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THERAPEUTIC AND SAFETY ASPECTS OF AMRITA (TINOSPORA CORDIFOLIA LINN.) IN DIABETES MELLITUS

Medha Lakkawar[1], Anand More[2], Shalini Rai[3], Sandeep Tiwari[4]

[1]PG Scholar, [2]HOD and Professor, [3]Assistant Professor, [4]Assocciate Professor, Roga Nidana Evum Vikriti Vigyana Department, All India Institute of Ayurveda, New Delhi. India

Corresponding Author: lakkawarmedha@gmail.com

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ABSTRACT

Tinospora cardifolia Linn. is a well-known medicinal plant used to treat a variety of ailments in traditional medicine. The common names are *Amrita*, *Guduchi* and it belongs to the Menispermaceae family. Chemical contents of *T. cordifolia* include alkaloids, diterpenoid lactones, steroids, glycosides aliphatic chemicals, and polysaccharides. Diabetes mellitus is a metabolic condition marked by a loss of glucose homeostasis caused by abnormalities in insulin production, insulin action, or both, resulting in impaired glucose metabolism and other energy-producing fuels such as lipids and protein. Diabetes is a collection of disorders with long-term consequences that damage the eyes, kidneys, heart, and skin, notably the blood vessels and nerves. **Aim**: The aim of the present review was to explore and document the therapeutic hypoglycemic, antidiabetic activity, and safety of the *Tinospora cordifolia* Linn. plant. Based on current discoveries, this paper provides an overview of the active components and biological functions of *T. cordifolia* in diabetes management. **Material and Method**: A systematic search approach through an electronic database was used to gather articles on the therapeutic antidiabetic effect and safety of *Tinospora cordifolia* (TC). **Observation and Result:** The anti-diabetic benefits of *Amrita* (TC) are due to biologically active phytoconstituents isolated from various parts of the plant, such as alkaloids, tannins, cardiac glycosides, flavonoids, saponins, and steroids. The plant is attributed with Extrapancreatic activity through inhibition of gluconeogenesis & glycogenolysis, mitigation of oxidative stress; and intrapancreatic activity by promoting insulin secretion and improving the pathological status of diabetics. *Tikta, Kashaya rasa, Ush-*

na virya, Kledashoshaka, and *Agnideepana* properties of *Guduchi* increase *Dhatwagni* leading to the removal of *Bahu drava shleshmata and Kleda* from *dhatus* which ultimately breaks the pathogenesis of *Prameha* (Diabetes mellitus). **Conclusion:** *Tinospora cordifolia* is a therapeutically effective and safe drug that can prevent, cure, reverse or even delay the progression of diabetic pathology.

Keywords: Amrita, Ayurveda, Diabetic Mellitus, Hypoglycemia, Review, Safety, *Tinospora cordifolia* Linn.

INTRODUCTION

Tinospora cordifolia Linn. commonly known as *Guduchi* or *Giloya* belonging to the family Menispermaceae, is a large, deciduous, climbing shrub found throughout India. Alkaloids, diterpenoid lactones, steroids, glycosides aliphatic compounds, polysaccharides are the chemical constituents from different parts of *T. cordifolia*. In ancient Indian literature, Ayurveda *Guduchi* is a widely used medicine for its general tonic, antispasmodic, anti-inflammatory, antiarthritic, anti-allergic, and anti-diabetic properties.[1] Also, Guduchi improves the immune system and the body's resistance to infections and is reported as a rejuvenating drug.[2] Many of the pre-clinical and clinical studies reported its antihyperlipidemic, antiglycemic, antioxidant, antitoxic, anticancer, immunomodulatory action, etc. *T. cordifolia* has been listed amongst 29 highly prioritized medicinal plants of agro-climatic zone 8 (Rajasthan, U.P., and M.P.) of India as identified by the National Medicinal Plant Board, New Delhi, Government of India. This plant has also been listed among 178 medicinal plant species in high Volume Trade by NMPB, New Delhi, India.[3] Diabetes mellitus is a metabolic syndrome, initially characterized by a loss of glucose homeostasis resulting from defects in insulin secretion, insulin action, or both resulting in impaired glucose metabolism and other energy-yielding fuels such as lipids and protein.[4] With the progression, the chronicity of the disease is associated with several complications like a cardiovascular, renal, neurological, ocular, failure of different organs.[5] In contemporary science, different oral hypoglycaemic drugs are available with insulin but, long-term use of these can cause severe complications in the future. *T. cordifolia* is a potent drug in Ayurveda used to combat diabetes. Its anti-diabetic property is explained by the name *Pramehaghna, Pramehahara, Mehaghna,* and *Mehahara.*[6,7,8,9,10] Its anti-diabetic properties have also been mentioned by the Indian Ayurvedic Pharmacopoeia.[11] The present review encompasses the therapeutic anti-hyperglycemic action and safety aspect of *T. cordifolia* in light of available pre-clinical and clinical studies.

Material and Method:

- **Search criteria:**

Articles on hypoglycaemic action and safety aspects of *T. cordifolia* were collected using a stepwise search process through an electronic database of PubMed, Google Scholar, Science Direct, Springer, and net surfing using the keywords 'Management', 'Diabetics, 'Amrita', 'Guduchi', '*Tinospora cordifolia'*, 'Treatment', 'Hypoglycaemia', 'Antihyperglycemic, 'Preclinical, 'clinical trial', 'Original research articles,' 'Safety' and their different combination and permutations.

- **Selection of Article:**

Open access, full-length article published in English focusing on intervention studies i.e., original research articles, clinical trials, and review articles of Ayurveda without any custom range of publications were included in the study. A total of 12 articles full filling the above criteria were selected for review.

Observations and Results:

The whole matter retrieved from above is presented in the four-sub heading as below -

A. Therapeutic efficacy in relation to DM

T. cordifolia has been shown to have hypoglycemic, antidiabetic, and hypolipidemic efficacy in preclinical studies, each with a different mode of action. *T. cordifolia* has only been studied in one clinical trial on diabetics and it demonstrated a modest hypoglycemic and hypolipidemic impact.

- **Preclinical studies:**

The detail of preclinical studies along with animal model, dosage form, extract, result, and activity are depicted in table 1.

- **Clinical study:**

In the accessible sources, only one therapeutic clinical trial was documented. In this trial, *T. cordifolia* stem powder was administered in 30 diagnosed cases of type 2 diabetes at a dose of 50mg/kg/day. The results demonstrated a significant reduction in blood sugar levels ($p<0.01$), though these remained slightly raised in some patients. Total cholesterol, VLDL cholesterol, triglyceride showed a significant reduction trend while HbA-1c and LDL cholesterol showed a non-significant declining trend. HDL cholesterol showed a very mild increasing trend.[24] It suggests that long-term intervention may yield superior effects.

B. Safety aspects of *Tinospora cordifolia*:

T. cordifolia's biosafety and "disease-modifying effectiveness" have been demonstrated in several preclinical and clinical studies. Extract of *T. cordifolia* has shown clinical efficacy in patients with liver diseases associated with ethanol intake. Data showed that *T. cordifolia* increased the retaining capacity of the liver and therefore, decreased the excretion of pyridoxine and niacin, which was due to liver regeneration and reduced oxidative burden. The antioxidant activity of *T. cordifolia* decreased urinary lipoamide levels and maintain the cell redox state.[25] One Ayurvedic polyherbal formulation 'Ilogen-Excel', which contains T. cordifolia as one of the constituents, is administered at the dose of 50 and 100 mg/kg for 60 days in Albino Wistar rats showed a significant decrease in blood glucose levels by increasing plasma insulin levels.[26]

- **Doses:**

T. cordifolia is documented to be safe at a dose of 500mg per day for a period of 21 days in healthy volunteers without any adverse change in haematological and biochemical investigations.[27] In examining the efficacy of *T. cordifolia* in allergic rhinitis, 300 mg of an aqueous extract was given 3 times daily for 8 weeks gave significant results.[28] Similar dosing of standardised aqueous Tinospora stem extract in the dose of 300 mg given three times daily (total dose of 900mg/day)was also adopted in HIV patients for six months.[29]

- **Toxicity:**

Nagral et al. recently presented a case series including six individuals who developed drug-induced liver injury (DILI) after consuming *T. cordifolia* in the form of boiled extracts, tablets, and syrup.[30] However, the aqueous extract of *T. cordifolia* has been reported to be nontoxic up to an oral dose of 2000 mg/kg in an acute toxicity evaluation in Wistar rats which is 10 times higher than the intended human therapeutic dose.[31]

- ***Caution over the look-alike of T.cordifolia reported with toxic adverse events - Tinospora crispa:***

Tinospora crispa (L.) Hook. f. & Thomson and *T. cordifolia both are from the* Menispermaceae family. *Tinospora crispa* gets mistakenly used instead of *T. cordifolia* due to similar leaves and appearance. A study reported *Tinospora crispa* with significant hypoglycaemic action by stimulating the secretion of insulin from β-cells.[32] However, a growing number of reports indicate that *Tinospora crispa* (TCP) can cause hepatotoxicity.[33,34]

C. Herb-Drug, Herb-Food interaction with-*Guduchi* (TC) in regard to Diabetes Mellitus:

The in-vivo pharmacokinetic and in-silico study demonstrated that oral co-administration of 100mg/kg hydroalcoholic extract of T. cordifolia and 20mg/kg Glimeperide in Wistar rats did not show any herb-drug interaction.[35] Another study also reported an increase in bioavailability of the hypoglycemic drug Glibenclamide when co-administered with *T. cordifolia*.[36] *T. cordifolia*-infused foods improve the storage stability and functionality of food without causing any negative interactions.[37,38]

D. The application of *T. cordifolia* to prevent and delay the onset of DM and its complications:

Administration of *T. cordifolia* prevents the rise in glucose level, insulin, triglycerides, and glucose-insulin index in the fructose-fed rats.[39] *T. cordifolia* has the potential to prevent diabetic retinopathy's

vascular problems, as well as limit the progression of cataracts and retinal vascular alterations.[40] Also, long-term usage of its various extracts and dosage forms may not create any side effects, instead, it helps to ease some diabetes consequences and complications.[41]

DISCUSSION

According to the current review, it is observed that *T. cordifolia* has a slight to moderate considerable blood glucose reducing impact. It has been reported that biologically active phytoconstituents are isolated from various portions of the plant, such as alkaloids, tannins, cardiac glycosides, flavonoids, saponins, and steroids, are responsible for its anti-diabetic properties.[42] These compounds act by their different target mechanism in diabetic conditions. Palmatine, jatrorrhizine, and magnoflorine are isoquinoline alkaloid-rich fractions from the stem that have been reported for insulin mimicking and insulin-releasing effects both in vitro (using rat pancreatic-cell line, RINm5F) and in vivo.[43] 'Berberine,' an isoquinoline alkaloid, decreases increased glucose levels as effectively as metformin by enhancing hepatic metabolism during insulin resistance, lowering blood sugar and cholesterol levels while maintaining blood pressure.[44] Tinosporin, isocolumbin, palmatine, tinocordiside, cordioside, and β-sitosterol are the compounds present in stem and root which are also reported to possess antidiabetic, antihyperlipidemic, and antioxidant properties.[45] The activity of the plant has been recorded in a variety of places, including the liver, fat, pancreatic cells, intestinal mucosa-L cells, muscle, and more. Extrapancreatic (mainly) and intrapancreatic processes are credited by the plant for treating diabetics' pathological status. [Graphic1]. Its extra pancreatic activities, such as liver glycogenesis/inhibited glycogenolysis, improved glucose uptake and utilization, inhibiting gluconeogenesis, inhibiting intestinal glucose absorption, inhibiting α-glucoside and α-amylase, mitigating oxidative stress, antioxidant properties, and tissue damage protection, appear to play a significant role in diabetes. Intrapancreatic activities include preventing and repairing cell integrity and functioning of β cells, encouraging endogenous insulin secretion/insulinotropic action, and lowering insulin resistance. *Guduchi* is a *vyadhipratyanikdravya* (a specific drug against the disease) drug for *Prameha* due to its *Pramehaghna* properties. In *Prameha* there is *Kapha* dosha predominance with *Meda dhatu* vitiation (*Bahuabadha Meda*). In the pathogenesis of *Prameha, Drava guna of Shleshma* (*Bahu drava shleshma*)[46] get increases which get pacify by *Tikta rasa* (bitter taste) and *Ushna virya* (hot potency) of *T. cordifolia*. *Kledashoshaka Tikta* and *Kashaya* (astringent taste) *rasa* and *Agnideepana* property of *Guduchi*, increase *Dhatwagni* of *Rasa, Rakt, Mansa, Meda dhatu*, thus eliminating excessive accumulated *Kleda* from *dhatus*. *Kledashoshana* property corrects the looseness of vitiated *Medo dhatu*. *Guduchi kwath* is described by *Sushruta* as a way to turn an incurable (*Asadhya*) diabetic into a controllable (*Yapya*) diabetic.[47] Coupled with the documented benefits of *T. cordifolia* in delaying the onset of DM, possibly preventing the disease, and also in delaying the vascular complications of DM, it is hypothesized that this plant can be employed as adjuvant therapy in the prevention of chronic disorders observed in DM, which are characterized by hyperglycaemia, hyperinsulinemia, etc. Very few studies were conducted to check the safety and therapeutic dose of *T. cordifolia* all of which have yielded positive results with no side effects. The classical dose of *T. cordifolia* is 3-6 grams in powder form and 50-100 ml in decoction form[48], although there has only been one research in humans using only 500 mg *T. cordifolia* without any harmful effects. The other two studies on HIV patients and allergic rhinitis have though used the dosage of 900gm/day in three divided doses, although the HIV study used it for 6 months duration, no adverse events have been reported in the study, which also documents its benefits. The study by Nagral et al. revealed significant knowledge gaps in drug-induced liver damage. He did not update on any additional medication taken by the patients or their liver function status before the patients started taking *T. cordifolia*. Similarly, the details of *T. cordifolia* in the commercially obtained syrup and tablet

were also not provided. It's difficult to link the *T. cordifolia* medication used by the case study patients to the observed hepatotoxicity due to the absence of strong causation between the two. With the documented benefits of *T. cordifolia* on other systems of the body as, it is quite probable that *T. cordifolia* can have a very significant role as a quaternary prevention strategy for preventing or delaying the onset of DM, as well as for better management and further prevention or delay in the onset of complications of DM. [Graphic 2] The studies on herb-drug interactions also report beneficial responses to coadministration of *T. cordifolia* with conventional treatment, which points toward the need for conduction of large-scale integrative RCTs on the same issue, in the scientific interest and benefits of patients.

CONCLUSION

Evidence from published trials suggests that T. cordifolia has several overlapping extra pancreatic (mainly) and intrapancreatic mechanisms of action that can prevent, cure, reverse or even delay the progression of diabetic pathology. In order to identify hypoglycaemic principles and comprehend the biological roles with safe and therapeutic doses, more study into the composition, isolation, purification, and characterization of bioactive products (active, natural principles, and crude extracts) is needed.

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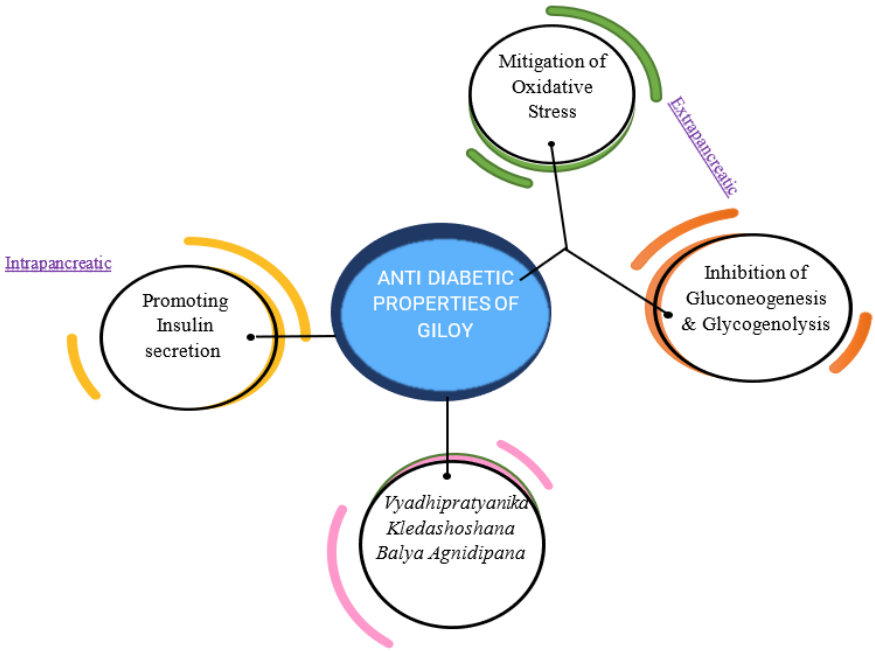
Table 1: Preclinical study

Reference	Animal model	Part used	Extract and Dose	Result and Activity
1[12]	Adult albino rats (Alloxan and Streptozotocin induced)	Stem	Methanolic extract Dose-150 mg/Kg	Antihyperglycemic action by enhancing the secretion of insulin or enhancing the transport of blood glucose to peripheral tissue.
2[13]	Adult Wister rats of both sexes	Stem	Ethanolic extract Dose-100mg/kg/day and 200 mg/kg/day	Both the doses exhibited a significant change in blood sugar levels- Antihyperglycemic action Significant ($p < 0.05$) reduction of the level of total cholesterol, triglycerides, LDLC, and VLDLC of diabetic rats and a significant increase in the level of HDL-C.
3[14]	The Wistar rat (Streptozotocin induced)	Stem	Aqueous extract Dose- 100 and 200 mg/kg	Significant reduction in serum glucose level by enhancing the Insulin level-Antihyperglycemic outcome
4[15]	Rats (Streptozotocin)	stem	Hexane, ethyl acetate, methanol Dose-250 mg/kg	Significant antihyperglycemic action by decreasing glycosylated hemoglobin level, reducing glucokinase and increasing glucose-6-phosphatase activity, improving insulin secretagogue effect, insulin and C-peptide levels show P-cells regeneration capacity of extracts.
5[16]	Rats (Normal and alloxan)	stem	Methanol Dose-500 mg/kg	Hypoglycemic result by 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 a significant decrease in fructose 1, 6-biphosphatase
6[17]	Wistar rats (Normal and glucose)	stem	Ethyl acetate, dichloromethane, chloroform and hexane extracts Dose-15mg/ml	Alpha-glucosidase inhibitor inhibits the salivary and pancreatic amylase, thus effectively reducing increased postprandial glucose level and showing a significant antihyperglycemic effect.
7[18]	Fed rats (Maltose)	leaves	Aqueous extracted saponarin, (alpha-glucosidase inhibitor) Dose-20.0-80.0 mg/kg	Saponarin (apigenin-6-C-glucosyl-7-O-glucoside) present in leaf inhibits activities of alpha-glucosidase and sucrase and result in hypoglycemic action.
8[19]	Swiss albino mice	Stem	Phosphate buffer, hexane, dichloromethane (DCM), chloroform Dose-520 mg/kg, orally.	In-vitro study- Hypoglycemic activity is reported by inhibiting α-amylase, α-glucosidase In-vivo study- Hypoglycemic activity is testified by improving the entry of glucose into the peripheral tissues, Decreases the activity of phosphorylase in the liver, thereby it may prevent the release of glucose into the blood.
9[20]	Albino Wistar rats	stem	Aqueous Dose-200mg/kg	Antihypertensive and antihyperlipidemic activity is testified. The mode of action of the drug is on extrapancreatic pathways rather than stimulating insulin secretion. Drug stimulate peripheral glucose utilization, retarding gluconeogenesis or decreasing the intestinal absorption of glucose. Ameliorated the degenerative changes in islets brought out by the T. cordifolia, indicating its capacity to regenerate the damaged cells. Significant increase in serum HDL-C level and reduction in total cholesterol and LDL.
10[21]	Albino rats	Stem	Aqueous and alcoholic extracts	Significant hypoglycemic effect was testified by increasing hepatic glycogen synthase and decreased glycogen phosphorylase activity. Not by the increase in serum insulin levels or regeneration of pancreatic β cells.
11[22]	Albino mice	Stem	Alcoholic extract	Significant decrease in glucose level The level of Urea, uric acid and creatinine was also restored to the greater extent.
12[23]	Wistar albino rats	Stem	Methanol	Significantly ($P < 0.01$) decreased the blood glucose level Significantly ($P < 0.01$) improved the body weight and protein levels Significantly ($P<0.01$) elevation in glycosylated hemoglobin due to improved glycemic control

Graphic 1: The Antidiabetic mechanism of action of T. cordifolia:



Graphic 2: The action of *T. cordifolia* on Diabetic complications