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Original article

Safety and efficacy of a polyherbal formulation for the management of dyslipidemia and hyperglycemia in patients with advanced-stage of type-2 diabetes

Mahdi Zarvandi[c], Hassan Rakhshandeh[a,b], Mohammad Abazari[c], Reza Shafiee-Nick[a,b], Ahmad Ghorbani[a,*]

[a] Pharmacological Research Center of Medicinal Plants, Mashhad University of Medical Sciences, Mashhad, Iran
[b] Department of Pharmacology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[c] Department of Persian Medicine, School of Persian and Complementary Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

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ABSTRACT

The present clinical trial was designed to evaluate the safety and efficacy of a polyherbal formulation (PHF) consisted of *Allium sativum, Aloe vera, Nigella sativa, Plantago psyllium, Silybum marianum and Trigonella foenum-graecum* for controlling dyslipidemia and hyperglycemia in patients with advanced-stage of type-2 diabetes.

An open-label phase I trial was carried out on 30 patients who had hyperlipidemia and hyperglycemia before the beginning of the trial in spite of receiving statins and oral hypoglycemic drugs. Patients were given one PHF sachet two times daily for 40 consecutive days. All subjects also continuously received their statins and oral hypoglycemic agents. Clinical assessments and laboratory findings were evaluated before starting treatment and at day 40.

Treatment with PHF had no significant effects on serum biochemical parameters related to liver and kidney functions, on hematological parameters related to erythrocytes, leukocytes, and platelets, and on body weight and blood pressure. After consumption of PHF, 2 patients complained of mild nausea, and 2 patients reported diarrhea. PHF significantly decreased fasting blood glucose and HbA1c from 162 ± 40 mg/dL to 146 ± 37 mg/dL and from $8.4 \pm 1.5\%$ to $7.7 \pm 1.1\%$, respectively. Also, it significantly decreased the level of LDL from 138 ± 25 mg/dL to 108 ± 36 mg/dL, and the level of triglycerides from 203 ± 47 mg/dL to 166 ± 58 mg/dL.

In conclusion, the present results demonstrated that the PHF was safe and efficacious in lowering the levels of blood glucose and serum lipids in patients with advanced-stage of type-2 diabetes.

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1. Introduction

Diabetes mellitus is still one of the major reasons of morbidity and mortality in both developed and developing countries. According to the WHO reports (June 2016), the global prevalence of diabetes among adults has increased from approximately 4.7% in 1980 to about 8.5% in 2014. It is estimated that 3.7 million patients died from consequences of diabetes and hyperglycemia in the year 2012, and without urgent action, this disease will be the 7th cause of death in 2030. Over time, diabetes results in serious complications such as nephropathy, neuropathy, retinopathy, and cardiovascular diseases in poorly controlled patients [1]. Currently, oral hypoglycemic (e.g. metformin and glibenclamide) and hypolipidemic (e.g. statins and fibrates) agents are the most widely used drugs for control of diabetes [2,3]. The clinical uses of these synthetic medications are accompanied with some unpleasant side effects including severe hypoglycemia, lactic acidosis, abdominal discomfort and peripheral edema for some oral hypoglycemic agents, and myopathy and hepatic toxicity in the case of hypolipidemic agents [2,4–6]. Furthermore, despite aggressive therapy with the currently available drugs, many patients do not reach the goal levels of blood glucose and lipids [7,8]. Therefore, the searches for finding new hypoglycemic and

Abbreviations: ALP, alkaline phosphate; ALT, alanine aminotransferase; AST, aspartate transaminase; FBG, fasting blood glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PHF, polyherbal formulation; T2D, type-2 diabetes; RBC, red blood cell WBC white blood cell.

* Corresponding author.
E-mail address: ghorbania@mums.ac.ir (A. Ghorbani).

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hypolipidemic agents with lesser side effects and more effectiveness are being continued in many laboratories.

Medicinal plants have always been a rich source for finding new therapies for human diseases. Antidiabetic effects of numerous plants were reported in animal studies and clinical trials [9–11]. Also, a number of polyherbal formulations have been shown to induce beneficial effects in the management of diabetes [12,13]. Recently, we published two review articles about medicinal plants that their antidiabetic actions are supported by several clinical trials [10,11]. Based on the literature results discussed in those articles and on our previous experiences in formulation of polyherbal compounds [12,14,15], six plants with potent hypoglycemic and hypolipidemic effects were chosen (*Allium sativum*, *Aloe vera*, *Nigella sativa*, *Plantago psyllium*, *Silybum marianum* and *Trigonella foenum-graecum*) for preparing a polyherbal formulation (PHF) for managing hyperglycemia and dyslipidemia in diabetic patients. The present clinical study aimed to evaluate the safety and efficacy of this PHF in patients with confirmed type-2 diabetes (T2D).

2. Materials and methods

2.1. Preparation of polyherbal formulation

The cloves of *A. sativum*, the leaves of *A. vera*, and the seeds of *N. sativa*, *P. psyllium*, and *T. foenum-graecum* were purchased from the local market (Sheikh-Al-Raeis, Mashhad city, Iran), and were authenticated by a botanist. The hydroalcoholic extract of *S. marianum* was purchased from Gol Darou Co (Iran). The *A. vera* leaf gel was dried under shade and powdered to a fine grade. The fresh cloves of *A. sativum* were crushed with a juicer, dried under shade, and powdered to a fine grade. The husk of *P. psyllium* seed was separated using a blender. The seeds of *N. sativa* and *T. foenum-graecum* were cleaned and powdered separately. Then, all the plant materials were passed through mesh # 60 (250 μm) and mixed together in specified proportions (Table 1) to get a uniform mixture. Each PHF sachet (6.4 g) consisted of a combination of 300 mg *A. sativum*, 300 mg *A. vera*, 1.8 g *N. sativa*, 1 g *P. psyllium*, 2.5 g *T. foenum-graecum*, and 500 mg *S. marianum* extract. The PHF sachets were stored at 4 °C until use.

2.2. Study design

The open-label Phase I clinical trial was carried out on 30 patients with T2D referred to Shahid Qodsi Diabetes Center in Mashhad, Iran (Clinical trial registration number: IRCT2014030116776N1). The study protocol was performed in accordance with the Declaration of Helsinki and subsequent revisions and approved by the ethics committee at Mashhad University of Medical Sciences. Informed written consent was obtained from each volunteer before the study.

Patients that met the following conditions were enrolled in this study: (1) were diagnosed as T2D at least for 2 years duration; (2) were >25 years old; (3) had low-density lipoprotein (LDL) ≥100 mg/dL; (4) triglycerides ≥ 150 mg/dL; (5) had been receiving hypolipidemic (statins) drugs for over three months; (6) had fasting blood glucose (FBG) > 140 mg/dL or HbA1c ≥ 7% (53 mmol/mol); (7) had been receiving oral hypoglycemic drugs (metformin and/or glibenclamide) for over three months. Patients were excluded from the trial if they had one of the following criteria: (1) had type-1 diabetes, gestational diabetes, or other specific types of diabetes; (2) were candidates for insulin therapy; (3) had taken other herbal supplements for control of diabetes during study; (4) suffered from severe renal or hepatic impairment; (5) had severe infection; (6); had a history of allergies to the plants of PHF; (7) had addiction to alcohol or narcotics; (8) was pregnant or lactating.

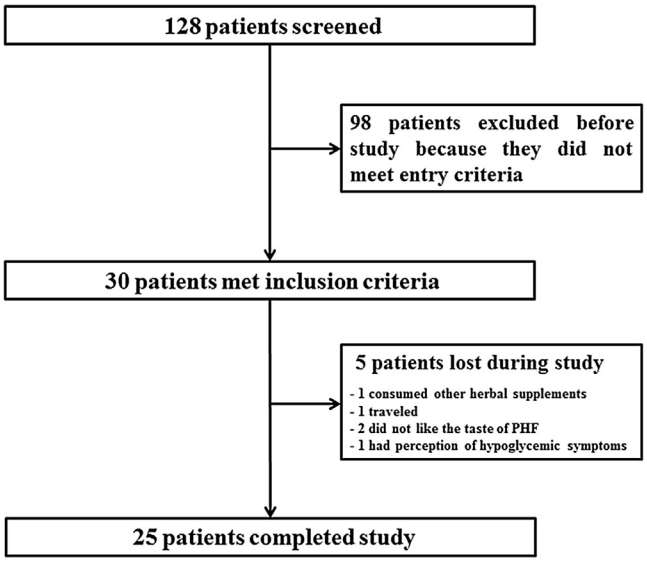

Fig 1. Patient recruitment and selection flow chart according to study protocol.

Fig. 1 shows the patient recruitment and selection flow chart. The selected patients were orally administered one sachet two times daily (before a meal) for 40 consecutive days. All subjects also continuously received their statins and oral hypoglycemic agents. Blood samples were obtained after an overnight fasting before starting treatment and at day 40.

2.3. Outcomes

Biochemical and hematological parameters including urea, creatinine, alkaline phosphate (ALP), aspartate transaminase (AST), and alanine aminotransferase (ALT), FBG, HbA1c, total cholesterol, LDL, high-density lipoprotein (HDL), triglycerides, white blood cell (WBC), red blood cell (RBC), hemoglobin, hematocrit, and platelets were determined as main parameters of the study. Also, all subjects were followed-up during the study for any unwanted symptoms related to the consumption of PHF (e.g. blood pressure, gastrointestinal signs, etc.).

Table 1
Plant materials used in the polyherbal formulation.

No	Botanical name	English name	Family	Part used	Composition (%)
1	*Allium sativum* L.	Garlic	Lilliaceae	Cloves juice	4.7
2	*Aloe vera* L.	Aloe vera	Lilliaceae	Leaf juice	4.7
3	*Nigella sativa* L.	Black seed	Ranunculacea	Seed powder	28.1
4	*Plantago psyllium* L.	Psyllium	Plantaginaceae	Seed husk	15.6
5	*Silybum marianum* L.	Milk thistle	Asteraceae	Seed extract	7.8
6	*Trigonella foenum-graecum* L.	Fenugreek	Leguminosae	Seed powder	39.1

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