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Functional potential of anti-diabetic medicinal plants

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Abstract
Diabetes is an escalating health problem and long-term use of synthetic drugs urges alternate choices such as herbal remedies having minimum side effects. Herbal drugs are effective in preventing the advancement of diabetes and related complications. Hence, research are advancing for maximum explorations of the hypoglycemic potential of herbs. Anti-diabetic activity of medicinal plants are mainly due to enhancement of insulin secretion and glucose utilization, reduction of antiglycation and insulin resistance. A few medicinal plants traditionally used for diabetic treatment proved scientifically for its antidiabetic action due to either of these functions are dealt in this review.

Keywords: Formulation, glycation, hypoglycemic, insulin, polyherbal, traditional

1. Introduction
Diabetes mellitus is one of the fastest surging global health emergencies of 21st century as stated by International Diabetes Federation (IDF). According to IDF, 463 million people have diabetes in 2019 worldwide and it is projected to reach 700 million by 2045 [1]. World Health Organisation has recognised diabetes as one among four priority noncommunicable disorders besides cancer, cardiovascular disorders and respiratory diseases [2].
Diabetes is a serious, long-term (or 'chronic') condition that occurs when there are raised levels of glucose in a person's blood because their body cannot produce any or enough of the hormone insulin, or cannot effectively use the insulin it produces. World Health Organisation had categorised diabetes into many types in which type I and type II are prominent. Apart from this, impaired glucose tolerance, gestational diabetes, monogenic diabetes etc. are the other types of diabetes [3]. It is also associated with several macrovascular complications such as coronary artery disease, peripheral arterial disease, stroke and microvascular complications such as diabetic nephropathy, neuropathy, retinopathy, diabetic ulcer etc. [4]. The therapeutic medications include metformin as the first line medication along with other drugs including alpha glucosidase inhibitors, thiazoliodinediones, sulphonylureas etc and insulin therapy [5].
Adopting better lifestyle, diet control and other nonpharmacological approaches *viz*, exercise meditation etc. can evidently delay or prevent the type II diabetes. Even different anti-diabetic medications including insulin therapy are available, the possible side effects and raising.
diabetes incidence especially in developing nations together necessitate the option for effective, safer and less costly approach [6].
The global use of Complementary Alternate Medicine (CAM) for diabetes treatment is increasing rapidly. CAM envisages health care approaches with a history of use or origins outside of mainstream medicine [7]. It includes the use of herbal medicines, dietary supplements and other therapies like yoga, meditation etc. Herbal antidiabetic agents has been in use for centuries and today it is used individually in prediabetic stage or along with conventional medicines as a combination therapy. A few herbal phytoresources and their proven scientific evidence for potential anti-diabetic activity are reviewed in this paper.

2. Antidiabetic medicinal plants
In India, the knowledge on anti-diabetic medicinal plants were prevalent from the era of pioneers like Charaka and Sushrutha. Numerous medicinal plants are used for prediabetes and diabetes along with allopathic medicine as it is therapeutically proven for hypoglycemic property. Most common functions of anti-diabetic phyto resources are i) to increase the secretion of insulin hormone, ii) to raise the glucose uptake and utilization, iii) to reduce protein glycation and iv) reducion of insulin resistance.

2.1 Insulin secretion enhancers

2.1.1 *Aegle marmelos* L. Correa. Roxb.: Indian bael

Aegle marmelos is an indigenous tree of India belongs to family Rutaceae and considered sacred as it symbolizes Lord Shiva hence called Shivaduma also. The Bael originated in Eastern ghats and central India and mainly found in tropical and sub-tropical region. It is a deciduous tree with characteristic trifoliate leaves and globose fruits having hard woody shell [8].

The antidiabetic compound of *Aegle marmelos* is Umbelliferone β- D-galactopyranoside which can increase the pancreatic secretion of insulin and the liver enzymes for glucose utilization [9]. Kumar (2013) reported that the Umbelliferone β- D- galactopyranoside isolated from stem bark of *Aeglemarmelos* have the potential to raise the insulin level in diabetic rats. The insulin level was found to be increasing in a dose dependant manner comparable to the standard drug glibenclamide. According to Birudu *et al.* (2020) high dose (500 mg) of methanolic leaf extract of *A. marmelos* can reduce blood glucose level in alloxan induced diabetic rats comparable to the standard drug glimipiride (40 mg) [10]. Along with bark and leaves, fruits of Indian bael is also scientifically proven for promising hypoglycemic activity. The bael fruit pulp powder reduces both fasting and post prandial blood glucose in diabetic individuals undertaking diet control [11]. The fasting blood glucose level decreased from 153.4 mg/dl to 148 mg/dl and post prandial glucose showed a drop from 263 mg/dl to 255 mg/dl over a study duration of 60 days.

2.1.2 *Catharanthus roseus* L.: Madagascar periwinkle

Catharanthus roseus L.is an evergreen herbaceous annual or perennial named after Greek dialect meaning 'Pure flower'. It is an essential therapeutic plant of the family Apocyanaceae. It bears broad glossy green leaves and white to pinkish flowers. Periwinkle is a highly established antidiabetic, anticancerous and cytotoxic agent. It has been used in British West Indies for treating diabetic ulcers [12].

The antidiabetic compounds present in *Catharanthus roseus* are Vindoline and Vindogentianine. Vindoline is found to increase the insulin level in mouse insulinoma cell line (MIN6). Vindoline at a concentration higher than 50 µM can raise the insulin secretion to the maximum level [13]. According to Alkreathy and Ahmad (2020), *Catharanthus roseus* ethanolic extract combined with the ursolic acid exhibits high levels of insulin production. The combination using equal proportions of *Catharanthus roseus* ethanolic extract and ursolic acid (25 mg: 25 mg) hiked the insulin production from 5.93 µU/ml to 13.65µU/ml in diabetic rats. This proved the scope of *Catharanthus roseus* and ursolic acid combination as a feasible alternate therapy [14].

2.1.3 *Gymnema sylvestre* (Retz.) R. Br ex Schultes.: Sugar destroyer /Australian cowplant

Gymnema sylvestre is a perennial woody vine originated from tropical Asia is a prime phyto resource for diabetic cure since time immemorial. In Sanskrit *Gymnema sylvestre* is called as 'Madhunashini', which literally means sugar destroyer. It is habituated in the tropical forests of central and Southern India [15].

Gymnemic acid-I present in *G. sylvestre* could protect high glucose treated mouse insulinoma (MIN-6) cells from apoptosis via inhibition of phosphorylation activity of mTOR (Mammalian target of rapamycin) [16]. Recently, five new pregnane glycosides (Gymsylosides A-E) and four known oleananesaponins were isolated and identified among which 200Mm Gymsyloside-C exhibited maximum antidiabetic potential [17].

An antioxidant rich herbal tea [18] and a polyherbal dietary supplement GlucoSupreme [19] containing *G. sylvestre* leaves were developed for diabetic patients. Hydro alcoholic leaf extract of *G. sylvestre* stimulate GLP-1(Glucagon like peptide) and enhances proglucagon expression in ileum followed by Insulin Receptor (IR) expression in pancreas of diabetic rats resulting glucose reduction [20]. Sweetkick tablets developed using gymnemic acid could inhibit the sweet taste receptors and hence desire and pleasantness for consuming high sugar sweet foods could be reduced [21].

2.2 Glucose uptake and utilization enhancers

2.2.1 *Emblica officinalis* L. Indian gooseberry/ Amla

Emblica officinalis known as 'Vitamin C capsule of nature', is a tree belongs to the family Euphorbiaceae. It is a deciduous tree with pinnate leaves, greenish yellow flowers and spherical fruits with six vertical stripes. The whole tree is medicinally important including root, bark, leaves, flowers, fruits and seeds.

Variya *et al.* (2019) reported gallic acid as the antidiabetic compound in *Emblica officinalis.* Gallic acid promotes the glucose uptake in 3T3-L1 adipocytes when measured using a fluroscent glucose analogue, 2- NBDG [22]. The dry fruit powder of amla possess antidiabetic effect when the blood glucose parameters of diabetic rats were compared by treating with amla dry fruit powder and standard drug, glipizide.The glycosylated haemoglobin content reduced from 0.99% to 0.43% in amla powder treated group [23].

2.2.2 *Nardostachys jatamansi* (D. Don.) DC. Indian spikenard

Nardostachys jatamansi (D. Don.) DC. is a critically endangered and primitive aromatic perennial herb belonging to Valerianaceae family. It is habituated in Alpine Himalayas region in India, Tibet and China. The rhizomes are densely covered with silky reddish brown fibrous remains of petiole of radical leaves. It possess immense medicinal properties prominently nerve disorders like hysteria. Jatamansic acid and jatamansone possess antidiabetic properties.

Jatamansi extract is found to be lowering blood glucose in diabetic rats by suppressing gluconeogenesis. The enzymes promoting gluconeogenesis such as glucose-6-phosphatase and Phosphoenolpyruvate carboxy kinase (PEPCK) in Streptozotocin induced diabetic rats. Also jatamansi extract could lower glycosylated haemoglobin and raise insulin secretion in diabetic rats [24]. Prevention of type I diabetes was observed when β-cell rupture was induced using streptozotocin after the pretreatment with jatamansi extract as intraperitonial injection. It also protected β-cells from cytokine toxicity in RINm5F cells and islets [25].

2.2.3 *Tinospora cordifolia (Willd.)* Hook f. & Thomas: Heart leaved moonseed

Tinospora cordifolia commonly known as, Guduchi or giloy is a dioecious perennial climber with immense medicinal benefits. It is habituated in tropical areas of Indian subcontinent. Fresh stem has green succulent bark covered by thin brown bark. Leaves are heart shaped and flowering occurs in racemes. Male flowers occur in clusters while female flowers are solitary. Fruits have the size and shape of a large pea.

Magnoflorine isolated from *T. cordifolia* stem exhibited high *in vitro* α-amylase and α- glucosidase inhibitory action [26]. A polyherbal formulation containing *T.cordifolia* stem, *Gymnema sylvestre* leaves, *Pterocarpus marsupium* bark and *Trigonella foenum- graceum* seeds exhibited reduction in blood glucose, glycosylated haemoglobin and increased plasma insulin level in diabetic rats [27]. Oral consumption of guduchi leaf powder reduced blood glucose and improvement in body weight of diabetic patients [28]. *T. cordifolia* can be a good candidate for using in support therapy since its extract combined with standard drugs recorded high blood glucose reduction in diabetic [29].

2.3 Antiglycation agents

2.3.1 *Aloe barbadensis* Miller: Indian Aloe

Aloe barbadensis or *Aloe vera* is a perennial succulent spreads by producing offsets commonly known as 'Plant of immortality'. It is originated from Eastern & Southern Africa and North-West Himalayan areas. *Aloe vera* leaves occur as thick rosettes without stem or in short stem. Leaves are serrated, plumpy and green to grey- green in colour. It blooms during summer in pendulous spikes.

High molecular fraction of *Aloe vera* is proved to decrease blood glucose and lipid profile effectively [30]. Aloe emodin-8- O- glycoside is the anti-diabetic compound present in *Aloe vera*and it caused increases glycogen synthesis in L6 myotubes and 3T3L1 adipocytes [31] *A. vera* is a good contender in support therapy as well since, in combination with the standard drug it effected a synergestic blood glucose and LDL cholesterol reduction [32]. Besides, *A. vera*extract could reduce the production of Advanced Glycation End-products (AGE's) and inhibit protein glycation consequently prevented diabetic complications. *A. vera* methanolic extract exhibited alpha amylase and alpha glucosidase enzyme inhibition too [33].

2.3.2 *Ocimum* sp.

Ocimum sp. known as 'queen of herbs' is a genus of aromatic annual and perennial herbs belonging to the family Lamiaceae. It is the native to the temperate and tropical regions of all continents with greatest number of species in Africa. Ocimum includes at least 30 species which have established in tropics and sub-tropical regions among which *Ocimum basilicum, Ocimum grattisimum* and *Ocimum tenuiflorum* is found to be having high antidiabetic potential.

O. basilicum (Basil) is proved to have diabetes induced renal disorder in rats. Besides glucose lowering and antioxidant action, basil extract exhibited protective effect on kidney against diabetes induced nephropathy [34]. The major antidiabetic compounds of *O. basilicum* and *O. grattissimum* are eugenol and several phenolic compounds like caftaric acid, caffeic acid, chicoric acid, rosemarinic acid etc. Phenolic compounds were tested for insulin secretion property in pancreatic islets of rats incubated with high dose of glucose. All compounds recorded increased secretion of insulin among which caftaric acid posessed maximum insulin secretion effect [35].

O. grattissimum is found to be effective against placentomegaly and fetal macrosomia, the usual complications in gestational diabetes. Administration of extract to pregnant diabetic rat exhibited a protective effect on gestational diabetes and cardiovascular health [36]. Prolonged administration of *O. grattissimum* aqueous extract reduced diabetes in rats [37].

Ethyl-acetate butanol fraction of *O. tenuiflorum* exhibited maximum inhibition of alpha amylase enzyme [38]. A polyherbal preparation using *Momordica charantia, Eugenia jambolana and O. sanctum* is found to lower blood glucose levels in alloxan induced diabetic rats [39]. Silver nanoparticles of *O. tenuiflorum* and O. basilicum showed high inhibition of alpha amylase and alpha glucosidase enzymes which in turn reduces blood glucose [40].

2.4 Insulin resistance reducers

2.4.1 *Andrographis paniculata* (Burm. F.) Wall. Ex Nees. : Green chiretta

Andrographis paniculata is an erect anuual herb commonly known as kalmegh or 'King of Bitters', belonging to Acanthaceae family. Plants globally. The slender stems with lance shaped leaves and small flowers in racemes are its identifying characters.

Thakur *et al* (2018) [41] reported Andrographolide and Didehydroandrographolide (deAND) as the potent antidiabetic agent. Didehydroandrographolide (deAND) and andrographolide is found to reduce the level of TNFα (proinflammatory cytokine) in the highfat diet induced diabetic rats [41]. deAND and andrographolide could be a remedy for hyperglycemia and hyperinsulinemia in rats. Insulin resistance of these compounds measured as HOMA-IR value also found to be the least [42].

3. Conclusion

Diabetes has become a major global health problem. Active experimentations and day to day update about the potential antidiabetic medicinal plants are on track worldwide. A few medicinal plants and scientific evidences of its functional role imparting anti-diabetic property is discussed. Recent advancements including development of micro, nano formulations, support therapy etc. are increasing since need for safer and effective solution is preferred rather than long term use of harmful drugs.

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