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Review Article

Review on Plants for Management of Diabetes in India: An Ethno-Botanical and Pharmacological Perspective

Shikha Dixit*, Sugandha Tiwari

ABSTRACT

Background: Diabetes mellitus is a prevalent chronic disease, which is recognized as a common threat to health in the last decade, especially in Asia. It is a lifestyle disease which may cause a number of complications in the body of humans like cardiac failure and dysfunctioning of urinary tract. **Materials and Methods**: The data is obtained from various search tools and electronic databases like, scientific literature, Google scholar, Google, Pubmed, Web of science and Scopus. **Results:** Major therapy for diabetes is insulin, oral-antidiabetic drugs, and herbal treatment. However, insulin and oral anti-diabetic drugs come with a number of side effects and cannot be afforded by people with below poverty line. The herbal medicines have performed a satisfactory clinical practice for the management of diabetes mellitus. Moreover, pharmacological & phytochemical screening of medicinal plants has also witnessed the hypoglycaemic effects of these plants in treating diabetes mellitus. Majority of the modern drugs like metformin, atropine, digitalis, etc. are also originated from plants. **Conclusion**: The current paper presents a review of medicinal plants used for diabetes management in India. The therapeutic potential, ethnobotanical use, and their pharmacological evaluations are highlighted for harnessing the anti-diabetic potential of these plants by the Indian healthcare system.

Key words: Diabetes management, India, Ethnopharmacology, Herbal drugs.

Shikha Dixit*, Sugandha Tiwari

Department of Botany, DGPG College, CSJMU Kanpur, INDIA.

Correspondence

Shikha Dixit

Department of Botany, DGPG College, CSJMU Kanpur, INDIA.

Phone no: 6306845929

E-mail: dixitshikha0730@gmail.com

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INTRODUCTION

Diabetes mellitus is one of the major challenges across the globe, resulting in great financial and medical burden to the patients [1]. As per WHO, the worldwide prevalence of diabetes was recorded as 8.8% in 2017 whereas, 1.6 million deaths occurred owing to diabetes in 2016 [2,3]. According to International Diabetes Federation (IDF), the diabetic population of the globe will reach to 629 million by 2045, which was recorded as 425 million in 2017 [4]. Moreover, Nagarathna *et al.* [5] stated that the diabetic population of India is projected to reach 79.4 million by 2030. Chen *et al.* [6] reported continent wise prevalence of DM which is depicted in Figure 1. The Indian subcontinent has risen as the capital of this epidemic disease. Here, the estimated prevalence of diabetes in age group 20-79 of Bangladesh is 9.85%, India 8.31%, Sri lanka 7.77%, Pakistan 6.72%, whereas it is recorded as 3.03% for the nepal [7]. The age-related prevalence of diabetes in India is higher in comparison to some other populations [8]. The Indians posses increased insulin level at a given BMI, which signalizes peripheral insulin resistance due to higher body fat percentage [9]. The prime factors for contributing increased level of type II diabetes and hyperinsulinemia in Indians are low muscle mass, typical abdominal deposition pattern, racial predisposition and excessive body fat [10].

Generally, diabetes occurs in various forms but type I, type II and gestational are the dominating ones [11]. Type I diabetes occurs when beta cells does not produces sufficient amount of insulin. It is detected more in children whereas, type II occurs when insulin receptors are unable to use the produced insulin. However, type II is more common form which is found in the majority of the patients.. It occurs due to lack of disciplined lifestyle like lack of physical activity, unhealthy diet, stress, obesity. Gestational diabetes occurs during pregnancy [12]. The vital cause for diabetes is metabolic dysregulation of carbohydrate, which leads to impaired insulin action, defect in insulin secretion or both [13]. Polydipsia, frequent urination, headaches, weight loss, high level of sugar in urine, fatigue are some of the common symptoms of diabetes [14]. Uncontrolled diabetes management results in number of complications affecting both microvascular and macrovascular. Microvascular complications includes nephropathy (kidney damage), retinopathy (eye damage), neuropathy (nerves damage) and macrovascular includes peripheral vascular disease (poor circulation to the limb), cardiovascular diseases (risk of heart attack), cerebrovascular disease (risk of stroke) [15].

Diagnosis of Diabetes mellitus

The diagnosis of early diabetes includes Glycosylated Haemoglobin (HbA1C), Glucose Tolerance Test (GTT), Fasting Plasma Glucose (FPG), Postprandial Plasma Glucose (PPG) test [16]. GTT helps to diagnose gestational diabetes, pre-diabetes, insulin resistance or reactive hypoglycemia. FPG & PPG level reflect the state of recent glycemia, whereas HbA1c level reflects chronic glycaemia. As per American Diabetes Association (ADA), HbA1c should be less than 7%

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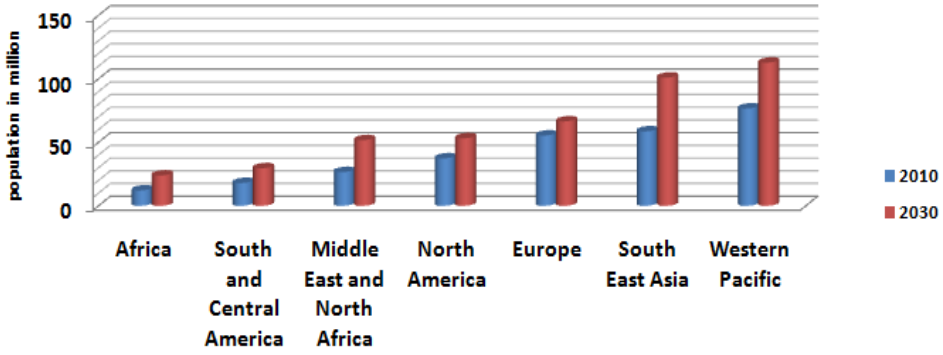

Figure 1: Continent wise diabetic population of the world.

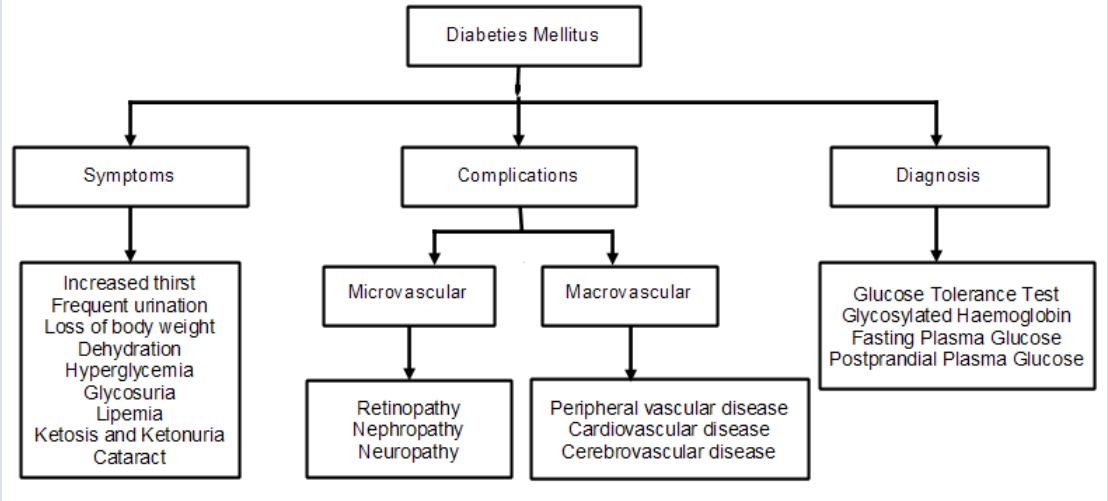

Figure 2: Symptoms, complications and diagnosis of diabetes mellitus.

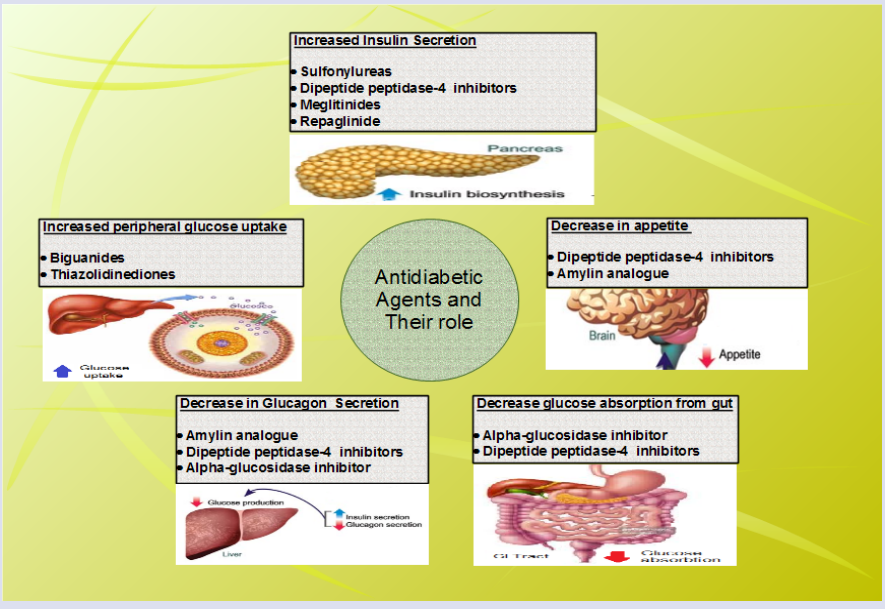

Figure 3: Oral antidiabetic agents and their role in treating diabetes mellitus.

whereas, fasting plasma glucose (FPG) should be 70-130 mg/dl (3.9-7.2) mmol/l) for glycemic control. Moreover, the postprandial glucose (PPG) should be under 180 mg/dl (<10mmol/l) [17].

Current treatments of Diabetes mellitus

The major treatments for DM are conventional therapy, complementary therapy and alternative medication as described in Table 1. Conventional therapy includes chemically synthesized oral antidiabetic drugs and insulin whereas, complementary therapy includes yoga and acupuncture. However, herbal medication is based on plant formulations. The various oral anti-diabetic drugs such as Metformin, α-glucosidase inhibitors, Dipeptidyl peptidase-4 (DPP), Biguanides, Sulphonylureas, Meglitinides and Thiazolidinediones are diverse in their mode of action, endurability and safety profiles [18]. The recommended first choice for the treatment of diabetes is metformin however, high glucose level requires administration of insulin [19]. Insulin is also known as principal hormone, as it regulates level of blood glucose. It transfers blood glucose to tissues. The storage of insulin in body takes place in units of 6 molecules and its active form is a monomer. According to UK Prospective diabetes study, the standard treatment for type 1, some forms of type II, and gestational diabetes is insulin and its analogue [20]. In addition, Sulphonylureas and meglitinides stimulates pancreas to increase the release of insulin. Thiazolidinediones reforms insulin activity, whereas α-glucosidase inhibitors check digestion and absorption of carbohydrate from the gut. Biguanides acts by promoting glucose utilization and reducing hepatic glucose production, DPP-4 inhibits glucagon release and increases insulin secretion [21,22]. Currently, some advanced classes of drugs are also available such as SGLT-2i therapy based on exendin (exenatide once in a week) [23] and glucagon-like peptide (GLP)-1 analogue (taspoglutide and liraglutide) [24]. Further, Sodium-glucose co-transporters 2 inhibitors (SGLT2i) are an experimental group of synthetic drugs which exerts hypoglycemic effect. In renal proximal tubules it inhibits glucose reuptake, and thus induces glycosuria. Furthermore, SGLT2 inhibition reduces blood pressure, weight and has renal and cardiac benefits in individuals with preserved renal function [25]. Athyros *et al.* [2] in his study reported that GLP-1 analogue, SGLT-2i, and metformin as better than other classes of antidiabetic drugs. In addition these also possess some cardiovascular benefits.

Adverse effects of oral antidiabetic drugs

Now a days, several oral antidiabetic drugs are available which have either adverse effects or sub-optimal effects on different body parts [32] such as long term use of metformin causes vit B12 deficiency [33]. Also, it increases risk of lactic acidosis in patients who have pulmonary, cardiac or renal insufficiency or have any history of liver disorder [34]. However, sulfonylureas, glizatones and some DPP-4 inhibitors can induce heart failure [35]. Thus, key challenge in the management of DM is the treatment without any adverse effect. Some oral antidiabetic drugs and there effects have been tabulated in Table 2.

Herbal remedy

As per WHO, approximately 90% of the diabetic patients from developing countries primarily rely on the plants and their products for the management of diabetes mellitus [41,42]. Also, there are about 21,000 medicin1al plants species available across the world out of which about 2500 plant species have been reported from India [45]. Among these, 800 plants have have been reported with antidiabetic potential [44]. The medicinal properties of these plants have been established due to numerous bioactive compounds such as minerals, saponins, tannins, alkaloids, terpenoids, phenols, anthraquinones and flavonoids [45]. Furthermore, a wide collection of data & documentation of traditional system of medicine helped in scientific investigation on drug development. Although, there is no drug which can cure diabetes completely but green medicines are safe as compared to synthetic drugs [46]. Furthermore, some common and potent medicinal plants with antidiabetic activity having Indian origin are bael (Aegle marmelos), garlic *(Allium sativum),* neem *(Azadirachta indica),* beet *(Beta vulgaris),* mustard (Brassica juncea), sadabahar (Catharanthus roseus), ivy guard (Coccinia indica), banyan tree *(Ficus benghalenesis),* gurmar *(Gymnema sylvestre),* gurhal *(Hibiscus rosa-sinesis),* jamun *(Syzygium cumini),* mango *(Mangifera indica),* karela *(Momordica charantia),* giloy *(Tinospora cordifolia),* kari patta (Murraya koeningii), tulsi *(Ocimum sanctum),* pomegranate (*Punica granatum*), methi *(Trigonella foenum-graecum)* [7]. Due to natural origin & less side effects, use of these traditional plants is increasing day by day in developed & developing countries. Although, botanicals play a crucial role in the treatment of diabetes, however, it requires more exploration for drug development from natural resources. The current review article has an objective to collect various ethno-botanical data of the medicinal plants having hypoglycemic activity and to provide present scientific information of these plants. Some of the commonly used antidiabetic plants and their preparation in various ethnobotanical studies of India are presented in Table 3.

Pharmacological activities of some anti-diabetic plants

Acacia catechu (L.f.) Wild.

Bhatia *et al.* [55] reported that oral administration of ethanolic extract of A. catechu hard wood at 250 mg/kg elicits significant antihyperglycemic

Table 1: Current therapies for treatments of Diabetes mellitus.

Antidiabetic Medication	Route of administration	Therapy	Ref.
Insulin	Oral/Injectable	Insulin therapy is benefitcial for long term glucose control as monotherapy as well as in conjunction with other oral antidiabetic medication	21
Orthodox Anti-diabetic drugs	Oral	Oral antidiabetics like α-glucosidase inhibitors, DPP-4 inhibitors, Biguanides, Sulphonylureas, Meglitinides and Thiazolidinediones lowers blood glucose level through different mechanism.	26
SGLT-2 inhibitors	Oral	It is an experimental group of drugs that helps kidney to decrease the blood glucose level. It possess minimal adverse effects and few beneficial side effects such as it decreases dehydration, polyuria, weight loss and hypertension.[5]	27
GLP-1 analogue	Injectable	It is a synthetic and incretin based therapy which regulate sugar by stimulating insulin secretion and inhibiting glucagon secretion.	28, 29
Yoga	-	Bhastrika Pranayama, Surya namaskar, Padmasana, Bhujangasana, Trikonasana, Shavasana, Sukhasana, Pawanmuktasana, Dhanurasana, Pashimottanasana, and Ardhmatsyendrasana are helpful in controlling Diabetes mellitus. Yoga lowers down both fasting blood sugar (FBS) and postprandial blood sugar (PPBS)	30
Herbal drugs	Oral	They act like insulin or act on insulin secreting β-cells or act by modifying glucose utilization or by some other mechanism.	31

Table 2: Adverse effects of allopathic dugs for Diabetes mellitus.

Antidiabetic Agent	Name of Drug	Adverse Effect	Reference
Insulin	Regular insulin Isophane insulin	Weight gain, hypoglycaemia	23,36
α-glucosidase inhibitors	Acarbose Miglitol	Diarrhoea, bloating or flatulence	23,37
Biguanides	Metformin Phenformin	Dyspepsia and lactic acidosis	16,38
Dipeptidyl peptidase-4 (DPP-4)	Sitagliptin Saxagliptin	Suppressor of neoplasm, increased risk of tumors and cancers	23,38
Sulphonylureas	Tolbutamide Chlorproamide Glipizide Glimepiride	Weight gain &hypoglycaemia	23,36
Thiazolidinediones	Rosiglitazone Pioglitazone	Liver and heart diseases	16,37
Meglitinides	Repaglinide Nateglinide	Weight gain & hypoglycaemic	23,36
SGLT-2i	Empagliflozin Dapagliflozin	Polyuria, hypotension, genital infections, dehydration, and risk of fracture and amputation	25,39
GLP-1 analogue	Exenatide Liraglutide	Nausea, vomiting, diarrhea, pancreatitis and thyroid cancer.	40

Table 3: Some Indian Medicinal Plants with Potential Anti-diabetic Activity.[4,47-54]

S. N.	Botanical Name	Common Name	Family	Habit	Part Used	Ethanobotanical Use
1.	Acacia catechu (L.f.) Wild.	Babool	Leguminosae	Tree	Bark	Decoction of bark
2.	Aegle marmelos (L.) Correa	Bael	Rutaceae	Tree	Leaf	Extract of leaf
3.	Adhatoda vasica Nees	Malabar nut	Acanthaceae	Shrub	Root, Leaf	Decoction of root and leaf
4.	Allium sativum L.	Garlic	Amaryllidaceae	Herb	Leaf, Bulb	Leaf and bulb consumed raw
5.	Aloe vera (L.) Burm.f.	Aloe	Liliaceae	Herb	Leaf	Gel eaten raw
6.	Antidesma diandrum Retz.		Euphorbiaceae	Shrub	Leaf	Boiled extract
7.	Ananas comosus (L.) Merr.	Ananas	Bromeliaceae	Herb	Whole plant	Leaf decoction and fresh fruit pulp
8.	Argemone Mexicana L.	Poppy	Papaveraceae	Herb	Stem	Curry made from stem
9.	Asparagus racemosus L.	Shatavari	Liliaceae	Climber	Root	Tuberous root juice
10.	Azadiracta indica Juss.	Neem	Meliaceae	Tree	Leaf, Seed	Leaves antidiabetic
11.	Beta vulgaris L.	Beet	Amaranthaceae	Herb	Root	Root extract
12.	Bombax ceiba L.	Shimul	Bombacaceae	Tree	Flower, Stem, Bark	Decoction
13.	Brassica juncea (L.) Czern	Mustard	Brassicaceae	Herb	Seed	Seed powder with milk
14.	Cajanus cajan (L.) Millsp.	Pigeon pea	Fabaceae	Shrub	Seed	Cooked seeds taken as food
15.	Cassia tora L.	Tora	Leguminosae	Herb	Seed	Shade dried seed powder
16.	Catharanthus roseus (L.) G. Don	Sadabahar	Apocynaceae	Herb	Flower	2-3 flowers taken with aloe juice
17.	Citrullus lanatus (Thunb.) Matsum. & Nakai	Watermelon	Cucurbitaceae	Vine	Seed	Fruit pulp
18.	Coccinia indica Wight & Arm.	Ivy gourd	Cucurbitaceae	Climber	Fruit	Used as antidiabetic
19.	Curcuma longa L.	Turmeric	Zingiberaceae	Herb	Rhizome	8 g of grinded turmeric mixed in water taken with ½ teaspoon of honey after meal
20.	Cyperus rotundus L.	Mutha	Cyperaceae	Herb	Rhizome	Fresh juice
21.	Ficus benghalensis L.	Banyan Tree	Moraceae	Tree	Fruit, Bark	Fruits as antidiabetic
22.	Gymnema sylvestre (Retz.) R.Br.Ex Sm.	Gurmaar	Apocynaceae	Climber	Leaf	Leaf powder with jaggery powder taken orally
23.	Hemidesmus indicus (L.) R.Br.	Anantmool	Apocynaceae	Shrub	Root	Decoction
24.	Hibiscus rosa-sinensis L.	China rose	Malvaceae	Shrub	Leaf	Tender fresh leaf juice

25.	Ichnocarpus frutescens (L.) R.Br.	Black creeper	Apocynaceae	Shrub	Root	Powder of root
26.	Lantana camara L.	Wild sage	Verbenaceae	Shrub	Leaf, Fruit	Consumed raw
27.	Mangifera indica L.	Mango Tree	Anacardiaceae	Tree	Seed	Dry kernel powder mixed with cow's milk
28.	Momordica charantia L.	Karela	Cucurbitaceae	Vine	Whole Plant	Extract of whole plant and fruit juice
29.	Murraya koeningii (L.) Spreng.	Kari patta	Rutaceae	Tree	Leaf	Leaf juice
30.	Ocimum sanctum L.	Holy Basil	Lamiaceae	Sub-shrub	Leaf	Leaf powder with honey
31.	Punica granatum L.	Pomegranate	Lythraceae	Tree	Fruit	Fruit
32.	Schima wallichiiv (DC.) Korth.	Needlewood Tree	Theaceae	Tree	Leaf	Fresh extract
33.	Scoparia dulcis L.	Goatweed	Plantaginaceae	Herb	Whole plant	Decoction of whole plant
34.	Sesbania sesban (Jacq.) W. Wight	Jayanti	Fabaceae	Shrub	Leaf	Leaf decoction
35.	Syzygium cumini (L.) Skeels	Jamun	Myrtaceae	Tree	Seed	Dried seed powder
36.	Terminalia chebula Retz	Hortokhi	Combretaceae	Tree	Seed	Seed powder and decoction
37.	Trigonella foenum- graceum L.	Methi	Leguminosae	Herb	Seed	Filtrate of soaked seeds
38.	Tinospora cordofilia (Willd.) Miers	Giloya	Menispermaceae	Climber	Whole Plant	Crushed leaf juice
39.	Xanthium indicum Koenig in Roxb.	Burweed	Asteraceae	Herb	Leaf	Vegetable made from young leaves
40.	Zingiber officinale Roscoe	Ginger	Zingiberaceae	Herb	Rhizome	Small amount of dried powdered rhizome mixed in curries & soups, taken with milk in empty stomach

property in normal glycemic and streptozotocin induced diabetic rats. Two fractions of ethanolic extract of A. catechu bark comparable to chloroform, petroleum ether, acetone and aqueous extract shows markable anti-hyperglycemic property in alloxan-induced diabetic rats at 2 dose of 200 mg/kg and 400 mg/kg. The study included various parameters such as glucose, creatinine, low density lipoprotein, high density lipoprotein, urea, serum triglyceride and serum cholesterol [56].

Aegle marmelos (L.) Correa

The leaf extract using aqueous solvent shows significant normalization of lipid parameters and blood glucose level at 300 mg/kg in streptozotocin induced diabetic mice. In vitro, this extract also releases insulin, thus reflects hypoglycemic activity [57]. In non-insulin dependent diabetic patients oral administration of A. marmelos leaves lowers down blood glucose level at a dose of 5g/day [58]. Callus and leaf in methanolic extract reveals antidiabetic property at a dose of 1g/kg in rabbits which were induced diabetic using streptozotocin. This doesn't show any activity in chloroform, benzene and petroleum ether extracts [59].

Allium sativum L.

Dineshkumar *et al.* [60] studied the hypolipidemic and antidiabetic activity in diabetic patients when treated with aqueous extract of A. sativum via oral administration . The treatment of 1% solution/kg of A. sativum in alloxan induced rabbits witnesses anti-hyperglycemic activity [61]. In addition, alcoholic extract administration of A. sativum decreases concentration of Candida albicans in kidney and liver homogenates in infected, normol and experimentally induced (streptozotocin) diabetic rats [62]. 500 mg/kg dose of DRF/AY/5001, a herbal formulation of A. sativum shows hypoglycaemic activity in normal, epinephrine induced and alloxan induced hyperglycemic rats [63].

Aloe vera (L.) Burm.f.

Leaf gel of A. vera shows a significant increase in liver glycogen and body weight whereas, it decreases normalized serum lipids and urine and blood glucose level [64]. Moreover, an administration of ethanolic extract of Aloe vera gel (300 mg/kg) for 21 days possess markable antihyperlipidaemic activity in streptozotocin induced diabetic rats [65]. Misawa *et al.* [66] isolated phytosterols, cycloartanol and lophenol from Aloe vera leaf gel that reduces sugar level for 44 days in type II diabetic animal model at 25g/kg/day . In addition, oral administration of A. vera leaf (8 weeks) in mice shows significant reduction of plasma glucose in Type 1 diabetes [67].

Azadirachta indica Juss.

Leaf extract administration of A. indica normalizes lipid parameters and blood glucose thus, elicits antidyslipidemic and antihyperglycemic property in streptozotocin induced diabetic rats [68,69]. Atangwho *et al.* [70] demonstrated that leaf extract of A. indica in combination with Vernonia amygdalina elevates insulin level thus possesses antihyperglycemic property in diabetic rats . Moreover, polyherbal formulation of A. indica and Momordica charantia leaf (400 mg/kg) shows remarkable antihyperlipidemic and antidiabetic effect [71].

Beta vulgaris L.

Oral administration of B. vulgaris extract on alternate days for 1 month showed remarkable antidiabetic action by reducing cholesterol and triglyceride in 4 groups diabetic, control, diabetic + extract and control + extract in streptozotocin induced animals [72]. Mzoughi *et al.* [73] evaluated in vitro antioxidant and enzyme inhibitory activities (α-glycosidase and α-amylase) in ethanol extract of B. vulgaris leaves, thus revealed prominent role as antihyperglycemic agent.

Brassica juncea (L.) Czern

Anand *et al.* [74] in his study demonstrated that administration of 200 mg/kg aqueous extract of B. juncea seeds daily for 1 month in streptozotocin induced diabetic rats elicits remarkable antihyperlipidaemic and antidiabetic effect. Administration (for 21 days) of B. juncea extract in combination with metformin treated diabetes mellitus by controlling cholesterol and triglyceride level in body. The study was performed in four groups namely, normal, normal+streptozotocin, streptozotocin+metformin and streptozotocin + B. juncea extract where, the dose of metformin and plant extract was 75 and 450 mg/kg respectively [75].

Cajanus cajan (L.) Millsp.

In alloxan induced diabetic rats the methanolic extract of C. cajan leaves elicits decrease in fasting sugar level at two doses of 400 mg/kg and 600 mg/kg [76]. In a study made by Manzo and Vitor, showed significant

antihyperglycemic activity when normal glycemic mice were fed with ethanolic extract of C. cajan leaves [77].

Catharanthus roseus (L.) G. Don

Tiong *et al.* [79] in his study isolated four alkaloids from C. roseus leaf extract using dichloromethane solvent that possess ameliorated glucose ingestion in pancreatic beta-TC6 cells of mouse [78]. Moreover, extract of C. roseus elicits antidiabetic potential by reducing serum protein and blood glucose in alloxan induced rats . Methanolic extract of P. granatum leaf and twig in 1:1 possess antidiabetic action in STZ induced diabetic rat [80,81].

Gymnema sylvestre (Retz.) R.Br.Ex Sm.

The leaf extract of G. sylvestre act as therapy for type II diabetes as in vitro it stimulates insulin secretion with the help of isolated human islets of langerhans and MIN6 beta-cell line [82]. The administration of aqueous leaf extract (400-800 mg/kg) of G. sylvestre possesses hypoglycemic and hypolipidemic property in alloxan induced diabetic rats [83]. Wei *et al.*[84] isolated conduritol from stem of G. sylvestre possesses antidiabetic activity by elevating splencia, pancreas, thymus index or retarding the atrophy of splencia, pancreas, thymus of the experimentally induced (alloxan) diabetic rats. Moreover, a novel bioactive compound dihydroxy gymnemic triacetate isolated from acetone extract of G. sylvestre elicits antihyperlipidemic and hypoglycemic effect in streptozotocin induced diabetic rats [85].

Hemidesmus indicus (L.) R.Br.

Nandy *et al.* [86] in his study stated that oral administration (30days) of ethanolic extract of H. indicus root restored the haemoglobin, blood glucose, protein, plasma insulin level. Also, it restored the detained activities of pancreatic enzymes to normal situation in alloxan induced rats [86]. Studies on H. indicus reported the hypoglycaemic effect of rhizome extract due to various phytocompounds viz. hemidine, hemidesminine, hemidesmin-I and hemidesmin-II. Some other phytconstituents such as sterols, tannins, flavonoids, volatile oils and glycosides have also been reported which contribute in antidiabetic potential [87].

Hibiscus rosa-sinesis L.

Rehana *et al.* [88] in his investigation synthesized a nanoparticle of zinc oxide (ZnO) by using various plant extracts viz. *Hibiscus rosa-sinesis, Moringa oleifera, Azadirachta indica, Tamarindus indica* and *Murraya koenigii.* The study screened the α-glucosidase and α-amylase action of ZnO nanoparticles that reduced the side effects and toxicity of the drugs used to treat diabetes. Five fractions isolated from the leaf extract of H. rosa-sinensis using ethanol solvent reveals antihyperlipidemic and antidiabetic action in non-obese diabetic mouse [89]. In addition, acute and sub acute treatment of diabetes in alloxan induced diabetic rats, through two doses (250 and 500 mg/kg) of ethanol extract of H. rosa-sinensis flowers shows remarkable reduction in blood glucose [90].

Lantana camara L.

Administration of methanolic extract (200 and 400 mg/kg) of L. camara leaf shows significant antihyperlipidemic and antidiabetic activities by controlling parameters such as low density lipoprotein, high density lipoprotein, total cholesterol and triglycerides [91]. Kumar *et al.* [92] studied the antidiabetic effect of ethanolic extract of L. aculeate root in rats injected with alloxan. Moreover, Venkatachalam *et al.* [93] studied remarkable antihyperglycemic property of methanolic extract of L. camara fruit on the basis of HbA1c profile, body weight and histopathological studies of normal and streptozotocin induced diabetic rats.

Mangifera indica L.

The aqueous extract of M. indica stem bark elicits hypoglycemic activity when intraperitonealy administrated (50-800 mg/kg) in STZ induced diabetic rats [94]. Li *et al.* [95] isolated mangiferin, a polyphenol from M. indica plant that prevents diabetic nephropathy progression. They also observed the improvement in renal function of diabetic nephropathy rat model. Furthermore, oral administration of M. indica peel extract at a concentration of 200 mg/kg elicits remarkable antihyperlipidemic and antidiabetic effect in streptozotocin induced diabetic rats [96]. The study of Wang *et al.* [97] demonstrated the role of mangiferin in preventing diabetes induced nephropathy progression in STZ induced diabetic rats. The study also focused on the protection of podocyte through autophagy in glomerulus of diabetic rat [97].

Momordica charantia L.

Sathishsekar and Subramanian investigated the role of seed extract of M. charantia in reducing (150 mg/kg) renal and hepatic thiobarbituric acid reactive substances, hydroperoxides and fasting blood glucose. The study also witnessed a significant reduction in superoxide dismutase, glutathione-s-transferase, catalase, reduced glutathione and glutathione peroxidase in the kidney and liver of diabetic rats [98]. Alcalase hydrolysate, a phytoconstituent from M. charantia possessed higher hypoglycaemic property in comparision to pancreatin hydrolysate [99]. Wang *et al.* [100] established a comparable study between Indian and Chinese M. charantia by measuring various parameters such as total triterpene, totat phenol, antidiabetic activity and antioxidant property using reducing power, free radical scavenging, α-glucosidase inhibition and α-amylase inhibition assays. Furthermore, subcutaneous administration of alcoholic extract and fresh juice of M. charantia fruit causes hypolipidemic, hepato-renal protective and antidiabetic effect in experimentally induced (alloxan) diabetic rats [101].

Ocimum sanctum L.

Three new phytoconstituents namely, ocimarin, ocimumosides A and ocimumoside, isolated from leaves of O. sanctum revealed anti-stress activity. Out of which, ocimumosides A shows anti-stress property by controlling plasma corticosterone, adrenal hypertrophy, plasma creatine kinase and hyperglycemia [102]. Aerial part extract of O. sanctum using two solvents (chloroform and hydro alcohol) witnessed the antidiabetic effect in alloxan induced diabetic rats at two doses of 250 and 500 mg/kg [103,104]. Furthermore, triterpenoid which was isolated from aerial part extract (Hydro alcoholic) of O. sanctum at 20 mg/kg dose shows antidiabetic effect in alloxan induced diabetic rats [105].

Punica granatum L.

Huang *et al.* [106] reported that, oral administration of flower extract of P. granatum reduces glucose loading induced ameliorates level of plasma glucose in Zucker diabetic fatty rats at 500 mg/kg. 200 mg/kg dose of P. granatum fruit peel extract controls all the adverse effects thus possesses anti-peroxidative and antidiabetic potential in alloxan mice [92]. Moreover, oral administration of P. granatum flower extract using aqueous solvent elevates oxidative stresses, lipid parameters and blood glucose in STZ induced diabetic rats [107]. In addition, McFarlin *et al.* [108] administrated the seed oil of P. granatum that reduced the lipid parameters and blood glucose in mice.

Scoparia dulcis L.

Pamunuwa *et al.* [109] investigated the antidiabetic effect of S. dulcis through curbing of PPAR-γ, ameliorated insulin secretion and α-glucosidase inhibition. The study reported the presence of various compounds viz. scutellarein, luteolin, glutinol, coixol, apigenin, scoparic acid A and scoparic acid D responsible for antidiabetic potential. Scoparic

acid D, (diterpenoid) isolated from S. dulcis ethanol extract reflects antihyperglycaemic activity by normalizing level of plasma insulin in STZ induced diabetic Wistar rats at 10, 20 and 40 mg/kg for15 days [110]. Furthermore, oral administration of S. dulcis plant extract shows remarkable hypoglycemic activity when orally administrated (100 and 200 mg kg^{-1}) in alloxan induced diabetic mice. The study presented a comparative analysis between plant extract and metformin treatment of diabetes [111].

Tinospora cordifolia (Willd.) Miers

Patel *et al*. demonstrated the antidiabetic potential of T. cordifolia stem extract using various solvents viz. methanol, ethyl acetate and hexane, by decreasing blood sugar in STZ induced diabetic rats at 250 mg kg^{-1} [112]. Dihar, a polyherbal formulation consisting of eight plants viz. Gymnema sylvestre, Momordica charantia, Syzygium cumini, Emblica officinalis, Curcuma longa, Azadirachta indica, Enicostemma littorale and T. cordifolia remarkably decreases lipid peroxidation level and ameliorates activity of antioxidant enzymes in STZ induced diabetic rats [113]. T. cordifolia stem extract using chloroform, dichloromethane, ethyl acetate and hexane solvents were analysed for α-glucosidase inhibition action which resulted that only dichloromethane extract have 100% α-glucosidase inhibition [114]. In addition, saponarin isolated from T. cordifolia leaf extract elicits hypoglycemic effect at 20-80 mg kg^{-1} dose [115].

Trigonella foenum-graecum L.

Oral administration of T. foenum-graecum ethanol extract reflects antidiabetic property at dose of 0.1, 0.25 and 0.5 g/kg in STZ induced diabetic rats by controlling triacylglycerol, creatinine, serum glucose, uric acid, urea, total cholesterol, alanine aminotransferase and aspartate aminotransferase [116]. Losso *et al*. reported that intake of T. foenum-graecum seeds (5%) incorporated in bread in a diet controlled diabetic subject elicits significant reduction in blood glucose [117]. In addition, oral administration (4 or 8 g) of fiber yielded from T. foenum-graecum to healthy obese subjects results in enhanced satiety and reduced energy ingestion [118]. T. foenum-graecum seed extract using ethanol solvent shows dose dependent hypoglycemic property relative to oral antidiabetic drugs in alloxan induced diabetic rats at 2, 1, 0.5 and 0.1 g/kg doses [119-121]. Furthermore, 4-hydroxyisoleucine, an amino acid extracted from T. foenum-graecum possesses antidiabetic and insulinotropic properties by controlling glucose level or liver damage in STZ induced rats [122].

CONCLUSION

In traditional medical system, a number of medicinal plants have been recorded which have offered a promising line for the treatment of diabetes mellitus. Many of them have been explored and scientifically validated. However, for the majority of plant species, there is still a need of reverse pharmacology to validate their efficacy and potential. Some of the plants such as, *Syzygium cumini, Aegle marmelos, Aloe vera, Azadiracta indica, Zingiber officinale, Murraya koeningii, Gymnema sylvestre, Momordica charantia* and *Allium sativum* have witnessed their varying level of hypoglycemic activity. In addition, these plants have also found effective in controlling the complications of diabetes. Further, more studies may be targeted in isolation, identification and characterization of bioactive constituents of medicinal plants. The outcomes of current study may serve as an initiation point for potential antidiabetic drug development. This review may help in reverse pharmacology and development of safe therapeutic drugs for the treatment of diabetes, a devastating disease.

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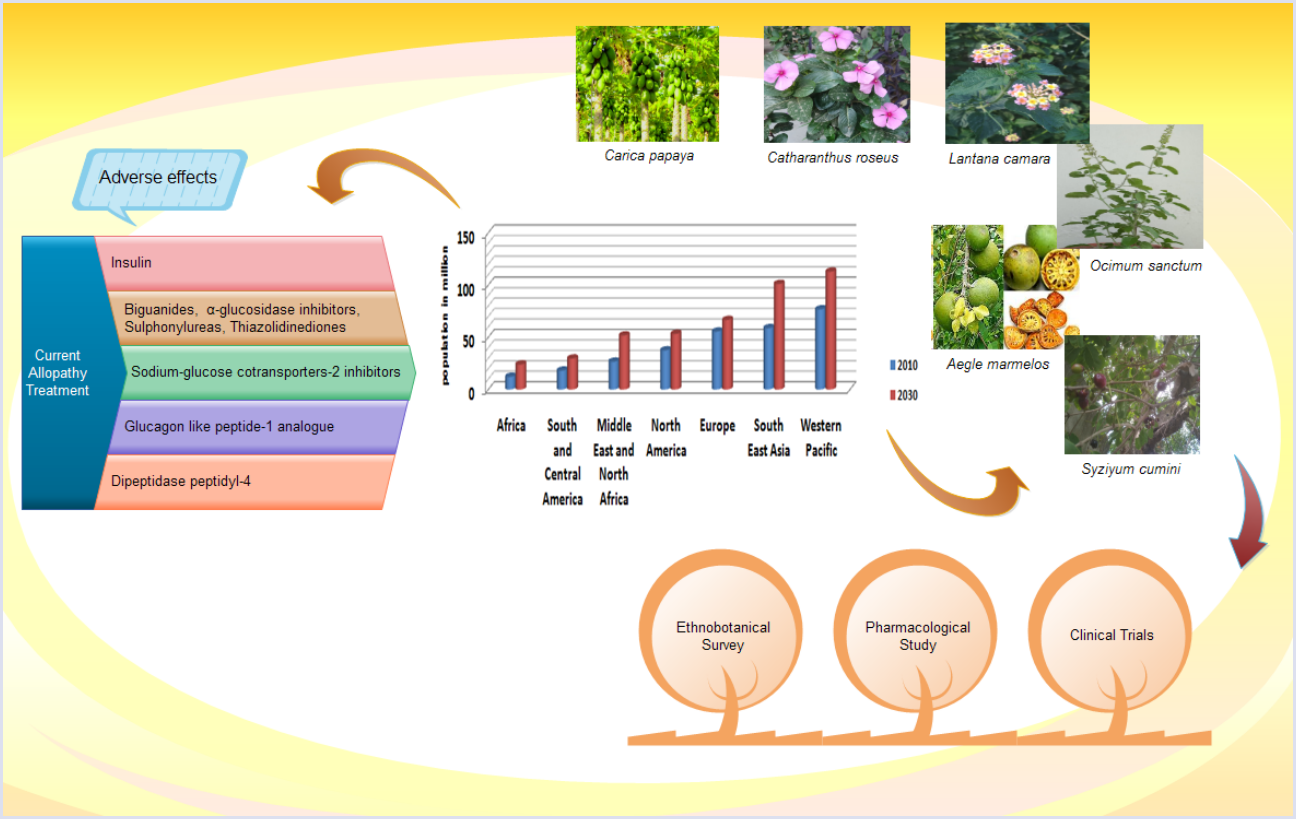
GRAPHICAL ABSTRACT



ABOUT AUTHORS

Shikha Dixit is a research scholar in the department of Botany, Chhatrapati Shahu Ji Maharaj University (CSJMU) Kanpur, India. She is an active researcher in the field of herbal medicine and ethno-pharmacology. She has published a number of research articles in the field of herbal medicine and anti-diabetic plants. She is active reviewer of many reputed journals.

Sugandha Tiwari received her PhD from CSJMU Kanpur. She is currently an associate professor in the department of botany CSJMU Kanpur. She has published a number of research articles in the field of anti-diabetic plants, and ethno-pharmacology. She is also active reviewer of many reputed journals. Her research interest includes plant science, herbal medicine and pharmacology.

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