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Anti-Diabetic Potential of Selected Indian Traditional Medicinal Plants – An Updated Review

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Abstract

The number of diabetes mellitus cases is rapidly increasing worldwide and its complications are a major cause of disability and hospitalization, posing a significant financial burden. Diabetes mellitus is a complex and a fast growing medical problem throughout the globe, in both developed and developing countries. As per WHO report, diabetes is a multifarious group of disorders that disturbs the metabolism of carbohydrates, fat and protein and results in a shortage or lack of insulin secretion and/or reduced sensitivity of the tissue to insulin. In order to manage the diabetic condition, various synthetic drugs have been developed, but each has their own drawbacks / side effects. So, the natural way of treating / managing diabetic condition through medicinal herbs received attention all over the world. In India, certain herbs like *Andrographis paniculata*, *Cassia auriculata*, *Curcuma longa*, *Murraya koenigii*, *Phyllanthus emblica, Trigonella foenum-graecum*and*Salacia oblonga*havebeen employed to manage diabetic condition in various traditional systems of medicine. Even though several research woks have been conducted on the efficacy of these medicinal plants, information are scattered. Hence, the present review focused on summation of anti-diabetic potential of medicinal herbs which are used in Indian system of medicine with scientific evidences.

Key words: Diabetes, Herbs, Medicine, Indian traditional plants

INTRODUCTION

Diabetes is the preponderant global epidemic affecting 8.3% of the global population. It is estimated that by 2030, diabetes will be the world's seventh leading cause of death [1]. Despite advances in understanding and management of this metabolic disorder, the rate of morbidity and mortality due to this disorder is increasing every year. Approximately 285 million people have been diagnosed with diabetes mellitus worldwide and this figure is expected to double by the year 2030 [2].

The hyperglycaemic manifestations of diabetes could result in various vascular complications such as neuropathy, nephropathy, retinopathy, and cardiomyopathy, which are major sources of morbidity and mortality associated with diabetes. The key pathogenic events underlying the hyperglycemia-associated vascular complications include oxidative stress, inflammation, and associated pathophysiologic pathways [3]. Oxidative stress-induced activation of various cellular pathways and resultant inflammatory episodes contributes to the endothelial damage in the blood capillaries of organs such as the retina, peripheral neurons, and kidneys leading to retinopathy, neuropathy, and nephropathy, respectively.

Various antidiabetic drugs such as biguanides, sulfonylureas, meglitinides, thiazolidinediones, alpha-glucosidase inhibitors, incretinmimetics, dipeptidyl peptidase-IV inhibitors and insulin are currently available to reduce, control and manage diabetes mellitus. Most classes of these pharmaceutical drugs have serious side/adverse effects [4 - 6]. This scenario drives researcher to search for novel, alternative, safe and plant based drugs to overcome diabetic problems including various secondary complications.

In this connection, herbal medicines have long been used effectively in treating diabetes in Asian communities and throughout the world. Natural products have received considerable attention for the management of diabetes and its complications [7 - 9] which have reached epidemic levels worldwide [10]. The World Health Organization Expert Committee on diabetes also recommended that traditional medicinal plants be further investigated as they are frequently considered to be free from toxic and side effects [11]. Traditional antidiabetic plants might provide new oral hypoglycemic solution, which can counter the high cost and poor availability of the current medicines/present day drugs for many rural populations particularly in developing countries. However, detailed information regarding the efficacy, mechanism of action and safety of plant drugs are needed for further translational investigations.

In this context, we have reviewed the anti-diabetic potential of herbals, which are cost-effective, locally available and traditionally used in our Indian system of medicine such as *Andrographis paniculata*, *Cassia auriculata*, *Curcuma longa*, *Murraya koenigii*, *Phyllanthus emblica, Trigonella foenum-graecum* and *Salacia oblonga*. Since all these herbal ingredients are practiced in our traditional medicinal system the herbal drug will be economic, safe and human-friendly.

Andrographis paniculata

The genus *Andrographis* which belongs to the Acanthaceae family comprises of about 40 species (Figure 1). Only a few are popular for their use in folk medicine for assorted health concerns. Among these *Andrographis paniculata* (Burm.f.) Wall. Nees. is used in ancient oriental and Ayurvedic medicine. *A. paniculata*, commonly known as King of Bitters or kalmegh, is an annual, branched, erect handsome herb running half to one meter in height. It is native to peninsular India and Sri Lanka and is also distributed in different regions of Southeast Asia, China, America, West Indies and Christmas Island. It is cultivated because of its well known medicinal value and it grows well in most soil types thus it is widely distributed [12].

The aerial parts and roots of the plant have been widely used as traditional medicine in China, India, Thailand and other Southeast Asian countries to treat many maladies. It is known as King of Bitters (English), Mahatikta (Sanskrit), Kiryato (Gujarati), Mahatita (Hindi), Kalmegh (Bengali), or Fah Talai Jone (Thai) [13]. A wide array of studies has been conducted by researchers, especially in Asia, following reports about the medicinal properties possessed by this plant mostly according to traditional medical practitioners in ayurvedic medical system. Phytochemical studies have revealed that *A. paniculata* contains diverse compounds including labdane diterpenoid lactones, flavonoids and miscellaneous compounds.

The aerial parts of this plant have been used for centuries in Asia as traditional medicine for the treatment of various ailments. It has been used by traditional medical practitioners for stomach-ache, inflammation, pyrexia, and intermittent fevers. The whole plant has been used for several applications such as antidote for snake-bite and poisonous stings of some insects, and to treat dyspepsia, influenza, dysentery, malaria and respiratory infections [14]. The leaf extract is a traditional remedy for the treatment of infectious disease, fever causing diseases, colic pain, loss of appetite, irregular stools and diarrhea [15]. In Malaysia, a decoction of the aerial parts is used to treat common cold, hypertension, diabetes, cancer, malaria and snakebite. It is an important constituent of at least 26 Ayurvedic formulas in Indian pharmacopoeia. In traditional Chinese medicine, it is seen as the cold-property herb used to rid the body of heat and fever and to dispel toxins from the body. In Ayurvedic medicinal system, tribals of Tamilnadu, India use this herb for a variety of ailments like dysmenorrhoea, leucorrhoea, pre-natal and post-natal care, complicated diseases such malaria, jaundice, gonorrhea and general ailments like wounds, cuts, boils and skin diseases [16 - 18] *A. paniculata* has various compounds in its aerial parts and roots and these are often used in extracting its active principles [19, 20]. Phytochemical studies of *A. paniculata* have led to the isolation of various plant metabolites. Notable among these metabolites are the terpenoids (entalabdane diterpene lactones) which account for a large proportion of its components and therapeutic activity. Other categories of compounds that have also been isolated include flavonoids (flavones), noriridoides, xanthones, polyphenols and trace and macro elements. Diterpenoids are distributed in and have been isolated from the aerial parts and roots of this plant. Of the diterpenoids that have been identified and isolated from *A. paniculata*, andrographolide is the most prominent in occurrence and quantity [21]. Dominant diterpenoids other than andrographolide which have been isolated mostly from the aerial parts of *A. paniculata* include deoxyandrographolide and neoandrographolide. Flavones are the major flavonoids that have been isolated from the aerial parts, roots and whole plant of *A. paniculata* such as 5, 7, 2', 3'-tetramethoxyflavone, 5-hydroxy-7, 2', 3'-trimethoxy flavones, 5-hydroxy-7, 2', 6'trimethoxyflavone, 7-O-methyldihydrowogonin, 7-O-methylwogonin, Dihydroskullcapflavone [22, 23]. Several miscellaneous compounds have been isolated, especially, from the roots of *A. paniculata* such as xanthones, 8-dihydroxy-3,7-dimethoxy-xanthone, 4,8-dihydroxy-2,7-dimethoxy-xanthone, 1,2-dihydroxy-6,8-dimethoxyxanthone and 3,7,8-trimethoxy-1-hydroxy-xanthone [24]. Five rare noriridoids designated as andrographolide A-E, along with curvifloruside were isolated from the roots of *A. paniculata* [25].

Antidiabetic potential of different parts of *A. paniculata* was studied in different diabetic animal models (Table 1). The aqueous extract (50 mg/kg) of *A. paniculata* raw material produced a significant ($P<0.05$) reduction (52.9%) in blood glucose level in streptozocin-induced hyperglycaemic rats. Freeze dried material of *A. paniculata* (6.25 mg/kg body weight), however, produced a more significant ($P<0.001$) reduction (61.81%) in blood glucose level. The results further showed that the aqueous extract of *A. paniculata* did not produce significant reduction in blood glucose level in normo-glycemic rats [26, 27] revealed the antidiabetic activity of *A. paniculata* by *in vitro* cell line model. Andrographolide was reported to ameliorate the diabetic retinopathy by inhibiting retinal angiogenesis and inflammation [28].

Ethanolic extracts of *A. paniculata* and andrographolide were reported to decrease the expression of glucose transporters (Glut 4) [29]. Chloroform fraction of *A. paniculata* was found to alter the glucose metabolism and diabetogenic gene expression [30]. Various mechanisms of anti-diabetic action of *A. paniculata* were revealed through research studies such as insulin resistance through down-regulation of NF-κB signalling pathway [31], inhibits TNFα-induced ICAM-1 expression via suppression of NADPH oxidase activation and induction of HO-1 and GCLM expression through the PI3K/Akt/Nrf2 and PI3K/Akt/AP-1 pathways [32], *in vitro* α-glucosidase and α-amylase enzyme inhibitory effects of *A. paniculata* extract and andrographolide [33 - 35]. Andrographolide was reported to prevent on the development of diabetes in autoimmune diabetic NOD mice [36]. Effect of andrographolide and ethanol extract of *A. paniculata* on liver glycolytic, gluconeogenic, and lipogenic enzymes were shown in type 2 diabetic rat model [34]. Protective effects of *A. paniculata* against endothelial dysfunction in diabetic rats were studied by Dandu and Inamdar [37]. Insulin-releasing action of *A. paniculata* was demonstrated by Wibudi *et al*. [38].

Cassia auriculata

Cassia auriculata L. is an erect annual or biennial shrub found throughout India in open areas of forest (Figure 1). The leaves are bitter, astringent, acrid, thermogenic, haematinic, constipating and expectorant. Seeds are also bitter, stringent, acrid, cooling, ophthalmic, diuretic, alexeteric and vulnerary. The leaves are used for ulcer, leprosy and skin diseases. Flowers are useful in diabetes and throat problems and the fruit is useful in controlling vomit. The leaf is used in the traditional systems of Indian medicine for curing jaundice, liver diseases, leprosy and ulcer [39, 40]. The powdered flower bud is used as herbal tea for diabetic patients and it also improves the complexion in women [41].

Figure 1: Anti-diabetic plants used in Indian systems of traditional medicine

Andrographis paniculata

Curcuma longa

Trigonella foenum-graecum

Salacia oblonga

Murraya koenigii

Cassia auriculata

Phyllanthus emblica

Table 1. Anti-diabetic effect of Indian traditional medicinal plants

S. No.	Plant	Model	Reference
1	*Andrographis paniculata* (Burm.f.) Wall. Nees.	Streptozotocin induced diabetic rats	[179 - 185]
		Alloxan-induced hyperglycemic rats	[186 - 192]
		Sucrose-induced type-2 diabetic adult male rat	[193]
		High-fructose-fat-fed rats	[194 - 196]
2	*Cassia auriculata* L.	Streptozotocin-induced rat model	[197 - 209]
		Alloxan-induced diabetic rats	[210 - 219]
		Galactose-fed rat model	[220]
3	*Curcuma longa* L.	Alloxan-induced diabetes rats	[221 - 224]
		Streptozotocin-induced rats models	[225 - 232]
		Streptozotocin-nicotinamide diabetic rats	[233]
		High fat diet fed rats	[234]
		Genetically diabetic KK-Ay mice	[235, 236]
4	*Murraya koenigii* (L.) Sprengel	Streptozotocin induced diabetic rats	[237 - 241]
		Alloxan-induced diabetic rat models	[242 - 246]
5	*Trigonella foenum-graecum* L.	Streptozotocin-induced diabetic rats	[247 - 252]
		Alloxan-induced rat model	[253 - 259]
		Nitrate-induced diabetes rat model	[260]
		Human model	[261]
6	*Salacia oblonga* Wall.	*In vitro* maltase, sucrose and alpha-glucosidase	[262, 263]
		Streptozotocin-induced diabetic rats	[264 -266]
		Zucker diabetic fatty rats	[267]
		Diabetic nephropathy	[268]
		Glucose homeostasis	[269]
		Diabetic vascular complications	[270]

It has been used in Ayurvedic medicine as Avarai Panchaga choornam and the main constituent of kalpa herbal tea [42]. In Sri Lanka, among herbal teas that are consumed most frequently the dried flowers of *C. auriculata* are considered to be beneficial for individuals suffering from diabetes, constipation and urinary tract diseases [43]. Different parts of this plant is used by various tribal people of India for the treatment of body heat and cuts [44], asthma and cough, dysentery, rheumatism and tooth-ache and skin diseases. In Andhra Pradesh, this plant is used to treat conjunctives and renal disorders [45].

Anti-diabetic effect of flower extract of *C. auriculata* was investigated in different animal models (Table 1). Blood glucose lowering effect of flowers was studied by Pari and Latha [46]. Flower extract showed hypoglycaemic response towards maltose ingestion and also concurrently suppressed insulin activity [47]. It showed hypoglycaemic effect as one of the ingredients of polyherbal formulations like Dianex [48], Hyponidd [49, 50]. Effect of *C. auriculata* against diabetic related complications like diabetic nephropathy [51] was reported. Alpha glucosidase inhibition, insulinogenic action and amelioration in the carbohydrate metabolic pathways by *C. auriculata* extracts was investigated as a mechanism of its anti-diabetic action [52 - 55].

Curcuma longa

Turmeric (*Curcuma longa* L.; family: Zingiberaceae) is a perennial, tropical plant and native to Asia (Figure 1). The deep orange-yellow turmeric powder is a commonly used spice in Southeast Asian and Middle Eastern countries. In India, curcumin has a long history of use as an Ayurvedic medicament particularly to treat various inflammatory conditions as it is the active principle of turmeric [56], which comprises 0.3% to 5.4% of raw turmeric [57]. Curcumin is a hydrophobic low-molecular-weight flavonoid, extracted from dried rhizomes of turmeric [58].

Various diabetic rat models were employed to prove the anti-diabetic effect of turmeric (Table 1). Oral administration of various dosages of curcumin (80 mg/kg body weight for 21 days [59] and 45 days [60]; 60 mg/kg BW for 14 days [61]; 90 mg/kg BW for 15 days [62]. In addition, oral administration of turmeric aqueous extract (300 mg/kg BW) [63] or curcumin (30 mg/kg BW) for 56 days [64] resulted in a significant reduction in blood glucose in STZ-induced diabetes model in rats. In high fat diet induced insulin resistance and type 2 diabetes models in rats. Oral administration of curcumin (80 mg/kg BW) for 15 and 60 days, respectively, showed an antihyperglycemic effect and improved insulin sensitivity [65]. Dietary curcumin (0.5% in diet) was also effective in ameliorating the increased levels of fasting blood glucose, urine sugar, and urine volume in STZ induced diabetic rats [66]. Effect of aqueous extract of *C. longa* in diabetes induced neuropathic [67] and diabetic retinopathy was analysed [68]. Antidiabetic potential of a by-product from curcumin production industry (spent turmeric oleoresin) was investigated [69]. Effects of *C. longa* on postprandial plasma glucose and insulin in healthy subjects were evaluated by Wickenberg *et al*. [70] and Sukandar *et al*. [71].

The possible mechanisms of the effect of curcumin on glycemia in diabetes models may be explained firstly by curcumin attenuates tumor necrosis factor-α (TNF-α) levels [72]. It also inhibits nuclear factor-kappa B (NF-κB) activation [73] and protein carbonyl, lipid peroxidation, and lysosomal enzyme activities (N-acetyl-β-d-glucosaminidase, β-d-glucuronidase, β-d-galactosidase) [74]. In addition, curcumin can decrease the levels of thiobarbituric acid reactive substances (TBARS) and the activity of sorbitol dehydrogenase (SDH). Second, curcumin has the ability of induction of peroxisome proliferator-activated receptor gamma (PPAR-γ) activation [75]. Curcumin also can elevate plasma insulin level and increase lipoprotein lipase activity [76]. Third, curcumin is involved in activating of enzymes in liver, which are associated with glycolysis, gluconeogenic, and lipid metabolic process, and activating nuclear factor erythroid-2-related factor-2 (Nrf2) function as well [77]. Anti-glycation property of *C. longa* fruits was reported by Jain *et al*. [78] and Khan *et al*. [79]. Ghorbani *et al*. [80] revealed the anti-hyperglycemic and insulin sensitizer effects of turmeric and its principle constituent curcumin. Ponnusamy *et al*. [81] discovered bisdemethoxycurcumin from *C. longa* rhizome as a potent small molecule inhibitor of human pancreatic α-amylase while other showed that turmeric volatile oil inhibits key enzymes linked to type 2 diabetes [82, 83]. Aqueous extract of *C. longa* rhizome showed stimulation of insulin release [84]. Rungseesantivanon *et al*. [85] demonstrated that curcumin supplementation improves diabetes-induced endothelial dysfunction associated with decreased vascular superoxide production. Muscarinic M-1 cholinoceptors was activated by curcumin to increase glucose uptake into skeletal muscle [86]. Similarly, curcumin activates AMPK and suppresses gluconeogenic gene expression in hepatoma cells [87]. Effect of curcumin on hyperglycemia-induced vascular endothelial growth factor expression was studied [88].

Murraya Koenigii

Murraya koenigii (L.) Sprengel, belongs to the family Rutaceae, commonly known as curry-leaf tree, is a native of India, Sri Lanka and other south Asian countries (Figure 1). It is found almost everywhere in the Indian subcontinent, it shares aromatic nature, more or less deciduous shrub or tree up to 6 m in height and 15-40 cm in diameter with short trunk, thin smooth grey or brown bark and dense shady crown. Most part of plant is covered with fine down and has a strong peculiar smell. *M. koenigii* is genus of tree, native to tropical Asia from Himalaya foothill's of India to Sri Lanka eastward through Myanmar, Indonesia, Southern China and Hainan. It is having grey color bark, longitudinal striatations on it and beneath it white bark is present.

Phytochemical screenings revealed the presence of phytochemicals such as carbohydrates, alkaloids, sterols, tannins, volatile oils, saponins, anthroquinone glycosides and flavanoids in this plant [89]. Leaves are aromatic and contain proteins, carbohydrates, fiber, minerals, carotene,

nicotinic acid and vitamin C. The leaves contain high amount of oxalic acid, leaves also contains crystalline glycosides, carbazole alkaloids, koenigin and resin. Fresh leaves contain yellow colored volatile oil conversely also rich in vitamin A and calcium [90]. It also contains girinimbin, iso-mahanimbin, koenine, koenigine, koenidine and koenimbine. Mahanimbicine, bicyclomahanimbicine, phebalosin, coumarine as Murrayone imperatoxin etc are isolated from leaves. Triterpenoid alkaloids like cyclomahanimbine and tetrahydromahanmbine are also present in the leaves. Murrayastine, murrayaline, pypayafolinecarbazole alkaloids and many other chemical compounds have been reported in the leaves of *M. koenigii*. Bark mainly contains the carbazole alkaloids as murrayacine, murrayazolidine, murrayazoline, mahanimbine, girinimbine, koenioline and xynthyletin. The pulp of fruits generally contain 64.9% moisture, 9.76% total sugar, 9.58% reducing sugar, 0.17% non reducing sugar and negligible amount of tannin and acids. It also contains 13.35% of vitamin C. The pulp of fruits contain trace amount of minerals 1.97% phosphorus, 0.082% potassium, 0.811% calcium, 0.166% magnesium and 0.007% iron. It also contain remarkable amount of protein [89].

Anti-diabetic effect of *M. koenigii* leaf extracts was evaluated in different animal models (Table 1). Hepatoprotective and antioxidant effects of *M. koenigii* in streptozotocin-diabetic rats was investigated [91]. Glycemic effect of *M. koenigii* was studied [92 - 96]. Islet protective and insulin secretion property of *M. koenigii* in streptozotocin-induced diabetic mice was analyzed [97, 98]. Efficacy of *M. koenigii* leaf extract on immune-modulatory [99], antioxidant [100, 101], impaired gastrointestinal motility [102] diabetic nephropathy [103, 104] were proven. Antidiabetic effect of mahanimbine (carbazole alkaloid) from *M. koenigii* was analyzed [105].

Phyllanthus emblica

Phyllanthus emblica L. (syn. *Emblica officinalis*), commonly known as Indian gooseberry or Amla, family Euphorbiaceae, is a main herbal drug utilized in Indian traditional systems of medicine (Figure 1). It is used equally as a medicine and as a tonic to build up lost energy and vigor. *P. emblica* is extremely nutritious and might be a chief dietary source of vitamin C, amino acids, and minerals [106]. Entire parts of the plant are used for medicinal purposes, particularly the fruit, which has been used in Ayurveda as a powerful rasayana and in customary medicine for the treatment of diarrhea, jaundice, and inflammation. The fruit is used either alone or in combination with other plants to treat many ailments such as common cold and fever; as a diuretic, laxative, liver tonic, refrigerant, stomachic, restorative, alterative, antipyretic, anti-inflammatory, hair tonic; to prevent peptic ulcer and dyspepsia, and as a digestive. Moreover, plant parts show antidiabetic, hypolipidemic, antibacterial, antioxidant, antiulcerogenic, hepatoprotective, gastroprotective, and chemopreventive properties [107]. *P. emblica*is one of the most extensively studied plants and reports suggest that it contains tannins, alkaloids, and phenolic compounds. It has been reported that fruits of *P. emblica* contains higher amount of vitamin C and considerably higher concentrations of most minerals, protein and amino acids like glutamic acid, proline, aspartic acid, alanine, cystine and lysine. Vitamin C levels are more than those in oranges, tangerines, or lemons. Fresh pericarp of *E. officinalis* contains higher amount of hydrolysable tannins like emblicanin A and B, punigluconin, pedunculagin. Activity-directed fractionation and purification process identified phytochemicals present in *P. emblica*such as gallic acid, methyl gallate, corilagin, furosin and geraniin. Phytochemical investigations revealed that *P. Emblica* contains higher amount of flavonoid like quercetin. Fruits were also analyzed for their alkaloids like phyllantine and phyllantidine. The fruit also contains gallic acid, ellagic acid, chebulinic acid, chebulagic acid, emblicanin A, emblicanin B, punigluconin, pedunculagin, citric acid, ellagotannin, trigallayl glucose, pectin, 1-O-galloyl-β-D-glucose, 3,6-di-O-galloyl-D-glucose, chebulagic acid, corilagin, 1,6-di-O-galloyl-β-D-glucose, 3 ethylgallic acid (3 ethoxy 4,5 dihydroxy benzoic acid), and isostrictiniin. It also contains flavonoids such as quercetin, kaempferol 3 O-α-L (6″ methyl) rhamnopyranoside and kaempferol 3 O-α-L (6″ ethyl) rhamnopyranoside. Recently, β-glucogallin as a novel aldose reductase inhibitor from *P. emblica* [108].

Siddha, Unani Tibetan, Sri Lankan, and Chinese systems of medicine utilize *P. emblica* as a powerful rasayana (rejuvenator) and to be useful in delaying the degenerative as well as a senescence process. It helps to increase longevity, improve digestion and to treat constipation. It also diminishes fever, cleanses the blood, decreases cough, eases asthma, strengthens the heart, benefits the eyes, encourages hair growth, invigorates the body, and augments the intellect, as per the Ayurvedic system of medicine. In several folk medicines the fruits, which are astringent, are beneficial in treating ophthalmic problems, dyspepsia, gastritis, hyperacidity, constipation, colitis, hemorrhoids, hematuria, menorrhagia, anemia, diabetes, cough, asthma, osteoporosis, premature graying of hair, weakness and fatigue. *P. emblica* is also stated to have hepatoprotective, cardioprotective, diuretic, laxative, refrigerant, stomachic, restorative, alterative, antipyretic, and anti-inflammatory properties. Besides being a hair tonic, *P. emblica* also prevents peptic ulcer dyspepsia, and is a digestive medicine [109].

Anti-diabetic action of *P. emblica* was investigated in allaxon induced diabetic mice [110] and streptozotocin-induced rat model [111, 112] evaluated the anti-hyperglycemic properties of *P. emblica* fruit in normal as well as diabetic human volunteers (Table 1). The results indicated a significant decrease in fasting and 2 h post-prandial blood glucose levels on the 21st day in both normal and diabetic subjects receiving 1, 2 or 3 g *P. emblica* powder per day as compared with their baseline values. Tiwari *et al.* [113] demonstrated that *P. emblica* extracts not only attenuated the diabetic condition but also reversed neuropathic pain through modulation of oxidative-nitrosative stress in diabetic rats. Even Kumar *et al.* [114] investigated flavonoid rich fruit extract of *P. emblica* in

type II diabetes induced diabetic neuropathy in male Sprague-Dawley rats. It was observed that oral administration of a 1:1 mixture of Epigallocatechin gallate and *P. emblica* extract for 3 months significantly improved antioxidant defense as well as diabetic and atherogenic indices in uremic patients with diabetes [115].

Trigonella foenum-graecum

Fenugreek (*Trigonella foenum-graecum* L.), an annual legume crop belonging to the family of Fabaceae is native to an area extending from Iran to northern India (Figure 1). The crop has now been introduced to parts of Africa, Mediterranean Europe, West and South Asia, North America, South America and parts of Australia [116]. The distinctive cuboid, yellow-to-amber colored seeds are used both whole and in powdered form and often roasted to reduce their bitterness and enhance their flavour, they are frequently encountered in the cuisines of the Indian subcontinent. The seeds are used in the preparation of pickles, vegetable dishes, daals, and in recent trend as a spice adjunct [117]. The appetizing fragrance and seasoning sweet flavor has been of great values and will still continue to enhance food intake [118]. The fresh leaves, sprouts, and microgreens are used as vegetables and are an ingredient in some Indian curries. The sprouted seeds and microgreens are used in salads and they provide natural food fiber and other nutrients required in human body [119]. The high levels of fiber make this plant is beneficial to digestion and it also has the ability to modify food texture. Furthermore it is widely used for the associated therapeutic and chemopreventive activities such as antibacterial, anticancer, antiulcer, anthelmintic, hypocholesterolemic, hypoglycemic, antioxidant, and antidiabetic effects.

This plant is a unique functional food crop. The chemical constituents of both seed and leaves have made them valuable as food and medicine, in addition to being a rich source of nutrients (macronutrients and micronutrients), it delivers various phytochemicals (non-nutritive plant chemicals that have protective or disease preventive properties) which confer the medicinal values as well as impart the popular spicy flavour [120]. The nutritional value includes several aspects that may be grouped into two categories: organoleptic properties and nutritious contents. Seeds of this plant are known and popular for their strong spicy flavour, in addition the high fiber contents [121]. The dried leaves are used as a quality flavour for meat, fish and vegetable dishes. Sotolon is the major chemical responsible for distinctive sweet smell and the seed contains volatile oil and fixed oil in small quantities [122]. As it has been widely used as traditional food, functional food and nutraceuticals, it provides natural food fiber and other nutrients required in body [119]. In terms of protein contents, it has a chemical composition that mimics milk in its ratio between protein and amino acids contents [123]. The endosperm is rich in protein such as globulin, histidine, albumin and lecithin [124]. The protein fraction is lysine-rich and comparable in quality to that of soybean protein [125]. This plant could functionally promote health because of the high content of amino acid 4- hydroxyisoleucine which has high potential for insulin-stimulating activity [126]. This high protein content and quality should be looked into in qualitative and quantitative improvement of this crop which could greatly impart population with low protein intake especially in some developing countries. Seeds are rich in carbohydrates and especially mucilaginous fiber which is comprised mainly of galactomannans. They are actually popular for fiber and a rich source of soluble dietary fiber content. It contains 50 % fiber (30 % soluble fiber and 20 % insoluble fiber) [127]. Non-starch polysaccharides constitute fiber content. It is no exception from other vegetable in high contents of vitamins and minerals; it is relatively low in mineral content when compared with the vitamin content however it has some of them in good amounts such as phosphorus and sulphur [128]. High occurrence of calcium, iron and zinc has also been reported in curry made from fenugreek [129]. With reference to micronutrient content, it is especially rich in choline. Both the seed and leaves contain high levels of vitamin C, nicotinic acid and riboflavin, while the seed is rich in thiamin and folic acid but the leaves contain little or no folic, β- carotene, a precursor of vitamin A is present in the leaves at relatively high amount.

Preliminary animal and human trials suggest possible hypoglycaemic and antihyperlipedemic properties of fenugreek seed powder taken orally. It has been well known to be used as antidiabetic remedy for both type I and II diabetes and has been extensively used as a source of antidiabetic compounds, from its seeds, leaves and extracts in different model systems [130]. About 25-50 g seeds were given to diabetic patients daily in diet to prevent and manage long term complications of diabetes and studies have been made about the glycemic index of fenugreek recipes which showed that the soluble fiber has significantly reduced the glycemic index [131]. On the other hand, water extract of seeds has higher hypoglycemic and antihyperglycemic potential and for this reason it may be used as a supplementary medicine to treat the diabetic population by significantly reducing the dose of standard drugs. Since fenugreek seeds are a source of protein, they can replace pulses in the diets of diabetics. Inclusion of 25-50 g seeds in the diet of diabetic patients (taken daily) can be an effective supportive therapy in the management of diabetes. The bioactive compounds with respect to diabetic conditions include the galactomannan-rich soluble fiber fraction which may be responsible for the antidiabetic activity of the seeds [132].

Anti-diabetic activity of fenugreek was evaluated in different models (Table 1). Hypoglycemic effect was proven in different forms on experimental rats [133, 134]. Pharmacodynamic interaction of fenugreek on sero-biochemical parameters was investigated in diabetic Sprague-Dawley rats [135]. Role of this plant in the prevention of type 2 diabetes mellitus in prediabetes was investigated by Gaddam *et al*. [136]. Seed was reported to attenuates the diabetic nephropathy [137 - 140], diabetic neuropathy [141], inflammation and oxidative stress [142 - 144] and immunostimulant activities [145]. Antidiabetic effect of trigonelline [146, 147], GII [148 - 150], omega-3 fatty acids [151], trigonelline and diosgenin were analysed

[152 - 154], galactomannans [155] and soluble dietary fibre fraction [156] from seeds were reported. Fenugreek extract was reported to enhance the antidiabetic activities of glibenclamide [157, 158].

Salacia oblonga

Salacia oblonga Wall. is widely distributed in south region of India and Sri Lanka (Figure 1). Itis a perennial straggling plant belongs to the family Hippocrateaceae (Common name: Ponkoranti) found in foot hills of the mountain of Eastern and Western Ghats of Tamilnadu and Kerala up to 1000 m. It is a climbing shrub, leaves are elliptic in shape, flowers are small, axillary, short pedunculate, head or branched cymes with 5-6 cm in dia. The root of *Salacia oblonga* is used for the treatment of rheumatoid arthrities and allergic conditions. The fruits are used as a diatery supplement and as a tribal anti-diabetic medicine [159]. Root is extensively used for treating Diabetes Mellitus by Siddha Practitioners and also it has been used as a remedy for Gonorrhea, rheumatism, itch, Asthma, thirst and ear diseases in Tamilnadu and Kerala. *S. oblonga* is proved to be antiseptic, besides nephroprotective, cardiac fibrosis inhibitor, hypolipidemic and also useful in hepatic steatosis and as an anti-microbial, anti-inflammatory, antioxidant and antidiabetic agent [160, 161] revealed the sucrose inhibitory effect of herbal tea that containing *S. oblonga* was claimed to be beneficial as a dietary supplement. Similarly, Collene *et al*. [162] determined the nutraceutical value of *S. oblonga* extract and suggested that it could be a good supplement to decrease glycemia. The glucose lowering capacity of *S. oblonga* was evaluated in streptozotocin-induced diabetic rats [163]. *In vitro* antioxidant activity of methanolic extract of *S. oblonga* was investigated by Basu *et al*. [164]. Phytopharmacological aspects of Salacia chinensis was investigated by Deokate and Khadabadi [165].

Two thiosugars isolated from *S. oblonga* extract, salacinol and kotalanol, also reveal *in vitro* inhibitory effects against maltase, isomaltase, and sucrase, with potent effect against sucrase than the alpha-glucosidase. Due to reduction of the enzymatic breakdown of di-, tri-, and oligosaccharides by alpha-glucosidase, carbohydrate absorption is decreased, attenuating the postprandial glycemic response. The undigested di-, tri-, and oligosaccharides pass through the small intestine into the colon where they are digested by the colonic microflora producing gaseous by products, which is demonstrated by the increased breath hydrogen responses [166]. Lowering of postprandial glycemia by *S. oblonga* extract has been observed in rats fed either maltose or sucrose, but not glucose, which is consistent with its alpha-glucosidase inhibitory effect in the small intestine. According to a study performed by Rossi *et al*. [167] which explained glucose lowering efficacy of different salacinol derivatives model obtained by substituting sulphur with selenium or increasing the sulphated chain, but these derivatives were less effective.

Huang *et al*. [168], in an another study conducted demonstrated that oral administration of water extract of *S. oblonga* to Zucker diabetic fatty rats lowered plasma triglyceride and total cholesterol levels, increased HDL-c levels and reduced triglyceride, non-sterified fatty acids and the ratio of fatty droplets to total tissue. It is observed that extract of *S. oblonga* improves postprandial hyperglycemia and hepatic steatosis in Zucker diabetic fatty rats (Table 1). Huang *et al*. [168] demonstrated that *S. oblonga* extract functions as a PPAR-alpha activator, providing a potential mechanism for decrease in postprandial in a series of *in vivo* and *in vitro* studies. Shimoda *et al*. [169] and Tanimura *et al*. [170] revealed suppression of post parandial blood glucose level by water extract of *S. reticulata*. α-Glucosidase inhibitory activity of *S. chinensis*was reported by Yoshikawa *et al*. [171]. Salacinol, kotalanol and kotalagenin 16-acetate showed a stronger inhibition of the increased serum glucose levels [172]. Grover *et al*. [173] investigated the effects of *S. oblonga* in diabetic nephropathy while Welles [174] studied oxidative stress in glucose homeostasis. Minami *et al*. [175] studied the effect of five member sugar moiety on glycogen-degrading enzymes. Huang *et al*. [176] evaluated the potentials *S. oblonga* extract in diabetic related vascular complications.

Salacia extracts exhibited free radical scavenging, antioxidant and hepatoprotectant activities [177]. In human studies, Salacia extracts have been shown to decrease plasma glucose and insulin levels, decrease HbA1c, and modulate serum lipid levels with no adverse effects being reported. Similar results have been demonstrated in rat and mouse models as well as *in vitro* systems. Safety of *S. reticulata* and other *Salacia* species as *S. oblonga* and *S. chinensis*in rats and mice indicate that extracts are exceedingly safe. No clinical studies have examined the effects of Salacia extracts on human weight loss, although weight loss and decreases in weight gain have been demonstrated in animal models. Hydroalcoholic extracts of the stem of selected plants were found to possess different levels of antioxidant status. Anti diabetic efficacy was evaluated in the STS induced diabetic rats [178].

CONCLUSION

This review clearly indicates the therapeutic usefulness of various Indian traditional medicinal plants to treat / manage diabetic complications. The beneficial effects shown by all the presently described medicinal plants might be due to their multiple mechanisms of action. The experimental evidence of therapeutic efficacy confirms the anti-diabetic potential of Indian medicinal plantsResults of these experimental studies can stand as a bridge for further clinical studies and / or lead for the development of better therapeutic natural remedies for prevention and treatment of diabetic complications.

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