EFFICACY OF SIDDHA HERBO-MINERAL FORMULATION ULOGA CHENDURAM FOR TYPE 2 DIABETES MELLITUS – A NON-RANDOMIZED OPEN CLINICAL TRIAL

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Abstract

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia which causes serious damage to the heart, blood vessels, eyes, kidneys, and nerves. According to WHO, about 422 million people are affected by diabetes worldwide. The possible adverse reactions of present-day antidiabetic drug demand newer alternatives for the management of diabetes, improving the quality of life and prevention of diabetic complications.

Objective: To evaluate the efficacy of Siddha traditional formulation Uloga Chenduram for patients with Type 2 Diabetes Mellitus

Materials and methods: A non-randomized, open clinical trial was carried out on 30 patients at Ayothidoss Pandithar Hospital after obtaining approval from the ethical committee. Uloga chenduram was given to the diabetic patient for 90 days along with Triphala chooranam as an adjuvant. The efficacy of the drug was evaluated by assessing clinical symptoms, HbA1c, fasting, and postprandial blood glucose tests before and after treatment for all patients.

Results: The result showed statistically significant improvement in clinical symptoms, with mean reduction in HbA1c from 10.00% to 6.8% ($p < 0.0073$). The mean reduction in fasting, and postprandial blood glucose tests after treatment with Uloga chenduram was from 161.3mg/dl to± 24.31 to 121.56 ± 16.67mg/dl ($p < 0.0001$) and 264.90 ± 45.47mg/dl to 200.24 ± 40.51 mg/dl ($p < 0.0001$) respectively.

Conclusion: Uloga chenduram was effective in the management of Type 2 Diabetes Mellitus in terms of its antidiabetic effects and hypolipidemic effects.

Keywords : Uloga chenduram, Siddha, Type 2 Diabetes Mellitus, Herbo-mineral drug, Non-randomized open clinical trial

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1. Introduction

Diabetes mellitus [DM] is a major public health problem worldwide. Current global estimates indicate that this condition affects 415 million people and is set to escalate to 642 million by the year 2040[1]. This prevalence is expected to rise to 366 million people by the year 2030[2].In diabetes, chronic hyperglycemia in synergy with the other metabolic aberrations can cause damage to various vital organ systems, leading to the development of disabling and life-threatening health complications, most prominent of which are microvascular [Rretinopathy, nnephropathy and neuropathy] and macrovascular complications leading to increased risk of cardiovascular diseases[3].

Several categories of drugs that have been currently used for the treatment of diabetes can act by multiple different mechanisms, such as stimulation of the release of insulin, reduction of hepatic glucose output, and enhancement of the peripheral uptake of glucose[4]. The major issue relies on the regular usage of some diabetic medications resulting in possible adverse effects such as gastrointestinal distress, myalgia, headache, uurinary tract infection, dizziness, etc[5]. So, a potential alternate therapy is highly needed to ensure the safety of chronic usage. The worldwide use of complementary and traditional medicines for managing diseases such as diabetes has rapidly increased over the last decade. It is reported that up to 72.8% of people with diabetes used herbal medicine, dietary supplements, and other alternate therapies[6]. This has led to increased demand for traditional medicines with antihyperglycemic activity having lesser side effects. Siddha medicine is one of the traditional systems of medicine that is prevalent in Tamil Nadu for centuries. In Siddha literature, diabetes is comparable with 'Madhumegam' or 'Neerizhivu'[7]. As per Yugi, Mathumegam exhibits the following symptoms like polyuria, nocturia, polydipsia, polyphagia, body pain, weight loss, tiredness, burning feet, and genital pruritis[8], these symptoms can be correlated with Non-Insulin Dependent Diabetes Mellitus [NIDDM].

Uloga chenduram is a Siddha Herbo-mineral formulation indicated for Madhumegam in Siddha literature. It consists of Uloga manduram [ferrousoferric oxide], the juice of Naval pattai [Syzygium cumin.Linn] and juice of Karisalai [Eclipta prostate.Linn][9]. The previous studies on the above ingredients showed that they have an antihyperglycemic property[10,11]. But the clinical documentation of the study drug in the treatment of diabetes has not yet been studied. So, the present study was conducted to evaluate the anti-hyperglycemic efficacy of Uloga chenduram through a non-randomized open clinical trial.

Methodology

1.1. Study design and Site of study: A non-randomized, open clinical trial was carried out in the General medicine department OPD of Ayothidoss Pandithar Hospital, National Institute of Siddha, Tambaram Sanatorium, Chennai-47 for 12 months by the standards of Good Clinical Practices. (Figure.1)

1.2. Ethical consideration: The study was conducted after obtaining approval from the Institutional Ethical Committee (IEC) of the National Institute of Siddha (IEC NO: NIS/IEC/14/2018-19/3-20.09.18). The trial was registered before the initiation of the trial in the clinical trial registry of India with Reg.no CTRI/ REF/2019/09/028190 (Registration date: 22/09/2019).

After explaining the purpose of the study, details of the study drug, benefits, and potential risks to the participants in their vernacular language, written consent was obtained from the patients.

1.3. Intervention:

1.3.1. Trial drug: Uloga chenduram was taken as a trial drug. Details of the Intervention are illustrated in Table.1. The essential raw ingredients for the preparation of Uloga chenduram were purchased from a reputed raw drug store in Chennai's Paris Corner and verified by the responsible official of the gunapadam department, NIS.

The botanist at NIS Chennai validated the Naavalpattai (Bark of Syzygium cumini L.) and Kaiyaan (Wedelia Chinensis (Osbeck) Merr.) that were collected from Pallavaram. The purification and preparation of medicine were done at the National Institute of Siddha's lab, Chennai. The drug was prepared as per the Siddha text "Agathiyar attavanai vaagadam"[9,12].

Table.1.Details of study drug Uloga Chenduram

S.NO	Details	Drug profile
1	Name of Trial drug	Uloga chendhuram
2	Route of administration	Oral

3	Dose	488 mg, twice a day, After food
4	Adjuvant	Tripala chooranam
5	Vehicle	Water
6	Duration	90days (45+45)
7	Drug holiday	7 days (after completion of 45 days)
8	Ingredients	1.Purified uloga manduram [ferrouso ferric oxide]-336gm 2.Naaval pattaichaaru [Juice of Syzygium cumini L.]-672 ml 3.Kaiyaanchaaru [juice of Wedelia chinensis [Osbeck] Merr.]-672 ml 4.Tripala decotion -672 ml
9	Reference	Agasthiyar attavanai vaagadam

1.3.2. Literature evidences on the antidiabetic property of study drug ingredients

Nguyen Phuong thao et.al found a new cyclohexyl ethanoic derivative isolated from the leaves of Wedelia chinensis [osbeck] Merr. found to possess highly significant α-amylase and α-glucosidase inhibitory activities compared to standard drug acarbose[13]. Tripathi and Kohli studied the antidiabetic activity of Syzygium cumini [L.] [stem bark] on streptozotocin [STZ]-induced diabetic Wistar albino rats with various Syzygium cumini [L.] extract for 3 weeks lead to significant reductions in fasting blood glucose levels as compared to that of the standard glibenclamide diabetic controls[14]. Y. K. Murali et.al studied the Water extract of dry fruits of Terminalia chebula gaertn. improves glucose tolerance test in streptozotocin-induced diabetic rats[15]. Kannan VR et al. showed oral administration of methanolic extract of Terminalia chebula gaertn. fruits and seeds exhibited dose-dependent reduction in blood glucose of streptozotocin-induced diabetic rats both in short-term and long-term study[16].

Sabu M.C et al. and Senthilkumar GP et al reported that Triphala extract has reduced the blood sugar level in normal and alloxan [120mg/kg] induced diabetic rats significantly[16,17]. Prabhu Srinivasan et.al evaluated the Anti-diabetic activity of quercetin extracted from Phyllanthus emblica L. fruit in streptozotocin-induced diabetic rats resulted in a significant decrease in blood glucose and urine sugar levels, with a considerable rise in plasma insulin and hemoglobin levels[18].From the previous studies, it was concluded that all the ingredients of the study drug were known for their Antidiabetic-property. Hence the medicine has properties of all these activities and acts as a whole drug in the management of Neerizhivu [Diabetes]. Screening of the anti-diabetic potential activity of Uloga Chenduram showed a significant level of α-amylase and α-glucosidase enzyme inhibition properties in the tested models[19].

1.3.3. Eligibility criteria for participants

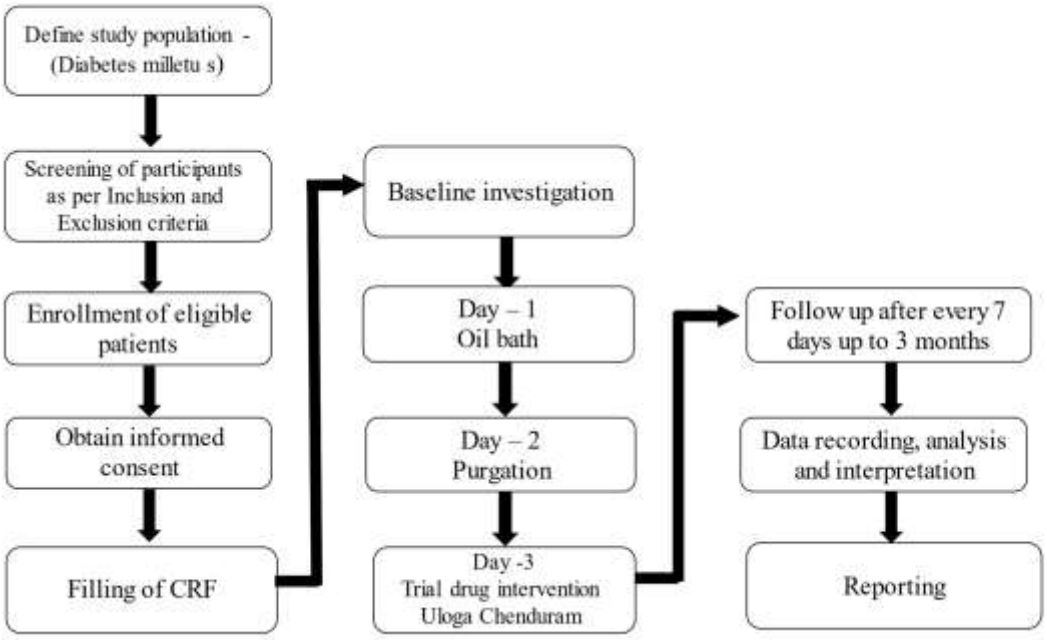
The inclusion criteria consisted of diagnosed diabetic patient based on WHO diabetic criteria of both sexes aged between 31 to 70 with elevated HbA1C > 6.5 and < 10% and having clinical features such as polyuria, nocturia, polydipsia, polyphagia, body pain, tiredness, weight loss, burning feet, genital pruritus was screened and 30 patients fulfilling the inclusion criteria were included in the trial. WHO Diabetic diagnostic criteria: Blood sugar –fasting > 126 and = < 200 mg /dl (or) Postprandial Blood Sugar > 200 mg/dl and = < 350 mg /dl

The exclusion criteria consist of ppatient's with secondary hypertension., IDDM (Insulin Dependent Diabetes Mellitus), secondary diabetes mellitus, coronary artery diseases, pregnant woman, lactating mother, central nervous disorder, secondary thyroid disorder, gestational diabetes mellitus, existing renal failure indicated by elevated serum creatinine levels and the subjects those who are not willing to give informed consent were excluded.

1.3.4. Study Procedure

In this study, the trial drug Uloga chenduram was given to patients for a period of 90 days with 7 days of drug holiday after the completion of 45 days. The patients were instructed not to use any other medications during the study without the investigator's approval. They were advised to follow up every seventh day of the week. Patients were further followed up for 3 months after completion of the trial. On day 1, patients are advised to take an oil bath. On day 2, Purgation was recommended for all patients based on their body constitution. Patients were advised to take rest and normal diet on day 3. From day 4, the trial drug was given as started. 488 mg of Uloga chenduram was given twice a day for 90 days along with Triphala chooranam as an adjuvant (Fig-1).

Fig-1 . Flow chart on methodology of Clinical study



1.3.4. Data collection and analysis

Before the enrollment, the patient's personal details, physical examinations like height, weight, blood pressure, characters (Gunangal), Sensory and motor organs, Eight unique diagnostic tools of Siddha (Envagai thervu), Uyir thaathukkal (vatha, pitta,kapha), Siddha urine examination (neerkuri), body status (Thega ilakanam) were done. The blood investigations such as HbA1C, fasting blood glucose, postprandial blood glucose, and Lipid profile were done before and after the intervention. We interpret the result as good control if blood levels decrease by 1 to 2.5% from the baseline value of the patient, as moderate control if it decreases by 0.1-0.9 % from the baseline values of the patient, and others considered as a poor control.

The data collected was analyzed using STATA software. The level of significance of the probability value was taken as 0.05. Descriptive data were made using tables/graphs. Student t-test was employed to determine the significance of blood sugar before and after treatment.

2. Results

In the present study, the Siddha medicine Uloga Chenduram was tested and analysed to find a solution and prevent the complications of Neerizhivu by using Non randomized open clinical trial. The study aimed to regulate the deranged humor and to control elevated blood glucose levels and restore the optimum HbA1c range. Uloga chenduram was given with Tripala chooranam in warm water for 90 days. Laboratory investigation was done on the 0^{th}, and 90^{th} day for the clinical assessment. The baseline data of study participants were illustrated in Table-2.

Table.2. Baseline data of Study population

S. NO	Baseline data	Category	Frequency (No. of cases)	Percentage
1	Gender	Male	14	46.67%
		Female	16	53.33%
2	Age	20-30	0	0%
		31-40	5	16.67%
		41-50	13	43.33%
		51-60	9	30%
		61-70	3	10%
3	Weight	Under weight	0	0%
		Normal weight	15	50%
		Over weight	15	50%

4	Chronicity of illness (in years)	0-1 1-3 3-5 5-10	4 5 11 10	13.33% 16.67% 36.67% 33.33%
5	Thega ilakanam (Body constituent)	Vatha pitham Pitha vatham Vatha kabam Kaba vatham	2 9 2 17	6.67% 30% 6.67% 56.66%
6	Gunam (Character)	Sathuvam (Pure elements) Rasatha (Active elemental) Thamo (Elements of self benefits)	0 26 4	0 86.67% 13.33%

Though previously published data reports that diabetes is more prevalent in males (2.3 %), than in females equals to 1.4 %, the gender difference in our present study may be due to the small sample size .[20] Most of our study sample were diagnosed diabetics since 3-5 years(n=11,36.67%)

According to Siddha concept of body constitution (Thega ilakkanam) most of the cases (n=17, 56.6%) were vatha kapham which is responsible for the clinical features of diabetes as listed in Table-3 such as nocturia , polydipsia, polyphagia, body pain, tiredness, weight loss and burning feet as all of them are directly proportional to altered vatham and altered kapham results in chronicity and a predilector for the diabetic complication. Though the chief cause cause of diabetes as per Siddha is the derangement of Pitham humor, as Sage Theraiyar says "Pakar pitham vinthaiyalaathu megam vaarathu" in pini mutharkaaranam. Initially increased Pitha humor enhances Vaayu, then affects Iyam and Vali. Thus mukutram (Vali, Azhal,Iyam) gets affected which then affects the functions of seven Udal thathukkal [seven body constituents][12]. So, the diabetic drug has the potential to normalize pitha kutram and strengthen the seven Udal thathukkal.[21]The study drug Uloga chenduram consists of Uloga manduram [ferrousoferric oxide], the juice of Naval pattai [Syzygium cumin.Linn] and juice of Karisalai [Eclipta prostate.Linn][9]. Naaval pattai reduces pitham, Manduram, and Karisalai balances kabam and vatham. Thus, Uloga chenduram balances the Mukutram, thus strengthening the seven udal thaathukkal[13].

Table.3. Assessment of the efficacy of Trial drug based on clinical features

Clinical features	Before treatment (No. of cases)	After treatment (No. of cases)
Nocturia	10 (33.33%)	9 (30%)
Polydipsia	12 (40%)	12 (40%)
Polyphagia	0	0
Body pain	30 (100%)	28 (93.33%)
Tiredness	28 (93.33%)	25 (83.33%)
Weight loss	2 (6.67%)	2(6.67%)
Burning Feet	20 (66.67%)	17 (56.67%)
Genital Pruritus	5 (16.67%)	5 (16.67%)

Table.4. Assessment of the efficacy of Trial drug based on Blood investigations

Blood parameter and Treatment status	Mean ± Standard deviation	Significance
HbA1c – BT	10.0049 ± 1.0442	t = 5.044, p <0.0073 Two-fold Significant
HbA1c – AT	6.8837 ± 0.5621	
Fasting blood glucose – BT	161.3333 ± 24.3137	t = 48.70, p <0.0001

Fasting blood glucose – AT	121.5667 ± 16.6727	Two-fold Significant
Postprandial blood glucose - BT	264.9014 ± 45.4730	t = 39.59, p <0.0001 Significant
Postprandial blood glucose - AT	200.2459 ± 40.5179	
Total cholesterol – BT	202.3259 ± 28.7561	t = 18.25, p = <0.0001 Significant
Total cholesterol – AT	172.5293 ± 40.6024	
HDL – BT	46.2121 ± 8.00979	t = 15.10, p = 0.0001 Two-fold Significant
HDL – AT	54..9282 ± 5.8779	
LDL – BT	120.779 ± 20.9958	t = 13.21, p = 0.0002 Significant
LDL – AT	99.2144 ± 24.5715	
Triglycerides – BT	157.5495 ± 108.3414	t = 19.25, p = < 0.0001 Significant
Triglycerides – AT	126.1179 ± 42.3727	

AT- After treatment; BT- Before treatment; HbA1c – Glycated Haemoglobin; HDL – High density lipoprotein; LDL – Low density lipoprotein

HbA1c can be performed at any time of the day and do not need any prior preparation such as fasting. It reflects the average plasma glucose over the previous eight to 12 weeks [22] Because of these properties, HbA1c has been recognized as the preferred screening, diagnosing and prognostic test for assessing glycaemic control in people with diabetes.[23] In our study, out of 30 cases, 23 cases (76.67%) showed good glycemic control by a decrease in HbA1c level of 1 to 2.5% and 4 cases (13.33 %) showed moderate control by a decrease of 0.1-0.9 % HbA1c level and 3 cases (10%) showed poor control. The average HbA1c at the start of treatment and after the treatment were 10.0049% and 6.8837% respectively and it is two-fold significant statistically (p<0.0073) as shown in (Table.4). Moreover, studies report that HbA1c measurement as a predictor of prevalent retinopathy, and can be targeted as a better tool for predicting microvascular complications.[24] Since the study drug shows two fold significance in the reduction of HbA1C level, it can be considered as an effective drug in the prevention of microvascular complications

Further, diabetes mellitus is considered as an established risk factor for coronary heart disease and ischaemic stroke. Among the various investigations, fasting blood glucose has been reported to be log-linearly and importantly associated with risk of vascular disease at all concentrations, including below the threshold for diabetes of 7 mmol/L.[25] The significant reduction in fasting blood glucose level in n=29 out of N=30 cases (96.67%) and the two fold significance (p<0.0001) in the level of fasting blood glucose level before and after treatment 161.33mg/dl and 121.57mg/dl respectively as shown in Table.4 indicates that the study drug can have the ability to reduce the cardiovascular risks associated with diabetes.The fact can be supported by reduction in total cholestrol level (202.32mg/dl), LDL level (120.77mg/dl) and triglycyride level (157.54mg/dl) to 172.52,54..92mg/dl and 126.11mg/dl respectively. And the increase in HDL from 46.21 to 54.92 mg/dl. There was also a significant decrease postprandial blood glucose level, in 93.34% of cases (n=28) and the average post prandial blood sugar before and after treatment was 264.90 mg/dl and 200.25mg/dl respectively, which is (p<0.0001) statistically significant. (Table.4). Throughout the study period and follow up, there was no report of any adverse effect such as hypoglycemia and its symptoms.

This study result showed that out of 30 patients, 23 cases [76.67%] had Good improvement, 4 cases [13.33%] had moderate improvement and 3 [10%] cases had poor prognosis based on HbA1c level. There is a statistically two-fold significant difference between before and after treatment on average HbA1c, fasting blood sugar, and average HDL levels and it has a significant difference between Postprandial blood sugar, Total cholesterol, LDL, Triglycerides which promotes Uloga chenduram as a better antidiabetic agent. Besides its antidiabetic action it is also a double-edged sword in decreasing the lipid profile and therefore can be considered as a two-in one formulation as an antidiabetic and a lipid-lowering drug with profound benefits.

Limitations

The present study had small sample size, short-term follow-up of patients and no comparison group which can be considered as the limitations of present study.

3. Conclusion

Diabetes mellitus is the most common metabolic disorder all over the world and its incidence is increasing day by day due to a sedentary lifestyle and unhealthy food habits and stress. Based on the study result, it is concluded that the trial drug Uloga chenduram effectively controls blood glucose levels as evidenced by a significant reduction in HbA1c levels, lipid profile and improves the patient's general health with no observable adverse events during the course of treatment. So, it can be considered as a safe traditional drug with anti-diabetic action. Further, RCT studies and safety

studies are needed in a large population to reinforce it as an evidence-based medicine.

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