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Review Article

AN OVERVIEW ON ANTI DIABETIC ACTIVITY OF SIDDHA MEDICINAL PLANTS

ARUNVANAN.M[1*], SASI.S.K[2], MUBARAK.H[3], KANAGARAJAN.A[3]

[1] PG scholar, Dept.of Noi Naadal,GSMC, Palayamkottai,[2] Lecturer, Dept.of Noi Naadal, GSMC, Palayamkottai, [3] SCRU, Palayamkottai,
***Corresponding author, E.mail:** arunsiddhalayam@gmail.com

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ABSTRACT

Siddha system of medicine, one of the ancient medical systems has the great potential of medicinal resources as repository since ages. Diabetes is a major lifestyle disorder, the prevalence of which is increasing globally. Diabetes mellitus is compared with *Madhumegam* in Siddha literature. Most of the contemporary drugs work on insulin metabolism and several metabolic pathways to reduce hyperglycaemic conditions. The conventional Siddha drugs works on the same platform through its basic principles. Siddha medicinal plants which are having hypoglycaemic activity by involving various metabolic pathways are taken in to account and considered for a review. This process will create some new ideas in the avenue of research.

Keywords: Siddha, *Madhumegam*, Diabetes mellitus.

BACKGROUND

Neerizivu noi, one of the clinical entities is comes under *Neer Perugal Noikal* (polyuric conditons). *Madhumegam* is one among them compared to Diabetes mellitus(ICMR 2002 guidelines) reveals there may be more than 10 million population will suffer by this metabolic disorder. Siddha pharmacopeia comprises more than 1000 medicinal plants to cure various diseases. This article focus in order to bring out Siddha medicinal plants which are commonly identifiable, easy to avail all time, with lesser adverse effect, cost effective and with evident research data favoring anti diabetic activity.

***Madumegam* (Diabetes mellitus)**

Saint *Yugi* describes 20 types of *Mega noigal* of which 4 in *Vatham* (wind), 6 in *Pitham* (fire) and 10 in *Kabam* (water). *Madhumegam* is one among the 6 *Pitha mega noikal*. According to Siddha, *Madhumegam* is characterized by excessive and frequent urination, sweet odour of urine, identified by the presence of ants and house flies at the urinated place, recognizing smell of sugar when urine is heated , loss of weight, resulting in the gradual deterioration of the *Udalthathus* (7 body humours). The literature says the etiological factors will be of excessive sexual indulgence, over eating, laziness, and depression, desire to the worldly things, heredity, and high intake of ghee, milk, toddy, meat, tasty fishes and food with sweet taste[55]. In general the therapeutic advice may be of low calorie diet, exercise and managing with appropriate medicines, In Siddha system the treatment modality lies on the medicines, life style changes and exercise comprised of mind and body like Yogam(Yogic exercises), Some of the potent anti diabetic herbs which are commonly used in Siddha medicines are taken into account in order to establish its recent research findings for Diabetes mellitus and to prevent complications. The familiar Siddha medicines prescribed for diabetes are *Avarai Kudineer* (decoction), *Madhumega Chooranam* (Fine powder), *Thetran Chooranam, Seenthil Chooranam, Naaval Chooranam.*

Materials and methods

The review process is adopted to collect the research papers of various Siddha medicinal plants through available online peer reviewed and indexed journals. The Siddha aspect of the medicinal plants is furnished in the *Table 1* followed by the scientific data favoring anti diabetic activity are mentioned. The scientific data are summarized in to Invivo and Invitro studies.

In-vivostudies

Avarai (*Cassia auriculata*)

Flower extract of *Cassia auriculata*, increased plasma insulin and improved specific insulin binding in streptozotocin induced diabetic rats[1] (L. Pari *et al*.) n-butanol fraction[2] (S. J. Surana *et al*) and ethanol extract of *C.auriculata* exhibited significant reduction ($p<0.001$) in blood glucose levels in alloxan induced rats with remarkable increase in plasma insulin[3](F Lukmanul Hakkim *et al*).

Kondrai (*Cassia fistula*)

Hexane, aqueous extracts of *Cassia fistula*[4] (Nirmala. A *et al)* and gold nano particles[5] from stem bark- increased insulin secretion and decreased blood glucose levels in animals with streptozotocin-induced diabetes (P Daisy *et al*.).

Naaval (*Syzygium cumini*)

Ethanolic extract of whole fruit of *Syzygium cumini*-lowered blood glucose concentration probably by stimulating insulin secretogouge activity and increased the glycogen store in muscles of normal rats[6] (Rahul Gupta *et al*). Cuminoside- reduced fasting blood glucose level[7] (Farswan M *et al*.). Mycaminose- reduced blood glucose level[8] (A. Kumar).Water extract of pulp of *Syzygium cumini* stimulates release of insulin and inhibition of insulinase activity[9] (Achrekar,S *et al*) . Stigmasterol from *S.cumini* has significant effect on lowering serum glucose concentration with a concomitant increase in insulin level[10](Panda *et al)* Lupeol from *S.cumini* showed elevated Serum insulin level and concomitant reduction of glycated haemoglobin, serum glucose and nitric oxide[11](Gupta *et al*). The ethanolic extract and the compounds JB1 = 3, 15-dihydroxy Δ3 androstene [16, 17-C] (6' methyl, 2'- 1,3-dihydroxy-1-propene) 4H pyran from S.cumini have potent anti diabetic activity by reducing blood glucose level and the compound JB2=3-hydroxy androstane [16, 17-C] (6' methyl,2'-1-hydroxy-isopropene-1-yl) 4, 5, 6 H pyran have significant anti diabetic activity by reducing blood glucose level in alloxan induced diabetic rats[12]. Ethanolic extracts of seeds of *S. cuminii* were shown to reverse the pancreatic cell damage caused by alloxan[13] (Sigogneau-jagodzinski MP *et al*). *S. cumini* bark extract exhibited antidiabetic activity by significantly ($p<0.05$) lowering blood glucose (84.30±4.25) and urine sugar levels, also showed significantly ($p<0.05$) elevated levels of plasma insulin (10.29±0.59) and C-peptide (236.50±11.87) in Streptozotocin induced Diabetic rats[14] (Saravanan G *et al*).

Kadalazhingil (*Salacia reticulata*)

Methanol fraction of *Salacia reticulata* to alloxan diabetic rats improved glucose tolerance and significantly reduced fasting blood glucose, fructosamine, and glycosylated hemoglobin levels. This suggests that the hypoglycemic effect of *Salacia reticulata* in alloxan diabetic rats may involve an extrapancreatic effect on glucose

production or clearance[15] (Ruvin Kumara *et al*). Mangiferin, one of the main components in *Salacia* species (Li *et al*. 2004), has been reported to be potent α-glucosidase inhibitors that have been shown to inhibit increases in serum glucose levels[16] (Yoshikawa *et al*. 2001). Mangiferin from *S. reticulata* directly acts on liver cells and suppresses the gluconeogenic pathway resulting in decreased fasting blood glucose level in diabetes mice[17] (Im *et al*. 2008). Aqueous extract of *S. reticulata* strongly inhibited the activities of α-glucosidase and α-amylase, but not that of β-glucosidase[18] (Shimoda *et al*. 1998). Antidiabetic property of *Salacia* is partially attributed to intestinal α-glucosidase inhibitory activity[19] (Yuhao *et al*. 2008), furthermore, inhibition of this enzyme delays glucose absorption into the blood and suppresses postprandial hyperglycemia, resulting in improved glycemic control[20] (Heacock *et al. 2005*) Water extract of *salacia reticulata* inhibited the postprandial elevation of plasma glucose, insulin levels and intestinal α -glucosidase activities in mice[21] (Kyoji yoshino *et al*).

Koraikilangu (*Cyperus rotundus*)

Antidiabetic activity ($p<0.001$) was found at a dose of 300 mg/kg in acetone fraction of *Cyperus rotundus* in alloxan induced diabetic rats[22] (Nishikant A Raut *et al*).

Kottam (*Costus speciosus*)

Eremanthin isolated from *Costus speciosus* showed reduced plasma glucose level($p<0.05$) in streptozotocin induced diabetic male Wistar rats, also oral administration of Eremanthin significantly decreased glycosylated hemoglobin (HbA_1c), serum total cholesterol, triglyceride, LDL-cholesterol and at the same time markedly increased plasma insulin, tissue glycogen, HDL-cholesterol and serum protein[23] (Eliza J *et al*).

Maruthu (*Terminalia arjuna*)

Ethanolic stem bark extract restored all the lipids and glucose parameters to near normal values in alloxan induced diabetic rats [24](*B. Ragavan et al*). Ethanol extract of *T. arjuna* significantly ($p<0.05$) improved oral glucose tolerance, decreased fasting serum glucose level ($p<0.05$) also decreased serum total cholesterol ($p<0.01$) and triglyceride ($p<0.001$) significantly in streptozotocin-induced type 2 diabetic model rats[25] (Morshed *et al*). The significantly ($p<0.001$) altered levels of liver hexokinase, pyruvate kinase, lactate dehydrogenase (LDH), glucose-6-phosphatase and fructose-1,6-diphosphatase in diabetic rats were brought back to the near normal by the extract of *T. arjuna* , also it produced significant hypoglycemic activity by increasing glycolysis and repressing gluconeogenesis in diabetic animals and is correlated with the significant down regulation of lipid levels[26] (Manonmani Ganapathy *et al*).Methanol extract of *Terminalia arjuna* resulted in prominent reduction in blood sugar level, normalization of serum biochemical profiles, significant modulation of lipid peroxidation, endogenous nonenzymatic (GSH), and enzymatic (CAT) antioxidant and detoxification systems in streptozotocin induced diabetic rats[27](Moulisha Biswas *et al*).

The level of fasting blood glucose (FBG), glycated hemoglobin (HbA1C), total cholesterol (TC), triglycerides (TG), low density lipoprotein-cholesterol (LDL-C) and very low density lipoprotein-cholesterol (VLDL-C) significantly decreased while high density lipoprotein cholesterol (HDL-C) and hepatic glycogen were increased in streptozotocin induced type 2 diabetic rats treated with *T.arjuna* extract. Moreover, treatment with *T.arjuna* extract significantly ($P < 0.05$) ameliorated thiobarbituric reactive substances (TBARS), malonaldehyde (MDA) and protein carbonyl (PC), and glutathione (GSH), glutathione-s-transferase (GST) and catalase (CAT) in liver and pancreas of HFD/STZ group. Blood urea nitrogen (BUN), serum creatinine (Scr) and alkaline phosphatase (ALP), which were decreased significantly ($P < 0.05$) by TA treatment [28] (Kehkashan Parveen *et al*). Ethanolic extract of *T. arjuna* bark, resulted in significant decrease of blood glucose and in a decrease in the activities of glucose-6-phosphatase, fructose-1,6-disphosphatase, aldolase and an increase in the activity of phosphoglucoisomerase and hexokinase in tissues of alloxan induced diabetic rats[29](B ragavan *et al*).

Venthayam (*Trigonella foenum-graecum*)

Administration of *Trigonella foenum-gr*aecum extract in alloxan-induced diabetic rats showed decrease in blood glucose ($p<0.05$), serum cholesterol, ($p<0.05$), SGOT and SGPT levels[30] (Renuka C *et al*).

Keezanelli (*Phyllanthus amarus*)

Oral administration of Ethanolic leaf extract of *Phyllanthus amarus* resulted in a significant ($P<0.05$) decline in blood glucose and significant recovery in body weight of diabetic mice. There was also a significant ($P<0.05$) reduction in the activities of glucose-6-phosphatase and fructose-1-6-disphosphatase in liver, also there was significant ($P<0.05$) increase in the activity of glucokinase in liver of diabetic mice [31](A. A. Shetti *et al*). The extract of *P. amarus* noted in reducing the blood sugar in alloxan diabetic rats[32] (Raphael KR *et al*).

Seenthil (*Tinospora cordifolia*)

The treatment of *Tinospora cordifolia* methanolic extract significantly ($P<0.01$) decreased the blood glucose level, also prevented ($P<0.01$) the elevation of glycosylated haemoglobin and cholesterol levels in diabetic rats which could be due to the result of improved glycemic control proved by *Tinospora cordifolia.* The same extract also improved the activity of liver hexokinase ($P<0.01$) and the activity of fructose 1, 6- bi- phosphatase and glucose 6 phosphatase were found to be restored to normal ($P<0.01$) level [33](v. sivakumar *et al*)

Manjal (*Curcuma longa*)

Administration of water or Ethanolic *curcumin* extracts found to bring blood glucose , plasma insulin, total haemoglobin ,glycosylated haemoglobin , AST and ALT levels of liver and kidney malondialdhyde (MDA), antioxidant enzymes superoxide dismutase and catalase (SOD and CAT) to normal[34] (Azza A *et al*). Administration of freeze dried rhizome powder of *curcuma longa* dissolved in milk on streptozotocin induced diabetic rats resulted in increased HDL, Hb ($p<0.05$) with significant decrease in the levels of blood glucose, lipid profile and hepatoprotective enzymes ($p<0.001$)[35] (p k rai *et al*). Role of Turmeric powder on alloxan induced diabetic rats showed significantly decreased levels of urea, uric acid and creatinine to near normal ($p<0.05$) thereby protecting the rats from diabetic nephropathy[36](Amouoghli *et al*). The *Curcuma longa* rhizomes EtOH extract significantly suppressed an increase in blood glucose level in type 2 diabetic KK-A(y) mice [37](Minpei Kuroda *et al*)

Kariveppilai (*Murraya koenigii*)

Murraya koenigii ethanolic extract possesses significant hypoglycemic potential than glibenclamide in STZ-induced diabetic rats. Which showed decreased levels of blood glucose, glycosylated hemoglobin, urea, uric acid, creatinine and the plasma insulin level revealed the insulin stimulatory effect of the extract[38] (Arulselvan P *et al*). Feeding of diet containing *M. koengii* leaves in mild and moderate diabetic rats induced by alloxan showed a maximal reduction in the blood glucose level ($P<0.05$ and 0.005)[39] (Yadav S *et al*).The effect of Mahanimbine (carbazole alkaloid from *Murraya koenigii* leaves) on streptozotocin-induced diabetic rats showed decrease in the elevated fasting blood sugar, triglycerides, low density lipoprotein, very low density lipoprotein levels ($P < 0.05$) and increased high density lipoprotein[40] (B. Dineshkumar *et al*). Aqueous and methanol extract of *Murraya koenigii* on alloxan-induced diabetic rats showed significant reduction ($P<0.05$) in blood glucose levels and significant increase in Plasma insulin suggests that the hypoglycemic effect may be mediated through stimulating insulin synthesis and/or secretion from the beta cells of pancreatic islets of Langerhans[41](Vinuthan m. k *et al*).

Paagal (*Momordica charantia*)

Saponin fraction of *Momordica charantia* in alloxan induced diabetic rats showed decrease in blood glucose ($p<0.05$), increase in the level of insulin ($p<0.05$) and glycogen synthesis ($p<0.01$) also the glucose tolerance was raised in normal rats[42] (Yingzi wang *et al*). Aqueous extract of country and hybrid variety of *M. charantia* in diabetic rats resulted in a significant reduction in blood glucose, glycosylated hemoglobin, lactate dehydrogenase, glucose-6-phosphatase,

fructose-1,6-bisphosphatase and glycogen phosphorylase, and a concomitant increase in the levels of hemoglobin, glycogen and activities of hexokinase and glycogen synthase[43] (Sekar DS *et al*).

Kadukkai (*Terminalia chebula*)

Oral administration of ethanolic extract of *Terminalia chebula* on STZ induced diabetic rats reduced the blood glucose and glycosylated hemoglobin, also increased plasma insulin level reveals the insulin stimulating action of the extract. The glycogen and carbohydrate metabolizing enzymes were returned normal. The morphological changes in mitochondria, endoplasmic reticulum of pancreatic beta cells and number of secretory granules of beta cells were normalized[44] (Senthil kumar *et al*). The aqueous extract of the fruits of *Terminalia chebula* reduced the elevated blood glucose ($p<0.01$) and significantly reduced the increase in glycosylated hemoglobin (HbA1c) ($p<0.01$) in STZ induced diabetic rats, a decline in the hepatic and skeletal muscle glycogen content were partly prevented[45] (murali *et al*).

The long and short term usage of the chloroform extract of *T. chebula* seeds resulted in reduction of blood glucose which is probably mediated through enhanced secretion of insulin from the β-cells of Langerhans or through extra pancreatic mechanism also a Significant renoprotective activity was observed[46] (Nalamolu Koteswara Rao *et al*).

Thandrikai (*Terminalia belerica*)

The continuous administration of *T.belerica* fruits against alloxan induced hyperglycemia rats showed Significant reduction of glucose level and increased levels of antioxidant enzymes such as Superoxide dismutase, glutathione reductase and catalase were observed in blood and liver[47] (Sabu M. C *et al*). The Hexane, Ethylacetate and Methanolic extracts of *T.belirica* fruit at Streptozotocin induced rats showed significantly ($p<0.05$) increased plasma insulin, C-peptide and glucose tolerance levels, body weight, serum total protein. In addition the plant extracts significantly decreased the serum levels of total cholesterol, triglycerides, low density lipoprotein cholesterol, urea, and uric acid and creatinine in diabetic rats[48] (Latha P.C.R *et al)*.

Nellikai (*Phyllanthus emblica*)

Ethanolic extract of *P.emblica* showed dose dependenent reduction in blood glucose level, also the cholesterol, triglyceride and other hepatic markers are reduced in alloxan induced diabetic rats[49] (*Mittal M et al*). Aqueous fruit extract, of *Phyllanthus emblica* Linn significantly decreased the blood glucose level ,also induced hypotriglyceridemia by decreasing TG levels, the extract was also found to improve liver function by normalizing the activity of liver-specific enzyme alanine transaminase (ALT)[50](Shamim A *et al*). The aqueous extracts of *Phyllanthus emblica* fruits significantly ($P<0.05$) reduced serum glucose, glycosylated hemoglobin, cholesterol, triglycerides, urea and creatinine but increased serum insulin, HDL-cholesterol and protein in alloxan-induced diabetes mellitus in rats[51] (M. Rajathi *et al*).

In-vitro studies

Naaval (*Syzygium cumini*)

Water extract of pulp of *S. cumini* stimulates release of insulin and inhibition of insulinase activity[9] (Achrekar,S *et al*).

Kariveppilai (*Murraya koenigii*)

Mahanimbine – a carbazole alkaloid from *Murraya koenigii* leaves showed appreciable alpha amylase inhibitory effect and weak alpha glucosidase inhibitory effects when compared with acarbose[40] (B. Dineshkumar *et al*).

Manjal (*Curcuma longa*)

The Ethanol extract of *Curcuma longa* stimulated human adipocyte differentiation in a dose-dependent manner and showed human peroxisome proliferator-activated receptor (PPAR)-gamma ligand-binding activity in a GAL4-PPAR-gamma chimera assay. Curcumin, demethoxycurcumin, bisdemethoxycurcumin, and ar-turmerone mainly contribute to the effects via PPAR-gamma activation[37] (Minpei Kuroda *et al*).

Kadukkai (*Terminalia chebula*)

The In-vitro studies of aqueous extract of the fruits of *Terminalia chebula* with pancreatic islets showed that the insulin release was nearly two times more than that in untreated diabetic animals[45](murali *et al*). The highest inhibitory effect of tannins isolated from the alcoholic extract of fruits of *Terminalia chebula* was noted with porcine pancreatic amylase and potato starch as substrate. This result was comparable to that of Acarbose which is a very effective antidiabetic agent[52] (Mukherjee S *et al*).

Table1: Selected medicinal plants with Siddha aspect.

S.no	Tamil name	Botanical name	Taste (S/ T/ P)[54 *]	Pacifies (V,P,K)[53,**]
1	*Avarai*	*Cassia auriculata*	**S**- *Thuvarppu* **T**- *Thatpam* **P**- *Inippu*	Pitham and Kapham
2	*Kondrai*	*Cassia fistula*	**S**- *Thuvarppu,kaippu* **T**- *Veppam* **P**- *Karppu*	Pitham and Kapham
3	*Naaval*	*Syzygium cumini*	**S**- *Thuvarppu* **T**- *Thatpam* **P**- *Karppu*	Pitham and Kapham
4	*Kadalazhingil*	*Salacia reticulata*	**S**- *Thuvarppu,* **T**- *Thatpam* **P**- *Karppu*	Pitham and Kapham
5	*Koshtam*	*Costus speciosus*	**S**- *kaippu* **T**-*Veppam* **P**-*Karppu*	Pitham,Kapham
6	*Marudu*	*Terminalia arjuna*	**S**- *Thuvarppu* **T**- *Thatpam* **P**- *Karppu*	Kapham
7	*Venthayam*	*Trigonella foenum-graecum*	**S**- *Kaippu* **T**- *Thatpam* **P**- *Karppu*	Pitham,Kapham
8	*Keezanelli*	*Phyllanthus amarus*	**S**-*Thuvarppu, kaippu, Pulippu, Inippu* **T**-*Thatpam* **P** -*Inippu*	Vatham,Pitham and Kapham
9	*Seenthil*	*Tinospora cordifolia*	**S**- *Kaippu*	Pitham,Kapham

			T- *Veppam* **P**- *Karppu*	
10	*Manjal*	*Curcuma longa*	**S**- *Karppu,Kaippu* **T**- *Veppam* **P**- *Karppu*	Pitham,Kapham
11	*Kariveppilai*	*Murraya koenigii*	**S**- *Karpu,* **T**- *Veppam* **P**- *Karpu*	Kapham
12	*Paagal*	*Momordica charantia*	**S**- *Kaippu* **T**- *Veppam* **P**- *Karppu*	Pitham,Kapham
13	*Kadukkai*	*Terminalia chebula*	**S**-*Thuvarppu, kaippu, Karppu,pulippu, Inippu* **T**-*Veppam* **P** -*Inippu*	Vatham,Pitham and Kapham
14	*Thandrikai*	*Terminalia belerica*	**S**- *Thuvarppu* **T**- *Veppam* **P**- *Inippu*	Pitham,Kapham
15	*Nellikai*	*Phyllanthus emblica*	**S**-*Pulippu,Thuvarppu,Inippu* **T**-*Thatpam* **P**-*Inippu*	Vatham, Pitham and Kapham

*** S – Suvai (Taste), T – Thanmai (Character), P - Pirivu (Division); ** V – Vatham, P -Pitham, K- Kapham; Inippu(Sweet), Pulippu (Sour), Kaippu (Bitter), Karppu (Pungent), Thuvarppu (Astrigent), Veppam (Hot), Thatpam (Cold)**

DISCUSSION

By observing Table 1, it denotes the *Thuvarppu and Kaippu* (Astringent and Bitter) are the predominant tastes, so it pacifies diseases of *Pitham* , it is inferred that *Madhumegam* comes under *Pitha* diseases which can be managed by administering the medicinal plants given in this review. The In-vivo and In-vitro studies of the above Siddha medicinal plants revealing its antidiabetic activity through pancreatic and extra pancreatic mechanism coincides with the medicines mentioned in the Siddha literatures, in addition to this action the same drugs also preventing diabetic complications, exhibits anti lipidemic activity (increasing HDL and decreasing LDL), and prevents the damage of hepatic cells via its anti oxidant activity.

CONCLUSION

It is essential to evaluate the studies on individual Siddha medicinal plants as well as Siddha formulations supporting anti diabetic activity in every step of the metabolic pathway of the disease in order to establish its clinical usage globally. Clinical documentation of compound Siddha formulations must be encouraged to promote mass level utilization for the society with minimal expenditures.

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