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Antidiabetic claims of *Tinospora cordifolia* (Willd.) Miers: critical appraisal and role in therapy

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PEER REVIEW

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Comments
Over all, the paper is informative. This is worth to be published as the readers would be benefitted and learn the properties of *T. cordifolia* which is widely used as anti-diabetic medicine.
Details on Page 74

ABSTRACT

Currently, available conventional options for diabetes mellitus have certain limitations of their own, and options from medicinal plants with antihyperglycemic activities are being searched to meet the need. Antidiabetic properties of *Tinospora cordifolia* are highly appreciated in Ayurveda and even in recent modern researches. Several studies on its extracts (*viz.* immune-modulatory, anti-hyperglycemic, antioxidant, adaptogenic, hepatoprotective, hormone regulator *etc.*) and isolated phytoconstituents (like tinosporin, berberine, jatrorrhizine *etc.*) have reported that it is a preventive and curative antidiabetic herb, which are substantiated by clinical trials. Scattered information pertaining to antidiabetic potential of *Tinospora* is reported. Present review encompasses (i) in-depth information of reported antidiabetic activities of the plant in light of available experimental and clinical studies, and (ii) understanding on the possible mechanism of its action in combating the complex pathology of diabetes.

KEYWORDS
Diabetes mellitus, *Guduchi,* Herbal remedies, *Tinospora cordifolia,* Traditional medicine

1. Introduction

Diabetes mellitus is a chronic metabolic disorder caused by defective insulin secretion, resistance to insulin action, or a combination of both[1]. Hyperglycemia, an inevitable consequence of diabetes, is the source of most deleterious effects associated with this disease along with alteration in glucose and lipid metabolism and modification in liver enzyme levels. The treatment goals have evolved significantly over the past decades from preventing imminent mortality, to alleviating symptoms, to normalize glucose levels with the intent of forestalling diabetic complications.

It is the fact that diabetes can't be cured completely as it has never been reported that someone had recovered totally from it. If it is so, then why to opt for the conventional antidiabetic drugs that are either expensive or often related with adverse effects[2]. Ayurvedic herbs provide better alternatives, owing to lesser side-effects and low cost[3]. World Health Organization has also substantiated the utilization of herbal remedies to combat diabetes[4].

Tinospora cordifolia (Willd.) Miers (*T. cordifolia*), commonly known as *Guduchi*, is a highly potent herb used in Ayurveda to combat diabetes and keep the function of various organs in harmony. Various Ayurvedic texts and Nighantu (lexicons/ Ayurvedic materia medica) have described its anti-diabetic usages under various names *viz. Pramehaghna*, *Pramehahara*, *Mehaghna* and *Mehahara*[5-9]. Ayurvedic Pharmacopoeia of India has also cited its antidiabetic utility[10]. Tribals of Korkus (Melghat, Maharashtra, India) have been using the herb for polyuria, diabetes and fever[11]. Various dosage forms of *Guduchi* and wide array of its derived products (active, natural principles and crude extracts) have been mentioned/used in traditional system of medicine and have reported anti-diabetic activity experimentally or clinically in numerous scientific journals. These constituents directly or indirectly affect various metabolic cascades and influence the level of glucose.

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Though plentiful researches were carried out during the past decades, only scattered information exploring its antidiabetic activity is accessible. The present review highlights the reported antidiabetic potential of the plant and to understand its probable mode of its action.

2. Methodology

Published information from several articles, of which few review articles and cross-references were collected. Recent developments in antidiabetic research on *Tinospora*, covering all available records and articles in Pubmed, Scopemed, Dhara online and other allied databases including fields of pharmacology, biomedicine and health were also rationally reviewed and taken into study for the report. The search criteria were restricted to the roles of plant in diabetes and related complications, by probing Ayurvedic claims in light of published experimental and clinical outcomes in this regard.

3. Phytochemical antidiabetic virtues

It has been reported to mediate its anti-diabetic potential through myriad of biologically active phytoconstituents isolated from different parts of plant, including alkaloids, tannins, cardiac glycosides, flavanoids, saponins and steroids[12,13]. These compounds have been reported to encompass different target activities in diabetic conditions, thus enabling the potential application in experimental and clinical research. The isoquinoline alkaloid rich fraction from stem, includes palmatine, jatrorrhizine, and magnoflorine which have been reported for insulin mimicking and insulin releasing effect both *in vitro* (using rat pancreatic β-cell line, RINm5F) and *in vivo*[14]. Another isoquinoline alkaloid 'berberine' has been tested and used successfully in experimental and human diabetes. It lowers elevated glucose level as effectively as metformin. It also inhibits FOXO1, which integrates insulin signaling with mitochondrial function, thus improving hepatic metabolism during insulin resistance and metabolic syndrome. By adenosine monophosphate-activated protein kinase activation, it decreases the blood sugar and cholesterol level and maintains the blood pressure[15-18]. Besides, tinosporin, isocolumbin, palmatine, tinocordiside, cordioside and β-sitosterol compounds present in stem and root which are also reported to possess antidiabetic, antihyperlipidemic and antioxidant properties (Figure 1)[19].

4. Experimental studies

4.1. In vivo studies

Pharmacological studies have proven *in vivo* antidiabetic potential of various extracts of *T. cordifolia* and shown in Table 1[20-48]. Aqueous extract of stem obtained from another species of *Tinospora*-'*Tinospora crispa*' also reported to possess antihyperglycemic effect probably by stimulation of insulin release via modulation of β-cell and Ca^{2+} concentration[49]. Borapetoside C isolated from *Tinospora crispa* (5 mg/kg, *i.p.*) attenuated the elevated plasma glucose in diabetic mice, increased glucose utilization, delayed the development of insulin resistance and then enhanced insulin sensitivity. The activation of insulin-induced IR-Akt-GLUT2 expression in liver and the enhancement of insulin sensitivity may have contributed to the hypoglycemic action of borapetoside C[50].

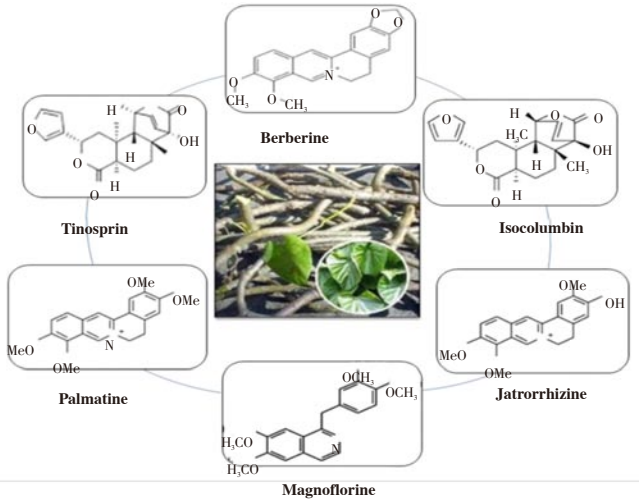

Figure 1. Phytochemical antidiabetic virtues of *T. cordifolia.*

One Ayurvedic polyherbal formulation 'Ilogen-Excel', which contains *T. cordifolia* as one of the constituents, administered at the dose of 50 and 100 mg/kg for 60 d which has shown significant decrease in blood glucose levels and increase in plasma insulin, hepatic glycogen and total hemoglobin. The root extract of plant lowered the levels of glycosylated hemoglobin, plasma thiobarbituric acid reactive substances, hydroperoxides and ceruloplasmin in diabetic rats[51]. A herbomineral formulation 'Hyponidd' is reported for its hypoglycemic potential as well as antioxidant activity and the results are comparable with earlier reports on this plant[52]. Hypoglycemic activity of polyherbal formulation 'Trasina' is reported due to the superoxide dismutase (SOD) activity of pancreatic islet cells in the rats. The formulation induces a dose related decrease in hyperglycemia and augments islet SOD activity[53]. Another polyherbal Ayurvedic formulation of the plant, 'Dihar', showed significant antihyperglycemic, antihyperlipidemic and antioxidant effects in rats. There was a significant decrease in reduced glutathione, SOD, catalase levels and increase in thiobarbituiric acid reactive species levels in the liver[54].

4.2. In vitro studies

In Ehrlich ascites tumor cells model, water, ethanol and methanol extracts of the herb showed glucose uptake-stimulatory activity[55]. The leaf powder sample effectively absorbed glucose and retarded its diffusion across dialysis membrane. The maximal glucose diffusion retardation index was exhibited by it. All these mechanisms might create a concerted function in lowering the rate of glucose absorption so as to decrease postprandial blood glucose concentration[56]. Initiation and restoration of cellular defense anti-oxidant markers including SOD, glutathione peroxidase and glutathione, inhibition of glucose 6-phosphatase and fructose 1, 6-diphosphatase, restoration of glycogen content in liver were reported in *in vitro* studies[39].

Table 1

Antidiabetic pharmacological profile of *T. cordifolia*.

Part	Extract	Drug-induced diabetes (Animal model)	Dosage (mg/kg)	Treatment	Effect	Proposed mechanism/remarks	References
Root	Aqueous	Alloxan-rats	400.0	*p.o.* for 21-120 d	Antihyperglycemic	Effects on key metabolic enzymes involved in carbohydrate metabolism, significant glycemic control in mild and moderate type diabetes	[20]
	Aqueous	Alloxan-rats	-	*p.o.*	Hypoglycemic	Increases in body weight, total hemoglobin and hepatic hexokinase; decreases in hepatic glucose-6-phosphatase, serum acid phosphatase, alkaline phosphatase, and lactate dehydrogenase	[21]
	Aqueous	Alloxan-rats	400.0	-	Hypoglycemic	Its effect equivalent to only 1 IU/kg of insulin	[22]
	Alcoholic	Alloxan-rats	100.0	*p.o.* for 6 weeks	Hypoglycemic	To reduce blood and urine glucose levels and prevent weight loss	[23]
	Aqueous	Alloxan induced diabetic cataract-rats	400.0	*p.o.* for 2 months	Hypoglycemic	Decreases of 38.01% and 40.41% in serum glucose levels after 1 and 2 month treatment, respectively	[24]
	Alcoholic, aqueous	Fasted albino rats	-	-	Hypoglycemic	To reduce fasting blood glucose by initiating endogenous insulin secretion, glucose uptake, inhibition of peripheral glucose release	[25]
	Aqueous	Alloxan-rats	2.5, 5.0	*p.o.* for 6 weeks	Significant hypoglycemic action	Reduction in serum and tissue cholesterol, phospholipids and free fatty acids.	[26]
	Aqueous	Streptozotocin-rats	-	*p.o.* for 6 weeks	Significant antihyperglycemic	Significant reduction in blood and urine glucose	[27]
	Alcoholic	Alloxan-rats	100.0	*p.o.* for 6 weeks	Significant antihyperglycemic,	Normalized the antioxidant status of heart, brain, liver and kidney, restores the antioxidant defence	[28,29]
	Aqueous, alcoholic	Fasting and adrenaline induced hyperglycaemia-rabbits	-	*p.o.*	Hypoglycaemic	Decreases the blood glucose level and increases glucose tolerance	[15]
	Methanol	Aloxan and streptozotocin-rats	150.0	*p.o.*	Significant hypoglycaemic	The extract without showing toxicity in acute toxicity study	[30]
	Hexane, ethyl acetate, methanol	Streptozotocin-rats	250.0	*p.o.* for 100 d	Significant antihyperglycemic	To decrease glycosylated hemoglobin level, reduce glucokinase and increased glucose-6-phosphatase activity, and to improve insulin secretagogue effect, insulin and C-peptide levels which shows β-cells regeneration capacity of extracts	[31]
	Methanol	Normal and alloxan-rats	500.0	*p.o.* for 6 weeks	Significant hypoglycemic	Significant decreases in blood glucose, glycosylated hemoglobin and cholesterol (P<0.05); increases in body weight and protein (P<0.01), hepatic enzyme hexokinase activity increased, glucose-6-phosphatase and significant decrease in fructose 1, 6-biphosphatase	[32]
	Aqueous, alcoholic	Streptozotocin-albino rats	200.0, 400.0	*p.o.* for 30 d	Antihyperglycemic	To modulate renal tissue morphology and ameliorate activity of key gluconeogenic enzymes and to improve renal functions	[33]
	Ethanolic	Fasted albino rats	250.0	*p.o.* for 1 d	Hypoglycemic action	About 30% reduction in blood sugar	[34]
	Aqueous	Adrenaline induced hyperglycaemia in rabbits	10.0	-	Antihyperglycemic effect	To significantly inhibit hyperglycaemia	[35]
Stem	Ethanolic	Alloxan-rats	250.0	Single dose, *p.o.*	Hypoglycemic activity	Significant effect within 1 week	[36]
	Aqueous, alcoholic	Streptozotocin-albino rats	200.0, 400.0	*p.o.* for 30 d	Antihyperglycemic	Act by increasing hepatic glycogen synthase and decreasing glycogen phosphorylase activity	[37]
	Ethyl acetate, dichloromethane, chloroform and hexane extracts	Normal and glucose-loaded Wistar rats	15.0	*p.o.*	Antihyperglycemic	Alpha glucosidase inhibitor, to inhibit the salivary and pancreatic amylase, thus effectively reducing increased postprandial glucose level	[38]
	Isoquinoline alkaloid rich fraction	Normal and glucose-loaded Wistar rats	50.0, 100.0, 200.0	*p.o.*	Antihyperglycemic	Insulin-mimicking and insulin-releasing effect *in vitro* and *in vivo*	[39]
	Hydoalcoholic extraction (70% ethanol, 30% water)	High fat diet fed and streptozotocin-Sprague-Dawley rats	100.0, 200.0	*p.o.* for 14 d	Antihyperglycemic	To mitigate oxidative stress, promote insulin secretion, inhibit gluconeogenesis and glycogenolysis	[40]
	Aqueous	Alloxan induced diabetic rats	500.0	*p.o.* for 40 d	Antihyperglycemic	Significant decreases in blood glucose, glycosylated haemoglobin, urea, cholesterol (P<0.05), and increases in protein and glycogen (P<0.01), extract with nontoxic and well tolerated.	[41]
	Aqueous	High-fructose diet (66% fructose) induced diabetic Wistar rats	400.0	*p.o.* for 60 d	Antihyperglycemic	To prevent rise in glucose levels by 21.3%, insulin by 51.5%, triglycerides by 54.12% and glucose-insulin index by 59.8%; to alleviate insulin resistance and oxidative stress; to improve glucose and lipid metabolism	[42,43]
Leaves	Aqueous, alcoholic, chloroform	Normal and alloxan induced diabetes in rabbits	50.0, 100.0, 200.0	*p.o.* for 1 d	Dose dependent hypoglyce mic	Action similar to glibenclamide and insulin	[44]
	Aqueous extracted saponarin, (alpha-glucosidase inhibitor)	Maltose-fed rats	20.0-80.0	*p.o.*	Hypoglycemic	To show saponarin (apigenin-6-C-glucosyl-7-O-glucoside) with competitive inhibition on activities of alpha-glucosidase and sucrase of different origins	[45]
	Alcoholic and aqueous	Streptozotocin- mice	400.0	*p.o.* for 50 d	Hypoglycemic	Amelioration of diabetic neuropathy and gastropathy	[46]
Whole plant	Aqueous	Streptozotocin-mice	200.0	*p.o.* for 40 d	Hypoglycemic	To reduce plasma glucose concentration by 7.45% through increasing glucose metabolism; to prevent polyuria, rise in urinary albumin levels and renal hypertrophy as well	[47]
	Aqueous	Alloxan-rats and rabbits	400.0	*p.o.*	Hypoglycemic	To regulate glucose metabolism	[48]

5. Beneficial role in diabetic complications and related conditions

5.1. Diabetic retinopathy

Plant extract (250 mg/kg for 24 weeks) in rats reduces blood glucose and inhibits over-expression of angiogenic and inflammatory mediators (angiogenic markers-vascular endothelial growth factor, protein kinase C and anti-inflammatory markers tumor necrosis factor alpha and interleukin-1 beta), which are distinct markers of diabetic retinopathy. Moreover, it also prevents retinal oxidative stress and restores antioxidant enzyme levels and provides evidence for its safety and efficacy in the management of experimental diabetic retinopathy[57].

5.2. Cataract

Root extracts (400 mg/kg) prevented experimental diabetic cataract in rats. Total decrease of 38.01% in serum glucose levels after 1 month and decrease of 40.41% after 2 month of oral treatment were observed[24].

5.3. Diabetic neuropathy and gastropathy

Stem extracts showed amelioration of experimental diabetic neuropathy and gastropathy in rats by oral administration[47]. Aqueous extract of stem prevented hyperalgesia in rats and showed aldose reductase inhibitory activity *in vitro* (with an IC_{50} of 103 μg/mL)[58]. Clinical trials with aldose reductase inhibitor, sorbinil (Pfizer-CP45634) have demonstrated significant improvement in the pain relief, motor and sensory nerve conduction velocities with minimum toxicity in patients with neuropathy. Role of aldose reductase inhibitor in the treatment of symptomatic, somatic and autonomic neuropathies complicating diabetes has been established[59].

5.4. Diabetic nephropathy

Plant extracts (200 mg/kg orally for 40 d) attenuated progression of renal damage and prevented polyuria, rise in urinary albumin levels and renal hypertrophy as well in mice[47]. Consumption of a diet containing *Tinospora* at the 5% level ameliorates changes in kidney chondroitin sulphate/dermatan sulphate in diabetic rats[60]. It was also found effective in modulation of morphology and some gluconeogenic enzymes activity in diabetic rat kidney[33].

5.5. Diabetic ulcers

A randomized controlled study on plant extract as an adjuvant in surgical treatment of diabetic foot ulcers is proved to be highly beneficial in immunomodulation for ulcer healing. Thus, it speeds up the recovery[61].

5.6. Protection against brain, heart, liver and kidney damage in chronic diabetes

The plant exerted neuro-protection by modulating the antioxidant system in rat hippocampal slices subjected to oxygen glucose deprivation. Its strong neuro-protective and free radical scavenging actions may be an effective therapeutic tool against ischemic and glucose deprived brain damage in chronic diabetes[62,63]. Alcoholic root extract has antioxidant defense mechanism in experimental rats. Root extract is reported to normalize the antioxidant status of heart, brain, liver and kidney at a dose of in alloxan-rats and the effect is more prominent than glibenclamide and insulin. Decreased concentrations of glutathione, glutathione peroxidase and SOD, catalase activity are reported in heart and brain of diabetes rats[25,26]. The cardioprotective activity of an herbal formulation "Caps HT2", which contains methanol extract of *Tinospora* as a component, has shown antioxidant, anticoagulant, platelet anti-aggregatory, release of lipoprotein lipase, anti-inflammatory and hypolipidemic activity in rats[64].

5.7. Hyperlipidaemia

Hyperglycemia and hyperlipidaemia coexists in diabetes. Administration of aqueous root extract in diabetic rats for 6 weeks results in a significant reduction of serum and tissue cholesterol, phospholipids and free fatty acids[23,26].

5.8. Weight loss

Aqueous and alcoholic extract of root prevented weight loss and resulted in weight gain in rats[21,23].

5.9. Cardioprotective activity

Ayurveda describes *Hridya* (cardioprotective) properties and its use in *Hridroga* (cardiac disorders)[8,9]. A dose-dependent reduction in infarct size and in serum and heart lipid peroxide levels was observed with treatment of *T. cordifolia* in ischemia-reperfusion-induced myocardial infarction in rats[65]. The stem extract has been normalized alterations in the lipid metabolism caused by diabetes mellitus in streptozotocin-induced diabetic rats indirectly benefiting the heart[66].

5.10. Impotency and genitourinary troubles

Impotency, erectile dysfunction and loss of libido are common complications in diabetes, affecting the person both medically as well as socially. Hydroalcoholic and aqueous extracts of stem (400 mg/kg body weight) showed significant aphrodisiac activity on male Wistar albino rats as evidenced by increase in number of mounts, penile erection index, ejaculatory behavior and mating performance. Stem extracts decreased blood urea concentration in

uremia, weight of ventral prostate, relieved urinary infections and dissolved urinary calculi[67,68]. Benefit in urinary tract infections does not have evidence of direct antibacterial action, but is likely to have a correlation with its anti-inflammatory and immune-modulating activities.

5.11. Diabetic osteoporosis and anti-arthritic

Nowadays osteoporosis and arthritis are also important issues in the milieu of frailty in elder diabetics. Bone loss in tibia slower than that in controls was demonstrated in rats treated with *Tinospora* extracts (10 mg/kg body weight), and showed osteoprotective effect. Serum osteocalcin and cross-laps levels were significantly reduced. This suggests its potential use as an anti-osteoporotic agent[69]. Aqueous extracts exerted a significant anti-inflammatory and analgesic effect on cotton pellet granuloma and formalin induced arthritis models. Its effect was comparable with indomethacin and its mode of action appeared to resemble that of a non-steroidal anti-inflammatory agent, which supports its usage in various painful arthritic conditions[70].

5.12. Gastrointestinal protection in old age

Gastrointestinal troubles are common ailments in old age. Pharmacological evidences support the gastrointestinal protective role of *Tinospora* along with potential efficacy in relieving nonspecific diarrhea, dysentery, peptic ulcer and abdominal pain[71]. These studies can explain traditional claims of symptomatic relief in dyspepsia, belching, bloating, flatulence or stomach pain relating to term '*Ajirna*' or '*Agnimandya*' in Ayurvedic literature[72].

6. Role in gestational diabetes

Gestational diabetes increases the incidences of congenital anomalies, morbidity, and mortality in the mother and her fetus/newborn. In experimental diabetic rats, dietary supplements of the plant during pregnancy attenuated embryopathy and provided significant protection against diabetes-induced maternal and fetal oxidative stress. The plant extract significantly counterbalanced the diabetes-associated oxidative stress in maternal liver by lowering the levels of malondialdehyde and reactive oxygen species (in neutrophil cells) and the increased levels of glutathione and total thiols[73].

7. Clinical evidences

The effect of the aqueous leaf digest (10 g/200 mL water) on post-prandial blood glucose levels in type-2 diabetics was determined. The herb is found to exhibit a significant ability to reduce blood sugar levels in human subjects[74]. Its hypoglycaemic potential was substantiated by a similar response observed in another study, wherein two Ayurvedic dosages form *viz*. *Guduchi Ghana* (solidified aqueous extract) and *Guduchi Satva* (sedimented starchy aqueous extract) which exerted significant hypoglycemic and anti-hyperglycaemic activity along with significant relief in signs and symptoms of type-2 diabetics. Statistically, *Guduchi Ghana* was proved to be more effective than *Guduchi Satva* to control glycemic level[75]. Two or more clinical studies reported on Kwatha (decoction) and Churna (fine powder) of *Guduchi*, also supports its antidiabetic potential[76,77]. Another clinical study has shown that *Guduchi* plays an important role in normalization of altered liver functions (alanine transaminase, aspartate transaminase) and the herb was found to be safe for therapeutic usage (dose: 500 mg/d, duration: 21 d, subjects: healthy individuals); thus via improving the function of hepar, the herb regulates the carbohydrate and lipid metabolism[78].

All these studies corroborate with the results of earlier animal studies and establish its use as a safe anti-diabetic agent in Ayurvedic system of medicine.

8. Contemporary studies to decode the mode of action

Tinospora is a renowned immunomodulator[79,80], adaptogenic[81], antioxidant[82], free radical scavenging[83], hepatoprotective and hormone regulation agent[84], proving it an preventive as well as curative anti-diabetic herb par excellence. Some of its activities via these peripheral mechanisms are detailed as follows.

8.1. Suppression of oxidative stress

Hyperglycemia-induced oxidative stress promotes auto-oxidation of glucose to form free radicals. The generation of free radicals beyond the scavenging abilities of endogenous antioxidant defense may further result in macrovascular and microvascular dysfunctions in the body[85]. Activity of plant in countering oxidative stress is well established[74].

8.2. Immunomodulation to ameliorate diabetes

Owing to the multifaceted immune modulatory potential, *Tinospora* has the ability to impact a plethora of diseases, including diabetes. Diabetes is accompanied by various autoimmune mechanisms, leading to progressive loss of pancreatic islet β cells[86]. During the initial phase of autoimmune destructive process, some viable β cells produce enough insulin. By time, nearly all β cells are destroyed and the patient becomes totally exogenous insulin dependent. *Tinospora* improves immuno response, by which the autoimmune process could be halted or reversed. Thus, several goals can be achieved including deactivation of islet-reactive lymphocytes, correction of inflammatory milieu that injures islets, promoting lymphocytic activation, and restoration of adequate islet mass. Immunomodulatory activity of plant is reported via various mechanisms, such as activation macrophages via Toll-like receptor 6 signaling, nuclear factor kappa-light-chain-enhancer of activated B cells translocation and cytokine production leading to increase in granulocyte-macrophage colony-stimulating factor, which leads to leukocytosis and improves neutrophil function[79,80,86].

8.3. Stress buster

Stress and depression is an common occurrence in old age and it may sometimes unmask diabetes, by causing blood glucose levels to rise[87]. Mental stress can cause the imbalance of hormonal and

nervous regulation and make the susceptible to disorders including diabetes mellitus[88]. The herb is mentioned as a '*Medhya Rasayana*' (memory enhancer) and for '*Bhrama*' (vertigo) in Ayurveda. It is supported by current evidences that *Tinospora* exhibits anti-stress activity by normalization of stress-induced biochemical changes in norepinephrine, dopamine, and 5-hydroxytryptamine in experimental rat models and improves the level of 5-hydroxyindoleacetic acid (a metabolite of 5-hydroxytryptamine) in mice with ethanolic root extracts[89,90]. Depression is characterized by decreased levels of monoamines in brain like norepinephrine, serotonin, and dopamine. The mechanisms of anti-stress and antidepressant activities of *Tinospora* relate to interaction with alpha-1 adrenergic, dopaminergic (D2), serotonergic, and metabotropic transmembrane receptors for gamma-aminobutyric acid leading to increasing levels of norepinephrine, dopamine, serotonin, and gamma-aminobutyric acid. Potentiation of brain monoamines by inhibition of monoamine oxidase is another suggested mechanism proving it as an effective stress buster and restorer to health[91].

8.4. Nutritional supplementation

Along with rich protein and dietary fibre contents, appreciable levels of major and minor elements namely Zn, Mn, Cl, K, Ca, Ti, Cr, Fe, Co, Ni, Cu, Br, and Sr are found in this herb, which act as micronutrients for health restoration and alleviate degenerative processes in diabetes[92,93]. Crude values for food content in *Tinospora* include high fibre (15.19%), sufficient protein (4.5%-11.2%), sufficient carbohydrate (61.66%), and low fat (3.1%). Nutritive value is 292.54 calories per 100 g. It has high potassium (0.845%) (regulatory function of nerve impulses), high chromium (0.006%) (regulation of carbohydrate utilization pathophysiological alterations in diabetes), sufficient iron (0.28%) (to improve haematopoietic functions especially in diabetic nephropathy where erythropoietin release from kidney is compromised), and sufficient calcium (0.131%) (regulatory functions in nervous, cardiovascular, and musculoskeletal systems)[94].

8.5. Raising life quality of diabetics

The rejuvenating approach by its aforesaid properties might be linked to achieve better quality of life with increased life span in diabetics. Type 2 diabetes more typically develops with increasing age[95]. Senile dementia involves deteriorating effect on brain cells which reduces the life quality of diabetics. The usefulness of plant extracts as a cognitive enhancer is substantiated by its potent *in vitro* acetylcholinesterase inhibitory activity[96]. Its role in preventing oxidative stress associated with infections was suggested with reference to catalase, glutathione-s-transferase, glutathione peroxidase, glutathione reductase, SOD, and polyphenoloxidase[97]. Beside aforesaid activities, *Tinospora* also acts as hematinic, rejuvenator and tonic, which justify its beneficial role in general debility, fatigue, old age.

9. Clinically desirable drug interactions

Although *Tinospora* is less likely to have drawbacks of the conventional drugs used for diabetes, the concepts of herb-drug interactions should also be kept in mind. No negative herb-drug interaction is reported till date, but more studies in this area remain yet to be accomplished. Concurrent administration of *Tinospora* with metformin showed beneficial pharmacokinetic as well as pharmacodynamic interaction leading to enhancing antihyperglycemic and antihyperlipidemic activities[98]. Plant alkaloid berberine has been shown to boost the effects of metformin and 2,4-thiazolidinedione, and can partly replace the commercial drugs, which could lead to a reduction in toxicity and side effects of the latter[99]. In Ayurveda, decoction of *Tinospora* stem is used as a medium of '*Shodhana*' process (relates to combining a substance with another substance to enhance its activity and to help counter some of its unwanted effects) to purify *Guggul* (*Commiphora wightii*), which is an vital component of various Ayurvedic antidiabetic formulations. *Tinospora* enhanced the activity of *Guggul*. When used alone, the effect of *Guggul* significantly decreased. Use of *Tinospora* combinations has a potential basis for clinically desirable drug interactions[71,100,101].

10. Toxicity and safety concerns

Although extensive works have been conducted on this herb, no conspicuous information on toxicity is available so far[102]. The herb is considered to be safe in dosage mentioned[103].

11. Discussion

Recent antidiabetic studies on *Tinospora* are consistent with its ancient and traditional use in diabetes. Current review outlined various pharmacological and clinical evidences which indicated that it had mild to moderate, but significant, blood glucose lowering effect. The long-term use of its various extracts and dosage forms may be advantageous over chemical drugs in alleviating some of the chronic manifestations and complications caused by diabetes. Additionally, its use in conjunction with conventional drug treatments, such as a chemical agent or insulin, permits the use of lower doses of drug and/or decreased frequency of administration which decreases the side effects most commonly observed.

In nutshell, *Tinospora* not only maintains glycemic control like those conventional drugs but possesses multiple target actions obliterating the complex diabetic pathology and remote apparent metabolic complications. Multiple sites of action of the plant were reported, such as liver, fat, pancreatic β cells, intestinal mucosa-L cells, muscle *etc*. It possesses multiple beneficial activities via several extrapancreatic (primarily) and intrapancreatic mechanisms attributed to improving the pathological status of diabetics. Its extrapancreatic activities such as glycogenesis/inhibited glycogenolysis in liver, improving glucose uptake and utilization, inhibiting gluconeogenesis, inhibiting intestinal glucose absorption, inhibiting α-glucoside and α-amylase, mitigating oxidative stress, antioxidant properties and protection against tissue damage, seem to contribute profoundly to diabetes. The intrapancreatic actions involve preventing and restoring integrity and functioning of β cells, promoting endogenous insulin secretion/insulinotropic action and reduction of insulin resistance. Earlier studies reveal activities of its extracts in preventing, treatment or postponing the secondary diabetic complications. Thus, it works on all preventive, curative and restorative aspects of management, inevitably needed to counter diabetes. None of conventional synthetic drugs can provide all aforesaid beneficial properties. Present review warrants more investigation into the composition, isolation, purification, and characterization of bioactive products (active, natural principles, and crude extracts) to present in it for

identification of hypoglycaemic principles and to elucidate the biological roles of other herbs in this regard.

Since the plant showed beneficial pharmacokinetic and pharmacodynamic interaction with synthetic antidiabetic drugs. The dose and frequency of diabetes medication might need to be changed/trim down, as its administration along with diabetes medications might cause blood sugar to go too low. Blood sugar should be monitored closely. *Tinospora* in combination with other agents in Ayurvedic formulations has '*Shodhana*' process (mentioned earlier) and supportive evidence from a modern pharmacological study[71,101]. Exploring the possibility of specific additive or synergistic effects of *Tinospora* with other substances and the pharmacokinetic and pharmacodynamics of such combinations will help to establish rationale behind combination formulations of *Tinospora*.

Although evidence from animals and humans consistently supports the anti-diabetic claims of *Tinospora* in Ayurvedic literature, multi-centric large scale clinical trials would be more confirmatory, especially for in depth cause-effect evaluations, routing the mechanism of action and to evaluate the safety and interaction with conventional drugs when both are administered simultaneously. None of adverse reactions in the plant is found so far. Thus, it was been proved as a safe tool to manage diabetes.

12. Perspectives and future directions

Tinospora must be thoroughly investigated in clinically manifested hyperglycaemia in the wake of ethnomedicinal antidiabetic usages. Studies on true dose response relationship of the action of the plant remain to be established. A consorted management approach by bridging *Tinospora* and synthetic drugs would be highly desirable, which will not only ensure good glycemic control when supported by suitable diet and life style regimen mentioned for diabetes, but also will aid to delay its complications. It can also be used as a supportive drug with other synthetic drugs as an adjuvant, to enhance their activity and to alleviate their possible side effects.

Future trials with similar antidiabetic herbs should be encouraged, and better identification criteria to screen the potential candidates for antidiabetic treatment should be established. It is a general belief that a synergism between two or more plant extracts enhances the physiological potential of bio-organic substances. A combination of different plant extracts is often preferred over single extract. Therefore, its extracts can be combined with other highly potent antidiabetic herbs such as *Trigonella foenum graecum, Emblica officinalis, Momordica charantia etc*. More *in vivo* and *in vitro* investigations should be encouraged in order to validate the antidiabetic activity of the identified plants claimed by the traditional healers and ancient literatures. Present review strongly emphasizes the optional and rational uses of traditional herbal medicines in this regard.

To our surprise, an integrated approach towards understanding the probable mode of action and elucidating mechanistic aspects of the herb is lacking. Without routing mechanism of action, it will be difficult for modern medicine to accept herbal formulations in mainstream therapeutics. Therefore, approaches for studying the effect of herbs should include the whole system, and mechanistic studies elucidating the multiple pharmaco-dynamic targets.

13. Conclusion

Present review spotlights the classical antidiabetic claims of *Tinospora* and their validation by contemporary researches. Evidences from reported studies suggest its multi-faceted effects to prevent, reverse, or even delay the sequences of diabetes pathology via many overlapping extrapancreatic (primarily) and intrapancreatic mechanism of actions. Few tranditional and available management options are expensive and often associated with negative side effects. Therefore, *Tinospora* and analogous potent herbs provides better alternatives which have usually less toxic and affordable. This review can be used for further research as well as clinical purpose.

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Conflict of interest statement

We declare that we have no conflict of interest.

Comments

Background

Diabetes mellitus is the most common endocrine disorder of the world and one of the major risk factors for cardiovascular disease. Around 300 million population across the globe is expected to suffer from diabetes by the year 2025. Several anti-diabetic drugs are already in market which proves to be beneficial to these patients, but with the recent trends of over use of hypoglycemic drugs, the chances of resistance and complications arise. Moreover, the drugs dosage needs to be increased in patients due to its sensitivity and effectiveness in a long term use of one type of drug. So people are now switching to Ayurvedic and herbal medicines which have fewer side effects and are also cost effective with minimal contraindications. The current study is designed to evaluate the anti-diabetic properties of *T. cordifolia* which is quite promising reaseach studies conducted on its extracts (*viz*. immune modulatory, anti-hyperglycemic, antioxidant, adaptogenic, hepatoprotective, hormone regulator) and its phytoconstituents (like tinosporin, berberine, jatrorrhizine *etc*.) proving it as a preventive as well as curative anti-diabetic herb, which are substantiated by clinical trials.

Research frontiers

This is a review article, so no question of cutting edge research. It

is a combination of findings from research studies putting together in this paper.

Related reports

Anti-diabetic properties of *T. cordifolia* have been documented since 2003. It is a review article written well by comprising of all the facts of *T. cordifolia.*

Applications

It is obvious that the extract of *T. cordifolia* can be used in several complications including diabetes.

Peer review

Over all, the paper is informative. This is worth to be published as the readers would be benefitted and learn the properties of *T. cordifolia* which is widely used as anti-diabetic medicine.

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