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Clinical Evaluation of Siddha Formulation Pereechangai Nei in the Management of Madhumegam (Type 2 Diabetes Mellitus)

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Abstract
Pereechangai nei is a medicated ghee formulation mentioned in Siddha literatures for management of Madhumegam (Type-2 Diabetes mellitus). For its scientific validation this drug was studied for its therapeutic effectiveness in Madhumegam patients. Its well designed protocol was approved by Institutional Ethics Committee and the study been enrolled in Clinical Trial Registry of India. The clinical study was conducted as an Prospective, open label clinical trial in OPD of Ayothidoss pandithar Hospital of National Institute of Siddha Chennai. Based on the inclusion criteria 40 Madhumegam patients (Type-2 Diabetes mellitus) were enrolled in this study. Informed consent was obtained from each patient before study initiation. Pereechangai nei of 5ml dose was administered orally twice a day before food for a period of 90 days and advised to follow the prescribed dietary regimen. All the baseline data, Laboratory investigations were recorded in the prescribed Case Report Form of each patient. Blood sugar level in fasting and postprandial was done once in 30 days and HbA1c was done before treatment (0th day) and after treatment (90th day). The clinical assessment was recorded once in 10 days. Student 't' test was employed to test the significance of treatment using before and after treatment data on HbA1c, Clinical symptoms, Blood sugar fasting and postprandial. The level of significance probability 0.05 was used to test the treatment difference and the values are statistically extremely significant with score ($p < 0.0001$).

Keywords: Madhumegam, Type -2 Diabetes mellitus, Azhinjiathikashayam, Clinical trial, Siddha medicine
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***Keywords:** HbA1c, Madhumegam, Medicated ghee, Siddha literature, Type-2 Diabetes mellitus.*

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I. Introduction

In Siddha system of medicine, Madhumegam is a type of Meganeer which is characterized by passing of sweet urine as per Saint Yugi. Based on the derangement of three vital humours, "Meganeer" is classified into twenty types in which four comes under Vatham, six under Pitham and ten under Kabam. The One called Madhumegam (Honey urine) comes under Pitham type.

In Siddha system of medicine, Saint Yugi mentioned Madhumegam as one of the type of Meganeer, which is characterized by passing of sweet urine. Also, based on the derangement of three vital humours, "Meganeer" is classified into twenty types in which four comes under vatham, six under pitham and ten under kabam. Madhumegam (Honey urine) comes under pitham type. As per the text Agasthiar 1200 ,Madhumegam is characterized by the symptoms of excessive urination with sweetness (polyurea), excessive thirst (polydypsea), excessive hunger (polyphagia), and significant weight loss. The text also mentions the causes for the disease as, excessive indulgence in sex, increased body heat (pitham), excessive food intake like fish, ghee, milk, toddy etc., physical inactivity, stress and genetic factors to name few. These causes and symptoms can be correlated with Type 2 Diabetes mellitus in modern system of medicine.

According to World Health Organisation (WHO), the number of people with diabetes has raisen to 422 million and 1.6 million deaths are directly attributed to diabetes each year. WHO estimates that DM as the seventh leading cause of death. Treatment for such life style disorders for prolonged duration with synthetic drugs add to the concern of adverse drug reactions and several side effects. Here comes the major role of traditional systems like siddha with its holistic approach and with herbal medicines of no or least side effects

adds immense potential and demand for its use these days. This is considered as a boon for middle and low income countries who are majorly been affected.

In siddha classical texts, many herbal, mineral, herbomineral formulations have been mentioned for the treatment of Madhumegam. One among such classical text called, "Therayar Maha Karisal" mentions about "Pereechangai nei'' a polyherbal medicated ghee formulation recommended exclusively for the treatment of Madhumegam. The ingredients of "PEREECHANGAI NEI"" includes Phonex *dactilifera,linn* (Dry Fruit) , roots of Pavonia *odorata* , Plumbago *indica*, Trichosanthus *cucumerina*, Hemidesmus *indicus*, Aerva *lanata*, Cassia *fistula* ,Michelia *champaca* , Strigus *lutea* , Zingiber *officinale*(Rhizome) , fruits of Piper *nigrum* , Piper *longum*, Elettaria *cardamomum*, Syzygium *aromaticum*, (Bud) and cow's ghee have been identified for their individually proven Antihyperglycemic activity. This study records its therapeutic efficacy clinically in Madhumegam patients.

II. Materials And Methods

The clinical study was conducted using a standard protocol, after obtaining the approval of the Institutional Ethical Committee (IEC) (NIS/ IEC/9/2014-15/6-26.08.2015). It is an Open Clinical Trial conducted at Ayothidoss Pandithar Hospital OPD.NO.1 Dept of Maruthuvam (Medicine), National Institute of Siddha, Tambaram sanatorium, Chennai.

Subject selection: Patients reporting at the OPD of Ayothidass Pandithar Hospital with symptoms of inclusion criteria will be subjected to screening test and documented by using screening proforma. After screening of 90 patients diagnosed as Madhumegam (Type 2 Diabetes mellitus), 40 cases were selected to this trial. Before enrollment into the trial the informed consent was obtained from all the study participants.

Inclusion criteria:

- Age : 30-55 yrs.
- Sex : male & female
- Fresh/Old cases will be included
- HbA1C >6.5
- Patients who is already under siddha medication for mathumegam.
- Diabetes with Hypertension
- Symptoms of Polyuria, Nocturia, Polydipsia, Polyphagia, Body pain, Weight gain, Tiredness, Burning feet and genital pruritus. Patients who fulfil any of the above three criteria will be included in the clinical trial.

Exclusion criteria

- IDDM (Insulin Dependent Diabetes Mellitus)
- HbA1C>9
- Cardiac diseases
- Pulmonary diseases
- Renal diseases
- Thyroid dysfunctions
- Gestational diabetes
- Other endocrine abnormalities
- Patient who are not willing to give blood sample
- Patients under allopathy medication
- Patients developed any complications of Diabetes Mellitus.

Withdrawal criteria

- Intolerance to the drug and development of any serious adverse reactions during drug trial.
- Poor patient compliance and defaulters.
- Patient turned unwilling to continue in the course of clinical trial.
- Increase in severity of symptoms, Uncontrolled blood sugar level

Conduct of study

All the patients were given unique registration card having patient's Registration number of the study, Address, Phone number and investigator's contact number etc. All the baseline findings, vitals, clinical signs and symptoms (Increased frequency of Urination (polyuria), Thirst (polydipsia), Excessive hunger (polyphagia), Body pain, Tiredness, Burning feet, Generalized/genital pruritis, Dull pain in the testis, Yellow coloured urine) and laboratory data (Haematology, Blood biochemistry, Lipid profile, LFT& RFT, HbA1c, Urine analysis) and

in siddha aspect En vagai thervugal were recorded in the Case Report Form (CRF) before (i.e., 0th day), commencement of the trial.

Each study drug packages contain 100ml of Pereechangai nei . Patients were advised to take 5ml before food every day for two times for 90 days. At each visit (once in 10 days for 90 days) the patients were given the above drug packages for 10 days of treatment. At each visit the patients were advised to bring back the unconsumed drugs and return to the investigator. Each visit, the patient's vitals and clinical assessments were recorded in the case report form by the investigator. Laboratory investigations were done at the end of the treatment.

III. Observation:

1.Age distribution: [table: 1]

Age	No of cases	Percentage%
30-40	14	35
41-50	22	55
51-55	4	10

Among the 40 cases treated 14 cases (35%) belonged to 30-40 years, 22 cases (55%) belonged to 41-50 years and 4 cases (10%) belonged to 51- 55 years.

2..Sex distribution: [table: 2]

Patients	No of cases	Percentage (%)
Male	17	42.5%
Female	23	57.5%

Among 40 cases of both sexes selected, 17 cases (42.5%) were Male and 23 cases (57.5%) were Female.

3.Religion status: [table:3]

Religion	No of cases	Percentage (%)
Hindu	34	85
Muslim	3	7.5
Christian	3	7.5

Among 40 cases 34 cases (85%) were Hindus, 3 cases (7.5%) were Muslims, and 3 cases (7.5%) were Christians.

4.Educational status: [table: 4]

Educational status	No of cases	Percentage (%)
Literate	26	65
Illiterate	14	35

Among 40 cases 26 cases (65%) were literate, 14 cases (35%) were Illiterate.

5.Occupational status: [table: 5]

Occupation	No of cases	Percentage (%)
Homemakers	20	50
Employees	13	32.5
Businessmen	4	10
Teachers	2	5
Driver	1	2.5

Among 40 cases 20 cases (50%) were Homemakers, 13 cases (32.5%) were working as employees, 4 cases (10%) were Bussinessmen, 2 cases (5%) were Teachers, and 1case (2.5%) was Driver. Homemakers are more affected, this be can due to excess workload and stress.

6.Marital status: [table: 6]

Marital status	No of cases	Percentage (%)
Married	40	100
Unmarried	0	0

Among 40 cases, all 40 cases (100%) were married.

7.Socio- economic status: [table: 7]

S.No	Economic status	No of cases	Percentage (%)
1.	Middle class	26	65
2.	Poor	8	20
3.	Rich	6	15

Among 40 cases 26 cases (65%) were from middle class family, 8 cases (20%) were from poor socio- economic status and 6 cases (15%) were from Rich.

8.Menopausal status: [table:8]

Menopause	No of cases	Percentage (%)
Attained	12	52
Not Attained	11	48

Among 23 female cases ,12 cases(52%) were attained menopause 11 cases(48%) were not attained menopause,.

9.Family history: [table: 9]

Family history	No of cases	Percentage (%)
Nil Family history	28	70
Positive family history	12	30

Among 40 cases 28 cases (70%) had nil relevant family history and 12 cases (30%) had positive family history of type 2 diabetes.

10.Personal habits: [table: 10]

Personal habits	No of cases	Percentage (%)
Non smokers & non alcoholic	33	83
Non Alcoholic	5	12
Non smokers	2	5

Among 40 cases 33 cases (83%) were Non smokers & Non Alcoholic, 5 cases (12%) were alcoholic and 2 were (5%) were smokers.

11.Food habits: [table: 11]

Food habits	No of patients	Percentage (%)
Non Vegetarian	0	75
Vegetarian	10	25

Among 40 cases Non vegetarian (30 cases i.e 75%) are more prone to Madhumegam than vegetarian (10 cases i.e 25%).

12.Chronicity of illness: [table: 12]

S.No	Duration of illness (Years)	No of cases	Percentage (%)
1.	0- 1	18	45
2.	Above 1 & upto 3	16	40
3.	Above 3 & upto 5	5	12.5
4.	Above 5 & 10	1	2.5

Among 40 cases, 18 cases (45%) had the history up to 0-1 year only. 16 cases (40%) suffered for >1-3 yrs, 3 cases (12%) for >3-5 yrs and 1case (3%) for >5-10 yrs.

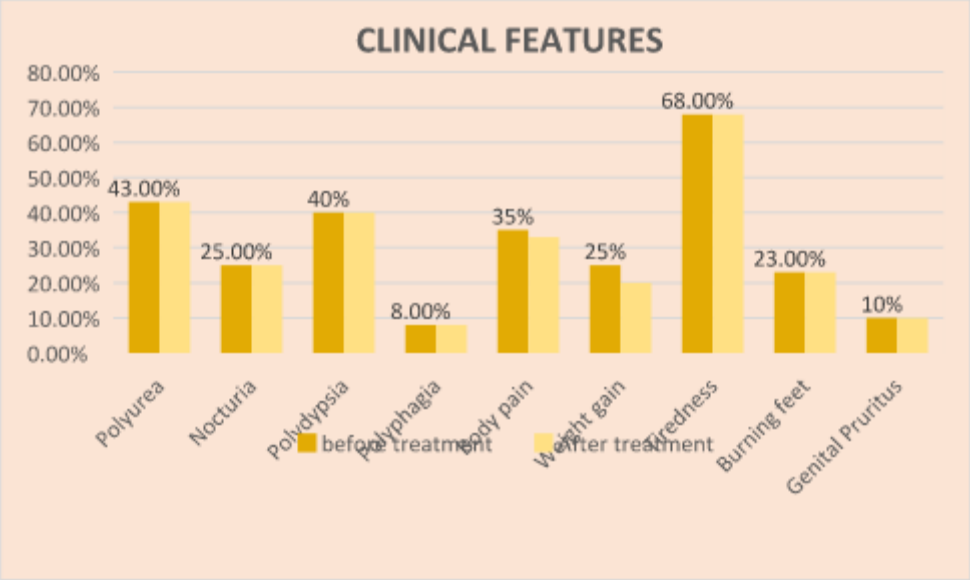
13. Past treatment history: [table: 13]

Past Treatment History	No of cases (%)	Duration of Treatment
Siddha only	20(50%)	8 months to 3 yrs
Allopathy with Siddha	15(38%)	1month to 3 yrs
No treatment history (Newly diagnosed)	5(12%)	Nil

Among 40 cases, 20 cases (50%) were under siddha treatment only, 15 cases (38%) had taken allopathic treatment in the past and were gradually shifted siddha treatment and 5(12%) cases had no past treatment history since they were newly diagnosed with diabetes.

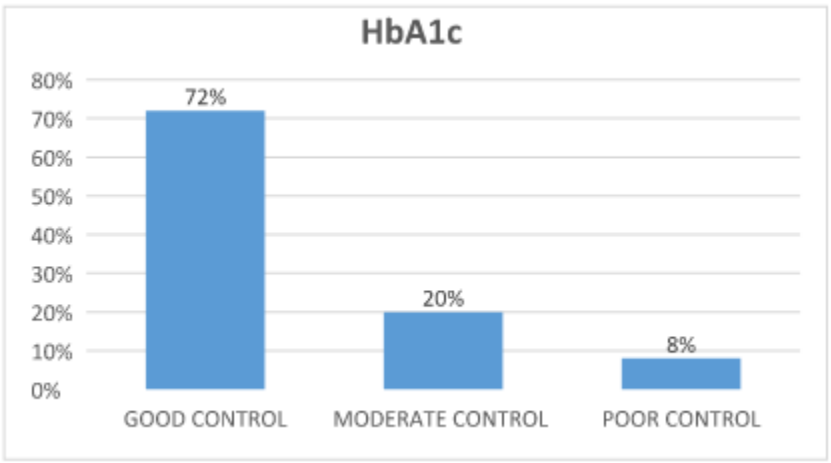
14.Clinical features: [table 14]

S.No	Clinical features	No. of cases Affected before treatment [%]	No. of cases improved after treatment [%]
1	Polyuria	17 [43%]	17[43%]
2	Nocturia	10 [25%]	10 [25%]
3	Polydypsia	16 [40%]	16 [40%]
4	Polyphagia	3 [8%]	3 [8%]
5	Body pain	14 [35%]	13 [33%]
6	Weight gain	10 [25%]	8 [20%]
7	Tiredness	27 [68%]	27 [68%]
8	Burning feet	9 [23%]	9 [23%]
9	Genital pruritis	4 [10%]	4 [10%]



15.HbA1c Results: [Table 15]

HbA1c	No of cases [Percentage %]
Good control	29 [72.5%]
Moderate control	8 [20%]
Poor control	3 [7.5%]



Good control: 1- 2.5 % decrease from its base level,
Moderate control: 0.1-0.9 % decrease from its base level,
Poor control: No change or Increase from its base level.

Results from fasting blood sugar:

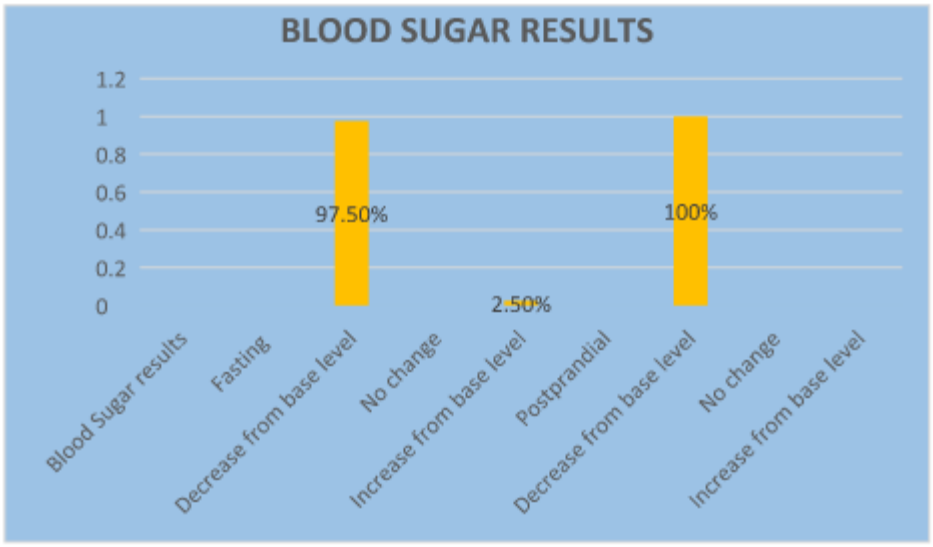
Fasting Blood Sugar	No of cases [%]
Decrease from its base level	39[97.5%]
No change from its base level	0[0%]
Increased from its base level	1 [2.5%]

Regarding Fasting blood sugar of the 40 cases, 39 cases (97.5%) decreased from its base level, and 1 case (2.5%) showed increase from its base level.

Results from Postprandial blood sugar:

Postprandial blood sugar	No of cases [Percentage %]
Decreased from its base level	40 [100%]
No change from its base level	0 [0%]
Increased from its base level	0 [0%]

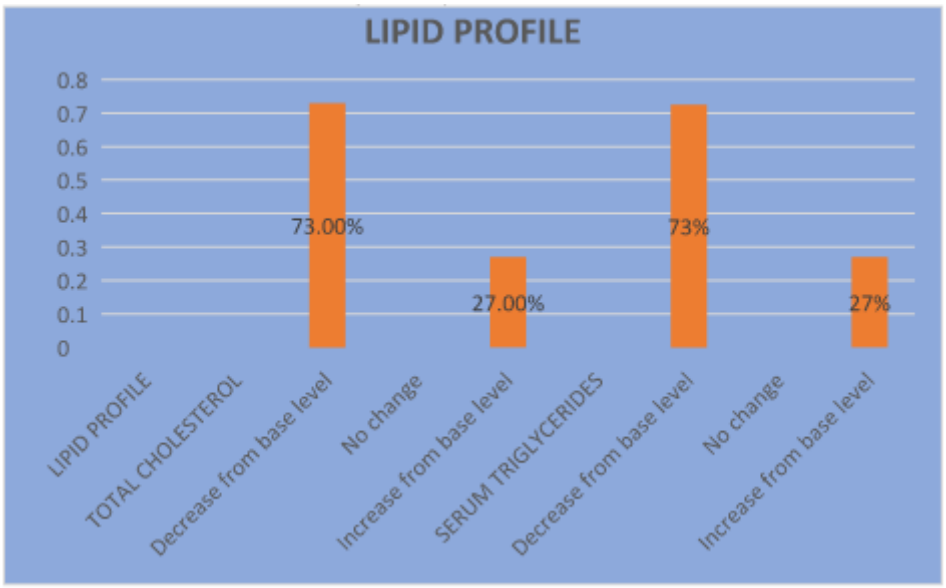
Regarding postprandial blood sugar of the 40 cases, 40 cases (100%) showed increase from its base level.



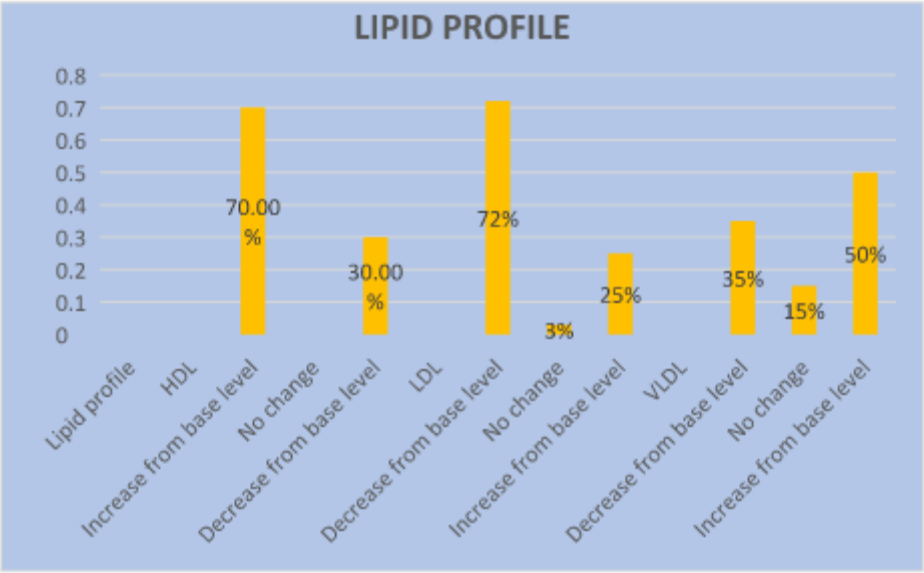
Results from Total cholesterol:

Total cholesterol	**No of cases [percentage%]**
Decrease from its base level	29 [73%]
No change from its base level	0[0%]
Increased from its base level	11[27%]

- Regarding Total cholesterol of the 40 cases, 29 cases (72.5%) showed decrease from its base level and 11 cases(27.5%) showed increase from its base level.
- Regarding Serum Triglycerides of the 40 cases, 29 cases (72.5%) showed decrease from its base level and 11 cases(27.5%) showed increase from its base level.



- Regarding HDL of the 40 cases, 28 cases (70%) showed increase from its base level and12 cases (30%) showed reduction from its base level.
- Regarding LDL of the 40 cases, 29 cases (72.5%) showed decrease from its base level , 1 case (2.5%) showed no change and 10 (25%) showed increase from its base level.
- Regarding VLDL, Out of 40 cases, 14 cases (35%) showed decrease from its base level, 6 cases (15%) showed no change and 20 cases (50%) showed reduction from its base level.



STATISTICAL ANALYSIS:

The collected data was analyzed using STATA software.The level of significance of probability value was taken as 0.05. Student 't' test was employed to determine the significance of blood sugar at before and after treatment.

Mean ±Standard deviation of HbA1c - Before and after treatment

Treatment status	Mean ±Std deviation	Significance
HbA1c before	8.075 ± 0.658	t = 8.4895, p <0.0001
HbA1c after	6.988 ± 0.473	Extremely Significant

Mean ±Standard deviation of Fasting Blood sugar - Before and After treatment

Treatment status	Mean ±Std deviation	Significance
FA before	163 ± 33.5	t = 7.81, p <0.0001
FA-- after	115 ± 20	Significant

Mean ±Standard deviation of Post prandial Blood sugar - Before and After treatment

Treatment status	Mean ±Std deviation	Significance
PP before	283 ± 44.8	t = 8.40, p <0.0001
PP after	201 ± 42.5	Significant

Mean ±Standard deviation of Total cholesterol - Before and After treatment

Treatment status	Mean ±Std deviation	Significance
T.C before	191 ± 33.9	t = 2.14, p = 0.036
T.C after	176 ± 30.3	Significant

Mean ±Standard deviation of HDL - Before and After treatment

Treatment status	Mean ±Std deviation	Significance
HDL before	48.4 ± 9.34	t = -2.27, p = 0.026
HDL after	52.6 ± 7.40	Significant

Mean ±Standard deviation of LDL - Before and After treatment

Treatment status	Mean ±Std deviation	Significance
LDL before	108 ± 21	t = 1.49, p = 0.14
LDL after	101 ± 19.1	Not significant

Mean ±Standard deviation of Triglycerides - Before and After treatment

Treatment status	Mean ±Std deviation	Significance
TGL before	168 ± 61.2	t = 2.07, p = 0.042
TGL after	144 ± 39.6	Significant

IV. Discussion

Prevalence of diabetes mellitus (DM) is rapidly rising throughout the globe at an alarming rate, where India leads with largest number of diabetics and became "diabetes capital of the world." Currently available conventional options for diabetes have certain limitations; considering which options from alternative medicines are being searched to meet the need. Siddha, the most traditional system of Indian subcontinent hold huge number of remedies that are in use for centuries in the treatment of diabetes and associated complications. The current clinical study was aimed to revalidate the actual efficacy of one such formulation in treatment of DM.

Also from January, 2020, the world is facing an unprecedented outbreak of coronavirus disease 2019 (COVID-19) caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Data from the early months of 2020 suggest that most people with COVID-19 have comorbidities, the most prevalent of which are diabetes, cardiovascular disease, and hypertension. A significant association with worse outcomes is seen in people with these comorbidities.Studies have also shown that COVID-19 is associated with hyperglycaemia particularly in the elderly with type 2 diabetes.

In this scenario those competitive drugs exerting multiactions as antiviral, antidiabetic, immunomodulatory, as nutrient for disease prone vulnerable groups and more are in real need. Unknowingly, all these requisite criteria suites very likely to centuries old Siddha medicines formulated by Siddhars in their texts. One among them, a classical text called, ‟Therayar Maha Karisal" mentions about "PEREECHANGAI NEI"‟ a polyherbal medicated ghee formulation recommended exclusively for the treatment of Madhumegam(Type2 DM).The herbal ingredients in Pereechangai Nei are found to possess antidiabetic activity along with antioxidant, antihyper lipidemic and hepatoprotective activities which can indirectly act upon glucose metabolism thereby aiding in controlling blood sugar levels and by preventing its long term complications.

- The Antidiabetic activity of Date fruit was evaluated using normo glycemic and hyperglycemic Sprague dawley rats with two doses (300 and 600mg/kg) against control, disease control and standard drug (Glibenclamide 2.5mg/kg).
- Pavonia odorata root studied for antidiabetic activity at a dose level of 100 mg/kg of CHCl3, 100mg/kg of EtOAc and 200mg/kg of MeOH in Alloxan induced diabetic rats is proven.
- Anti diabetic activity of Plumbago zeylanica root studied on GLUT4 translocation in STZ-induced diabetic rats.
- Antidiabetic activity of Trichosanthus cucumerina studied in STZ- induced diabetic rats, with continuous administration; there was a gradual reduction in FBS (by 56.8% on day 14 and by 64.4% on day 28).
- Hemidesmus indicus exhibits significant antidiabetic activity by restoring glucose metabolizing enzymes, hepatic microsomal protein and hepatic cytochrome P-450-dependent monooxygenase enzyme systems to near normal level in experimentally induced diabetic rats.
- Anthraquinones, flavon-3-ol derivatives in Cassia fistula studied using invitro assays such as alpha amylase inhibition assay and glucose diffusion assay suggest its Antidiabetic activity.
- Dry Ginger, has chemical constituents Gingerol, Zingerine, Zingeberine. Its oral administration as ethanolic extract of ginger (800 mg/kg) significantly decreases fasting blood glucose level after 1 hour treatment in an STZ-type 1 diabetic rat model.
- Anti diabetic activity of Syzygium aromaticum flower buds EtOH extract significantly suppressed an increase in blood glucose level in type 2 diabetic KK-A(y) mice and contribute to its hypoglycemic effects via PPAR-γ activation.
- The bioavailability enhancing activity of Piperine enhances further targeted delivery of the drug for action. The ghee acts as a carrier of nutrients to be absorbed across the cell membrane. Ghee contains 8% saturated fatty acids and its digestibility coefficient is 96% than other fats. It contains anti-oxidants like beta carotene 600IU and vitamin E. Researches on models of Sprague Dawley rats, showed that no effect of 5-10% ghee supplemented diets on Serum cholesterol and triglycerides. Cow ghee increases only the ‘good’ (HDL) and not the ‘bad’ cholesterol (LDL) level, because it is capable of increasing the range of vitamins soluble in fat, like Vitamin E and thereby prevents the oxidation of LDL.
- Thus the potency and efficiency of a drug is further enhanced.

The Qualitative study for pereechangai nei was done in Biochemistry lab, NIS and the results are as follows, of **Calcium, Sulphate, Fluoride and Oxalate, Carbonate, Starch, Reducing Sugar, Iron, Ammonium, Oxyquinole, Pyrocatechol, Antipyrine, Aliphatic aminoacid, Meconic acid** and absence of heavy metals such as lead, arsenic and mercury etc., which are essential to fulfill the therapeutic need.

Physico chemical analysis for pereechangai nei was done in the tamil nadu Dr.M.G.R. Medical university, Guindy, Chennai.The results were, **0% loss on drying, 0.9% total ash value, 0.5% acid insoluble ash, 0.45% water soluble ash, 18% alcohol soluble extraction** were reported.

Premilinary phytochemical analysis of the extracts of pereechangai nei showed presence of saponins, carbohydrates, protein, flavonoids, diterpenes, fat and fixed oils, quinines.

Heavy metal analysis was done for pereechangai nei at VS laboratory results shown that arsenic, mercury, lead, cadmium, copper were within the permissible limit(WHO/FDA permissible limits for ASU).

The microbial load revealed below detection limit, specific pathogen such as E.coli,Salmonella spp, S.aureus, Pseudomonas aeruginosa were Absent per g of Pereechangai nei, aflotoxin by GCMS and Pestiside Residue by GCMS were Studied in Pereechangai nei. Aflatoxin Content B2 is Present in Pereechangai nei Other Aflatoxin B1,G1,G2 and all pesticide residue revealed Below Detection Limit.

The TLC & HPTLC of Pereechangai nei was evaluated at Regional research unit of unani , Royapuram, Chennai showed TLC plate was developed using Toluene: Ethyl acetate: Formic acid (8.2: 1.8: 0.1) as mobile phase. After development allow the plate to dry in air, record the finger print and densitometric chromatogram of the two batch samples of the single compound scanned at 254 and 366 nm.

V. Conclusion

Clinical study revealed that the trial drug possessed good clinical improvement in 29 cases (72.5%) of cases.8(20%) of cases had moderate results and 3 cases(7.5%) of cases had poor prognosis through its HbA1c level study.The evidence of statistical report shows the average reduction of HbA1c from the start of treatment 8.075 to 6.988 at the end of treatment respectively and it is extremely significant. ($p<0.0001$). Physiochemical values are within limits, HPTLC fingerprint could serve as a marker. It is concluded by this study that Pereechangai nei is safe,efficacious and cost effective potent pure herbal drug in the management of Madhumegam. Pereechangai nei though it is a ghee preparation it did not increase total cholesterol or triglycerides, instead it increased HDL and lowered TGL levels which is evident through the clinical data. Thus Pereechangai nei serve as a promising antidiabetic drug for future research in the treatment of Diabetes mellitus. The study may be undertaken with the same drug for a prolonged period in more number of cases and it can be explored in large sample size for further research.

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CONFLICTS OF INTEREST: None declared.

Bibliography

[1]. Dr.R.Thiyagarajan,Therayar Maha Karisal-1st Edition, 2009 publication, Pg.no.146,147.
[2]. Yogi Munivar, Yoogi Vaithiya Chinthamani, 2nd Edition, 2005 publication, Pg.no: 145,149,155,156.
[3]. K.N.Kuppuswamy mudaliyar, Siddha Maruthuvam Pothu, 6th Edition, 2004 publication , Pg.no:509-521.
[4]. "Purificatication of raw drugs"-Kannusami pillai -Sigichaa rathnadeepam,part-1,Edition:2007,page no:33.
[5]. Davidson's "Principles and practice of medicine" - 21st edition ,Page.no.7.
[6]. Prof.V.Seshiah, A Handbook on Diabetes mellitus, 7th edition 2016 publication,Pg.no.12,16-27.
[7]. Bailey CJ. New pharmacological approaches to glycaemic control. Diabetes Review. 1999;7:94–113.
[8]. Ahmed S, Khan RA, Jamil S, Afroz S. Report - Antidiabetic effects of native date fruit Aseel (Phoenix dactylifera L.) in normal and hyperglycemic rats. Pak J Pharm Sci. 2017 Sep;30(5):1797-1802.
[9]. Mahalingam Gayathri , Krishnan Kannabiran Hypoglycemic activity of *Hemidesmus indicus* R. Br. on streptozotocin-induced diabetic rats Int J Diabetes Dev Ctries2008 Jan-Mar; 28(1): 6–10.
[10]. Vetrichelvan T, Jegadeesan M. Anti-diabetic activity of alcoholic extract of *Aerva lanata* (L.) Juss Juss. ex Schultes in rats. J Ethnopharmacol. 2002;80:103–7.
[11]. Soundiramani Balraj, R. Indumathy, Dr. N. Jayshree & M. Sakthi Abirami. EvaluationofInvitro Anti-diabetic Activityof Various Root Extract ofCassia fistula L.Imperial Journal of Interdisciplinary Research (IJIR) Vol-2, Issue-6, 2016 ISSN: 2454-1362, http://www.onlinejournal.in
[12]. J. A. O. Ojewole, "Analgesic, antiinflammatory and hypoglycaemic effects of ethanol extract of Zingiber officinale (Roscoe) rhizomes (Zingiberaceae) in mice and rats," Phytotherapy Research, vol. 20, no. 9, pp. 764–772, 2006
[13]. M. P. Rani, M. S. Krishna, K. P. Padmakumari, K. G. Raghu, and A. Sundaresan, "Zingiber officinaleextract exhibits antidiabetic potential via modulating glucose uptake, protein glycation and inhibiting adipocyte differentiation: an in vitro study," Journal of the Science of Food and Agriculture, vol. 92, no. 9, pp. 1948–1955, 2012.
[14]. Shanmugam Manoharan, Simon Silvan, Krishnamoorthy Vasudevan, and Subramanian Balakrishnan Antihyperglycemic and Antilipidperoxidative Effects of *Piper longum* (Linn.)Dried Fruits in Alloxan Induced Diabetic Rat ,Journal of Biological Sciences,Volume 7 (1): 161-168, 2007
[15]. Kuroda M, Mimaki Y, Ohtomo T, Yamada J, Nishiyama T, Mae T, Kishida H, Kawada T. Hypoglycemic effects of clove (Syzygium aromaticum flower buds) on genetically diabetic KK-Ay mice and identification of the active ingredients.J Nat Med. 2012 Apr;66(2):394-9. doi: 10.1007/s11418-011-0593-z. Epub 2011 Oct 11.
[16]. Atal CK, Dubey RK, Singh J. Biochemical basis of enhanced drug bioavailability by piperine: evidence that piperine is a potent inhibitor of drug metabolism. J Pharmacol Exp Ther. 1985;232:258-262.
[17]. Bhardwaj RK, Glaeser H, Becquemont L, Klotz U, Gupta SK, Fromm MF. Piperine, a major constituent of black pepper, inhibits human P-glycoprotein and CYP3A4. J Pharmacol Exp Ther. 2002;302:645–650.
[18]. Nagashree S, Archana KK, Srinivas P, Srinivasan K, Sowbhagya HB,Anti-hypercholesterolemic influence of the spice cardamom (Elettaria cardamomum) in experimental rats. J Sci Food Agric. 2017 Aug;97(10):3204-3210.
[19]. Ankita Mahakalkar, Pranita Kashyap, Ram Bawankar& Bhushan Hatwar, The Versatility of Cow Ghee- An Ayurveda Perspective, American Journal of Drug Delivery and Therapeutics, 2014,1:1, 028-034.

[20]. India Pharmacopeia I Volume I, Government of India, Ministry of Health and Family welfare, Indian Pharmacopeia commission, 2014.
[21]. Pharmacopoeial Laboratory for Indian Medicine (PLIM) Guideline for standardization and evaluation of Indian medicine which include drugs of Ayurveda, Unani and Siddha systems. Department AYUSH .Ministry of Health & Family Welfare, Govt. of India.
[22]. Indian standard methods of sampling and test for oils and fats Indian standard institution New Delhi 47-50. 1964
[23]. Brain KR, Turner TD. The Practical Evaluation of Phytopharmaceuticals. Bristol:Wright- Scientechnica; 1975:36-45
[24]. Ganesh N. Sharma K, Nitin S, Jyotsana S. Phytochemical screening and estimation of Total Phenolic Content in *Aeglemarmelos*Seeds. *Int J PharmaClinc Res*.2011; 3(2): 27-29.
[25]. Olajire A. A and Azeez L Total antioxidant activity, phenolic, flavonoid and ascorbic acid contents of Nigerian vegetables., 2011; 2(2) 022-029,African Journal of Food Science and Technology.
[26]. Protocol for testing of ayurvedic, siddha & unani medicines, Government of India, Department of AYUSH, Ministry of Health & Family Welfare, Pharmacopoeial laboratory for indian medicines, ghaziabad.
[27]. Kumar A, Lakshman K, Jayaveera KN, Sheshadri Shekar D, Narayan Swamy VB, Khan S, Velumurga C .In Vitro α-Amylase Inhibition and Antioxidant Activities of Methanolic Extract of Amaranthus Caudatus Linn. Oman Med J. 2011 May; 26(3):166-70.
[28]. Deutschlander MS, van de Venter M, Roux S, Louw J, Lall N. Hypoglycaemic activity of four plant extracts traditionally used in South Africa for diabetes. J Ethnopharmacol. 2009;124:619–24.

Pallala Iswarya, et. al. "Clinical Evaluation of Siddha Formulation Pereechangai Nei in the Management of Madhumegam (Type 2 Diabetes Mellitus)." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 19(8), 2020, pp. 55-64.