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Validation of Anti-diabetic Potential of *Avirai kudineer* a Siddha herbal formulation-A Review

Rajalakshmi K[1], Christian GJ[2], Shanmuga Priya P[3], Jeeva Gladys R[4]
[1(]*Department of Siddha,, The Tamilnadu DR. MGR. Medical University, Chennai, India)*
[2(]*Department of Pathology, (Noi Nadal), National Institute of Siddha, Chennai, India.)*
[3(]*Department of Toxicology (Nanjunool, National Institute of Siddha, Chennai, India.)*
[4(]*Research fellow, The Tamilnadu DR. MGR. Medical University, Chennai, India)*

Abstract: *Indian medicinal plants are profoundly used in the ancient Siddha system of medicine. These plants are attaining an immense interest in the field of research, due to their safety, efficacy and easy acessibility. Avirai Kudineer is being widely used in this traditional system of medicine whose scientific aspects are only minimally explored. The current review focuses on the phytochemical screening and various in-vitro and in-vivo studies on Cassia auriculata (Avirai), Cassia fistula (Kondrai), Syzygium cumini (Naval), Salacia reticulata (Kadalazhinjil), Saussurea lappa (koshtam), Terminalia arjuna (Marutham) and Cyperus rotundus(Korai kizhangu) which are the ingredients of Avirai Kudineer. The present analysis is based on the anti-diabetic studies of the ingredients categorizing them as inhibitors of carbohydrates digesting enzymes (alpha-amylase inhibitors, alpha-glucosidase inhibitors), inhibitors of intestinal glucose absorption and stimulators of insulin secretion and cellular uptake enhancers of glucose. The review validates that all ingredients of Avirai kudineer have anti-hyperglycemic potential based on the data collected in Siddha literature and recent researches and therefore vouches Avirai Kudineer as a successful Siddha formulation in the treatment and improving the quality of life of both Pre-diabetic and Diabetic patients.*

Keywords*: Anti-diabetic Plants, Avirai Kudineer, Alpha-amylase inhibitor, Alpha-glucosidase inhibitor, Siddha*

I. Introduction

Diabetes mellitus is a complex metabolic syndrome with an absolute or relative deficiency of insulin resulting in disturbed intermediary metabolism and manifestations. Diabetes mellitus affects all body systems and the main brunt is borne by eyes, kidneys, skin and nerves. The World Health Organization (WHO) estimates that by 2025, worldwide, there will be 300million diabetics. India, by then will be a home to more than 57million diabetics. Present diabetic Population in India is estimated approximately as 32 million of which Type 2 Diabetes caused by insulin resistance is the commoner type comprising 90% of Diabetics[1].Before the advent of modern medicine, the people of South India used Siddha system of medicine to combat this complex metabolic disorder recognized by them as *Madhumegam* and were protected from the onslaughts of this disease for centuries. But now, this indigenous treatment for diabetes has lost its sheen and it is high time that we rediscover these age-old Siddha herbal remedies to tackle this metabolic disorder. The two major concerns in the usage of presently available synthetic anti-diabetic drugs are the side effects caused and the drug resistance on prolonged usage[2]. Hence, there is a demand for new dimensions in filling the gap of lack of scientific explanations in traditional medicines thereby identifying newer health care strategies to combat this multifactorial disease.

II. Materials And Methods

This review article adopts the bibliographic search, scrutinizing the anti-diabetic potential and phytochemical analysis of the ingredients of *Avirai kudineer* from online peer reviewed Journals and Classical textbooks obtained through multiple accepted databases such as (Google scholar, Pub med, Scopus, Science direct, Research gate, Elsevier). A focused collection has been made to evaluate the target action of phytoconstituents at molecular level with search words such as Cassia auriculata, Cassia fistula, Syzygium cumini, Salacia reticulata, Cyperus rotundus, Costus speciosus, Terminalia arjuna, alpha-amylase inhibitors, alpha-glucosidase inhibitors, inhibitors of intestinal glucose absorption, stimulators of insulin secretion and various in-vitro and in-vivo studies of ingredients of *Avirai kudineer*. This review article also analyses and discusses the Siddha classical literature and Siddha Materia medica for the *tridosha* concepts of diabetes in Siddha and its treatment methodology along with scientific explanations.

2.1. Carbohydrate metabolism and formation of glucose

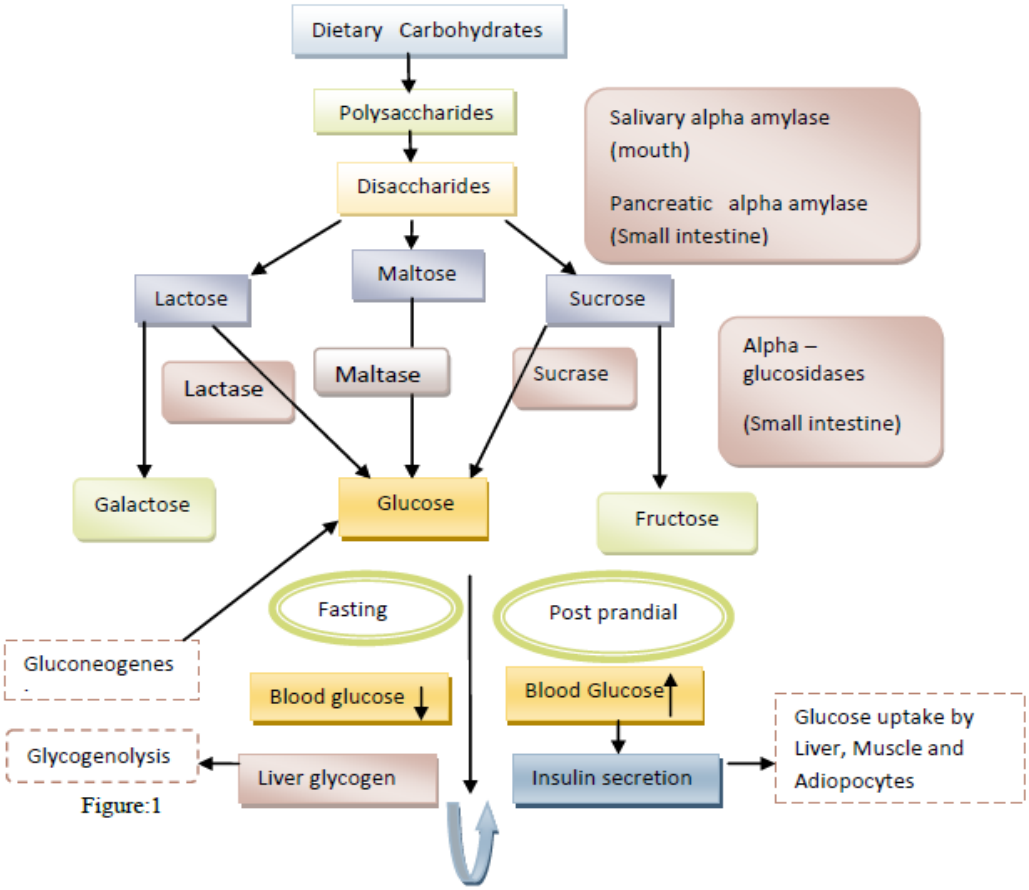

Figure:1

Glucose is the key regulator of insulin secretion. It must be metabolized in beta cells to stimulate insulin secretion. This is achieved by a series of regulatory steps. Dietary Carbohydrates are digested by carbohydrate digesting enzymes alpha-amylase and alpha-glucosidase and forms glucose in the gastrointestinal tract which is absorbed in the blood stream by passive and active mechanism (Fig.1). Normally, in the fed state, a rise in blood glucose level stimulates insulin secretion from pancreatic beta cells which is a normal mechanism. This hormone initiates glucose uptake into specific target tissues primarily liver, muscle and adipocytes, promotes glucose oxidation and glycogen deposition in liver and muscle and the incorporation of glucose (as glycerol) into triglycerides in adipocytes. All these activities together are responsible for lowering the elevated plasma glucose resulting from intake of a meal.

In contrary, there is decrease in glucose and insulin level in the fasting state, therefore Glucose is then mobilized from glycogen stores in the liver (glycogenolysis) or formed from smaller, non-sugar precursor molecules (gluconeogenesis). This occurs in the liver and to be a lesser extent, kidneys and is under the control of glucagon a counter hormone whose level rise as those of insulin fall and vice versa. Hence, when glucagon levels are high and insulin levels are low, gluconeogenesis and glycogenolysis are stimulated and glucose enters the blood stream[3].

2.1.1. Role of Carbohydrate digesting enzymes Alpha-amylase and Alpha-glucosidase

The Main source of glucose in diet is Polysaccharides. Polysaccharides are acted upon by alpha-amylase present in Saliva and Pancreatic juice. Serum amylase present in pancreatic juice is more powerful and it is released in small intestine breaking down starch into disaccharides and glucose before leaving the duodenum[3]. Alpha-glucosidase is a collective term of a membrane bound enzyme of small intestinal villi involved in the breakdown of alpha linkages of Oligosaccharides and disaccharides into glucose. These enzymes include maltase, iso maltase, sucrase, lactase, and alpha dextrinase. The Monosaccharides glucose, fructose and galactose are the final products of carbohydrate digestion that are rapidly absorbed in the first half of the small intestine. In the presence of inhibitors, digestion occurs throughout the small intestine resulting in slower absorption of Monosaccharides and blunting of postprandial glucose rise**.** Therefore, a search for compounds

that can inhibit alpha-amylases or intestinal alpha-glucosidases is regarded as one of the therapeutic approaches for developing Novel anti-diabetic agents[3].

III. Rationale For Anti-Diabetic Agent

From the foregoing, the following mechanisms have been proposed for an agent that would lower or control plasma glucose levels. i. Inhibition of carbohydrate digesting enzymes alpha-amylase and alpha-glucosidase. ii. Impairment of glucose uptake from small intestines. iii. Stimulation of insulin secretion from beta cells of the pancreas. iv. Insulin mimic or insulin sensitizing activity at target tissues in liver, skeletal muscles and adipocytes. v. Antagonism of glucagon activity[3]. Present day Oral hypoglycemic agents such as sulfonyl ureas, Biguanides, Thiazolidinediones, Alpha-amylase inhibitors and alpha-glucosidase inhibitors are synthetic molecules which are effective in diabetes, but they have their limitations and side effects[4].

IV. *Avirai Kudineer* And Its Significance

The flora of India is abounded with herbs for the treatment for diabetes, of which more than 400 plants have been recommended as anti-diabetic agents[5]. *Avirai Kudineer* is one of the most reputed Siddha polyherbal formulations consisting of seven ingredients which are being used traditionally in south India as a time-tested Anti-diabetic formulation. It has its source in the Classical Siddha Literature "*Theraiyar Kudineer*"[5] and it is also found in the Siddha literature "*Gunapadam mooligai vaguppu*" (Siddha Materia medica), which mentions the significance of this herbal decoction in the last line of poetic description of *Avirai kudineer* as, "*Kaviri neerum vatri kadal neerum vatrumthanaey*"[6] which means "river and oceans would become as dry lands". This emphasizes the high potential of this herbal decoction to interfere with the osmotic diuresis and renal complications of diabetes, resulting from increased blood glucose level.

4.1. Phytochemical screening and in vitro anti-diabetic action of Ingredients

Table: 1

S.no	Botanical name / Parts used	Tamil name	Antidiabetic Phytoconstituents	Antidiabetic Action
1.	Cassia auriculata (Whole plant)	Avirai	Tannins, flavanoids, saponin,terpenoids,alpha tocopherol[7]	Alpha- amylase and alpha-glucosidase inhibition[8].
2.	Cassia fistula (bark, leaves)	Kondrai	Flavanoid, Proanthocyanidin, Lupeol, saponin, Tannin,Triterpenoid[9]	Alpha -amylase inhibition, Stimulate or regenerate beta cell for insulin secretion [9,10].
3.	Syzygium cumini (seeds)	Naaval	Flavanoid**,** myricetin, ellagic acid, Tannin, Jambosine, Jamboline [11, 12, 13].	Inhibits intestinal glucose uptake [11].
4.	Salacia reticulata (Whole plant)	Kadalazhinjil	Salacinol, Kotanalol,Salaretin**,** quercetin, [14,15].	Alpha-glucosidase inhibition [14].
5.	Cyperus rotundus (Rhizome)	Korai kizhangu	Flavanoids,Tannins, Saponins, Cyperene, Nor cyperone, beta sitosterol [16].	Inhibits alpha- amylase and alpha- glucosidase [17].
6.	Costus speciosus (Rhizome)	Koshtam	Eremanthin, Saponins, Triterpenes, beta sitosterol [18]**.**	Stimulates insulin secretion and tissue glucose uptake [18].
7.	Terminalia arjuna (Bark)	Marutham	Flavanoids,Tannins , Triterpenoid saponins Arjunolic acid,Arjungenin,luteolin, Arjungenin, Arjunic acid [19, 20].	Alpha- amylase inhibition and alpha- glucosidase inhibition [19, 20].

4.2. In vivo Anti-diabetic studies on Individual ingredients of Avirai kudineer

4.2.1. Cassia auriculata

Pari et al., studied the effect of Cassia auriculata flowers on blood sugar levels of streptozotocin induced diabetic rats and observed that oral administration of 0.45g/Kg body weight of aqueous extract of flower for 30 days resulted in significant decrease in blood glucose and an increase in plasma insulin. And reported that Cassia auriculata 0.45g/kg body weight was found to be comparable with glibenclamide[21]. Latha M et al., evaluated the antihyperglycemic effect of Cassia auriculata flower and its effect on key metabolic enzymes involved in carbohydrate metabolism. The study revealed that Cassia auriculata flower extract at a dose of 0.45/kg body weight for 30 days suppressed gluconeogenic enzymes and increased hexokinase activity. It also resulted in decreased blood glucose, Glycosylated hemoglobin and increased plasma insulin level and lipid levels in diabetic rats[22].

Gupta S et al., evaluated the antihyperglycemic and hypolipidemic activity of aqueous extract of Cassia auriculata leaves in streptozotocin diabetic rats. Cassia auriculata leaf extract 100, 200 and 400 mg/kg doses were given for 1 day to determine antihyperglycemic activity and 400 mg/kg dose was administered daily for 3 weeks to assess glycemic control and hypolipidemic effect. Antihyperglycemic effect was resolute by the reduction in fasting blood glucose by 13.9% and 17.4% in mild and severely diabetic rats respectively at 400 mg/kg after 5th hour of administration. After 3 weeks of administration of the leaf extract, reduction in fasting blood glucose and glycosylated haemoglobin was observed at 400mg/kg. This study indicates that the decoction of Cassia auriculata leaves will be effective in the treatment of Type II diabetes along with hyperlipidemia [23]. Another study by S.J.Surana et al., revealed that the n-butanol fraction of hydromethanolic extract of cassia auriculata flowers showed an anti hyperglycemic activity in Wistar male rats. 0.20g/kg alloxan was administered in rats with blood glucose level 250-300mg/dl and the elevated blood glucose was confirmed after 48 hours The results concluded that the n-butanol fraction of hydromethanolic extract of Cassia auriculata flowers showed anti hyperglycemic activity in 30 days which is comparable with Standard drug Phenformin. It also reduced serum lipids and proteins to normal level indicating its hypolipidemic action[24].

Shipra Gupta et al., observed that administration of Cassia auriculata leaf extract at a dose of 400mg/kg once a day for 15 days showed the enhanced activity of hepatic hexokinase and phosphofructokinase and suppressed glucose-6-phosphatase and fructose-1,6-bisphosphatase in both mildly and severely streptozotocin induced diabetic rats[25]. Sharada nalla et al., in 2012 demonstrated the anti-diabetic activity of ethanolic extract of Cassia auriculata leaves. Diabetes was induced by administration of streptozotocin–nicotanimide and after 72 hours blood glucose was determined. Animals with blood glucose level 126mg/dl were included in the study. A dosage of 400mg/kg extract of Cassia auriculata leaves showed anti-diabetic activity after 15 days of administration in streptozotocin–nicotanimide induced diabetic rats[26].

Ethanolic extract of Cassia auriculata roots at doses of 300 and 600 mg Kg^{-1} body weight in cisplatin and gentamycin induced renal injury in animals caused a significant reduction in blood urea, serum creatinine and normalization of histopathological changes[27]. Another study conducted by Pai Aruna et al., revealed that ethyl acetate extract of Cassia auriculata seed reduced pancreatic thiobarbituric acid reactive substances (TBARS) **($p<0.05$)** significantly and fasting blood glucose in alloxan induced diabetic rats which are comparable with tolbutamide[28].

4.2.2. Cassia fistula

Narendra silawat et al., performed a study to identify the mechanism of action of Cassia fistula leaf extract for hypoglycemic, OGTT in two dose levels 200 and 400mg/kg with glibenclamide (0.5mg/kg) as a standard drug.The extract at both doses was found to be equally effective hence the dose of 200mg/kg may be appropriate for diabetic. The study also indicated that it takes 1 hour for the active ingredient or its metabolite to enter the circulation and target tissues to bring out hypoglycemic effect and maintained for 2.30 hours. Studies on isolated Psoas muscle indicated Cassia fistula leaf extract enhanced the uptake of glucose in muscle tissue in a short time of 30 minutes in the absence of insulin and the effect was more in the presence of insulin. The direct effect in the absence of insulin on Psoas muscle indicates that the extract has either insulin like effect on Psoas muscle or direct stimulatory effect on the enzymes involved in the metabolism of glucose. A Decrease in lipid peroxidation was observed in Cassia fistula which may be due to the result of its OH Scavenging produced by $fecl_2$-H_2O_2 and H_2O_2 in the reaction system. The study showed an elevation in GSH extract which contributes Cassia fistula to have potent antioxidant potential[29]. A study conducted at Malaysia evaluated the anti-diabetic effects of methanolic and aqueous extract of bark, leaf, flower and pods of Cassia fistula in Normoglycemic and streptozotocin-nicotinamide induced type II diabetic Sprague-Dawley rats. In Normoglycemic rats blood glucose levels were estimated in the fasting condition after the administration of extracts at 1st, 2nd, 4th and 8th hour. Bark methanolic extract showed the hypoglycemic effect starting from 2nd to 8th hour. Leaf methanolic extract showed the hypoglycemic effect starting from 4th to 8th hour but not effective as glibenclamide. In type II diabetes mellitus rats, bark methanolic extract showed anti hyperglycemic effect similar to glibenclamide from the 7th day with maximum efficacy on the 21st day. Leaf and bark methanolic extract showed increased serum insulin and decreased HbA1C levels. In this study, the pods did not exhibit any hypoglycemic effect. Methanolic extract of bark and leaves showed significant anti-hyperglycemic activity than other parts[30].

4.2.3. Syzygium cumini

A comparative study on anti-diabetic activity of methanolic extract and ethyl acetate extract of Syzygium cumini seeds in streptozotocin induced diabetic rats from mycaminose, a compound extracted from Syzygium cumini seeds. The results confirmed the anti-diabetic activity in methanolic extract of Syzygium cumini seeds at the dose of 200 and 400mg/Kg when administered for 15 days[31]. Mycaminose, isolated from Syzygium cumini seed possess anti-diabetic property whose mechanism of action is similar to that of Glibenclamide which is a drug that stimulate insulin secretion from beta cells of pancreas[32]. Another interesting

study evaluated the syzygium cumini seeds for insulin resistance and beta cell dysfunction in a high-fat diet in Streptozotocin induced diabetic rats. Administration of Syzygium cumini seeds decreased serum glucose and insulin resistance at 400mg/kg in Wistar albino rats [33].

4.2.4. Salacia reticulata

Methanolic extract of Salacia reticulata root bark showed hypoglycemic activity in alloxan induced diabetic rats when given for 120 days. It may involve an extra pancreatic effect on glucose production or clearance. It also reduced glycosylated hemoglobin levels, fructosamine, fasting blood glucose and improved glucose tolerance[34].Administration of Salacia reticulata extracts was observed to reduce blood aldohexose which persisted up to five hours, suggesting its anti-diabetic potential[35]. A Study of hydro-alcoholic extract of Salacia reticulata at the dose of 500mg/kg per orally, reduced the blood serum aldohexose level considerably when compared to the management cluster in corticosteroid evoked hypoglycemic model[36]. A Water soluble fraction (25-100mg/kg per orally) from the roots and stems of Salacia reticulata powerfully restrained elevated blood serum aldohexose level with the administration of sucrose or malt sugar[37]. Mangiferin an active ingredient of Salacia and its glucosides resulted in the reduction in blood aldohexose levels at a dose of 30mg/kg per os for 2 weeks[38].

4.2.5. Cyperus rotundus

Evaluation of effect of Cyperus rotundus in the treatment of diabetes on alloxan induced hyperglycemia in rats showed that oral daily administration of 500mg/kg of the extract (once a day for seven consecutive days) significantly lowered the blood glucose levels. The anti hyperglycemic activity can be attributed to its antioxidant activity as it showed the strong DPPH Radical scavenging action in vitro[39]. The rhizome of this plant has been reported to play a major role in the protection of neurodegenerative disorders due to its antioxidant and free radical scavenging properties[40].

Wound contraction rate was delayed in diabetic rats compared to normal (non-diabetic) rats throughout the study. A Study on Cyperus rotundus ethanolic extract on wound healing showed a statistically significant dose dependent wound contraction rate. Further, Standard glibenclamide and two doses of Cyperus rotundus extract hastened the epithelialization period (13 and 11 day) compared to 18 days in diabetic rats. The extract exhibited dose dependent effect in hastening wound healing. Among the two doses, high dose (400mg/Kg) produced faster healing effect[41].

4.2.6. Costus speciosus

A Study conducted in STZ (Streptozotocin) induced diabetic rats which were given Costus speciosus root extract in doses of 200, 400 and 600 mg/Kg body weight and 600 microgram/ Kg body weight of the standard drug glibenclamide for 4 weeks revealed that Costus speciosus root extract 400 and 600 mg/Kg body weight induced a decrease in blood glucose and an increase in serum insulin levels[42]. A study in Tamil Nadu separated a compound from Costus speciosus named Eremanthin identified by gas chromatography mass spectrometer (GCMS). Administration of eremanthin at different doses (5, 10, 20mg/kg b.w) was given for 60 days in Streptozotocin (STZ) induced diabetic male Wistar rats. Eremanthin at the dose of 20mg/kg b.w decreased glycosylated haemoglobin levels and decreased lipid levels [43]. Another study in 2009 isolated a compound from Costus speciosus named costunolide and was administered orally at the dose of 20mg/kg against streptozotocin induced diabetic rats. This study revealed it reduced HbA1C levels in 30 days which suggests Costunolide to be more potent than Eremanthin [44]**.** Ethanolic extract of costus speciosus rhizome reduced the plasma glucose levels in alloxan induced diabetic rats at the dose of 200mg/kg in 14 days[45].

4.2.7. Terminalia arjuna

Blood glucose level of the control, the HFD/STZ group and the HFD/STZ + TA (Terminalia arjuna) groups were studied at different time points (0, 30, 60 and 120 min) after oral administration of glucose (2 g/kg). In the HFD/STZ group, the peak increase in blood glucose level was observed after 60 min and remained high over next 60 min. Terminalia arjuna treatment significantly ($P < 0.05$) decreased blood glucose level at 60 and 120 min in the HFD/STZ + TA group compared to the HFD/STZ group. Further, the HbA1c level was also found to be significantly increased in HFD/STZ group compared to control rats while Terminalia arjuna treatment decreased the level of HbA1c. The study supports that Terminalia arjuna might enhance glucose utilization by peripheral tissues and increase the glycogen stores in the liver. Also, the HFD/STZ-model of diabetes exhibited abnormalities in lipid metabolism as evidenced from the significant elevation of serum TC, TG, LDL-C, VLDL-C and reduction of HDL-C levels. Treatment with Terminalia arjuna for four weeks significantly reduced the TC, TG, LDL-C, VLDL-C level and significantly increased HDL-C levels in HFD/STZ indicating its hypolipidemic action[46]. A study on antioxidant activity of Terminalia arjuna showed, that the antioxidant enzymes (GST and CAT) activity was decreased significantly in HFD/STZ group. Whereas

the treatment with Terminalia arjuna significantly improved these antioxidant enzymes activities in HFD/STZ + TA group. The Acetone extract of Terminalia arjuna showed hypoglycemic activity in alloxan induced diabetes mellitus in Wistar albino rats at the dose of 500mg/kg for 2 weeks[47].

Ethanolic extract Terminalia arjuna bark 1.25g/kg was administered to Streptozotocin induced male long Evan diabetic rats for consecutive 21 days and determined the anti-hyperglycemic activity. It reduced the post prandial hyperglycemia but not significantly when fed with glucose load in the acute test. In chronic test after 21 days it significantly ($p < 0.05$) reduced the blood glucose level when fed with glucose load. It also possessed hypolipidemic activity[48]. Ethanolic extract of Terminalia arjuna bark showed anti-diabetic effect ($p < 0.05$) in alloxan induced diabetic rats by oral administration at the dose of 200mg/kg and 500mg/kg for 30 days. The activities of glycolytic enzymes hexokinase, aldolase and phosphoglucoisomerase were evaluated. Activities of hexokinase, phosphoglucoisomerase were decreased and aldolase was increased after the administration of Terminalia arjuna extract[49].

4.2.8 Toxicity profile

Toxicity studies (Acute, Sub chronic) that were carried out on Cassia auriculata[50] Cassia fistula[51], Syzygium cumini[52], Salacia reticulata[53], Cyperus rotundus[54], Clostridium speciosus[55] and Terminalia arjuna[56]using rat models assure that they have high margin of safety when administered in doses several times of what is suggested for humans. No significant adverse effect was noted in blood chemistry, body weight or behavior. And no histopathological changes were observed. Therefore all ingredients of Avirai Kudineer are found to be safe without any side effects. However Salacia reticulata was found to enhance post implantation losses and LBW in pregnancy and should not be used in gestational diabetes.

4.2.9 Biochemical studies on hypoglycemic effect of Avirai kudineer

V.Bhavapriya et al., in 2001, has carried out a study on anti diabetic effect and biochemical analysis of Avirai kudineer in experimental animal models of alloxan induced male Wistar albino rats. After 15 days of treatment blood was collected and the results show that AK treated rats had significantly increased tolerance for glucose and the maximum glucose tolerance was noted after 30min of loading glucose. The biochemical parameters urea, creatinine and cholesterol have been significantly normalized and the decreased protein values during diabetes were found to increase in AK treated rats, insisting its positive effect on renal function. Moreover it also increased the hexokinase activity up to 82% which is higher when compared to a study on Syzygium cumini which increased hexokinase activity by 72.7%. Therefore study suggests that the hypoglycemic effect of Avirai kudineer is attributed to the additive effects and synchronicity of the individual ingredients which can reverse the diabetic status when used as a polyherbal formulation than used singly[57].

V. Siddha Concept Of Diabetes

Tridosha (*Vatham*, *Pitham* and *Kabam*) is the basic physiology in which the Siddha system of medicine solely stands. These unique humours operate constantly between environment and individual and are required to maintain the integrity of a living system. Diabetes mellitus is grouped under *Pitha* disorders of "*Mega*" disease. *Mega* disease translates into an excessive discharge of urological secretion and excretions. Diabetes mellitus is directly referred to as '*Madhumegam'* in the above classification made by *Sage Yugi* as a nectar sweet polyuria condition.This clinical entity is characterized with symptoms such as excessive and frequent urination, sweet odour in urine, presence of ants and house flies at the urinated place, loss of weight resulting in gradual deterioration of the body. According to Siddha system of medicine, *Madhumegam* results due to predominantly deranged humors, *pitham* and *kabam*, due to alteration in the lifestyle and dietary habits[58].

5.1 Treatment methodology in Siddha and its scientific explanation

Table: 2

Altered humours in DM	Pacifying tastes		
Pitham	Astringent	Sweet	Bitter
Kapham	Pungent	Astringent	Bitter

According to Siddha system of medicine the pharmacological action of a drug primly depends on its taste and its action potentials of character (*Gunam*) and potency (*Veeriyam*) after digestion, through which the drug has the ability to enhance or suppress the deranged humours. Therefore for anti-diabetic action the tastes bitter and astringent are preferred which would pacify the predominantly altered humours, *pitham* and *kabam*

(Table: 2)[59]. Upon analyzing the data collected from various phytochemical researches on medicinal plants, plant based phenols, flavanoids, isoflavones, alkaloids, terpenes and saponins are responsible for the bitterness or astringency of these plants. Higher molecular weight polyphenols known as tannins are astringent and lower molecular weight phenolic compounds tend to be bitter. Flavanoids tend to be bitter depending upon the glycoside chain present in it[60]. These phytoconstituents were found to ameliorate the persistent hyperglycemia, oxidative stress and modulate various metabolic pathways which might attribute to the management of diabetes and its complication [61].

VI. Discussion

Enzyme inhibitors can be a target potential in the areas of disease control and their treatments, as enzymes catalyze the most important biochemical pathways[62]. Upon screening the in vitro studies of individual herbs of *Avirai kudineer* it is evidently clear that almost all ingredients are capable of inhibiting the carbohydrate digesting enzymes alpha-amylase and alpha-glucosidase which is one of the anti-diabetic therapeutic approaches in the management of blood glucose. As inhibition of Amylase and glucosidase enzymes can significantly decrease the postprandial increase of blood glucose after a mixed carbohydrate diet and therefore it is considered to be an important strategy in the management of blood glucose[63].

All most all ingredients of *Avirai kudineer* are found to have saponins, Tannins and flavanoid phytochemicals. According to a molecular level study, Tannin extracts has shown promising anti-diabetic effects with potential alpha-amylase and alpha-glucosidase inhibition activities. Moreover it also induces glucose transport through activation of the insulin mediated signaling pathway and inhibits adipocyte differentiation hence the key genes involved in the adipogenesis process is inhibited. These combined activities make Tannins as an ideally suited prototypic compound to develop novel pharmaceuticals that can treat Hyperglycemia, without concomitant weight loss or gain[64, 65]**.** Furthermore upon dealing with the molecular mechanisms causing diabetic micro vascular complications, the Polyol pathway involving the enzyme Aldose reductase enzyme play a very important role. Hence, Phytochemicals which are reported to have potent Aldose reductase inhibiting activity were found to have protective as well as prophylactic role in diabetic micro vascular complications such as Diabetic neuropathy, Nephropathy and Retinopathy. There is also considerable evidence that the diabetic complication is also contributed by oxidative stress which results in the production of free radicals leading to tissue injury. An increase in Lipid peroxidases in plasma may be one of the important factors in the development of vascular complications and atherosclerosis in diabetic patients who are high cardiovascular risk group. Carotenoid (Lutein, and Oligomeric proanthocyanidins) and Flavanoids (quercetin, myricetin, rutin, ellagic acid) might prove to be important for alternative diabetic treatment or reduction of the risk of the disease and have been proved to inhibit lens Aldose reductase activity in rats and there by inhibited the Polyol pathway induced oxidative stress leading to a protective effect on diabetic cataract rats[66].

Saponins and its group triterpenoids or steroidal glycoalkaloid stimulates the release of insulin and blocks the formation of glucose in the blood stream. The protective effects of saponins on the early stage of diabetic nephropathy in rats have been reported due to the strong ability to reduce lipid peroxidases and increase in antioxidant enzymes in diabetic rats. Saponins improve glucose and lipid homeostasis by restoring the deregulated glycolytic and gluconeogenic enzymes in the diabetic state through the activation of AMP-Activated protein kinase(AMPK) which plays a Key role for regulating carbohydrate and fat metabolism[67].

In vitro studies mentioned in this review, reveal that among the seven ingredients of *Avirai Kudineer*, Cassia auriculata, Cassia fistula, Salacia reticulata, Cyperus rotundus and Terminalia arjuna has either or both alpha-amylase and alpha-glucosidase inhibitory activity. Syzygium cumini shows inhibition of intestinal glucose uptake and Costus speciosus is reported to stimulate insulin secretion and tissue glucose uptake. Thus all of them act synergistically as effective anti-diabetic agents. In vivo studies of Cassia auriculata flowers, leaf and root extracts on diabetic rats, reports it to have significant antihyperglycemic effect as it decreases the blood glucose, glycosylated hemoglobin level and increases the plasma insulin level and also protects from diabetic nephropathy. Its noteworthy anti-diabetic potential makes it a vital herb which owes to the name of this herbal decoction as *Avirai kudineer*. In vitro Studies on Cassia fistula and Syzygium cumini have shown to posses anti hyperglycemic effects similar to that of glibenclamide and increase the insulin levels. In vitro Studies on Salacia reticulata extracts has shown to reduce aldohexose level suggesting its anti-diabetic potential and studies on Cyperus rotundus has been reported to have hypoglycemic potential and it also hastened the wound healing effect in diabetic rats which supports its efficacy in diabetic ulcers. Studies on Cyperus rotudus also report it to play a major role in the protection of neurodegenerative disorders. In vitro studies on Costus speciosus reduced the blood glucose level and increased the secretion of insulin. In vitro studies on Terminalia arjuna decreased HbA1C levels in diabetic rats and enhances the peripheral uptake of glucose in tissue and increases the glycogen storage in Liver. Therefore all these results unveil the fact that *Avirai kudineer* not only influences the causal component of diabetes (i.e. Blood sugar) but also the effect component of molecular pathology (i.e. polyol pathway effect and antioxidant potential) which may contribute to the prevention of diabetic complication by

reducing the oxidative stress and tissue injury. Hence it can be concluded that *Avirai kudineer* is a polyherbal formulation with multi-nodal anti diabetic actions and may serve as a potent anti diabetic agent.

VII. Conclusion

Through this review, the plants Cassia auriculata (Avirai), Cassia fistula (Kondrai), Syzygium cumini (Naval), Salacia reticulata (Kadalazhinjil), Saussurea lappa (koshtam), Terminalia arjuna (Marutham) and Cyperus rotundus (Korai kizhangu) which are the ingredients of *Avirai Kudineer* have been shown to have varying degrees of Anti-diabetic, antioxidative, vascular regenerative and hypolipidemic actions. Hypoglycemic effects and pharmacological actions of *Avirai kudineer* as mentioned in Siddha literature based on its tastes as well as its scientific explanations have demonstrated its significance in the control of diabetes and its complications. Therefore it necessitates to carryout collaborative research and clinical trials to overcome the present day challenges of diabetes mellitus and for the development of plant-based drugs particularly *Avirai kudineer* which is relatively safe, efficient and economical on prolong usage than their analogues.

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