A REVIEW ON DIABETES MILLETUS AND THE HERBAL PLANTS USED FOR ITS TREATMENT

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ABSTRACT

Over the last century human life style and food habits have drastically changed which lead to various chronic diseases. Diabetes mellitus is one such disease which is causing serious problems to human health. Diabetes Mellitus is a metabolic disorder characterized by hyperglycemia due to defect in insulin secretion, insulin action or both. Over the last century human life style and food habits have drastically changed which lead to various chronic diseases. Diabetes mellitus is one such disease which is causing serious problems to human health. Around 200 million people around the world are being diagnosed with diabetes according to WHO statistics diabetes is the sixth leading cause of disease-related death in the world. On long standing it leads to many micro and macro vascular complications. The microvascular complications of diabetes includes nephropathy, retinopathy, and neuropathy. In type-1 diabetes the first signs of these complications may develop during adolescence, particularly if insulin is insufficient in the body. Similar complications may occur in the later life of patients with type-2 diabetes. They frequently occur during the time of diagnosis.2

INTRODUCTION

Diabetes Mellitus is a metabolic disorder characterized by hyperglycemia due to defect in insulin secretion, insulin action or both. Over the last century human life style and food habits have drastically changed which lead to various chronic diseases. Diabetes mellitus is one such disease which is causing serious problems to human health.1 Around 200 million people around the world are being diagnosed with diabetes according to WHO statistics diabetes is the sixth leading cause of disease-related death in the world. On long standing it leads to many micro and macro vascular complications. The microvascular complications of diabetes includes nephropathy, retinopathy, and neuropathy. In type-1 diabetes the first signs of these complications may develop during adolescence, particularly if insulin is insufficient in the body. Similar complications may occur in the later life of patients with type-2 diabetes. They frequently occur during the time of diagnosis.2

History of diabetes

diabetes disease is prevalent since approximately 1550BC. An Egyptian doctor defined a unknown rare disease as a disease that causes the patient to lose weight rapidly and urinate frequently. This is considered to be the first definition to the diabetes mellitus. The name diabetes was coined by the Greek Physician Artextus (30-90AC). He recorded the disease with symptoms such as constant thirst (polydipsia), loss of weight and excessive urination (polyuria). He named the condition ‘diabetes’, which means ‘a flowing through’. After this period, diabetes name is rarely mentioned. Indeed, it seems to have a mystery or incredibly during the Middle Ages. The first reference to the disease came from Avicenna, the famous Arabian Physician. He described the complications of the disease in detail, and how it got progressed (Amos et al 2006). Around this period, ‘uroscopy’ came into existence as a way of identifying disease (betterley C et al 1983). The colour, and odour of the urine were examined to establish the disease of the patient. Some physicians even tasted the urine of patients, and this apparently lead how to the second name, mellitus, meaning ‘honey’ in Latin.6

During the early 19th Century, chemical tests have been devised through which it was possible to detect excess sugar in the urine. Despite many therapies had been proposed, in the absence of a cause, they proved unsuccessful. In 1920 an American called Moses Barron linked the Langerhans cells with the basis of diabetes mellitus6. Based up on the research of Barron, a doctor called Frederick Banting conducted critical experiments linking the pancreas and diabetes. Banting discovered an essential hormone named insulin, named after the ‘islands’ of cells described by Langerhans. Banting and one of his colleagues were recognised for their achievement and were awarded Nobel Prize. Throughout the 20th century, treatment of the disease has advanced drastically.

Although prevention and management remains difficult for diabetes mellitus, the life of an average diabetic is becoming both longer and easier due to advanced treatments which are being used now a days15.

Diabetes mellitus occurrence in the world

Diabetes mellitus is estimated to increase from 4.0 percent in the year 1995 to 5.4 percent by the year 2025. The number of people with diabetes mellitus in the world will increase from 135 million in 1995 to 300 million in the year 2025. According to statistics, there will be a 42 percent increase, from 51 million to 72 million, in the developed countries and 70% increase, from 84 to 228 million, in the developing countries. There are three major types of diabetes.
1) Type-I (Insulin dependent diabetes mellitus).
2) Type-II (Non-insulin dependent diabetes mellitus).
3) Gestational diabetes mellitus.

Type I or Insulin Dependent Diabetes Mellitus:

In insulin dependent diabetes mellitus, insulin is completely absent because the pancreas lacks cells or contains defective cells. This condition occurs in genetically susceptible individuals from an autoimmune response that selectively destroys pancreatic cells. Their life spans are drastically reduced up to one third as a result of degenerative complications like kidney dysfunction, nerve impairment, and cardiovascular complications as well as blindness.4 This arises from the metabolic control provided by periodic insulin injection. The usual rapid onset of the indications of insulin dependent diabetes mellitus suggested that the autoimmune attack on the pancreatic cells is responsible for the shorter duration of this disease. However the disease persists for several years as the immune system slowly destroys the pancreatic cells. when >80% of these pancreatic cells have been destroyed it leads to classic symptoms of diabetic disease.5 It usually occurs after 30 years of age, but Peak incidence occurs during puberty, around 12-14 years in boys and 10-12 years of age in girls. The main signs and symptoms include hyperglycemia, increased thirst and hunger, frequent urination, weight loss, ketoadiasis .6

Type-II or Non-insulin Dependent Diabetes Mellitus

Non insulin dependent diabetes mellitus is characterized by reduced insulin secretion in response to glucose levels and Insulin resistance which leads to the inefficient absorption of glucose into the cell for energy. It is present in 90% of the diagnosed cases of diabetes and affects 10% of the population above 65 years of age, usually occurs
in obese individuals. These individuals have normal or even greatly elevated insulin levels. Perhaps, the elevated insulin production results from overeating (obesity is almost always the result of overeating). It eventually suppresses the synthesis of insulin receptor (a plasma membrane bound glycoprotein). This hypothesis concludes that diet alone is usually sufficient to control this type of diabetes.12

Gestational diabetes mellitus

Gestational diabetes mainly develops during the time of pregnancy. It results due to the hormonal changes in pregnancy which can change the body ability to use insulin leading to carbohydrate intolerance. It results in hyperglycemia of variable severity. It usually disappears after the birth of child, and does not clarify that the child will be born with diabetes.13

Diabetic complications

Diabetes mellitus also causes "microvascular" complications leading to the small blood vessels damage. Diabetic retinopathy, affects blood vessel formation in the retina of the eye, can lead to problems in vision like reduced vision, and potential blindness.10 Diabetic nephropathy, the complication of diabetes on the kidneys, can lead to the risk of larger amounts of protein in the urine, and gradually leading to chronic kidney disease requiring dialysis. Diabetic neuropathy is the complication of diabetes affecting the nervous system, most commonly causing numbness, and pain in the feet and also increasing the risk of skin damage due to altered sensation.11 Diabetic neuropathy is a vascular disease affecting circulation of blood in the legs, contributing to the risk of diabetes-related foot problems (such as diabetic foot ulcers) that are difficult to treat and occasionally require amputation.14

Importance of herbal plants in the treatment of diseases

Nature always stands as a golden mark to exemplify the outstanding phenomena of one race depending on other for food. Natural products from plant, animal and minerals have been the basis of the treatment of human disease from the times immemorial. Today it is estimated that about 80 % of people in developing countries are still depending on traditional medicine based largely on species of plants and animals. Herbal medicines are currently in demand and their necessity is increasing eventually. About 500 plants with medicinal use are mentioned in ancient literature by Theophrastus and 800 plants have been used in indigenous systems of medicinal system17. India is a rich depository of medicinal plants are used in traditional medical treatments. The various indigenous systems of medicine such as Siddha, Ayurveda, Unani and Allopathy use several plant species to treat different diseases. The use of plant medicines is becoming popular due to toxic and side effects of allopathic drugs. This led to sudden increase in the number of herbal drug industries.19 Herbal medicines are the major remedy in traditional systems of medicine have been used in medicine since ages. The practices are continuing till today because of its biomedical benefits as well as its cultural beliefs in many parts of world. It have made a great contribution towards maintaining human health care system.19

In India around 20,000 medicinal plant species have been recorded but more than 500 traditional plant communities use about 800 plant species for curing different diseases. Currently 80% of the world population rely on plant-derived medicine for the first line of primary health care because it has no side effects. Plants are important sources of medicines. Presently about 25% of pharmaceutical prescption in the United States contain at least one plant-derived ingredient. In the 20th century, roughly 121 pharmaceutical products were formulated based on the traditional knowledge obtained from various pharmacopeias.20 There are many evidences that many herbal plants are used for the treatment of diabetes mellitus. Plant families which are confirmed to show hypoglycemic activity include:

- Leguminosae, lamiacae, Liliacae, cucurbitaceae, asteraceae, moraceae, rosaceae, euphorbiaceae, araliaceae, polygalaceae, asclepiadaceae, meliaceae etc.14 Many clinical studies have confirmed the therapeutical importance of medicinal plants in the treatment of diabetes mellitus disease. The effect of the medicinal plants may delay the diabetic complications and rectify the metabolic abnormalities. However during the past few decades new bioactive compounds are being isolated from the hypoglycemic plants. They showed hypoglycemic activity with more efficacy and are used in effective treatment of diabetes mellitus.22

List of plants used for the treatment of diabetes mellitus

<table>
<thead>
<tr>
<th>S_no</th>
<th>Botanical name</th>
<th>Common name</th>
<th>Family</th>
<th>Plant part used</th>
<th>Reference</th>
</tr>
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<tbody>
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<td>Artemisia pallens27</td>
<td>Davana plant</td>
<td>Compositae</td>
<td>Aerial parts</td>
<td>Subramani et al 1996</td>
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<td>Aegle marmelos28</td>
<td>Bael fruits</td>
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<td>Aqueous leaf extract</td>
<td>Sachdeva et al 2001</td>
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<td>Liliacae</td>
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<td>Augest et al 1973</td>
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<td>Annonaceae</td>
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<td>Murraya koenigii</td>
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<td>Rutaceae</td>
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<td>Dioscorea dumetorum20</td>
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<td>Cerasaceae</td>
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<td>Cucurbitaceae</td>
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<td>Eugenia jambolana29</td>
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<td>Myrtaceae</td>
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<td>China rose</td>
<td>Malvaceae</td>
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<td>Pomegrante</td>
<td>Punicaceae</td>
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<td>Chenopodiaceae</td>
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<td>Canovaia ensiformis31</td>
<td>Horse bean</td>
<td>Leguminosae</td>
<td>Aqueous extract of seeds</td>
<td>Enyikwela et al 1991</td>
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</table>
Artemisia pallens

It is commonly called as davana belonging to family Compositae. Methanolic extract of aerial parts of plants are responsible for anti diabetic activity. In glucose fed hyperglycemic rats and also in alloxan induced diabetic rats methanolic extract (100mg/kg given orally) reported antihyperglycemic activity. Cadinol α-terpine, dysentery, diabetes.

Aegle marmelos

It is commonly called as onion belonging to family Lilliaceae. Allium cepa belongs to family Alliaceae. A.marmelos are cholesteremic, anti inflammatory, anti oxidant, aphrodisiacs, antihyperglycemic as well as hypotensive activity 78. It is commonly called as Indian cinnamon belonging to family Lauraceae. Asian gingseng, Allicin is a biologically active against diabetic activity. It increases utilization of glucose either by direct glucose stimulation or by acting like insulin for glucose uptake 88. Many bioactive compounds have been isolated from this plant. Extensive chemical investigations on various parts of the tree have been carried out and more than 100 compounds have been isolated 57. Many of these compounds including skimmianine, agelin, lupeol, cineole, citral, corinellol, cuminaldehyde (4-isopropylbenzaldehyde), eugenol, maresin, marmesin, marmesol, luvangetin, auranpt, psoralen, mannelide, fagarine, mainin and tamin have been proved to be biologically active against various major and minor diseases including cancer, malaria and gastro-duodenal disorders. The presence of Aeglin, lupeol, eugenol, marmesin constituents were found to be cause of its property of preventing myocardial damage due to diabetes mellitus. The antioxidant property of the Amarmelos leaf, play a vital role in delaying, intercepting or preventing oxidative reactions, catalysed by free radicals. This antioxidant activity might be due to the presence of phenolic compounds such as flavonoids, phenolic acids and phenolic diterpenes 77.

Allium cepa

It is commonly called as onion belonging to family Lilliaceae. Hypoglycemic activity reported in ether soluble fraction of onion (0.25mg/kg/p.o) in streptozotocin induced diabetic rabbits. The bulb part containing s-methyl cysteine sulfoxide, s-allyl cysteine sulfoxide has anti diabetic activity. It lowers blood glucose levels and has potent anti oxidant activity which may account for hypoglycemic potential 98. Seven compounds were isolated from the ethanol extract of the seeds of Allium cepa, their structures were elucidated by physico-chemical properties and spectroscopic analysis as tannic acid, N-trans-furaloyl tyramine, beta-sitosterol-3 beta-glucopyranoside-6-palmitate, sitosterol, daucosterol, tryptophane, psoralen, mannelide, fagarine, mainin and tamin have been proved to be biologically active against various major and minor diseases including cancer, malaria and gastro-duodenal disorders. The presence of Aeglin, lupeol, eugenol, marmesin constituents were found to be cause of its property of preventing myocardial damage due to diabetes mellitus. The antioxidant property of the Amarmelos leaf, play a vital role in delaying, intercepting or preventing oxidative reactions, catalysed by free radicals. This antioxidant activity might be due to the presence of phenolic compounds such as flavonoids, phenolic acids and phenolic diterpenes 77.

Caesalpinia bonducella

It is commonly called Chinese cinnamon belonging to family Leguminosae. The aqueous ethanolic seed extract has hypoglycemic activity reported in streptozotocin induced diabetic rabbits. Hypoglycemic activity reported in chronic type II diabetic model with increase in secretion of insulin. Bargent, caesalpinin A, α and β amyrin lupeol increases the release of insulin from pancreatic cells 106. Four cassane diterpenes, designated bonducellpins A,B,C & D were isolated 27; two new cassane diterpenes, named caesaldekarins F & G have been isolated & identified; α-amyrin, β-amyrin, lupeol and lupeol acetate have been identified and isolated. The leaves are anthelminthic, emmenagogue and febrifuge, and are useful in elephantiasis, intestinal worms, splenomegaly, hepatomegaly, amenorrhoea, dysmenorrhoea, fevers and pharyngodynia.

Swertia chiranta

It is commonly called indian gentian belonging to family Gentianaceae. Hexane fraction of plant has blood sugar lowering effect. Swchnerin (50mg/kg/po) given to streptozotocin induced (35mg/kg/i.v) albino rats. Insulin releasing effect of hexane fraction of plant (250mg/kg/po) is given for 28 days in albino rats shown significant raise in glycogen. Amargentin, swchnerin, chirantin, geniopinor stimulates insulin release from islets of langerhans by osteoporosis treatment. Antihyperlipidaemic and anticholesterol activities of the drug were observed after oral administration of minced bulbs, a water extract, the essential oil (100 mg/kg), or the fixed oil to rabbits or rats. The active antiallergic and anti-inflammatory constituents of onion are the flavonoids (quecetin and kaempferol). The flavonoids act as anti-inflammatory agents because they inhibit the action of protein kinase, phospholipase A2, cyclooxygenase, and lipoxygenase, as well as the release of mediators of inflammation (e.g. histamine) from leukocytes 75.
depleting aldehyde fuschin stained β-granules and immune stained insulin

**Mucuna pruriens**

It is commonly called velvet bean belonging to family Leguminosae. Alcoholic extract of plant (100, 200, 400mg/kg/day) is given to alloxanized rats reported significant glucose lowering effect. Hypoglycemic activity of paint extract (200mg/kg) reported on daily feeding of extract for 40 days in streptozotocin induced diabetic mice. Murcune, murcunidine, β siosterol, possibly act through stimulation of release of insulin or by direct insulin like action due to presence of trace elements like manganese, zinc etc. The main plant chemical found in Mucuna pruriens include alkaloids, alkalaminic, arachic acid, behenic acid, beta carboline, beta sitosterol, butofenine, cystine, dopamine, fatty acids, flavones, galactose D, gallic acid, genistin, glutamic acid, glutathione, glycine, histidine, hydroxyl genistin, 5- hydroxyl tryptamine, isoleucine, L- dopa, linoelic acid, linoelic acid, lysine, mannose D, methionine, 6- methoxynaran, mucunadine, mucumin, mucunine, murenic acid, niacin, nicotine, oleic acid, palmitic acid, palmitoleic acid, phenylalanine, pruriendine, prurienine, riboflavin, saponins, serine, serotonin, stearic acid, stizolamine, threonine, trypsin, tryptamine, tyrosine, valine and vernolic acid. Mucuna pruriens is used for facial paralysis and nervous disorders, muscular pain, sterility, gout, menstrual disorder, diabetes and cancer.

**Ocimum sanctum**

It is commonly called belonging to family Lamianae. Leaf power extract (20mg/kg for 30 days) has plasma glucose lowering activity in streptozotocin induced diabetic animals revealing the effect of the extract on three enzymes of carbohydrate metabolism namely glucokinase, hexokinase, and phosphofructokinase. Eugenol, carvacrol, linalool, carophylline, fisicosterol has potent hypoglycemcic hypolipidemic effects in normal and diabetic rats. Administration of leaf extract lead to decrease in plasma glucose level by 24.6%. Ocimum sanctum Linn. contains major essential oils such as eugenol, carvacrol, nerol and eugenol methyl ether. Leaves have been reported to contain ursolic acid, apigenin, luteolin, isorhamnetin, luteolin-7-O-glucuronide, luteolin-7-0-glucuronide, and mooludistin. The ethanol extract (90%) of the leaves showed heaptoprotective effect against paracetamol-induced liver damage.

Endophytes have been found virtually in every plant studied, where they colonize the internal tissues of their host plant and can form a range of different relationships including symbiotic, mutualistic, commensalistic to pathogenic. Endophytes in plants can originate from the rhizosphere or phyllosphere however, some may be transmitted through the seed. Endophytic bacteria can promote plant growth and yield and also can act as biocontrol agents. Endophytes can also be beneficial to their host by producing a range of bioactive compounds that could be harnessed for potential use in medicine, agriculture or industry.

Endophytic microorganisms from medicinal plants are a potential source of a diverse array of bioactive metabolites which can be potential for the development of novel drugs. Many authors have isolated endophytic microbes from various medicinal plants with antioxidant, antibacterial, antimicrobial, anticancer, anti diabetic, immune suppressant activity. Further many more examples in which endophytes producing various secondary metabolites such as taxol, asperagenase, camptothecin, as anticancer compounds and antibiotics useful in the pharmaceutical industry etc. Endophytes have been found to possess a novel potent molecules such as antibiotics, alkaloids and anti diabetic showing insulin mentic effect by oral route.

**Hibiscus rosa chinesis**

It is commonly called china rose belonging to family malvaceae. Alcoholic leaf extract (250mg/kg/p.o) given for seven consecutive days has shown hypoglycemcic activity in hyperglycemic rats. Hypoglycemcic activity of single dose of ethanol extract of plant in glucose loaded rats at 120 min and blood glucose lowering effect after repeated administration for seven consecutive days at 30, 90, and 120 min after glucose loading. Stimulates insulin secretion from pancreatic beta cells and utilizes glucose uptake by direct stimulation of glucose uptake or the mediation of enhanced insulin secretion.

**Trigonella foenum graecum**

It is commonly known as "Fenugreek" in English and " Methi" in Hindi, is a member of family Fabaceae. The plant is grown throughout India. It is a medicinal plant claiming to possess number of therapeutic uses. Leaves and seeds are used as an antioxidant, anti inflammatory and antipyretic. Fenugreek seeds contains only minute quantities of an essential oil. Furthermore, n-alkanes, sesquiterpenes, alkanes and lactones were reported. The dominant aroma component in fenugreek seeds is a hemiterpenoid y-lactone. Among the non volatile components of fenugreek seeds, the furosterol glycosides are probably responsible for the bitter taste. Among the several more compounds yet identified, steroles and diosgenine derivatives (of potential interest for the pharmaceutical industry) and trigonellin (N-methyl pyridinium-3-carboxylate, 0.4%) are most worth noting. Trigonella foenum graecum has an antidiabetic activity in which the hypoglycemic effect has been confirmed by several investigators. From the seeds of T. foenum-graecum an unusual amino acid, 4-hydroxyisoleucine, has been isolated, which significantly decreased the plasma triglyceride levels. Fenugreek is a food with traditional medicinal use in diabetes. Beneficial effects have been demonstrated in diabetic animals and both insulin-dependent and non-insulin-dependent diabetic subjects In vitro effect of fenugreek extracts on intestinal sodium-dependent glucose uptake and hepatic glycogen phosphorylase A. The aqueous and alcoholic extracts of Trigonella foemnum-graecum leaf were tested for hypoglycemic activity in normal and alloxan-diabetic rats Apart from these activities immunomodulatory, anti-inflammatory and antipyretic activity are also found. This traditional Indian Anti-Diabetic Plants Attenuate Progression of Renal Damage.

**Tinospora cardifolia**

Tinospora cordifolia belonging to the family Menispermaceae is commonly known as "Guduchi" and "Giloya" in Hindi. It is found throughout tropical India, ascending to an altitude of 1000 ft. The stems are rather succulent with long Filiform leaves, small, yellow and seeds are curved. Main chemical constituents are berberine Giloin, tinosporadine, tinosporinin, tinosporic acid and tinosporol. It is used in venereal disease and as antiperiodic, anti inflammatory, diuretic, antiallergic and anti-diabetic. The extract of stem is useful in skin diseases . Dry barks of T. cordifolia has antispasmodic, antipyretic anti leprotic properties . A definite blood glucose lowering effect within two weeks has been confirmed in alloxan diabetic albino rats. Blood glucose values are brought down close to normal fasting level using herbal samples, twice or thrice daily, as needed. While evaluating comparative hypoglycemic activity of the experimental herbal samples, significant blood glucose lowering activities are observed. The stem of the Tinospora cordifolia is one of the constituents of several ayurvedic preparations. The root and stem of T. cordifolia are prescribed in combination with other drugs as an antitode of snake bite and scorpion sting.

**Momordica charantia**

It is commonly called as kugua, karela bitter gourd belonging to family cucurbiteae. It is a popular herbal resource to treat diabetes. It increases the mitosis of pancreatic cells and partially recover the destroyed cells. Various medicinal properties are confirmed by several investigators. From the seeds of Tinospora cordifolia membraneous and cordate, the flowers, small, yellow and seeds are curved. Main chemical constituents are berberine Giloin, tinosporadine, tinosporinin, tinosporic acid and tinosporol. It is used in venereal disease and as antiperiodic, anti inflammatory, diuretic, antiallergic and anti-diabetic. The extract of stem is useful in skin diseases . Dry barks of T. cordifolia has antispasmodic, antipyretic anti leprotic properties . A definite blood glucose lowering effect within two weeks has been confirmed in alloxan diabetic albino rats. Blood glucose values are brought down close to normal fasting level using herbal samples, twice or thrice daily, as needed. While evaluating comparative hypoglycemic activity of the experimental herbal samples, significant blood glucose lowering activities are observed. The stem of the Tinospora cordifolia is one of the constituents of several ayurvedic preparations. The root and stem of T. cordifolia are prescribed in combination with other drugs as an antitode of snake bite and scorpion sting.
Gymnema sylvestre

Gymnema sylvestre is a large woody, much branched climber with pubescent young parts in dry forest up to 600 m height. Gymnema sylvestre (400mg/day) is given to alloxaan induced diabetic rats. Its leaf has been widely used in Ayurvedic traditional medicine and is bitter, acid, thermogenic, anti-inflammatory, anaodyne, digestive and liver tonic. It is also known for its antidiabetic, anticancer and antimicrobial properties. It is rich in phytochemicals such as alkaloids, flavonoids, saponins, carbohydrates and phenols with highest concentration of saponins being 5.5%. 19

Azadirachta indica

It is commonly called as neem belonging to the family meliaceae. Azadirachta indica is the most useful medicinal plant in India. It possesses anti-inflammatory, antibacterial, antiarthritic, hypoglycemic, antiluceral, antifungal, antimalarial, antitumour and diuretic properties. 20 The phytochemical constituents reported are alkaloids, tannins, coumarin, proteins, stigmasterol, flavonoids, polyphenols, saponins and sugars. 21

Conclusion

Diabetes mellitus is a chronic disease which leads to various complications on long standing. Allopathic medicines are not effective in treating the disease leading to various adverse effects. Hence medicinal plants are the best alternative for the treatment of diabetes mellitus. The plant species have proved their efficacy in reducing blood glucose levels. Discovery of novel compounds can be developed through extensive research work on bioactivity of various constituents. In near future herbal plants will play a crucial role in modern system of medicine.

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