REVIEW ARTICLE

A Comprehensive Review on Natural Remedies for Diabetes: A Metabolic Disorder

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Abstract

The metabolic syndrome (MetS) is a group of metabolic imbalances that involves hypertension, central obesity, insulin resistance, and atherogenic dyslipidemia. It is linked to an increased risk of diabetes and atherosclerotic and non-atherosclerotic cardiovascular disease (CVD). MetS has gained significant importance recently due to the exponential increase in obesity worldwide. The two main causes of this kind of syndrome are an increase in high-calorie, low-fiber fast food consumption and a decrease in physical activity owing to mechanised transportation and sedentary leisure activities. The syndrome contributes to the spread of diseases such as type 2 diabetes, coronary artery disease, stroke, and others. Herbal treatments have a long history of use in the treatment and prevention of disorders, including diabetes, when compared to conventional medicine. Diabetes is one of the world's most serious public health issues. Diabetes mellitus is a syndrome marked by hyperglycemia, changes in lipid, carbohydrate, and protein metabolism, and long-term consequences affecting the eyes, kidneys, cardiovascular system, and nervous system. From thousands of years plants and their derivatives are being used for treatment of diabetes and continue to provide mankind with new remedies. Also recently increase in number of people suffering from diabetes worldwide and several associated complications leads to pay more attention towards remedies of diabetes. Hence a review of conventional and recently explored plants useful in treatment of diabetes concised and aimed to revert back to the conventional plant benefits and utilization of medicinal plants.

Keywords: Antidiabetic, Diabetes Mellitus, Hypoglyceamic, Medicinal plants.

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INTRODUCTION

Before the introduction of insulin in 1922, the treatment of diabetes mellitus relied on dietary measures which included the use of traditional plant therapies. Many traditional plants were successfully used for the treatment of diabetes.[1-3] Although, the active principles of various classes of chemical compounds have been isolated from plants; some remain to be identified.[4] The World Health Organization has recommended that traditional plant treatment for diabetes.[5] An antidiabetic agent could act by enhancing insulin secretion and or by improving insulin action.[6] Nowadays, the use of complementary and alternative medicine and consumption of botanicals have been increasing.[7]

Diabetes is a condition in which the body either does not produce enough insulin or cannot use insulin properly. Insulin is a naturally occurring hormone in the blood that is necessary for providing our cells with energy to function. Insulin helps sugar (glucose) to move from the blood stream into the cells. When glucose cannot enter our cells, it builds up in the blood (hyperglycemia), leading to damage of organs.

Most of the people with diabetes have "type II diabetes "(adult onset diabetes) this means that the body does not produce enough insulin or the insulin is not able to transfer glucose into the cell. In contrast, people with" type I diabetes" (juvenile onset diabetes) have a condition where the body does not produce any insulin at all. People with type I diabetes need insulin injection and close monitoring to control their blood sugar levels.[8] Banting an orthopedic surgeon and C.H. Best a medical student extracted insulin for the 1st time on 30th June 1921 (Table 1).

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Historical works on oral pills was done by laboratories in France in 1944 and oral pills containing sulfonyl urea derivatives were introduced in 1955 by Franke and Fuchs.[9,10] According to the diabetes atlas published by the International Diabetes Federation (IDF), there are an estimated 40 million people with diabetes in India in 2007 and this number is predicted to rise to almost 70 million by 2025 by which time every 5th diabetic subject in the world would be an Indian.[11] Table 2 describing the differentiable points between the both types of diabetes.[12]

Table 1: Various milestones in the history of diabetes mellitus

1500 BC	Papyrus describes abnormal polyurea and was bought by Eberus in Luxor
500 BC	Diabetes described (honey urine) in ayurveda of sushrut.
1682 AD	Brunner observed polydypsia and polyurea in pancreactectomized dog.
1869 AD	Islets described by langerhans.
1921 AD	Pauleso extracted insulin, banting and best extracted insulin, purified it and used to treat diabetes in dog.

Table 2: Comparison chart between type I and type II dependent diabetes mellitus[12]

Factors	*IDDM (type I)*	*IDDM(type II)*
Primary disease	Islet cells	Insulin receptors
Presence of genetic factor	Yes	No
Average age at onset	<40	>40
Ketosis	Common	Hardly encountered
Pancreatic cell antibody	Present	Absent
Insulin treatment	Always required	Not always required
Body weight loss	Profound	Minimal
History of symptoms	Abrupt and severe	Gradual and insidious
Frequency	0-20%	80-90%

Clinical Aspects of Diabetes

Millions of people have diabetes and don't even know it because the symptoms develop so gradually, people often don't recognize them. Some people, particularly pre-diabetics, have no symptoms at all. Diabetics may have some or none of the following symptoms:[13]

- Frequent urination
- Excessive thirst
- Extreme hunger
- Unexplained weight loss
- Sudden vision changes
- Tingling or numbness in hands or feet
- Poor circulation
- Poor sleep
- Feeling very tired much of the time
- Irritability
- Very dry skin
- More infections than usual
- Sores that are slow to heal[12]

India leads a world with the largest number of diabetic subjects of being termed diabetes capital of the world, as per WHO, India will be the nation with the highest number of diabetes in the world by 2030 followed by China and then USA. This is an alarming sound as far as the heath system of India is concerned.[14]

Table 3: India's status at 2030 as per WHO

Ranking	*Country*	*People with diabetes (in millions) 2000*	*People with diabetes (in millions) 2030*
1.	India	31.7	79.4
2.	China	20.8	42.3
3.	USA	17.7	30.3

Not only India but the entire Indian subcontinent and south East Asia are at higher predisposition to diabetes as shown in WHO database. The economic burden to be felt by all these nations is surely going to affect their growth.[15]

Diabetes - A Disease to a Disorder

Diabetes is a long-term illness that affects the way your body converts food into energy. The majority of the food you eat is converted to sugar (also known as glucose) and absorbed into your bloodstream. When your blood sugar levels rise, your pancreas is prompted to release insulin. Insulin is a key that allows blood sugar to enter your body's cells and be used as energy. Changes in these chemical levels could be harmful to human health. Diabetes develops as a result of this.

Experts advise people to maintain their blood glucose levels in following ways,

- Fasting blood sugar levels of 80 to 130 mg/dL (4.4 to 7.2 mmol/L) (before meals)
- 180 mg/dL (10.0 mmol/L) or less 2 hours following a meal
- A1C levels in the blood should be less than 7%.

*Because vigorous treatment to achieve these goals raise the risk of hypoglycemia (low blood sugar), these targets are altered for some persons who are more susceptible to hypoglycemia, such as the elderly.

*After taking chronic treatments for the management of diabetic conditions hurts the effectivity of body either to use produced Insulin or unable to produce insulin.

Diabetes and Its Complications

Complications Related to Artery Damage[16]

Diabetes causes damage to both large and small arteries. This artery damage results in medical problems that are both common and serious:

- **Cardiovascular disease**. Diabetics have up to a 400% greater chance of heart attack or stroke. Heart disease and stroke cause about 65% of deaths among people with diabetes. These deaths could be reduced by 30% with improved care to control blood pressure and blood glucose and lipid levels.
- **Amputations**. About 82,000 people have diabetes-related leg and foot amputations each year. Over 60% of non-traumatic lower limb amputations are diabetes related. Foot care programs that include regular examinations and patient education could prevent up to 85% of these amputations.
- **Kidney disease**. About 38,000 people with diabetes develop kidney failure each year. Treatment to better

Table 4: Herbal Drugs used in control of Diabetes

SN	*Common name*	*Scientific name*	*Part Used*	*Chemical constituents*	*Pharmacological action*
1.	Garlic[17-20]	*Allium sativum*	Bulbs	Scormine, allylthiofructosid , uronic acid	Antioxidant, increase secretion and slow the degradation of insulin.
2.	Aloe Vera[21-23]	*Aloe barbadensis mill*	Leaves	Aloin, isobarbaloin, Emodin,aloe-emodin.	Cathartic, lower fasting blood glucose levels and HbA1c. after- sun lotion, treat burns and to promote wound healing.
3	Ninjin, Ginseng[24-27]	*Panax ginseng*	Rhizome	Panaxadial, panaxatriols.	Decreases in fasting blood glucose
4.	Tulsi[19,28-30]	*Ocimum sanctum*	Whole plant	Eugenol, carvacol, caryophyllin, eugenol methyether.	Positive effect on postprandial and fasting glucose, enhances the functioning of beta cells, and facilitates the insulin secretion process.
5.	Fenugreek [18,32,33]	*Trigonella foenum graecum*	Seeds	Glycosides, quercetin, luteolin	Improved glycaemic control.
6.	Indian aconite[34]	*Aconitum ferox wall ex. Ser*	Roots	Napelline ,picro-aconine ,benzyl aconine ,homo napelline.	Diaphoretic,diuretic,antiperiodic,antipyretic and antidiabetic action.
7.	Bale tree[35,36]	*Aegle marmelos coor.*	Leaves and root	Tannin phlobtannins aegeline ,flavon-3-ols,leucoanthocyanins.	Hypoglycemic activity.
8..	Onion[18,37-40]	*Allium cepa linn*	Bulbs	Allyl propyl disulphide, cycloallin, propylsulfenic acid	Diuretic, stimulating, expectorant, antiflatulance and reduce blood sugar.
9.	Neem tree[41-43]	*Azadiracta indica A. Juss.*	Leaves	Salani , nimbin, nimbidin.	Reduction of blood glucose level
10.	*Vinca rosea*[44-45]	*Catharanthus roseus*	Whole plant	Alkaloids, urosilic acid, leurosine, previne, mitraphyllime.	Antidiauretic activity, hypoglyconic activity, reduce blood sugar.
11.	Ivy gourd[46,47]	*Coccinia indica*	Roots	Stigmost-7en-3-one, lupeol	Hypoglycemic activity.
12.	Carrot[48]	*Daucus carota linn.*	Roots	Sterol, alpha pinene, myrcene, limonene	Reduce blood sugar level.
13.	Tea[18,49]	*Camellia sinensis (L)*	Leaves	Caffeine, theobromine, theophylline, thease .	Reduce blood sugar level.
14.	Vidhadaki[34]	*Rourea santaloides W.and A.*	Roots		Antidiabetic activity
15.	Sarpagandha[19]	*Rauwolfia serpentiana*	Roots	Reserpine ,ajmaline, serpentinine, rescinnamine	Stimulates the hypoglycemic effect of insulin as well as the hyperglycemic effect of adrenaline in normal subjects.
16.	Mentha oil[50]	*Mentha piperita*	Leaves	Menthol, menthone, menthofuran,	Antidiabetic activity.
17.	Eucalyptus[51-54]	*Eucalyptus globules*	Leaves	Cineole, pinene, camphene,	Hypoglycemic effect.
18.	Cascara bark[55]	*Rhamnus pershiana*	Bark	Barbaloins, chrysaloins, emodin.	Hypoglycemic effect.
19.	Evening prime rose[56-58]	*Oenothera biennis*	Fixed oil from seeds.	Lenolinic acid, gamma linolinic acid, oleic acid, palmitic acid.	Diabetic neuropathy.
20.	Maiden hair tree[59-61]	*Gingko biloba*	Dried leaves	Flavanol, monoglycoside, diglycosides, triglycosides of kaempferol	Early stage diabetic neuropathy

21	Karela[18,58,62-64]	*Momordica charantia*	Fresh green fruits	Charantin, momordicin, ascorbic acid.	Lower blood sugar levels.
22.	Gudmar[18,58,65,66]	*Gymnema sylvestre*	Leaves	Pentriacontane, hentriacontane, phytin, resin, tartaric acid.	Hypoglycemic effect.
.23.	Malbar kino[58,67,68]	*Peterocarpus marsupium*	Dride juice of plant	Kino tannic acid, kinored, K-pyrocatechin, resin gallic acid.	Hypoglycemic action.
24.	Kalmi dalchini[69-72]	*Cinnamomum zeylanium*	Dried inner bark of shoot.	Phlobatannins, mucilage, cinnamaldehyde, eugenol..	Effectively support healthy glucose metabolism.
25.	Black plum (jamun)[67,68-73,74]	*Syzygium cuminii*	Seeds, leaves, fruits.	Ellagic acid, isoquercitin, quercetin, Acetyloleanolic acid	Hypoglycemic action.
26.	Guduchi[75,76]	*Tinospora cordifolia*	Dried stems	Tinocordiside, syringin, tinosporic acid, tinosporal.	Hypoglycemic action.
27.	Turmeric[68-76]	*Curcuma longa*	Rhizome	Curcumin, alpha pinene, beta pinene, camphene, zingiberene.	Lower blood sugar, increase glucose metabolism, increase insulin activity.
28.	Zinger[76]	*Zingiber officinale*	Rhizome	Alpha zingiberene, beta bisabolene, alpha farnesene, alpha curcumene.	Control blood sugar level.
29.	Snake root[77-81]	*Polygala senega*	Dried roots	Salicylates, triterpenes, saponins.	Hypoglyceamic action
30.	Marian thistle[50]	*Silybum marianum*	Dried ripe fruits free from pappus	Flavanolignans, silymarin, silybin, isosilybin, silycristine.	Reduce blood sugar levels.
31.	Nettle[50,82]	*Radix uriteae dioical*	Dried roots and rhizomes	Phenyls, propains, lignans, fatty acid.	Produce antidiabetic action.
32.	Bear berry[50-72]	*Arctosta-phylous uva-ursi*	Dried leaves	Hydroquinone derivatives, rbutin, methylarbutica,gallic acid.	Lowers the risk of diabetic complication.
33.	Peanut[18]	*Arachis hypogaea*	Seeds	Glycerides of fatty acids, oleic, linoleic, stearic and palmitic acid.	Keep blood sugar level down.
34.	Bitter apple[83,84]	*Citrullus colocynthis*	Fruits	Alpha elaterin, colocynthin, colocynthidin	It shows insulinotropic effect.
35.	Banaba[85-86]	*Lagerstroemia speciosa*	Fruit	Colosolic acid and maslinic acid .	Glucose transpoter activator.
36.	Bitter almond[87]	*Prunus amygdalus*	Seeds	Bland fixed oil ,protein, enzymes, emulsion,amygdalin.	Shows hypoglyceamic acid.
37.	Ashvagandha[88]	*Withania somnifera*	Roots and stem	Withanine, somniferine, somnine, somniferinine	Decrease blood glucose level.
38.	Coriander[89]	*Coriandrum sativum*	Seeds	Coriandrol, coriandryl acetate, pinene.	Reduce hyperglyceamia.
39.	Jira[90]	*Cuminum cyminum*	Fruits	Cuminaldehyde, alpha pinene,beta pinene, cuminic alcohol.	Shows antidiabetic effect.

40.	Mustard[91]	*Brassica juncea*	Leaves and seed	Fixed oil, protein, glycoside-sinigrin.	Increase activity of glycogen synthetase and decrease in glycogenolysis.
41.	Davana oil[92]	*Artemisia pallens*	Aerial part of plant	Davanone, artemone, non-davanone,cineol	Produce reduction in glycemia.
42.	Sweet potato leaves[93]	*Ipomoea batatas*	Leaves	Anthocyanins, chlorogenic acid, caffeic acid,	Produce a reduction in hyperinsulinemia
43.	Isabgol[71,94,95]	*Plantago ovata*	Dried seeds	Mucilage, pentosan, aldobionic acid, fixed oil	Antidiabetic activity.
44.	Amla[67,71]	*Emblica officinalis*	Dried and fresh fruits	Vitamin c, phyllemblin, tannin ,phosphorous, iron, calcium.	Hypoglycemic action.
45.	Shilajit[96]	*Herbomineral drug*	Fissures of iron rich rock	Albuminoids, fatty acids, trace elements, fulvic acid -7methoxy- carboxy biphenyl.	Counteracts diabetes and regulates blood supply of glucose.
46.	Marsh Mallow[18]	*Althaea officinalis*	Roots	Starch, mucilage pectin.	Keep blood sugar level down.
47.	Bay laurel[18]	*Laurus nobilis*	Leaves	Eucalyptol, terpenes, ger aniol,terpeneol,methyle ugenol.	Body uses insulin more effectively.
48.	Saptrangi[67,97,98]	*Salacia oblonga*	Roots and stem	Alpha glucosidase, salicinol, katalonol-9.	Show inhibitory activity on aldose reductase.
49.	Chitra[67,99]	*Berberis aristata*	Stem bark	Berberine, berbamine, aromaline, palmatine.	Stimulates pancreas to pump more insulin into blood.
50.	Bilberry[72]	*Vaccinium myrtillus*	Leaves	Anthocyanoside glycoside – myrtillin	Lowers the risk of diabetic complications like diabetic cataract and retinopathy.
51.	Mango leaves[100,101]	*Mangifera indica*	Leaves	Protocatechuic acid, catechin, mangiferin, alanine, glycine kinic acid.	Lowers blood sugar levels.
52.	Curry leaves, methi neem[91]	*Murraya koenigii*	Leaves	Girinimbine, murrayanine, murrayafoline- A.	Decrease glycogenolysis and gluconeogenesis.
53.	Barley[102]	*Hordeum vulgare*	Seeds	Protein, maltose and amylotytic enzymes.	Mobilize insulin in NIDDM subjects.
54.	Chirata[103-105]	*Swertia chirayita*	Flowering herb	Xanthone, swerchirin	Blood sugar lowering effect.
55.	Kidney beans[18,106]	*Phaseolus vulgaris*	Seeds	Soluble fiber	Reduces the rise in blood sugar after meals.
56.	Common Fig leaf [107,108]	*Ficus carica*	Leaves	Ficusin, psoralen, 8methoxy psoralen.	Decrease in hyperglyceamia, facilitates glucose uptake
57.	Nopal ,prickly pear cactus[109,110]	*Opuntia streptacantha*	Whole plant	Xylose, galactose, mucilage, arabinose, kaempferol.	Intestinal glucose uptake may be affected by some properties of the plant, and animal studies have found significant decreases in postprandial glucose and HbA1c.
58.	Goat's Rue[111,112]	*Galega Officinalis*	Whole plant	Galegine, tannins, chromium.	Support the maintenance of balanced glucose in the bloodstream.
59.	Insulina vegetal,pedra hume caa.[113-115]	*Myrcia uniflora*	Leaves	Flavanone glycosides –myrciacitrins I and II acetophenone glucosides- myciaphenones A and B	herbs as tea infusions suggest that their hypoglycaemic effects are overrated.

60.	Common horse–chestnut[116,117]	*Aesculus hippocastanum L.*	Seeds	Five triterpene oligologlycosides named escins-Ia, Ib, IIa, IIb and IIIa	These compounds showed hypoglycaemic activity. Greater hypoglycaemic activities were obtained with escins IIa and IIb.

control blood pressure and blood glucose levels could reduce diabetes-related kidney failure by about 50%.

- **Eye disease and blindness**. Each year, 12,000–24,000 people become blind because of diabetic eye disease, including diabetic retinopathy. Diabetes is the leading cause of new cases of blindness among adults 20–74 years old. Screening and care could prevent up to 90% of diabetes-related blindness.
- **Sexual Dysfunction**. Approximately 70% of all adult males with diabetes currently suffer or will experience sexual dysfunction or impotence.

Complications Related to Neuropathy[16]

Diabetes reduces or distorts nerve function, causing a condition called neuropathy. The two main types of neuropathy are:

- Peripheral (affects nerves in the toes, feet, legs, hands, and arm)
- Autonomic (affects nerves that helps regulate digestive, bowel, bladder, heart, and sexual function)

Symptoms include: Tingling, burning sensation, weakness.

Herbal Remedies- A Weapon Against Diabetes

Around 60% of the world's population uses traditional medicines derived from medicinal plants. This article focuses on the use of Indian herbal medications and plants in the treatment of diabetes, particularly in India. Diabetes is a serious human disease that affects people from all walks of life in a variety of countries. It is proven to be a big health issue in India, particularly in metropolitan areas. Despite the fact that there are a variety of techniques to reducing the negative effects of diabetes and its secondary complications, herbal formulations are favored due to their low cost and lack of side effects. A list of medicinal plants used to treat diabetes that has been shown to have anti-diabetic and other therapeutic benefits, as well as herbal medications.[31]

Using herbal remedies and plant derivatives to help in the treatment of diabetes should certainly not be discounted. Although numerous 'miracle herbal cure' companies exist, and champion the ability of herbal compounds to supplement insulin as a treatment, the herbs and plant derivatives listed below have largely been employed traditionally by native people in the treatment of diabetes (Table 4).

Allium sativum

Allium sativum is more commonly known as garlic, and is thought to offer antioxidant properties and micro-circulatory effects. Allium may cause a reduction in blood glucose, increase secretion and slow the degradation of insulin.[118]

Aloe vera

Aloe Vera is a widely used as an after-sun lotion, to treat burns and to promote wound healing. It is well-regarded as a 'healing herb.' In some parts of the world, dried aloe vera sap and gel (taken from the inner portions of the leaves) are used traditionally to treat diabetes. Aloe vera may be able to lower fasting blood glucose levels as well as HbA1c.[118]

Bauhinia forficata and Myrcia uniflora

Bauhinia forficata grows in South America, and is used in Brazilian herbal cures. This plant has been referred to as 'vegetable insulin.' *Myrcia uniflora* is also widely employed in South America. Studies utilising the herbs as tea infusions suggest that their hypoglycaemic effects are overrated.[118]

Chromium picolinate

Is a mineral supplement and highly absorbable nutritional form of chromium - an essential nutrient for sugar and fat metabolism. The adequate daily dietary intake for chromium is 50 to 200 micrograms, but most diets contain less than 60% of this intake! Chromium has been studied with regards to its supportive action on insulin production. In one controlled study, subjects were administered a placebo or 100 or 500 micrograms of *Chromium picolinate* two times per day for four months. Those subjects receiving 100 micrograms twice per day demonstrated no significant improvements, while the group receiving 500 micrograms twice per day saw significant benefits in the glucose/insulin system.[119]

Coccinia indica

Coccinia indica is also known as the 'ivy gourd' and grows wild across the Indian subcontinent. Traditionally employed in ayurverdic remedies, the herb has been found to contain insulin-mimetic properties (i.e.; it mimics the function of insulin). Significant changes in glycemic control have been reported in studies involving *Coccinia indica*.[118]

Ficus carica

Ficus carica, or fig-leaf, is well known as a diabetic remedy in Spain and South-western Europe. Studies on animals suggest that fig-leaf facilitates glucose uptake. The efficacy of the plant is, however, still yet to be validated in the treatment of diabetes.[118]

Gymnema sylvestre

It is also known as the 'sugar killer' as it is said to remove the taste for sweet foods. More recently, *Gymnema Sylvestre* has been shown to be helpful in maintaining healthy blood glucose levels within the normal range. *Gymnema sylvestre* has been linked to the promotion of pancreatic health in animal studies.[118]

Galega officinalis (Goat's Rue)

It is an herb that was traditionally used in medieval Europe to help support pancreatic health and maintain healthy insulin levels, and has more recently been investigated in clinical trials. Studies have also suggested that this potent herb may help to support the maintenance of balanced glucose in the bloodstream.[118]

Ginseng species

In some studies utilising American ginseng, decreases in fasting blood glucose were reported. Varieties include Korean ginseng, Siberian ginseng, American ginseng and Japanese ginseng. In some fields the plant, particularly the panax species, are hailed as 'cure-all,' as is the case with many of the herbs employed around the world in the treatment of diabetics.[118]

Ginkgo biloba

It is an herb that dates back about 200 million years! It has survived mainly in Oriental temple gardens, where it is highly prized in Chinese Traditional Medicine. Studies have investigated *Ginkgo biloba* as a natural antioxidant with regards to cardiac health. Furthermore, this herb has been shown to have great supportive capabilities with regards to the maintenance of healthy blood glucose levels within the normal range.[118]

Momordica charantia

Momordica charantia goes under a variety of names and is native to some areas of Asia, India, Africa and South America. Marketed as charantia, it is also known as karela or karolla and bitter melon. The herb may be prepared in a variety of different ways, and may be able to help diabetics with insulin secretion, glucose oxidation and other processes. Acute effects on blood glucose levels have also been reported.[118]

Ocimum sanctum

Ocimum sanctum is an herb employed in traditional ayurverdic practises, and is commonly known as holy basil. A controlled clinical trial showed a positive effect on postprandial and fasting glucose, and experts predict that the herb could enhance the functioning of beta cells, and facilitate the insulin secretion process.[118]

Opuntia streptacantha

Opuntia streptacantha (nopal) is commonly known as the prickly-pear cactus in the arid regions where it grows. Inhabitants of the Mexican desert have traditionally employed the plant in glucose control. Intestinal glucose uptake may be affected by some properties of the plant, and animal studies have found significant decreases in postprandial glucose and HbA1c.[118]

Silibum marianum

Silibum marianum is also known as milk thistle, and is a member of the aster family. Silymarin contains high concentrations of flavinoids and antioxidants, some of which may have a beneficial effect on insulin resistance. The role of milk thistle in glycaemic control is little understood.[118]

Syzygium cuminii Skeels

Jaman *(Syzygium cuminii* L. Skeels) is an evergreen fruit tree belonging to family Myrtaceae. It is a minor fruit crop of tropical and subtropical region. Mature fruit is fleshy, purplish berry 20 mm in diameter and up to 25 mm long containing a single seed. Some fruits have 2 to 5 seeds tightly compressed within a leathery coat and some are seedless. The fresh fruits are used for diabetes.[120]

Trigonella foenum graecum

Trigonella foenum graecum is known as fenugreek and is widely grown in India, North Africa, and parts of the Mediterranean. Of the few non-controlled trials that have been carried out on type 2 diabetics, most report improved glycaemic control. Further study is certainly warranted. [118]

Vaccinium myrtillus

Bilberry is an herb which has been used in recent times with several active constituents isolated from the berries and leaves of the bilberry plant, including anthocyanoside flavonoids (anthocyanins), vitamins and pectins, which are found in the berries, and quercetin, catechins, tannins, iridoids, and acids, which are found in the leaves. Bilberry also has excellent anti-oxidant properties due to high levels of anthocyanosides, further increasing the supportive health benefits of this remarkable herb. Regular use of Bilberry helps to support healthy vision as well as the health of the tiny blood capillaries which carry oxygen to the eyes. [118]

Further herbs that have been studied, and may have positive effects for diabetic patients include berberine, *Cinnamomym tamala*, curry, *Eugenia jambolana*, gingko, *Phyllanthus amarus, Pterocarpus marsupium, Solanum torvum,* and *Vinca rosea*. [118]

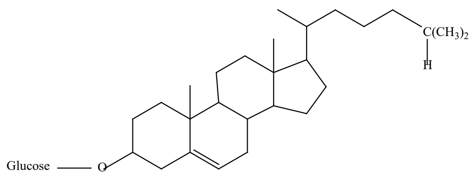
Role of Herbal Pharmacophores Against Diabetes

Home remedies have been utilized for a long period of time and continue to play an important role as complementary and alternative therapy. Furthermore, some novel bioactive compounds derived from plants have shown antidiabetic action with greater efficacy than oral hypoglycemic medications utilised in clinical therapy in recent years. Traditional medicine has had an excellent clinical track record and has a promising future in the treatment of diabetes mellitus. According to the World Health Organization, preventing diabetes and its complications is not just a huge challenge for the future, but also necessary if universal health is to be achieved.

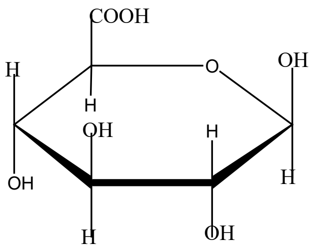
Studies on conventional Marker, their Chromatographic studies and Characterization

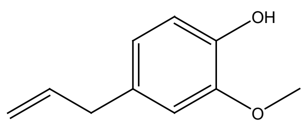
Charantin

Charantin is a typical cucurbitane-type triterpenoid in *M.*



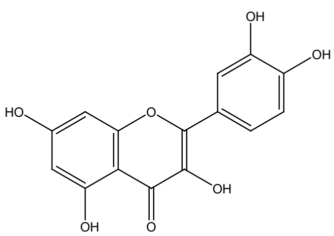
HARANTIN





EUGENOL

URONIC ACID



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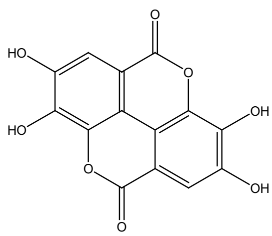

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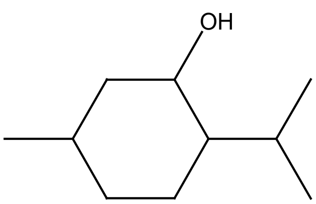

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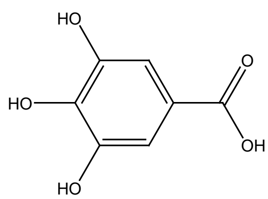
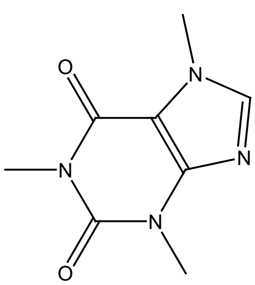
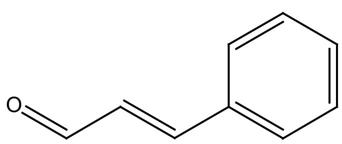


GALLIC ACID



CAFFEINE



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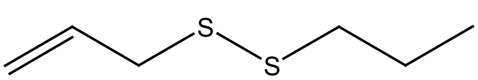

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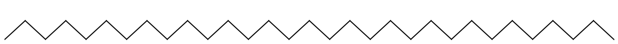

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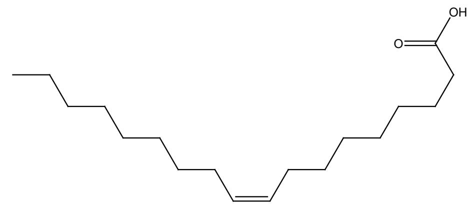
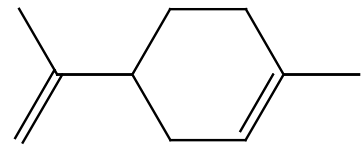


OLEIC ACID



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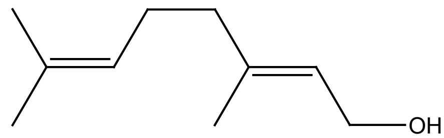

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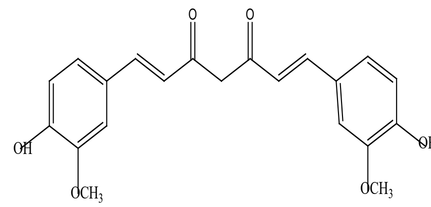

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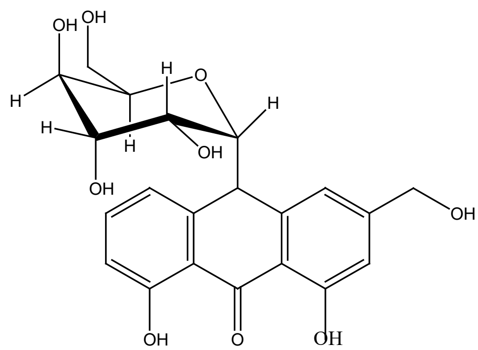
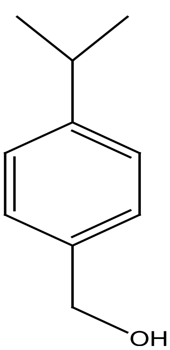
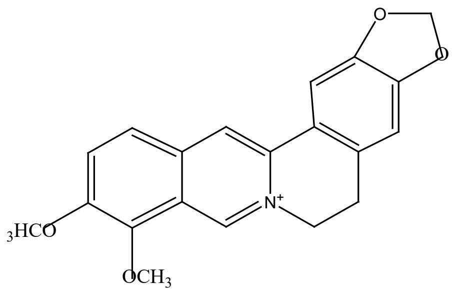


BARBALOIN



CUMINIC AlCOHOL



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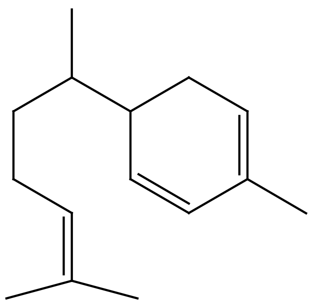
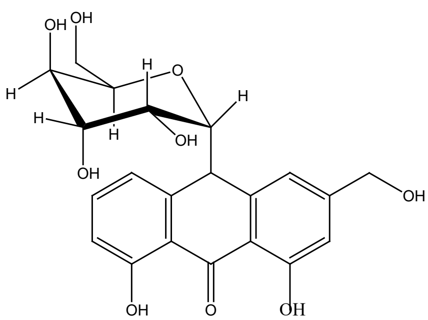
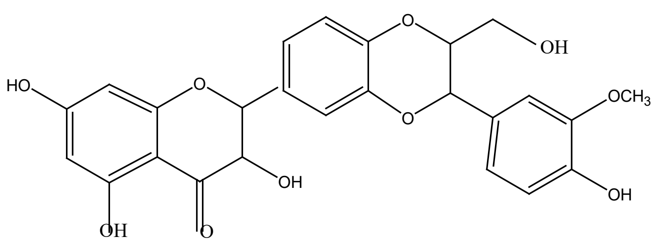


ZINGIBERENE



ALOIN



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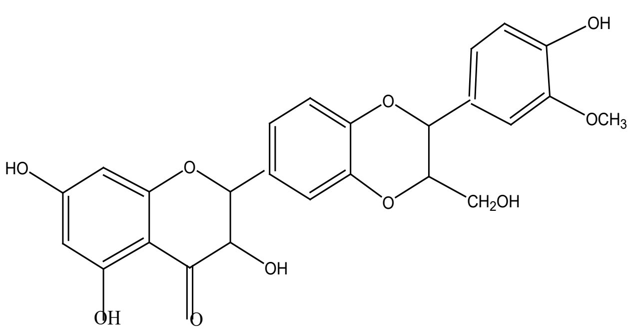
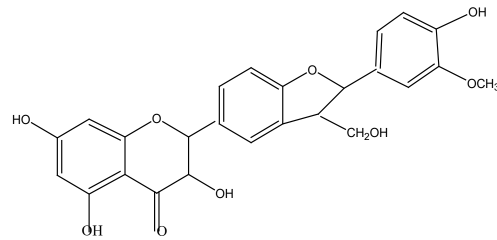
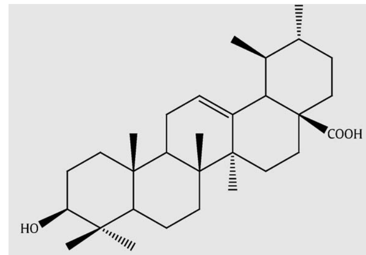
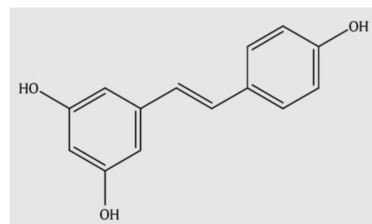


ISOSILYBIN

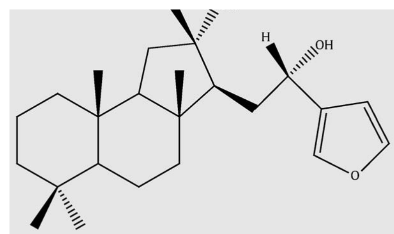


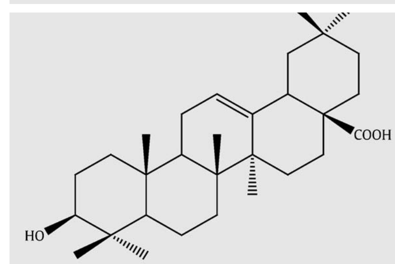
SILYCHRISTIN



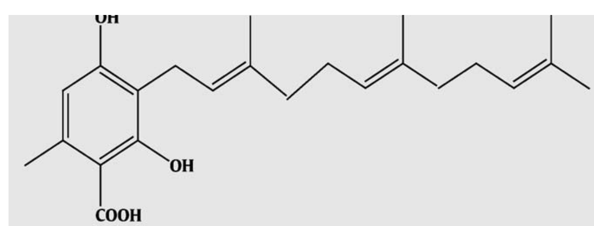


URSOLIC ACID RESVERATROL

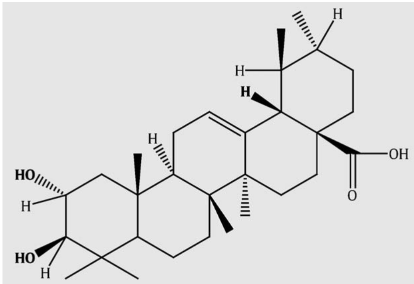


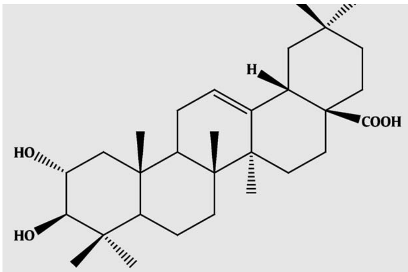


HYRTIOSAL OLEANOLIC ACID

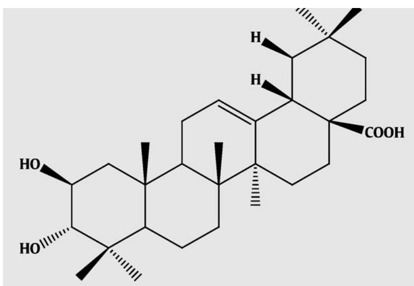


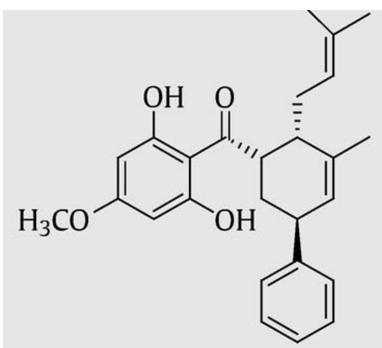
GRIFOLIC ACID





COROSOLIC ACID MASLINIC ACID





BREDEMOLIC ACID PANDURATIN A

charantia and is a potential substance with antidiabetic properties. This compound is a mixture of two compounds, namely, sitosteryl glucoside and stigmasteryl glucoside.

Chromatographic and Characterization Studies

An efficient method, pressurized liquid extraction (PLE) of charantin from fruits of *M. charantia* using ethyl alcohol has been established. A high performance thin layer chromatography (HPTLC) method for quantitative estimation of charantin in small, big, dried fruits used in formulations and different marketed antidiabetic polyherbal formulations (PHF) was developed in 2006. It was found that the HPTLC method was reproducible, accurate and precise and detects charantin concentration at nanogram level. The developed HPTLC method would be an important tool in the quality control method of polyherbal formulations.[121]

Recent Studies on Markers, their Chromatographic studies and Characterization

Berberine: A comprehensive metabonomic method, in combination with fingerprint analysis and target analysis have performed to reveal potential mechanisms of berberine action in the treatment of patients with type 2 diabetes and dyslipidemia.

Chromatographic and characterization studies: Ultra-performance liquid chromatography and quadrupole time-of-flight tandem mass spectrometry (UPLC Q-TOF MS) coupled with pattern recognition analysis were used to identify changes in global serum metabolites. Compared with placebo, patients before and after berberine treatment were separated into distinct clusters as displayed by the orthogonal signal correction filtered partial least-squares discriminant analysis (OSC-PLS-DA) score plot, which indicated changes in circulating metabolites after berberine treatment. Among them, free fatty acids changed markedly. These were further quantified by UPLC combined with single quadrupole mass spectrometry (UPLC SQ MS). There was a highly significant decrease in the concentrations of 13 fatty acids following berberine administration. 10 fatty acids also differed statistically from placebo.[122,123]

Fatty acids: Palmitic acid, Stearic acid and Oleic acid, are all very important bioactive molecules. They are not only the main energy source as nutrients, but also signaling molecules in various cellular processes. The long-term high level of these fatty acids in plasma may have more contribution to lipotoxicity than other NEFAs for their great influence on discrimination between DM-2 and controls.

Chromatographic and characterization studies: A new strategy, metabolomics, was firstly applied to research of dynamic plasma fatty acid metabolic profiling and biomarkers of DM-2. The application of GC/MS coupled with partial least squares-linear discrimination analysis (PLS-LDA) of data with variable weight scanning makes it possible to classify DM-2 patients and health controls and, further, to establish a 3 dimensional PLS-LDA model to visual represent alterations of non-esterified fatty acid (NEFA) metabolic profiles of type 2 diabetic patients treated with rosiglitazone for about 3 months. Furthermore, the combination of multivariate approach and GC/MS data-mining metabolite identification program results in a very powerful tool for metabolomics research.[124]

Mechanism of Action

Insulin signaling pathway

Insulin binding causes conformational change of insulin receptor (IR) and activates the intrinsic tyrosine kinase

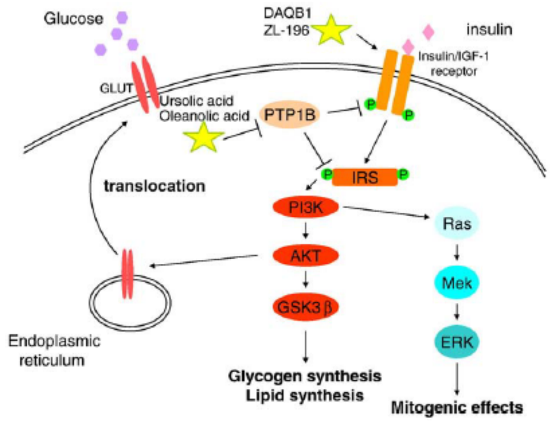


Fig.1: Enhancing insulin secretion through FFA receptors:

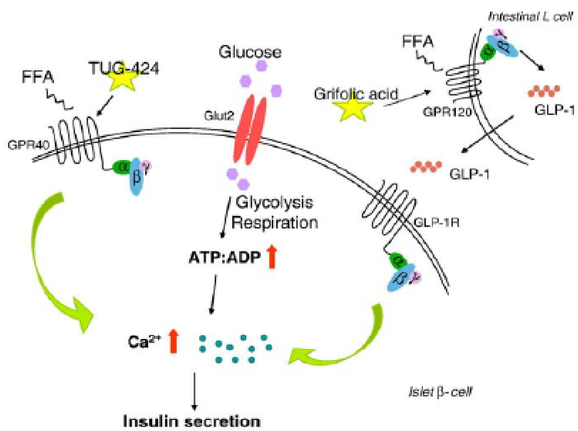


Fig 2: Carbohydrate metabolism pathway

activity of IR (Fig 1). IR phosphorylates the downstream signaling molecules including insulin receptor substrate (IRS). Protein tyrosine phosphotase 1B (PTP1B) inactivates IR and IRS through dephosphorylation of their tyrosine sites. IRS activates PI3K, which subsequently activates Akt and glycogen synthase kinase (GSK) 3â pathway to regulate glycogen and lipid synthesis and stimulate glucose uptake. PI3K also regulates cell proliferation through Ras/MEK/ERK pathway. Small molecules including DAQB1 and ZL-196 could directly activate insulin receptor tyrosine kinase (IRTK) and mimic the glucotropic effects of insulin without exerting mitogenic effects. Ursolic acid, olenolic acid and other derivatives could inhibit PTP1B thereby enhancing insulin signaling pathway.[125]

Increased glucose level elevates cellular ATP: ADP ratio through enhanced glycolysis and respiration (Fig 2). Increase of ATP: ADP ratio up regulates intracellular calcium level thus stimulating insulin secretion. GPR40, which is expressed in islet â-cells, is activated by FFA binding and stimulates intracellular calcium accumulation through G-proteins signaling cascade. TUG-424 was identified as a GPR40 agonist. FFA binding activates GPR120 in intestinal L cells and stimulates glucagon like peptide-1 (GLP-1) secretion. GLP-1 activates GLP-1R in islet â-cells and increase calcium levels through G-proteins signaling cascade. Grifolic acid

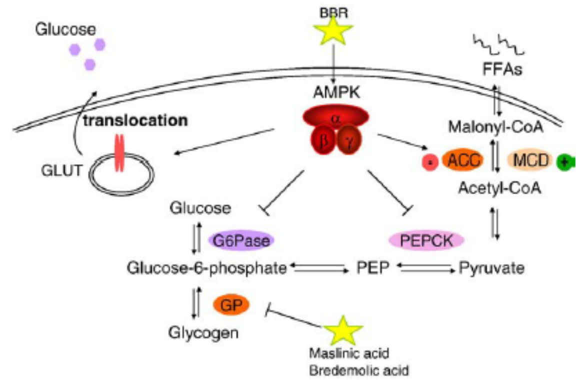


Fig 3: Peroxisome proliferators activated receptors (PPARs) involved metabolic regulation

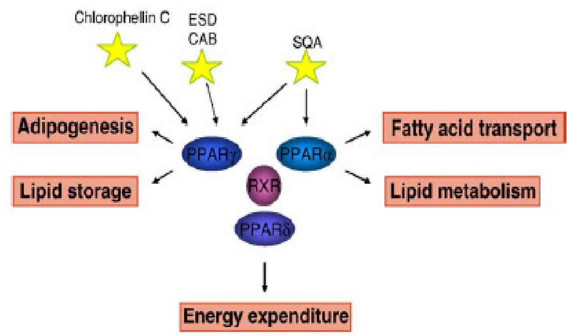


Fig 4: ER stress and inflammation related pathways

derivatives were determined as GPR120 partial agonists.[125]

AMP-activated protein kinase (AMPK) acts as a central energy sensor. Activated AMPK deactivates gluconeogenic enzymes PEPCK and G6Pase thereby decreasing hepatic glucose production (Fig 3). It increases glucose uptake by inducing glucose transporters (GLUT4 and GLUT1). AMPK also stimulates lipid metabolism by decreasing malonyl CoA levels through inhibiting acetyl CoA carboxylate (ACC) and activation of malonyl CoA decarboxylase. Berberine (BBR) was reported to exert beneficial effects on diabetes through activating AMPK. Glycogen phosphorylase (GP) is the key enzyme for glycolysis; it generates glucose through glycogen breaking down. Maslinic acid, bredemolic acid and their related derivatives inhibit GP activity, mimicking the action of insulin in stimulating hepatic glycogen synthesis.[125]

PPARá regulates fatty acid metabolism and transport. PPARã regulates adipogenesis and lipid storage (Fig 4). PPARä is involved in fat oxidation, energy expenditure and lipid storage. Agents that target more than one PPAR isoform and selective PPAR modulators (SPPARMs) are expected to improve efficacy and reduce side effects. SQAand some of its derivatives were identified as PPARá/ã dual agonists. Chlorophellin C was discovered to be a potent PPARã agonist. ESD and CAB were identified as PPAR ã partial agonist or antagonist.[125]

Inflammatory cytokines, lipids and ROS can activate inflammatory signaling pathways including, JNK and IKK,

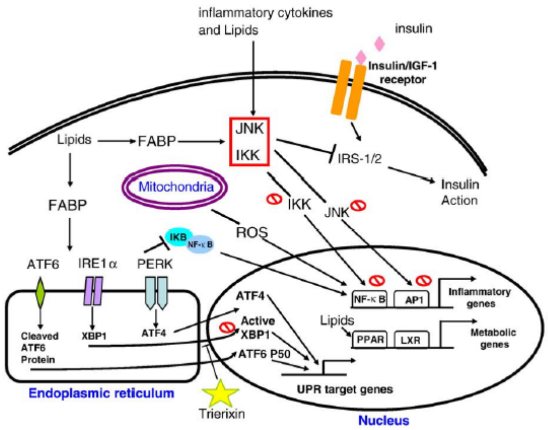


Fig 5: Molecular Effects of cytokines and lipids on Diabetes Prognosis

which in turn inhibit insulin action. PERK activates IKK and inhibits insulin action through a series of transcriptional events mediated by NF-êB. JNK and IKK aggravate inflammatory response by regulating transcription through NF-êB and AP-1, respectively. On the other hand, PPAR and LXR families can promote nutrient transport and lipid metabolism, while moderate inflammation and stress. FABP coordinates the distribution and action of lipids. Three crucial UPR signaling pathways including PERK, IRE1 and ATF6 are involved, which lead to the expression of UPR target genes. The effective interventions are indicated by symbol "Ø" in red.[125]

FUTURE PROSPECTS

Despite many advances in the development of antidiabetic and hypoglycemic agents, an ideal drug for treating diabetes is still a distant reality. As traditional plant medicines are used throughout the world for a range of diabetic complications since long time. If plants are to be used according to their original traditional method, the WHO guidelines on their use should be applied to rationalize that use, and to ensure consistency, efficacy and safety of these products. In spite of the various challenges encountered in the medicinal plant based drug discovery, Natural products compounds discovered from medicinal plants (and their analogues thereof) have provided numerous clinically useful drugs and still remain as an essential component in the search for new medicines. So, these traditionally used plants can be exploited effectively in order to find New Chemical Entity for treatment of diabetes. The review of such medicines might offer a natural key to unlock a diabetologist's pharmacy for the future. In order to prevent this alarming health problem, the development of research into new hypoglycemic and potentially antidiabetic agents is of great interest. Many new bioactive drugs isolated from plants having hypoglycemic effects showed antidiabetic activity equal and sometimes even more potent than known oral hypoglycemic agents such as daonil, tolbutamide and chlorpropamide. However, many other active agents obtained from plants have not been well characterized. More investigations must be carried out to evaluate the mechanism of action of medicinal plants with antidiabetic effect.

CONCLUSION

Diabetes is a condition that has been known to man for millennia and causes significant morbidity and mortality in humans. Despite major advancements in T2D research and the introduction of anti-diabetic medicines, no solutions have been discovered. T2D therapies abound in medicinal herbs, which have long been employed in alternative and complementary medicine systems. The process through which herbal medicines work are yet unknown. T2D therapies are evolving, and they are generally effective. Multiple metabolic pathways are thought to be modulated. Herbal medicines are popular because of their safety and varied targeting actions. In T2D, treatments are effective treatment options. We're here to help. Some plant-derived substances that have been proven T2D can be prevented and treated by regulating insulin levels. Systematic data on the structure, activity, and modes of action of these plants and chemicals will pave the way for antidiabetic medication research and development.

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