23 (2015) 555–561

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevierhealth.com/journals/ctim

Effects of a standardized *Ayurvedic* formulation on diabetes control in newly diagnosed Type-2 diabetics; a randomized active controlled clinical study

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ARTICLE INFO

Article history:
Received 16 June 2014
Received in revised form 4 June 2015
Accepted 4 June 2015
Available online 9 June 2015

Keywords:
Polyherbal formulation
Type-2 diabetes
Clinical research
Herbal remedies

ABSTRACT

Objectives: The purpose of this study was to investigate the efficacy of a standardized polyherbal formulation consists of aqueous extracts from six herbs, in patients with Type-2 diabetes mellitus.
Design: Randomized, active control study.
Interventions: 93 patients, newly diagnosed with Type-2 diabetes mellitus were randomly allocated to group 1 (received polyherbal capsules 500 mg/day, up titrated weekly to a maximum of 3 g/day) and group 2 (received Metformin 500 mg/day, up titrated weekly to a maximum of 2 g/day).
Main outcome measures: The primary endpoint was effect on the change from baseline in blood glucose (Fasting blood Glucose and Postprandial blood glucose), and glycosylated hemoglobin (HbA1c). The secondary outcome includes the effect on lipid levels, liver enzymes and renal function test.
Results: After 24 weeks, mean laboratory measured fasting and post prandial blood glucose showed a decrease of 25.52% and 24.22% in polyherbal formulation (PHF) treated group, compared to 31.46% and 24% decrease in Metformin treated group (estimated treatment difference −10.8; 95% CI −22.63 to 1.03 and −0.36; −12.1 to 11.38, respectively). Reduction in HbA1c was also similar for PHF and Metformin (estimated treatment difference 0.01; 95% CI −0.51 to 0.53). However, the decrease in the mean total cholesterol level was more pronounced in PHF treated group (estimated mean difference 61.3; 95% CI 55.32 to 67.28) than Metformin treated group (estimated mean difference 41.12; 95% CI 34.92 to 47.32). Also, there was statistical significance between the treatment groups in total cholesterol level at the end of six months treatment (estimated treatment difference 20.18; 95% CI 12.34 to 28.02).
Conclusion: The study demonstrated that daily intake of this PHF decreased the glycemic level and improved lipid homeostasis, while maintaining the other serum biochemical levels to the normal, and therefore it may be useful for the patients with Type-2 diabetes. This trial is registered in the Clinical Trials Registry – India (CTRI) (CTRI/2014/03/004490).

1. Introduction

Diabetes mellitus is emerging as a major crippling disease, affecting more than 370 million people across the globe.[1] It is a state of chronic hyperglycemia, traditionally been categorized into Type-1 (inadequate insulin secretion due to loss in β cells) and Type-2 diabetes (resistance to insulin action). This conception is expanded with the realization that many different overlapping mechanism can lead to diabetes and therefore diabetes is now considered as a heterogeneous disease with multiple etiologies.[2] Tuami et al. discuss the importance of key factors contributing to this heterogeneity, including age at onset for both Type 1 and Type 2 diabetes, obesity, and the role of genetic factors.[3,4] Unrestrained blood glucose gives rise to severe problems like lactic acidosis, diabetic ketoacidosis, or hyperosmolar non-ketotic syndrome whereas long term complications of diabetes include macro vascular and

Abbreviations: T2DM, Type-2 diabetes mellitus; PHF, polyherbal formulation; FBG, fasting blood glucose; PPBG, postprandial blood glucose; HbA1c, glycosylated hemoglobin; HPLC-PDA, High performance liquid chromatography with Diode-Array detection.

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http://dx.doi.org/10.1016/j.ctim.2015.06.005
0965-2299/

micro vascular complications such as retinopathy, nephropathy, peripheral neuropathy and autonomic neuropathy (including gastrointestinal, genitor-urinary, cardiovascular symptoms and sexual dysfunction).[2]

Despite great progression made in understanding the pathophysiology and treatment therapies, the mortality rate is still very high and therefore World Health Organization classify diabetes as one of the four priority non communicable diseases among cardiovascular, cancer and chronic respiratory disease.[5] The current trend of treatments include oral medications (sulfonylurea, biguanide, α-glucosidase inhibitors), insulin analogs (long and rapid acting) and insulin pens and pumps.[1] These anti-diabetic agents have certain side effects such as weight gain and hypoglycemia.[6] Therefore, recently focus has been shifted toward plants and plant based medicines in curing such chronic diseases, as they are believed to be less toxic. Around the world millions of people are using traditional medicines and formulations based on *Ayurveda* as front line medicinal product for diabetes.[7] *Ayurveda*, which means "science of life", is a traditional Indian system of medicine that has been documented and practiced since 3000 B.C.[8] It is an alternative form of medicine, composed of elements of physiology, pathology, pharmacology, material medica and surgery.[9] *Ayurveda* recommends many plant based preparations for management of several diseases.[10] In fact there is a growing acceptance of traditional medicines all over the world, for being a rich bio resource of therapeutic leads for pharmaceutical companies. However, without proper standardization and validation on effectiveness and the possible risks, these traditional medicines cannot be used.[11]

The present study was carried out to investigate one such polyherbal formulation (PHF) in capsule dosage form, consists of six herbal extracts viz. *Berberis aristata, Cyperus rotundus, Cedrus deodara, Emblica officinalis, Terminalia chebula and Terminalia bellirica*. Relying and respecting the holistic approach of Ayurveda, the plant materials in PHF were selected on the basis of their pharmacological attributes. For example, in the treatment of diabetes, *B. aristata* regulates the glucose homeostasis through decreased gluconeogenesis and oxidative stress,[12] *C. rotundus* and *C. deodara* may be useful in reduction of blood glucose,[13] *E. officinalis, T. chebula* and *T. bellirica* may be useful for their anti-hyperlipidemic effect.[14] In this way, the multiple manifestations due to diabetes can be specifically targeted using a polyherbal agent.

This PHF was earlier tested for its efficacy and safety against hyperglycemia in streptozotocin induced diabetic rats (in the name of *Diabcap*, proprietary name given by the procuring source, Herbal Medicinal Products Department, Council of Scientific & Industrial Research-Central Institute of Medicinal and Aromatic Plants, Lucknow, India. The name *diabcap* is subjected to change).[15] However, up till now it has not been analyzed whether this polyherbal formulation (PHF) has similar effects in humans. Therefore, the objective of the study was to find out if the PHF had the glucose lowering effect on human, as observed with administration of this PHF to the streptozotocin diabetic rats.

In this study, a randomized pilot clinical study was carried out to assess the safety and efficacy of this PHF in comparison to standard drug Metformin in patients, newly diagnosed with Type-2 diabetes.

2. Materials and methods

2.1. Study drug

The PHF was prepared in capsule dosage form by the Herbal Medicinal Products Department, Council of Scientific & Industrial Research-Central Institute of Medicinal and Aromatic Plants, Lucknow (India). Each 500 mg of capsule (size 0) contain water extracts from *B. aristata* (83.3 mg), *C. rotundus* (83.3 mg), *C. deodara* (83.3 mg), *E. officinalis* (83.3 mg), *T. chebula* (83.3 mg) and *T. bellirica* (83.3 mg). The anti-diabetic activity on streptozotocin induced diabetic rats of the PHF was assessed by Awasthi et al.[15], the dose of 0.3 g/kg body weight in rats shows anti-hyperglycemic activity, which is equivalent to 3 g/day dose in humans.[16]

2.2. Quantitative chromatographic analysis.

2.2.1. Sample preparation

Accurately weighed 10 mg of lyophilized polyherbal extract was dissolved in 1 ml mixture of methanol/water (8:2 v/v) and ultrasonicated (Sonic Vibra-Cell VCX750) for 20 min at room temperature. The sample was then centrifuged at 15000 rpm for 10 min, supernatant was filtered through a 0.22 μm syringe filter (PVDF, GELMAN, USA) and subjected to HPLC analysis. For quantitative analysis of PHF, Berberine, Gallic acid and Quercetin were purchased from Sigma Aldrich and used as reference compounds. A stock solution with a concentration of 1 mg ml^{-1} of Berberine, Gallic acid and Quercetin was prepared in methanol.

2.2.2. Chromatographic conditions

Waters HPLC instrument (Waters Corporation, Milford, MA, USA) equipped with an on-line degasser, a 717 plus auto sampler, temperature control module, 2996 photodiode array detector (PDA) and waters 600 pump was used. Waters Empower 2 software (Waters Co., Milford, MA, USA) was used for data acquisition and integration. Separation was carried out using Waters XBridge C 18 column (5 μm, 4.6mm × 250 mm) with XBridge C18 guard cartridge (5 μm, 4.6 × 20 mm). The column was maintained at 25 °C throughout the analysis. All the solvents used in the present study were of HPLC grade.

A gradient elution was carried out at a flow rate of 0.8 ml/min with Water: orthophoshphoric acid (100:0.01 v/v, pH was adjusted to 3.4 by triethanolamine) as solvent A, Methanol as solvent B and Acetonitrile as solvent C. The optimized gradient elution was as follows; run was started with 90% A, 1 % B and 9% C and gradually changed to 10% A, 60% B and 30% C in 30 min.

2.3. Ethics statement

Ethical approval for the study was obtained from the Institutional Ethics Committee of King George's Medical University, Lucknow (U.P.), India (No. 56 E.C.M.11B/P12). The study was conducted following the guidelines of Declaration of Helsinki and reported as per Consolidated Standards of Reporting Randomized Clinical Trials (CONSORT) statement.[17] Written informed consent was obtained from all the participants before entry in the study.

2.4. Study participants

160 newly diagnosed Type 2 diabetic patients, aged between 20 and 60 years of either sex were recruited from the Department of Medicine, King George's Medical University, Lucknow, Uttar Pradesh, India. Diagnosis of diabetes were in accordance to the criteria set in Standards of Medical Care in Diabetes-2010.[18] The exclusion criteria were Type 1 diabetics, cardiovascular diseases, pregnancy, patients having serum creatinine level >1.2 mg/dL and the patients who had any history of taking oral hypoglycemic medication prior to the study.

2.5. Study design

This is an interventional, prospective, randomized clinical study. Recruited participants were randomized into two treatment groups (groups 1 and 2), on the basis of minimization of differences for age, sex, and body mass index (BMI).[19] Randomization was