

Role of *Tinospora cordifolia* in metabolic health disorders: An updated review

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REVIEW ARTICLE

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ABSTRACT

The use of various herbal drugs in India has been widely developed in recent years. Guduchi (*Tinospora cordifolia*) belonging to family Menispermaceae has a tremendous amount of bioactive principles in exploring nutraceuticals from natural source. *T. cordifolia* is considered as an important herbal drug of traditional system of Indian Medicines. The herb is also well known for its therapeutic efficacy in treatment of various diseases viz. dyspepsia, diabetes, fever, urinary problems, jaundice, chronic diarrhoea, cardiac disease, dysentery, helmenthiasis, skin diseases, leprosy, thyroid and various metabolic diseases. Present review highlights the antidiabetic, hypolipidemic activity of Guduchi and their validation through existing literature, experimental studies. The plant is reported to have various alkaloids, glycosides, steroids and terpenoids. The current study is undertaken to explore and review its role on metabolic disorders.

Keywords: *Tinospora cordifolia*, Guduchi, metabolic disorder, antidiabetic, hypolipidemic

1. Introduction

The global population is facing a surge in metabolic and lifestyle disorders, and the contemporary system of medicine is having limited efficacy to manage these disorders in effective and safe manner. (1-3) Metabolism is the breaking down of food to its simpler components: proteins, carbohydrates (or sugars), and fats. Metabolic disorders occur when these normal processes become disrupted. Disorders in metabolism can be inherited, in which case they are also known as inborn errors of metabolism, or they may be acquired during your lifetime. (4) Type 2 Diabetes Mellitus (T2DM) is a cluster of abnormal metabolic paradigms with the essential feature of hyperglycaemia and is dubbed as the disease of “premature ageing”. Incidence of T2DM is rising all over the world at worrying rate, despite, comprehensive and coordinated effects of World Health Organization (WHO), International Diabetes Federation and Several Social Science Agencies. (5) 6.6 % of the world population was affected by this disease in 2010 with an estimated 285 million carriers and the number may become almost double

(552 million) by 2030. India is facing an even grimmer scenario. On the basis of affected population, both in terms of percentage and numbers India has significantly more patients than China and other neighbouring countries and is often referred to as the diabetic capital of the world. (6)

Metabolic syndrome is a cluster of conditions that occur together, increasing your risk of heart disease, stroke and type 2 diabetes. These conditions include increased blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels. Metabolic syndrome is closely linked to overweight or obesity and inactivity. It's also linked to a condition called insulin resistance. Normally, your digestive system breaks down the foods you eat into sugar. Insulin is a hormone made by your pancreas that helps sugar enter your cells to be used as fuel. In people with insulin resistance, cells don't respond normally to insulin and glucose can't enter the cells as easily. As a result, your blood sugar levels rise even as your body churns out more and more insulin to try to lower your blood sugar. (7)

Ayurveda holistic dietary and lifestyle management approaches and regimens of natural product based medicines offers time-tested and effective solutions for diabetes and related metabolic disorders. (8-10) *Ayurveda* explains metabolic disorders as *agnivaishamya* (problems in digestion, absorption). This condition occur due to vitiation of digestive fire, this can happen due to *doshic* imbalance a condition occur due to blockage in the individual channels of metabolism, as a result of this excess or improper digestion and absorption occur, and results in disease. (11) *Tinospora cordifolia* (*Guduchi*) is one of the components of several traditional formulations with potent rejuvenating, immunomodulatory, cytoprotective, and antioxidant properties that help to manage disordered physiological processes of body. (12-14) *Tinospora cordifolia* (*Guduchi*) composed of so many different chemicals constituents that might have effect on various system of human body. Different experimental or clinical studies have shown its effect as antioxidant, immunomodulatory, anticancerous, anti-diabetic, anti hyperlipidemic. So many scientific evidences are also available for its anti-diabetic potency, anti hyperlipidemic properties associated with cardioprotective agent on various animal and human models. Various classical *Ayurvedic* texts and *Nighantu* (*Ayurvedic* materiamedica) have described its anti-diabetic usages under various names viz. *Pramehaghna*, *Pramehahara*, *Mehaghna* and *Mehahara*. (15-19) *Ayurvedic Pharmacopoeia of India* has also cited its antidiabetic utility. (20) Tribals of Korkus (Melghat, Maharashtra, India) have been using the herb for polyuria, diabetes and fever. (21) Various dosage forms

of *Guduchi* and wide array of its active, natural principles and crude extracts have been used in traditional system of medicine and have reported anti-diabetic, anti-hyperlipidemic activity experimentally or clinically in numerous scientific journals. These constituents directly or indirectly affect various metabolic cascades and influence the level of glucose. (22) The present review highlights the efficacy of *Tinospora* on various metabolic disorders.

2. Collection of Data

Published information on *Tinospora cordifolia* were collected from several review articles, experimental studies and some cross-references were collected. Recent developments research on role of *Tinospora cordifolia* on various metabolic disorders (Table 1), covering all available records and articles in Pubmed, Scopemed, Dhara and other associated databases including fields of pharmacological research articles were also reviewed. Present review article is restricted to the role of plant in metabolic disorders.

3. Discussion

Tinospora cordifolia (Family: Menispermaceae), a well-known medicinal plant of *Ayurveda* is used in therapeutics as a single herb as well as is an essential ingredient of several polyherbal *Ayurvedic* formulations. (23, 24) Time-to-time several classical dosage forms of *Tinospora cordifolia* are being developed by adopting classical pharmaceutical doctrines of *Ayurveda*. (25-28) These dosage forms are being used in traditional practice as a rejuvenative, health promotive, as well as curative medicine in wide range of disorders. (29-31)

Table 1. Pharmacological effects of *Tinospora cordifolia* in different metabolic disorders

Part	Extract	Experimental/ Clinical	Dose	Duration for Treatment	Effect
Root	Aqueous	Alloxan-rats	400 mg/kg	3 to 15 weeks	Antihyperglycemic. (32)
Root	Aqueous	albino rats	2.5gm/kg, 5gm/kg,	6 weeks	Lowers the serum glucose level. (33)

			7.5gm/kg		
Root	Alcoholic	Alloxan rats	400mg/kg	4months	Lowers the plasma glucose level. (34)
Stem	Alcoholic	Alloxan rats	500mg/kg	6weeks	Decreased glucose- 6-phosphatase, fructose 1, 6- bi- phosphatase. (35)
Stem	Alcoholic	Alloxan rats	20ml/kg	2 to 30 days, twice day	Hypoglycemic effect. (36)
Stem	Aqueous, Ethanol, Methanol	Albino mice (Ehrlich ascites tumor (EAT) cells)	1-100mg	-	Glucose uptake stimulatory activity of the lyophilized extracts of <i>T. cordifolia</i> viz; aqueous, ethanol and methanol were evaluated for glucose uptake at different dosages. (37)
Root	Alcoholic	Alloxan rats	100mg/kg	6 weeks	Hypoglycemic effect. (38)
Root	Methanolic	Alloxan, streptomycin induced rat	150mg/kg	-	Hypoglycemic effect. (39)
Stem bark	Alcoholic	Albino rat	250mg/kg	90days	Hypoglycemic effect. (40)
Stem	Alcoholic	Human	125mg/kg, 250mg/kg	1 to 2 weeks	Non –significant result on serum glucose level. (41)
Stem	Isoquinoline alkaloid rich fraction	Normal and glucose-loaded Wistar rats 50.0, 100.0, 200.0	50 mg/kg, 100 mg/kg, 200 mg/kg	-	Hypoglycemic effect via mechanisms of insulin releasing and insulin-mimicking activity. (42)
Stem	Hydoalcoholic extraction	High fat diet fed and streptozotocin-Sprague Dawley rats	100mg/kg, 200 mg/kg	14 days	Anti-diabetic potential through mitigating oxidative stress, promoting insulin secretion. (43)
Stem	Aqueous	Alloxan induced diabetic rats	500 mg/kg	40days	Activity of hexokinase enzyme was significantly increased whereas glucose 6 phosphatase and fructose 1,6-biphosphatase significantly decreased. (44)
Stem	Aqueous	High-fructose diet (66% fructose) induced	400mg/kg	60 days	Role against fructose-induced insulin resistance and oxidative stress. (45)

		diabetic Wistar rats			
Stem	Aqueous, alcoholic, chloroform	Normal and alloxan induced diabetes in rabbits	50 mg/kg, 100mg/kg, 200mg/kg	1 day	Dose dependent hypoglycemic Action similar to glibenclamide and insulin. (46)
Leaves	Aqueous	Maltose-fed rats	20 mg/kg , 80 mg/kg	-	Hypoglycemic effect. (47)
Leaves	Alcoholic, aqueous	Streptozotocin-mice	400 mg/kg	50 days	Hypoglycemic effect. (48)
Leaves	Aqueous	Streptozotocin-mice	200 mg/kg	40 days	Hypoglycemic effect. (49)
Whole plant	Aqueous	Alloxan-rats and rabbits	400 mg/kg	-	Hypoglycemic effect. (50)
Stem	Aqueous	Human	250 mg/kg	10 days	Cardioprotective properties of vaso dilatation, cardiotoxicity. (51)
Stem	Aqueous	Human	150 mg/kg, 300 mg/kg	28 days	Decreases in blood pressure and Heart rate. (52)
Stem	Alcoholic	Rats	-	7 days	Cardioprotective activity of T. cordifolia in limiting ischemia-reperfusion induced myocardial infarction. (53)
Stem	Alcoholic	Human	500mg	60 days	Dyslipidemic features declined by 28.6%, metabolic syndrome decreased by 13.73%. (54)
Root	Aqueous	Male albino rats	2.5 gm/kg, 5gm/kg	30 days	Hypolipidemic potential. (55)
Root	Aqueous	Male albino rats	2.5 gm/kg	6 weeks	5.0 g/kg body weight showed highest hypolipidaemic effect. (56)
Stem	Powder	Human	50mg/kg	15 days	Decrease in the level of Serum Lipoprotein Profile. (57)
Stem	Aqueous	Human	3gm	14 days	Antihypertriglyceridemic activity. (58)
Leaf	Powder	Human	2gm	60 days	Very effective for maintaining haemoglobin level and total erythrocyte count. (59)
Stem	Powder	Human	6gm	60 days	It brings equilibrium of

					Dosha, Dhatu, Mala in the body by bringing equilibrium of all the vitiated Dhatus also MedaDhatu to Sama (equilibrium) state. (60)
Whole plant	Aqueous	Human & rats	-	1 week	Hypoglycaemic effect. (61)

4. Antidiabetic

Experimental and clinical studies, have proven significant role of various extracts *Tinospora cordifolia* as antidiabetic, dyslipidemic, cardiogenic, cardioprotective as shown in Table 1. Aqueous extract of stem obtained from another species of *Tinospora*- '*Tinosporacrispa*' also documented to possess the antihyperglycaemic effect is probably due to stimulation of insulin release via modulation of beta-cell Ca^{2+} concentration. This insulinotropic effect of *T. crispa* is physiological proposes that the extracts contain compounds which could be used in the treatment of type II diabetes. (62) From reference 32- 50, various experimental or clinical studies, proved its role as hypoglycemic activity by insulin mimicking or some other pathway to reduce plasma glucose level. A study done in Malaysia, on another species of *Tinospora cordifolia* named, *Tinosporacrispa* extract was taken orally by Type 2 (non-insulin-dependent) diabetic patients to treat hyperglycaemia. It claimed its hypoglycaemic property by adding aqueous extract to the drinking water of normal and alloxan-diabetic rats. After one week of observation, fasting blood glucose levels were significantly lower and serum insulin levels were significantly higher in treated diabetic animals compared to untreated diabetic control. This insulinotropic action of *T. crispa* was further investigated in vitro using isolated human or rat islets of Langerhans and HIT-T15 cells. In static incubations with rat islets and HIT-T15 B cells, the extract induced a dosage dependent stimulation and potentiation of basal and glucose-stimulated insulin secretion respectively. This insulinotropic effect was also evident in perfused human and rat islets

and HIT-T5 B-cells, the rate of HIT-T15 glucose utilisation was not affected by incubation with *T. crispa*, suggesting that the cells were viable throughout. These are the first studies to provide biochemical evidence which substantiates the traditional claims for an oral hypoglycaemic effect of *Tinosporacrispa*, and which also show that the hypoglycaemic effect is associated with increased insulin secretion. (61) In Ehrlich ascites tumor cells model, water, ethanol and methanol extracts of the herb, demonstrated the glucose uptake-stimulatory activity. (62)

5. Cardioprotective

From table 1, reference 51-53 *Tinospora cordifolia* claimed to have beneficial role on cardiac activity. Aqueous and Hydro-alcoholic extracts of *Tinospora cordifolia* were administered and vital parameters, assessment of cardiac profiling were performed using cold pressor test (CPT), tilt table and platelet aggregation tests. The CPT induced arterial stiffness was counteracted by treatment with single dose and multiple doses of aqueous and hydro-alcoholic extracts *Tinospora cordifolia*. Treatment with single doses and multiple doses of aqueous and hydro-alcoholic extracts *Tinospora cordifolia* produced increase in cardiac output. (51) *Tinospora cordifolia* is known as an adaptogen, as it increases the resistance of the body to physical, chemical, and biological stress and builds energy, general vitality. It is observed that the aqueous extract of *Tinospora cordifolia* when administered on daily basis has shown improvement (increasing trend) in distance, and max speed, VO_2 max and muscle power in the presence of physical stress. *Tinospora cordifolia* has mainly down-regulated the over activity of

sympathetic nervous system. (52) The experimental study had done on models of myocardial ischemia-reperfusion (I/R) injury have shown dose dependent reduction in infarct size and in lipid peroxide levels of serum. The heart tissues were observed with the prior treatment of *Tinospora cordifolia* with various doses. (53)

6. Hypolipidemic

From table 1, *Tinospora cordifolia* have proven its hypolipidemic effect on both experimental and clinical studies. (54-58) *Tinospora cordifolia* indicated in the treatment of diabetes and obesity; both of which are associated with each other. It has been evaluated for their anti-diabetic and anti-obese potency. *Tinospora cordifolia* contains multiple bioactives, which were identified to interact with multiple proteins involved in the pathogenesis of diabetes/obesity, i.e., isocolumbin with adiponectin, β -sitosterol with cholesteryl ester transfer protein, tinocordiside with lamin, berberine with JNK1, β -sitosterol & isocolumbin with peroxisome proliferator-activated receptor- γ , berberine with suppressor of cytokine signaling, isocolumbin with pancreatic α -amylase, isocolumbin with α -glucosidase, and β -sitosterol with aldose reductase.. The study suggested the probable modulation in multiple pathways in diabetes and obesity. (54) The other study indicated that *Tinospora cordifolia* stem extract was able to ameliorate the derangements in lipid metabolism which were associated with diabetes mellitus in streptozotocin induced diabetic rats towards normal level. It revealed the usefulness and beneficial value of this herb by enhancing HDL cholesterol levels and lowering the LDL and VLDL cholesterol levels, in treating hyperlipidemia. (55) The aqueous extract of root of *Tinospora cordifolia* has hypoglycemic effect, which significantly reduces the serum liver enzymes and prevents the weight gain. (56) Another study done type 2 diabetic patients, resulted significant decrease in the level of fasting blood sugar, total cholesterol, β lipoproteins and triglycerides. The decrease in lipids and

apoprotein levels of β lipoproteins was accompanied with stimulation of plasma lecithin cholesterol acyltransferase (LCAT). It showed promising result as an hypolipidemic agent. (57)

Hypertriglyceridemia is an independent risk for cardiovascular diseases. *Tinospora cordifolia* is composed of so many alkaloids which can lower the triglycerides without side effects. A pilot study was done on patients, which significantly depleted the levels of marker hyperglyceridemia. (58)

A clinical study was found that, leaf powder of *Tinospora cordifolia* was taken water have shown significant increase in haemoglobin and total erythrocyte count. It might significant role to treat the anaemia. (59) This botanical and its several developed formulations are thus were explored and established having promising potential in the management of wide range of metabolic

7. Conclusion

In conclusion *Tinospora cordifolia* could prove an excellent substitute for multidrug therapy which is currently recommended for management of various metabolic disorders. *Tinospora cordifolia* and its various dosage forms are reported to possess multi-targeted biological properties to manage diabetes, lipid disorders and related ailments. Rich bioactive phytoconstituents of this plant play a vital role in expression of its wide range of beneficial effects in metabolic disorders.

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Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

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