosphate dehydrogenase, lactate dehydrogenase and HK showed a significant increase in their levels, whereas a significant decrease was observed in the levels of gluconeogenic enzymes, G6Pase and alanine aminotransferase in treated diabetic rats. Serum creatinine and urea levels were also significantly declined. This investigation demonstrated promising antidiabetic activity of Coscinium fenestratum.

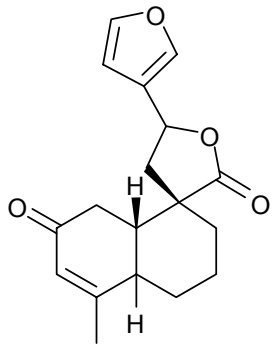
Costus speciosus (Costaceae), Nephrolepsis tuberosa (Nephrolepidaceae) and Stephania hernandifolia (Menispennaceae)

The rhizome of Costus speciosus, the tuber of Nephrolepsis tuberosa, and the bulb of Stephania hernandifolia, used by the local people and traditional healers in the Eastern Himalayan belt, were studied for their effects on serum

glucose levels in nondiabetic and diabetic rat models at different prandial states (Mosihuzzaman et al., 1994). The results indicated that these three plants have interesting possibilities as a source of per os hypoglycemic agents.

Croton cajucara (Euphorbiaceae)

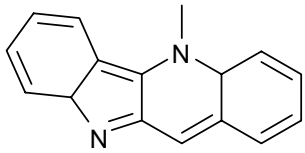
Trans-Dehydrocrotonin (t-DCTN), a 19-nor-clerodane diterpene isolated from the bark of Croton cajucara demonstrated a significant hypoglycemic activity in alloxan-induced diabetic rats, but not in normal rats (Farias et al., 1997). The above mentioned compound also effectively lowered the blood sugar levels in glucose fed normal rats. The hypoglycemic effect of t-DCTN was almost comparable to that produced by glibenclamide, a clinically used drug. The results indicated the antihyperglycemic potential of t-DCTN.



trans-hydrocortin

Cryptolepis sanguinolenta (Asclepiadaceae)

Cryptolepine, an indoloquinolone alkaloid isolated from Cryptolepis sanguinolenta, was found to significantly lower glucose when given per os to a mouse model of diabetes (Luo et al., 1998). The antihyperglycemic effect of cryptolepine leaded to a significant decline in plasma insulin concentration, associated with evidence of an enhancement in insulin-mediated glucose disposal. Finally, cryptolepine increased glucose uptake by 3T3-L1 cells.



cryptolepine

Cucurbita ficifolia (Curcurbitaceae)

In Mexico, this plant is consumed widely and several dishes and candies are prepared with its seeds or fruit and its consumption is related to the treatment of diabetes (the healers recommend the ingestion of the fruit macerated in water). Acute hypoglycemic effects of freeze-dried juice of Cucurbita ficifolia fruits were studied in healthy and alloxan-diabetic mice and when the juice was administered by i.p. route it showed an acute hypoglycemic effect in alloxan-diabetic mice (Alarcon-Aguilar et al., 2002). In addition, daily per os administration of this preparation showed a highly significant normalization of the glycemia.

Cuminum nigrum (Apiaceae)

The seeds of Cuminum nigrum were screened phytochemically and were found to contain 8% flavonoids and 0.01% alkaloids. When studied for their effect on blood glucose levels in normoglycemic and alloxan diabetic rabbits after per os administration, the obtained data indicated that the total flavonoid contents of Cumimum nigrum seeds exhibited considerable hypoglycemic activity and may therefore be responsible for the reported antidiabetic activity of the seeds (Ahmad et al., 2000). Furthermore, it was conceivable that the Cuminum nigrum flavonoids possessed insulin-inducing properties.

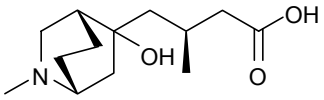
Dendrobium candidum (Orchidaceae)

According to reported data, Dendrobium candidum do not decrease the serum glucose concentrations and insulin levels in normal mice (Wu et al., 2004). However, it could increase serum insulin levels and decrease serum glucagons concentrations in STZ-diabetic rats. The results of immunohistochemical stain demonstrated that the number of islet β cells was increased and that of islet α cells was decreased in STZ-diabetic rats. It could also decrease the serum glucose concentrations and increase liver glucogen contents in adrenaline-induced hyperglycemic mice. Dendrobium candidum has obvious anti-hyperglycemic effects in adrenaline-induced hyperglycemic mice and STZ-diabetic rats. Its mechanism of action probably involves the stimulation of the secretion of insulin from β cells and the inhibition of the secretion of glucagons from α cells and it can probably decrease the decomposition of liver glucogen and increase the synthesis of liver glucogen.

Dioscorea dumetorum (Dioscoreaceae)

Whereas the alkaloid-containing fraction was hypoglycemic in fasting normal mice, the whole extract and the fractions containing steroidal derivatives showed significant hypoglycemic activities in fasting normal mice or rabbits and in fasting alloxan-diabetic rabbits (Undie & Akubue 1986). The hypoglycemic action of the glycosidic portion, in particular, was prompt and potent in normal as well as in severely alloxan-diabetic rabbits, suggesting thereby, the possibility of obtaining a compound that could act in conditions of even severe insulin lack.

Dioscoretine, isolated from the methanol extract of Dioscorea dumetorum tubers, when administered i.p. to normal and alloxan diabetic rabbits produced significant hypoglycemic effects and the hypoglycemic effects were compared to those of tolbutamide (Iwu et al., 1990).



dioscoretine

Eclipta alba (Asteraceae)

Eclipta alba, an indigenous medicinal plant, has a folk (Siddha and Ayurvedha) reputation in rural southern India as a hypoglycemic agent. The reported study on alloxan diabetic rats clearly showed that the per os administration of Eclipta alba possessed potent antihyperglycemic activity (Ananthi et al., 2003).

Terminalia chebula (Compretaceae), Terminalia belerica (Compretaceae) and Emblica officinalis (Euphorbiaceae)

Methanolic extracts of Terminalia chebula, Terminalia belerica, Emblica officinalis and their combination named 'Triphala' (equal proportion of the above three plant extracts) are being used extensively in Indian system of medicine for atherosclerosis, cancer, diabetes and liver cirrhosis. They were found to inhibit lipid peroxide formation and to scavenge hydroxyl and superoxide radicals in vitro (Sabu & Kuttan 2002).

Enicostemma littorale Blume (Gentianaceae)

Pills prepared from Enicostemma littorale were administered to 84 patients with type II diabetes for three months (Umesh et al., 2004).

Estimation of various biochemical parameters showed that Enicostemma littorale reduced blood glucose as well as serum insulin levels and prevented the progression of the long-term complications in diabetic patients. Significant improvement in kidney function, lipid profile and blood pressure was observed suggesting that Enicostemma littorale is an effective antidiabetic herbal.

The whole plant aqueous extract was tested for its hypoglycemic activity on normoglycemic, hyperglycemic and alloxan induced diabetic rats after administration via gastric intubation (Vijayvargia et al., 2000). In the case of diabetic rats, the fall of blood sugar after 30 days treatment with the aqueous extract was found to be significant. The decrease in the plasma glucose level was accompanied with a decrease in the level of glycosylated haemoglobin and of the G6Pase activity in liver.

Marrubium vulgare (Lamiaceae), Rubus imperialis (Rosaceae) and Wedelia paludosa (Acanthaceae)

The hypoglycemic effect of four Brazilian medicinal plants (Marrubium vulgare, Rheedia gardneriana, Rubus imperialis and Wedelia paludosa) was studied on alloxan-induced diabetic rats (Novaes et al., 2001). The aqueous extract of these plants was intragastrically administered to diabetic rats. The results showed that all plants studied significantly lowered the blood glucose levels. These results suggested that these four medicinal plants could be an adjunct agent in the treatment of diabetes mellitus.

Equisetum myriochaetum (Equisetaceae)

Popularly known as “cola de caballo”, it is traditionally used for the treatment of type II diabetes mellitus, especially in the southern Mexico. A decoction of the aerial parts of the plant is prepared and consumed as a herbal tea (“agua de uso”).

The hypoglycemic effect of the aqueous as well as the butanolic extracts prepared from aerial parts of Equisetum myriochaetum was examined as a single per os dose in STZ- diabetic rats (Andrade-Cetto et al., 2000).

The hypoglycemic effect of the aqueous extract from aerial parts of Equisetum myriochaetum was analyzed in 11 recently diagnosed type II diabetic patients (Revilla et al., 2002). The results demonstrated that the aqueous extract of the aerial parts of Equisetum myriochaetum showed a hypoglycemic effect in type II diabetic patients starting 90 min after its per os administration.

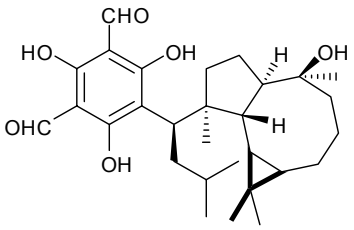
Eruca sativa (Cruciferae)

Clinical research has confirmed the efficacy of several plant extracts in the modulation of oxidative stress associated with diabetes mellitus. Oil of Eruca sativa seeds was tested for prevention and treatment of diabetes mellitus induced experimentally by alloxan injection (El-Missiry & El-Gindy 2000). It was suggested that Eruca sativa seeds oil could be used as antidiabetic supplement in cases of diabetes mellitus. This may be related to its antioxidative properties and to the consequent increase in hepatic GSH.

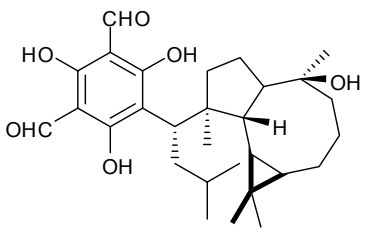
Eucalyptus globulus Labill. and Eucalyptus macrocarpa (Myrtaceae)

Eucalyptus globulus (Tasmanian Bleu Gum) is used as a traditional treatment for diabetes. In this study (Gray & Flatt 1998), incorporation of eucalyptus in the diet reduced the hyperglycemia and associated weight loss of STZ-diabetic mice. These data indicated that Eucalyptus globulus represents an effective antihyperglycemic dietary adjunct for the treatment of diabetes and a potential source for discovery of new per os active agent(s) for future therapy of diabetes mellitus.

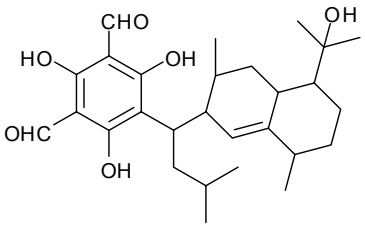
In a related study, four phloroglucinol derivatives, macrocarpals A, B, D, and G have been isolated from Eucalyptus macrocarpa and their inhibitory activity against porcine lenses ALR2 was reported (Murata et al., 1992). Some phloroglucinol derivatives were also obtained by synthesis and the relationship between structure and activity has also been reported.



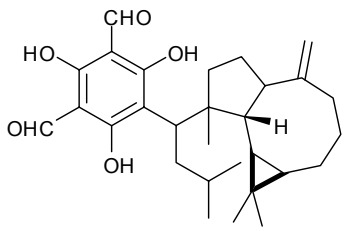
macrocarpal A



macrocarpal B



macrocarpal D



macrocarpal G

Eugenia jambolana Lam. (Myrtaceae)

In India, the decoction of kernels of Eugenia jambolana is used as a household remedy for diabetes. The hypoglycemic activity of different parts of Eugenia jambolana (Indian black berry) seeds such as whole seed, kernel, and seed coat was studied on STZ-diabetic rats after per os administration (Rave et al., 2004). Whole seed showed a moderate hypoglycemic effect, and seed coat did not show any hypoglycemic effect.

Euphrasia officinale (Scrophulariaceae)

The effects of the aqueous extract of the leaf of Euphrasia officinale, administered per os, on blood glucose levels in normal and alloxan-diabetic rats were investigated (Porchezhian et al. 2000). The treatment of alloxan-induced diabetic rats reduced the increased glucose levels, while the extract was devoid of hypoglycemic effect in normal rats.

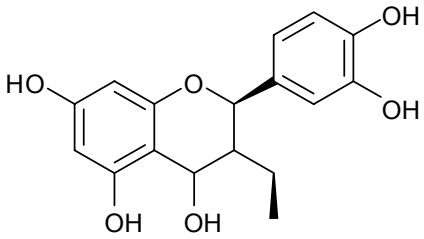
Ferula persica (Apiaceae), Paronychia argentea (Caryophyllaceae) and Pistacia atlantica (Anarcadiaceae)

Ferula persica, Paronychia argentea and Pistacia atlantica are three of the plants widely recommended by the herbalists and used for their hypoglycemic activity in Jordan. Aqueous extracts of these plants were tested in vitro for their alpha amylase inhibitory activity and in vivo for their hypoglycemic activity in normoglycemic and STZ-diabetic rats (Hamdan & Afifi 2004). Although the three plants were advocated for their hypoglycemic effects in Jordanian traditional herbal medicine; none of them showed significant hypoglycemic activity compared to the untreated animals. Paronychia argentea and Pistacia atlantica showed significant alpha amylase inhibitory activity while Ferula persica did not demonstrate any alpha amylase inhibitory activity. The main conclusion of this work was the concern over the unjustified claims of the uses of some herbal medicine in Jordan and possibly in other countries.

Ficus bengalensis L. (Moraceae)

A glycoside of leucopelargonidin, leucodelphinidin, isolated from the bark of Ficus bengalensis demonstrated significant hypoglycemic, hypolipidemic and serum insulin raising effects in moderately diabetic rats with close similarities to the effects of the minimal dose of glibenclamide (Cherian & Augusti 1993). The main difference observed in their effects was

that the former significantly enhanced the fecal excretion of sterols and bile acids while the later had no such action.



leucopelargonidin
leucodelphinidin: 3-O-alpha-ramnoside

Ficus carica (Moraceae)

The hypoglycemic effect of an aqueous extract of Ficus carica leaves was studied in STZ-diabetic rats (Perez et al., 1998). The extract induced a significant hypoglycemic effect after either per os or i.p. administration. Body weight loss was prevented in treated diabetic rats and the survival index was significantly affected by plasma insulin levels. Results showed that Ficus carica aqueous extract had a clear hypoglycemic activity in treated versus non-treated diabetic rats.

The effect of a decoction of leaves of Ficus carica as a supplement to breakfast, was studied in type I diabetes mellitus patients (Serraclara et al., 1998). It was concluded that the addition of Ficus carica to diet could help to control postprandial glycemia.

Ficus racemosa (Moraceae)

The glucose-lowering efficacy of a methanol extract of the stem bark of Ficus racemosa was evaluated both in normal and alloxan-induced diabetic rats after per os administration (Bhaskare Rao et al., 2002). The methanol extract at the doses examined exhibited significant hypoglycemic activity in both experimental animal models when compared with the control group. The activity was also comparable to that of the effect produced by a standard antidiabetic agent, glibenclamide. The present investigation established pharmacological evidence to support the folklore claim that it is an antidiabetic agent.

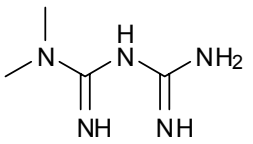
Fraxinus excelsior (Oleaceae) and Silybum marianum (Asteraceae)

The hypoglycemic effect of the aqueous extracts of Fraxinus excelsior seed and Silybum marianum aerial part was investigated in normal and

STZ-diabetic rats after per os administration (Maghrani et al., 2004). The aqueous extracts of both plants exhibited potent hypoglycemic and anti-hyperglycemic activities in normal and STZ rats, respectively, without affecting basal plasma insulin concentrations.

Galega officinalis L. (Leguminosae)

Galega officinalis (French lilac) was used in folklore medicine to treat symptoms now ascribed to type II diabetes. Galega officinalis was found to be rich in guanidine, a substance with blood glucose-lowering activity that formed the chemical basis of metformin (Vuksan et al., 1990). This insulin sensitizing drug was introduced in 1957 by Jean Sterne (1909–1997), a physician and clinical pharmacologist at the Hôpital de la Pitie in Paris. Sterne selected dimethylbiguanide (metformin) for clinical development and proposed the name "Glucophage" ("glucose eater"). His results were published in 1957 (Sterne 1957) and the rest is history as nowadays metformin is the only example of an approved antidiabetic drug that was developed from a herbal source with a long history of use and reputed to be the most widely prescribed agent in the treatment of diabetes.



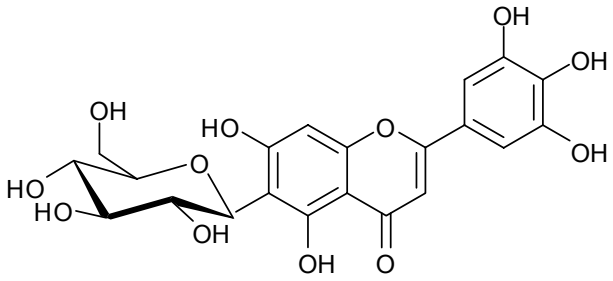
Metformin

It must be noted that while endless pharmacological studies (Baley and Day 2004) have been conducted so as to monitor the safety profile of metformin, its natural ancestor, Galega officinalis is a Class A Federal Noxious Weed in 35 states of America, and appears on the database of poisonous plants (USDA Natural Resources Conservation Service; Poisonous Plant Database. U.S. Department of Health and Human Services. U.S. Food & Drug Administration, Center for Food Safety & Applied Nutrition. Office of Plant and Dairy Foods and Beverages). At this point Paracelsus quote: '*The right dose differentiates a poison from a useful medicine*' is the most appropriate conclusion or comment for the above mentioned irony.

Gentiana olivieri Griseb. (Gentianaceae)

Hypoglycemic effect of Gentiana olivieri flowering herbs on per os administration were studied using in vivo models in normal and STZ-diabetic rats (Ekrem et al., 2005). Through in vivo bioassay-guided fractionation the

plant processes isoorientin, a known C-glycosylflavone that was isolated from the ethyl acetate fraction as the main active ingredient. Isoorientin exhibited significant hypoglycemic and antihyperlipidemic effects.



isoorientin

Ginkgo biloba (Ginkgoaceae)

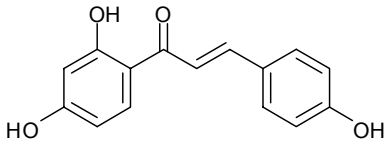
Gingo biloba is one of the oldest living tree species, dating back more than 200 million years and the extracts from dried leaves of younger trees are used in complementary therapies for a variety of diseases including diabetes. A glucose tolerance test was undertaken before and after ingestion of Ginkgo biloba extract for three months in 20 individuals (Kudolo 2000). It seems that Ginkgo biloba may increase insulin release.

Rubus fructicosis L. (Rosaceae) and Globularia alypum L. (Globulareaceae)

The present study investigated the effect of per os administration of the aqueous extract of Rubus fructicosis and Globularia alypum leaves on blood glucose levels in normal and STZ-diabetic rats (Maghrani & Eddouks 2002). The findings indicated that the extracts from both plants represented an effective blood glucose lowering and a potential source for discovery of new per os active component(s) for a therapeutical use.

Glycyrrhizae radix (Fabaceae)

Traditionally in Japan, some kampo medicines (traditional oriental herbal prescriptions) have long been used for the treatment of diabetic neuropathy. Some ALR2 inhibitors are included among these herbal prescriptions. Among these, GU-17 from Glycyrrhizae radix, identified as isoliquiritigenin, had the most potent ALR2 inhibiting activity in vitro (Aida et al., 1990). The results suggested that isoliquiritigenin may be effective in preventing diabetic complications.



isoliquiritigenin

Gongronema latifolium (Asclepiadaceae)

Gongronema latifolium is a rainforest plant, which has been traditionally used in the South Eastern part of Nigeria for the management of diabetes. The results of a reported study suggested that the extracts from Gongronema latifolium leaves could exert their antidiabetic activities through their antioxidant properties (Ugochukwu & Bababy 2002).

The aqueous and ethanolic extracts were tested in order to evaluate their effect on renal oxidative stress and lipid peroxidation in non-diabetic and STZ-diabetic rats after per os administration (Ugochukwu & Makini 2003). The ethanolic extract appeared to be more effective in reducing oxidative stress, lipid peroxidation, and increasing the GSH/GSSG ratio, thus confirming the ethnopharmacological use of Gongronema latifolium in ameliorating the oxidative stress found in diabetics and indicating promise of possible use in lessening morbidity in affected individuals.

The antihyperglycemic effects of aqueous and ethanolic extracts from Gongronema latifolium leaves was also investigated on glucose and glycogen metabolism in liver of non-diabetic and STZ-diabetic rats (Ugochukwu & Bababy 2003). The data showed that the ethanolic extract from the plant's leaves had antihyperglycemic potency, which was suggested to be mediated through the activation of HK, PFK, G6PD and inhibition of GK in the liver.

Gymnema sylvestre (Asclepiaceae), Eugenia jambolana (Myrtaceae), Momordica charantia (Curcurbiceae), Azadirachta indica (Meliaceae), Cassia auriculata (Fabaceae), Aegle marmelose, Withania somnifera (Solanaceae) and Curcuma longa (Zingeberaceae)

Dianex, a polyherbal formulation consisting of the aqueous extracts of Gymnema sylvestre, Eugenia jambolana, Momordica charantia Azadirachta indica, Cassia auriculata, Aegle marmelose, Withania somnifera and Curcuma longa was screened for hypoglycemic activity in normal and STZ-diabetic mice (Mutalik et al., 2005). Dianex was administered per os and produced significant hypoglycemic activity in both normal and diabetic mice in acute and long-term studies. The body weight of diabetic mice

was significantly increased with all tested doses of Dianex. The elevated triglycerides, cholesterol, urea and creatinine levels in diabetic mice were decreased. Hence, Dianex may be useful in the treatment of diabetes mellitus.

Gymnema sylvestre (Asclepiadaceae)

Gymnema sylvestre is a woody plant found in tropical forests of India and Africa and for more than 2000 years people chewed its leaves to treat "madhu meha" ("honey urine"). Used in Ayurvedic medicine, it is thought to destroy a person's ability to discriminate sweet taste and therefore is often called "gurmar" or "sugar destroyer" (Shane-McWhorter 2001).

Two water soluble extracts obtained from the leaves of Gymnema sylvestre, were tested in STZ-diabetic rats after per os administration for their effects on blood glucose homeostasis and pancreatic endocrine tissue (Shanmugasundaram et al., 1990). This herbal therapy appears to bring about blood glucose homeostasis through increased serum insulin levels provided by repair/regeneration of the endocrine pancreas.

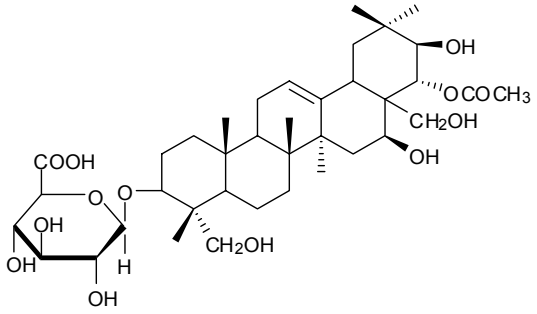
Also, the effectiveness of the water extract from the leaves of Gymnema sylvestre, in controlling hyperglycemia was investigated in 22 type II diabetic patients as conventional per os anti-hyperglycemic agents (Baskaran et al., 1990). The obtained data suggested that the β cells may be regenerated/repaired in type II diabetic patients on the extract's supplementation. This was supported by the raised insulin levels in the serum of patients after the supplementation.

Furthermore, the antihyperglycemic action of a crude saponin fraction and five triterpene glycosides (gymnemic acids I-IV and gymnemasaponin V) derived from the methanol extract of leaves of Gymnema sylvestre was investigated in STZ-diabetic mice (Sugihara et al., 2000). The results indicated that insulin-releasing action of gymnemic acid IV, administered i.p., may contribute to the antihyperglycemic effect by the leaves of Gymnema sylvestre. Gymnemic acid IV may be an anti-obese and antihyperglycemic prodrug.

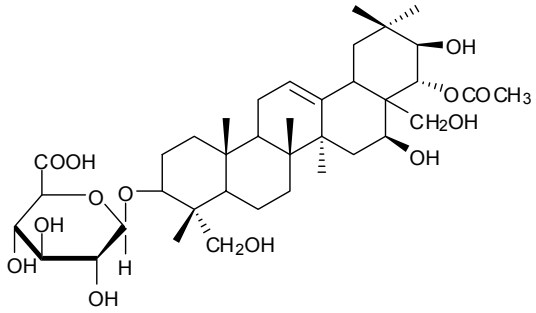
From the glycosidic fraction of the leaves of Gymnema sylvestre, six triterpene glycosides, gymnemosides a, b, c, d, e, and f, were isolated together with other known triterpene glycosides (gymnemic acids). The inhibitory activity of each triterpene glycoside on the glucose uptake in rat small intestine fragments was examined, in order to determine its impact on the increase of serum glucose level in glucose-loaded rats (Yoshikawa et al., 1997).

It was found that Gymnemic acids II and III showed potent inhibitory activity on glucose uptake. Gymnemoside b and gymnemic acids III, V, and

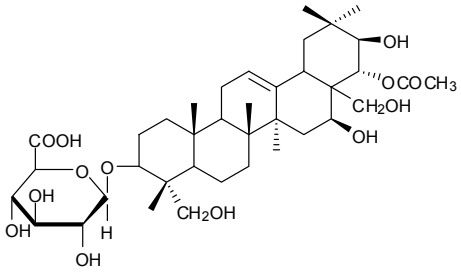
VII were found to exhibit a little inhibitory activity against glucose uptake, and the principal constituents, gymnemic acid I and gymnemasaponin V, lacked this activity. It is noteworthy that, although Gymnema saponin constituents such as Gymnemic acids II and III show no effect on serum glucose levels in oral-loaded rats, they exhibit potent inhibitory activity on the glucose uptake and further studies need to be contacted.



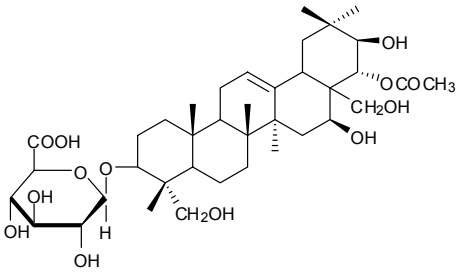
gymnemic acid I



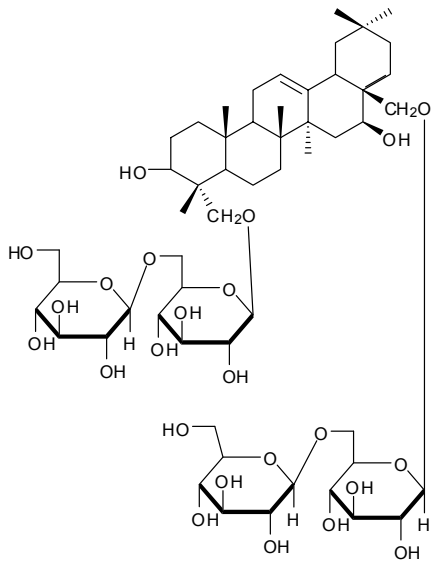
gymnemic acid II



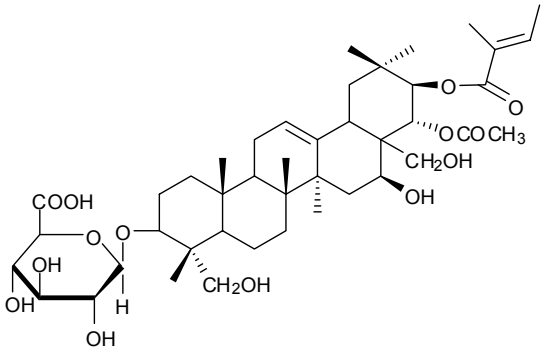
gymnemic acid III



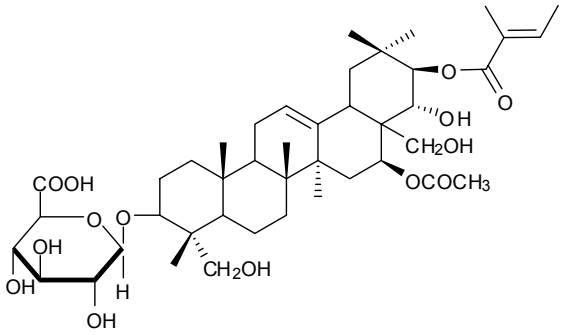
gymnemic acid IV



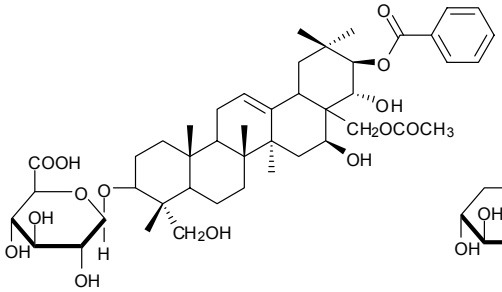
gymnemosaponin V



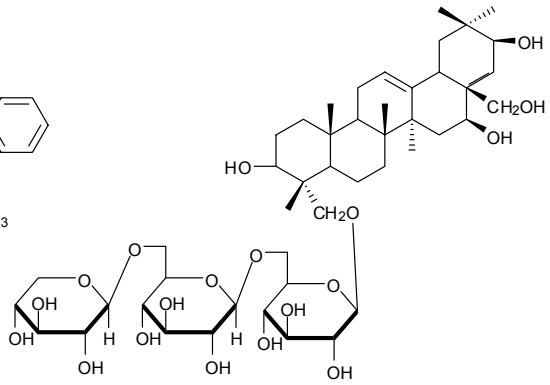
gymnemoside a



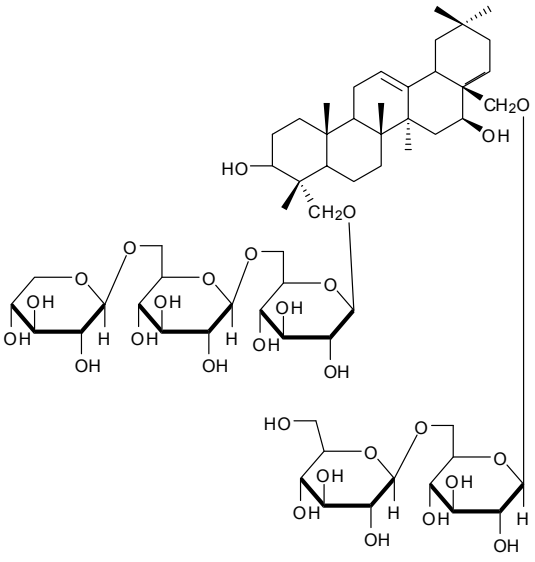
gymnemoside b



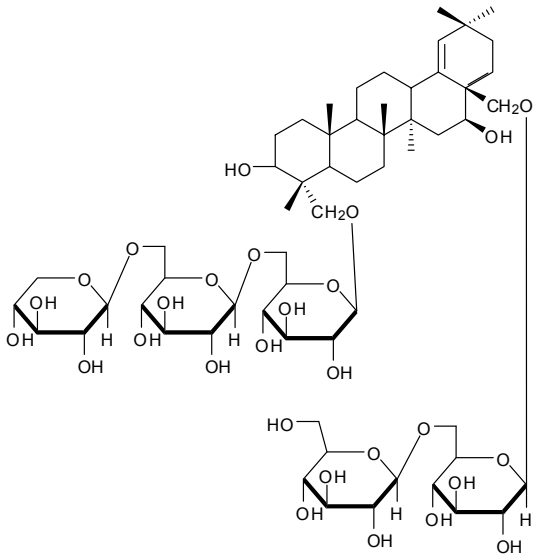
gymnemoside c



gymnemoside d



gymnemoside e



gymnemoside f

Gymnema montanum (Asclepiadaceae)

The effect of Gymnema montanum leaves extracts, a sparse plant used in the ancient period of India, was studied after per os administration on alloxan-induced hyperlipidemia in male Wistar rats (Anathan et al., 2003a).

These data indicated that Gymnema montanum represents an effective antihyperglycemic and antihyperlipidemic adjunct for the treatment of diabetes and a potential source of discovery of new per os active agent for future therapy.

The effects of Gymnema montanum on blood glucose levels, plasma insulin levels, and the carbohydrate metabolic enzymes was studied in alloxan diabetic rats (Anathan et al 2003b). Per os administration of the alcoholic extract of Gymnema montanum reduced the blood glucose levels. This clearly showed its antidiabetic efficacy, which was better than that of glibenclamide.

Gynura procumbens (Asteraceae)

An ethanolic extract of the leaves of Gynura procumbens was obtained, and the effects of its per os administration on STZ-diabetic rats was investigated (Zhang & Tan 2000; Akowuah et al., 2002). The results indicated that the leaves of Gynura procumbens may have biguanidine-like activity.

Harpagophytum procumbens (Pedaliaceae)

South Africa is blessed with a rich floral biodiversity of medicinally useful plants. One such plant is Harpagophytum procumbens. It is widely used in South African traditional medicine for the treatment, management and/or control of a variety of human ailments. The plant extract produced dose-dependent, significant reductions in the blood glucose concentrations of both fasted normal and fasted diabetic rats (Mahomed et al., 2005). The results of this experimental animal study indicated that Harpagophytum procumbens root aqueous extract possesses hypoglycemic properties, and lend pharmacological support to the suggested folklore uses in the management of type II diabetes mellitus in some communities of South Africa.

Helicteres isora (Sterculiaceae)

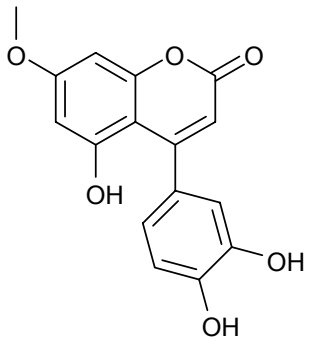
Helicteres isora root juice has been used in the treatment of diabetes by several ethnic groups in different parts of India. A reported study suggests that the extract of Hericteres isora has insulin-sensitizing and hypolipidemic activity and has the potential for use in the treatment of type II diabetes (Chakrabarti et al., 2002).

Hericium erinaceus (Hericaceae)

Recent studies have showed that many types of mushroom, may exert important biological effects in humans, including antioxidant activities, regulation of blood lipid levels and reduction of blood glucose levels. In a reported study, a methanol extract of the fruiting bodies of Hericium erinaceus was concentrated to remove the solvent, yielding a residue (referred to as HEM) which was added to the diet of the experimental animals (Wang et al., 2004). The hypoglycemic effects of feeding HEM to STZ-diabetic rats were studied. Polydipsia was stronger in induced diabetic rats not fed with HEM than in those receiving HEM. Rats fed with HEM had significantly lower blood glucose levels than those not fed with HEM.

Hintonia latiflora (Rubiaceae)

A reported study confirmed the antidiabetic effect of the Hintonia latiflora bark (copalchi bark) extract in various animal species with hyperglycemia induced by different methods (Korec et al., 2000). By the use of the synthetically produced neoflavonoid, coutareagenin, the presented series of tests provided evidence that coutareagenin, one of the active substances contained in the Hintonia latiflora bark, produces a reduction of the diabetic elevated blood sugar levels. The native extract as a whole, however, has to be regarded as the active substance of Hintonia latiflora (Copalchi bark).



coutaraegenin

Hordeum vulgare (Gramineae)

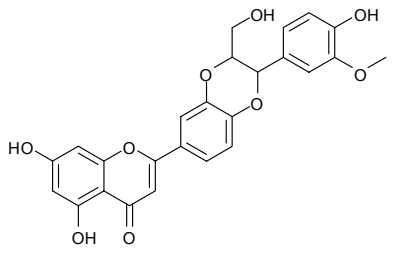
The alleged beneficial properties of Hordeum vulgare (barley) in the treatment of diabetes were investigated (Naismith et al., 1991). It was suggested that a factor other than the fibre content of the cereals may be responsible for the beneficial effect.

In adult diabetic rats, a diet containing barley had a modulating effect on the symptoms of diabetes (blood glucose concentration and water consumption) when compared with a starch or sucrose-based diet (Mahdi & Naismith 1991). It was postulated that the beneficial effect of barley might be explained by its very high content of chromium. Supplementation of the sucrose-based diet with an amount of trivalent inorganic chromium calculated to be equivalent to the available chromium in the barley-based diet abolished the differences in response to the diabetic state.

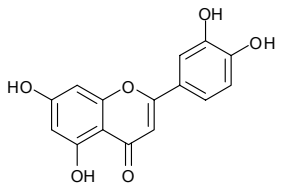
Also the postprandial glycemic response of Hordeum vulgare was studied in 18 healthy volunteers and 14 patients having type II diabetes mellitus (Shukla et al., 1991). The glycemic response to barley was significantly lower than that to white bread in both groups of subjects. However, the insulinemic response to barley was significantly lower than that to white bread in healthy subjects only. In type II diabetic subjects, there was a tendency for the response to barley to be higher than that to white bread 0.5 h after ingestion. Barley, with a low glycemic index, seemed to mobilize insulin in type II diabetic subjects. This makes it an especially suitable cereal for diabetic patients.

Hydnocarpus wightiana (Arcariaceae)

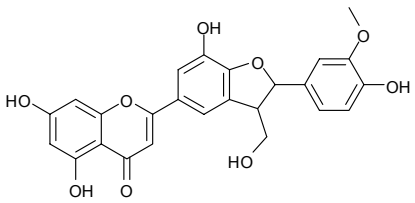
Hydnocarpus wightiana is advocated in the traditional medicine in India to possess strong antidiabetic activity. In the course of identifying bioactive fractions from Indian medicinal plants it was observed that the acetone extract of the seed hulls of Hydnocarpus wightiana possessed strong free radicals scavenging activity, alpha-glucosidase and moderate N-acetyl-beta-D-glucosaminidase inhibitory activities (Reddy et al., 2005). Further fractionation of the extract led to the isolation of hydnocarpin, luteolin and isohydnocarpin in substantial yields.



hydnocarpin



luteolin



isohydnocarpin

All the compounds showed strong free radical scavenging property. Furthermore, all the three compounds also showed varying degrees of alpha-glucosidase and N-acetyl-beta-D-glucosaminidase inhibitory activity, luteolin

being the superior. This study suggested that the presence of antioxidant molecules along with their enzyme inhibitory activities in the acetone extract of Hydnocarpus wightiana seed hulls may be responsible for the antidiabetic properties as advocated in the traditional medicine.

Hygrophila longifolia (Acanthaceae)

The extra-pancreatic effects of the hypoglycemic plant Hygrophila longifolia have been investigated in rats after per os administration (Fernando et al., 1998). The results obtained in the present study suggested that Hygrophila longifolia may exert hypoglycemic action by mechanisms similar to these of the sulphonylureas.

Hypoxis hemerocallidea (Hypoxidaceae)

A study was undertaken to examine the hypoglycemic effect of the aqueous extract of Hypoxis hemerocallidea corm (locally known as "African Potato") in normal (normoglycemic) and in STZ-induced diabetic rats after per os administration (Mahomed & Ojewole 2003). The results of this experimental animal study indicated that African potato possessed hypoglycemic activity; and thus lent credence to the suggested folkloric use of the herb to the control of type II diabetes mellitus in some communities of South Africa.

Ipomoea aquatica (Convolvulaceae)

This study was undertaken to compare the per os hypoglycemic activity of the aqueous extract of the vegetable Ipomoea aquatica ("sweet potato") with that of the known hypoglycemic drug tolbutamide in glucose challenged Wistar rats (Malalavidhane et al., 2001; Malalavidhane et al., 2003). The results showed that the aqueous extract of Ipomoea aquatica was as effective as tolbutamide in reducing the blood glucose levels of glucose-challenged Wistar rats.

Irvingia gabonesis (Irvingiaceae)

The effects of Dikanut (Irvingia gabonensis), an African viscous preparation, as supplement in the diet of eleven type II diabetic patients, was studied (Adamson et al., 1990). The dikanut supplement elicited hypolipidemic activity. The reduction in plasma lipids was primarily due to a decrease in LDL, VLDL-cholesterol and triglycerides levels. HDL-cholesterol was increased. The three ATPases of the erythrocyte membrane of the diabetic patients were significantly lower than in normal subjects. When dikanut was consumed by the diabetics for four weeks, the activities of the

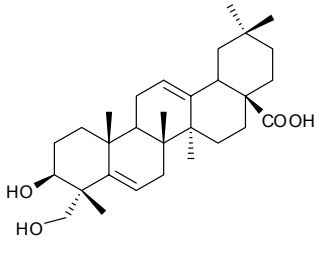
above enzymes increased significantly. The increases correlated well with significant reduction of plasma glucose levels. These desirable biochemical effects mediated by ingestion of a naturally-occurring dietary fibre were accompanied by improved clinical profile.

Juniperus communis (Cupressaceae)

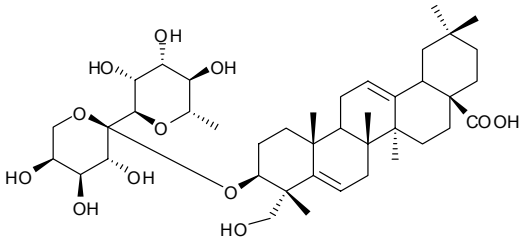
The hypoglycemic activity of a decoction from Juniperus communis (juniper berries) both in normoglycemic and in STZ-diabetic rats was studied (Sanchez et al., 1994). Juniper decoction decreased glycemic levels in normoglycemic rats through an increase of peripheral glucose utilization or a potentiation of glucose-induced insulin secretion. The per os administration of the decoction to STZ-diabetic rats resulted in a significant reduction both in blood glucose levels and in the mortality index, as well as the prevention of the loss of body weight. This effect seemed to be mediated by the peripheral action of juniper.

Kalopanax pictus (Araliaceae)

The stem bark of Kalopanax pictus, a tree growing in East Asian countries, has been traditionally used for the treatment of rheumatoid arthritis, neuronal pain and diabetes mellitus. To search for the anti-diabetic principle from the stem bark of Kalopanax pictus, seven kinds of chemical constituents including hedearagenin and its glycosides were isolated (Park et al., 1998). The anti-diabetic evaluation of these isolates in the STZ-diabetic rats exhibited, after i.p. administration, that kalopanaxsaponin A has a potent anti-diabetic activity in contrast to a mild activity of hedearagenin. In addition, significant hypocholesterolemic and hypolipidemic activities of kalopanaxsaponin A and hedearagenin were observed.



hedearagenin



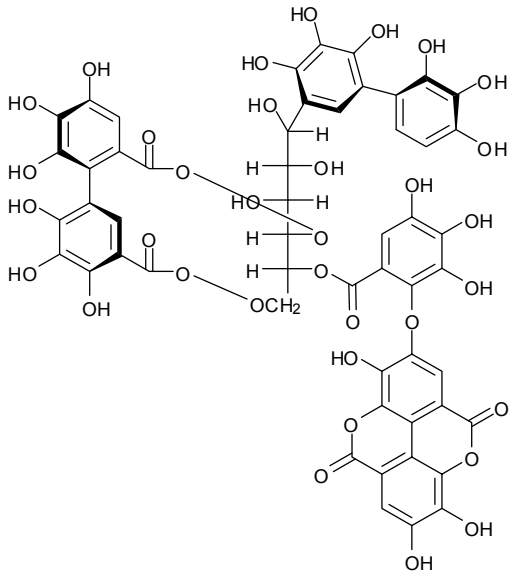
kalopanaxsaponin A

Lagerstroemia speciosa L. (Lythraceae)

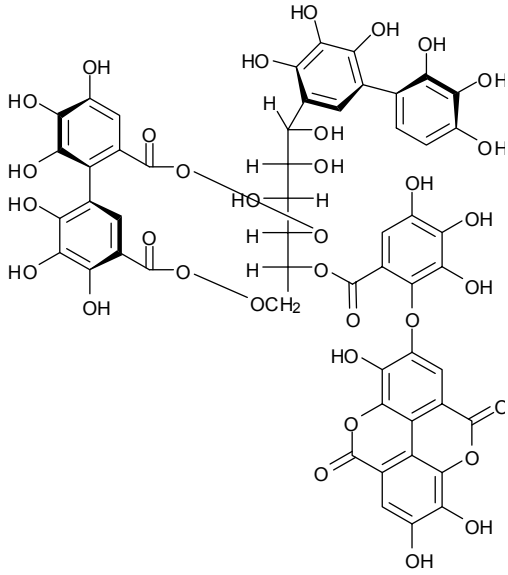
The hypoglycemic effects of Lagerstroemia speciosa, known by the Tagalog name “banaba” in the Phillipines, were studied using hereditary diabetic mice (type II, KK-AY/Ta Jcl) (Kakuda et al., 1996). The mice were

fed a test diet containing the hot-water extract from banaba leaves, the water eluent of the partial fraction unadsorbed onto HP-20 resin of the hot water extract, and the methanol eluent of the partial fraction adsorbed onto HP-20 resin of it for a feeding period of 5 weeks. It is suggested that the hot water extract and especially that adsorbed onto HP-20 resin, obtained from banaba leaves have beneficial effects on controlling of the level of plasma glucose in type II diabetes mellitus.

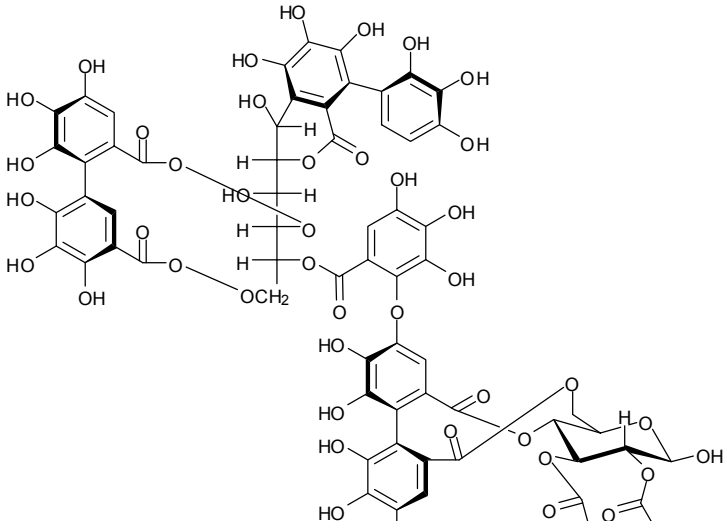
Glucose transport enhancers were searched for in Lagerstroemia speciosa and three active ellagitannins, lagerstroemin, flosin B and reginin A increased glucose uptake of rat adipocytes in vitro, and could be responsible for lowering the blood glucose level (Hayashi et al., 2002).



lagerstroemin

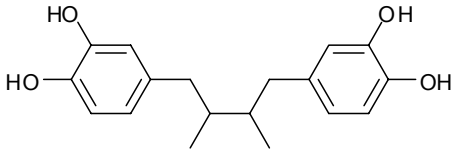


flosin B



Larrea tridentata (Zygophyllaceae)

An ethnomedically-driven approach was used to evaluate the ability of a pure compound, masoprocol, isolated from the creosote bush (Larrea tridentata) to lower plasma glucose concentration in two mice models of type II diabetes after per os administration (Luo et al., 1998). These data raised the possibility that masoprocol, or other lipoxygenase inhibitors, represents a new approach for the treatment of type II diabetes.



masopropol

Lepechinia caulescens (Labiatae)

The traditional preparation and the water extracts obtained from the flowers of Lepechinia caulescens were administered to fasting healthy mice i.p. (Roman-Ramos et al., 2001). The investigation results showed that only the traditional preparation and the water extract significantly reduce blood glucose levels after i.p. administration.

Lepidium sativum L. (Brassicaeae)

The hypoglycemic effect of an aqueous extract of Lepidium sativum seeds was investigated in normal and STZ-diabetic rats (Eddouks et al., 2005). It was concluded that the aqueous extract of Lepidium sativum exhibited a potent hypoglycemic activity in rats, after per os administration, without affecting the levels of plasma insulin concentration.

Leucas lavandulaefolia Rees (Labiatae)

The antidiabetic activity of Leucas lavandulaefolia extract on STZ-diabetic rats has been investigated (Saha et al., 1998). The extract caused a significant reduction of blood glucose levels in STZ-diabetic rats after per os administration.

Loranthus begwensis (Loranthaceae)

The African mistletoe, Loranthus bengwensis, has been widely used in Nigerian folk medicine to treat diabetes mellitus. The data indicated that

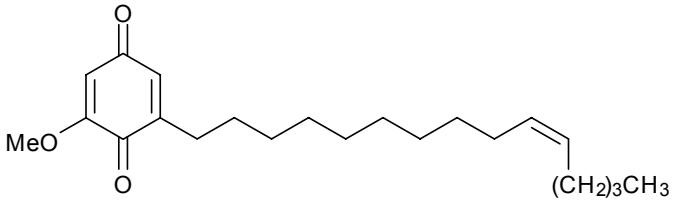
African mistletoe possessed significant anti-diabetic activity in STZ-diabetic rats when administered per os; its anti-diabetic activity appeared to be highly dependent on the host plant species (Obatomi et al., 1994).

Lupinus termis (Leguminoseae), Cymbopogon proximus (Halfa barr) (Gramineae) or Kammun quaramany (Zygophyllacae)

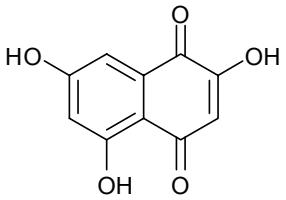
The effect of three species of hypoglycemic herbs on the lipid profile was investigated in plasma and liver tissues of diabetic and herbs' treated diabetic rats (Newairy et al., 2002). The obtained data demonstrated that the glycemic control of all of the three herbal suspensions was associated with their hypocholesterolemic effects on the hypercholesterolemia of the alloxan-induced diabetic rats. In conclusion, the Kammun quaramany showed the most potent effect.

Maesa lancelata (Myrsinaceae)

Maesanin and flaviolin were isolated from the fresh fruit of Maesa lancelata, which is a East African medicinal plant. These p-benzokinone derivatives showed in vitro inhibitory activity against rat lenses ALR2 (ALR2) (Haraguchi et al., 1996).



maesanin



flaviolin

Mangifera indica L. (Anacardiaceae)

The leaves of Mangifera indica (Mango) are used as an antidiabetic agent in Nigerian folk medicine. The effect of the aqueous extract of the leaves when administered per os on blood glucose level was assessed in normoglycemic, glucose-induced hyperglycemic and STZ-diabetic rats and the results of this study indicated that the aqueous extract of the leaves of Mangifera indica possess hypoglycemic activity (Aderibigbe et al., 1999; Aderibidge et al., 2001). This action may be due to an intestinal reduction of the absorption of glucose (carbohydrates).

Momordica charantia (Curcurbiceae), Melia azadirachta (Meliaceae), Pterocarpus marsupium (Fabaceae), Tinospora cordifolia (Menispermaceae), Gymnema sylvestre (Asclepiadaceae), Enicostemma littorale (Gentiaceae), Emblica officinalis (Euphorbiaceae), Eugenia jambolana (Myrtaceae), Cassia auriculata (Fabaceae) and Curcuma longa (Zingeberaceae)

Hyponidd is a herbomineral formulation composed of the extracts of ten medicinal plants (Momordica charantia, Melia azadirachta, Pterocarpus marsupium, Tinospora cordifolia, Gymnema sylvestre, Enicostemma littorale, Emblica officinalis, Eugenia jambolana, Cassia auriculata and Curcuma longa). Hyponidd was investigated for its possible antihyperglycemic and antioxidant effect in diabetic rats. The results showed that per os administration of hyponidd exhibits antihyperglycemic and antioxidant activity in STZ-induced diabetic rats (Babu et al., 2004).

Momordica charantia (Curcurbiceae)

Momordica charantia, commonly called bitter gourd, is a medicinal plant used in the Ayurvedic system of medicine for treating various diseases including diabetes mellitus. At present, unripe fruits, seeds and aerial parts of the plant have a widespread use as vegetable and phytomedicine in various parts of the world to treat diabetes (Umesh et al., 2005). Sodium orthovanadate is a well-known insulin mimetic and an antidiabetic compound. The results of a study suggested that Momordica fruit extract and sodium orthovanadate exhibit hypolipidemic as well as hypoglycemic effect in diabetic rats and their effect is pronounced when administered per os.

A hypoglycemic peptide, polypeptide-p, has been isolated from fruit, seeds, and tissue of Momordica charantia (Khanna et al., 1981). Polypeptide-p is a very effective hypoglycemic agent when administered s.c. to gerbils, languor, and humans.

Cerasee, a wild variety of Momordica charantia is traditionally prepared as a tea for the treatment of diabetes mellitus in the West India and Central America. To investigate a possible hypoglycemic effect, concentrated aqueous extracts of cerasee were administered to normal and STZ-diabetic mice (Bailey et al., 1985). In normal mice, i.p. administration of cerasee improved glucose tolerance after 8 hr, and in STZ-diabetic mice the level of hyperglycemia was reduced. Chronic per os administration of cerasee to normal mice for 13 days improved glucose tolerance. The cerasee extracts did

not significantly alter plasma insulin concentrations, suggesting that cerasee may exert an extrapancreatic effect to promote glucose disposal.

Investigations were carried out to evaluate the effect of Momordica charantia on the glucose tolerance of type II diabetic patients (Welihinda et al., 1986). The fruit juice of Momordica charantia was found to significantly improve the glucose tolerance of 73% of the patients investigated while the other 27% failed to respond.

The hypoglycemic effect of per os administered extracts of fruits of cultivated Momordica charantia (karela) was examined in normal and STZ-diabetic mice (Day et al., 1990). The results suggested that per os administered karela extracts lower glucose concentrations independently of intestinal glucose absorption and involve an extrapancreatic effect.

The Monocordia charantia extract seems to act like insulin or via insulin secretion from the pancreas, like the action of sulfonyl ureas (Higashino et al., 1992).

Morinda lucida Benth (Rubiaceae)

The hypoglycemic and anti-hyperglycemic activities of a methanol extract of Morinda lucida leaves were studied in normal and STZ-diabetic rats (Olajide et al., 1999). These results suggested that the leaves of Morinda lucida have a strong glucose lowering property when administered per os to STZ-treated rats.

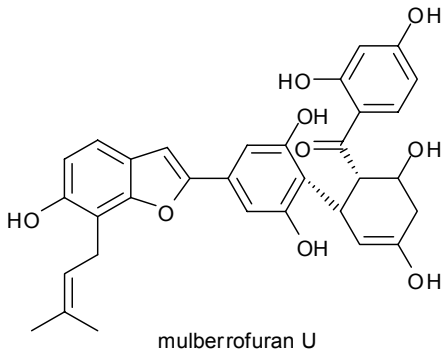
Moringa stenopetala (Moringaceae)

The hypoglycemic effect of Moringa stenopetala extract was assessed in nondiabetic rabbits by blood glucose analysis (Mahonnen et al., 1998). In vivo experiments were carried out in rabbits that received i.p. the test material and the standard, glibenclamide. The plant extract, although less potent than glibenclamide, was found to lower blood glucose concentration. The hypoglycemic effect was observed to increase with time and with an increase in the dose of the extract.

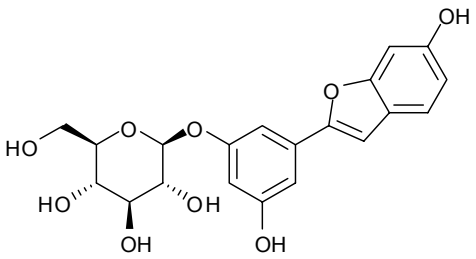
Morus insignis (Moraceae)

Ethyl acetate- and n-butanol-soluble fractions of the leaves of Morus insignis showed a significant hypoglycemic activity on STZ-diabetic rats after per os or i.p. administration (Basnet et al., 1993). From these hypoglycemic activity-showing fractions, two new compounds, mulberrofuran U and moracin M-3-O-beta-D-glucopyranoside were isolated, along with known compounds

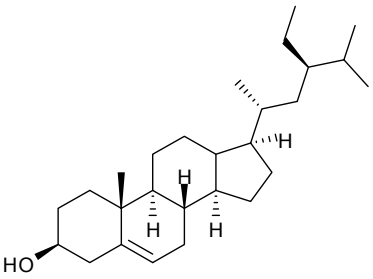
(beta-sitosterol, beta-sitosterol-3-O-beta-glucopyranoside, ursolic acid and quercetin-3-O-beta-glucopyranoside).



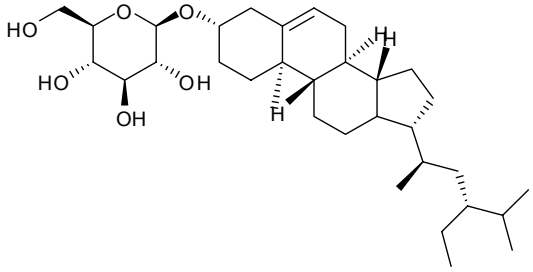
mulberrofuran U



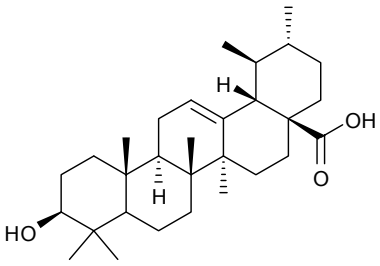
moracin M-3-O-beta-D glucopyranoside



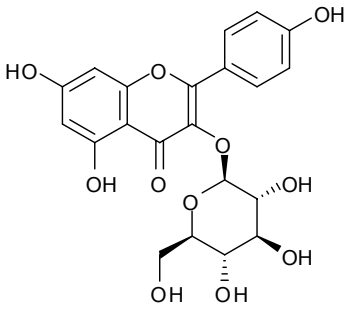
b-sitosterol



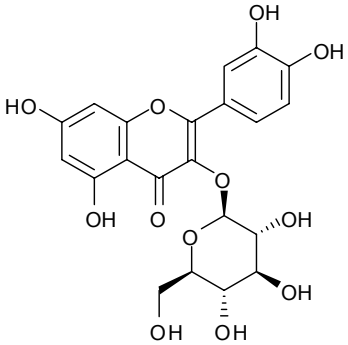
b-sitosterol-3-O-beta-glucopyranoside



ursolic acid



kaempferol-3-O-beta-glucopyranoside

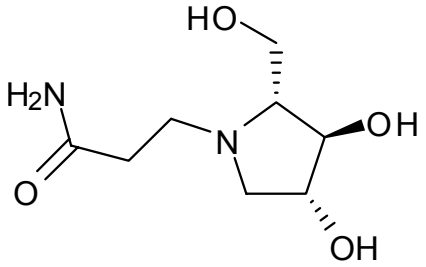


quercetin-3-O-beta-glucopyranoside

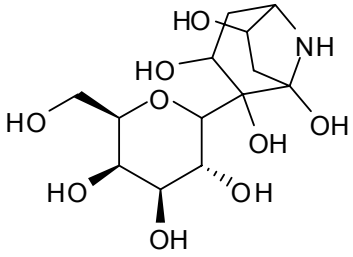
Morus alba L. (Moraceae)

A new glycoprotein was purified from the aqueous methanolic extract of the root bark of Morus alba, which has been used as a component of antidiabetic remedy in Oriental Medicine. This new glycoprotein was named as Moran 20K (Kim et al., 1999). The protein lowered blood glucose level in STZ-diabetic mice model and it also increased the glucose transport in cultured epididymis fat cells. The amino acid composition of the protein was analyzed, and the protein contained above 20% serine and cysteine, comparable to that of insulin. The actual molecular weight of the protein was determined as 21,858 Da.

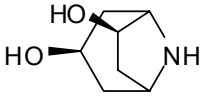
New polyhydroxylated alkaloids, (2R,3R,4R)-2-hydroxymethyl-3,4-dihydroxypyrrolidine-N-propionamide from the root bark of Morus alba L, D-galactopyranosyl-calystegine B and 3-beta,6-beta-dihydroxynortropane from the fruits, were isolated. Fifteen other polyhydroxylated alkaloids were also isolated (Yamashita et al., 2001). 1-Deoxynojirimycin, a potent alpha-glucosidase inhibitor, was concentrated by silkworms feeding on mulberry leaves. Some alkaloids contained in mulberry leaves were potent inhibitors of mammalian digestive glycosidases but not inhibitors of silkworm midgut glycosidases, suggesting that the silkworm has enzymes specially adapted to enable it to feed on mulberry leaves. The possibility of preventing the onset of diabetes and obesity using natural dietary supplements containing 1-deoxynojirimycin and other alpha-glucosidase inhibitors in high concentration is of great potential interest.



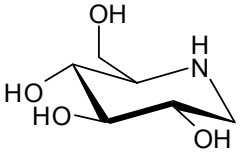
(2R,3R,4R)-2-hydroxymethyl-3,4- dihydroxypyrrolidine-N-propionamide



D-galactopyranosyl-calystegine B



3 beta,6 beta-dihydroxynortropane



1-deoxynojirimycin

Murraya koenigii (Rutaceae)

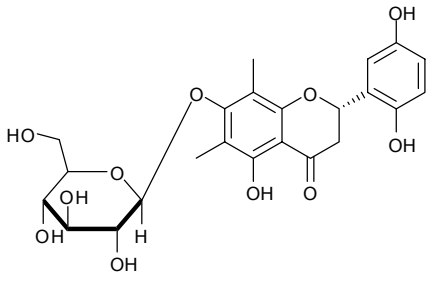
The aqueous extract of Murraya koenigii leaves has been studied in order to evaluate the hypoglycemic activity in normal and alloxan induced diabetic rabbits after per os administration (Kesari et al., 2005). This plant is promising as it is widely and regularly used in India and other tropical countries as a spice for food flavoring and as such it appeared to be without any side effects and toxicity. The findings from this study suggested that the aqueous extract of these leaves may be prescribed as adjunct to dietary therapy and drug treatment for controlling diabetes mellitus.

Musa sapientum (Musaceae)

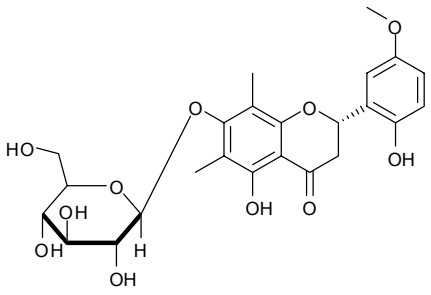
Musa sapientum, commonly known as banana, is widely used in Indian folk medicine for the treatment of diabetes mellitus. The flower extract prevented a decrease in body weight, and also resulted in a decrease in free radical formation in experimental animals after per os administration (Pari & Umamaheswari 2000). Thus the study showed that oral administration of banana flower extract had an antihyperglycemic action. The decrease in thiobarbituric acid reactive substances and the increase in reduced GSH, glutathione peroxidase, SOD and CAT clearly showed the antioxidant property of the flower extract.

Myrcia multiflora (Myrtaceae)

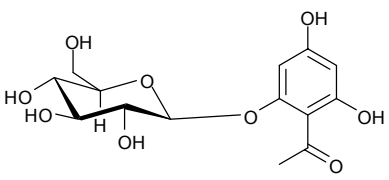
The leaves of Myrcia multiflora, which have been used as a specific medicine against diabetes with the popular name "plant insulin" in Brazil, were found to show inhibitory activities on ALR2 and alpha-glucosidase as well as on the increase of serum glucose level in sucrose-loaded rats and in alloxan-induced diabetic mice (Yoshikawa et al., 1998). From the ethyl acetate-soluble portion, new flavanone glycosides, myrciacitrins I and II, and new acetophenone glycosides, myrciaphenones A and B, were isolated together with several known compounds such as five flavonol glycosides, myricitrin, mearnsitrin, quercitrin, desmanthin-1, and guaijaverin. The principal components of this natural medicine including new glycosides, myrciacitrin I and myrciaphenone B, were found to show potent inhibitory activities on ALR2 and alpha-glucosidase.



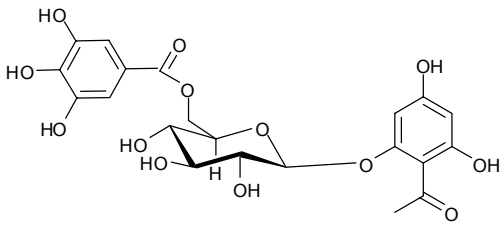
myrciacitrin I



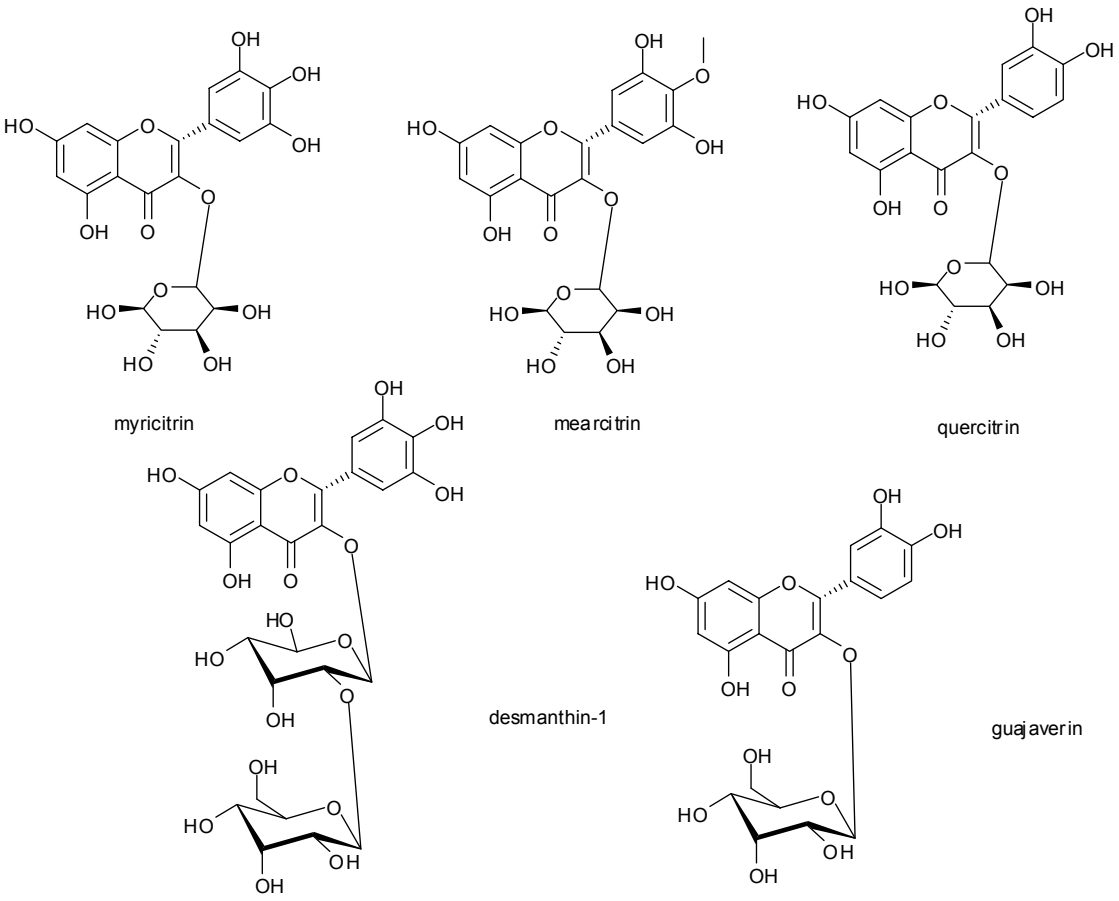
myrciacitrin II



myrciaphenon A



myrciaphenon B



Myrtus communis L. (Myrtaceae)

Myrtus communis leaves as well as the volatile oil (Myrtii Oleum) obtained from the leaves are used to lower the blood glucose level in type II diabetic patients in Turkish folk medicine (Sepici et al., 2004). The above observations showed that Myrtii oleum exerted hypoglycemic as well as mild hypotriglyceridemic activity in diabetic experimental animals after per os administration. The reduction in blood glucose level may be due to the reversible inhibition of glucosidases present in the brush-border of the small intestinal mucosa, the higher rate of glycolysis as envisaged by the higher activity of GK, as one of the key enzymes of glycolysis, and enhanced rate of glycogenesis as evidenced by the higher amount of liver glycogen present after the myrtii oleum administration.

Nelumbo nucifera (Nymphaeaceae)

Per os administration of the ethanolic extract of rhizomes of Nelumbo nucifera markedly reduced the blood sugar level of normal, glucose-fed hyperglycemic and STZ-diabetic rats, when compared with control animals

(Mukherjee et al., 1997). The extract improved glucose tolerance and potentiated the action of exogenously injected insulin in normal rats.

Ocimum sanctum L. (Lamiaceae)

Per os administration of alcoholic extract of leaves of Ocinum sanctum (Holy basil) led to marked lowering of blood sugar level in normal, glucose fed hyperglycemic and STZ-diabetic rats (Chattopadhyay et al., 1993). Further, the extract potentiated the action of exogenous insulin in normal rats.

Ocimum gratissimum (Lamiaceae)

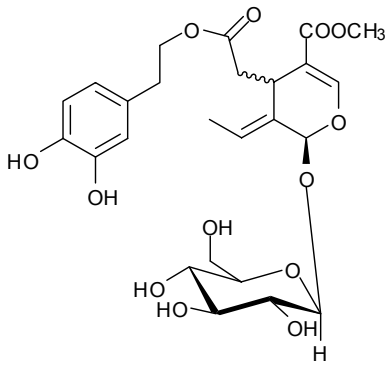
The hypoglycemic effect of the methanolic extract of Ocimum gratissimum leaves was evaluated in normal and alloxan-induced diabetic rats (Aguiyi et al., 2000). I.p. injection of the extract (400 mg/kg) significantly reduced plasma levels both in normal and diabetic rats.

Ocimum canum (Lamiaceae)

Aqueous extract of Ocimum canum, is used by some Ghanaians to manage diabetes mellitus. In vivo modulation of levels of fasting blood glucose by Ocimum canum extract was evaluated in type II diabetes mellitus using a genetically diabetic animal model, and its effects on glucose-stimulated insulin release in vitro were monitored using isolated rat pancreatic β islet cells (Nyarkoa et al., 2002). The results showed that fasting blood glucose levels and body weight decreased significantly in diabetic and non-diabetic mice, which were administered aqueous extract of Ocinum canum. In vitro, the extract significantly enhanced insulin release from isolated rat pancreatic β islet cells. These results could explain the use of Ocinum canum in Ghanaian folk medicine to manage diabetes mellitus.

Olea europaea (Oleaceae)

The hypoglycemic activity of olive leafs was studied (Gonzalex et al., 1992). Maximum hypoglycemic activity was obtained from samples collected in the winter months, especially in February. One of the compounds responsible for this activity was oleuropeoside. This compound also demonstrated antidiabetic activity in experimental animals with alloxan-induced diabetes after per os administration. The hypoglycemic activity of this compound may result from two mechanisms: (a) potentiation of glucose-induced insulin release, and (b) increased peripheral uptake of glucose.



oleuropeoside

Opuntia robusta (Cactaceae)

The influence of Opuntia robusta (prickly pear), a traditionally used dietary nutrient against diabetes mellitus among the American Indian population, was examined in 15 young patients suffering from familial heterozygous isolated hypercholesterolemia (Wolfram et al. 2001). After daily consumption of broiled edible pulp of prickly pear the findings indicated that the regular ingestion of Opuntia robusta was able to significantly reduce in vivo oxidation injury in a group of patients suffering from familial hypercholesterolemia. This traditional food of the American Indians thus may have a significant cardiovascular benefit.

Opuntia streptacantha Lemaire (Cactaceae)

Nopal stems (Opuntia streptacantha) are used as a food source in Mexico. To assess the hypoglycemic effect of the Opuntia streptacantha Lemaire (nopal), three groups of patients with type II diabetes mellitus were studied (Frati-Munari et al., 1988). This study showed that the stems of Opuntia streptacantha, when ingested, caused a hypoglycemic effect in the diabetic patients. The mechanism of this effect is unknown, but an increased insulin sensitivity was suggested.

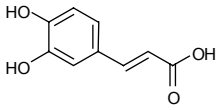
To assess the relationship between the doses of Opuntia streptacantha and its acute hypoglycemic action in diabetics, eight patients with type II diabetes mellitus were studied (Frati-Murati et al., 1989). A significant direct correlation was noticed between the doses and the hypoglycemic effect.

Origanum vulgare L. (Lamiaceae)

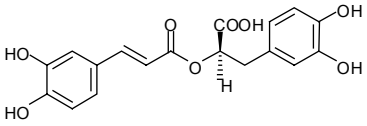
The effect of an aqueous extract of Origanum vulgare leaves on blood glucose levels was investigated in normal and STZ-diabetic rats (Lemhadri et al.,

2004). It was concluded that an aqueous extract exhibits an anti-hyperglycemic activity in STZ-diabetic rats without affecting basal plasma insulin concentrations.

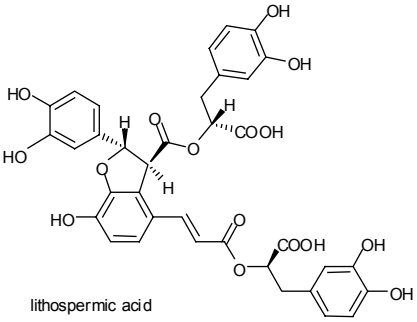
Five polar constituents of Origanum vulgare were investigated for their ability to inhibit ALR2, the first enzyme of the polyol pathway implicated in the secondary complications of diabetes (Koukoulitsa et al., 2006). Rosmarinic acid and lithospermic acid were the more active ALR2 inhibitors while caffeic acid was inactive.



caffeic acid



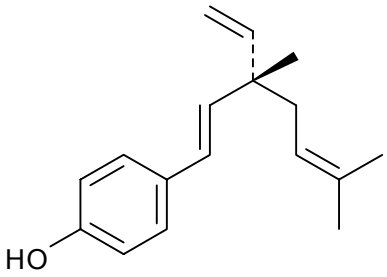
rosmarinic acid



lithospermic acid

Otholobium pubescens (Fabaceae)

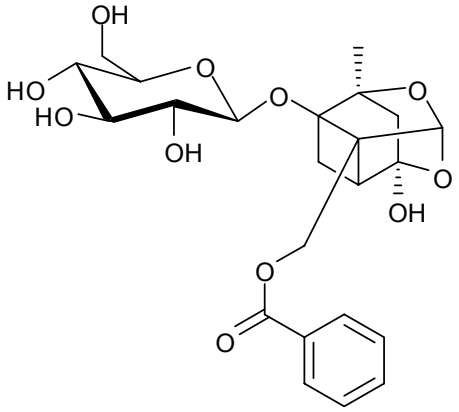
The known compound bakuchiol was isolated from an extract of Otholobium pubescens. Per os administration of backuchiol reduced blood glucose levels in a dose-dependent fashion in diabetic mice and did not display a hypoglycemic effect when tested in lean mice (Krenisky et al., 1999).



bakuchiol

Paeonia lactiflora Pall. (Panunculaceae)

Paeonia lactiflora root has been used in traditional Chinese medicine for more than a millennium, with claims of antispasmodic, tonic, astringent and analgesic properties. The principal bioactive ingredient, paeoniflorin, a monoterpene glucoside, was isolated from the root of Paeonia lactiflora (Shibata et al., 1963).



paeoniflorin

The roots produced a significant blood sugar lowering effect in STZ-diabetic rats after per os administration. Plasma insulin level was not changed in paeoniflorin-treated normoglycemic rats indicating an insulin-independent action. Also, the above mentioned glucoside reduced the elevation of blood sugar in glucose challenged rats. Increase of glucose utilization by paeoniflorin can thus be considered (Hsu et al., 1997).

Panax ginseng (Aralilaceae), Anemarrhena asphodeloides (Liliaceae), Glycyrrhiza glabra (Fabaceae)

The antihyperglycemic interaction (blend effect) of component herbs included in a traditional Chinese prescription, Byakko-ka-ninjin-to (BN; consisted of five herbs, ginseng, anemarrhena, licorice, gypsum and rice) was investigated using genetically obese diabetic KK-CA(y) mice and alloxan-diabetic mice (Kimura et al., 1999). The results indicated that the antihyperglycemic effects depend on four of the herbs (not gypsum) and Ca^{2+} in the blend.

Panax ginseng (Araliaceae)

Ginseng is well known to be a good tonic for health care. With two-dimensional regulation to blood glucose (to lower hyperglycemia and rise hypoglycemia, not to influence normal blood glucose), many active constituents have been isolated and some preparations of ginseng have been developed and used in clinical treatment of diabetes.

Some fractions extracted from ginseng radix caused hypoglycemic effect on alloxan diabetic mice after they were injected i.v. and the results indicated that some ginseng fractions stimulated insulin release, especially glucose-

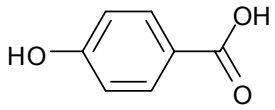
induced insulin release from pancreatic islets and thereby lowered the blood glucose level (Kimura et al., 1981).

In a double-blind placebo-controlled study, 36 type II diabetic patients were treated for 8 weeks with ginseng or placebo (Sotaniemi et al., 1995). Ginseng therapy elevated mood, improved psychophysical performance, and reduced fasting blood glucose and body weight. The 200mg dose of ginseng improved glycated hemoglobin and physical activity. Placebo reduced body weight and altered the serum lipid profile but did not alter fasting blood glucose. Therefore, ginseng may be a useful therapeutic adjunct in the management of type II diabetes mellitus.

A preliminary short-term clinical study was performed to assess whether American ginseng (Panax quinquefolius L) affects postprandial glycemia in humans (Vuksan et al., 2000). American ginseng attenuated postprandial glycemia in both diabetic and non diabetic groups after per os administration. For nondiabetic subjects, to prevent unintended hypoglycemia it may be important that the American ginseng be taken with the meal.

Pandanus odorus Ridl. (Pantadaceae)

Hypoglycemic activity-guided fraction led to the isolation of the known compound, 4-hydroxybenzoic acid, from Pandanus odorus (Thai name: Toei-hom) (Peungvicha et al., 1998a). This compound showed a hypoglycemic effect in normal rats after per os administration. Additionally, the compound increased serum insulin levels and liver glycogen content in normal rats.



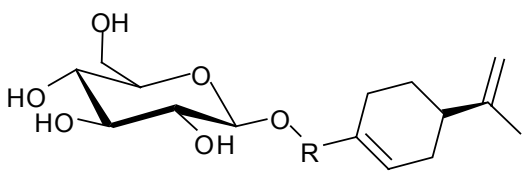
4-hydroxybenzoic acid

In STZ-diabetic rats per os administration of 4-hydroxybenzoic acid caused a decrease in plasma glucose levels dose-dependently. The compound did not affect serum insulin level and liver glycogen content in the diabetic model, but increased glucose consumption in normal and diabetic rat diaphragms. These results suggested that 4-hydroxybenzoic acid produced a hypoglycemic effect mediated by an increase in the peripheral glucose consumption (Peungvicha et al., 1998b).

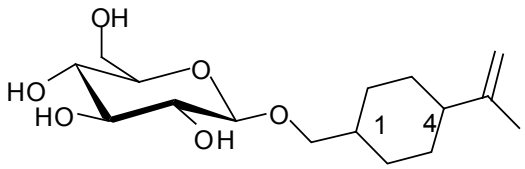
Perilla frutescens (Viridis)

Four monoterpene glycosides, perillosides A–D were isolated from the leaves of Perilla frutescens and were found to be inhibitors of rat lenses

ALR2 (Fujita et al., 1995). Perillosides A and C showed the highest inhibitory activity. Furthermore, derivatives of these monoterpene glycosides were synthesized and their activities on rat lenses ALR2 were determined to elucidate structure–activity relationships.



perilloside A: R=CH_2
perilloside B: R=CO



perilloside C:1,4-trans
perilloside D:1,4-cis

Phaseolus vulgaris (Fabaceae)

An investigation was carried out to evaluate the effect of Phaseolus vulgaris (white beans), an indigenous plant used in Unani and Ayurvedic medicine in India, on blood glucose, plasma insulin, cholesterol, triglycerides, free fatty acids, phospholipids, and fatty acid composition of total lipids in liver, kidney, and brain of normal and STZ-diabetic rats (Leelavinothan & Subramanian 2004). The results suggested that Phaseolus vulgaris exhibited hypoglycemic and hypolipidemic effects in STZ-diabetic rats after per os administration. It also prevented the fatty acid changes observed during diabetes.

Phellinus baumii (Hymenochaetaceae)

The antidiabetic effect of the crude exopolysaccharides produced from submerged mycelial culture of Phellinus baumii (mushroom) in STZ-diabetic rats was investigated (Hwang et al., 2005). The results suggested that per os administrated exopolysaccharides exhibited considerable hypoglycemic effect in STZ-induced diabetic rats and that they may be useful for the management of diabetes mellitus.

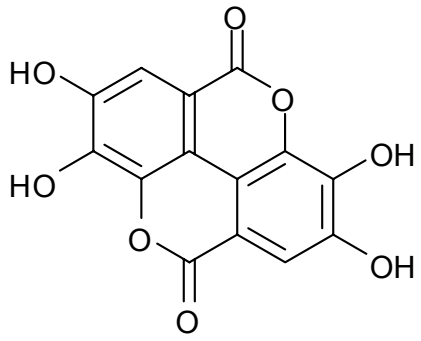
Phyllanthus amarus (Euphorbiaceae)

Diuretic, hypotensive and hypoglycemic effects of Phyllanthus amarus (syn. Phyllanthus niruri) on human subjects were assessed. Nine mild hypertensives (four of them also suffering from diabetes mellitus) were treated per os with a preparation of the whole plant of Phyllantus amarus for 10 days (Srividya & Periwal 1995). A significant reduction in systolic blood

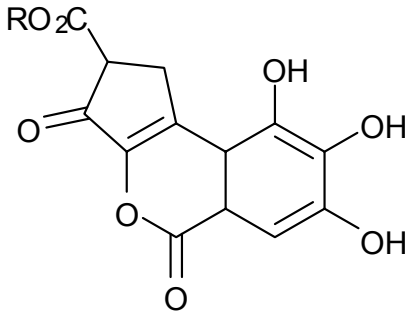
pressure in non-diabetic hypertensives subjects was noted. Blood glucose level was also significantly reduced in the treated group. Clinical observations revealed no harmful side effects. These observations indicated that Phyllanthus amarus is a potential diuretic, hypotensive and hypoglycemic drug for humans.

In contrast, the results from another study demonstrated that one week per os treatment with the aqueous extract of Phyllanthus amarus did not result the lowering of both fasting blood glucose level and postprandial blood glucose level in untreated type II diabetic patients (Mainen et al., 2001).

Ellagic acid and two more compounds, brevifolin and ethyl brevifolic carboxylate were isolated from Phyllanthus amarus and were found to inhibit rat lenses ALR2 (Shimizu et al., 1989).



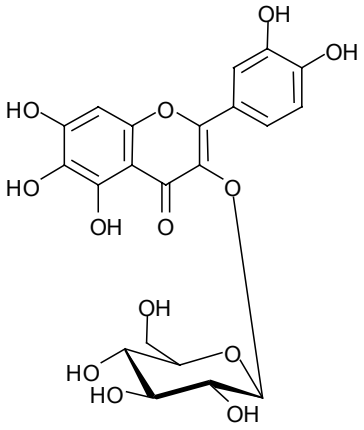
ellagic acid



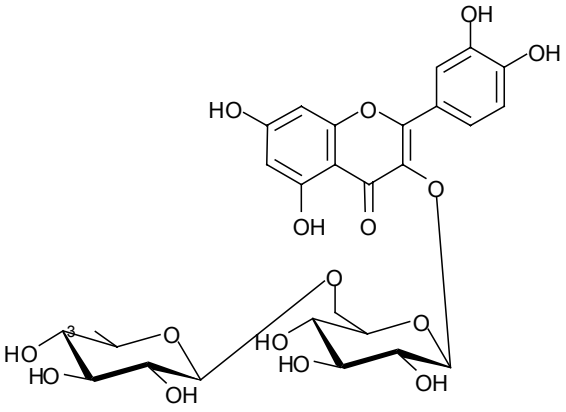
R=H: brevifolin
R=Et: ethyl brevifolin carboxylate

Phyllanthus sellowianus (Euphorbiaceae)

Phyllanthus sellowianus is a plant used in folk medicine as a hypoglycemic and diuretic agent. The reduction in blood glucose levels obtained with two certain fractions was similar to that observed with glibenclamide which was used as a reference for the hypoglycemic activity (Hnatyazyna et al., 2002). The tested fractions revealed the presence of flavonoid compounds, of which isoquercitrin and rutin were the major constituents, respectively. The possible involvement of these flavonoids in the hypoglycemic effect of the active fractions was discussed.



isoquercitrin



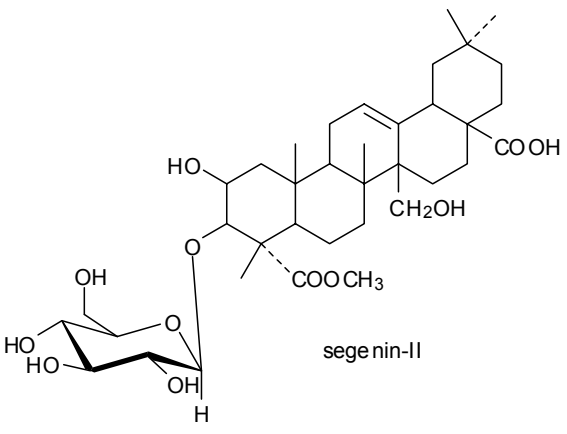
rutin

Piper sarmentosum Roxb. (Piperaceae)

The hypoglycemic effect of the water extract of the whole plant of Piper sarmentosum (Thai name: Chaplu) was examined in normal and STZ-diabetic rats (Peungvicha et al., 1998). These results demonstrated that the water extract of whole plant of Piper sarmentosum, when administered per os, has a hypoglycemic effect in rats.

Polygala senega L. (Polygalaceae)

The hypoglycemic effect of the rhizomes of Polygala senega was investigated in normal and KK-Ay mice, one of the model animals of type II diabetes mellitus (Kako et al., 1996). It was proposed that the hypoglycemic effect that occurred after i.p. administration was without altering the insulin levels and with the need of the presence of insulin in order to act. In addition, one of the active components of this hypoglycemic effect was identified as a triterpenoid glycoside, senegin-II (as a mixture of isomers).



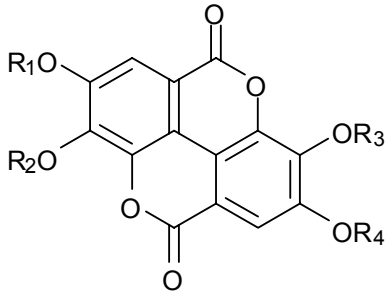
senegenin-II

Polygonatum officinale (Liliaceae)

The hypoglycemic effect of the rhizomes of Polygonatum officinale was investigated in both normal and STZ-diabetic mice (Kato 1994). The methanol extract of rhizomes of Polygonatum officinale reduced the blood glucose of normal mice after i.p. administration and also significantly lowered the blood glucose of STZ-diabetic mice. It also suppressed epinephrine-induced hyperglycemia in mice. In addition, the n-butanol fraction of the methanolic extract elicited a significant decrease in the blood glucose level of STZ-diabetic mice.

Potentilla candicans (Rosaceae)

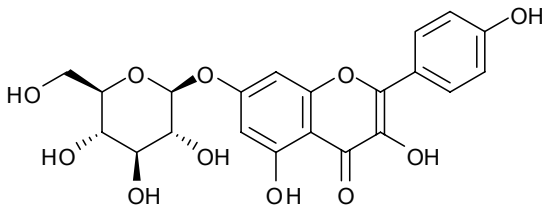
Two derivatives of ellagic acid have been isolated from "Sinfito", the root of Potentilla candicans, a plant traditionally used for the treatment of diabetic cataract and as an astringent in Mexico (Terashima et al., 1990). These derivatives have been found to inhibit in vitro ALR2.



Ellagic acid: $R_1=R_2=R_3=R_4=H$
A. $R_1=H$, $R_2=R_3=R_4=Me$
B. $R_1=SO_3K$, $R_2=R_3=R_4=Me$

Prunus davidiana (Rhamnaceae)

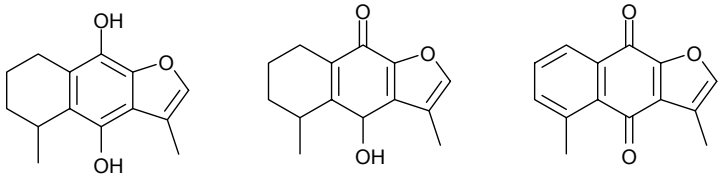
Blood glucose and total lipid levels in STZ-diabetic were determined after i.p. administration of a methanolic extract of Prunus davidiana stems and its main component, prunin (= naringenin 7-O-beta-D-glucoside) (Yokozawa & Oura 1991). From the data obtained it was concluded that i.p. administration of the methanolic extract and prunin produced a significant hypoglycemic effect. Total blood lipids were also decreased by these substances. Thus, it was suggested that this methanolic extract contained one or more hypoglycemic principles including the main flavanone glycoside, prunin, which can significantly reduce the levels of blood glucose and total lipids in STZ-diabetic rats.



narigenin 7-O-beta-D-glucoside

Psacalium decompositum (Asteraceae)

The hypoglycemic effect of the hexane, methanol and water extracts obtained from roots of Psacalium decompositum was investigated in fasting healthy mice (Alarcon-Aguilar 2002). Only the water extract significantly reduced blood glucose in a dose-dependent manner in normal mice after i.p. administration. This water extract was macerated with methanol obtaining a precipitate (WMP fraction), and it was studied in healthy and alloxan-diabetic mice. The WMP fraction showed significant hypoglycemic activity in healthy and mild diabetic mice, but the administration of this fraction to animals with severe diabetes did not cause any significant decrease in blood glucose levels. The main constituents of this fraction are the sesquiterpenouds cacacol, cacalone and maturine.



cacacol cacalone maurine

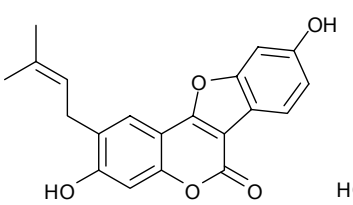
Psidium guajava (Myrtaceae)

During a screening of medicinal plants for inhibition of PTP1B, an extract from Psidium guajava leaves exhibited significant inhibitory effect on PTP1B (Oh et al., 2005). Thus, its antidiabetic effect on diabetic mice was evaluated. Taken together, it was suggested that the extract from Psidium guajava leaves possessed antidiabetic effect in type II diabetic mice model and this effect is, at least in part, mediated via the inhibition of PTP1B.

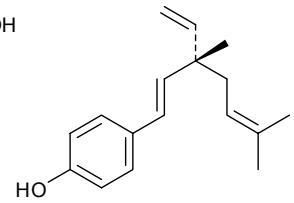
Psoralea corylifolia (Papilionaceae)

PTP1B plays a major role in the negative regulation of insulin signaling, and this establishes this protein as an attractive therapeutic target for diabetes. Bioassay-guided fractionation of the EtOAc-soluble extract of the seeds of

Psoralea corylifolia afforded two PTP1B inhibitory compounds, psoralidin and bakuchiol. (Kim et al., 2005).



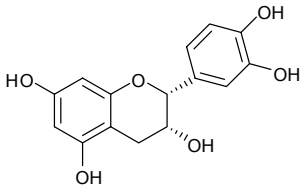
psoralidin



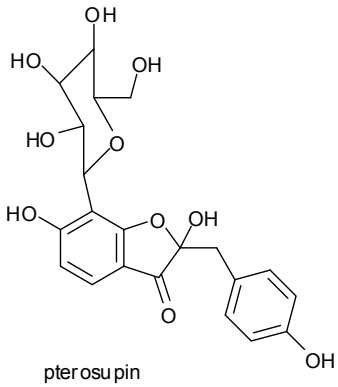
bakuchiol

Pterocarpus marsupium L. (Fabaceae) and Trigonella foenum-graecum L. (Leguminosae)

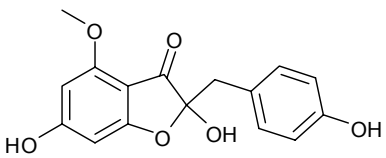
Insulin resistance (hyperinsulinemia) is now recognized as a major contributor to the development of glucose intolerance, dyslipidemia and hypertension in type II diabetic patients. Aqueous extracts of Pterocarpus marsupium bark and Trigonella foenum-graecum seeds have been shown to exert hypoglycemic/antihyperglycemic effect in experimental as well as in clinical settings (Grover et al., 2005). Results of this study, in addition to previous clinical benefits of Pterocarpus marsupium seen in type II diabetic subjects, are suggestive of usefulness of its bark in insulin resistance, the associated disorder of type II diabetes. Though several antidiabetic principles (epicatechin, pterosupin, marsupin and pterostilbene) have been identified, yet future studies are required to assert their efficacy and safety.



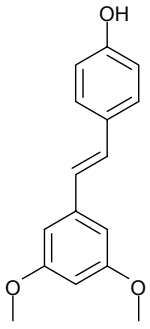
epicatechin



pterosupin



marsupin

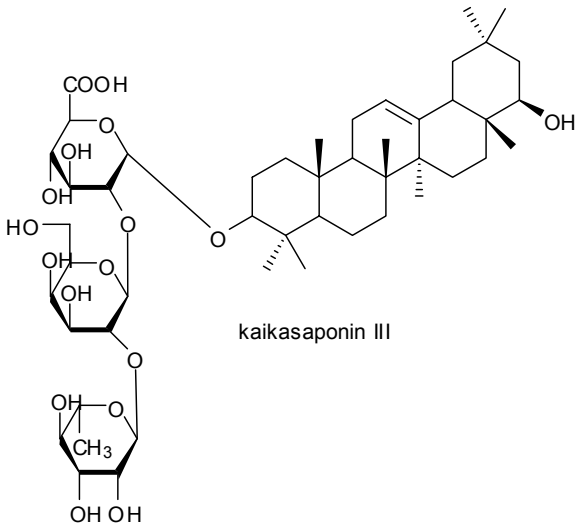


pterostilbene

Long-term complications are frequently developed in diabetes mellitus and are difficult to treat. Per os administration of the above two plant extracts exerted a favorable effect on body weight and blood glucose and on the course of cataract development. The effects were best with Pterocarpus marsupium. The exerted anti-cataract effect was evident from the decreased opacity index (Vatsa et al., 2004).

Pueraria thunbergiana (Leguminosae)

Pueraria thunbergiana has been used as a therapeutic agent for diabetes mellitus in traditional Korean medicine. The results suggested that its main constituent, kaikasaponin III (as a mixture of isomers), may exhibit its hypoglycemic and hypolipidemic effects by up-regulating or down-regulating antioxidant mechanisms via the changes in Phase I and II enzyme activities (Jongwon et al., 2004).



kaikasaponin III

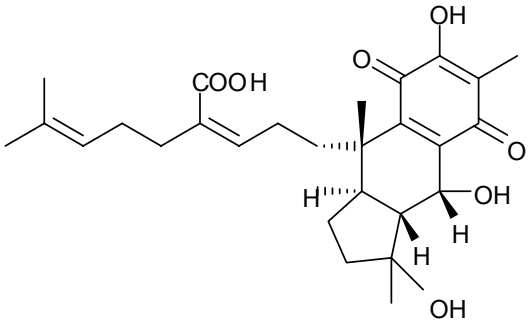
Punica granatum (Punicaceae)

Male flowers of Punica granatum are used for the treatment of diabetes mellitus in Unani medicine. Per os administration of its aqueous-ethanolic (50%, v/v) extract led to significant blood glucose lowering effect in normal, glucose-fed hyperglycemic and alloxan-induced diabetic rats (Jafri et al., 2000).

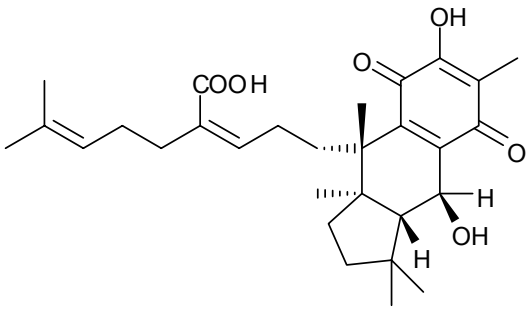
Pycnanthus angolensis Warb (Myristicaceae)

Two new compounds, pycnanthuquinone A and pycnanthuquinone B, were isolated from leaves and stems of the African plant, Pycnanthus angolensis Warb. Pycnanthuquinones A and B are the first representatives of

a novel terpenoid-type quinone skeleton, and both compounds possessed significant antihyperglycemic activity (Fort et al., 2000). Pycnanthuquinones A and B were tested for antihy-perglycemic activity in diabetic mice by per os administration. Blood glucose lowering effects were observed for both compounds.



pycnanthuquinone A



pycnanthuquinone B

Retama raetam (Fabaceae)

The effect of the aqueous extract of Retama raetam on blood glucose levels was investigated in fasting normal and STZ-diabetic rats after single and repeated per os administration (Maghrani et al., 2003). These findings suggested that the aqueous extract of Retama raetam possessed significant hypoglycemic effect in both normal and STZ-diabetic rats.

The purpose of another study was to determine the underlying mechanism of the hypoglycemic activity of an aqueous extract perfusion of Retama raetam in normal and STZ-diabetic rats after p.o. administration (Maghrani et al., 2005). It was concluded that an aqueous extract perfusion caused a potent inhibition of renal glucose reabsorption. This renal effect was at least one mechanism to explain the observed hypoglycemic activity of this plant in normal and diabetic rats.

Rubus fructicosis L. (Rosaceae), Globularia alypum L. (Globulariaceae)

The present study investigated the effect of per os administration of the aqueous extract of Rubus fructicosis and Globularia alypum leaves on blood glucose levels in normal and STZ-diabetic rats (Maghrani et al., 2002). In normal rats, single and repeated per os administration of Rubus fructicosis lowered significantly the blood glucose levels, while, Globularia alypum treatment did not change blood glucose levels. In STZ-diabetic rats, single

and repeated per os administration of both plant extracts produced significant decrease of blood glucose levels. Both treatments did not affect insulin secretion both in normal and STZ-diabetic rats, indicating that mechanism(s) by which these plants decrease blood glucose levels is extra-pancreatic at least, for the doses used. In addition, the acute toxicity study revealed that the aqueous extracts may be considered relatively safe. These findings indicated that Rubus fructicosis and Globularia alypum represent effective blood glucose lowering and a potential source for discovery of new per os active compound(s) for future therapy.

Salacia reticulata (Hippocrateaceae)

Salacia reticulata, a plant distributed in Sri Lankan and Indian forests, has been used as a supplementary food in Japan to prevent obesity and diabetes. Polyphenolic compounds may be involved in its antiobesity effects in rats through inhibition of fat metabolizing enzymes and enhanced lipolysis (Yoshikawa et al., 2002).

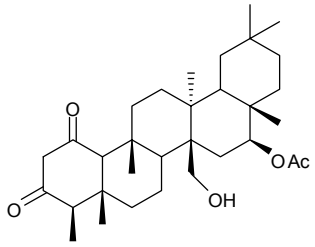
The hypoglycemic activity of the aqueous extract of the root bark of Salacia reticulata (known as kotala himbatu) has been confirmed in the normal healthy rat model (Kumara et al., 2005). The results suggested that the hypoglycemic effect of Salacia reticulata in alloxan diabetic rats after per os administration may involve an extrapancreatic effect on glucose production or clearance.

Salacia oblonga Wall (Celastraceae)

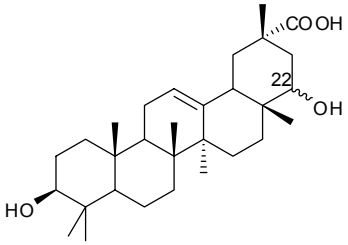
Salacia oblonga, known as Chundan, is distributed in the southern regions of India and the roots of Salacia oblonga have been extensively used as a remedy for gonorrhea, rheumatism, itch, asthma, and diabetes in the Ayurvedic system of traditional Indian medicine.

The petroleum ether extract of the root bark of Salacia oblonga Wall was studied in STZ-diabetic rats for anti-lipid peroxidative activity after i.p. administration (Krishnakumar et al., 1999; Krishnakumar et al., 2000). The results suggested that Salacia oblonga root bark extract possessed anti-diabetic and anti-peroxidative principles, and may be of value in the treatment of diabetes and associated cardiovascular complications.

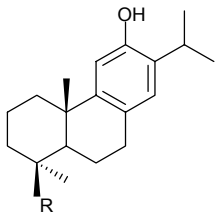
Also, three triterpenoids, kotalagenin 16-acetate, maytenfolic acid, 3α,22α-dihydroxyolean-12-en-29-oic acid and two diterpenoids, 19-hydroxyferruginol and lambertic acid, were isolated from the root of Salacia oblonga Wall and showed inhibitory activity on rat lenses ALR2 (Matsuda et al., 1999).



kotalagenic 16-acetate



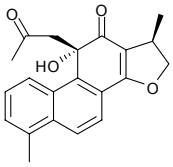
maytentolic acid: 22β-hydroxy
3α22α dihydroxyolean-12-en-29-oic acid: 22a-hydroxy



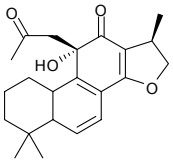
19-hydroxyferruginol: R=CH_2OH
lambetic acid: R=COOH

Salvia miltiorhiza (Lamiaceae)

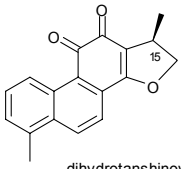
"Danshen", the dried root and rhizome of Salvia miltiorhiza is a plant that is officially listed in the Chinese Pharmacopoeia and is widely used for treatment of hematological abnormalities, heart diseases, menstrual disorder, miscarriage, hepatitis, and swelling. Seven abietane-type diterpenoids, danshenols A and B, dihydrotanshinone I, tanshinone I, cryptotanshinone, tanshinone IIA and (-)-danshexinkun A, were isolated from this plant. All these compounds showed inhibitory activity against rat lenses ALR2 with danshenol A being the strongest inhibitor (Kasimu et al., 1997; Tezuka et al., 1997).



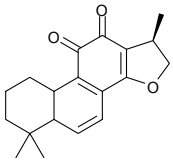
danshenol A



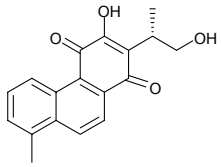
danshenol B



dihydrotanshinove
Δ^{15} tanshione I

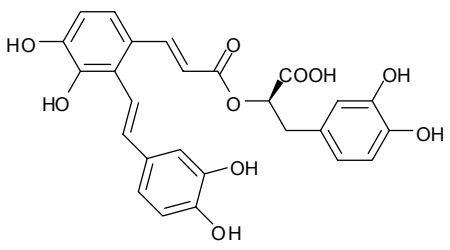


cryptotanshione
Δ^{15} tanshione IIA

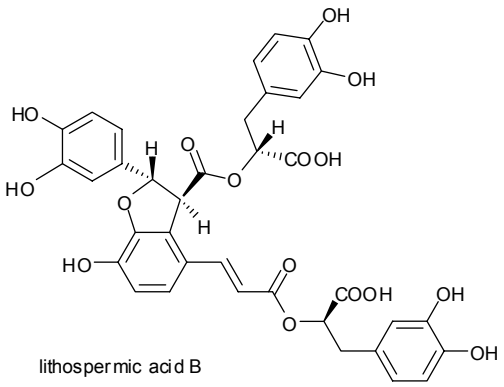


(-)-danshexinkum

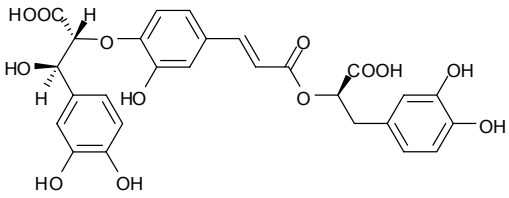
Salvianolic acid A, isolated from Salvia miltiorhiza, has been reported to have ALR2 inhibitory activity. Thus, the rat lenses ALR2 inhibitory activity of seventeen Salvia plants has been examined (Du et al., 1995; Kasimu et al., 1998). Four compounds were isolated from the root of Salvia deserta (Xinjiang-Danshen), lithospermic acid B, salvianolic acid K, salviaflaside and rosmarinic acid. They all were reported as ALR2 inhibitors.



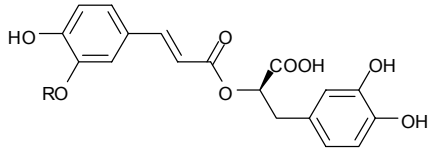
salvionolic acid A



lithospermic acid B



salvionolic acid K



salviaflaside: R=Glc
rormarinic acid: R=H

Sanguis draxonis (Acacae)

The extracts of Sanguis Draxonis, a kind of natural plant exudates, have been prescribed for handling diabetic disorders as a Chinese traditional medicine. Surprisingly, these exudates were found to be a good material for per os insulin delivery. In conclusion, the results demonstrated that Sanguis draxonis elicits a long-term hypoglycemic effect significantly after per os administration in STZ-diabetic rats and it can be considered as a stable and effective system for per os insulin delivery (Zhenqinga et al., 2004).

Sclerocarya birrea (Anacardiaceae)

In order to appraise some of the ethnomedical uses of Sclerocarya birrea, the present study was undertaken to investigate the analgesic, anti-inflammatory and anti-diabetic properties of the plant's stem-bark aqueous extract in experimental models of pain, inflammation and diabetes mellitus (Ojewole 2004). The results of this experimental study on rats indicated that Sclerocarya birrea stem-bark aqueous extract possessed analgesic, anti-inflammatory and hypoglycemic properties after per os administration. These findings gave pharmacological support to the suggested folkloric uses of the plant's stem-bark in the management and/or control of pain, inflammatory conditions, and type II diabetes mellitus in some communities of South Africa.

Scoparia dulcis L. (Scrophulariaceae)

Scoparia dulcis, commonly known as Sweet Broomweed, is widely used in Indian folk medicine for the treatment of diabetes mellitus. Per os administration of the aqueous extract of the Scoparia dulcis leaves for 45 days in experimental animals resulted in a significant reduction in blood glucose, glycosylated haemoglobin and an increase in total haemoglobin (Pari & Venkateswaran 2002). The aqueous extract also prevented a decrease in the body weight. A per os glucose tolerance test was also performed in diabetic rats, in which there was a significant improvement in glucose

tolerance in animals treated with aqueous extract of the plant and the effect was comparable to that of glibenclamide.

A significant increase in the activities of plasma insulin, SOD, CAT, glutathione peroxidase, glutathione-S-transferase and reduced GSH was observed in brain on treatment with Scoparia dulcis plant extract (Pari & Latha 2004). Since the study of induction of the antioxidant enzymes is considered to be a reliable marker for evaluating the antiperoxidative efficacy of a medicinal plant, these findings suggested a possible antiperoxidative role for Scoparia dulcis plant extract. Hence, in addition to antidiabetic effect, Scoparia dulcis possessed antioxidant potential that may be used for therapeutic purposes.

Another study further confirmed the antihyperglycemic effect of the plant extract and also demonstrated the consistent strong antioxidant properties of Scoparia dulcis used in the traditional medicine (Latha et al., 2004).

In experimental diabetes, enzymes of glucose and fatty acid metabolism are markedly altered. The effect of Scoparia dulcis L. plant extract was investigated on hepatic key metabolic enzymes of carbohydrate metabolism in STZ-diabetic rats (Pari & Latha 2004). The results indicated that the aqueous extract of Scoparia dulcis, when administered using intragastric tube, showed antihyperglycemic effect by attenuating the above biochemical alterations in STZ-induced diabetes.

Scoparia dulcis has been documented as a traditional treatment of diabetes. The obtained results revealed the possible therapeutic value of Scoparia dulcis for the better control, management and prevention of diabetes mellitus progression (Latha et al., 2004).

Smallanthus sonchifolius (Asteraceae)

Smallanthus sonchifolius (yacon), originating from South America, has become popular in Japan and in New Zealand for its tubers. The plant is also successfully cultivated in Central Europe in the Czech Republic in particular. Its aerial part is used in Japan and in Brazil as a component in medicinal teas. Based on this, the aqueous leaf extracts have been studied in vitro for their hypoglycemic activity (Valentoval et al., 2004) using rat hepatocyte primary cultures. The observed combination of radical scavenging, cytoprotective and anti-hyperglycemic activity indicated a possible use of Smallanthus sonchifolius leaves in the prevention and treatment of chronic diseases involving oxidative stress and diabetes.

In another study, the hypoglycemic effect of the water extract of the leaves of Smallantus sonchifolius (yacon) was examined in normal, transiently hyperglycemic and STZ-diabetic rats after per os or i.p.

administration. The results showed that yacon water extract produces an increase in plasma insulin concentration (Aybar et al., 2001).

Solanum lycocarpum (Solanaceae)

In Brazil, a preparation obtained from the fruits of Solanum lycocarpum, popularly known as 'fruta-de-lobo' (wolf-fruit), has been widely employed for diabetes management, obesity and to decrease cholesterol levels. The medicinal preparation consists of the green fruits which are ground in water and filtered. The white "gum" deposited is decanted and slowly dried providing a powder which is commercialized in capsules with the name "polvilho-de-lobeira". Through phytochemical analysis of this phytomedicine and the fruit of Solanum lycocarpum polysaccharides were found as the main components. Some of the polysaccharides slowed gastric emptying and act on the endocrinous system affecting the liberation of gastrointestinal hormones, lowering blood glucose levels. The hypocholesterolemic activity could be due to the increased fecal bile acid excretion as well as to the action of the short-chain fatty acids, coming from fermentation, on the synthesis of delta-aminolevulinate and by the increase of the cholesterol 7-alpha-hydroxylase and 3-hydroxy-3-methylglutaryl CoA reductase synthesis (DalAgnol & Lino von Poser 2000).

On the other hand, the hypoglycemic effect induced by the starch obtained from the unripe fruits of Solanum lycocarpum was investigated after per os administration on diabetic mice (Oliveira et al., 2003). The results did not provide evidence for a hypoglycemic effect associated with the polysaccharide fraction of Solanum lycocarpum in either normal or hyperglycemic mice. These data stresses the need for adequate pharmacological investigation of the natural products widely used in folk medicine.

Sorbus domestica (Rosaceae)

Sorbus domestica fruits are shelf grown at the mountainous regions of the northern Greece and consumed by the local population, not only as a nutritious food, but also traditionally as an antidiabetic agent, as it is believed to prevent diabetic symptoms (Termetzi et al., 2008). A study was conducted in order to demonstrate in vitro these traditional uses of Sorbus domestica fruits as well as to compare the different ways people use it and highlight their significance in the diet as protective agents against the above mentioned pathologies. The diethyl ether and the ethyl acetate fractions showed high

ALR2 inhibitory activity, without important differences between the different maturity stages of the fruits. The obtained data emphasized the fruits' potent pharmacotherapeutical role against the long-term diabetic complications (Termetzi et al., 2007).

Spergularia purpurea (Caryophyllaceae)

In order the underlying mechanism of the hypoglycemic activity of the aqueous extract of Spergularia purpurea to be determined, it was tested in diabetic mice after per os administration. The obtained data indicated that the aqueous extract of Spergularia purpurea inhibited endogenous glucose production in mice. This inhibition was at least one mechanism explaining the observed hypoglycemic activity of this plant in diabetic animals (Eddouks et al., 2003).

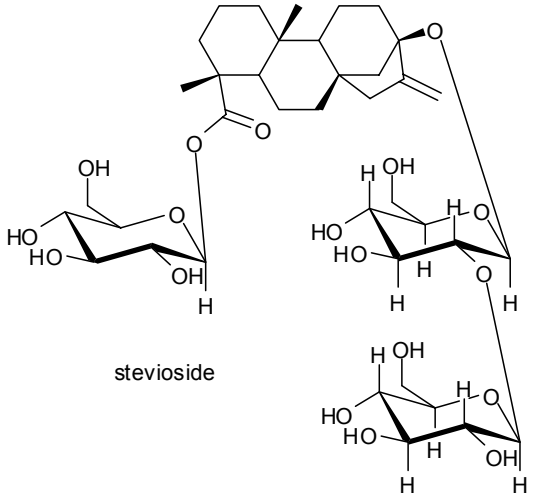
Spinacea oleracea L. (Salsolaceae)

A study was performed in healthy rabbits subjected to weekly s.c. glucose tolerance tests after intragastric administration of water, tolbutamide or traditional preparation of Spinacea oleracea The results showed a significant decrease in the area under glucose tolerance curve and the hyperglycemic peak (Roman-Ramos et al., 1995).

Stevia rebaudiana Bertoni (Compositae)

Stevioside is present in the plant Stevia rebaudiana. Plant extracts have been used for the treatment of diabetes in, for example, Brazil, although a positive effect on glucose metabolism has not been unequivocally demonstrated. The acute effects of stevioside in type II diabetic patients when administered per os were studied. It was found that stevioside reduces postprandial blood glucose levels in type II diabetic patients, indicating beneficial effects on the glucose metabolism. Stevioside may be advantageous in the treatment of type II diabetes (Gregersen et al., 2004).

The effects of stevioside on the glucose and insulin metabolism in normal rats and STZ-diabetic rats were studied. Stevioside was able to regulate blood glucose levels by enhancing not only insulin secretion, but also insulin utilization in insulin-deficient rats; the latter was due to decreased PEPCK gene expression in rat liver by stevioside's action of slowing down gluconeogenesis (Chen et al., 2005).



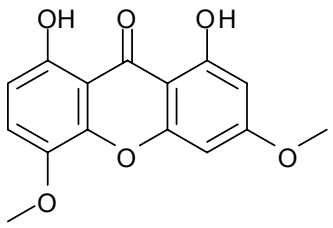
stevioside

Sutherlandia frutescens (Fabaceae)

Sutherlandia frutescens is widely used in South African traditional medicine for the management and/or control of a plethora of human ailments. In order to scientifically apprise some of the ethnomedical uses of Sutherlandia frutescens, a study was undertaken to investigate the analgesic, anti-inflammatory and antidiabetic properties of the plants shoot aqueous extract in experimental animal models (Ojewole 2004). The results of this experimental animal study suggested that the plant's shoot aqueous extract possesses analgesic, anti-inflammatory, and hypoglycemic properties, and thus lend pharmacological credence to the suggested folkloric uses of the herb in the management and/or control of painful, arthritic and other inflammatory conditions, as well as for type II diabetes mellitus in some communities of South Africa.

Swertia chirayita (Gentianaceae)

A xanthone was isolated from the hexane fraction of the Swertia chirayita plant, swerchirin. It has a very significant blood sugar lowering effect after per os administration in fasted, fed, glucose loaded, and tolbutamide pre-treated albino rat models (Bajpai et al., 1991).



swerchirin

Syzygium cumini L. (Myrtaceae)

The effect of feeding along with diet of different fractions obtained from the seeds of Syzygium cumini was tried on fasting blood glucose and glucose tolerance in normal and alloxan diabetic rats (Pandey et al., 2002). The observations indicated that the hypoglycemic effect of Syzygium cumini seeds, administered per os, was due to water soluble gummy fibre. The water insoluble neutral detergent fibre and other constituents of the seeds had no significant hypoglycemic effects.

Syzygium aromaticum (Myrtaceae)

Syzygium aromaticum (commonly referred to as clove) extract acts like insulin in hepatocytes and hepatoma cells by reducing PEPCK and G6Pase gene expression. Much like to insulin, clove-mediated repression is reversed by PI3K inhibitors and NAC inhibitors. The results demonstrated that consumption of certain plant-based diets may have beneficial effects for the treatment of diabetes and indicate a potential role for compounds derived from clove as insulin-mimetic agents (Prasadb et al., 2005).

Syzygium cordatum (Myrtaceae)

The present study investigated the hypoglycemic effect of Syzygium cordatum leaf extract in non-diabetic and STZ-diabetic rats when injected into the central lateral ventral. Syzygium cordatum leaf extract contains compounds that could be effective in mild diabetes mellitus or in cases of glucose tolerance impairment (Musabayane et al. 2005).

Syzygium cumini and Syzyrium jambos (Mystaceae)

The use of alternative therapies to treat diabetes, including teas prepared with different vegetables, is widespread in Brazil. In Porto Alegre, a southern city of Brazil, the tea prepared from leaves of Syzygium cumini or Syzyrium jambos has been reported to be used frequently by diabetic patients. The postulated antihyperglycemic effect of the Syzyrium cumini was investigated in three experiments. In the first, a randomized, parallel, placebo controlled trial, tea prepared from leaves of Syzygium cumini did not present any antihyperglycernic effect in 30 non diabetic young volunteers submitted to a glucose blood tolerance test. In the animal experiments, the effect of increasing doses of the crude extract prepared from leaves of the plant and administered with oro-gastric tube, on the post-prandial blood glucose level

of normal rats and STZ-diabetic rats was tested. These results do not rule out hypoglycemic effects in patients with type II diabetes mellitus, but strongly suggest that this herb can not be recommended for an antihyperglycemic treatment (Teixeira et al., 2000).

Telfaria occidentalis (Compositae)

The hypoglycemic effect of the aqueous extract of the leaves of Telfaria occidentalis was assessed in normoglycemic, glucose induced hyperglycemic and STZ-diabetic diabetic mice. The results of this study indicated that the aqueous extract of the leaves of Telfaria occidentalis possess hypoglycemic activity after per os administraton (Aderibidge et al., 1999).

Tetrapleura tetraptera (Fabaceae)

The fruit of Tetrapleura tetraptera is frequently used in Tropical African traditional medicine for the management and/or control of an array of human ailments, including arthritis and other inflammatory conditions, asthma, diabetes mellitus, hypertension, epilepsy and schistosomiasis. The present study was undertaken to examine the anti-inflammatory and hypoglycaemic effects of Tetrapleura tetraptera fruit aqueous extract in rats. Fresh egg albumin-induced pedalo edema and STZ-induced diabetes mellitus were used as experimental test models of inflammation and diabetes. The plant extract was administered per os and produced dose-dependent, significant reductions in the blood glucose levels of both fasted normal and fasted diabetic rats. The results of this experimental animal study indicated that Tetrapleura tetraptera fruit aqueous extract possesses anti-inflammatory and hypoglycaemic properties. The experimental findings lend pharmacological credence to the suggested folkloric uses of the plant's fruit in the management and/or control of arthritis and other inflammatory conditions, as well as in type II diabetes mellitus in some Yoruba-speaking communities of South-Western Nigeria (Ojewolea & Adewunmib 2004).

Teucrium polium (Labiatae)

The aqueous extract of Teucrium polium has long being used in Iran as a hypoglycemic aid without any knowledge about its probable side effects and mode of action. In an effort to assess the claimed hypoglycemic property of the herb and to derive some knowledge about the mechanism of action, the crude extract was administered per os to a group of STZ-diabetic rats for six consecutive weeks (Esmaeli & Yazdanparast 2004). The obtained data

indicated that Teucrium polium crude extract is able to enhance insulin secretion and that the plant extract, probably without metabolic transformation, is able to reduce high blood glucose levels through enhancing insulin secretion by the pancreas.

Teucrium laurifolia (Labiatae)

Teucrium laurifolia (Purple flower strain) were tested for hypoglycemic activity in rats (Aritajat et al., 2004). The results showed that high blood glucose levels of diabetic rats were associated with severe destruction of β cells (insulin-secreting cells) in the islet of Langerhans. The 15-day-treatment of Teucrium laurifolia extract decreased levels of blood glucose in diabetic rats. Whether Teucrium laurifolia leaf contains insulin-like substance(s) which directly act as hypoglycemic agents, or contains substances that induce the regenerative process of β cells remained to be further investigated.

Trigonella foenumgraecum (Leguminoseae)

Trigonella foenumgraecum (fenugreek) seeds, a common condiment used in Indian homes, have been found to diminish hyperglycemia in normal and STZ-induced diabetic rats after per os administration. Fasting blood glucose, urinary sugar excretion, serum cholesterol and triglyceride levels in diabetics were significantly reduced. Clinical symptoms like polyuria, polyphagia and polydypsia were improved. These effects of fenugreek seeds seemed to be due to the gum fibre present in them. Fenugreek was reported to be absolutely safe for consumption based on a long-term animal study (Udayasekhara 1996).

Urtica dioica (Urticaceae)

The blood glucose lowering effect of Urtica dioica (stinging nettle) as a medicinal plant has been noted in old writings such as those of Avicenna. It was demonstrated that the active fraction named F1, caused a marked increase in insulin secretion (Bijan et al., 2003). A simultaneous assay of glucose showed that the increase in insulin level was associated with a decrease in glucose level. Furthermore, the active component of Urtica dioica was found to increase the levels of insulin in blood serum in normal and STZ-diabetic rats that were injected i.p. with the active ingredient of the extract. The results showed that the blood lowering effect of the extract was due to the enhancement of insulin secretion by Langerhance isletes.

Vaccinium myrtillus L. (Ericaceae), Taraxacum officinale (Asteraceae), Cichorium intybus L. (Compositae), Juniperus communis L. (Cuphessaceae), Centaurium umbellatum Gilib. (Genianaceae), Phaseolus vulgaris L. (Fabaceae), Achillea millefolium L. (Asteraceae), Morus nigra L. (Moraceae), Valeriana officinalis L. (Valeranaceae) and Urtica dioica L (Urticaceae)

Treatment with the plant extract P-9801091 (is an antihyperglycemic preparation containing Myrtilli folium (Vaccinium myrtillus L.), Taraxaci radix (Taraxacum officinale), Cichorii radix (Cichorium intybus L.), Juniperi fructus (Juniperus communis L.), Centaurii herba (Centaurium umbellatum Gilib.), Phaseoli pericarpium (Phaseolus vulgaris L.), Millefolii herba (Achillea millefolium L.), Mori folium (Morus nigra L.), Valerianae radix (Valeriana of ficinalis L.) and Urticae radix (Urtica dioica L)) resulted to statistically significant changes in antioxidative defense occurred in an experimental model of short-term diabetes mellitus. The treatment with the plants extract that was mixed with laboratory chow led to a significant increase in the catalytic concentration of GSTs in the liver of diabetic mice and a decrease in MDA concentration, which could be explained by its antihyperglycemic effect. Hyperglycemia in diabetes mellitus is responsible for the development of oxidative stress (via glucose auto-oxidation and protein glycation), which is characterized by increased lipid peroxide production and/or decreased antioxidative defense. (Petevski et al., 2003)

Viscum album (Viscaceae)

The acute hypoglycemic effect of water and ethanolic extracts of three Viscum album (subspecies: album, austriacum, abietis) were investigated in normoglycemic and STZ-diabetic rats (Orhan et al., 2005). The extracts were administered to the experimental animals per os using a gastric gavage needle The findings obtained in the experiments demonstrated that European mistletoe (Viscum album L.) subspecies possessed potent antihyperglycemic and antioxidant activity depending on the host plant.

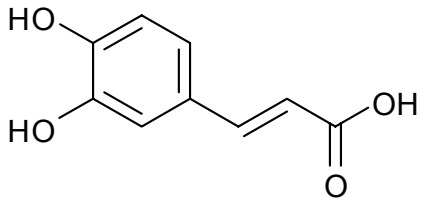
Withania somnifera (Solanaceae)

Hypoglycemic, diuretic and hypocholesterolemic effects of roots of Withania somnifera were assessed on human subjects (Radhika et al., 2000). Six mild type II diabetic subjects and six mild hypercholesterolemic subjects

were treated per os with the powder of roots of Withania somnifera. Suitable parameters were studied in the blood and urine samples of the subjects along with dietary pattern before and at the end of treatment period. Decrease in blood glucose, increase in urine sodium, urine volume, significant decrease in serum cholesterol, triglycerides, LDL and VLDL cholesterol were observed indicating that the root of Withania somnifera is a potential source of hypoglycemic, diuretic and hypocholesterolemic agents. Clinical observations revealed no adverse effects.

Xanthium strumarium (Compositae)

The antihyperglycemic effect of caffeic acid, one of the phenolic compounds contained in the fruit of Xanthium strumarium, was investigated (Hsu et al., 2000). After an i.v. injection of caffeic acid into diabetic rats of both STZ-induced and insulin-resistant models, a dose-dependent decrease of plasma glucose was observed.

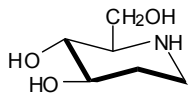


caffeic acid

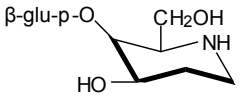
However, a similar effect was not shown in normal rats. An insulin-independent action of caffeic acid can thus be considered. In addition, this compound reduced the elevation of plasma glucose levels in insulin-resistant rats receiving a glucose challenge test. Also, glucose uptake into the isolated adipocytes was raised by caffeic acid in a concentration-dependent manner. The increase of glucose utilization by caffeic acid seemed to be responsible for the lowering of plasma glucose.

Xanthocercis zambesiaca (Leguminosae)

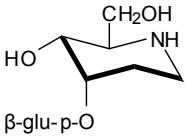
The aqueous and methanol extract of the leaves and root of Xanthocercis zambesiaca and eight structurally related nitrogen-containing sugars, were evaluated, after i.p. administration, for antihyperglycemic effects in STZ-diabetic mice (Nojima et al., 1998). The insulin-releasing effects of fagomine were also investigated and it increased plasma insulin level in STZ-diabetic mice and this induced potentiation of insulin release may partly contribute to antihyperglycemic action.



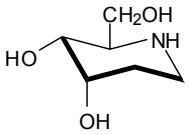
fagomine



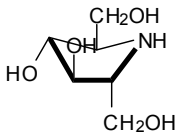
4-O-β-O-glucopyrano-sylfogomine



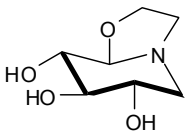
3-O-β-O-glucopyranosylflagomine



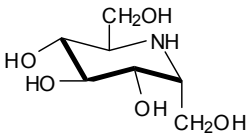
3-epifagomine



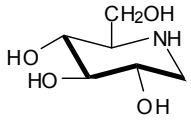
2,5-dideoxy-2,5-imino-D-mannitol



castonospermine



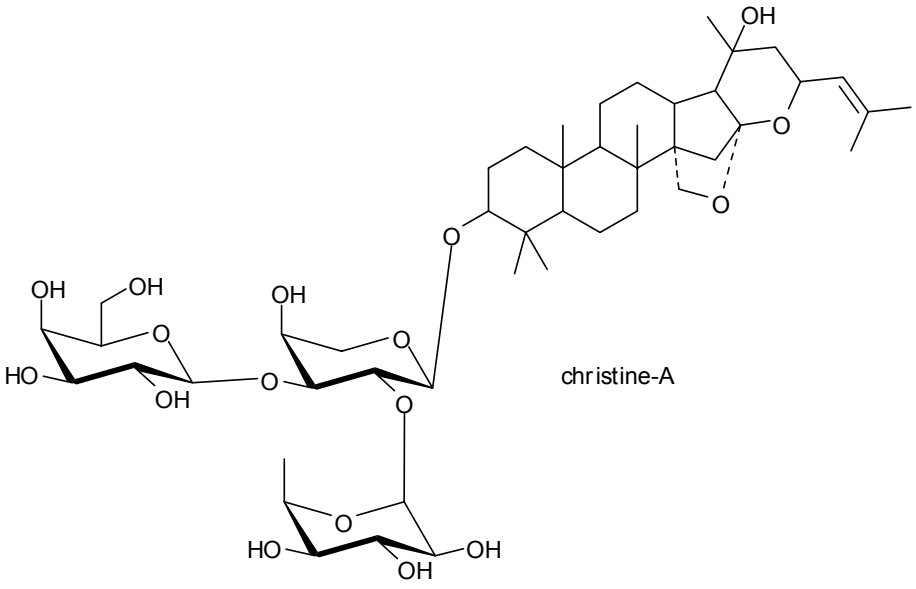
a-homonojirimycin



1-deoxynojirimycin

Zizyphus spina-christi (Rhamnaceae)

Zizyphus is one of the plants commonly used in Egyptian folk medicine for the treatment of different diseases. The effect of the butanol extract of Zizyphus spina-christi leaves as well as christinin-A, its principle saponin glycoside, was investigated in normal and STZ-diabetic rats (as a mixture of isomers) (Glombitza et al., 1994). In normal rats, treatment in both cases for one and four weeks produced insignificant changes in all studied parameters. However, in diabetic rats, treatment with the remedies significantly reduced serum glucose level, liver phosphorylase and G6Pase activities, and significantly increased serum pyruvate level and liver glycogen content after 4 weeks' treatment. There was also marked improvement in glucose utilization in diabetic rats. Serum insulin and pancreatic cAMP levels showed significant increase in diabetic rats treated for a period of 4 weeks with the butanol extract.



christine-A

Abbreviations

AGEs: advanced glycation end products; ALR2: aldose reductase; CAT: catalase; G6Pase: glucose-6-phosphatase; G6PD: glucose 6-phosphate dehydrogenase; GK: glucokinase; GLUT4: glucose transport protein, isozyme 4; GSH: glutathione; GST: glutathione S-transferase; HDL: high density lipoprotein; HK: hexokinase; HMGR: HMG CoA reductase; i.m.: intramascular; i.p: intraperitoneal; i.v.: intravenous; IDDM: insulin dependent diabetes mellitus (type I); Km: Michaelis constant for enzymatic reactions; LDL: low density lipoprotein; LOX: lipoxygenase; MDA: malondialdehyde; MDH: malate dehydrogenase; NAC: N-acetylcysteine; NIDDM: non insulin dependent diabetes mellitus (type II); PEPCK: phosphoenolpyruvate carboxykinase; per os: orally; PFK: phosphofructokinase; PI3K: phosphatidylinositol 3 kinase; PTP1B: protein tyrosine phosphatase 1B; s.c.: subcutaneous; SOD: superoxide dismutase; STZ: streptozotocin; TGF: T-cell growth factor; VLDL: very low density lipoprotein.

References

1. Abdel-Hassan IA, Abdel-Barry JA, Tariq MS. "The hypoglycemic and antihyperglycemic effect of citrullus colocynthis fruit aqueous extract in normal and alloxan diabetic rabbits". *J. Ethnopharmacol.* 2000; 71(1-2): 325-330.
2. Adamson I, Okafor C, Abu-Bakare A. "A supplement of Dikanut (Irvingia gabonesis) improves treatment of type II diabetics". *West Afr. J. Med.* 1990; 9(2): 108-115.
3. Aderibigbe AO, Emudianughe TS, Lawal BA. "Antihyperglycemic effect of Mangifera indica in rat". *Phytother. Res*. 1999; 13(6): 504-507.
4. Aderibigbe AO, Emudianughe TS, Lawal BA. "Evaluation of the antidiabetic action of Mangifera indica in mice". *Phytother. Res*. 2001; 15(5): 456-458.
5. Aderibigbe AO, Lawal BA, Oluwagbemi JO. "The antihyperglycamic effect of Telfaria occidentalis in mice". *Afr. J. Med. Med. Sci*. 1999; 28(3-4): 171-175.
6. Aguiyi JC, Obi CI, Gang SS, Igweh AC. "Hypoglycemic activity of Ocimum gratissimum in rats". *Fitoterapia* 2000; 71(4): 444-446.
7. Ahmad M, Akhtar MS, Malik T, Gilani AH. "Hypoglycemic action of the flavonoid fraction of Cuminum nigrum seeds". *Phytother. Res*. 2000; 14(2): 103-106.
8. Aida K, Tawata M, Shindo H, Onaya T, Sasaki H, Yamaguchi T, Chin M, Mitsuhashi H. "Isoliquiritigenin: a new ALR2 inhibitor from glycyrrhizae radix". *Planta Med.* 1990; 56(3): 254-258.
9. Ajabnoor MA. "Effect of aloes on blood glucose levels in normal and alloxan diabetic mice". *J. Ethnopharmacol.* 1990; 28(2): 215-220.
10. Akhtar MS and Iqbal J. "Evaluation of the hypoglycemic effect of Achyranthes aspera in normal and alloxan-diabetic rabbits ". *J. Ethnopharmacol*. 1991; 31(1): 49-57.

11. Akowuah GA, Sadikun A, Mariam A. "Flavonoid Identification and Hypoglycemic Studies of the Butanol Fraction from Gynura procumbens". *Int. J. Pharmacogn*. 2002; 40(6): 405-410.
12. Alarcon-Aguilar FJ, Hernandez-Galicia E, Campos-Sepulveda AE, Xolalpa-Molina S, Rivas-Vilchis GF, Vazquez-Carrillo LI, Roman-Ramos R. "Evaluation of the hypoglycemic effect of Cucurbita ficifolia Bouche´ (Cucurbitaceae) in different experimental models". *J. Ethnopharmacol*. 2002; 82: 185-189.
13. Alarcon-Aguilar FJ, Jimenez-Estrada M, Reyes-Chilpa R, Roman-Ramos R. "Hypoglycemic effect of extracts and fractions from Psacalium decompositum in healthy and alloxan-diabetic mice". *J. Ethnopharmacol.* 2000; 72(1-2): 21-27.
14. Alarcon-Aguilar FJ, Roman-Ramos R, Jimenez-Estrada M, Reyes-Chilpa R, Gonzalez-Paredes B. Flores-Saenz JL. "Effects of three Mexican medicinal plants (Asteraceae) on blood glucose levels in healthy mice and rabbits". *J. Ethnopharmacol*. 1997; 55: 171-177.
15. Ali AA, Mohamed MH, Kamel MS. "Studies on Securigera securidacea (L.) Deg. Et Dprfl. Fabaceae) seeds, an antidiabetic Egyptian folk medicine". *Pharmazie* 1998; 53: 710-715.
16. Almeida RN, Filho JM, Naik SR. "Chemistry and pharmacology of an ethanol extract of Bumelia sartorum". *J. Ethnopharmacol*. 1985; 14(2-3): 173-185.
17. Al-Shamaony L, Al-Khazraji SM, Twaij HA. "Hypoglycemic effect of Artemisia herba alba. Effect of a valuable extract on some blood parameters in diabetic animals". *J. Ethnopharmacol*. 1994; 43(3): 167-171.
18. Ananthan R, Latha M, Pari L, Ramkumar KM,, Baskar CG, Narmatha Bai V. "Effect of Gymnema montanum on Blood Glucose, Plasma Insulin, and Carbohydrate Metabolic Enzymes in Alloxan-Induced Diabetic Rats". *J. Med. Food*. 2003b; 6(1): 43-49.
19. Ananthan R, Latha M, Ramkumar KM, Pari L, Baskar C, Narmatha Bai V. "Effect of Gymnema montanum Leaves on Serum and Tissue Lipids in Alloxan Diabetic Rats Experimental Diabesity". *Research*, 2003a; 4(3): 183-189.
20. Ananthi J, Prakasam A, Pugalendi KV. "Antihyperglycemic activity of Eclipta alba leaf on alloxan-induced diabetic rats". *Yale J. Biol. Med.* 2003; 76(3): 97-102.
21. Andallu B, Radhika B. "Hypoglycemic, diuretic and hypocholesterolemic effect of winter cherry (Withania somnifera, Dunal) root". *Indian J. Exp. Biol*. 2000; 38(6): 607-609.
22. Andrade-Cetto A, Heinrich M. "Mexican plants with hypoglycemic effect used in the treatment of diabetes". *J. Ethnopharmacol*. 2005; 99: 325-348.
23. Andrade-Cetto A, Wiedenfeld H, Revilla MC, Sergio IA. "Hypoglycemic effect of Equisetum myriochaetum aerial parts on streptozotocin diabetic rats". *J. Ethnopharmacol*. 2000; 72(1-2): 129-133.
24. Andrade-Cetto A, Wiedenfeld H. "Hypoglycemic effect of Acosmium panamense bark on streptozotocin diabetic rats". *J. Ethnopharmacol*. 2004; 90: 217-220.
25. Andrade-Cetto A, Wiedenfeld H. "Hypoglycemic effect of Cecropia obtusifolia on streptozotocin diabetic rats". *J. Ethnopharmacol*. 2001; 78: 145-149.

26. Anjel de la Fuenta J, Manzanaro S. "ALR2 inhibitors from natural sources". *Nat. Prod. Rep*. 2003; 20: 243-251.
27. Aritajat S, Wutteerapol S, Saenphet K. "Anti-diabetic effect of Thunbergia laurifolia Linn. aqueous extract". *Southeast Asian J. Trop. Med. Public Health* 2004; 35(Suppl 2): 53-58.
28. Asano N, Yamashita T, Yasuda K, Ikeda K, Kizu H, Kameda Y, Kato A, Nash RJ, Lee HS, Ryu KS. "Polyhydroxylated alkaloids isolated from mulberry trees (Morusalba L.) and silkworms (Bombyx mori L.)". *J. Agric. Food Chem*. 2001; 49(9): 4208-4213.
29. Augusti KT. "Antidiabetic effects of a glycoside of leucopelargonidin isolated from Ficus bengalensis Linn.Cherian ". *Indian J. Exp. Biol*. 1993; 31(1): 26-29.
30. Aybar MJ, Sanchez Riera AN, Grau A, Sanchez SS. 'Hypoglycemic effect of the water extract of Smallantus sonchifolius (yacon) leaves in normal and diabetic rats". *J. Ethnopharmacol*. 2001; 74(2): 125-132.
31. Babu PA, Suneetha G, Boddepalli R, Vasantha Lakshmi V, Sudha Rani T, RamBabu Y and Srinivas K. "A Database of 389 medicinal plants for diabetes". *Bioinformation* 2006; 1(4): 130-130.
32. Babu PS, Stanely Mainzen Prince P. "Antihyperglycemic and antioxidant effect of hyponidd, an ayurvedic herbomineral formulation in STZ-diabetic rats". *J. Pharm. Pharmacol*. 2004; 56(11): 1435-1442.
33. Bailey CJ, Day C, Turner SL, Leatherdale BA. "Cerasee, a traditional treatment for diabetes. Studies in normal and streptozotocin diabetic mice". *Diabetes Res*. 1985; 2(2): 81-84.
34. Bailey CJ, Day C. "Metformin: its botanical background". *Pract. Diab. Int*. 2004; 21(3): 115-117.
35. Bailey CJ, Day C. "Metformin: its botanical background". *Pract. Diab. Int.* 2004; 21(3): 115-117.
36. Bajpai MB, Asthana RK, Sharma NK, Chatterjee SK, Mukherjee SK. "Hypoglycemic effect of swerchirin from the hexane fraction of Swertia chirayita". *Planta Med*. 1991; 57(2): 102-104.
37. Baskaran K, Kizar Ahamath B, Radha Shanmugasundaram K, Shanmugasundaram ER. "Antidiabetic effects of a leaf extract from Gymnema sylvestre in non-insulin-dependent diabetes mellitus patients". *J. Ethnopharmacol*. 1990; 30(3): 295-300.
38. Basnet P, Kadota S, Terashima S, Shimizu M, Namba T. "Two new 2-arylbenzofuran derivatives from hypoglycemic activity-bearing fractions of Morus insignis". *Chem. Pharm. Bull*. (Tokyo). 1993; 41(7): 1238-1243.
39. Bhaskara R, Murugesan T, Sinha S, Saha BP, Pal M, Mandal SC. "Glucose lowering efficacy of Ficus racemosa bark extract in normal and alloxan diabetic rats". Phytother. Res. 2002; 16(6): 590-592.
40. Bnouham M, Ziyyat A, Mekhfi H, Tahri A, Legssyer A. "Medicinal plants with potential antidiabetic activity- A review of ten years of herbal medicine research (1990-2000)". *Int. J. Diabetes & Metabolism* 2006; 14: 1-25.
41. Bolkent S, Yanardag R, Tabakoglu-Oguz A, Ozsoy-Sacan A. "Effects of chard (Beta bulgaris L. var. cicla) extract on pancreatic B cells in streptozotocin-

diabetic rats: a morphological and biochemical study". *J. Ethnopharmacol*. 2000; 73: 251-259.
42. Budinsky A, Wolfram R, Oguogho A, Efthimiou Y, Stamatopoulos Y, Sinzinger H. "Regular ingestion of opuntia robusta lowers oxidation injury". *Prostaglandins Leukot. Essent. Fatty Acids*, 2001; 65(1): 45-50.
43. Campos KE, Diniz YE, Cataneo AC, Faine LA, Alves MJQF, Novelli ELB. "Hypoglycemic and antioxidant effects of onion, Allium cepa: dietary onion addition, antioxidant activity and hypoglycemic effects on diabetic rats". *Int. J. Food Sci. Nutr*. 2003; 54(3): 241-246.
44. Chakrabarti R, Vikramadithyan RK, Mullangi R, Sharma VM, Jagadheshan H, Rao YN, Sairam P, Rajagopalan R. "Antidiabetic and hypolipidemic activity of Helicteres isora in animal models". *J. Ethnopharmacol.* 2002; 81(3): 343-349.
45. Chakrabarti S, Biswas TK, Rokeya B, Ali L, Mosihuzzaman M, Nahar N, Azad Khan AK, Mukherjee B. " Advanced studies on the hypoglycemic effect of Caesalpinia bonducella F. in type I and 2 diabetes in Long Evans rats". *J. Ethnopharmacol*. 2003; 84: 41-46.
46. Chang SL, Chang CL, Chiang YM, Hsieh RH, Tzeng CR, Wu TK, Sytwu HK, Shyur LF, Yang WC. "Polyacetylenic compounds and butanol fraction from Bidens pilosa can modulate the differentiation of helper T cells and prevent autoimmune diabetes in non-obese diabetic mice". *Planta Med*. 2004; 70(11): 1045-1051.
47. Chattopadhyay RR. "Hypoglycemic effect of Ocimum sanctum leaf extract in normal and streptozotocin diabetic rats". *Indian J. Exp. Biol*. 1993; 31(11): 891-893.
48. Chempakam, B. "Hypoglycemic activity of arecoline in betel nut Areca catechu L". *Indian J. Exp. Biol.* 1993; 31: 474-475.
49. Chen TH, Chen SC, Chan P, Chu YL, Yang HY, Cheng JT. " Mechanism of the hypoglycemic effect of stevioside, a glycoside of Stevia rebaudiana". *Planta Med*. 2005; 71(2): 108-113.
50. Chithra P, Sajithlal GB, Chandrakasan G. "Influence of aloe vera on the healing of dermal wounds in diabetic rats". *J. Ethnopharmacol*. 1998; 59(3): 195-20.
51. Choi JS, Yokozawa T, Oura H. "Improvement of hyperglycemia and hyperlipemia in streptozotocin-diabetic rats by a methanolic extract of Prunus davidiana stems and its main component, pruning". *Planta Med*. 1991; 57(3): 208-211.
52. Choi1 J, Shin1 M, Park K-W, Lee K-T, Jung HJ, Lee MS, Park HJ. "Effect of Kaikasaponin III Obtained from Pueraria thunbergiana Flowers on Serum and Hepatic Lipid Peroxides and Tissue Factor Activity in the Streptozotocin-Induced Diabetic Rat". *J. Med. Food*. 2004; 7(1): 31-37.
53. Dall'Agnol R, Lino von Poser G. "The use of complex polysaccharides in the management of metabolic diseases: the case of Solanum lycocarpum fruits". *J. Ethnopharmacol*. 2000; 71(1-2): 337-341.
54. Das AV, Padayatti PS, Paulose CS. "Effect of leaf extract of Aegle marmelose (L.) Correa ex Roxb. on histological and ultra structural changes in tissues of streptozotocin induced diabetic rats". *Indian J. Exp. Biol.* 1996; 34(4): 341-345.
55. Day C, Cartwright T, Provost J, Bailey CJ. "Hypoglycemic effect of Momordica charantia extracts". *Planta Med*. 1990; 56(5): 426-429.

56. De Sousa E, Zanatta L, Seifriz I, Creczynski-Pasa TB, Pizzolatti MG, Szpoganicz B, Silva FR. "Hypoglycemic effect and antioxidant potential of kaempferol-3, 7-O-(alpha)-dirhamnoside from Bauhinia forficata leaves". *J. Nat. Prod*. 2004; 67(5): 829-832.
57. Diamond J. "The double puzzle of diabetes ". *Nature* 2003; 423: 599-602.
58. Diatewa M, Samba CB, Assah TC, Abena AA. "Hypoglycemic and antihyperglycemic effects of diethyl ether fraction isolated from the aqueous extract of the leaves of Cogniauxia podoleana Baillon in normal and alloxan-induced diabetic rats". *J. Ethnopharmacol*. 2004; 92(2-3): 229-232.
59. Du GH, Qiu Y, Tian YE, Zhang JT. "Prevention of galactose-induced cataractogenesis in rats by salvianolic acid A". *Acta Pharm.Sín*. 1995; 30: 561-566.
60. Eddouks M, Jouad H, Maghrani M, Lemhadri A, Burcelin R. "Inhibition of endogenous glucose production accounts for hypoglycemic effect of Spergularia purpurea in streptozotocin mice". *Phytomedicine* 2003; 10(6-7): 594-599.
61. Eddouks M, Lemhadri A, Michel JB. "Caraway and caper: potential anti-hyperglycemic plants in diabetic rats". *J. Ethnopharmacol*. 2004; 94(1): 143-148.
62. Eddouks M, Lemhadri A, Zeggwagh NA, Michel JB. "Potent hypoglycemic activity of the aqueous extract of Chamaemelum nobile in normal and STZ-diabetic rats". *Diabetes Res. Clin. Pract*. 2005; 67(3): 189-195.
63. Eddouks M, Maghrani M, Zeggwagh NA, Michel JB. "Study of the hypoglycemic activity of Lepidium sativum L. aqueous extract in normal and diabetic rats". *J. Ethnopharmacol*. 2005; 97(2): 391-395.
64. El-Fiky FK, Abou-Karam MA, Afify EA. "Effect of Luffa aegyptiaca (seeds) and Carissa edulis (leaves) extracts on blood glucose level of normal and streptozotocin diabetic rats". *J. Ethnopharmacol*. 1996; 50(1): 43-47.
65. El-Missiry MA, El Gindy AM. "Amelioration of alloxan induced diabetes mellitus and oxidative stress in rats by oil of Eruca sativa seeds". *Ann. Nutr. Metab*. 2000; 44(3): 97-100.
66. Esmaeili MA, Yazdanparast R. "Hypoglycemic effect of Teucrium polium: studies with rat pancreatic islets". *J. Ethnopharmacol*. 2004; 95: 27-30.
67. Fagot-Campagna A. & Narayan K. "Type 2 diabetes in children". *Br. Med. J*. 2001: 322: 377-387.
68. Farias RA, Rao VS, Viana GS, Silveira ER, Maciel MA, Pinto AC. "Hypoglycemic effect of trans-dehydrocrotonin, a nor-clerodane diterpene from Croton cajucara". *Planta Med*. 1997; 63(6): 558-560.
69. Farzami B, Ahmadvand D, Vardasbi S, Majin FJ, Khaghani Sh. "Induction of insulin secretion by a component of Urtica dioica leave extract in perifused Islets of Langerhans and its in vivo effects in normal and streptozotocin diabetic rats". *J. Ethnopharmacol*. 2003; 89: 47-53.
70. Fernando MR, Wickramasinghe N, Thabrew MI, Ariyananda PL, Karunanayake EH. "Effect of Artocarpus heterophyllus and Asteracanthus longifolia on glucose tolerance in normal human subjects and in maturity-onset diabetic patients". *J. Ethnopharmacol.* 1991; 31(3): 277-282.
71. Fernando MR, Wickramasinghe SMDN, Thabrew MI. "Extra Pancreatic Actions of Hygrophila longifolia". *Int. J. Pharmacogn*. 1998; 36(5): 352-356.

72. Fort DM, Ubillas RP, Mendez CD, Jolad SD, Inman WD, Carney JR, Chen JL, Ianiro TT, Hasbun C, Bruening RC, Luo J, Reed MJ, Iwu M, Carlson TJ, King SR, Bierer DE, Cooper R. "Novel antihyperglycemic terpenoid-quinones from Pycnanthus angolensis". *J. Org. Chem*. 2000; 65(20):6534-6539.
73. Fracchiolla G, Laghezza A, Piemontese L, Carbonara G, Lavecchia A, Tortorella P, Crestani M, Novellino E, Loiodice F. "Synthesis, Biological Evaluation, and Molecular Modelling Investigation of Chiral Phenoxyacetic Acid Analogues with PPARalpha and PPARgamma Agonist Activity". *ChemMedChem* 2007; 2: 641-654.
74. Frati-Munari AC, Del Valle-Martinez LM, Ariza-Andraca CR, Islas-Andrade S, Chavez-Negrete A. "Hypoglycemic action of different doses of nopal (Opuntia streptacantha Lemaire) in patients with type II diabetes mellitus". *Arch. Invest. Med. (Mex).* 1989; 20(2): 197-201.
75. Frati-Munari AC, Gordillo BE, Altamirano P, Ariza CR. "Hypoglycemic effect of Opuntia streptacantha Lemaire in NIDDM". *Diabetes Care*. 1988; 11(1): 63-66.
76. Fuentes NL, Sagua H, Morales G, Borquez J, San Martin A, Soto J, Loyola LA. "Experimental antihyperglycemic effect of diterpenoids of llareta Azorella compacta (Umbelliferae) Phil in rats". Phytother. Res. 2005; 19(8): 713-716.
77. Fugh-Beerman A. "Herb-drug interactions". *Lancet* 2000; 355: 134-138.
78. Fujisawa T, Ikegami H, Kawaguchi Y, Nojima K, Kawabata Y, Ono M, Nishino M, Noso S. Taniguchi H, Horiki M, Itoi-Babaya M, Babaya N, Inoue K, Ogihata T. "Common genetic basis between type I and type II diabetes mellitus indicated by interview-based assessment of family history ". *Diabetes Res. Clin. Pract.* 2004; 66S:S91-S95.
79. Fujita T, Ohira K, Miyatake K, Nakano Y, Nakayama M. "Inhibitory effect of perillosides A and C, and related monoterpene glycosides on ALR2 and their structure-activity relationships", *Chem. Pharm. Bull.* 1995; 43: 920-926.
80. Ghannam N, Kingston M, Al-Meshaal IA, Tariq M, Parman NS, Woodhouse N. "The antidiabetic activity of aloes: preliminary clinical and experimental observations". *Horm. Res*. 1986; 24(4): 288-294.
81. Glombitza KW, Mahran GH, Mirhom YW, Michel KG, Motawi TK. "Hypoglycemic and antihyperglycemic effects of Zizyphus spina-christi in rats". *Planta Med*. 1994; 60(3): 244-247.
82. Gonzalez M, Zarzuelo A, Gamez MJ, Utrilla MP, Jimenez J, Osuna I. "Hypoglycemic activity of olive leaf". Planta Med. 1992; 58(6): 513-515.
83. Gray AM, Flatt PR. "Actions of the traditional anti-diabetic plant, Agrimony eupatoria (agrimony): effects on hyperglycemia, cellular glucose metabolism and insulin secretion". *Br. J. Nutr*. 1998; 80(1): 109-114.
84. Gray AM, Flatt PR. "Antihyperglycemic actions of Eucalyptus globulus (Eucalyptus) are associated with pancreatic and extra-pancreatic effects in mice". *J. Nutr*. 1998; 128(12): 2319-2323.
85. Gregersen S, Jeppesen PB, Holst JJ, Hermansen K. "Antihyperglycemic Effects of Stevioside in Type II Diabetic Subjects". *Metabolism* 2004; 53(1): 73-76.
86. Grover JK, Vats V, Yadav SS. "Pterocarpus marsupium extract (Vijayasar) prevented the alteration in metabolic patterns induced in the normal rat by feeding an adequate diet containing fructose as sole carbohydrate". *Diabetes Obes. Metab*. 2005; 7(4): 414-417.

87. Grover JK, Yadav S and Vats V. "Hypoglycemic and antihyperglycemic effect of Brassica juncea diet and their effect on hepatic glycogen content and the key enzymes of carbohydrate metabolism". *Mol. Cell. Biochem.* 2002; 241(1-2): 95-101.
88. Halim EM. "Lowering of blood sugar by water extract of Azadirachta indica and Abroma augusta in diabetes rats". *Indian J. Exp. Biol*. 2003; 41(6): 636-640.
89. Hamdan II, Afifi FU. "Studies on the in vitro and in vivo hypoglycemic activities of some medicinal plants used in treatment of diabetes in Jordanian traditional medicine". *J Ethnopharmacol*. 2004; 93(1): 117-121.
90. Haraguchi H, Ohmi I, Kubo I. "Inhibition of ALR2 by maesanin and related p-benzoquinone derivatives and effects on other enzymes". *Bioorg. Med. Chem*. 1996; 4: 49-53.
91. Hayashi T, Maruyama H, Kasai R, Hattori K, Takasuga S, Hazeki O, Yamasaki K, Tanaka T. "Ellagitannins from Lagerstroemia speciosa as activators of glucose transport in fat cells". *Planta Med*. 2002; 68(2): 173-175.
92. Herrera-Arellanoa A, Aguilar-Santamarý L, Garcý B, Nicasio-Torresa P, Tortorielloa J. "Clinical trial of Cecropia obtusifolia and Marrubium vulgare leaf extracts on blood glucose and serum lipids in type II diabetics". Phytomedicine 2004; 11: 561-566.
93. Higashino H, Suzuki A, Tanaka Y, Pootakham K. "Hypoglycemic effects of Siamese Momordica charantia and Phyllanthus urinaria extracts in STZ-diabetic rats". *Nippon Yakurigaku Zasshi*. 1992; 100(5): 415-421.
94. Hikino H, Yoshizawa M, Suzuki Y, Oshima Y, Konno C. "Isolation and hypoglycemic activity of trichosans A, B, C, D, and E: glycans of Trichosanthes kirilowii roots". *Planta Med*. 1989; 55: 349-350.
95. Hnatyszyna O, Miñob J, Ferraroa G. Acevedob C. "The hypoglycemic effect of Phyllanthus sellowianus fractions in streptozotocin-induced diabetic mice". *Phytomedicine* 2002; 9(6): 556-559.
96. Hosseinzadeh H, Ramezani M, Danaei AE. "Antihyperglycemic effect and acute toxicity of Securigera Securidaca L. seed extracts in mice". *Phytother. Res*. 2002; 16(8): 745-747.
97. Hsu FL, Chen YC, Cheng JT. "Caffeic acid as active principle from the fruit of Xanthium strumarium to lower plasma glucose in diabetic rats". *Planta Med*. 2000; 66(3): 228-230.
98. Hsu FL, Lai CW, Cheng JT. "Antihyperglycemic effects of paeoniflorin and 8-debenzoylpaeoniflorin, glycosides from the root of Paeonia lactiflora". *Planta Med*. 1997; 63(4): 323-325.
99. Hsu HH, Chang CK, Su HC, Liu IM, Cheng JT. "Stimulatory effect of puerarin on alpha1A-adrenoceptor to increase glucose uptake into cultured C2C12 cells of mice". *Planta Med*. 2002; 68(11): 999-1003.
100. Hussain Z, Waheed A, Qureshi RA, Burdi DK, Verspohl EJ, Khan N, Hasan M. "The effect of medicinal plants of Islamabad and Murree region of Pakistan on insulin secretion from INS-1 cells". *Phytother. Res*. 2004; 18(1): 73-77.
101. Huxtable RJ. "The harmfull potential of herbal and other plant products". Drug Safety 1990; 5(Suppl. 1): 126-136.

102. Hwang HJ, Kim SW, Lim JM, Joo JH, Kim HO, Kim HM, Yun JW. "Hypoglycemic effect of crude exopolysaccharides produced by a medicinal mushroom Phellinus baumii in STZ-diabetic rats". *Life Sci.* 2005; 76(26): 3069-3080.
103. Iwu MM, Igboko OA, Okunji CO, Tempesta MS. "Antidiabetic and ALR2 activities of biflavanones of Garcinia kola". *J. Pharm. Pharmacol*. 1990; 42(4): 290-292.
104. Iwu MM, Okunji CO, Ohiaeri GO, Akah P, Corley D, Tempesta MS. "Hypoglycemic activity of dioscoretine from tubers of Dioscorea dumetorum in normal and alloxan diabetic rabbits". *Planta Med.* 1990; 56(3): 264-267.
105. Jafri MA, Aslam M, Javed K, Singh S. "Effect of Punica granatum Linn. (flowers) on blood glucose level in normal and alloxan-induced diabetic rats". *J. Ethnopharmacol*. 2000; 70(3): 309-314.
106. Jeong SI, Kwak DH, Lee S, Choo YK, Woo WH, Keum KS, Choi BK, Jung KY. "Inhibitory effects of Cnidium officinale Makino and Tabanus fulvus Meigan on the high glucose-induced proliferation of glomerular mesangial cells". *Phytomedicine*, 2005; 12(9): 648-655.
107. Jouad H, Maghrani M, Eddouks M. "Hypoglycemic effect of Rubus fructicosis L. and Globularia alypum L. in normal and STZ-diabetic rats". *J. Ethnopharmacol*. 2002; 81(3): 351-356.
108. Kako M, Miura T, Nishiyama Y, Ichimaru M, Moriyasu M, Kato A. "Hypoglycemic effect of the rhizomes of Polygala senega in normal and diabetic mice and its main component, the triterpenoid glycoside senegin-II". *Planta Med*. 1996; 62(5): 440-443.
109. Kakoulitsa C, Zika Ch, Geromichalos GD, Demopoulos VJ, Skaltsa H. "Evaluation of ALR2 inhibition and docking studies of some secondary metabolites, isolated from Origanum vulgare L. ssp. hirtum". *Bioorg. Med. Chem*. 2006; 14: 1653-1659.
110. Kakuda T, Sakane I, Takihara T, Ozaki Y, Takeuchi H, Kuroyanagi M. "Hypoglycemic effect of extracts from Lagerstroemia speciosa L. leaves in genetically diabetic KK-AY mice". *Biosci. Biotechnol. Biochem.* 1996; 60(2): 204-208.
111. Kamalakkanan N, Rajadurai M, Stanely Mainzen Prince P. "Antihyperlipidaemic effect of Aegle marmelos fruit extract in streptozotocin-induced diabetes in rats". *J. Sci. Food Agr*. 2004; 85(4): 569-573.
112. Kamalakkanan N, Rajadurai M, Stanely Mainzen Prince P. "Effect of Aegle marmelos Fruits on Normal and Streptozotocin-Diabetic Wistar Rats". *J. Med. Food* 2003; 6(2): 93-98.
113. Karageuzyan KG, Vartanyan GS, Agadjanov MI, Panossian AG, Hoult JR. "Restoration of the disordered glucose-fatty acid cycle in alloxan-diabetic rats by trihydroxyoctadecadienoic acids from Bryonia alba, a native Armenian medicinal plant". *Planta Med*. 1998; 64(5): 417-422.
114. Kasimu R, Basnet P, Tezuka Y, Kadota S, Namba T. "Danshenols A and B, new ALR2 inhibitors from the root of Salvia miltiorhiza bunge ". *Chem. Pharm. Bull*. 1997; 45: 564-566.
115. Kasimu R, Tanaka K, Tezuka Y, Gong ZN, Li JX, Basnet P, Namba T, Kadota S. "Comparative study of seventeen Salvia plants: ALR2 inhibitory activity of

water and MeOH extracts and liquid chromatography- mass spectrometry (LC-MS) analysis of water extracts ". *Chem. Pharm. Bull*. 1998; 46: 500-504.
116. Kasuga S, Ushijima M, Morihara N, Itakura Y, Nakata Y. "Effect of aged garlic extract (AGE) on hyperglycemia induced by immobilization stress in mice". *Nippon Yakurigaku Zasshi*. 1999; 114(3): 191-197.
117. Kato A, Miura T. "Hypoglycemic action of the rhizomes of Polygonatum officinale in normal and diabetic mice". *Planta Med*. 1994; 60(3): 201-203.
118. Kesari AN, Gupta RK, Watal G. "Hypoglycemic effects of Murraya koenigii on normal and alloxan-diabetic rabbits". *J. Ethnopharmacol*. 2005; 97(2): 247-251.
119. Khanna P, Jain SC, Panagariya A, Dixit VP. "Hypoglycemic activity of polypeptide-p from a plant source". *J. Nat. Prod*. 1981; 44(6): 648-655.
120. Kim ES, Park SJ, Lee EJ, Kim BK, Huh H, Lee BJ. "Purification and characterization of Moran 20K from Morus alba". *Arch. Pharm. Res*. 1999; 22(1): 9-12.
121. Kim HS, Kim YH, Hong YS, Paek NS, Lee HS, Kim TH, Kim KW, Lee JJ. "a-Glucosidase inhibitors from Commelina communis". *Planta Med*. 1999; 65(5): 437-439.
122. Kim HY, Oh JH. "Screening of Korean forest plants for rat lens ALR2 inhibition". *Biosci. Biotechnol. Biochem.* 1999; 63(1):184-188.
123. Kim YC, Oh H, Kim BS, Kang TH, Ko EK, Han YM, Kim BY, Ahn JS. "In vitro protein tyrosine phosphatase 1B inhibitory phenols from the seeds of Psoralea corylifolia". *Planta Med*. 2005; 71(1): 87-89.
124. Kimura I, Nakashima N, Sugihara Y, Fu-jun C, Kimura M. "The antihyperglycemic blend effect of traditional chinese medicine byakko-ka-ninjin-to on alloxan and diabetic KK-CA(y) mice". *Phytother. Res.* 1999; 13(6): 484-488.
125. Kimura M, Waki I, Chujo T, Kikuchi T, Hiyama C, Yamazaki K, Tanaka O. "Effects of hypoglycemic components in ginseng radix on blood insulin level in alloxan diabetic mice and on insulin release from perfused rat pancreas". *J. Pharmacobiodyn*. 1981; 4(6): 410-417.
126. Kimura M, Waki I, Tanaka O, Nagai Y, Shibata S. "Pharmacological sequential trials for the fractionation of components with hypoglycemic activity in alloxan diabetic mice from ginseng radix". *J. Pharmacobiodyn.* 1981; 4(6): 402-409.
127. Konno C, Murakami M, Oshima Y, Hikino H. "Isolation and hypoglycemic activity of panaxans Q, R, S, T and U, glycans of Panax ginseng roots". *J. Ethnopharmacol*. 1985; 14(1): 69-74.
128. Korec R, Heinz Sensch K, Zoukas T. "Effects of the neoflavonoid coutareagenin, one of the antidiabetic active substances of Hintonia latiflora, on streptozotocin-induced diabetes mellitus in rats". *Arzneimittelforschung* 2000; 50(2): 122-128.
129. Korotkova VD, Perelygina AA, Trumpe TE, Sokolov SIa, Lobanova AM. "Arfazetin in the treatment of diabetes mellitus". *Probl. Endokrinol*. (Mosk). 1988; 34(4): 25-28.
130. Koyama Y, Abe K, Sano Y, Ishizaki Y, Njelekela M, Shoji Y, Hara Y, Isemura M. "Effects of green tea on gene expression of hepatic gluconeogenic enzymes in vivo". *Planta Med*. 2004; 70(11): 1100-1102.

131. Krenisky JM, Luo J, Reed MJ, Carney JR. "Isolation and antihyperglycemic activity of bakuchiol from Otholobium pubescens (Fabaceae), a Peruvian medicinal plant used for the treatment of diabetes". *Biol. Pharm. Bull.* 1999; 22(10):1137-1140.
132. Krishnakumar K, Augusti KT, Vijayammal PL. "Anti-Peroxidative and Hypoglycemic Activity of Salacia Oblonga Extract in Diabetic Rats". *Int. J. Pharmacogn*. 2000; 38(2): 101-105.
133. Krishnakumar K, Augusti KT, Vijayammal PL. "Hypoglycemic and anti-oxidant activity of Salacia oblonga Wall. extract in STZ-diabetic rats". *Indian J. Physiol. Pharmacol*. 1999; 43(4): 510-514.
134. Kudolo GB. "The effect of 3-month ingestion of Ginkgo biloba extract on pancreatic β cell function in response to glucose loading in normal glucose tolerant individuals". *J. Clin. Pharmacol*. 2000; 40: 647-654.
135. Kumar GR, Reddy KP. "Reduced nociceptive responses in mice with alloxan induced hyperglycemia aftergarlic (Allium sativum Linn.) treatment". *Indian J. Exp. Biol*. 1999; 37(7): 662-666.
136. Kumara NKVM, Pathirana RN, Pathirana C. "Hypoglycemic Activity of the Root and Stem of Salacia reticulata var. Î²-diandra in Alloxan Diabetic Rats". *Int. J. Pharmacogn*., 2005; 43(3): 219-225.
137. Kumari K, Augusti KT. "Antidiabetic and antioxidant effects of S-methyl cysteine sulfoxide isolated from onions (Allium cepa Linn) as compared to standard drugs in alloxan diabetic rats". *Indian J. Exp. Biol.* 2002; 40(9): 1005-1009.
138. Latha M and Pari L. "Antihyperglycemic effect of Cassia auriculata in experimental diabetes and its effects on key metabolic enzymes involved in carbohydrate metabolism". *Clin. Exp. Pharmacol. P.* 2003; 30(1-2): 38-42.
139. Latha M, Pari L, Sitasawad S, Bhonde R., "Scoparia dulcis, a traditional antidiabetic plant, protects against streptozotocin induced oxidative stress and apoptosis in vitro and in vivo". *J. Biochem. Mol. Tox.* 2004; 18(5): 261-272.
140. Lathaa M, Pari L. "Sandhya Sitasawadb, Ramesh Bhondeb Insulin-secretagogue activity and cytoprotective role of the traditional antidiabetic plant Scoparia dulcis (Sweet Broomweed)". *Life Sci*. 2004; 75: 2003-2014.
141. Lee Y, Kim H, Choi HS, Kang BH, Han YB, Kim SJ. "Effects of water extract of 1:1 mixture of Phellodendron cortex and Aralia cortex on polyol pathway and oxidative damage in lenses of diabetic rats". *Phytother. Res*. 1999; 13(7): 555-560.
142. Lemhadri A, Zeggwagh NA, Maghrani M, Jouad H, Eddouks M. "Anti-hyperglycemic activity of the aqueous extract of Origanum vulgare growing wild in Tafilalet region". *J. Ethnopharmacol*. 2004; 92(2-3): 251-256.
143. Lemhadri A, Zeggwagh NA, Maghrani M, Jouad H, Michel JB, Eddouks M. " Hypoglycemic effect of Calamintha officinalis Moench. in normal and STZ-diabetic rats". *J. Pharm. Pharmacol*. 2004; 56(6): 795-799.
144. Lemus I, García R, Delvillar E, Knop G. "Hypoglycemic activity of four plants used in Chilean popular medicine". *Phytother. Res*. 1999; 13(2): 91-94.
145. Li M, Qu W, Wang Y, Wan H, Tian C. "Hypoglycemic effect of saponin from Tribulus terrestris". *Zhong Yao Cai* 2002; 25(6): 420-422.

146. Li WL, Zheng HC, Bukuru J, De Kimpe N. "Natural medicines used in the traditional Chinese medical system for therapy of diabetes mellitus". *J. Ethnopharmacol*. 2004; 92: 1-21.
147. Liu IM, Liou SS, Lan TW, Hsu FL, Cheng JT. "Myricetin as the active principle of Abelmoschus moschatus to lower plasma glucose in STZ-diabetic rats". *Planta Med*. 2005; 71(7): 617-621
148. Liu KZ, Li JB, Lu HL, Wen JK, Han M. "Effects of Astragalus and saponins of Panax notoginseng on MMP-9 in patients with type II diabetic macroangiopathy". *Zhongguo Zhong Yao Za Zhi* 2004; 29(3): 264-266.
149. Luo J, Chuang T, Cheung J, Quan J, Tsai J, Sullivan C, Hector RF, Reed MJ, Meszaros K, King SR, Carlson TJ, Reaven GM. "Masoprocol (nordihydroguaiaretic acid): a new antihyperglycemic agent isolated from the creosote bush (Larrea tridentata)". *Eur. J. Pharmacol*. 1998; 346(1): 77-79.
150. Luo J, Fort DM, Carlson TJ, Noamesi BK, nii-Amon-Kotei D, King SR, Tsai J, Quan J, Hobensack C, Lapresca P, Waldeck N, Mendez CD, Jolad SD, Bierer DE, Reaven GM. " Cryptolepis sanguinolenta: an ethnobotanical approach to drug discovery and the isolation of a potentially useful new antihyperglycemic agent". *Diabet. Med*. 1998; 15(5): 367-374.
151. MacFarlance IA, Bliss M, Jackson JG, Williams G. "The history of diabetes mellitus. In textbook of diabetes". (eds Pichup, j. Williams G.) Blackwell, London 1997, 2nd edn, vol. I, pp 1-21.
152. Maghrani M, Lemhadri A, Jouad H, Michel JB, Eddouks M. "Effect of the desert plant Retama raetam on glycemia in normal and STZ-diabetic rats". *J. Ethnopharmacol*. 2003; 87(1): 21-25.
153. Maghrani M, Michel JB, Eddouks M. "Hypoglycemic activity of Retama raetam in rats". *Phytother. Res.* 2005; 19(2):125-128.
154. Maghrani M, Zeggwagh NA, Lemhadri A, El Amraoui M, Michel JB, Eddouks M. "Study of the hypoglycemic activity of Fraxinus excelsior and Silybum marianum in an animal model of type I diabetes mellitus". *J. Ethnopharmacol*. 2004; 91(2-3): 309-316.
155. Mahdi GS, Naismith DJ. "Role of chromium in barley in modulating the symptoms of diabetes". *Ann. Nutr. Metab.* 1991; 35(2): 65-70.
156. Mahomed IM, John AO. "Ojewole Analgesic, anti-inflammatory and antidiabetic properties of Harpagophytum procumbens DC (Pedaliaceae) secondary root aqueous extract". *Phytother. Res*. 2005; 18(12): 982-989.
157. Mahomed IM, Ojewole JA. "Hypoglycemic effect of Hypoxis hemerocallidea corm (African potato) aqueous extract in rats". *Methods Find Exp. Clin. Pharmacol*. 2003; 25(8): 617-623.
158. Makonnen E, Hunde A, Damecha G. "Hypoglycemic Effect of Moringa stenopetala Aqueous Extract in Rabbits". *Phytother. Res*., 1998; 11(2): 147-148.
159. Malalavidhane S, Wickramasinghe SMDN, Jansz ER. "An aqueous extract of the green leafy vegetable Ipomoea aquatica is as effective as the per oshypoglycemic drug tolbutamide in reducing the blood Sugar levels of Wistar rats". *Phytother. Res*., 2001; 15(7): 635-637.
160. Malalavidhane TS, Wickramasinghe SMDN, Perera MSA, Jansz ER. "Per os hypoglycemic activity of Ipomoea aquatica in streptozotocin-induced, diabetic wistar rats and Type II diabetics". *Phytother. Res.,* 2003; 17(9): 1098-1100.

161. Matsuda H, Cai H, Kubo M, Tosa H, Iinuma M. " Study on anti-cataract drugs from natural sources. Effects of buddlejae flos on in vitro ALR2 activity". *Biol. Pharm. Bull*. 1995; 18(3): 463-466.
162. Matsuda H, Murakami T, Yashiro K, Yamahara J, Yoshikawa M. "Antidiabetic principles of natural medicines. IV. ALR2 and α-glucosidase inhibitors from the roots of Salacia oblonga WALL. (Celastraceae): Structure of a new friedelane-type triterpene, kotalagenin 16-acetate". *Chem. Pharm. Bull.* 1999; 47(12): 1725-1728.
163. Miura T, Ichiki H, Iwamoto N, Kato M, Kubo M, Sasaki H, Okada M, Ishida T, Seino Y, Tanigawa K. "Antidiabetic activity of the rhizome of Anemarrhena asphodeloides and active components, mangiferin and its glucoside". *Biol. Pharm. Bull*. 2001; 24(9): 1009-1011.
164. Moshi MJ, Lutale JJK, Rimoy GR, Abbas ZG, Josiah RM, Swai ABM. "The effect of Phyllanthus amarus aqueous extract on blood glucose in non-insulin dependent diabetic patients". *Phytother. Res*. 2001; 15(7): 577-580.
165. Mosihuzzaman M, Nahar N, Ali L, Rokeya B, Khan AK, Nur-E-Alam M, Nandi RP. "Hypoglycemic effects of three plants from eastern Himalayan belt". *Diabetes Res*. 1994; 26(3): 127-138.
166. Mukherjee PK, Maiti K, Mukherjee K, Houghton PJ. "Leads from Indian medicinal plants with hypoglycemic potentials". *J. Ethnopharmacol*. 2006; 106: 11-28.
167. Mukherjee PK, Saha K, Pal M, Saha BP. "Effect of Nelumbo nucifera rhizome extract on blood sugar level in rats". *J. Ethnopharmacol*. 1997; 58(3): 207-213.
168. Murata M, Yamakoshi Y, Homma S, Arai K and Nakamura Y. "Isolation and characterization of macrocarpals B-G antibacterial compounds from Eucalyptus macrocarpa". *Biosci. Biotechnol. Biochem.* 1992; 56: 2062-2065.
169. Musabayane CT, Mahlalela N, Shode FO, Ojewole JAO "Effects of Syzygium cordatum (Hochst.) [Myrtaceae] leaf extract on plasma glucose and hepatic glycogen in STZ-diabetic rats". *J. Ethnopharmacol.* 2005; 97: 485-490.
170. Mutalik S, Chetana M, Sulochana B, Devi PU, Udupa N. "Effect of Dianex, a herbal formulation on experimentally induced diabetes mellitus". *Phytother. Res*. 2005; 19(5): 409-415.
171. Nagda KK, Deshmukh B. "Hemagglutination pattern of galactose specific lectin from Pedilanthus tithymaloides in diabetes mellitus". *Indian J. Exp. Biol*. 1998; 36(4): 426-428.
172. Naik SR, Barbosa Filho JM, Dhuley JN, Deshmukh V. "Probable mechanism of hypoglycemic activity of bassic acid, a natural product isolated from Bumelia sartorum". *J. Ethnopharmacol*. 1991; 33(1-2): 37-44.
173. Naismith DJ, Mahdi GS, Shakir NN. " Therapeutic value of barley in the management of diabetes". *Ann. Nutr. Metab*. 1991; 35(2): 61-64.
174. Nammi S, Boini MK, Lodagala SD and Behara RB. " The juice of fresh leaves of Catharanthus roseus Linn. reduces blood glucose in normal and alloxan diabetic rabbits". *BMC Complementary and Alternative Medicine* 2003; 3: 4-7.
175. Narendhirakannan RT, Subramanian S, Kandaswamy M. "Mineral content of some medicinal plants used in the treatment of diabetes mellitus", *Biol. Trace Elem. Res*. 2005; 103(2): 109-115.

176. Newairy AS, Mansour HA, Yousef MI, Sheweita SA. "Alterations of lipid profile in plasma and liver of diabetic rats: effect of hypoglycemic herbs". *J. Environ. Sci. Health B*. 2002; 37(5): 475-484.
177. Nicasio P, Aguilar-Santamaría L, Aranda E, Ortiz S, González M. "Hypoglycemic effect and chlorogenic acid content in two Cecropia species". *Phytother. Res*. 2005; 19(8): 661-664.
178. Nicola WG, Ibrahim KM, Mikhail TH, Girgis RB, Khadr ME. "Role of the hypoglycemic plant extract cleome droserifolia in improving glucose and lipid metabolism and its relation to insulin resistance in fatty liver". *Boll. Chim. Farm*. 1996; 135(9): 507-517.
179. Nojima H, Kimura I, Chen FJ, Sugihara Y, Haruno M, Kato A, Asano N. " Antihyperglycemic effects of N-containing sugars from Xanthocercis zambesiaca, Morus bombycis, Aglaonema treubii, and Castanospermum australe in streptozotocin-diabetic mice". *J. Nat. Prod*. 1998; 61(3): 397-400.
180. Novaes AP, Rossi C, Poffo C, Pretti Junior E, Oliveira AE, Schlemper V, Niero R, Cechinel-Filho V, Burger C. "Preliminary evaluation of the hypoglycemic effect of some Brazilian medicinal plants". *Therapie*, 2001; 56(4): 427-430.
181. Nyarkoa AK, Asare-Ananeb H, Ofosuhenea M, Addyc ME. "Extract of Ocimum canum lowers blood glucose and facilitates insulin release by isolated pancreatic β-islet cells". Phytomedicine 2002; 9(4): 346-351.
182. Obatomi DK, Bikomo EO, Temple "Anti-diabetic properties of the African mistletoe in STZ-diabetic rats". *J. Ethnopharmacol*. 1994; 43(1): 13-17.
183. Obatomi DK, Bikomo EO, Temple VL. "Anti-diabetic properties of the African mistletoe in STZ-diabetic rats". *J. Ethnopharmacol*. 1994; 43(1): 13-17.
184. Obatomi DK, Oye AAA, Jangber ZN. "Temple Metabolic and Renal Changes Following the Ingestion of African Mistletoe Extract in Rats". *Phytother. Res*. 1998; 11(2): 171-173.
185. Oh WK, Lee CH, Lee MS, Bae EY, Sohn CB, Oh H, Kim BY, Ahn JS. "Antidiabetic effects of extracts from Psidium guajava". *J. Ethnopharmacol*. 2005; 96(3): 411-415.
186. Ojewole JA. " Hypoglycemic effect of Clausena anisata (Willd) Hook methanolic root extract in rats". *J. Ethnopharmacol*. 2002; 81(2): 231-237.
187. Ojewole JA. "Analgesic, antiinflammatory and hypoglycemic effects of Sutherlandia frutescens R. BR. (variety Incana E. MEY.) [Fabaceae] shoot aqueous extract Methods". *Find Exp. Clin. Pharmacol*. 2004; 26(6): 409-411.
188. Ojewole JAO. "Evaluation of the analgesic, anti-inflammatory and anti-diabetic properties of Sclerocarya birrea (A. Rich.) Hochst. stem-bark aqueous extract in mice and rats". *Phytother. Res*. 2004; 18(8): 601-608.
189. Ojewolea JAO, Adewunmib CO. "Anti-inflammatory and hypoglycemic effects of Tetrapleura tetraptera (Taub) [fabaceae] fruit aqueous extract in rats". *J Ethnopharmacol*. 2004; 95: 177-182.
190. Okyar A, Can A, Akev N, Baktir G, Sutlupinar N. "Effect of Aloe vera leaves on blood glucose level in type I and type II diabetic rat models".*Phytother. Res*. 2001; 15(2): 157-161.

191. Olajide OA, Awe SO, Makinde JM, Morebise O. "Evaluation of the anti-diabetic property of Morinda lucida leaves in streptozotocin-diabetic rats". *J. Pharm. Pharmacol*. 1999; 51(11): 1321-1324.
192. Oliveira AC, Endringer DC, Araujo RJ, Brandao MG, Coelho MM. "The starch from Solanum lycocarpum St. Hill. fruit is not a hypoglycemic agent". *Braz. J. Med. Biol. Res*. 2003; 36(4): 525-530.
193. Onderoglu S, Sozer S, Erbil KM, Ortac R, Lermioglu F. "The evaluation of long-term effects of cinnamon bark and olive leaf on toxicity induced by streptozotocin administration to rats. *J. Pharm. Pharmacol.* 1999; 51(11): 1305-1312.
194. Orekhov AN, Grunwald J. "Effects of garlic on atherosclerosis". *Nutrition.* 1997; 13(7-8): 656-663.
195. Orhan DD, Aslan M, Sendogdu N, Ergun F, Yesilada E. "Evaluation of the hypoglycemic effect and antioxidant activity of three Viscum album subspecies (European mistletoe) in streptozotocin-diabetic rats". *J. Ethnopharmacol*. 2005; 98: 95-102.
196. Oshima Y, Sato K, Hikino H. "Isolation and hypoglycemic activity of quinquefolans A, B, and C, glycans of Panax quinquefolium roots". *J. Nat. Prod*. 1987; 50(2): 188-190.
197. Palanichamy S, Nagarajan S, Devasagayam M. "Effect of Cassia alata leaf extract on hyperglycemic rats". *J. Ethnopharmacol*. 1988; 22(1): 81-90.
198. Pandey M, Khan A. "Hypoglycemic effect of defatted seeds and water soluble fibre from the seeds of Syzygium cumini (Linn.) skeels in alloxan diabetic rats". *Indian J. Exp. Biol*. 2002; 40(10): 1178-1182.
199. Parameshwar S, Srinivasan KK, Mallikarjuna Rao C. "Oral Antidiabetic Activities of Different Extracts of Caesalpinia bonducella Seed". *Int. J. Pharmacogn*. 2002; 40(8): 590-595.
200. Pari L, Latha M. "Antihyperglycemic Effect of Scoparia dulcis: Effect on Key Metabolic Enzymes of Carbohydrate Metabolism in Streptozotocin-Induced Diabetes". *Int. J. Pharmacogn*. 2004; 42(8): 570-576.
201. Pari L, Latha M. "Protective role of Scoparia dulcis plant extract on brain antioxidant status and lipidperoxidation in STZ diabetic male Wistar rats". *BMC Complementary and Alternative Medicine* 2004; 4: 16-19.
202. Pari L, Ramakrishnan R, Venkateswaran S. "Antihyperglycemic effect of Diamed, a herbal formulation, in experimental diabetes in rats". *J. Pharm. Pharmacol*. 2001; 53(8): 1139-1143.
203. Pari L, Satheesh MA. "Antidiabetic Effect of Boerhavia diffusa: Effect on Serum and Tissue Lipids in Experimental Diabetes". *J. Med. Food,* 2004; 7(4): 472-476.
204. Pari L, Umamaheswari J. "Antihyperglycemic activity of Musa sapientum flowers: effect on lipid peroxidation in alloxan diabetic rats". *Phytother. Res*. 2000; 14(2): 136-138.
205. Pari L, Venkateswaran S. "Hypoglycemic activity of Scopariadulcis L. extract in alloxan induced hyperglycemic rats". *Phytother. Res*. 2002; 16(7): 662-664.
206. Pari L, Venkateswaran S. "Protective Role of Phaseolus vulgaris on Changes in the Fatty Acid Composition in Experimental Diabetes". *J. Med. Food*, 2004; 7(2): 204-209.

207. Park HJ, Kim DH, Choi JW, Park JH, Han YN. "A potent anti-diabetic agent from Kalopanax pictus ". *Arch. Pharm. Res*. 1998; 21(1): 24-29.
208. Pepato MT, Baviera AM, Vendramini RC and Brunetti IL. "Evaluation of toxicity after one-months treatment with Bauhinia forficata decoction in STZ-diabetic rats". *BMC Complementary and Alternative Medicine* 2004; 4: 7-10.
209. Pepato MT, Baviera AM, Vendramini RC, Perez Mda P, Kettelhut Ido C, Brunetti IL. "Cissus sicyoides (princess vine) in the long-term treatment of streptozotocin-diabetic rats". *Biotechnol. Appl. Biochem.* 2003; 37(Pt 1): 15-20.
210. Pérez C, Domínguez E, Ramiro JM, Romero A, Campillo JE, Torres MD. "A study on the glycemic balance in streptozotocin-diabetic rats treated with an aqueous extract of Ficus carica (fig tree) leaves". *Phytother. Res*. 1998; 10(1): 82-83.
211. Perez RM, Perez C, Zavala MA, Perez S, Hernandez H, Lagunes F. " Hypoglycemic effects of lactucin-8-O-methylacrylate of Parmentiera edulis fruit". *J. Ethnopharmacol*. 2000; 71(3): 391-394.
212. Petlevski R, Hadzija M, Slijepcevic M, Juretic D, Petrik J. "Glutathione S-transferases and malondialdehyde in the liver of NOD mice on short-term treatment with plant mixture extract P-9801091". *Phytother. Res*. 2003; 17(4): 311-314.
213. Peungvicha P, Temsiririrkkul R, Prasain JK, Tezuka Y, Kadota S, Thirawarapan SS, Watanabe H. "4-Hydroxybenzoic acid: a hypoglycemic constituent of aqueous extract of Pandanus odorus root". *J. Ethnopharmacol.* 1998a; 62(1): 79-84.
214. Peungvicha P, Thirawarapan SS, Temsiririrkkul R, Watanabe H, Kumar Prasain G, Kadota S. "Hypoglycemic effect of the water extract of Piper sarmentosum in rats". *J. Ethnopharmacol*. 1998; 60: 27-32.
215. Peungvicha P, Thirawarapan SS, Watanabe H. "Possible mechanism of hypoglycemic effect of 4-hydroxybenzoic acid, a constituent of Pandanus odorus root". *Jpn. J. Pharmacol*. 1998b; 78(3): 395-398.
216. Poisonous Plant Database. U.S. Department of Health and Human Services. U.S. Food & Drug Administration, Center for Food Safety & Applied Nutrition. Office of Plant and Dairy Foods and Beverages. http://vm.cfsan.fda.gov/~djw/plantnam.html.
217. Ponnachan PT, Paulose CS, Panikkar KR. "Effect of leaf extract of Aegle marmelose in diabetic rats". Indian J Exp Biol. 1993; 31(4): 345-347.
218. Porchezhian E, Ansari SH, Shreedharan NK. "Antihyperglycemic activity of Euphrasia officinale leaves". *Fitoterapia* 2000; 71(5): 522-526.
219. Prasadb RC, Herzogb B, Boonec B, Simsc L, Waltner-Lawa M. "An extract of Syzygium aromaticum represses genes encoding hepatic gluconeogenic enzymes". *J. Ethnopharmacol*. 2005; 96: 295-301.
220. Punitha IS, Rajendran K, Shirwaikar A, Shirwaikar A. "Alcoholic stem extract of Coscinium fenestratum regulates carbohydrate metabolism and improves antioxidant status in streptozotocin-nicotinamide induced diabetic rats". *Evid. Based Complement. Alternat. Med*. 2005; 2(3): 375-381.
221. Puri D. "The insulinotropic activity of a Nepalese medicinal plant Biophytum sensitivum: preliminary experimental study". *J. Ethnopharmacol*. 2001; 78(1): 89-93.

222. Pushparaj P, Tan CH, Tan BK. "Effects of Averrhoa bilimbi leaf extract on blood glucose and lipids in streptozotocin-diabetic rats". *J. Ethnopharmacol*. 2000; 72(1-2): 69-76.
223. Pushparaj PN, Tan BK, Tan CH. "The mechanism of hypoglycemic action of the semi-purified fractions of Averrhoa bilimbi in streptozotocin-diabetic rats". *Life Sci*. 2001; 70(5): 535-547.
224. Qian DS, Zhu YF, Zhu Q. "Effect of alcohol extract of Cornus officinalis Sieb. et Zucc on GLUT4 expression in skeletal muscle in type II (non-insulin-dependent) diabetic mellitus rats". *Zhongguo Zhong Yao Za Zhi*. 2001; 26(12): 859-862.
225. Rajasekaran S, Sivagnanam K, Ravi K, Subramanian S. "Hypoglycemic Effect of Aloe vera Gel on Streptozotocin-Induced Diabetes in Experimental Rats". *J. Med. Food*. 2004; 7(1): 61-66.
226. Rave K, Sivagnanam K, Subramanian S. "Anti-Diabetic Activity of Eugenia jambolana Seed Kernels on STZ-diabetic rats". *J. Med. Food*. 2004; 7(2): 187-191.
227. Reddy SV, Tiwari AK, Kumar US, Rao RJ, Rao JM. "Free radical scavenging, enzyme inhibitory constituents from antidiabetic Ayurvedic medicinal plant Hydnocarpus wightiana Blume". *Phytother. Res*. 2005; 19(4): 277-281.
228. Revilla MC, Andrade-Cetto A, Islas S, Wiedenfeld H. "Hypoglycemic effect of Equisetum myriochaetum aerial parts on type II diabetic patients". *J. Ethnopharmacol*. 2002; 81: 117-120.
229. Rollo J. "An account of two cases of the diabetes mellitus, with remarks as they arose during the progress of the cure". C. Dilly, London, 1797.
230. Roman-Ramos R, Contreras-Weber CC, Nohpal-Grajeda G, Flores-Saenz JL, Alarcon-Aguilar FJ. "Blood Glucose Level Decrease Caused by Extracts and Fractions from Lepechinia caulescens in Healthy and Alloxan-diabetic Mice". *Int. J. Pharmacogn*. 2001; 39(4): 317-321.
231. Roman-Ramos R, Flores-Saenz JL, Alarcon-Aguilar F. "Antihyperglycemic effect of some edible plants". *J. Ethnopharmacol*. 1995; 48: 25-32.
232. Russell KRM, Morrison EY, Ragoobirsingh D. "The effect of annatto on insulin binding properties in the dog". *Phytother. Res*. 2005; 19(5): 433-436.
233. Sabu MC, Kuttan R. "Anti-diabetic activity of medicinal plants and its relationship with their antioxidant property". *J. Ethnopharmacol*. 2002; 81: 155-160.
234. Saha K, Mukherjee PK, Das J, Mandal SC, Pal M, Saha BP. "Hypoglycemic activity of Leucas lavandulaefolia Rees. in STZ-diabetic rats". *Phytother. Res*. 1998; 11(6): 463-466.
235. Sanchez de Medina F, Gamez MJ, Jimenez I, Jimenez J, Osuna JI, Zarzuelo A. "Hypoglycemic activity of juniper berries". Planta Med. 1994; 60(3): 197-200.
236. Satyanarayana S, Sarma GS, Ramesh A, Sushruta K, Srinivas N. " Evaluation of Herbal Preparations for Hypoglycemic Activity in Normal and Diabetic Rabbits". *Int. J. Pharmacogn*. 2003; 41(6): 466-472.
237. Seema PV, Sudha B, Padayatti PS, Abraham A, Raghu KG, Paulose CS. "Kinetic studies of purified malate dehydrogenase in liver of streptozotocin-diabetic rats and the effect of leaf extract of Aegle marmelose (L.) Correa ex Roxb". *Indian J. Exp. Biol*. 1996; 34(6): 600-602.

238. Sepici A, Gürbüz I, Çevik C, Yesilada E. "Hypoglycemic effects of myrtle oil in normal and alloxan-diabetic rabbits". J Ethnopharmacol. 2004; 93: 311-318.
239. Serraclara A, Hawkins F, Perez C. "Hypoglycemic action of an per osfig-leaf decoction in type-I diabetic patients". *Diab. Res. Clin. Pract*. 1998; 39: 19-22.
240. Sezika E, Aslana M, Yesiladaa E, Ito S. "Hypoglycemic activity of Gentiana olivieri and isolation of the active constituent through bioassay-directed fractionation techniques". *Life Sci*. 2005; 76: 1223-1238.
241. Shane-McWhorter L. "Biological complementary therapies: a focus on botanical products in diabetes". *Diabetes Spectrum* 2001; 14(4): 199-208.
242. Shanmugasundaram ER, Gopinath KL, Radha Shanmugasundaram K, Rajendran VM. "Possible regeneration of the islets of Langerhans in streptozotocin-diabetic rats given Gymnema sylvestre leaf extracts". *J. Ethnopharmacol*. 1990; 30(3): 265-279.
243. Sharma SR, Dwivedi SK, Swarup D. "Hypoglycemic, antihyperglycemic and hypolipidemic activities of Caesalpinia bonducella seeds in rats". *J. Ethnopharmacol*. 1997; 58(1): 39-44.
244. Sheela CG, Augusti KT. "Antidiabetic effects of S-allyl cysteine sulphoxide isolated from garlic Allium sativum Linn". *Indian J. Exp. Biol*. 1992; 30(6): 523-526.
245. Sheela CG, Kumud K, Augusti KT. "Anti-diabetic effects of onion and garlic sulfoxide amino acids in rats". *Planta Med*. 1995; 61(4): 356-357.
246. Shibata S, Nakahara M, Aimi N. "The constituents of Japanese and Chinese crude drugs. IX. Paeoniflorin. A glucoside of Chinese peony roots". *Chem. Pharm. Bull*. 1963; 11: 379-391.
247. Shimizu M, Horie S, Terashima S, Ueno H, Hayashi T, Arisawa M, Suzuki S, Yoshizaki M, Morita N. "Studies on ALR2 inhibitors from natural products. II. Active components of a Paraguayan crude drug "Para-parai mí," Phyllanthus niruri". *Chem. Pharm. Bull*. 1989; 37: 2531-2533.
248. Shirwaikar A, Rajendran K, Dinesh Kumar C, Bodla R. "Antidiabetic activity of aqueous leaf extract of Annona squamosa in streptozotocin-nicotinamide type II diabetic rats". *J. Ethnopharmacol*. 2004; 91(1): 171-175.
249. Shirwaikar A, Rajendran K, Kumar DC. "Per osAntidiabetic Activity of Annona squamosa Leaf Alcohol Extract in NIDDM Rats". *Int. J. Pharmacogn*. 2004; 42(1): 30-35.
250. Shirwaikar A, Rajendran K, Punitha IS. "Antidiabetic activity of alcoholic stem extract of Coscinium fenestratum in streptozotocin-nicotinamide induced type II diabetic rats". *J. Ethnopharmacol*. 2005; 97(2): 369-374.
251. Shukla K, Narain JP, Puri P. "Glycemic response to maize, bajra and barley". *Indian J. Physiol. Pharmacol.* 1991; 35: 249-254.
252. Silva FR, Szpoganicz B, Pizzolatti MG, Vieira Willrich MA, De Sousa E. "Acute effect of Bauhinia forficata on serum glucose levels in normal and alloxan-induced diabetic rats". *J. Ethnopharmacol*. 2002; 83: 33-37.
253. Singh SN, Vats P, Suri S, Shyam R, Kumria MML., Ranganathan S, Sridharan K. "Effect of an antidiabetic extract of Catharanthus roseus on enzymic activities in streptozotocin induced diabetic rats". *J. Ethnopharmacol*. 2001; 76: 269-277.
254. Sotaniemi EA, Haapakoski E, Rautio A. "Ginseng therapy in non-insulin-dependent diabetic patients". *Diabetes Care*. 1995; 18(10): 1373-1375.

255. Srividya N, Periwal S. “Diuretic, hypotensive and hypoglycemic effect of Phyllanthus amarus”. *Indian J. Exp. Biol.* 1995; 33(11): 861-864.
256. Sterne J. «Du nouveau dans les antidiabetiques. La NN dimethylamine guanyl guanide (N.N.D.G.)”. *MarocMed* 1957; 36: 1295-1296.
257. Subramoniam A, Pushpangadan P, Rajasekharan S, Evans DA, Latha PG, Valsaraj R. “Effects of Artemisia pallens Wall. on blood glucose levels in normal and alloxan-induced diabetic rats”. *J. Ethnopharmacol.* 1996; 50(1): 13-17.
258. Sugihara Y, Nojima H, Matsuda H, Murakami T, Yoshikawa M, Kimura I. “Antihyperglycemic effects of gymnemic acid IV, a compound derived from Gymnema sylvestre leaves in streptozotocin-diabetic mice”. *J. Asian Nat. Prod. Res*. 2000; 2(4): 321-327.
259. Sung-Hee Cho, Tae-Hee Kim, Nan-Hee Lee, Ho-Sang Son, Il-Jin Cho, Tae-Youl Ha “ Effects of Cassia tora Fiber Supplement on Serum Lipids in Korean Diabetic”. *J. Med. Food*, 2005; 8(3): 311-318.
260. Swanston-Flatt SK, Day C, Bailey CJ, Flatt PR. “Evaluation of traditional plant treatments for diabetes: studies in streptozotocin diabetic mice”. *Acta Diabetol. Lat*. 1989; 26(1): 51-55.
261. Swanston-Flatt SK, Day C, Bailey CJ, Flatt PR. “Traditional plant treatments for diabetes. Studies in normal and streptozotocin diabetic mice”. *Diabetologia*. 1990; 33(8): 462-464.
262. Swanston-Flatt SK, Day C, Flatt PR, Gould BJ, Bailey CJ. “Glycemic effects of traditional European plant treatments for diabetes. Studies in normal and streptozotocin diabetic mice”. *Diabetes Res*. 1989; 10(2): 69-73.
263. Teixeira CC, Rava CA, Mallman da Silva P, Melchior R, Argenta R, Anselmi F, Almeida CR, Fuchs FD. “Absence of antihyperglycemic effect of jambolan in experimental and clinical models”. *J. Ethnopharmacol.* 2000; 71(1-2): 343-347.
264. Terashima S, Shimizu M, Nakayama H, Ishikura M, Ueda Y, Imai K, Suzui A, Morita N. “Studies on ALR2 inhibitors from medicinal plant of "sinfito," Potentilla candicans, and further synthesis of their related compounds”, *Chem. Pharm. Bull*. 1990; 3: 2733-2736.
265. Termentzi A, Alexiou P, Demopoulos VJ, Kokkalou E. “Antioxidant effect and inhibitory activity against ALR2 enzyme of sorbus domestica fruits’ extracts”. 2nd World Congress on Prevention and Therapies against Obesity: Latest Advances on Natural Ingredients, Pasteur Institute, Paris, June 2007.
266. Termentzi A, Kefalas P, Kokkalou E. “LC–DAD–MS (ESI+) analysis of the phenolic content of orbus domestica fruits in relation to their maturity stage”. *Food Chem*. 2008; 106: 1234-1245.
267. Tezuka Y, Kasimu R, Basnet P, Namba T, Kadota S. “ALR2 inhibitory constituents of the root of Salvia miltiorhiza Bunge”. *Chem. Pharm. Bull*. 1997; 45: 1306-1311.
268. Tunali T, Yarat A, Yanardag R, Ozcelik F, Ozsoy O, Ergenekon G, Emekli N. “The effect of chard (Beta vulgaris L. var. cicla) on the skin of streptozotocin induced diabetic rats”. *Pharmazie*. 1998; 53(9): 638-640.
269. Twaij HA, Al-Badr AA. “Hypoglycemic activity of Artemisia herba alba”. *J. Ethnopharmacol*. 1988; 24(2-3): 123-126.

270. Udayasekhara Rao P. "Short term nutritional and safety evaluation of fenugreek". *Nutr. Res*. 1996; 16: 1495-1505.
271. Ueda H, Kawanishi K, Moriyasu M. "Effects of ellagic acid and 2-(2,3,6-trihydroxy-4-carboxyphenyl)ellagic acid on sorbitol accumulation in vitro and in vivo". *Biol. Pharm. Bull*. 2004; 27(10): 1584-1587.
272. Ugochukwu NH, Babady NE. "Antihyperglycemic effect of aqueous and ethanolic extracts of Gongronema latifolium leaves on glucose and glycogen metabolism in livers of normal and STZ-diabetic rats". *Life Sci*. 2003; 73(15): 1925-1938.
273. Ugochukwu NH, Babady NE. "Antioxidant effects of Gongronema latifolium in hepatocytes of rat models of non-insulin dependent diabetes mellitus". *Fitoterapia* 2002; 73: 612-618.
274. Ugochukwu NH, Cobourne MK. "Modification of renal oxidative stress and lipid peroxidation in STZ-diabetic rats treated with extracts from Gongronema latifolium leaves". *Clinica Chimica Acta* 2003; 336: 73-81.
275. Umesh M, Upadhyay 1, Ramesh K. Goyal. "Efficacy of Enicostemma littorale in type II diabetic patients". *Phytother. Res*. 2004; 18(3): 233-235.
276. Undie AS, Akubue PI. "Pharmacological evaluation of Dioscorea dumetorum tuber used in traditional antidiabetic therapy". *J. Ethnopharmacol*. 1986; 15(2): 133-144.
277. USDA Natural Resources Conservation Service. Plants profile. http://plants.usda.gov/cgi_bin/plant_search.cgi.
278. Valentová K, Moncion A, De Waziers I, Ulrichová J. "The effect of Smallanthus sonchifolius leaf extracts on rat hepatic metabolism". *Cell Biol. Toxicol.* 2004; 20(2): 109-120.
279. Vatsa V, Yadava SP, Biswasb NR, Grovera JK. "Anti-cataract activity of Pterocarpus marsupium bark and Trigonella foenum-graecum seeds extract in alloxan diabetic rats". *J. Ethnopharmacol*. 2004; 93: 289-294.
280. Venkateswaran S, Pari L. "Effect of Coccinia indica leaves on antioxidant status in STZ-diabetic rats". *J. Ethnopharmacol*. 2003; 84: 163-168.
281. Venkateswaran S, Pari L. "Effect of Coccinia indica on Blood Glucose, Insulin and Key Hepatic Enzymes in Experimental Diabetes". *Int. J. Pharmacogn*. 2002; 40(3): 165-170.
282. Verspohl EJ. Bauer K, Neddermann E. "Antidiabetic effect of Cinnamomum cassia and Cinnamomum zeylanicum In vivo and In vitro". *Phytother. Res*. 2005; 19(3): 203-206.
283. Viana GS, Medeiros AC, Lacerda AM, Leal LK, Vale TG, Matos FJ. "Hypoglycemic and anti-lipemic effects of the aqueous extract from Cissus sicyoides". *BMC Pharmacol*. 2004; 4: 9-12.
284. Vijayvargia R, Kumar M, Gupta S. "Hypoglycemic effect of aqueous extract of Enicostemma littorale Blume (chhota chirayata) on alloxan induced diabetes mellitus in rats". *Indian J. Exp. Biol*. 2000; 38(8): 781-784.
285. Vuksan V, Sievenpiper JL, Koo VY, Francis T, Beljan-Zdravkovic U, Xu Z, Vidgen E. "American ginseng (Panax quinquefolius L) reduces postprandial

glycemia in nondiabetic subjects and subjects with type II diabetes mellitus". *Arch. Intern. Med*. 2000; 160(7): 1009-1013.
286. Vuksan V, Sievenpiper JL. "Herbal remedies in the management of diabetes: lessons learned from the study of ginseng". *Nutr. Metab. Cardiovasc. Dis*. 2005; 15(3):149-160.
287. Wadood A, Wadood N, Shah SA. "Effects of Acacia arabica and Caralluma edulis on blood glucose levels of normal and alloxan diabetic rabbits". *J. Pak. Med. Assoc*. 1989; 39(8): 208-212.
288. Wang JC, Hu SH, Wang JT, Chen KS, Chia YC. "Hypoglycemic effect of extract of Hericium erinaceus". *J. Sci. Food Agr*. 2004; 85(4): 641-646
289. Welihinda J, Karunanayake EH, Sheriff MH, Jayasinghe KS. "Effect of Momordica charantia on the glucose tolerance in maturity onset diabetes". *J. Ethnopharmacol*. 1986; 17(3): 277-282.
290. Witters L. "The blooming of the French lilac". *J. Clin. Invest.* 2001; 108: 1105-1107.
291. Wu HS, Xu JH, Chen LZ, Sun JJ. "Studies on anti-hyperglycemic effect and its mechanism of Dendrobium candidum". *Zhongguo Zhong Yao Za Zhi*. 2004; 29(2): 160-163.
292. Yadav UCS, Moorthy K, Baquer NZ. "Combined treatment of sodium orthovanadate and Momordica charantia fruit extract prevents alterations in lipid profile and lipogenic enzymes in alloxan diabetic rats". *Mol. Cell. Biochem*. 2005; 268(1-2): 111-120.
293. Yamahara J, Mibu H, Sawada T, Fujimura H, Takino S, Yoshikawa M, Kitagawa I, "Biologically active principles of crude drugs. Antidiabetic principles of Corny fructose in experimental diabetes induced by streptozotocin". *Yakugaku Zasshi* 1981; 101: 86-90.
294. Yasuda K, Kizu H, Yamashita T, Kameda Y, Kato A, Nash RJ, Fleet GW, Molyneux RJ, Asano N. "New sugar-mimic alkaloids from the pods of Angylocalyx pynaertii". *J. Nat. Prod*. 2002; 65(2): 198-202.
295. Yi YH, Gu JQ, Xiao K, Wang ZZ, Lin HW. "Studies on triterpenoids and their glycosides from Aralia dasyphylla". *Miq Yao Xue Xue Bao*. 1997; 32(10): 769-72.
296. Yokozawa T, Nakagawa T. "Inhibitory effects of Luobuma tea and its components against glucose-mediated protein damage". Food and Chemical Toxicology 2004; 42: 975-981.
297. Yong WU, Jing-ping OU-YANG, Ke WU, Ya WANG, Yun-feng ZHOU, Chong-yuan WEN "Hypoglycemic effect of Astragalus polysaccharide and its effect on PTP1B". *Acta Pharmacologica Sinica*, 2005; 26(3): 345-347.
298. Yoshikawa M, Murakami T, Kadoya M, et al. "Medicinal foodstuffs. III. Sugar beet. (1): Hypoglycemic oleanolic acid oligoglycosides,betavulgarosides I, II, III, and IV, from the root of Beta vulgaris L. (Chenopodiaceae)". *Chem. Pharm. Bull. (Tokyo)* 1996; 44: 1212-1217.
299. Yoshikawa M, Murakami T, Kadoya M, Li Y, Murakami N, Yamahara J, Matsuda H. "Medicinal foodstuffs. IX. The inhibitors of glucose absorption from the leaves of Gymnema sylvestre R. BR. (Asclepiadaceae): structures of gymnemosides a and b". *Chem. Pharm. Bull. (Tokyo).* 1997; 45(10): 1671-1676.
300. Yoshikawa M, Murakami T, Yashiro K, Matsuda H. "Kotalanol, a potent alpha-glucosidase inhibitor with thiosugar sulfonium sulfate structure, from antidiabetic

ayurvedic medicine Salacia reticulate". *Chem. Pharm. Bull. (Tokyo)* 1995; 46: 1339-1340.
301. Yoshikawa M, Shimada H, Nishida N, Li Y, Toguchida I, Yamahara J, Matsuda H. "Antidiabetic principles of natural medicines. ALR2 and alpha-glucosidase inhibitors from Brazilian natural medicine, the leaves of Myrcia multiflora DC. (Myrtaceae): structures of myrciacitrins I and II and myrciaphenones A and B". *Chem. Pharm. Bull. (Tokyo).* 1998; 46(1): 113-119.
302. Yoshikawa M, Shimoda H, Nishida N, Takada M, Matsuda H. "Salacia reticulata and its polyphenolic constituents with lipase inhibitory and lipolytic activities have mild antiobesity effects in rats". *J. Nutr*. 2002; 132(7): 1819-1824.
303. Yu BC, Hung CR, Chen WC, Cheng JT. "Antihyperglycemic effect of andrographolide in STZ-diabetic rats". *Planta Med*. 2003; 69(12): 1075-1079.
304. Zhang XF, Tan BK. "Anti-diabetic property of ethanolic extract of Andrographis paniculata in streptozotocin-diabetic rats". *Acta Pharmacol. Sin*. 2000; 21(12): 1157-1164.
305. Zhang XF, Tan BK. "Effects of an ethanolic extract of Gynura procumbens on serum glucose, cholesterol and triglyceride levels in normal and STZ-diabetic rats". *Singapore Med. J.* 2000; 41(1): 9-13.
306. Zhenqinga H, Zhenxia Z, Chuanxinb Z, Meic H. "Use of natural plant exudates (Sanguis Draxonis) for sustained per osinsulin delivery with dramatic reduction of glycemic effects in diabetic rats". *J. Control. Release* 2004; 97: 467-475.
307. Zimmet P, Alberti KGMM, Show J. "Global and societal implications of the diabetes epidemic". *Nature* 2001; 414: 782-787.