International Journal for Pharmaceutical Research Scholars (IJPRS)

V-3, I-1, 2014 ISSN No: 2277 - 7873

RESEARCH ARTICLE

Efficacy and Safety Profile of Siddha Compound Madhumega choornam (MMC) in Type II Diabetic Patients

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Manuscript No: IJPRS/V3/I1/00061, Received On: 05/02/2014, Accepted On: 12/02/2014

ABSTRACT

Madhumega choornam (MMC) is a well-known polyherbal Siddha formulation. It is in practice for the treatment of Madhumegam (diabetes) for more than four decades. Present study was undertaken to evaluate antidiabetic activity of MMC, containing seven herbs viz., *Murraya koenigii, Terminalia chebula, Emblica officinalis, Tinospora cordifolia, Syzygium cumini, Cyperus rotundus* and *Phyllanthus niruri*, in type 2 diabetes individuals of Tamil Nadu, South India. This study is an open, non-comparative, non-randomized, phase IV clinical trial spanning 20 weeks. About 95 subjects of age range between 20-65 years with fasting plasma glucose (FPG) between 126-149mg/dl and two-hour postprandial plasma glucose (PPPG) between 200-299 mg/dl were included in the study. Fasting plasma glucose and postprandial glucose, glycosylated hemoglobin, lipid profile, heamatology, renal and liver function test were performed at baseline and at the end of 20th week. A paired t-test was used to assess the statistical significance between baseline and final measurements. Paired t-test revealed that the fasting ($p=0.046$) and postprandial blood glucose ($p<0.001$) and HbA1c ($p<0.001$) showed significant reduction after MMC intervention. The liver, renal functions along with the hematological parameters were well within the normal range. The results suggest MMC to be beneficial for the treatment of type 2 diabetes, further follow-up studies are warranted to confirm the safety aspects of MMC use.

KEYWORDS

Antidiabetic, Siddha medicine, Safety

INTRODUCTION

Diabetes is characterized by hyperglycemia and associated with microvascular, macrovascular and neuropathic complications. Treatment and care of diabetes represents a substantial portion of the national health care expenditure and exerts a considerable national and global disease burden.

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According to WHO estimates the global prevalence of diabetes mellitus is >346 million and in 2010 it was projected that diabetes accounted for 12% of health expenditures or at least $376 billion-a figure likely to hit $490 billion in 2030.[1] A recent Indian study reported that in Tamil Nadu state comprises 4.8 million diabetic individuals which has been extrapolated to whole country as 62.4 million.[2] Sulfonylureas, biguanides, alpha-glucosidase inhibitors, thiazolidinediones, and meglitinides

are some drug categories used in oral therapy. As there are several limitations on current drug therapies, alternative Ideal therapies with anti-diabetic activity and similar degree of efficacy without the troublesome side effects have been researched extensively.

Madhumega choornam (MMC) is a well-known polyherbal formulation from Siddha medicine, one of the traditional medical systems in India.[3] The Siddha drug, MMC is in vogue in Government run Siddha hospitals of Tamil Nadu, South India for more than five decades for the treatment of *Madhumegam* or *Neerizhivu* (*neer* means urine and *izhivu* means excessive loss). As per Siddha text, the word '*madhu*' literally means sweet, '*megam*' means venereal disease, '*choornam*' means powder. Hence MMC is traditionally given for the treatment of diabetes mellitus.

Newly industrialized countries including India are currently undergoing demographic and life style transition. This has resulted in increasing burden of non-communicable diseases and the cost involved in managing it. Increased incidence of the adverse effects and economic burden in the usage of modern system of medicine may be a reason for the interest in traditional medicine.[4] The WHO observation on traditional medicines made this research group to design interventional study on mild form of Diabetes mellitus (DM) by administering Siddha medicine.

In this context, we are conducting PURSE HIS study (**P**opulation study of **U**rban, **R**ural and **S**emi-Urban regions for the detection of **E**ndovascular disease and prevalence of risk factors and **H**olistic **I**ntervention **S**tudy) at Sri Ramachandra University, Chennai, Tamil Nadu. At the base-line level, we measured prevalence of risk factors for endovascular diseases in three strata of society (namely, urban, semi-urban and rural societies) and identify differences in profile of risk factors in these different settings. After identifying the risk factors the participants are selected on the basis of voluntary participation for intervention with Siddha polyherbal compound MMC (supplementary material). This study was aimed to evaluate the clinical efficacy and safety of the polyherbal compound MMC in the management of type 2 diabetes. This pilot study was an open, non-comparative, non-randomized, phase IV clinical trial, conducted at the PURSE-HIS research station, at Sri Ramachandra University, Porur, Chennai, India from January 2008-2010.

MATERIALS AND METHOD

The trial was conducted in accordance with the ethical principles that are consistent with Good Clinical Practice guidelines and obtained prior approvals before start of the trial from the Institutional Ethics Committee of Sri Ramachandra University, Porur, Chennai. The trial was registered in Clinical Trial Registry of India (CTRI/2011/04/001677). Participants were informed in Tamil language, regarding the trial, the expected benefits and their right to opt-out of trial at any time without prejudice. Informed written consent was obtained from each participant, prior to his/her inclusion into the trial. Before commencing the MMC trial all the subjects were advised diet based on their body mass index (for BMI < 25kg/m^2, 530 k.cal ; 25-30 kg/m^2 , 402 k.cal; >30 kg/m^2 , 275 k.cal) for six weeks. Subjects whose blood sugar levels still higher after six weeks of diet were included in the study, but no recommendations on diet were given during trial period. About 95 subjects of age range between 20-65 years with fasting plasma glucose (FPG) between 126-149mg/dl and two-hour postprandial plasma glucose (PPPG) between 200-299 mg/dl were included in the study. The subjects with history of serious adverse effects or hypersensitivity reactions to the medication such as rashes, diarrhea, vomiting etc., and history of treatment with other anti-hyperglycemic drugs, active liver disease or hepatic dysfunctions, higher serum creatinine (> 2.5 mg/dl) and serious or unstable medical or psychological condition are excluded from the study.

Fasting blood sample was collected after an overnight fast of at least 10 hours and postprandial blood sample was collected two hours after breakfast. From each participant 5-

10 ml of blood was collected from the antecubital vein at the PURSE HIS research station and transported to the central laboratory using appropriate cold storage precautions. The samples were used to analyze the plasma glucose, glycosylated hemoglobin (HbA1c), serum lipid profile, blood urea nitrogen, serum creatinine, Serum glutamic oxaloacetic transaminase (SGOT), Serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase, total proteins, albumin, bilirubin and routine hematological analysis was done using the standard kits. On the same day after collection of blood specimen the participants were clinically examined by both physicians from allopathy and Siddha medicine. A Siddha physician examined the participants according to the principles and practice of the system.[3]

All enrolled participants were recommended the diet with respect to their BMI and advised to take 2 MMC capsules with water (dose of 500mg prepared by Arogya Healthcare Pvt. Ltd., Chennai-10) thrice a day before food. They were advised not to take any other anti-diabetic drugs during the study period of 20 weeks. All participants were followed at every 4 weeks and blood samples were taken for analyzing blood sugar. At the end of 20th week along with blood sugar, lipid profile, heamatology, renal and liver function test were performed. During each visit, body weight, blood pressure, cardiovascular and respiratory system were examined clinically. During each visit adverse effects present if any were documented

Statistical Analysis

All data were analyzed using the SPSS 16.0 (Chicago, IL, USA). Data were expressed as means and standard deviation. The significance of the difference between the means of the baseline and the final examinations was tested using the paired "t" test. A probability value of < 0.05 was considered to be statistically significant.

RESULTS

There were 95 subjects of whom 57 (60 %) were women and 38 (40%) men. The mean (SD) age was 47.4 (10.1) years. The mean body weight at baseline is 64.93±10.29 Kg, after 20 weeks there was a significant weight reduction of 0.536 Kg with 95% confidence interval of 0.258, 0.814 Kg. When compared with the baseline visit, 20 weeks of MMC intervention showed significant reduction in the fasting ($P = 0.046$), postprandial PG ($P < 0.001$) and HbA1c ($P < 0.001$) levels (Table 1). Cholesterol, TGL, LDL, HDL and Cholesterol HDL ratio were significantly lowered in follow-up examinations compared to the baseline estimations (Table 1). After excluding 23 individuals who were on anti-hypertensive drugs, the systolic (SBP) and diastolic blood pressure (DBP) also showed significant differences between baseline and follow-up examinations. The SBP at baseline is 134±22.6 and it has been reduced to 120±16.9 after 20 weeks of MMC intervention ($p<0.001$). Similarly DBP also reduced from 83±10.7 to 75±8.8 after intervention ($p<0.001$). Analysis of variables related to renal and liver function tests in the study participants between the baseline and follow-up examinations showed significant reduction in SGOT, SGPT, albumin, alkaline phosphate and total protein levels, however the values were still well within the normal clinical range (Table 2). No statistically significant differences were found between baseline, follow-up Bilirubin, BUN and serum creatinine levels (Table 2). Observation of hematological variables in the study group showed no significant differences in hemoglobin level, packed cell volume (PCV), total and differential blood count and erythrocyte sedimentation rate (ESR) (Table 3).

Table 1: Blood sugar levels before and after MMC intervention

	Initial visit	After 20 weeks	p value
FBS (n=95)	138.31±33.46	130.24±30.18	0.046
PPBS (n=95)	244.16±67.66	200.42±65.02	<0.001
HbA1C (n=95)	7.73±1.15	7.29±1.19	<0.001

Table 2: Lipid profile in the study participants

	Initial visit	After 20 weeks	p value
Cholesterol(mg/dl)	192.08±38.47	174.96±32.50	<0.001
TG (mg/dl)	166.32±85.05	139.09±65.79	<0.001
HDL(mg/dl)	41.32±7.74	39.78±8.18	0.039
LDL(mg/dl)	125.57±32.99	115.39±26.12	0.002
Chol/HDL ratio	4.74±1.06	4.52±0.91	0.031

TGL: Triglyceride HDL: High-density lipoprotein; LDL: Low-density lipoprotein; Chol/HDL: cholesterol to HDL cholesterol

Table 3: Liver and renal function variables in the study participants

	Initial visit	After 20 weeks	p value
SGOT (U/L)	22.97±10.91	18.78±7.24	<0.001
SGPT (U/L)	42.08±14.24	37.97±10.90	0.004
Alkaline Phosphate (U/L)	104.74±25.37	100.14±28.06	0.047
Total Protein (gm/dl)	7.68±0.53	7.39±0.44	<0.001
Albumin (gm/dl)	3.94±0.29	3.84±0.27	<0.001
Total Bilirubin (mg/dl)	0.59±0.28	0.59±0.27	0.915
Direct Bilirubin (mg/dl)	0.12±0.05	0.12±0.04	0.177
BUN(mg/dl)	8.98±2.79	8.89±2.94	0.780
Serum Creatinine (mg/dl)	0.79±0.20	0.83±0.20	0.074

BUN: Blood urea nitrogen; SGOT: serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase

Table 4: Hematological variables in the study participants

	Initial visit	After 20 weeks	p value
Hb (gm/dl)	13.21±1.96	13.00±1.77	0.243
PCV (%)	45.47±47.43	39.08±4.61	0.284
ESR (mm/1hr)	21.71±14.53	20.10±14.54	0.361
TLC (cumm)	7709.68±1922.23	7581.77±1990.51	0.520
Polymorphs (%)	57.05±6.97	56.73±10.44	0.807
Lymphocytes (%)	32.82±6.25	32.18±6.42	0.355
***Eosinophils* (%)**	4.94±4.27	4.69±3.28	0.539
Monocytes (%)	5.15±1.98	5.41±1.76	0.417

Hb: hemoglobin; PCV: packed cell volume; ESR: Erythrocyte sedimentation rate; TLC: Total leucocyte count; FBS: fasting blood sugar; PPBS: postprandial blood sugar.

DISCUSSION

Preliminary phytochemical analysis performed following the standard protocol revealed the presence of phenolic compounds, tannins, flavones, proteins, glycosides, reducing sugars, anthroquinones, quinines, alkaloids and saponins. Batch-to-batch variations were minimized to meet the standards of quality, safety and efficacy. For this MMC was standardized against Gallic acid (3,4,5-trihydroxybenzoic acid) which possesses wider biological activity and also present in majority of the herbs (*Emblica officinalis, Terminalia chebula, Syzygium cumini* and *Phyllanthus niruri)* using HPTLC method.[6] The MMC was also screened for heavy metal content and it is found to be within permissible limits as per WHO and FDA guidelines (Lead 328.6 ppb, Arsenic 1.089 ppb and Mercury 26.3 ppb). Preclinical studies conducted for acute oral toxicity [as per OECD test guideline – 423 (2001)], in female Sprague Dawley rats, revealed that MMC falls in Category -5 in Globally Harmonized System [2000 mg/kg < LD_{50} < 5000mg/kg] (data unpublished).

We evaluated the traditional Siddha drug *Madhumega choornam* for its anti-hyperglycemic action through an open trial of 20 weeks. From the observations of the present study it is clear that the MMC significantly reduced the fasting and postprandial blood glucose. Furthermore, significant reduction in the HbA1c provides a rationale for the use of MMC in the management of diabetes. MMC also demonstrated a significant reduction in the lipid profile of the study participants. The systolic and diastolic BP was also lowered significantly after 20 weeks. The liver, renal functions along with the hematological parameters were well within the normal range, demonstrating that MMC safe to use as anti-hyperglycemic medication.

Reduction in the fasting and postprandial blood glucose along with HbA1c is expected, because the individual herbs are known to have hypoglycemic action. Incorporation of *Murraya koenigii* leaves (10% w/v) in the diet of normal rats for 60 days resulted in hypoglycaemia associated with increased hepatic glycogen contents due to increased glycogenesis and decreased glycogenolysis and gluconeogenesis.[7] Furthermore, dietary supplementation with curry leaves has been shown to increase lecithin cholesterol acyltransferase activity which is involved in effective atheroprotection.[8] Treatment with chloroform extracts of *M. koenigii* showed glucosidase inhibition and islet protection in the murine diabetic model.[9] In contrast to this Murraya leaf extracts from different polarity solvents failed to lower the blood glucose raised by streptozotocin in rats.[10] *Terminalia chebula* contains maltase inhibitory principles[11] and exhibited significant antidiabetic and renoprotective effects.[12] Analysis of α-glucosidase inhibitory activity *in vitro* revealed that the *Terminalia chebula* acts as a potential α-glucosidase inhibitor and exhibit antidiabetic properties.[13]

In Streptozotocin induced type 2 diabetes rats, the dose of 300 mg/kg of aqueous *Emblica officinalis* seed extract produced a maximum fall of blood glucose.[14] *Tinospora cordifolia* methanolic extract significantly reduced the fasting blood glucose level and glycosylated hemoglobin in Streptozotocin induced diabetic rats by regenerating the damaged pancreas and thereby stimulation of insulin secretion in β-cells.[15] An alkaloid fraction derived from *Tinospora cordifolia* could exhibit potential anti-hyperglycemic effect in alloxan induced diabetic rats.[16] In streptozotocin induced diabetic rats *Syzygium cumini* bark extract could effectively elevated plasma insulin levels, C-peptide and reduced the blood glucose concentration indicating that both the pancreatic and the extrapancreatic mechanisms might be involved in its antidiabetic action.[17] Further, positive insulin staining that could be observed in the pancreatic duct and connective tissue in the pancreas of *Syzygium cumini* treated animals indicating that it can stimulate the development of insulin positive cells.[18,19] In contrast to this no effect for *Syzygium cumini* in the treatment of type 2 diabetes was also observed.[20]

Hydro-ethanolic extract of *Cyperus rotundus* significantly reduced the blood glucose level in alloxan induced diabetic rats.[21] Experimental evaluation of the anti-diabetic property of *Phyllanthus niruri* has shown that the aqueous crude extract of *Phyllanthus niruri* exhibited hypoglycaemic effect in diabetic rats.[22] In addition to this oral administration of the extract to normal rats reduced fasting blood glucose and also suppressed the postprandial rise in blood glucose in normal rats indicating its inherent hypoglycaemic and anti-hyperglycemic property.[23] The polyherbal formulations contain a variety of active components and all the constituents provide synergistic action and thus enhance the therapeutic value. In fact approximately 6-10g of *Madhumega choornam* (MMC) per day is in practice for treating madhumegam (T2DM) at Government run Siddha hospitals. In the present study we could observe a significant reduction in fasting and PPG levels even at a lower dose of 3g/day. Our recent study demonstrated that the polyphenols in madhumega chooranam is responsible for its anti-diabetic action.[24] Further comprehensive chemical and pharmacological investigations are needed to elucidate the active principle that exhibit hypoglycemic effect in MMC.

Our result showed that there is a significant reduction in the bodyweight, lipid profile, systolic and diastolic BP after 20 weeks of intervention indicating its antihyper-lipidemic and antihypertensive potentials. Although some of the herbs used in the MMC preparation are known for its antihyperlipidemic and antihypertensive activities[25], the exact role of MMC in controlling the lipid metabolism and hypertension is to be delineated. The use of herbal drugs has seen a rapid increase as they provide wide biological activity, have good safety margins and are available at affordable cost. One potential limitation of our study is that we could not evaluate long-term adverse effects of MMC because of the short treatment period. Although our trial size is small, after 20 weeks of intervention, haematological indices, liver and renal functions are well within the normal range demonstrating the safe use of MMC as anti-diabetic medication, further follow-up studies with larger sample sizes and long-duration are warranted to confirm the safety aspects of MMC use.

AKNOWLEDGEMENT

This research work was supported by a grant from Drugs and Pharmaceutical Research Programme under technology development and transfer division of Department of Science and technology, Government of India (Project no. VI-D&P/151/06-07/TDT). We would like to thank Dr. P. Manickam (National Institute of Epidemiology), Dr. M. V. Mahadevan (National Institute of Siddha) for technical assistance and Mrs. Pearline Suganthi peter for statistical analyses.

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