4. REVIEW OF LITERATURE

Diabetes mellitus, a metabolic disorder, is becoming a serious threat to health of people. The prevalence of diabetes mellitus is expected to reach up to 4.4% in the world by 2030[1]. The people with diabetes in the world are expected to approximately double between 2000 and 2025. India leads the world with largest number of diabetic subjects being termed as 'diabetes capital of the world' [2-3]. Plants have been used since time immemorial for medicinal purposes and form the origin of much of modern Pharmacotherapy. Many plants are reported to be useful in the treatment of Diabetes mellitus.

"Aavarai kudineer formulation"[23] is a polyherbal Siddha formulation useful in the treatment of Diabetes. Literature survey on Aavarai kudineer formulation was carried out from various books, journals reputed libraries and also from various websites, online publishers on ethnobotony, pharmacognosy, phytochemistry and pharmacological aspects. The literature review revealed that the "Aavarai kudineer formulation" is scientifically under explored. Further the ingredients of "Aavarai kudineer formulation" have been proved to be Hypoglycemic, Anti-hyperglycemic, Anti-diabetic and Hypo-cholestrolemic. Phyto-formulation studies of "Aavarai kudineer formulation" have not been carried out till date.

Aavarai kudineer formulation consists of fine powders of leaves of *Cassia auriculata* (Aavarai ilai) & *Cassia fistula* (Kondrai ilai), seeds of *Syzygium cumini* (Naval kottai), roots of *Salacia chinensis* (Kadal azhingil), rhizomes of *Costus speciosus* (Koatam) & *Cyprus rotundus* (Korai kizhangu), bark of *Terminalia arjuna* (Marutham pattai). Polyherbal formulation in powdered form where the botanical ingredients are not

more than ten can be evaluated microscopically. The hypoglycemic activity of various extract and various parts of some individual ingredients of Aavarai kudineer formulation has already been reported. In the present investigation Exo-morphology, Histo-morphology, Powder microscopy, Toxicity/safety profile, Preliminary phyto-chemical and Phyto-analytical, Physico-chemical constants, Pre-formulation, Phyto-formulation studies, and Pharmacological screening of the selected formulation has been carried out.

The review of literature of the seven raw materials of the Siddha official antidiabetic formulation "Aavarai Kudineer" is presented here in alphabetical order.

1. Literature review of *C. auriculata*

- Annie., *et al.,* (2005)[36] studied the effect of *Cassia auriculata* Linn. Root extract on Cisplatin and Gentamicin-induced renal injury.
- Ganesh Kumar., *et al*., (2011)[37] studied the facile green synthesis of gold nanoparticles using leaf extract of potent antidiabetic plant *Cassia auriculata.*
- Gupta., *et al.,* (2009)[38] studied the protective role of *Cassia auriculata* leaf extract on hyperglycemia-induced oxidative stress and carried out toxicity studies.
- Ira Thabrew., *et al*., (2004)[39] studied the effects of *Cassia auriculata* and *Cardiospermum halicacabum* tea's on the steady state blood level and toxicity of Carbamazepine.
- Kumaran., *et al.,* (2007)[40] studied the antioxidant activity of *Cassia auriculata* flowers.

- Nageswara Rao., *et al*., (2000)[41] studied the constituents of *Cassia auriculata* (The isolation and spectral data of di-(2-ethyl) hexyl phthalate (1) from *Cassia auriculata* leaves are reported).
- Prasanna., *et al*., (2009)[42] studied the anti-cancer effect of *Cassia auriculata* leaf extract *in vitro* through cell cycle arrest and induction of apoptosis in human breast and larynx cancer cell lines.
- Rajesh Ramasamy., *et al.,* (2011)[43] studied the immunomodulatory activity of polyphenols derived from *Cassia auriculata* flowers in aged rats.
- Sabu., *et al*., (2002)[44] studied the effect of *Cassia auriculata* Linn. on serum glucose level, glucose utilization by isolated rat hemi-diaphragm.
- Solomon Habtemariam., *et al.,* (2011)[45] studied antioxidant compounds from a South Asian beverage and medicinal plant, *Cassia auriculata.*
- Suman Bala Sharma., *et al.,* (2009)[46] studied the antihyperglycemic and hypolipidemic activity of aqueous extract of *Cassia auriculata* L. leaves in experimental diabetes.
- Surana., *et al*., (2008)[47] studied the antihyperglycemic activity of various fractions of Cassia auriculata Linn.in Alloxan diabetic rats.
- Vasanthi Nachiappan., *et al.,* (2013)[48] studied the antihyperlipidemic activity of *Cassia auriculata* flowers in triton WR 1339 induced hyperlipidemic rats.
- Yesu Raj., *et al.,* (2012)[49] studied the chemical compounds investigation of *Cassia auriculata* seeds.
- Yesu Raj., *et al.,* (2012)[50] reviwed that medicinal value of avaram (*cassia auriculata linn.*).

2. Literature review of *C. fistula*

- Becker., *et al*., (2002)[51] studied the antioxidant activity of Indian Laburnum (*Cassia fistula* L.) stem bark, leaves, flowers and fruit pulp.
- Bhakta., *et al*., (2001)[52] evaluated the hepatoprotective activity of *Cassia fistula* leaf extract.
- Devang J Pandya., *et al*., (2012)[53] studied the pharmacognostic and phytochemical evaluation of leaves of *Cassia fistula*.
- Gupta., et al., (2000)[54] studied the antitumor activity of methanolic extract of *Cassia fistula* L. seed against Ehrlich Ascites Carcinoma.
- Haq Nawaz Bhatti., *et al*., (2007)[55] carried out the Kinetic studies for Ni(II) biosorption from industrial waste water by *Cassia fistula* (Golden Shower) biomass.
- Ignacimuthu., (2011)[56] studied the antifeedant and larvicidal activities of Rhein isolated from the flowers of *Cassia fistula* L.
- Ignacimuthu and Duraipandiyan., (2007)[57] studied the antibacterial and antifungal activity of *Cassia fistula* L.
- Malpani., *et al.*,(2010)[58] studied the antidiabetic activity and carried out the phytochemical investigation of *Cassia fistula* Linn. bark.
- Malpani., *et al.*,(2010)[59] studied the antidiabetic activity of *Cassia fistula* Linn. bark in Alloxan induced diabetic rats.
- Manonmani., *et al*., (2005)[60] studied the antioxidant activity of *Cassia fistula* (Linn.) flowers in alloxan induced diabetic rats.

- Praveen kumar sehgal., (2006)[61] studied the wound healing potential of *Cassia fistula* on Infected Albino Rat Model.
- Sivanesan Karthikeyan., (2007)[62] Studied the Effect of *Cassia fistula* Linn. leaf extract on diethylnitrosamine induced hepatic injury in rats.
- Thirumal., et al., (2012)[63] Studies the pharmacognostical, phytochemical and pharmacological review of *Cassia fistula* Linn.

3. Literature review of *S. cumini*

- Abd El-Moneim M. R. Afify., *et al*., (2011)[64] studied the anticancer and antioxidant activities of *Syzygium cumini (*pomposia).
- Adriana Z. Mercadante., *et al*., (2011)[65] Identified the bioactive compounds from jambolana (*Syzygium cumini*) and evaluated the antioxidant capacity evaluation in different pH conditions.
- Balakrishnan., *et al*., (2006)[66] studied the *in vitro* glucose uptake activity of *Aegles marmelos* and *Syzygium cumini* by activation of Glut-4, PI3 kinase and PPARγin L6.
- Bhagyalakshmi Neelwarne., *et al*., (2007)[67] studied the chemical nature, stability and bioefficacies of anthocyanins from fruit peel of *Syzygium cumini* Skeels.
- Bhagyalakshmi Neelwarne., *et al*., (2008)[68] studied the efficient amelioration of carbon tetrachloride induced toxicity in isolated rat hepatocytes by *Syzygium cumini* Skeels extract.
- Bigoniya., *et al*., (2012)[69] carried out the pharmacognostical and physico-chemical standardization of *Syzygium cumini* and *Azadirachta indica* seeds.

- Bratati De., *et al*., (2005)[70] studied the *in vitro* study of antioxidant activity of *Syzygium cumini* fruits.
- Chandra, S., *et al*., (2001)[71] studied the anti-inflammatory activity of *Syzygium cumini* bark.
- Claudio Coimbra Teixeira., *et al.,* (1997)[72] studied the effect of *Syzygium cumini* (L.) skeels on post-prandial blood glucose levels in non-diabetic rats and rats with Streptozotocin-induced diabetes mellitus.
- Emad A Shalaby., *et al*., (2011)[73] studied the acaricidal activity of different extracts of *Syzygium cumini* L. Skeels (Pomposia) against *Tetranychus urticae* Koch.
- Ganesh Chandra Jagetia and Manjeshwar Shrinath Baliga., (2002)[74] proved that *Syzygium cumini* (Jamun) reduces the radiation-induced DNA damage in the cultured human peripheral blood lymphocytes: a preliminary study.
- Himesh Soni., *et al*., (2011)[75] carried out pharmacognostic studies of the leaves of *Syzygium cumini* Linn.
- Jasmin., and Daisy., (2007)[76] evaluated the hypoglycemic and hypolipidimic activity of methonolic extract of seeds of *Eugenia jambolana* in Streptozotocin induced diabetic rats.
- Jitender Sharma., *et al*., (2007)[77] studied the production of Tannase from *Aspergillus ruber* under solid-state fermentation using jamun (*Syzygium cumini*) leaves.

- Kanaka Latha Alikatte., *et al*., (2012)[78] studied the antiamnesic activity of *Syzygium cumini* against Scopolamine induced spatial memory impairments in rats.
- King., *et al*., (2007)[79] carried out the equilibrium and kinetic studies of removal of lead from aqueous solution using *Syzygium cumini* L.
- King., *et al*., (2008)[80] carried out the equilibrium and kinetic studies biosorption of Zinc on to *Syzygium cumini* L.
- Krishna Murti., *et al*., (2012)[81] carried out the exploration of preliminary phytochemical studies of Seed of *Syzygium cumini.*
- Kumar., *et al*., (2009)[82] studied the phytochemicals investigation on a Tropical Plant, *Syzygium cumini* from Kattuppalayam, Erode District, Tamil Nadu, South India.
- Kumpati Premkumar., *et al*., (2011)[83]studied the role of *Syzygium cumini* seed extract in the chemoprevention of *in vivo* genomic damage and oxidative stress.
- Márcio M. Coelho., *et al*., (2005)[84] studied the effect of the extracts and fractions of *Baccharis trimera* and *Syzygium cumini* on glycaemia of diabetic and non-diabetic mice.
- Md. Fahim Kadir., *et al*., (2012)[85] evaluated the anti-diabetic phytochemicals in *Syzygium cumini* (L.) Skeels (Family: Myrtaceae).
- Muniappan Ayyanar and Pandurangan Subash-Babu., (2012)[86] reviewed the phytochemical constituents and traditional uses *of Syzygium cumini* (L.) Skeels.

- Puspita sari., *et al*., (2012)[87] studied the colour properties, stability and free radical scavenging activity of jambolana (*Syzygium cumini*) fruit anthocyanins in a beverage model system: Natural and co-pigmented anthocyanins.
- Rao., *et al*., (2011)[88] studied the modeling of kinetics of Cd (II) adsorption on *Syzygium cumini L* leaf powder in a fixed bed mini column.
- Ravi., *et al.,* (2004)[89] have studied the anti-diabetic activity of *Eugenia jambolana* seed kernels on Streptozotocin –induced diabetic rats.
- Shafi., *et al*., (2002)[90] studied the antibacterial activity of *Syzygium cumini* and *Syzygium travancoricum* leaf essential oils.
- Sharma., *et al.,* (2003)[91] demonstrated hypoglycemic and hypolipidimic effect of ethanolic extract of seeds of *Eugenia jambolana* in Alloxan –induced diabetic rats.
- Shivashankara., *et al*., (2013)[92] studied the antidiabetic and hypoglycemic effects of *Syzygium cumini* (Black Plum).
- Vasanth Kumar., *et al*., (2007)[93] carried out the equilibrium and kinetic studies on the removal of lead from aqueous solution using *Syzygium cumini* L.
- William Zito., *et al*., (2008)[94] studied the α-Glucosidase inhibitory activity of *Syzygium cumini* (Linn.) Skeels seed kernel in vitro and in Goto–Kakizaki (GK) rats.

4. Literature review of *S. chinensis*

- Krishnan and Rangaswami., (1967)[95] studied the proanthocyanidins of *Salacia chinensis* Linn.
- Masakazu Kobayashi., *et al*., (2012)[96] studied the effects of *Salacia chinensis* extract on reproductive outcome in rats.

- Masayuki Yoshikawa., *et al*., (2008)[97] studied the absolute stereostructures of three rare D:B-friedobaccharane skeleton triterpenes from the leaves of *Salacia chinensis.*
- Moorthy Kannaiyan., *et al*., (2012)[98] studied the antimicrobial activity of the ethanolic and aqueous extracts of *Salacia chinensis* Linn. against human pathogens.
- Osamu Muraoka., *et al*., (2010)[99] quantitatively determined the potent α-glucosidase inhibitors, salacinol and kotalanol, in *Salacia* species using liquid chromatography–mass spectrometry.
- Yuhao Li., *et al*., (2008)[100] studied the *Salacia* root,as a unique Ayurvedic medicine, meeting multiple targets in diabetes and obesity.

5. Literature review of *C. speciosus*

- Akhila., *et al*., (1987)[101] studied the direct cyclisation of squalene to 5α-stigmast-9(11)-en-3β-ol via $\Delta^{9(11)}$ lanosterol in *costus speciosus*.
- Anand Akhila and Madan M. Gupta., (1987)[102] studied the biosynthesis and translocation of Diosgenin in *Costus speciosus.*
- Phytochemical and antimicrobial studies of *Costus Speciosus* (Koen.) was carried out by Aparna Saraf., (2007)[103]
- Binny., *et al.*, (2010)[104] studied the anti-inflammatory and antipyretic properties of the rhizome of *Costus speciosus* (koen.) sm.
- Chaturvedi., *et al*., (1984)[105] studied the proliferation of shoot tips and clonal multiplication of *Costus speciosus* in long-term culture.

- Choudhury Najma., *et al*., (2012)[106] studied the effect of *Costus speciosus* Koen on reproductive organs of albino mice.
- Dobey Subodh., *et al*., (2010)[107] evaluated the diuretic activity of aqueous and alcoholic extracts of rhizomes of *Costus speciosus* Linn. in wister albino rats.
- Ignacimuthu., *et al*., (2009)[108] evaluated the antidiabetic and antilipidemic effect of eremanthin from *Costus speciosus* (Koen.)Sm., in STZ-induced diabetic rats.
- Jasmin and Narasimhacharya., (2008)[109] evaluated the antihyperglycemic and hypolipidemic effects of *Costus speciosus* in Alloxan induced diabetic rats.
- Kentaro Inoue., *et al*., (1996)[110] studied the conversion of furostanol glycoside to spirostanol glycoside by β-glucosidase in *Costus speciosus.*
- Madan M. Gupta., *et al*., (1981)[111] studied the 5α-Stigmast-9(11)-en-3β-ol, a sterol from *Costus speciosus* roots.
- Madan M. Gupta., *et al*., (1981)[112] studied the aliphatic hydroxyketones and diosgenin from *Costus speciosus* roots.
- Madan M. Gupta., *et al*., (1982)[113] studied the aliphatic compounds from *Costus speciosus* roots.
- Nitin Verma and Khosa., (2012)[114] standardized the *Costus speciosus* rhizomes with special reference to its pharmacognostical and HPTLC studies.
- Savarimuthu Ignacimuthu., *et al*., (2009)[115] studied the normo-glycemic and hypolipidemic effect of Costunolide isolated from *Costus speciosus* (Koen ex. Retz.) Sm. in Streptozotocin-induced diabetic rats.

- Sheo B. Singh and Raghunath S. Thakur., (1982)[116] studied the Costusoside-I and Costusoside-J, two new furostanol saponins from the seeds of *Costus speciosus*
- Shruti Srivastava1., *et al*., (2011)[117] wrote a review on *Costus speciosus* (Keukand).
- Shukla., *et al*., (1990)[118] studied the Drechslerol-C, a phytotoxin produced by *Drechslera maydis*, the causitive organism of leaf blight of *Costus speciosus.*
- Shukla., *et al*., (1987)[119] studied the Drechslerol-A, a new phytotoxic metabolite produced by *Drechslera maydis*, a strain from *Costus speciosus.*
- Tschesche and Pandey., (1978)[120] studied the steroidal saponins of *Costus speciosus.*
- Umar Mahmood., *et al*., (1984)[121] studied the benzoquinones from *Costus speciosus* seeds.
- Yutaka Ebizuka and Kentaro Inoue., (1996)[122] studied the purification and characterization of furostanol glycoside 26-*O*-*β*-glucosidase from *Costus speciosus* rhizomes.
- Yutaka Ebizuka., *et al*., (1996)[123] studied the molecular cloning and bacterial expression of a cDNA encoding furostanol glycoside 26-*O*-*β*-glucosidase of *Costus speciosus.*

6. Literature review of *C. rotundus*

- Barreto and Evans., (1995)[124] studied the Mycobiota of the weed *Cyperus rotundus* in the state of Rio de Janeiro, with an elucidation of its associated *Puccinia* complex.
- Divya Kumari Kajaria., *et al*., (2012)[125] evaluated the antimicrobial activity and bronchodialator effect of a polyherbal drug–Shrishadi containing Shirisha (*Albezzia lebbeck*), Nagarmotha (*Cyprus rotandus*) & Kantakari (*Solanum xanthocarpum*).
- Meena., *et al*., (2010)[126] wrote a review on *Cyperus rotundus* - A Potential Herb.
- Nishikanth, A R and Naresh, J G., (2006)[127] studied the antidiabtic activity of hydro-ethanolic extract of *Cyperus rotundus* in alloxan induced diabetic rats.
- Rai puneetkumar., (2010)[128] carried out the preliminary phytochemical investigation of *Cyperus rotundus* Linn. Rizhome.
- Sri Ranjani Sivapalan & Prince Jeyadevan., (2012)[129] studied the physico-chemical and phyto-chemical constituents of rhizome of *Cyperus rotundus* linn.

7. Literature review of *T. arjuna*

- Anjaneyulu and Rama Prasad., (1982)[130] carried out the chemical examination of the roots of *Terminalia arjuna* and determined the structures of arjunoside III and arjunoside IV, two new triterpenoid glycosides.
- Anjaneyulu and Rama Prasad., (1983)[131] studied the structure of Terminic acid, a dihydroxytriterpene carboxylic acid from *Terminalia arjuna.*
- Anu T. Singh., *et al*., (2008)[132] studied the protective effects of *Terminalia arjuna* against Doxorubicin-induced cardiotoxicity.
- Behl., *et al*., (1999)[133] studied the influence of planting density on growth and biomass productivity of *Terminalia arjuna* under sodic soil sites.
- Bharani., (1995)[134] studied the salutary effect of *Terminalia arjuna* in patients with severe refractory heart failure.
- Bhutani and Pawar., (2005)[135]studied the effect of oleanane triterpenoids from *Terminalia arjuna* on the process of respiratory oxyburst.
- Chun-Ching Lin., *et al*., (2002)[136] studied the anti-herpes simplex virus type 2 activity of casuarinin from the bark of *Terminalia arjuna* Linn.
- Damodaran., (1987)[137] studied the ethnomedical significance of the arjun tree, *Terminalia arjuna* (Roxb.) Wight & Arnot.
- Dwivedi.S., *et al*., (2005)[138] studied the role of *Terminalia arjuna* in ischaemic mitral regurgitation.
- Farooq Anwar., *et al*., (2007)[139] studied the antioxidant activity of phenolic components present in barks of *Azadirachta indica*, *Terminalia arjuna*, *Acacia nilotica* and *Eugenia jambolana* Lam. Trees.

- Fayez., *et al*., (1998)[140] evaluated a tannin anti-cancer promotor from *Terminalia arjuna.*
- George R. Pettit., (1996)[141] studied the antineoplastic agents 338. The cancer cell growth inhibitory constituent of *Terminalia arjuna* (Combretaceae).
- Gollapalle Lakshminarayana shastry Viswanatha et al., (2010)[142] studied the antioxidant and antimutagenic activity of bark extract of *Terminalia arjuna.*
- Gupta., *et al*., (2002)[143] carried out the RP-LC of oleane derivatives in *Terminalia arjuna.*
- Ikhlas A. Khan., *et al*., (2010)[144] studied the Ursane triterpenoids from the bark of *Terminalia arjuna.*
- Jain., *et al*., (1998)[145] studied the Biomass production and soil amelioration in a high density *Terminalia arjuna* plantation on sodic soils.
- Kaur., *et al*., (2000)[146] studied the modulatory effects of a tannin fraction isolated from *Terminalia arjuna* on the genotoxicity of mutagens in *Salmonella typhimurium.*
- Kaur., *et al*., (2002)[147] studied the antimutagenic activity of acetone and methanol fractions of *Terminalia arjuna*.
- Kulshrestha Mayank Krishna and Karbhal Kamleshwar Singh., (2012)[148] Studied the Effect of different drying methods on the quality of the stem bark of *Terminalia arjuna (*Roxb.)
- Kumar and Maulik., (2013)[149] studied the effect of *Terminalia arjuna* on cardiac hypertrophy.

- Maulik., *et al*., (2001)[150] studied the effect of chronic treatment with bark of *Terminalia arjuna* on the isolated ischemic-reperfused rat heart
- Maulik., *et al*., (2005)[151] proved that *Terminalia arjuna* (Roxb.) protects rabbit heart against ischemic-reperfusion injury.
- Meikap., (2005)[152] studied the removal of chromium (VI) from dilute aqueous solutions by activated carbon developed from *Terminalia arjuna* nuts activated with zinc chloride.
- Niranjali Devara., *et al*., (2003)[153] studied the cardioprotective effect of the alcoholic extract of *Terminalia arjuna* bark in an *in vivo* model of myocardial ischemic reperfusion injury.
- Padmaa M. Paarakh., (2010)[154] wrote a review on *Terminalia arjuna* (Roxb.)Wt. And Arn.
- Parames C. Sil., *et al*., (2007)[155] studied the phytomedicinal activity of *Terminalia arjuna* against carbon tetrachloride induced cardiac oxidative stress.
- Parames C. Sil., *et al*., (2010)[156] studied the protective effect of the fruits of *Terminalia arjuna* against cadmium-induced oxidant stress and hepatic cell injury via MAPK activation and mitochondria dependent pathway.
- Rajeev Gupta., *et al*., (1997)[157] studied the Hypocholesterolaemic effects of *Terminalia arjuna* tree bark.
- Shi J. Liu., *et al*., (2011)[158] studied that aqueous extract, not organic extracts, of *Terminalia arjuna* bark exerts cardiotonic effect on adult ventricular myocytes.
- Shridhar Dwivedi., (2007)[159] studied the *Terminalia arjuna* Wight & Arn .as a useful drug for cardiovascular disorders.

- Sushma., (2003)[160] studied the comparative effect of oral administration and topical application of alcoholic extract of *Terminalia arjuna* bark on incision and excision wounds in rats.
- Tripathi., *et al*., (1992)[161] isolated Arjunolitin, a triterpene glycoside from *Terminalia arjuna.*
- Yadav and Rathore., (2001)[162] isolated new cardenolide from the roots of *Terminalia arjuna.*