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CLINICAL TRIAL OUTCOMES OF SIDDHA FORMULATION *PUNGAMPOOCHOORANAM* ON ITS EFFICACY AGAINST DIABETES MELLITUS – TYPE II (MADHUMEGAM): AN OPEN LABEL CASE STUDY IN 40 PATIENTS

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ABSTRACT
Diabetes Mellitus- Type II (DM-Type II) commonly known by its name Madhumegam in Siddha is a disease that affects more than 400 million people around the world. In 2040, there will be more than 640 million people with diabetes worldwide. The prevalence of TIIDM is expected to double within the next 20 years, due to the increase of the age, obesity and the number of ethnic groups of high risk in the population, with significant increases in cardiovascular disease, End-Stage Renal Disease (ESRD).Conventional anti-diabetic drugs used for clinical management of DM-Type II offers certain potential adverse effects upon long term usage which includes ketoacidosis, nausea, skin rashes, dermatitis, hypoglycemia etc. The use of herbal medicinal products and supplements has increased tremendously over the past three decades with not less than 80% of people worldwide relying on them for some part of primary healthcare. The main aim of the present investigation is to evaluate the anti-diabetic potential of the siddha formulation *PungampooChooranam* (PPC) in patients with TIIDM. A total of 40 patients who are recently identified with Type II diabetes along with secondary complication have been selected for the trial and were treated with PPC for the period of 48 days. The outcome of the study indicates that there was a significant reduction in clinical conditions such as Polyuria, Polyphagia, Polydipsia, Pruritis except emaciation among the patients. Structured monitoring of blood glucose is a greater systematic approach to the patient with TIIDM. It was observed from the data's of the present study that there was significant decrease in fasting and post prandial blood glucose level along with HbA1c level in patients treated with trial drug. Hence from the study it was concluded that the trial drug *PungampooChooranam* was therapeutically effective in clinical management of TIIDM (Madhumegam).

KEYWORDS: Type II diabetes mellitus, Madhumegam, *PungampooChooranam*, Fasting blood glucose, Post prandial blood glucose, HbA1c level.

1. INTRODUCTION
Diabetes mellitus (DM) is considered to be one of the oldest metabolic disorder known to man. It was first reported in Egyptian manuscript about 3000 years ago.[1] In 1936, the distinction between type I and type II DM was clearly made. Type II DM was first described as a component of metabolic syndrome in 1988.[2] Type 2 DM (formerly known as non-insulin dependent DM) is the most common form of DM characterized by hyperglycemia, insulin resistance, and relative insulin deficiency.

Type II diabetes mellitus is a chronic metabolic disorder in which prevalence has been increasing steadily all over the world. As a result of this trend, it is fast becoming an epidemic in some countries of the world with the number of people affected expected to double in the next decade due to increase in ageing population, thereby adding to the already existing burden for healthcare providers, especially in poorly developed countries.[3]

It is important to reiterate the staggering rate at which interest and use of herbal medicines is expanding. Over the past decade, the use of herbal medicines represents approximately 40% of all healthcare services delivered in

China while the percentage of the population which has used herbal medicines at least once in Australia, Canada, USA, Belgium, and France is estimated at 48%, 70%, 42%, 38%, and 75%, respectively.[4] In spite of the positive perception of patients on the use of herbal medicines and alleged satisfaction with therapeutic outcomes coupled with their disappointment with conventional allopathic or orthodox medicines in terms of effectiveness and or safety.[5-6]

Pongamiapinnata (Fabaceae) is popularly known as Indian beech in English.[7] Commonly known by its vernacularnameskaranj (Hindi), honge/karajata (Kannada), pungai (Tamil). As per the literature the extract of stem bark of *P. pinnata* (L.) showed antihyperglycaemic activity in diabetic mice.[8] Further, reports available that concomitant administration of synthetic oral hypoglycemic drugs along with *P. pinnata* produced synergistic effect in diabetic mice.[9] The preliminary phytochemical analysis showed the presence of alkaloids, terpenoids, triterpenes, flavonoids, steroids, and volatile oils.[10] It has been identified that Cycloart-23-ene-3*β*, 25-diol (B2) isolated from the stem bark of *P. pinnata* possesses antidiabetic activity in diabetic animals.[11] Cycloart-23-ene-3*β*, 25-diol improved the abnormalities of diabetic conditions in diabetic mice due to increased glucagon-like peptide 1 (GLP-1) insulin secretion[12] and has a protective effect on vital organs like heart and kidney.[13]

It was evident through literature survey that still now there is no proper clinical validation of *Pungampoo Chooranam* for TIIDM in diseased subjects. Hence the present investigation was pursued to establish the proper clinical evidence based data with respect to anti-diabetic potential of *PungampooChooranam* in diseased patients.

2. MATERIALS AND METHODS

2.1. Source of raw drugs

The herb *Pongamiapinnata* was collected from southern zone of Tamil Nadu, and other required ingredient is procured from a well reputed indigenous drug shop from Parrys corner, Chennai, Tamil Nadu, India .Herb were authenticated by the Pharmacognosist, SCRI Chennai, Tamil Nadu, India.

2.2. Ingredients

The siddha formulation *PungampooChooranam* (PPC) comprises of two main ingredients as listed below

1. Pungam flowers (*Pongamiapinnata*)
2. Cow's Ghee

2.3. Preparation[14]

The shade dried flowers of *Pongamiapinnata* were roasted slowly by adding little bit of cow's ghee. Then it is powdered and sieved using cloth.

Dosage : 2 gm twice a day
Adjuvant : Warm water
Duration: 48 Days

2.4. Study design

An open-labeled observational study comprises of 40 subjects with type II diabetes mellitus was chosen for the individualized in-depth evaluation. Protocol was approved by Goverment siddha medical college, Arumbakkam, Chennai, Tamil Nadu 600106 with referral approval number GSMC-CH-ME-4/2015/009. The entire study was conducted on patients at out-patient department of Govt Siddha Medical College, Chennai in the premises of Arignar Anna government hospital for Indian medicine and Homeopathy, Arumbakkam, Chennai-106, during the period of 2015-2017.

2.5. Selection criteria

Patients visiting the out-patient department of Govt Siddha Medical College Arumbakkam, Chennai-106 with the age 30-60 years who are recently identified (within 6 months) with Type II Diabetes with Blood Glucose level (Fasting) 126mg/dl - 140 mg/dl, 180mg/dl - 280 mg/dl Postprandial, 200mg/dl - 300mg/dl at random and HBA1C - 6.5% to 8% satisfying the inclusion criteria was selected for the study. Further patients consists of Diabetes accompanied by Polyuria, Polyphagia, Polydipsia, generalized tiredness, Fatigue, Peripheral neuritis, Itching all over the body were been included in the study population.

Patients with history of Insulin Dependent Diabetes Mellitus (IDDM), Cardiovascular Disease., Diabetic Nephropathy, Diabetic Retinopathy, Pregnant women, lactating mothers, T.B infection were excluded.

Drug Administration

Each subject was provided with 2 gm of trial drug *PungampooChooranam* with sufficient warm water for the period of 48 days further they were monitored for clinical improvement and other Compliance.

Clinical Study Assessment[15-18]

Each patient were subjected to the clinical investigation for evaluating the improvement in their disease condition through regular Blood Investigation such as Blood sugar (Fasting , Post Prandial and Glycaemic control through HbA1C level.

Statistical analysis

The statistical analysis was carried by using SPSS version 17 followed by non-parametric McNemar Test analysis. Probability P values < 0.05 were considered as significant.

3. RESULTS

3.1. Result analysis on Evaluation of clinical signs and symptoms before and after administration of trial drug in patients with TIIDM

Clinical assessment on compilation associated with TIIDM was considerably one of the important prime factors in elucidating the effectiveness of the therapy. Assessments were carried out by using the following clinical conditions such as Polyuria, Polyphagia,

Polydipsia, Pruritis Vulvae/ Balanitis, Itching present all over the body, Pain all over the body, Dryness of Mouth & Throat, Constipation, Emaciation, Skin infection and sleep disturbances. It was observed that there was a significant difference in most of the clinical parameters investigated after treatment with trial drug *PungampooChooranam* as listed in table no 1. Since the p value is significant in signs and symptoms except emaciation. There is significant reduction in signs and symptoms except emaciation among the patients for the treatment of Madhumegam (TIIDM).

Table 1: Result analysis on Evaluation of clinical signs and symptoms before and after administration of trial drug in patients with TIIDM.

S. No	Signs and Symptoms	Before Treatment		After Treatment	
		Total Number of Patients	Percentage Occurrence (%)	Total Number of Patients	Percentage Occurrence (%)
1.	Polyuria	40	100	7	17.5**
2.	Polyphagia	40	100	5	12.5**
3.	Polydipsia	40	100	4	10**
4.	Pruritis Vulvae/ Balanitis	04	10	0	0*
5.	Itching present all over the body	04	10	0	0*
6.	Pain all over the body	34	85	7	17.5**
7.	Dryness of Mouth & Throat	04	10	0	0*
8.	Constipation	08	20	0	0*
9.	Emaciation	04	10	3	7.5
10.	Skin infection	04	10	0	0*
11.	Disturbed Sleep	40	100	4	10**

McNemat test, C.I: 95%, *P<0.05; **P<0.001

3.2. Result analysis on Evaluation of Blood glucose and HbA1C level before and after administration of trial drug in patients with TIIDM

Structured monitoring of blood glucose is a greater systematic approach to the patient with TIIDM since it clearly reflects the clinical patterns of glycemia of the individuals. There was significant decrease in fasting blood glucose level of patient after treatment with trial drug. Which denotes the anti-hyperglycemic potential of the drug *PungampooChooranam* in patients with TIIDM. The data's were represented in table 2.

The performance of postprandial blood glucose has been observed to be beneficial in non-insulin-treated TIIDM patients. The data's obtained from the present investigation clearly shown that there was significant decrease in PP blood glucose level of patients exposed to *PungampooChooranam.* The data's were represented in table 2. Appropriate glucose control and reduction of glycosylated hemoglobin (HbA1c) levels are important for reduction of mortality because the primary cause of mortality in TIIDM. . There is significant reduction in HbA1C level among the patients after treatment with *PungampooChooranam* was observed as listed in table 2.

Table 2: Result analysis on Evaluation of Blood glucose and HbA1C level before and after administration of trial drug in patients with TIIDM.

Patient	Fasting blood sugar level in mg/dl		Postprandial blood sugar level in mg/dl		HbA1C	
	Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
1.	132	110	231	193	7.1	6.4
2.	138	120	233	191	7.3	6.2
3.	136	122	221	188	7.0	6.3
4.	131	119	202	168	6.9	6.4
5.	136	94	189	152	6.6	5.2
6.	139	124	242	218	8.0	7.9
7.	132	121	214	180	7.3	6.5
8.	129	97	230	188	7.2	6.4
9.	133	109	214	181	7.3	6.3
10.	130	106	219	186	6.9	6.1
11.	127	103	183	161	6.7	5.8
12.	140	132	263	217	8.0	7.8
13.	129	98	220	159	7.8	6.5
14.	126	98	227	161	7.1	6.4
15.	139	105	247	196	7.8	6.3

16.	133	111	188	143	6.7	5.7
17.	137	113	213	177	7.0	6.5
18.	127	95	185	157	6.8	5.7
19.	129	119	218	169	7.3	6.5
20.	138	114	220	173	7.4	6.8
21.	133	120	203	171	6.8	6.4
22.	131	109	226	180	7.0	6.7
23.	128	94	214	179	8.0	7.9
24.	135	108	245	208	7.8	7.5
25.	138	122	253	188	7.2	7.0
26.	140	130	258	203	8.0	7.6
27.	136	121	206	174	6.8	6.3
28.	131	105	186	166	6.7	5.8
29.	128	108	219	179	7.3	6.5
30.	136	114	226	187	7.4	6.8
31.	128	106	221	176	7.6	7.3
32.	133	117	228	179	7.5	7.1
33.	130	102	219	186	6.8	6.1
34.	128	97	228	176	7.9	7.6
35.	138	119	257	221	8.0	7.8
36.	131	98	184	168	7.1	5.9
37.	136	112	231	173	7.6	6.9
38.	133	123	222	182	8.0	7.3
39.	131	113	229	197	7.0	6.4
40.	134	119	237	181	6.9	6.6

4. DISCUSSION

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Metabolic abnormalities in carbohydrates, lipids, and proteins result from the importance of insulin as an anabolic hormone. Low levels of insulin to achieve adequate response and/or insulin resistance of target tissues, mainly skeletal muscles, adipose tissue, and to a lesser extent, liver, at the level of insulin receptors, signal transduction system, and/or effector enzymes or genes are responsible for these metabolic abnormalities.[19]

The global prevalence of diabetes in adults (20-79 years old) according to a report published in 2013 by the IDF was 8.3% (382 million people), with 14 million more men than women (198 million men *vs* 184 million women), the majority between the ages 40 and 59 years and the number is expected to rise beyond 592 million by 2035 with a 10.1% global prevalence. With 175 million cases still undiagnosed, the number of people currently suffering from diabetes exceeds half a billion. An additional 21 million women are diagnosed with hyperglycemia during pregnancy. The Middle East and North Africa region has the highest prevalence of diabetes (10.9%), however, Western Pacific region has the highest number of adults diagnosed with diabetes (138.2 millions) and has also countries with the highest prevalence.[20]

Many anti-diabetic drugs with different mechanisms of action are now available to treat type 2 diabetes mellitus, including sulfonylureas, glinides, thiazolidinediones, biguanides and α-glucosidase inhibitors. Recently, incretin-related drugs, such as dipeptidyl peptidase-4 (DPP-4) inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists[21], have been developed.

Metformin has long been considered the initial drug therapy choice in the treatment of type 2 diabetes mellitus (TIIDM). The most widely recognized clinical guidelines and consensus recommendations endorse its use when monotherapy is initially preferred to treat hyperglycemia.[22-25] Metformin is now widely prescribed as an anti-diabetic drug; however, there have been serious concerns about its adverse effects, especially ketoacidosis.[26]

Insulin secretagogues, including the sulfonylureas and meglitinides, have been used consistently as monotherapy for the treatment of TIIDM. Sulfonylureas, including glyburide, gliclazide, glipizide, and glimepiride or their predecessors have been used for the treatment of TIIDM since the 1960s.[27] The glucose-lowering effect of sulfonylureas is achieved by stimulation of insulin release from beta-cells within the pancreas and focuses primarily upon fasting blood glucose reduction although has some effects on post-prandial glucose as well.[28]

Sulfonylureas are usually well tolerated. The most common side effect is hypoglycemia, more common with long-acting sulfonylureas such as chlorpropamide and glibenclamide.[29-31] Other infrequent side effects that may occur with all sulfonylureas include nausea, skin

reactions such as erythema multiforme, exfoliative dermatitis and also, more rarely, photosensitivity.

GLP-1 receptor agonists are exogenous analogs promoting the incretin effect that is normally diminished in a patient with TIIDM.[32] Over the past few years, there have been numerous DPP-4 inhibitors approved for use in the treatment of hyperglycemia associated with TIIDM. The number of agents available differs depending on the country, but vildagliptin, sitagliptin, saxagliptin, alogliptin, and linagliptin are the most studied and readily available agents within this relatively new class of medications. Most common side effects to saxagliptinmonotherapy in headache, back pain, diarrhea, upper respiratory tract infection, naspharyngitis and hypoglycemia.

Overwhelming evidence from epidemiological, in vivo, in vitro, and clinical trial data indicates that the plant-based diet can reduce the risk of chronic diseases (e.g., cardiovascular disease, hypertension, diabetes, and cancer) due to presence of biologically active plant compounds or phytochemicals. Optimized nutrition through supplementation of diet with plant derived phytochemicals has attracted significant attention to prevent the onset of many chronic diseases including cardiovascular impairments, cancer, and metabolic disorder. These phytonutrients alone or in combination with others are believed to impart beneficial effects and play pivotal role in metabolic abnormalities such as dyslipidemia, insulin resistance, hypertension, glucose intolerance, systemic inflammation, and oxidative stress.

Pongamiapinnata comprises of biologically significant phytocomponents such as alkaloids, terpenoids, triterpenes, flavonoids, steroids further it was evident that this novel herb used extensively in formulating several siddha preparations. Further it possesses significant pharmacological activity such as anti-diabetic and protective activity in animal model. It was observed that there was a significant difference in most of the clinical parameters investigated such as Polyuria, Polyphagia, Polydipsia, Pruritis Vulvae/ Balanitis, Itching present all over the body, Pain all over the body, Dryness of Mouth & Throat, Constipation, Emaciation, Skin infection and sleep disturbances after treatment with trial drug *PungampooChooranam*

Many studies demonstrate that controlling plasma glucose level could prevent the progression of these complications, especially microvascular disease.[33-35] Because the fluctuations of plasma glucose level do not lend to easy analysis, we can use the HemoglobinA1c (HbA1c), which reflects the mean plasma glucose, in the last eight to 12 weeks.[36] Many recent studies have demonstrated that elevated postprandial plasma glucose effects the diabetes complications, primarily the in macrovascular complications more severely than elevated fasting plasma glucose.[37-40] Since fluctuations of fasting plasma glucose and postprandial could affect HbA1c, this study was performed to assess the relationship of fasting plasma glucose and two-hour postprandial on HbA1c. There was significant decrease in fasting, post prandial glucose level and glycosylated Hemoglobin (HbA1c) levels in patients after treatment with trial drug. Which denotes the anti-hyperglycemic potential of the drug *PungampooChooranam* in patients with TIIDM.

5. CONCLUSION

Present study were carried out in 40 patients affected with type II diabetes in regular clinical follow-up, further from the data's obtained from the present investigation it was clear that subjects treated *PungampooChooranam* at the dose of 2gm per day for 40 days has shown significant decrease in clinical symptoms associated with TIIDM. Control of glycemic index is the hall mark therapeutic goal in clinical management of TIIDM as an evident of this outcome of the present trial has substantiates that treatment with *PungampooChooranam* has significantly decreases the level of fasting, postprandial and HbA1c in the treated subjects. Hence it was concluded that siddha formulation *PungampooChooranam* may be considered as a drug of choice for better clinical management of TIIDM.

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