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A RANDOMIZED, DOUBLE-BLIND CLINICAL TRIAL OF POLY HERBAL TRADITIONAL DECOCTION FOR THE MANAGEMENT OF TYPE 2 DIABETES IN COMPARISON WITH STANDARD WESTERN TREATMENT

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ABSTRACT

Diabetes mellitus type 2 (Mathumekam) is a major health concern in the 21st century. Despite enormous advancements in contemporary science, there is a lack of reasonably safe and efficient medications available its management. The objective of this study was to evaluate the effectiveness of Poly Herbal Traditional Decoction containing 10 herbs namely, Senna auriculata (Root & bark), Cissampelos pareira (root), Ficus racemosa (bark), Terminalia arjuna (bark), Acacia arabica (bark), Syzygium cumini (bark), Curcuma longa (rhizome), Terminalia chebula (fruit pulp), Phyllanthus emblica (dry fruit), Terminalia bellirica (fruit pulp) in the management of Diabetes Mellitus Type 2 (DMT2). It was a double-blind, Randomized Control Trial conducted on 100 participants of DMT2 inadequately controlled by diet and exercise. The test drug was given to group-A participants (n=50) 5g added with 100ml (1 tumbler) boiled water for 10-15 minutes for 12 weeks and the standard western therapies (a drug alone or in combination with other hypoglycemic Western medicines based on the blood glucose level). The patients in group B (n=50) were received a placebo in addition to standard western treatment therapies. Primary outcome of the study was reduction of Glycosylated Hemoglobin (HbA1c) from baseline after three months, secondary outcomes were reduction of Fasting Blood glucose Level (FBG) and changes of Signs and symptoms of diabetes mellitus. The overall efficacy of the formulation was assessed in terms of reduction in fasting blood glucose level during the study period. At the end of the study, mean fasting blood glucose was reduced to 119.04 ±11.52 mg/dL and 176.90 ±13.91 mg/dL in test group and control group respectively. A reduction in mean fasting blood glucose was higher in Group I showing the overall therapeutic effectiveness of the test drug indicating that daily administration of Poly Herbal Traditional Decoction and standard Allopathic medical therapies for 03 months resulted in significant reductions of FBG. Similarly, Group I showed better improvement of the assessed diabetic signs and symptoms such as polydipsia, polyuria, polyphagia, fatigue, burning sensation in palm and soles in comparison to Group II during the study period. Moreover, the mean HbA1c (%) in Group I and Group II at baseline was 7.47 ±0.70 and 7.39 ±0.66 whereas at the end of 12 weeks of study the level of glycated haemoglobin in Group I and Group II was reduced to 5.03 ±0.53 and 6.79 ±0.51 respectively. No adverse events were reported throughout the trial period. This study concludes that the test drug (Poly

Herbal Traditional Decoction) was effective in T2DM in reducing FBG and HbA1c significantly in diabetic mellitus patients at 12 weeks of treatment.

Keywords: Diabetes mellitus type 2 (T2DM), Glycosylated Hemoglobin (HbA1c), Fasting Blood Glucose (FBG), Poly Herbal Traditional Decoction.

INTRODUCTION

Diabetes mellitus is a common disorder that has a major negative impact on human health. It is a disease of the lipid, protein, and carbohydrate metabolism that is characterized by persistent hyperglycemia, which can result in the development of severe, long-term complications. Hyperglycemia related to diabetes can be caused by a complete lack of insulin secretion (Type 1 DM), insulin action (Type 2 DM), or both [1]. The two main goals of type 2 diabetes treatment aim to decrease the insulin resistance and to increase insulin secretion. In the pathophysiology of the disease, it was found that a rapid rise in blood glucose levels, or hyperglycemia, occurs in people suffering from type 2 diabetes due to the rapid hydrolysis of starch mediated by pancreatic α-amylase and α-glucosidases followed by glucose uptake at the gut [2]. The capability of Allopathic oral hypoglycaemics to treat DM Type 2 is found to be less. Herbal medications are gaining popularity in comparison to commercially available drugs since they provide safer, more effective, and better results for treating a variety of health issues [3]. Therefore, finding more effective herbal or natural product formulations to treat the illness has become significantly important. Therefore, finding more effective herbal or natural product formulations to treat the illness has become significantly important. According to traditional methods, the combination of herbs (polyherbal) rather than a single herb is better for managing diabetes because of their synergism and less negative effects [3].

A decoction is one of the well-known and frequently utilized dosage form in Siddha medicine. Decoctions are often taken orally, and is absorbed very fast in the body. When taken as a dosage form, herbal decoctions can be used therapeutically in a wide range of disease. They are made using the method of boiling herbs to extract their water-soluble components, giving them the strongest activity of all the conventional medicinal preparation types. Decoctions are typically made from the tougher parts of plants, such as the roots, bark, and seeds. This is made by heating the necessary amounts of the powdered herbs with water for thirty minutes, or until the volume of the water is reduced to 1/4th of the initial volume. When heating, the vessel needs to be closed to prevent the therapeutically active components from evaporating out. The extract is then taken off from the heat and strained using a filter, and thus the prepared decoction is used either as a whole or after suitable dilution. Poly Herbal Traditional Decoction is used by Traditional Physicians for the treatment of Diabetes mellitus. Ingredients, method of preparation, and indication of this drug are obtained from an Ola- leaf Manuscript which was collected from the Batticaloa region as mentioned in the Ola-leaf manuscript written by Moothathampy Kathamuthu, Kokkadycholai in 1676 (The basic manuscript was written by Waihali Sinnathamy, Kalinkakudi, Puthur in 1518) and has been practiced in the area for more than 100 years. The decoction is prepared using different parts of the herbal ingredients.

Problem statement

The literature makes it clear that while there is evidence that diabetes complications can be avoided, the incidence of diabetes mellitus is still

rising. For over thousand years, traditional physicians have prescribed several medications for the treatment of diabetes mellitus. However, randomized controlled trials do not provide scientific evidence for the efficacy of these medications [4]. Clinical trials, particularly carefully planned randomized clinical trials (RCTs), are the cornerstone of evidence-based medicine and the primary requisite for the advancement of clinical medicine. Therefore, the purpose of this study is to investigate the hypothesis that using a test drug, Poly Herbal Traditional Decoction, in conjunction with regular allopathic treatment (a single medication or a combination of hypoglycaemic medications based on the blood glucose level / HbA1c) will result in a considerable reduction in blood glucose levels than the standard Allopathic medicine alone.

Background and Justification

According to estimates from the International Diabetes Federation, 463 million people worldwide have diabetes in 2019, and that number is expected to increase to 578 million by 2030 and 700 million by 2045 [5]. The majority of individuals in South East Asian nations are susceptible to diabetes, and according to data from Sri Lanka, one in every twelve adults are expected to have this disease condition. A dietary change that many food and dietetics organizations advise for diabetic patients is the consumption of low Glycaemic Index (GI) items. The term GI describes how blood glucose changes following the ingestion of meals having a high starch content. Comparing low-GI diets to high-GI foods, the former reduce insulin secretion by slowing the rise of postprandial blood glucose levels. Many epidemiological studies have shown that low GI foods are beneficial in reducing obesity and other non-communicable diseases. Blood sugar levels can be used to diagnose diabetes. A healthy person's blood sugar level should normally be between 80 and 100 mg/dl, and it can reach up to 160 mg/dl in the postprandial state. The Glycated Haemoglobin (HbA1c) Test, Oral Glucose Tolerance Test (OGTT), Finger Prick Blood Sugar Test, and Fasting Blood Sugar Level (FBS) Test are among the various laboratory procedures that can be performed to diagnose Diabetes mellitus [6].

Many medications are used to treat type 2 diabetes mellitus (T2 DM) in an effort to improve insulin secretion and glucose metabolism. The drugs that are frequently prescribed for T2 DM include biguanide, sulphonylureas, alpha-glucosidase inhibitors, tiazolidinediones, and lipitins [7]. The majority of these medications have comparable effects on circulating glucose levels and HbA1c in similar methods, but they vary in terms of their safety and pathophysiological consequences [8]. The recommended first-line treatment for type 2 diabetes is metformin. With its wide safety margin, it reduces the amount of glucose produced by the liver. The pursuit of alternative medicine utilizing natural or herbal sources for the treatment of type 2 diabetes has gained recognition in recent decades [9]. The use of complementary and alternative medicine has been pioneered by other factors, such as patient compliance. The role of nutritional therapy in preventing, controlling, and reducing the onset of complications from diabetes is becoming much importance. For this reason, it is crucial to avoid diabetes at all levels (Association, 2008). Most nations have widespread use of herbal medicines in their healthcare systems. According to World Health Organization (WHO) data, 80 percent of people in developing nations use herbal remedies for primary care. Similar to this, during the past 20 years, interest in herbal therapy has increased and herbal medications are currently in high demand in the developed world as well [10].

Medicinal herbs from India and China have been widely used for more than 2000 years to treat type 2 diabetes mellitus [11]. The herbal remedies work by altering the metabolism of glucose, lowering cholesterol levels, and promoting the release of insulin [12].

Conventional diabetes drugs are widely available; nevertheless, their expenses and possible adverse effects are greater than those of plant-based drugs. Many phytoconstituents having anti-diabetic properties, such as terpenoids, saponins, flavonoids, carotenoids, alkaloids, and glycosides, are found in medicinal plants. Numerous plants are abundant in bioactive chemicals that possess distinct pharmacological characteristics and do not result in unfavorable side effects. Communities in developing nations have long harbored great hopes for these plant remedies, and it is common to manage diabetes with inexpensive medicinal plants rather than prescription medications. The extracts from medicinal plants and herbs are currently employed due to their anti-diabetic properties. Numerous clinical studies have demonstrated conclusive evidence that medicinal plant extracts have anti-diabetic properties and aid in the restoration of pancreatic β-cell function [13]. In Sri Lanka, about 126 anti-diabetic herbs have been utilized to treat diabetes. However, despite the World Health Organization's recommendations for more research, the majority of these plants are utilized in traditional treatment systems without adequate scientific validation [14].

The research evidences showed that all of the parts of plants present in the "Polyherbal Traditional Decoction" possess hypoglycaemic effects with proven results and can be used as a potential anti-diabetic therapeutic agent. The purpose of this study is to test the hypothesis that, when combined with Poly Herbal Traditional Decoction (test drug), standard allopathic treatment (either a single medication or a combination of hypoglecaemic drugs based on the blood glucose level / HbA1c) will result in a higher reduction of Fasting Blood Sugar (FBS) than standard allopathic treatment given alone on the management of diabetes mellitus.

In this study, the test drug's efficiency in lowering HbA1c and Fasting Blood Sugar level while managing Diabetes Mellitus was shown. The results of the current study will be put into medical practice at Government or Private Siddha Ayurvedic hospitals for the management of Diabetes mellitus after the publication is done. The General Siddha Ayurvedic Physician will decide on the dosage and drug combination based on the levels of blood sugar and HbA1c.

Objectives

General Objective

To evaluate the hypoglycaemic action of the Poly Herbal Traditional Decoction

Specific Objective

O To determine the reduction of Glycosylated Hemoglobin (HbA1c)

O To determine the reduction of Fasting Blood Sugar (FBS)

O To determine the changes in following signs and symptoms

O Polyuria

O Polyphagia

O Polydepsia

METHODOLOGY

Collection and processing of plant material

The fresh parts of the plants were collected from Jaffna Districts and authenticated by Department of Kunapadam, Unit of Siddha Medicine, Trincomale Campus. The plant parts were cleaned well with running tap water. The ingredients were cut into small pieces in order to enhance the drying process and

will be dried in the shade for a favourable level until the final moisture content is less than 10% (w/w) or in a dryer. The dried parts were ground using the micro pulverizes, and were sieved (sieve no. 100) to get a fine powder such that 92 - 95 percent of the particle sizes remain less than 250 microns and 4 - 5 percent remains 425 microns.

The 5g of prepared powder was packed as sachet tea packets stored in air tight containers at room temperature and was used for the intervention study.

The trial drug and placebo drug were prepared at the hospital pharmacy.

Normal tea power was purchased from the local grocery shops and 5g of tea powder was packed as sachet tea packets stored in air tight containers at room temperature and was used for the intervention study.

Preparation of Decoction

The coarse powders of the 10 dried ingredients were obtained in the ratios as given in the Table 3-1 and were mixed accordingly. The mixed powder was packed in sachet packets each of weight 5g and was sealed to be used in the decoction preparation.

Table 3 1: List of ingredients present in the Poly-herbal Traditional Decoction with the quantities used

Name of plant ingredient	**Part used**	**Quantity used**
Senna auriculata	Root & bark	1 part
Cissampelos pareira	Root	1 part
Ficus racemosa	Bark	1 part
Terminalia arjuna	Bark	1 part
Acacia arabica	Bark	1 part
Syzygium cumini	Bark	1 part
Curcuma longa	Rhizome	1 part
Terminalia chebula	Fruit pulp	½ part
Phyllanthus emblica	Dry fruit	1 part

Terminalia bellirica	Fruit pulp	½ part

Freshly prepared, packed (as sachet tea packets) and stored coarse powder of the test drug (5g) was added with 100ml (1 tumbler) boiled water for 10-15 minutes.

Placebo tea powder (5g) was added with 100ml (1 tumbler) boiled water for 10-15 minutes.

The patients were instructed to remove the decoction powder packets and consume the decoction twice a day (morning and night) before meal.

Furthermore, the patients were advised to prepare the decoctions freshly on each day before the medicines are being consumed.

Study design

A double-blind, Randomized Control Trial was conducted at Diabetic Clinic in Diabetic Clinic of the Herbal Health Care Centre, Kokuvil, Sri Lanka. Ethical approval was obtained from the Institutional Ethics Review Committee of the Bandaranayake Memorial Ayurveda Research Institute (BMARI), Nawinna, Maharagama, Sri Lanka.

Inclusion criteria

The selected study participants were those;

- Patients diagnosed with type 2 diabetes not less than 6 months and not more than 24 months before baseline examination.
- Management by lifestyle with oral hypoglycemic agents or insulin or both
- All HbA1c > 6.5% (> 48 mmol/mol) within previous 3 months.
- Who were diagnosed with type 2 diabetes not less than 6 months and not more than 24 months and treated with oral hypoglycemic agents or insulin or both.
- Age between 30 – 70 years and
- Who have the ability to provide informed consent.

Exclusion Criteria

If any of the following are identified in a patient, he/she was excluded from the study. (These details will be crossed check with diagnosis card)

- Patients with Type I DM
- A previous HbA1c > 9.0% (> 75 mmol/mol)
- Uncontrolled hypertension (blood pressure > 180/110 mmHg)
- Unstable angina (class 4)
- A myocardial infarction in the past 6 months
- Two or more episodes of seizures
- Alcoholism or drug abuse documented in the chart
- Late-stage complications of diabetes or other chronic conditions, such as cirrhosis
- Inability to participate weekly session

Baseline Assessments and Investigations at the commencement of study

The following tasks were undertaken

1. A complete history was obtained.
2. Complete physical examination including vital signs, height, weight, measurement of Body Mass Index (BMI) was done.
3. Informed written consent was obtained.
4. Assessment of HbA1c and fasting Blood Sugar- A well trained and experienced nursing officer was withdraw and obtain 5 ml of blood from all participants, into a tube containing the anticoagulant, Ethylene Diamine Tetra-acetic Acid (EDTA). Venipuncture was performed minimally traumatic to minimize platelet activation and was done using a 23G needle and 5 ml syringe. The specimen was labeled with the patient's full name.

All samples were kept cool (at refrigerated temperatures, but not frozen) during storage and shipping to minimize changes in cells that can occur with storage. The sample was wrapped in paper towels, which was sent to Durdan's Hospital Laboratory, Jaffna, Sri Lanka.

Sample size

Since the test had been selected from the traditional Palm Ola leaf manuscript, there weren't any Randomized Clinical Trials carried out. Based on prior data from the clinical trial clinical efficacy and safety of metformin hydrochloride sustained-release (SR) tablet (II) produced by Dulening and the original metformin hydrochloride tablet produced by Glucophage in the treatment of Type 2 diabetes mellitus (T2 DM), randomized, open and parallel controlled clinical trial (Guo et al, 2021) the sample size was calculated. Hence 48% of patients in the control group and 68% of patients in the test group get lower HbA1C levels after 3 months, compared to baseline, to detect this increase with a power of 80% and statistical significance (α) of 0.05, and with a 10% dropout rate, 100 patients (50 per group) were enrolled [26].

Randomization, allocation concealment and blinding

The Primary Investigator was prepared 100 empty opaque envelopes, numbered sequentially from 1-100. These envelopes were handed over to a person who was generated the random allocation sequence. The random number list and random allocation sequence were generated by one of the colleagues of the researcher who was not involved in the research. A piece of paper containing the random allocation sequence (A or B) was folded and placed in the envelopes. Envelopes were sealed and kept in separate boxes. Randomization was done after getting all the reports. Participants were randomly assigned in a 1:1 ratio to the two arms such as the treatment arm and controlled arm. The research assistant who measures the weight, height, waist circumference, hip circumference of the participants was not aware whether the participants in the control group (II) or intervention groups (I).

Decoction powder packets labeled A (Poly Herbal Traditional Decoction) and B (Normal tea powder-placebo) were prepared by the Primary Investigator and kept in the pharmacy of hospital. Poly Herbal Traditional Decoction powder packets and placebo decoction powder packets were prepared by the investigator as described in 3.1. When participants meet the Medical Officer with the results of investigations each participant were prescribed the standard allopathic treatment and, in the sequence, given the appropriate sequentially numbered sealed envelope. After that, the participant was met the Pharmacist with the prescription for standard treatment along with the sealed envelope. The pharmacist was opened the envelope and issue the packets (Poly Herbal Traditional Decoction powder o normal tea powder) according to A or B printed on the piece of paper within the envelope.

A standard allopathic treatment was prescribed as per the prescription given by the Physician. Poly Herbal Traditional Decoction and Placebo powder were issued for one month.

The label (A or B) was removed by the pharmacist when he /she issues the medication. The open envelope was resealed with its contents (trial code and label which were removed from the decoction powder packets) by the pharmacist and kept safely at the pharmacy. Therefore, the investigator and participants were blinded to the allocation of participants to the treatment group (Poly Herbal Traditional Decoction) or control group (normal tea powder decoction as a placebo). Open labeled design was used for the standard treatment.

The patients were given a mobile contact number and requested to contact the investigator in the case of an adverse event. Unblinding was done who was developed any reaction (example a skin rash), suspect to be a reaction to the trial drug, and he/she was withdrawn from the study and appropriate management was provided.

All data were maintained with password-protected software and the password was kept confidentially by the researcher.

Treatment

There were two treatment arms (Group I & Group II)

The patients in the Group I were administrated standard Allopathic medical therapies from a diabetic clinic, a western hospital (that may be used alone or in combination with other hypoglycemic medications based on the blood glucose level / HbA1c for instance, metformin alone or metformin plus gliclazide), along with a test drug (Poly Herbal Traditional Decoction powder, 5g was added with 100ml (1 tumbler) boiled water for 10-15 minutes for two times a day before the meal. The patients in Group II were received a placebo tea powder (5g) was added with 100ml (1 tumbler) boiled water for 10-15 minutes for two times a day before the meal, in addition to standard Western treatment therapies (a drug alone or in combination with other hypoglycemic Western medicines based on the blood glucose level / HbA1c for instance, metformin alone or metformin plus gliclazide).

Outcomes

Primary outcome – HbA1c reduction in percentage from baseline after three months – It was compared the % of patients who had reduced HbA1C after three months compared to the baseline, in test group vs control group.

Secondary outcome – after one month and three months from base line

I. Reduction of Fasting Blood Sugar level in percentage

II. Reduction of Body Mass Index (BMI)

III. Changes of Signs and symptoms of diabetes mellitus

Instrument

An interviewer (researcher) administered a questionnaire or proforma (data collection form) was used to collect the data. The data collection form was prepared based on the specific objectives. In addition to responses to specific questions, notes were made on information obtained by examination and investigations.

Informed consent

The Investigator or Co-investigators were explained the study to the potential subject verbally, providing all pertinent information (purpose, procedures, risks, benefits, alternatives to participation, etc.), and the patient was allowed to ask questions regarding the research. Following this verbal explanation, the participants were provided with a study information sheet and must be afforded sufficient time to consider whether or not to participate in the research. After allowing the participant time to read the study information sheet, the Investigator was answered any additional questions the participant may have. When the subject is satisfied, the investigator was obtained the written informed consent to participate in the research.

Intervention

The intervention group (Group I) was received 100 ml of Poly Herbal Traditional Decoction two times a day before meals, in addition to their usual Western hypoglycemic medication. The patients were instructed to prepare the decoction as mentioned in section 3.2 in this proposal (preparation of decoction) before having the medicines.

This treatment protocol was given for 3 months.

Participants were instructed to continue their hospital follow-up. Participants were examined and investigated for primary and secondary outcomes at baseline, post-intervention 1 at 4 weeks, and post-intervention 2 at 3 months.

The control group (Group II) was given 100 ml of normal tea powder decoction (placebo) for two times a day before meals, in addition to their usual Western hypoglycemic medication. The patients were instructed to prepare the decoction as mentioned in section 3.2 in this proposal (preparation of decoction) before having the medicines. The control group patients were examined and investigated for primary and secondary outcomes at baseline, post-intervention 1 at 4 weeks and post intervention 2 at 3 months with no other interaction in between with study staff.

If the participant fails to consume the decoction (test/placebo) after the intervention, it was considered as "did not receive the intervention".

When participants discontinue the medicines due to the occurrence of adverse reactions or any other reasons, it was considered as "discontinued intervention".

When the participants fail to visit the hospital for the follow-up, it was considered as "lost to follow up". The investigators were tried to communicate the lost participants by telephone calls, postcards and through the family workers and they were requested to come back to the hospital to continue the treatment.

All interventions were carried out for three months for both Groups I and II.

Methods of Evaluation

Assessments of all variables were made at baseline, post-intervention 1 at 1 month and post intervention 2 at 3 months for all participants (Group I, and II).

Baseline testing was done after screening of study participants. From all study participants, baseline data were gathered by using data collection form and all baseline and post-interventions data were recorded in data collection sheet.

Table 3 2: List of investigations will be carried out in baseline and post interventions

Study test	Baseline	Post-intervention-1 (1 month)	Post-intervention-2 (3 months).
Presence of diabetes signs and symptoms	X	X	X
Weight (Kg)	X	x	X
Height (cm)	X		
Body mass index (BMI) (Kg/m^2)	X	x	X
Fasting blood sugar (FBS) (mg/dl)	X	x	x
HbA1c-	X	-	X

Confidentiality

The patient identification detail was appeared in the data collection sheet to facilitate follow-up only. It was not appeared in the data analysis document.

To protect participants' confidentiality, researcher was encrypted computer-based files, store documents (i.e., signed consent forms) in a locked file cabinet and remove personal identifiers from study documents as soon as possible. Files containing electronic data were closed when computers were left unattended.

All data were maintained with password-protected software and the password was kept confidential by the researcher. Summary of the data were published (individual data will appear only in data collection sheet). Data stored in a paper format was shredded. Data stored in an electronic form were destroyed by rewriting or reformatting.

Withdrawal and loss to follow-up

Withdrawal of subjects

The patients were given a mobile contact number and requested to contact the investigator in the case of an adverse event. Un-blinding will be necessary in those who were developed any reaction (for example a skin rash), suspect to be a reaction to the trial drug, and he/she was withdrawn from the study and appropriate management was provided. When participants discontinue the medicines due to the occurrence of adverse reactions or any other reasons, it was considered a "discontinued intervention".

When the participants fail to visit the hospital for the follow-up, it was considered as "lost to follow-up". The investigator was tired to communicate with the lost participants by telephone calls, postcards and through the family workers and they were requested to come back to the hospital to continue the treatment.

Lost to follow-up

The effects of lost to follow-up were minimized by adding 20% of additional sample to the sample size.

Data Analysis

Data were analyzed using statistical software SPSS (version 23). A probability of <0.05 was considered statistically significance for all tests. Continuous variables were tested for normality. Based on the normality, the relevant inferential statistic test was used. Descriptive analysis was performed for all variables. Mean differences of primary and secondary variables between two groups were assessed using independent sample t-test.

Conflict of interest

Since the Principal investigator is the employee of the Eastern University, Sri Lanka (funding organization for the current project) which has a motivation in subsequent commercialization of the product. Hence Agreement should be signed between the investigator and collaborator in order to define the basis for collaboration between the parties in areas of research and commercialization concerning.

Significant Financial Interests may arise in monetary value, equity interests (ownership) and intellectual property rights (patency, copy right).

Investigators must disclose their significant financial interests through Financial Interest Disclosure forms.

RESULTS AND OBSERVATION

Demographics and other baseline characteristics

A total of 100 participants completed the study. It was observed that participants had an average age 56.08 years (both sexes), average weight 62.3 (± 4.86) Kg, average BMI 24.3 (± 2.07) Kg/ square meter and average chronicity of 5.6 years (± 4.9) years at baseline were randomized into test group (n=50) and control group (n=50) (Fig. 4.1). It was also observed that 38 participants (38%) belonged to the age group of 41-50 years.

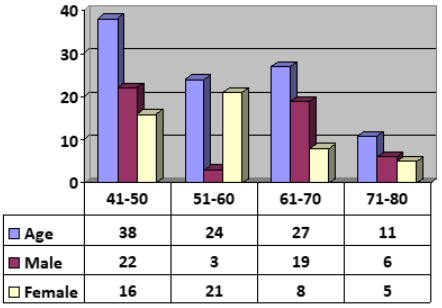

Fig. 4.1 — Distribution of participants according to sex & ages in both groups

Effect of test drug on the signs and symptoms of Diabetic mellitus

It was observed that the participants presented with the symptoms polyuria, polydipsia, polyphagia, sudden weight changes, burning sensation in palm and soles, and fatigue. In this study, Group I showed better improvement in polydipsia, polyuria, polyphagia, fatigue, burning sensation in palm and soles in comparison to Group II (Table 4.1).

Parameters	Before Treatment (BT)				After Treatment (AT)			
	Group I		Group II		Group I		Group II	
	No	Percentage (%)	No	Percentage (%)	No	Percentage (%)	No	Percentage (%)
Polyuria	34	68%	38	76%	21	42%	35	70%
polydipsia	29	58%	21	42%	11	22%	20	40%
polyphagia	19	38%	17	34%	9	18%	15	30%
sudden weight changes	5	10%	7	14%	4	08%	7	14%
burning sensation in palm and soles	38	76%	41	82%	5	10%	31	62%
Fatigue	15	30%	22	44%	4	08%	17	34%

Table 4.1: Effect of test drug on the signs and symptoms of Diabetic mellitus

Effect on fasting blood glucose (FBG)

In this study efficacy of the formulation was assessed in terms of reduction in fasting blood glucose level at 12 weeks of treatment in comparison to base line. In the Group I, mean fasting blood glucose was 217.04 ±13.82 mg/dL at base line whereas it was 218.9 ±13.94 mg/dL in the Group II. At the end of the study, mean fasting blood glucose was reduced to 119.04 ±11.52 mg/dL and 176.90 ±13.91 mg/dL in test group and control group respectively (Table 4.2). The result showed that a reduction in mean fasting blood glucose was higher in Group I at 12 weeks of treatment.

Fasting Blood Sugar	Before Treatment (BT)	First follow-up (end of first month)	Second follow-up (end of second month)	Third follow-up (end of third month)
Group I	217.04 ±13.82	200.44 ±15.01	175.64 ±14.46	119.04 ±11.52
Group II	218.9 ±13.94	210.64 ±14.84	193.90 ±14.84	176.90 ±13.91

Table 4.2: Effect on fasting blood glucose (FBG), (Mean ±SD)

Effect on Glycosylated Hemoglobin (HbA1c)

In this study efficacy of the formulation was assessed in terms of reduction in fasting blood glucose level at 12 weeks of treatment in comparison to base line. When mean HbA1c in both groups was compared, the difference in the mean HbA1c between test and control groups was significant ($p<0.05$). The mean HbA1c (%) in Group I and Group II at baseline was 7.47 ±0.70 and 7.39 ±0.66 whereas at the end of 12 weeks of study the level of glycated haemoglobin in Group I and Group II was reduced to 5.03 ±0.53 and 6.79 ±0.51 respectively (Table 4.3).

Groups	Baseline	After three months (end of third month)
Group I	7.47 ±0.70	5.03 ±0.53
Group II	7.39 ±0.66	6.79 ±0.51

Table 4.3: Effect on Glycosylated Hemoglobin (HbA1c)

Reduction of Fasting Blood Glucose (FBG) and Glycosylated Hemoglobin (HbA1c) before and after treatment with in a Group I and Group II

In this study efficacy of the formulation was assessed in terms of reduction in fasting blood glucose level and HbA1C at 12 weeks of treatment in comparison to base line. The mean difference between before and after treatment for fasting blood glucose for Group I and II were 43.4 and 41.344. The t value for Group I and II were 28.164 and 11.669 and the p value for both groups were 0.000.

Parameters	Mean		Std. Deviation		Std. Error Mean		95% Confidence Interval of the Difference				t		df		Sig. (2-tailed)	
(Before_ After treatment)	Grp I	Grp II	Group I	Group II	Group I	Group II	Lower		Upper		Group I	Group II	Group I	Group II	Group I	Group II
							Group I	Group II	Group I	Group II						
Pair 1-FBS	43.4	41.344	10.394	9.714	1.47	1.717	38.446	37.841	44.354	44.846	28.164	24.076	50	31	0.000	0.000
Pair 2-HBA1C	0.834	0.6188	0.3842	0.3551	0.0543	0.0628	0.5248	0.4907	0.7432	0.7468	11.669	9.857	50	31	0.000	0.000

Table 4.4: Effect on fasting blood glucose (FBG), (Mean ±SEM)

DISCUSSION

This Randomized Clinical Trial compared glycemic control, clinical outcome and amelioration of subjective symptoms in participants with diabetes mellitus type 2 treated with standard allopathic medical therapies and Poly Herbal Traditional Decoction in Group I and standard allopathic medical therapies and placebo in Group II participants. No adverse effects were reported during the four months of treatment. It's observed that both treatments resulted in sustained improvement in glycemic control. During the study event of hypoglycemia was not observed in both the groups. It was also observed that primary outcome to maintain normoglyceamia at 12 weeks of treatment was found significant. The Group I showed efficacy in terms of reduction in serum glucose at 12 weeks of treatment. These inferences are in line with other studies, wherein individual components of this formulation were efficacious in bringing down metabolic index [27].

Optimal treatment of type 2 diabetes mellitus requires a comprehensive and concerted approach. The management of the condition focuses on nutrition, exercise, and pharmacologic therapies to reduce the complications associated with hyperglycemia. In prediabetic and new-onset diabetes patients, nutrition therapy is of utmost importance to prevent for their deterioration of the condition [28].

The American diabetic association (International Expert Committee report) recommends HbA1c with a cut point ≥ 6.5% for diagnosing diabetes as an alternative to fasting plasma glucose as it provides a reliable measure of chronic glycemia and correlates well with the risk of long-term diabetes complications. Further, HbA1c is also a good predictor of lipid profile, providing additional benefits of identifying cardiovascular risk among diabetes patients [30]. The possible mechanism of action of the Poly Herbal Traditional Decoction to act as hypoglycemic and ameliorative to the symptoms may be hypothesized. The Poly Herbal formulation constituted of ten herbs having anti-diabetic activities acted synergistically to control and maintain normo-glycaemia.

Studies were conducted earlier with polyherbal formulations with varying contents and compositions for their antihyperglycemic potential. Senna auriculata (L.) Roxb, also known as Cassia auriculata is a plant belonging to Fabaceae family is a traditional medicinal plant,

widely used for the treatment of various ailments in Siddha system of medicine. The study Daisy et al, 2012, has shown the potent anti-diabetic activity that reduces blood sugar level in streptozotocin-(STZ) induced diabetic rats on oral administration of various extracts (hexane, ethyl acetate, methanol and aqueous extracts) of Senna auriculata bark. A per the study Kumar et al, 2022, the aqueous extract of Cissampelos pareira L. (Menispermaceae), root has the potential to reduce STZ-induced elevated blood glucose without affecting liver and kidney functions. The study Keshari et al, 2016, has shown proven effects of the stem bark of Ficus racemosa for its potential anti-diabetic activities. Similarly, Ragavan et al (2009), has shown the potential anti-diabetic action of the stem bark of the plant Terminalia arjuna extracts. The study Kumar et al showed that the ethanolic extract of Terminalia chebula fruit has the potential hypoglycaemic action on STZ- induced diabetic rats and the effect was found to be more effective than the standard drug glibenclamide used in the study. As per the study Gupta et al, 2019, ethyl acetate and aqueous extracts of Terminalia bellirica fruit was found to have considerable antioxidant and alpha-amylase inhibitory activity. In diabetic rats, both the extracts have shown blood glucose lowering activity coupled with improvement in body weight, lipid profile and renal function. Moreover, different test extracts of Acacia arabica bark were able to ameliorate the derangements in lipid metabolism caused by diabetes mellitus in alloxan induced diabetic rats towards normal level (Patil et al, 2011). The results the study Kumar et al, 2008 indicated that isolated compound 'Mycaminose', ethyl acetate and methanol extracts of the plant Syzygium cumini possess anti-diabetic effects against Streptozotocin (STZ)-induced diabetic rats. The results of the study Krup et al, 2013 indicated that Curcuma longa have an effect on insulin secretion and is effective in long term diabetes mellitus condition. The study Srinivasan et al, 2018 anti-hyperglycemic effect of quercetin - a major constituent of methanolic extracts of Phyllanthus emblica fruit in Streptozotocin (STZ)-induced diabetic rats was shown to have maximum decrease in blood glucose levels in the diabetic rats after 7 days of treatment.

CONCLUSION

The findings in this randomized clinical study demonstrates the potential of Poly Herbal Traditional Decoction as an alternative safe medication in the treatment of T2DM. It was also evident that Poly Herbal Traditional Decoction possesses a similar therapeutic response as compared to allopathic medical therapies. Future studies in a larger cohort may help in positioning the polyherbal formulation as an alternative to the standard treatment for type 2 diabetes. The study shown that Poly Herbal Traditional Decoction, with its steady influence on reducing the hyperglycemic index, is comparable with allopathic medical therapies.

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REFERENCES

Banani, D., Achintya, M. and Jayram, H. (2011). Management of Madhumeha (Diabetes mellitus) with current

evidence and intervention with Ayurvedic Rasausadhies.Indian Journal of Traditional Knowledge.[online] Volume 10(4), pp. 624-628.

Wild, S., Green, A., Sicree, R., King, H. (2004). Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 27. [online] Volume 1, pp. 1047-1053.

Gauttam, V. K., & Kalia, A. N. (2013). Development of polyherbal antidiabetic formulation encapsulated in the phospholipids vesicle system. Journal of advanced pharmaceutical technology & research, 4(2), 108.

Kumar S, Mittal A, Babu D, Mittal A. Herbal Medicines for Diabetes Management and its Secondary Complications. Curr Diabetes Rev. 2021;17(4):437-456.

Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: (2019) results from the International Diabetes Federation Diabetes Atlas. Diabetes Research Clinical Practice. 2019.

Verma, S., Gupta, M., Popli, H., & Aggarwal, G. (2018). Diabetes mellitus treatment using herbal drugs. International Journal of Phytomedicine, 10(1), 1-10.

Harrigan RA, Nathan MS, Beattie P. Oral agents for the treatment of type 2 diabetes mellitus: pharmacology, toxicity, and treatment. Ann Emerg Med. 2001;38(1):68–78.

Raz I. Guideline approach to therapy in patients with newly diagnosed type 2 diabetes. Diabetes Care. 2013;36.

Pandey A, Tripathi P, Pandey R, Srivastava R, Goswami S. Alternative therapies useful in the management of diabetes: a systematic review. J Pharm Bioallied Sci. 2011;3(4):504–12.

Alqathama, A., Alluhiabi, G., Baghdadi, H. (2020). Herbal medicine from the perspective of type II diabetic patients and physicians: what is the relationship?. BMC Complement Med Ther 20, 65.

Wang Z, Wang J, Chan P. Treating type 2 diabetes mellitus with traditional Chinese and Indian medicinal herbs. Evid Based Complement Alternat Med. 2013;2013:1–17.

Liu JP, Zhang M, Wang W, Grimsgaard S. Chinese herbal medicines for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2002. https://doi.org/10.1002/14651858.CD003642.pub2.

Verma, S., Gupta, M., Popli, H., & Aggarwal, G. (2018). Diabetes mellitus treatment using herbal drugs. International Journal of Phytomedicine, 10(1), 1-10.

Perera, H. K. I., Premadasa, W. K. V. K., & Poongunran, J. (2015). α-glucosidase and glycation inhibitory effects of costus speciosus leaves. BMC complementary and alternative medicine, 16(1), 1-9.

Nille Guruprasad C, Mishra Shardendu Kumar, Chaudhary Anand Kumar, Reddy K. R. C. (2021) Ethnopharmacological, Phytochemical, Pharmacological, and Toxicological Review on Sennaauriculata (L.) Roxb.: A Special Insight to Antidiabetic Property, Frontiers in Pharmacology.12.

Daisy, P., Feril, G. and Kani, J., 2012. Evaluation of antidiabetic activity of various extracts of Cassia auriculata Linn. bark on streptozotocin-induced diabetic wistar rats. International Journal of Pharmacy and Pharmaceutical Sciences, 4(4), pp.312-18.

Ankit Kumar, RavindraSemwal, AshutoshChauhan, RuchiBadoniSemwal, Subhash Chandra, DebabrataSircar, Partha Roy, Deepak Kumar Semwal (2002). Evaluation of antidiabetic effect of Cissampelospareira L. (Menispermaceae) root extract in streptozotocin-nicotinamide-induced diabetic rats via targeting SGLT2 inhibition, Phytomedicine Plus, 2(4).

Amit K. Keshari, Ghanendra Kumar, Priya S. Kushwaha, Monika Bhardwaj, Pranesh Kumar, AtulRawat, Dinesh Kumar, AnandPrakash, BalaramGhosh, SudiptaSaha, (2016). Isolated flavonoids from Ficusracemosa stem bark possess antidiabetic, hypolipidemic and protective effects in albino Wistar rats, Journal of Ethnopharmacology, 181. Pp. 252-262.

Ragavan, B., Krishnakumari, S. (2006)Antidiabetic effect ofT. arjuna bark extract in alloxan induced diabetic rats. Indian J ClinBiochem. 21, pp. 123–128.

Gandhipuram Periasamy Senthil Kumar, Palanisamy Arulselvan, Durairaj Sathish Kumar, Sorimuthu Pillai Subramanian. (2006). Anti-Diabetic Activity of Fruits of Terminaliachebula on Streptozotocin Induced Diabetic Rats. Journal of Health Science. 52(3). Pp,283-29.

Ashutosh Gupta, Ramesh Kumar, Abhay K. Pandey. (2020). Antioxidant and antidiabetic activities of Terminaliabellirica fruit inalloxan induced diabetic rats. South African Journal of Botany. 130. Pp.308-315.

Official Methods and Recommended Practices of the American Oil Chemists' Society (1993), AOC Press. Washington, DC

Lahorkar P, Ramitha K, Bansal V, Anantha Narayana DB. A comparative evaluation of medicated oils prepared using Ayurvedic and modified processes. Indian J Pharm Sci (2009). 71(6).

Association AD. Nutrition recommendations and interventions for diabetes. A position statement of the American Diabetes Association. Diabetes Care. 2008;31(Supplement 1):S61–78.

Guo LX, Liu GE, Chen L, Wang HF, Guo J, Zheng XL, Duan BH, Wang DZ, Zhu W, Wang K, Tan WS, Chen Q, Li QZ, Yang J, Zhang Q, Xie PF, Lei MX. (2021) Comparison of Clinical Efficacy and Safety of Metformin Sustained-Release Tablet (II) (Dulening) and Metformin Tablet (Glucophage) in Treatment of Type 2 Diabetes Mellitus. Front Endocrinol (Lausanne).

Pocock SJ. Clinical Trials: A Practical Approach. Wiley; 1983.

Basch E, Gabardi S, Ulbricht C. Bitter melon (Momordica charantia): a review of efcacy and safety. Am J Health Syst Pharm. 2003;60(4):356–9.

George CM, Brujin LL, Will K, Howard-Thompson A. Management of blood glucose with noninsulin therapies in type 2 diabetes. Am Fam Physician. 2015;92(1):27–34.

International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabe tes Care. 2009;32(7):1327–34.

Khan HA, Sobki SH, Khan SA. Association between glycaemic control and serum lipids profle in type 2 diabetic patients: HbA1c predicts dyslipidaemia. Clin Exp Med. 2007;7(1):24–9