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REVIEW ARTICLE

Indian Traditional medicinal plants as a source of potent Anti-diabetic agents: A Review

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Abstract

Objective The present review aims to provide an overview of traditional medicinal plants known to be of anti-diabetic potential.
Methods A literature search was conducted using the scientific databases including PubMed, EMBASE and google scholar and a total of fifty herbs have been described and their possible mechanism of anti-diabetic action has been mentioned. Among them, in-depth discussion on five most potent anti-diabetic herbs has been provided with respect to their mechanism of action, in-vivo studies and clinical efficacies.
Results The present review has highlighted the usefulness of the herbal source for the treatment and management of diabetes mellitus. With the help of previous literature published on *In-vivo* animal studies and human clinical studies; the effectiveness of *Gymnema sylvestre, Momordica charantia, Trigonella foenum graecum, Tinospora cordifolia and Curcuma longa* in the treatment and management of Diabetes has been proved.
Conclusion Based on this review it can be concluded that herbs can serve as more efficient, safer, and cost-effective adjuvant therapy in the management and treatment of diabetes. Further investigations mainly focusing on the isolation of phytocompounds from these herbs can lead to the discovery of newer antidiabetic agents.

Keywords Anti-diabetic · Diabetes mellitus · Herbs · Hyperglycaemia · Medicinal plants · Phytocompounds

Introduction

Diabetes mellitus is one of the most prevalent diseases found in all parts of the world and is becoming a serious threat to mankind's health [1]. It is a complex heterogeneous group of metabolic disorders including hyperglycemia and is associated with the imbalance in carbohydrate, protein, and lipid metabolism [2]. According to WHO, "Diabetes mellitus is a chronic disease caused by inherited and/or acquired deficiency in production of insulin by the pancreas, or by the ineffectiveness of the insulin produced. Such a deficiency results in increased concentrations of glucose in the blood, which in turn damage many of the body's systems, in particular the blood vessels and nerves" [3]. According to the recent data by International Diabetes Federation (IDF) Atlas claims that around 463 million adults are currently living with diabetes and estimates that there will be 578 million adults with diabetes by 2030, and 700 million by 2045 [4].

The management of diabetes mellitus is considered a global problem. In current allopathic therapy the oral hypoglycaemic agents and insulin, are subsequently used to control the diabetic conditions, however, complications associated with them, limited tolerability, cost, and other side effects reduce its wide acceptance. This could be the main reason for the shift of common people to Ayurveda form allopathic system nowadays [5].

Since ancient times traditional herbal drugs with multiple phytoconstituents and properties have been used as medicines for the treatment of a wide range of diseases [6]. Herbal medicines have been considered to be intrinsically safe, due to their natural occurrence, efficacy, and fewer side effects [7]. India has a long history of use of medicinal plants for the management of diabetes. World ethnobotanical information has reported the usage of about 800 plants for the control of diabetes mellitus, amongst them only 410 are experimentally proven for having anti-diabetic properties but the complete mechanism of action is available only for about 109 plants

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[8]. The treatment of diabetes using herbs has more advantageous effects and does not cause much side effects. These herbal drugs act by different mechanisms and consequently protect the β-cells during the diabetic condition and reduce the amount of glucose level in the blood [9].

This review aims to provide an overview of the use of medicinal plants in the management of diabetes, focusing on their mechanism of action. Furthermore, an emphasis on the five most commonly available and potent anti-diabetic herbs has been given. These include *Gymnema sylvestre*, *Momordica charantia*, *Trigonella foenum graceum, Tinospora cardifolia*, and *Curcuma longa*.

Methods

A literature search was conducted using the scientific databases including PubMed, EMBASE and google scholar. The aim was to identify published data on traditionally used medicinal plant for the treatment and management of Diabetes mellitus. The search terms used were "diabetes and plants", "traditional plants", "medicinal plants and diabetes", "anti-hyperglycemic plants", and "mechanism of anti-diabetic action". Based on the above criteria extensive literature search was carried out and a total of fifty herbs have been described with their possible mechanism of anti-diabetic action. Amongst the fifty herbs in-depth discussion on five most potent and easily available anti-diabetic herbs has been provided with respect to their mechanism of action, in-vivo studies and clinical efficacies.

Traditional anti-diabetic plants

Since the time of Charaka and Sushruta, traditional medicines have been used for the management of diabetes mellitus [10]. Medicinal plants have always been a valuable source of drugs and many of the currently available drugs such as aspirin, quinine, vincristine, vinblastine, and digitalis have been derived directly or indirectly from them [11]. Most of the anti-diabetic drugs derived from plants are from the phytochemical class of polyphenols, terpenoids, tannins, and steroids. These affect various metabolic cascades, which further affect the level of glucose in the human body [12].

A list of medicinal plants used traditionally for diabetes with proven anti-diabetic and related beneficial effects are compiled along with their family, active principles responsible for diabetes, mechanism of action and use (Table 1).

Amongst the fifty herbs described in Table 1 we have identified five most potent and easily available anti-diabetic herbs namely, *Gymnema sylvestre, Momordica charantia, Trigonella foenum graecum, Tinospora cordifolia and Curcuma longa*. In-depth discussion on these herbs has been provided with respect to their mechanism of action, in vivo studies and clinical efficacies. The rationale behind selection of these five herbs owes to their traditional usage, easy availability, effectiveness and most importantly to their proven clinical significance. The selected plants are a choice of herbal medicine in the treatment of diabetes. They are also utilized by multiple pharmaceutical herbal industries and most of the herbal anti-diabetic preparation consist of these herbs. Although there are other plants which are utilized in the diabetes management as folklore medicine but their commercial utilization is less as compare to the chosen five plants. Hence a need has been felt for understanding their various mechanism of actions and efficacy in management of diabetes.

Gymnema sylvestre

Gymnema sylvestre is an indigenous herb, belonging to the family Asclepiadaceae. It is popularly known as "gurmar" for its distinct property as sugar destroyer, it is a reputed herb in the Ayurvedic system of medicine. The plant is indigenous to western and central India, Australia, and tropical Africa [94].

Phytochemistry of *G. sylvestre*

G. sylvestre is a good source of a large number of bioactive substances. The leaves contain Triterpene saponins like gymnemic acids, gymnemasaponins, and gymnemasides. Apart from this, other phytoconstituents include flavones, anthraquinones, pentatriacontane, hentri-acontane, α and β-chlorophylls, phytin, stigmasterol, dquercitol, resins, etc. The major secondary metabolites present in Gymnema includes Gymnemic acid. The Gymnemic acids consist of numerous members termed as gymnemic acids I–VII, gymnemasaponins, and gymnemosides A–F. Gurmarin is another essential phytoconstituent isolated from *G. sylvestre* [95].

Mechanism of Action

Antidiabetic activity of Gymnemic acids appears to be due to a combination of mechanisms. It acts through stimulation in insulin secretion from the pancreas. It also shows a similar effect by delaying the glucose absorption in the blood. In the intestine it attaches to the receptor present in the external layer of the intestine, thereby preventing the absorption of sugar molecules by the intestine, resulting in low blood glucose levels [95]. In a study extract of the plant has showed its effectiveness in regeneration of pancreatic β cells [66]. Gymnemic acid the major phytocompounds present in the plant is reported to interact with glyceraldehyde-3-phosphate dehydrogenase (GAPDH), a key enzyme in glycolysis pathway [96]. Moreover, *G. sylvestre* has been reported to exhibit significant inhibitory activity against α-glucosidase; Fig. 1.

Table 1 List of Traditional plants used in management and treatment of Diabetes

Plant name	Family	Parts used	Active Principles	Mechanism of action	Uses	Reference
Acacia arabica	Leguminoceae	Bark	Gallic acid, pyrocatechol, (+)-catechin, (-) epigallocatechin-7-gallate, (-) epicatechin, quercetin, (+) catechin-5-gallate.	Act as secretagouge to release insulin	Hypoglycemic activity	[13, 14]
Achyranthes aspera	Amaranthaceae	Leaves, seeds.	Betaine, achyranthine, β ecdysone	Carbohydrate digestion and absorption	Hypoglycemic effect	[15, 16]
Adhatoda vasica	Acanthaceae	leaves	Vasicine Vasicinol	α-Glucosidase-inhibiting activity	Antidiabetic	[17, 18]
Aegle marmelose	Rutaceae	leaves	Aegelin, marmesin and marmelosin	Regeneration of pancreatic β cells and insulin secretion	Hypoglycaemic effect	[16, 19]
Ageratum conyzoides	Asteraceae	leaves	Mono- and sesquiterpenes	Increase peripheral utilization of glucose	Hypoglycaemic effect	[20, 21]
Allium cepa	Amaryllidaceae	bulb	S-methyl cysteine sulfoxide, S-allyl cysteine sulfoxide	Stimulates pancreatic β-cells	Hypoglycaemic effect	[22, 23]
Allium sativum	Amaryllidaceae	bulb	Allicin, apigenin, alliin	Stimulates pancreatic β-cells	Antidiabetic and anti-oxidant	[16, 23, 24]
Aloe barbadensis	Asphodelaceae	leaves	Aloin, barbaloin, isobarbaloine, aloetic acid.	Insulin secretion and synthesis	Hypoglycemic effect.	[16, 25]
Andrographis paniculata	Acanthaceae	Whole plant	Andrographolide,	Regeneration of pancreatic β cells, insulin secretion	Antidiabetic & hepatoprotective.	[26, 27]
Annona squamosa	Annonaceae	leaves	Acetogenin	Enhances insulin level from pancreatic islets, increased utilization of glucose in muscle.	Hypoglycemic and antihyperglycemic activities	[28, 29]
Areca catechu	Palmitaceae	Leaves, flowers, seeds	Nitrosamines, arecoline, arecaidine	Carbohydrate digestion and absorption	Hypoglycemic	[16, 30]
Azadirachta indica	Meliaceae	leaves	Azadirachtin, nimbolinin, nimbin, nimbidin, quercetin.	Improves the insulin signaling molecules and glucose utilization in the skeletal muscle.	Antidiabetic, Antibacterial, antioxidant	[31, 32]
Bacopa manneri	Serophulariacea	Aerial part	Bacosine, brahmine, bacopaside I, II, III, IV and V.	Increase in peripheral glucose consumption	Antihyperglycemic agent	[33, 34]
Bauhinia forficuta	Fabaceae	leaves	Kaempferitrin	Glycolysis, insulinonematic activity.	Hypoglycemic effect, antioxidant.	[35, 36]
Berberis aristata	Berberidaceae	Stem bark, roots, leaves	Barberin,	Glucose transport, carbohydrate digestion and absorption, DPP-IV inhibition	Hypoglycemic effect	[37, 38]
Boerhavia diffusa	Nyctaginaceae	leaves	Punarnavine, Boeravinone A-F	Increase in hexokinase activity, increase plasma insulin level, antioxidant	Antidiabetic	[39, 40]
Camellia sinensis	Thecaceae	leaves	Epigallocatechin-gallate, gallocatechin, epicatechin, (+) catechin, (−) epicatechin	Free radical scavenging activity, insulinonematic activity	Antihyperglycemic activity, antioxidant	[41, 42]
Caseria esculenta	Salicaceae	roots	Leucopelargonidin, Dulcitol, Beta sitosterole.	Insulin secretion	Antihyperglycemic activity	[43]
Cassia auriculata	Fabaceae	roots	Bis (2-ethyl hexyl) phthalate	α-Glucosidase-inhibiting activity	Antihyperglycemic effect	[44, 45]
Centella asiatica	Apiaceae	Whole plant	asiaticoside		Antihyperglycemic activity	[46, 47]
Coccinia indica	Cucurbitaceae	Aerial parts	- β- Amyrin Acetate, Lupeol, Cucurbitacin B, Taraxerone, Taraxerol, β-carotene, Lycopene,	Initiate insulin secretion, carbohydrate digestion and absorption.	Hypoglycemic effect.	[48, 49]
Commelina communis	Commelinaceae	Leaves, stem	1-deoxynojirimycin, (2*R*,3*R*,4*R*,5*R*)2,5-bis(hydroxym-ethyl)-3,4-dihydroxypyrrolidine	Inhibition of α-glucosidase	Antihyperglycemic agent.	[50, 51]
Curcuma longa	Zingiberaceae	rhizomes	Curcumin, termerone, germacrone, zingiberene	Inhibition of α-glucosidase, inhibition of GSK-3β	Antidiabetic, Antihyperlipidemic, antioxidant	[52, 53]
Cyprus rotandus	Cyperaceae	Whole plant	α cyperone, cyperene, cyperol.	Inhibites intestinal glucose absorption and promoting glucose consumption.	Hypoglycemic agent	[54, 55]
Emblica officinalis	Euphorbiaceae	fruits	Gallic acid, ellagic acid, vitamin c.	Hypoglycemic, Decreases lipid peroxidation, antioxidant.	Hypoglycemic and antioxidant.	[56, 57]
Enicostema littorale	Gentianaceae	Whole plant	Swertiamarin, apigenin, isovitexin, swertisin, saponarin, 5-o glucosylswertisin	Glucose-induced insulin release through K(+)-ATP channel.	Hypoglymcemic effect.	[58, 59]

Table 1 (continued)

Plant name	Family	Parts used	Active Principles	Mechanism of action	Uses	Reference
Ficus benghalensis	Moraceae	Bark, leaves	Leucocyanidin, pelarogonidin	Insulin secretion, glycogen synthesis	Antidiabetic	[60, 61]
Ficus racemosa	Moraceae	Bark, leaves	β-sitosterol, racemosic acid, Bergenin.	Glycogenolysis and gluconeogenesis	Hypoglycemic activity	[62, 63]
Glycyrrhiza glabra	Leguminoceae	roots	Glycyrrhizin, glycyrrhizic acid liquirtin, isoliquirtin.	Potent PPAR-γ ligand binding activity thus, reduces the blood glucose level	Hypoglycemic agent.	[64, 65]
Gymnema sylvestre	Asclepidaceae	leaves	Gymnenic acid, Stigmasterol, Gurmarin, betaine, gymnemosides.	Regeneration of pancreatic β cells, α-glucosidase inhibitor, insulin secretion	Antidiabetic agent.	[66–68]
Ginkgo biloba	Ginkgoceae	leaves	Kaempferol, isorhamnetin	Inhibition of α-amylase and α-glucosidase activity	Hypoglycemic agent.	[69]
Mangifera indica	Anacardiaceae	leaves	Mangiferin	α-Glucosidase-inhibiting activity	Hypoglycemic agent	[70]
Momordica charantia	Cucurbitaceae	fruits	Momordin, momordicine, charantin	Insulin secretion, glycogen synthesis	Hypoglycemic agent	[71, 72]
Morus indica	Moraceae	leaves	Chrysin, isoquercitrin	Insulin secretion	Hypoglycemic agent	[73]
Ocimum sanctum	Lamiaceae	leaves	Eugenol, trans-β ocimene, Carvacrol, linalool.	Insulin secretion, carbohydrate digestion and absorption	Hypoglycemic agent.	[74, 75]
Panax ginseng	Araliaceae	roots	Ginsenosides Rg2, panaxan A, B, C, D, E	Regeneration of pancreatic β cells, free radical scavenging	Antihyperglycemic activity	[76, 77]
Phyllanthus amarus	Phyllanthaceae	leaves	Brevifolin carboxylic acid, ethyl brevifolin carboxylate	α-Amylase inhibitory activity	Hypoglycemic, Anti-oxidant activity.	[78]
Pterocarpus marsupium	Leguminoceae	Stem wood	Marsupsin, pterosupin, pterostilbene	Insulinomematic activity	Antidiabetic	[79]
Swertia chirata	Gentinaceae	Whole plant	Amarogentin, swerchirin, chirantin	Stimulates insulin release from islets	Antihyperglycemic agent	[80]
Syzygium aromaticum	Myrtaceae	Flower buds	Eugenol, Caryophylline	Insulin secretion, carbohydrate digestion and absorption	Hypoglycemic agent	[81]
Syzygium cumini	Myrtaceae	Bark, seeds	Jambosine, jambolin, anthocyanins.	α-Glucosidase-inhibiting activity	Anti-hyperglycemic	[82]
Terminalia arjuna	Comberetaceae	Stem bark	Arjunic acid, arjunolic acid, gallic acid.	Stimulates insulin release from islets	Hypoglycemic ativity	[83]
Terminalia chebula	Comberetaceae	fruits	Gallic acid, chebulic acid, chebulanin, ellagic acid, chebulegic acid, chebulinic acid	Secretion of insulin from the β-cells.	Hypoglycemic ativity	[84]
Terminalia belerica	Comberetaceae	fruits	ß- sitosterol, gallic acid, ellagic acid, ethyl gallate, chebulaginic acid.	Insulin secretion, carbohydrate digestion and absorption	Hypoglycemic ativity	[85]
Tinospora cardifolia	Menispermaceae	Leaves and stem	Tinosporine, cordifolide, tinosporide, Barberin.	α-Glucosidase-inhibiting activity, glycolysis	Antidiabetic agent.	[86, 87]
Trigonella foenum graceum	Fabaceae	seeds	Trigonellin, Fenugreekine.	Regeneration of pancreatic β cells, insulin secretion	Antidiabetic activity.	[88, 89]
Vinca rosea	Apocynaceae	Whole plant	Catharanthine, vindoline, vindolinene vinblastine, vincristine	Regeneration of pancreatic β cells, insulin release	Hypoglycemic activity	[90]
Vitis vinifera	Vitaceae	Leaves, stem	E-resveratrol, E-ε-viniferin, anthocyanins.	Insulinonematic activity	Anti-hyperglycemic activity	[91]
Withania somnifera	Solanaceae	Leaves, roots	Withaferin A, withanolides	Insulin release from pancreatic β cells	Hypoglycemic activity	[92]
Zingiber officinalis	Zingiberaceae	rhizomes	Gingirol, shoagol, zingerone.	Increase insulin level & decrease fasting glucose level	Hypoglycemic activity	[93]

Antidiabetic effects of *Gymnema sylvestre*

Various in vivo animal studies and clinical expeiments have repeatedly shown hypoglycemic effects of leaves of G. sylvestre. In a study, the methanol extract of *G. sylvestre* leaf and callus showed pronounced anti-diabetic activity through the regeneration of β-cells [97]. Sugihara Y., et al. reported the antihyperglycemic effect of gymnemic acid IV, isolated from the leaves of *G. sylvestre*. The study reported that gymnemic acid IV decreased blood glucose levels by 13.5 − 60.0% within 6 hours of administration in comparison with glibenclamide, also increased plasma insulin levels was observed in STZ-diabetic mice at a concentration of 13.4 mg/kg due to gymnemic acid IV [66].

Momordica charantia

Momordica charantia also known as karela, the bitter guard is a flowering wine, belonging to family Cucurbitaceae. The herb is commonly used by Ayurvedic and other traditional systems of medicine as an anti-diabetic agent. The plant is widely cultivated in Asia, India, East Africa, and South America [72].

Phytochemistry of *M. charantia*

Bitter melon is rich in constituents such as glycosides, saponins, alkaloids, reducing sugars, resins, phenolic constituents, fixed oil, and free acids [98]. The main phytoconstituents present in *M. charantia* are charantine, charine, momordicin, momordin, cucurbitins, cucurbitacins momorcharins, etc. [72]. Most of the anti-diabetic potential of *M. charantia* is ascribed to Charantin. The hypoglycemic activity of the compound is similar to that of insulin [99].

Mechanism of action

M. charantia exerts its hypoglycemic effects via multiple mechanisms. The possible mechanism of the hypoglycemic action of *M. charantia* is mainly due to insulin secretion and glycogen synthesis [71, 72]. Some studies indicate that bitter melon may stimulate glucose utilization by peripheral and skeletal muscle, inhibit intestinal glucose uptake, and increase hepatic glycogen synthesis [72]. Hsin-Yi Lo et al., reported that seed extract of *M. charantia* regulates glucose metabolism mainly via the insulin signaling pathway [100]. In an experimental study using cell-based screening assay Hsueh-ling Cheng identified and reported that triterpenoids are the potential hypoglycaemic agents responsible for anti-diabetic action of the plant, also the underlying mechanism to bring about the action was attributed to AMP-activated protein kinase [101]; Fig. 2.

Antidiabetic effects of *M. charantia*

Experimental studies have confirmed the hypoglycaemic effect of *M. charantia* on various animal models. A study demonstrated the dose-dependent hypoglycaemic activity exhibited by methanolic fruit extract of *M. charantia* in alloxan-induced diabetic rats [102]. Mahmoud MF et al., studied the

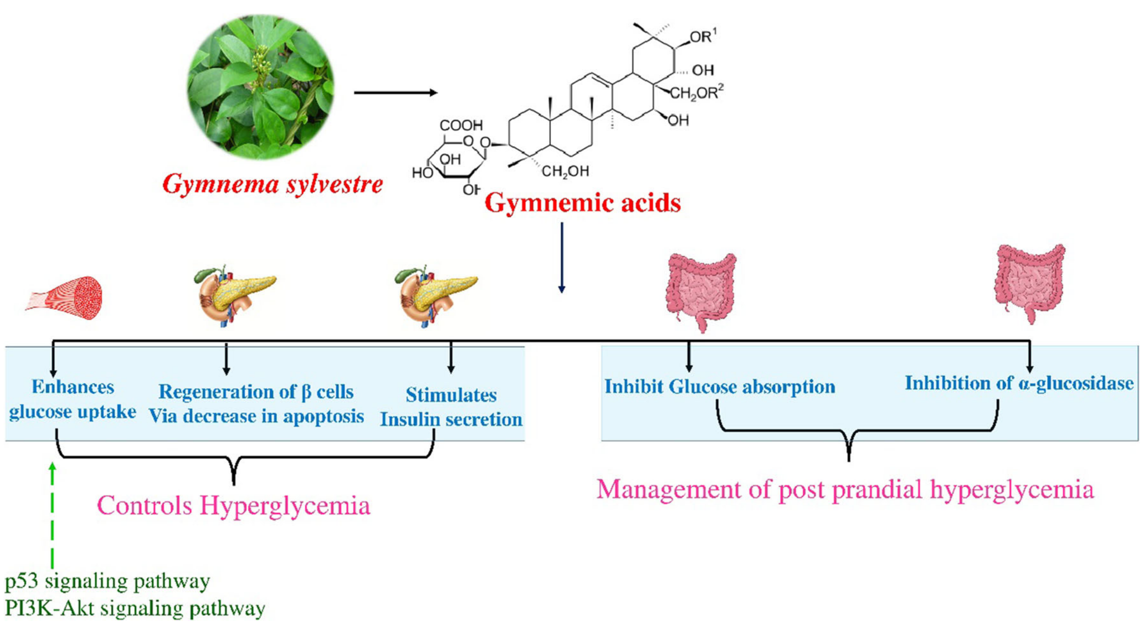

Fig. 1 Schematic representation of Probable molecular mechanism for anti-diabetic effect of *G. sylvestre*

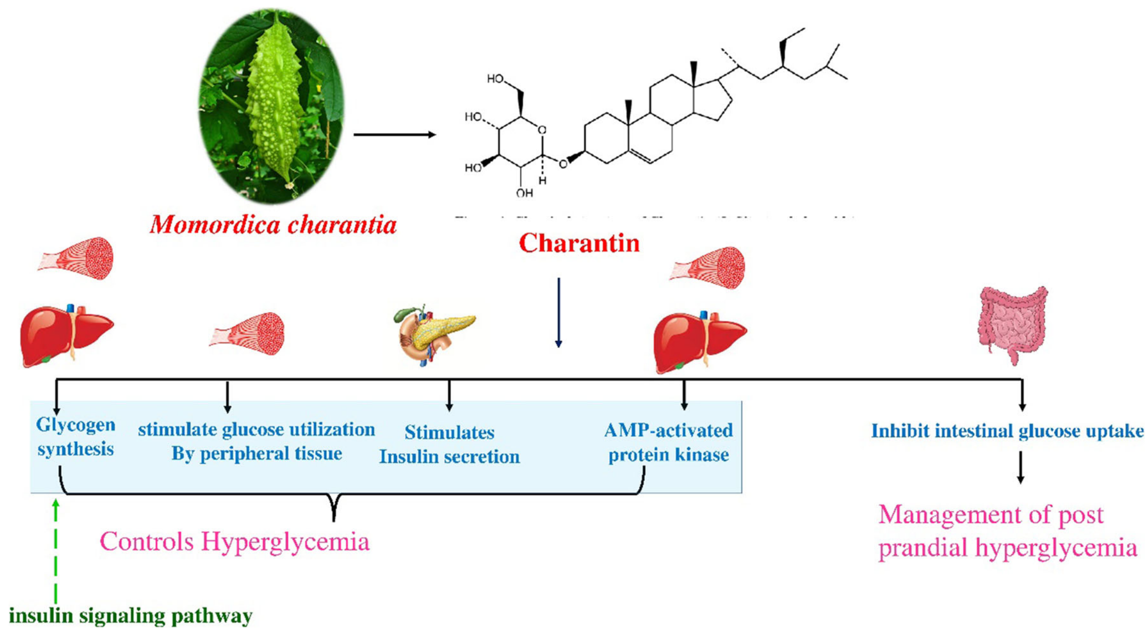

Fig. 2 Schematic representation of Probable molecular mechanism for anti-diabetic effect of *M. charantia*

antidiabetic activity of *M. charantia* fruit juice in streptozotocin-induced diabetic rats [103]. In an investigational study Joo-Hui Han et al., isolated four new cucurbitane-type triterpenoids (C1-C4) from the ethanol extract of *M. charantia* and investigated whether the compounds affect insulin sensitivity both in vitro and in vivo models. The results reported significant decreases in blood glucose level and enhanced glycogen storage by compound C2 in STZ-injected mice [104].

Trigonella foenum graceum

Trigonella foenum graceum also known as fenugreek is used primarily as an alternative therapy for diabetes. A member of the Fabaceae family, the plant cultivated in India and North African countries. The herb has a long history of usage as a potent anti-diabetic agent in Ayurvedic and folklore medicine [94, 105].

Phytochemistry of *T. foenum graceum*

The phytochemical studies have largely been focused on seeds. The main chemical constituents of seeds are alkaloids approximately 36%, steroidal saponins, mucilage, fibers [105]. Among the alkaloid content of fenugreek seed, Trigonelline is major phytoconstituents which is responsible for most of the activity of the herb. The mucilage (25–30%) is mostly a galactomannan. Steroidal saponins such as diosgenin and yamogenin constitute about 0.1–2.2%. Fenugreekine a sapogenin peptide ester is also present in the seeds. The free amino acids in the seeds are present as 4-hydroxyisoleucine, which is reported to have directly stimulated insulin [94, 106].

Mechanism of action

The mode of action of the herb is through Regeneration of pancreatic β cells and insulin secretion [88, 89]. A study reported the inhibitory role of Trigonelline on the activity of glycogen synthase kinase isoforms in the regulation of glycogen metabolism, to bring about the hypoglycaemic action [106]. Trigonelline has also been found to enhance glucose and lipid hemostasis via the improvement of the insulin signaling pathway [107]. Another possible mode of action of *T. foenum graecum*, are the Inhibition of glucose uptake, GLUT-4 translocation, and improved insulin resistance [108, 109]; Fig. 3.

Antidiabetic effects of *T. foenum graecum*

The pharmacological studies have proven the anti-diabetic potential of various extracts of *T. foenum graecum.* In a study, the ethanolic extract of fenugreek seeds was investigated for anti-diabetic action on streptozotocin-induced diabetic rats. The results demonstrated a significant decrease in serum glucose, total cholesterol, triacylglycerol, while an increase in serum insulin in diabetic rats was observed [110]. Shah et al., studied the hypoglycaemic effect of Trigonelline in alloxan-induced diabetic mice. They reported a reduction in blood glucose level and identified the presence of islet cells in the pancreatic duct suggesting its beneficial effect on β cells [111]. Multiple studies on seed extracts, raw powder, and active constituents by investigators have demonstrated the hypoglycaemic action of the herb, confirming its use as a potent herbal remedy for the management of diabetes.

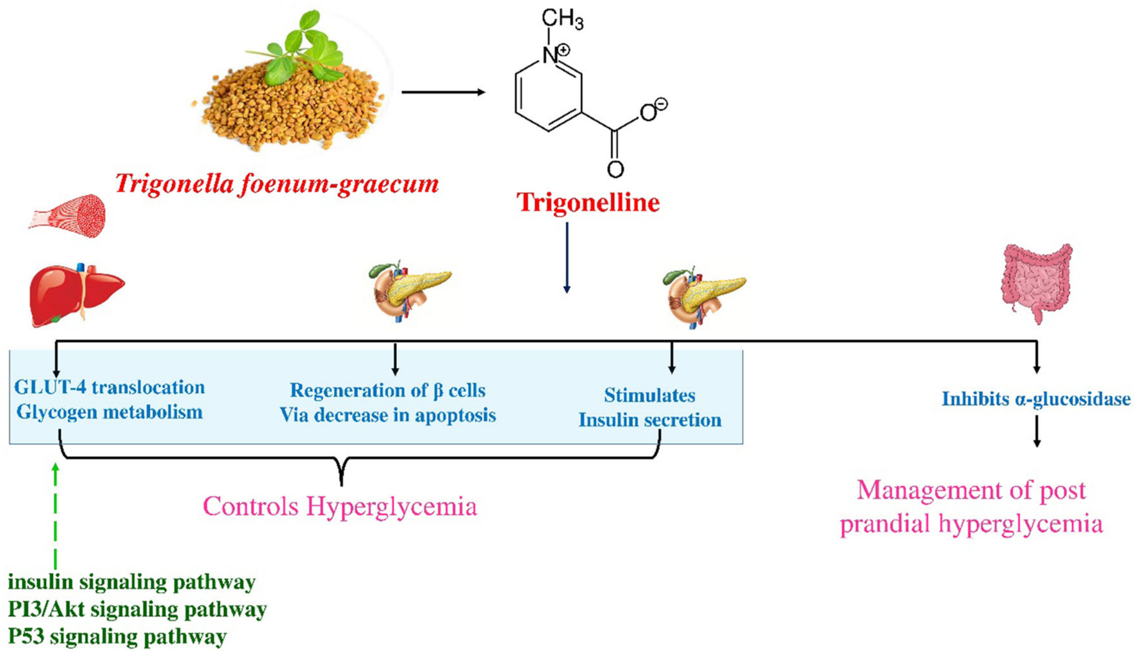

Fig. 3 Schematic representation of Probable molecular mechanism for anti-diabetic effect of *T. foenum-graecum*

Tinospora cordifolia

Tinospora cordifolia (Willd.) Miers, belonging to family Menispermaceae, is a potent herb used to combat diabetes. The herb reported to possess anti-diabetic activity in Ayurvedic literature and is present in many Ayurvedic formulations. The herb is commonly known as Guduchi and is indigenous to the tropical areas of India, Myanmar, and Sri Lanka [94].

Phytochemistry of *T. cordifolia*

T. cordifolia consists of a variety of phytoconstituents belonging to different classes such as alkaloids, glycosides, steroids diterpenoid, sesquiterpenoid, phenolics, proteins, etc. The major active constituents responsible for the anti-diabetic effect belongs to a class of alkaloids; these consist of Berberine, Palmatine, Tembetarine, Magnoflorine, Tinosporin. The other constituents present are Tinocordiside, Tinocordifolioside, Cordioside, Cordifolioside, Tinosporon, Tinosporides, etc. [94, 112].

Mechanism of Action

T. cordifolia is reported to act by a different mechanism of action. The possible mechanism to bring about hypoglycemic action is due to inhibition of α-glucosidase activity and glycolysis. In a study Chougale et al. reported the inhibitory effect of *T. cordifolia* on the α-glucosidase enzyme [86]. Joladarashi et al., proved the Glucose uptake-stimulatory effect of stem extracts of *T. cordifolia* by conducting experiments with Ehrlich ascites tumor cell model. The study reported the ameliorotary effect of *T. cordifolia* on GLUT 1 and GLUT 3 transporters involved in basal glucose uptake; suggesting it as a possible mechanism to exert the hypoglycemic effect [113]. Another study reported the insulin-releasing, insulin-sensitizing, and inhibition of gluconeogenesis as the possible mechanism exhibited by an alkaloidal fraction of *T. cordifolia* [114]; Fig. 4.

Antidiabetic effects of *T. cordifolia*

The stem has been the maximum investigated part of the plant for its anti-diabetic activity. It has been reported that methanol extract of *T. cordifolia* significantly reduces the fasting blood glucose levels in streptozotocin-induced diabetic rats. Improvement in the insulin and C-peptide levels were also reported which indicated the regeneration of β cells in the pancreas [115]. Manikkam et al. isolated a polysaccharide from methanolic extract of *T. cordifolia* stem and demonstrated the β-cell regenerative property of the isolated polysaccharide in streptozotocin-induced diabetic rats suggesting its usage as a potent hypoglycemic agent [116].

Curcuma longa

Curcuma longa Linn, belonging to family Zingiberaceae, is reported as a potent herb in Ayurveda system of medicine to combat diabetes. It is commonly known as Turmeric, Haldi,

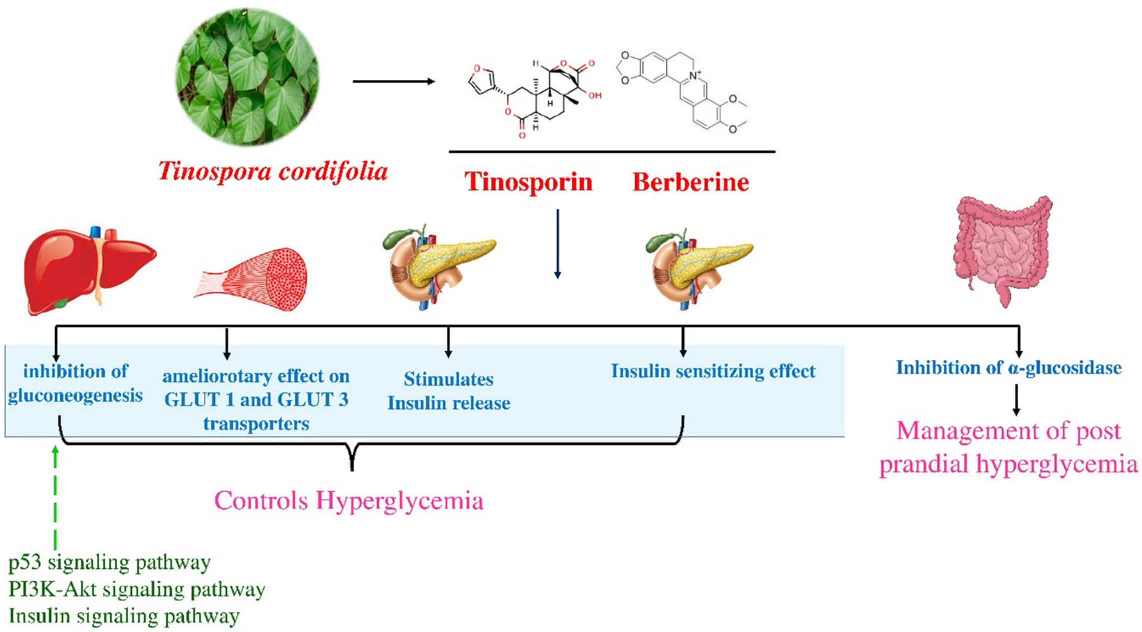

Fig. 4 Schematic representation of Probable molecular mechanism for anti-diabetic effect of *T. cordifolia*

Haridra, etc. The herb is native to India and is widely cultivated particularly in West Bengal, Tamil Nadu, and Maharashtra [94].

Phytochemistry of *C. longa*

The rhizomes of *C. longa* consist of a large number of phenolic compounds. Curcuminoids are the major active constituents present in the rhizomes. Curcuminoids are the mixture of three related compounds namely Curcumin, Demethoxycurcumin, and Bisdemethoxycurcumin among this curcumin constitute about 60% of total curcuminoids. Curcumin is a major active principle responsible for most of the biological activity of *C. longa* [94].

Mechanism of action

C. longa is known to exert the hypoglycemic action via different mechanisms, of which the most common being the inhibition of α-glucosidase and α-amylase enzyme [52, 117,

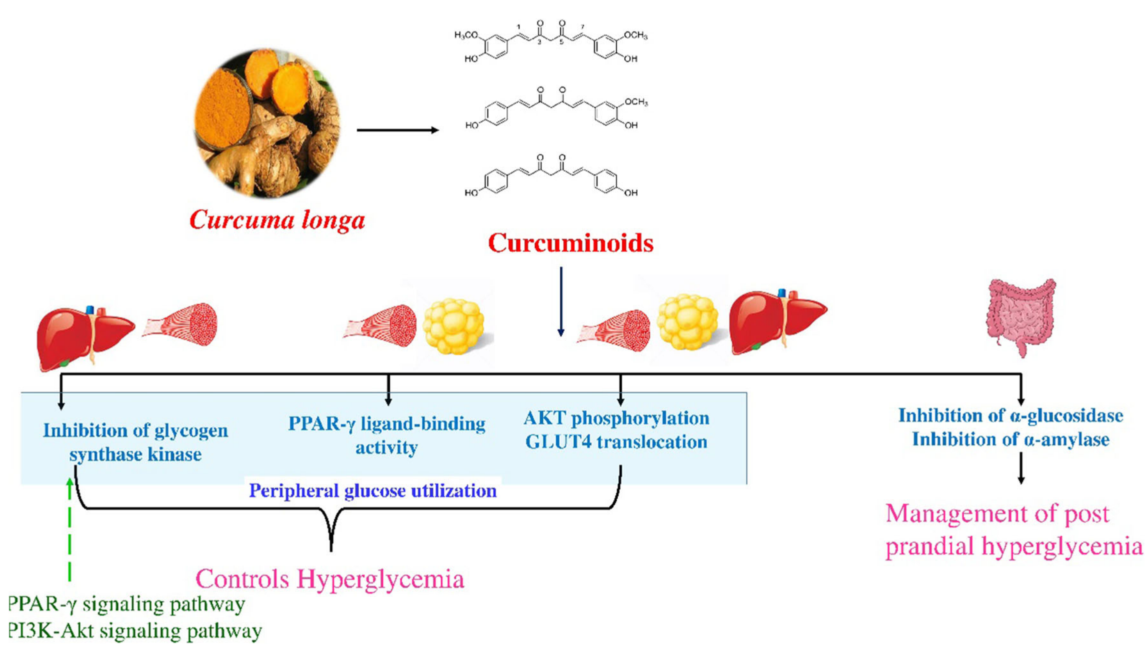

Fig. 5 Schematic representation of Probable molecular mechanism for anti-diabetic effect of *C. longa*

Table 2 Clinical studies on Anti-diabetic efficacy of selected five plants

Author (year)	Plant name	Study	Duration	Dose	Number (Cases/ Control)	Outcome	References
Gaytan Martinez L. et al., (2020)	*G. sylvestre*	RCT Double-blind	12 weeks	600 mg/day (GS capsule)	15/15	↓ 2-h OGTT (p = 0.003) and A1C (p = 0.025), ↑ insulin sensitivity	[122]
Al-Romaiyan A. et al., (2010)	*G. sylvestre*	Cohort study	2 months	1 gm/day (Novel GS extract)	11	↓ blood glucose ↑plasma insulin and C-peptide levels	[123]
Nanda Kumar S. et al., (2010)	*G. sylvestre*	quasi-experimental design	3 months	500 mg/day (GS capsule)	39/19	↓ blood glucose (fasting and post-prandial), and glycated hemoglobin	[124]
Trakoon-osot W. et al., (2013)	*M. charantia*	RCT Double-blind	16 weeks	6 g/day of MC dried-fruit pulp	19/19	↓ A1C from baseline (*p = 0.042*, ↓ of total advanced glycation end products (AGEs) in serum (p = 0.028)	[125]
Fuangchan A. et al., (2011)	*M. charantia*	Multicentric double-blind RCT	4 weeks	G1-500 mg/day, G2-1000 mg/day, G3-2000 mg/day, dry fruit pulp (G4-1000 mg/day metformin)	G1 = 33 G2 = 32 G3 = 31 G4 = 33	↓ fructosamine levels in G3 and G4.	[126]
Lim ST. et al., (2010)	*M. charantia*	RCT double-blind		G1- 60 mg/kg/day G2-80 mg/kg/day G3-100 mg/kg/day G4 = Placebo	G1 = 10 G2 = 10 G3 = 10 G4 = 10	G3 showed a more rapid (15 minutes) stimulation of insulin secretion than placebo	[127]
Najdi RA. et al. (2019)	*T. foenum graecum*	RCT	12 weeks	2 gm/day TGF	6/6	↑ fasting insulin level (P = 0.04).	[128]
Verma N. et al., (2016)	*T. foenum graecum*	Multicentric double-blind RCT	3 month	1000 mg/day Fenfuro (TGF seed extract) capsule	154	↓ fasting plasma, post-prandial blood sugar levels and HbA1c levels. ↑ fasting and post-prandial C-peptide levels.	[129]
Kumar V. et al., (2015)	*T. cordifolia*	RCT	15 days	50 mg/ kg body weight/ day TC stem powder	90	↓ fasting blood sugar	[130]
Roy K. (2015)	*T. cordifolia*	RCT	2 Months	500 mg/day encapsulated stem of TC	29/30	↓ HbA1c levels	[131]
Rahimi HR. et al., (2016)	*C. longa*	RCT Double-blind	3 months	80 mg/day Nano-curcumin (as nano-micelle)	39/41	↓ fasting blood sugar (p = 0.004) ↓ HbA1c levels (p = 0.02)	[132]
Chuengsamarn S. et al. (2012)	*C. longa*	RCT Double-blind	9 months	1500 mg/day curcuminoids capsule	119/116	↓ fasting plasma glucose and HbA1c levels (p = < 0.01), better β cell functions. ↑HOMA-β (p = < 0.01)	[133]
Na LX. et al. (2012)	*C. longa*	RCT Double-blind	3 months	300 mg/day curcuminoids	50/50	↓ fasting blood glucose (p < 0.01), HbA1c (p = 0.031), and insulin resistance index (HOMA-IR) (p < 0.01)	[134]

118]. Gutierres et al.., reported that increased levels of AKT phosphorylation and GLUT4 translocation in skeletal muscles could be the possible mechanism responsible for the antidiabetic activity of curcumin [53]. Kuroda et al., reported that the hypoglycemic effect exerted by curcumin, demethoxycurcumin, bisdemethoxycurcumin, and ar-turmerone is mainly attributed to PPAR-γ ligand-binding activity of the compound [119]. In a molecular docking study Yasser et al., reported that the hypoglycemic effects of curcumin may be due to the Inhibition of glycogen synthase kinase 3β [120]; Fig. 5.

Antidiabetic effect of *C. longa*

Various studies have shown the hypoglycemic activity of rhizomes of *C. longa*. Seo et al. investigated the glucose-lowering potential of curcumin in diabetic db/db mice. A significant decrease in blood glucose and HbA1c levels were observed in animals treated with curcumin. A further study reported the improvement in glucose homeostasis, glucose tolerance, and elevated plasm insulin levels by the administration of curcumin [121]. A study reported the suppression of increased blood glucose levels in Genetically Diabetic KK-A^y Mice by ethanolic extract *of C. longa* [119].

Clinical studies

Clinical trials plays an important role in accessing the safety and efficacy of a particular medication in humans. Based on the literature obtained on the clinical efficacy of the selected five herbs, only recent publications from the year 2010 onwards have been identified from the database search. The details of clinical experiments for the investigation of anti-diabetic effects of the five herbs has been summarized in Table 2.

Conclusion

Diabetes mellitus is the most common endocrine disorder marked by persistent hyperglycaemia resulting from impaired insulin production or insulin resistance. Regardless of all the developments in therapeutics, diabetes still remains a major cause of morbidity and mortality in the world. Allopathic therapies available currently for the treatment of diabetes have a number of serious side effects; consequently, there is a need for investigation of more effective and safer hypoglycaemic agents. Traditional medicine and ethno-botany have an ever-emerging role to play in the treatment and management of diabetes mellitus.

The present review has highlighted the usefulness of the herbal source for the treatment and management of diabetes mellitus. Around 50 herbs known for their usefulness in diabetes have been reviewed and a possible mechanism of the action exerted by them to bring about the anti-diabetic action has been highlighted. Among them, light has been shed upon 5 most potent anti-diabetic herbs with respect to their phytochemistry, underlying mechanism of action, and anti-diabetic effect exerted by them.

From the evidences gathered from literature it is noticeable that the herbs acts by various mechanism to bring about the anti-diabetic effect. As evident from the literature a single herbs displays multiple mechanism of action for example Regeneration of pancreatic β cells, inhibition α-glucosidase enzyme, insulin secretion, PPAR-γ ligand binding activity, etc. this may be due to the presence of a variety of phytoconstituents in a herb. This can in turn bring about the synergistic effects leading to reduction in hyperglycaemic action. As described in the review, most of the reported mechanism of actions exerted by the herbs have been described. In addition to that, more information on *G. sylvestre, M. charantia, T. foenum graecum, T. cordifolia and C. longa* has been provided owing to their extensive utilization by herbal industries for development of anti-diabetic products. By looking at the diverse phytoconstituents, their mechanism of action, and clinical evidences it is clear that these herbs possess anti-diabetic effect.

Based on this comprehensive overview we can conclude that herbal medicines can play a pivotal role in the management and treatment of diabetes with fewer side effects. More investigations mainly focusing on the isolation of phytocompounds from these herbs can lead to the discovery of newer anti-diabetic agents.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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