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CURRENT STATUS OF HERBAL DRUGS USED IN THE TREATMENT OF DIABETES MELLITUS

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ABSTRACT

Diabetes mellitus is a metabolic disorder widespread in all parts of the world and is becoming a serious threat for mankind. There are lots of chemical agents available for controlling & treating diabetic patients, but total recovery from diabetes has not been reported up to this date. In addition to adverse effects, drug treatments are not always satisfactory in maintaining euglycemia (normal concentration of glucose level in blood) and avoiding late stage diabetic complications. Alternative to these synthetic agents, plants provide a potential source of hypoglycemic drugs and are widely used in several traditional systems of medicine to treat this disease or are used as adjuvants to many allopathic antidiabetic drugs. Several medicinal plants have been investigated for their beneficial effects in different types of diabetes. Overall there has been great demand for plant products due to low cost, easy availability and lesser side effects. Some of the important plants are discussed here which have stood test of the time & proven beneficial in treatment of diabetes. One of the etiologic factors implicated in the development of diabetes and its complications is the damage induced by free radicals and hence an antidiabetic compound with antioxidant properties would be more beneficial. Therefore information on antioxidant effects of these medicinal plants is also included.

KEYWORDS: euglycemia, herbal drugs, antioxidant properties.

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia, abnormal lipid, and protein metabolism along with specific long-term complications affecting retina, kidneys

and nervous system. Diabetes mellitus has a significant impact on the health, quality of life and life expectancy of patients as well as on the health care system.

Diabetes mellitus has been recognized as a growing worldwide epidemic by many health advocacy groups including WHO. The WHO has estimated that diabetes will be one of the World's leading cause of death and disability within next quarter century. The statistics are alarming; 30 million people were diagnosed with diabetes worldwide in 1985, by 1995 the number had risen to 135 million, and at the current rate there will be some 300 million by the year 2025 as predicted by the WHO. It has been seen that every fourth person with diabetes is an Indian and India is known as the Diabetes Capital of the world. Urban population is mostly affected. A study from Kashmir's Sheri Kashmir Institute of Medical Sciences (SKIMS, Soura), a leading tertiary care hospital of Jammu and Kashmir, shows that 2.5 to 8% of the population is suffering from diabetes and 25 -26.5% people are in the prediabetic stage. Several drugs are available to decrease hyperglycaemia but these drugs have side effects. So the search for new drug/compounds is essential to overcome this chronic disease and problems associated with this.. It is still a challenge to medical community. Plant drugs and herbal formulations are considered to be very less toxic and with lesser side-effects than their synthetic counterparts.

CONVENTIONAL THERAPY

The general consensus on treatment of type 2 diabetes is that life style management must be at the forefront of therapy options. In addition to exercise, weight control and medical nutrition therapy, oral glucose lowering drugs, and injections of insulin are the conventional therapies. Pharmacological treatment is indicated when fasting glucose level exceeds 140mg/dl the postprandial glucose level exceeds 160 mg/dl or HbA_1C exceeds 8 %.[1]

PHARMACOLOGICAL TREATMENT AND LIMITATIONS

Oral glucose lowering drugs

Five classes of oral agents are approved for the treatment of diabetes. Oral therapy is indicated in any patient in whom diet and exercise fail to achieve acceptable glycemic control. Although initial response may be good, oral hypoglycemic drugs lose their effectiveness in a significant percentage of patients. The drug categories include sulfonylureas, biguanides, alpha-glucosidase inhibitors, thiazolidinediones, and meglitinides. These drugs have various side effects, e.g sulfonylureas cause weight gain due to

hyperinsulenemia[2,3] biguanides cause weakness, fatigue, lactic acidosis, alpha glucosidase inhibitors cause diarrhoea while thiazolidinediones may increase LDL-cholesterol level.

Insulin is usually added to an oral agent when glycemic control is suboptimal at maximal dose of oral medication. Weight gain and hypoglycemia are common side effects of insulin.[4,5] Vigorous insulin treatment may also cause an increased risk of atherogenesis.[6]

NEED AND SCOPE OF ALTERNATIVE MEDICINE

Regardless of the type of diabetes, patients are required to control their blood glucose with medication and by adhering to an exercise program and a dietary plan. Due to modernization of lifestyle, type 2 diabetes mellitus is becoming a major health problem in developing countries. Patients with type 2 diabetes mellitus are usually placed on a restricted diet and are instructed to undertake primarily weight control measures. If diet and exercise fail to control blood glucose at a desired level, pharmacological treatment is prescribed.[7] These treatments have drawbacks which range from adverse effects and development of resistance to lack of responsiveness in a large segment of patient population. Moreover, none of the glucose lowering agents is able to adequately control the hyperlipidemia that is frequently associated with the disease.

The limitation of currently available oral antidiabetic agents either in terms of efficacy/safety coupled with the emergence of the disease into global epidemic have encouraged health professionals from alternate system of medicine in developing countries particularly South east Asian countries to search for an alternative therapy that can manage diabetes more efficiently and safely.

MEDICINAL HERBS

As per ancient literature, more than 800 plants are reported to have antidiabetic properties.[8]. Ethanopharmacological surveys indicate that more than 1200 plants are used as traditional medicine for their allied hypoglycemic activity.[9] Indian Materia Medica has mentioned numerous dravyas which are reported to be effective in Madhumeha(diabetes).[10] The indigenous diet may not be useful in lowering the blood sugar to the same extent as insulin and other hypoglycemic agent do, but it has some other influences, which may be useful for the management of the disease and its complications.[11] In diabetes, some herbal alternatives are proven to provide symptomatic relief and assist in the prevention of the secondary complication of the disease. Some herbs have also been proven to help in regeneration of s-

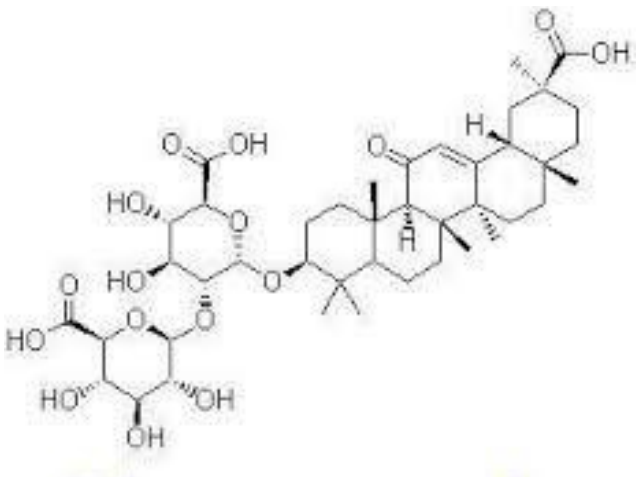
cells and in overcoming resistance.[12] In addition to maintaining normal blood sugar level, some herbs are also reported to possess antioxidant activity and cholesterol lowering action. The management of type 2 diabetes mellitus is possible with drugs that can lower the blood sugar level on one hand and restore the liver glycogen level on the other. In modern system of medicine, there is no drug, reported to possess these properties.[13] However, the hypoglycemic effect of some herbal extracts have been confirmed in human and animal models of type 2 diabetes and conventional drugs have been derived from the active molecule of these medicinal plants. Metformin, a less toxic biguanide and potent oral glucose lowering agent, was developed from *Galega officinalis* and is now extensively used to treat diabetes.[14,15]

Till now over 400 traditional plant treatments for diabetes have been reported[16], although only a small number of these have received scientific and medicinal evaluation to assess their efficacy. The following is a summary of several of the most studied and commonly used medicinal herbs.

1. *Momordica charantia* (Bitter gourd)

Also known as bitter melon, has been used extensively in folk medicine as a remedy for diabetes.[17] The blood sugar lowering action of fresh juice or unripe fruit has been established in animal experimental models as well as human clinical trials.[18]

It is composed of several compounds with confirmed antidiabetic activity. Alcohol-extracted charantin and M. charantia consisting of mixed steroids was found to be more potent than the oral hypoglycemic agent tolbutamide in an animal study.[19]



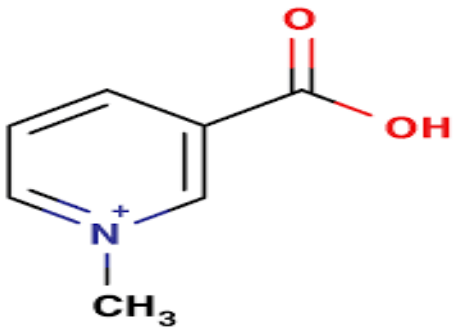
Charantin

2. *Trigonella foenum graecum* (Fenugreek, Methi)

Commonly known as Fenugreek, popular for its pungent aromatic properties, it is often used as a flavouring agent. It has been used as a remedy for diabetes, particularly in India. The active principle is in the defatted portion of the seed, which contains the alkaloid gonelline, nicotinic acid and coumarin. Several animal experimental studies confirmed the antidiabetic potential of *T. foeneum graecum*.[20,21,22]

Human studies have confirmed the glucose and lipid-lowering test.[23] At least 50% of seed is fiber based and may constitute another potential mechanism of Fenugreek's beneficial effect in diabetic patients.[24] Plant contains many steroid saponins, alkaloids (trigonillin) and furastanol glycosides known to have antidiabetic properties.

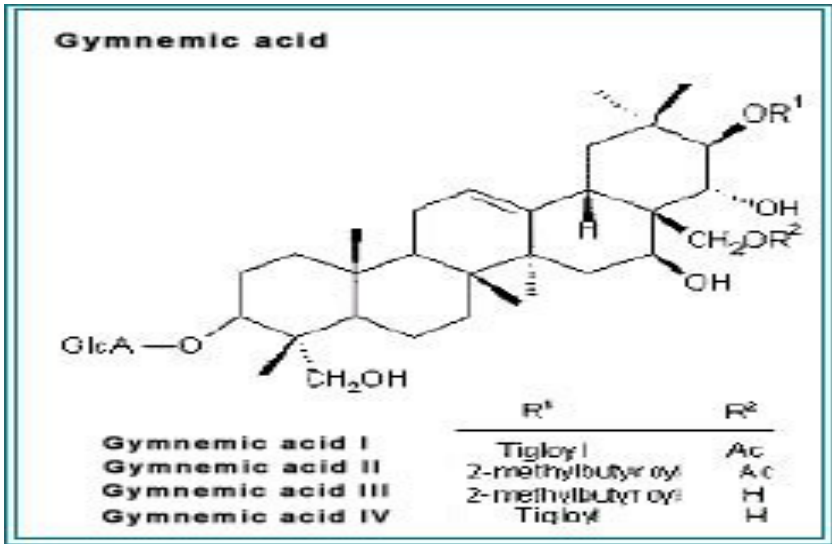
In type 2 diabetes patients, the ingestion of 15 g of powder of Fenugreek seeds soaked in water significantly reduced postprandial glucose levels during the glucose tolerance test.[25]



Trigonelline

3. *Gymnema sylvestre*

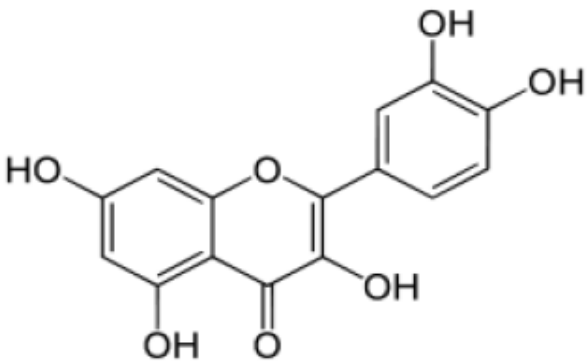
Commonly known as Gurnar, it has long been used as a treatment for diabetes. It appeared on the US market several years ago as a sugar blocker. In a study of type 2 diabetes, 22 patients were given 400 mg *Gymnema sylvestre* extract (gymnemic acid) daily along with their oral hypoglycemic drugs. All patients demonstrated improved blood sugar control. Twenty one of twenty two were able to discontinue oral medication and maintain blood sugar control with the Gymnema extract alone.[26] It was postulated that Gymnema sylvestre enhances the production of endogenous insulin.[27]



Gymnemic acid

4. *Azadirachta indica* (neem)

Commonly known as neem. It has been long used as a treatment for diabetes. Aqueous extract of neem leaves significantly decreases blood sugar level and prevents adrenaline as well as glucose-induced hyperglycaemia.[28] An aqueous leaf extract also reduced hyperglycaemia in streptozotocin induced diabetes and the effect is possibly due to presence of a flavonoid, quercetin.[29] The plant blocks the action of epinephrine on glucose metabolism, thus increasing peripheral glucose utilization.[30] It also increased glucose uptake and glycogen deposition in isolated rat hemi diaphragm.[31]

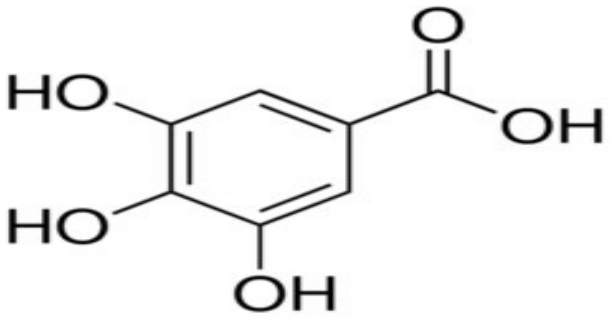


Quercetin

5. *Acacia Arabica* (Babul)

It is found all over india, mainly in the wild habitat. The plant extract acts as an antidiabetic agent by acting as secretagouge to release insulin. In a study it induced hypoglycemia in controll rats but not in alloxanized animals.[32] Powdered seeds of Acacia arabica when administered (2,3 and 4 g/kg body weight) to normal rabbits induced hypoglycemic effect by

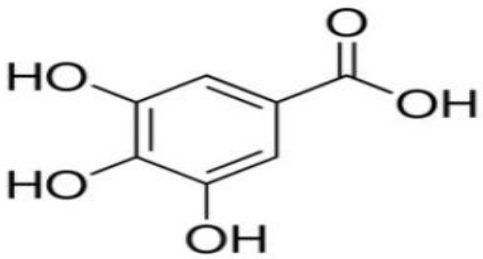
initiating release of insulin from pancreatic beta cells.[33] Plant contains gallic acid which is known for its anti**hyperglycaemic activity.**



Gallic acid

6. *Aegle marmelos* (Bengal Quince, Bel or Bilva)

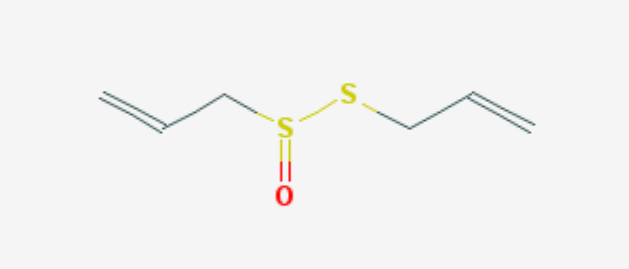
Administration of aqueous extract of Leaves improved digestion and reduced blood sugar and urea, serum cholesterol in alloxanized rats as compared to control. Besides exhibiting hypoglycemic activity, this extract also prevented peak rise in blood sugar at 1h in oral glucose tolerance test.[34] It contains several alkaloids, coumarins like marmelosine and terpenoids like phellandrene which are known to have antihyperglycaemic activity.



Marmellosin

7. *Allium cepa* (onion)

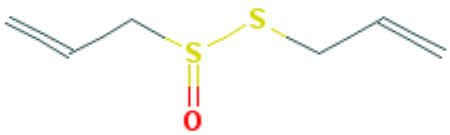
Allium cepa is known for Having antidiabetic activity as it contains quercitin (antidiabetic agent) which has been shown to possess antidiabetic activity in rabbits.[35] Allium cepa is also known to have antioxidant and hypolipidaemic activity as well. Administration of a sulfur containing amino acid from Allium cepa, S-methyl cysteine sulphoxide (SMCS) (200 mg/kg for 45 days) to alloxan induced diabetic rats significantly controlled blood glucose as well as lipids in serum and tissues and normalized the activities of liver hexokinase, glucose 6-phosphatase and HMG Co A reductase.[36,37] When diabetic patients were given single oral dose of 50 g of onion juice, it significantly controlled post-prandial glucose levels.[38]



S-allyl cysteine sulphoxide (allicin)

8. *Allium sativum* (garlic)

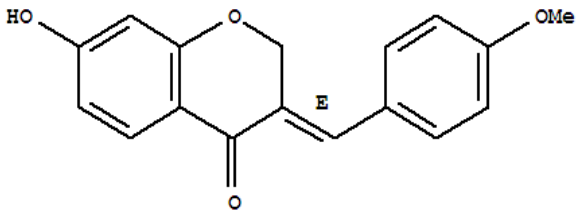
This is a perennial herb cultivated throughout India. Allicin, a sulfur-containing compound is responsible for its pungent odour and it has been shown to have significant hypoglycemic activity.[39] This effect is thought to be due to increased hepatic metabolism, increased insulin release from pancreatic beta cells and/or insulin sparing effect.[40] Aqueous homogenate of garlic (10 ml/kg/day) administered orally to sucrose fed rabbits (10 g/kg/day in water for two months) significantly increased hepatic glycogen and free amino acid content, decreased fasting blood glucose, and triglyceride levels in serum in comparison to sucrose controls.[41] S-allyl cystein sulfoxide (SACS), the precursor of allicin and garlic oil, is a sulfur containing amino acid, which controlled lipid peroxidation better than glibenclamide and insulin.[41] It also improved diabetic conditions. SACS also stimulated in vitro insulin secretion from beta cells isolated from normal rats.[42]



S-allyl cystein

9. *Caesalpinia bonducella*

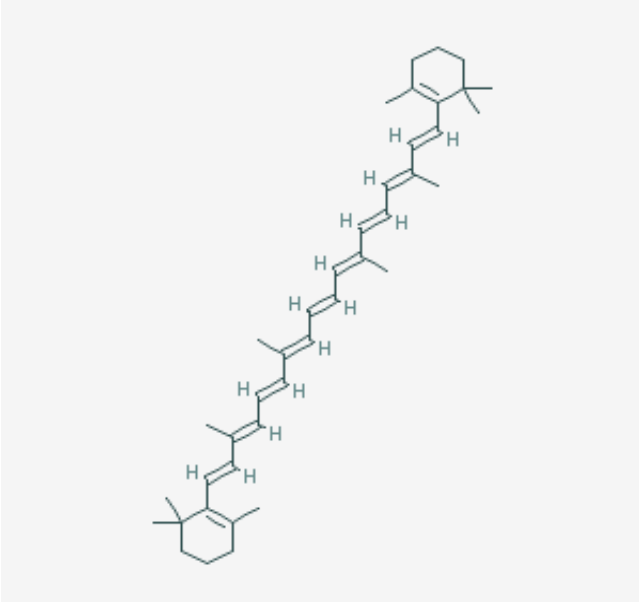
Caesalpinia bonducella is widely distributed throughout the coastal region of India and is used ethnically by the tribal people for controlling blood sugar. Both the aqueous and ethanolic extracts showed potent hypoglycemic activity in chronic type II diabetic models.[43] These extracts also increased glycogenesis thereby increasing liver glycogen content.[43] The antihyperglycemic action of the seed extracts may be due to the blocking of glucose absorption. Plant contains glycoside bonducellin and terpenoid caesallpin which are knwn to have antihyperglycaemic activity.



Bonducellin

10. ***Aloe vera and Aloe barbadensis***

Aloe, a popular houseplant, has a long history as a multipurpose folk remedy. The plant can be separated into two basic products: gel and latex. Aloe vera gel is the leaf pulp or mucilage, aloe latex, commonly referred to as aloe juice, is a bitter yellow exudate from the pericyclic tubules just beneath the outer skin of the leaves. Extracts of aloe gum effectively increased glucose tolerance in both normal and diabetic rats.[44] This action of Aloe vera and its bitter principle is through stimulation of synthesis and/or release of insulin from pancreatic beta cells.[45] This plant also has an anti-inflammatory activity in a dose dependent manner and improves wound healing in diabetic mice.[46] Besides, plant contains saponins, beta carotenes, salicylic acid, sterols etc. Some of them are known to have antioxidant & antidiabetic propertie



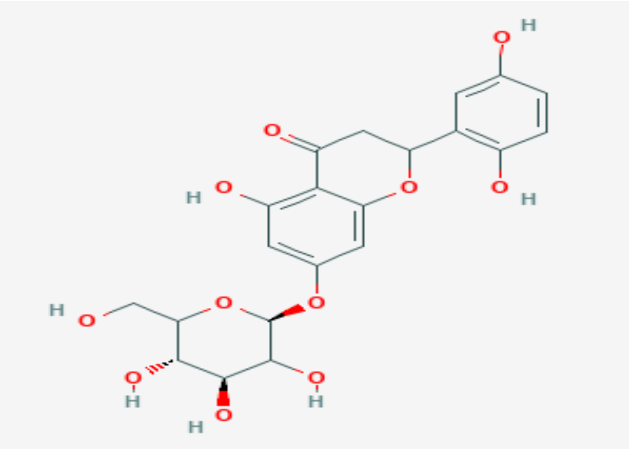
β carotene

11. *Capparis deciduas*

This is found throughout India, especially in dry areas. Hypoglycemic effect was seen in alloxanized rats when the rats were fed with 30% extracts of Capparis decidua (C. decidua) fruit powder for 3 weeks. This extract also reduced alloxan induced lipid peroxidation significantly in erythrocytes, kidney and heart. *C. decidua* was also found to alter superoxide dismutase and catalase enzyme levels to reduce oxidative stress.[47]

12. *Coccinia indica* (Ivy gourd, little gourd)

Dried extract of (*C. indica*) (500 mg/kg body weight) was administered to diabetic patients for 6 weeks. The extract restores the activities of enzyme lipoprotein lipase (LPL) (levels reduced) and glucose-6-phosphatase and lactate dehydrogenase, (levels raised) in untreated diabetics.[48] Plant root contains beta-amyrin, sponin coccinoside,beta sitosterol which are known to have antidiabetic activity.

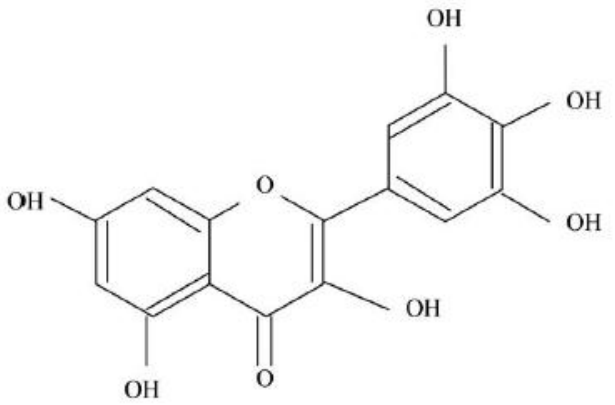


Coccinoside

13. *Eugenia jambolana* (Indian gooseberry, jamun)

Decoction of kernels of Eugenia jambolana is used as household remedy for diabetes. This also forms a major constituent of many herbal formulations for diabetes. Antihyperglycemic effect of aqueous and alcoholic extract as well as lypholized powder varies with different level of diabetes. In mild diabetes (plasma sugar >180 mg/dl) it shows 73.51% reduction, whereas in moderate (plasma sugar >280 mg/dl) and severe diabetes (plasma sugar >400 mg/dl) It shows 55.62% and 17.72% reduction respectively.[49] The plant is rich in compounds containing anthocyanins, Glucoside; ellagic acid, isoquercetin, kaemferol and myrecetin. The seeds are claimed to Contain alkaloid; jambosine, and glycoside jambolin or antimellin, which halt the diastatic conversion of starch into sugar. The extract of jamun pulp

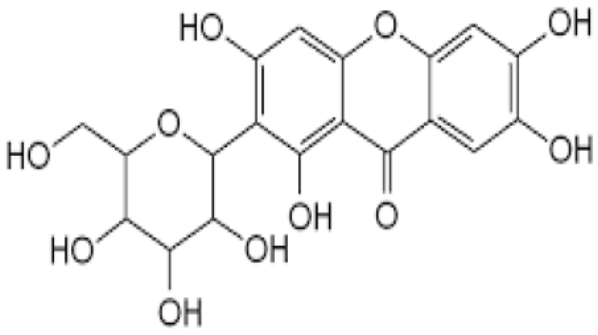
showed the hypoglycemic activity in streptozotocin induced diabetic mice within 30 min of administration while the seed of the same fruit required 24 h. The oral administration of the extract resulted in increase in serum insulin levels in diabetic rats. Insulin secretion was found to be stimulated on incubation of plant extract with isolated islets of Langerhans from normal as well as diabetic animals. These extracts also inhibited insulinase activity from liver and kidney.[50]



Jambolin

14. *Mangifera indica* (Mango)

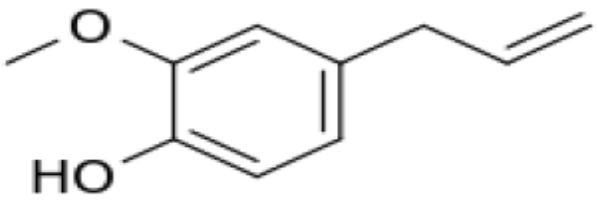
The leaves of this plant are used as an antidiabetic agent, besides it contains mangeferin, a compound known to have antidiabetic activity. Aqueous extract given orally did not alter blood glucose level in either normoglycemic or streptozotocin induced diabetic rats. However, antidiabetic activity was seen when the extract and glucose were administered simultaneously and also when the extract was given to the rats 1 hour before the glucose.[51] The results indicate that aqueous extract of *Mangifera indica* possesses hypoglycemic activity, which is attributed to intestinal reduction of the absorption of glucose.[51]



Mangiferin

15. *Ocimum sanctum*: (holy basil, tulsi)

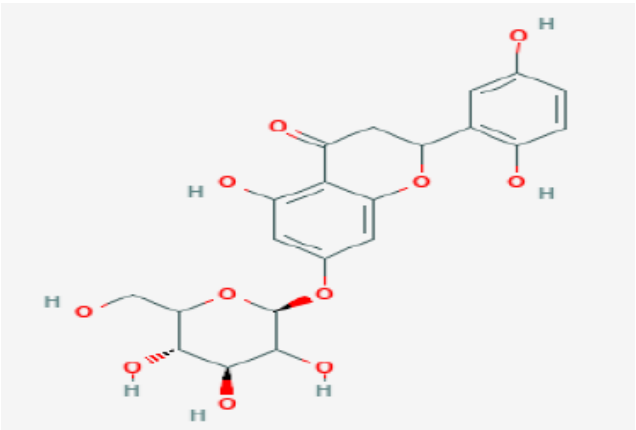
Commonly known as Tulsi, since ancient times, this plant is known for its medicinal properties. It contains eugenol, linalool, ursolic acid having anti-diabetic activities. The aqueous extract of leaves of *Ocimum sanctum* showed the significant reduction in blood sugar levels in both normal and alloxan induced diabetic rats.[52] Significant reduction in fasting blood glucose, uronic acid, total amino acid, total cholesterol, triglyceride and total lipid indicated the hypoglycemic and hypolipidemic effects of tulsi in diabetic rats.[53] Besides, the leaf of *Ocimum sanctum* is known to have antihyperglycaemic effects in experimental animals.[53]



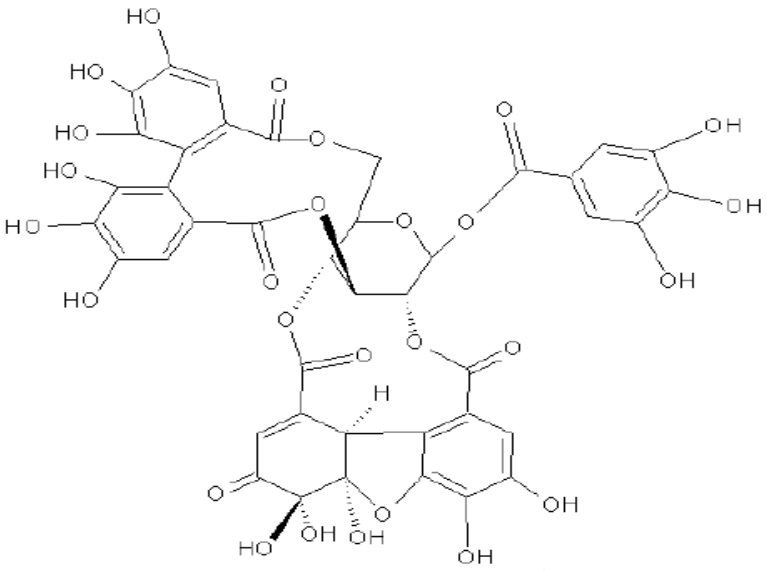
Eugenol

16. *Phyllanthus amarus* (bhuiawala)

It is a herb attaining height up to 60 cm, from family *Euphorbiaceae*. It is commonly known as bhuiawala. It is scattered throughout the hotter parts of India, mainly Deccan, Konkan and south Indian states. Traditionally it is used in diabetes therapeutics. Methanolic extract of *Phyllanthus amarus* was found to have potent antioxidant activity. This extract also reduced the blood sugar in alloxanized diabetic rats.[54] Besides, it contains tannins & ellagitannins like geranin, amarin which are known to have antidiabetic activity.



Coccinoside

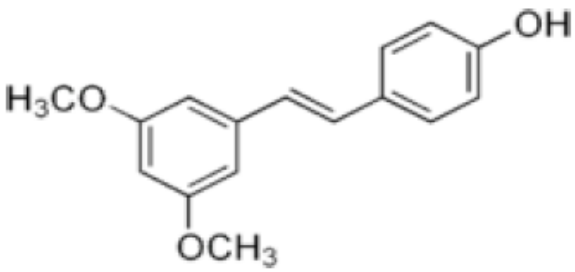


Geranin

17. *Pterocarpus marsupium* (Malabar kino)

It is a deciduous moderate to large tree found in India mainly in hilly region. Pterostilbene, a constituent derived from wood of this plant caused hypoglycemia in dogs[55,56]

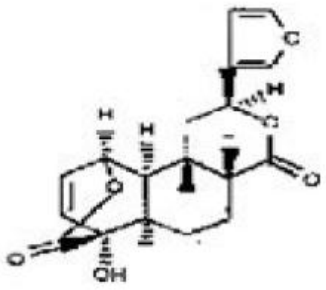
Hypoglycaemic activity of this extract is thought to be because of presence of tannates in the extract. Flavonoid fraction from *Pterocarpus marsupium* has been shown to cause pancreatic beta cell regranulation.[57] Epicatechin, its active principle, has been found to be insulinogenic, enhancing insulin release and conversion of proinsulin to insulin in vitro. Besides it contains pterostilbene also having antihypoglycaemic activity. Like insulin, (−) epicatechin stimulates oxygen uptake in fat cells and tissue slices of various organs, increases glycogen content of rat diaphragm in a dose-dependent manner.[58]



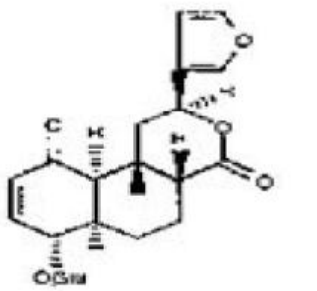
Pterostilbene

18. *Tinospora cordifolia* (Guduchi, heart leaved moon seed)

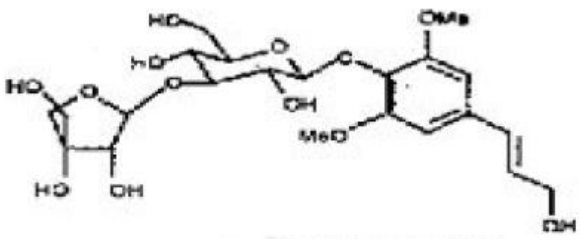
It is a large, glabrous, deciduous climbing shrub belonging to the Family *menispermaceae*. The plant contains columbin, tinosporaside & cordifolloside which are known to have antihypoglycemic activity. It is widely distributed throughout India and commonly known as Guduchi. Oral administration of the extract of *Tinospora cordifolia* (*T.cordifolia*) roots for 6 weeks resulted in a significant reduction in blood and urine glucose and in lipids in serum and tissues in alloxan diabetic rats. The extract also prevented a decrease in body weight.[59] *T.cordifolia* is widely used in Indian ayurvedic system of medicine for treating diabetes mellitus.[59,60] Oral administration of an aqueous *T.cordifolia* root extract to alloxan diabetic rats caused a significant reduction in blood glucose and brain lipids. Though the aqueous extract at a dose of 400 mg/kg could elicit significant anti-hyperglycemic effect in different animal models, its effect was equivalent to only one unit/kg of insulin.[61] It is reported that the daily administration of either alcoholic or aqueous extract of *T.cordifolia* decreases the blood glucose level and increases glucose tolerance in rodents.[61]



columbin



tinosporaside



Tinosporaside, Columbin, Cordifolloside

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