ORIGINAL ARTICLE

The Combination Effect of Five Herbal Drugs "Peganum Harmala, Quercus Infectoria, Vaccinium Myrtillus, Citrullos Colocynthis, Securigera Securidaca" on Blood Glucose

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Abstract

Objective: There are some studies about the good effects of herbal medicine on blood glucose. This study was designed to evaluate the synergism effect of Peganum Harmala (P.harmala), Quercus Infectoria (Q.i), Vaccinium Myrtillus (V.myrtillus), Citrullos Colocynthis (C.colocynthis), Securigera Securidaca (S.s) on blood glucosein type 2 diabetic patients.

Materials and Methods: Twenty four type 2 diabetic patients were enrolled in this cross over double- blinded clinical trial for receiving two months herbal medication and placebo. The subjects divided into two groups randomly. One group received herbal medication (the doses of 25mg/person of V.myrtillus, S.s and Mazoj and 62.5mg C.colocynthis, P.harmala) and the other group received placebo for 8 weeks. After washout period the herbal medication and placebo were replaced for the next 8 weeks. T-test and Chi-square were used for the comparison of variables between two groups.

Results: After two months, mean fasting blood glucose was 135±27.1 and 139±36.8 mg/dl, (*P*-value=0.64), and mean glycosylated hemoglobin was 6.5±0.75 and 6.6±0.97 percent, with herbal medication and placebo, respectively (*P*-value=0.51). About 15.4%of patients after herbal medication and 15.4 % after placebo consumption had 0.8% reduction in HbA1C (*P*-value=1/0). The mean HOMA IR index**,** after two months intervention with herbal medication or placebo**,** was 2.9±1.95 and 3.9±1.97, respectively (*P*-value=0.05).

Conclusion: low dose combination of P.harmala, Q.i, V.myrtillus, C.colocynthis, S.s may improve the insulin sensitivity and we did not find significant effect on blood glucose with low dose of this combination.

Keywords: Diabetes mellitus, Herbal medication, Insulin sensitivity, Glycosylated hemoglobin

Introduction

Diabetes mellitus is the most prevalent and costly chronic disease estimated up to 2025 which will get to 439 million diabetic patients (1-2). Diet, exercise and chemical glucose lowering medicine are used for blood glucose control but despite the use of multiple oral medications many patients suffer from high blood glucose and most

patients do not accept to use insulin injection(2). Uncontrolled diabetes mellitus is associated to serious micro and macrovascular complications (3-4). The use of herbal medicine is more accepted by the patients and many people use the herbal medicine without enough information about the efficacy or side effects of herbal medicine.

The use of medicinal plants has flourished as an alternative for the treatment of diabetes because modern medicines are tagged with several side effects and are also expensive. A multitude of herbs, medicinal plants and some compounds purified from them have been studied for the treatment of diabetes throughout the world .the herbal medicine mightprovide a basis of new synthetic antidiabetic analogues with potent activity. There are some studies about the acceptable effects of herbal medicine on blood glucose (5-6). This cross over double- blinded clinical trial was designed to evaluate the synergism effect of Peganum harmala (P.harmala), Quercusinfectoria (Q.i), Vacciniummyrtillus(V.myrtillus), Citrulloscolocynthis(C.colocynthis), Securigerasecuridaca(S.s) on blood glucose, this native herbal combination are used in our region for type two diabetic patients.

Materials and Methods

After approval the research by the Ethics Board Committee of Mazandaran University of Medical Sciences, Sari, Iran (IRCT code 138811143180N1), this cross over double-blinded clinical trial was conducted on 20 type 2 diabetic patients who referred to Diabetes Healthcare Center in Sari, Iran from 2008 to 2011.The calculated sample size was 19 cases according to α=0.05,β=0.9 and minimal detectable difference in mean of HbA1C 0.8. The inclusion criteria were age range of 30 to 80 years old and HbA1C$\leq$ 8% and no medication for diabetes control. Immune deficiency, pregnancy and lactation, cardiovascular disease, current use of corticosteroids and thiazide, uncontrolled thyroid dysfunction, acute infection, history of diabetic ketoacidosis, Cr>1.5 for male and>1.4mg dl for female, acute hepatitis, cirrhosis, proliferative retinopathy and severe weight loss (at least 10% during the last 6 months) were considered as exclusions criteria .All patients were entered into the study after giving an informed consent. The 0.8 percent glycosylated hemoglobin reduction and difference was considered as good response to intervention.

Plant Material

The plants were collected from Mazandaran (a Northern state in Iran) in November 2010 and dried in shadow followed by grinding. The selected plants were identified and confirmed by Department of Pharmacognosy. A voucher specimen has been deposited in Sari School of Pharmacy Herbarium. Fruits and seeds parts were dried at room temperature and powdered before encapsulation. Following the preliminary study, the doses of 25mg/person of V.myrtillus, S.s and Mazoj and 62.5mg C.colocynthis, P.harmala were chosen for the remaining of the study in order to evaluate the synergism effects of the plants on blood glucose. The placebo was lentil flour that was put in similar capsule. The maximum effects of V.myrtillus, S.s, Mazojand C.colocynthis, P.harmala were observed at a dose of 250mg/person and 125 mg/person o.p respectively.

Sequential sampling was used and all the participants filled out the consent form. Information about age, sex, history of hyperlipidemia and hypertension were recorded in a checklist. Blood pressure, weight and height were measured and BMI was calculated. A nutritionist explained diabetic diet for all the patients and they were advised to be on diet during the study. The patients were divided into two groups according to sequential entering. One group received herbal medicine and other group placebo for 8 weeks. After one week washout period the herbal medicine and placebo were replaced for the next 8 weeks. Blood pressure, fasting blood sugar (FBS), creatinine, serum lipids, serum insulin and HbA1C were measured at baseline

of each period. the patients did not know type of treatment for every period. The numbers of remained drugs were counted and their adverse effects and the laboratory tests were recorded by a physician who was blind about type of treatment. The measurement of FBS and HbA1C (as primary outcomes) and serum insulin, creatinine, lipids, weight and blood pressure (as secondary outcomes) were repeated after 8 weeks in each period. We utilized chromatography with Bio-system kit (Italy, CV<5%) for HbA1C, enzymatic calorimetric method with glucose Parsazmoon Co kit (Iran) for blood glucose, Screening ELISA Test with Hitachi autoanalizer using monobind kit(USA) for serum insulin levels. Insulin resistance was calculated through HOMA-IR methods (HOMA: Homeostasis model assessment method) (7).

Statistical Analysis

The data was entered into SPSS software for analysis. Descriptive statistics (mean and standard deviation) was used for quantitative variables and paired T-test for the comparison of quantitative and Chi-square for comparison of qualitative variables between two groups. Statistical significance was recognized at *P*-value<0.05.

Results

In this study, 24 diabetic patients (60% female) were enrolled. The mean age of the patients was 47 ± 6.9 years old. The mean of BMI was 28.5 ± 2.68 kg/m^2. Thirty five percent of the patients were hypertensive and 84.2 percent were suffering from hyperlipidemia. Table 1 shows the patients' data before intervention.

In the first period of study, four cases were excluded because of no compliance (two patients in herbal and 2 in the placebo group). Two months after treatment, mean fasting blood glucose was 135±27.1 and 139±36.8, (*P*-value=0.64), and mean glycosylated hemoglobin was, 6.5±0.75 and 6.6±0.97 (*P*-value=0.51), in herbal medicine and placebo groups, respectively. Two patients (15.4 %) after herbal medicine usage and also two cases after placebo consumption had more than 0.8% reduction in HbA1C (*P*-value=1/0). The reduction of HbA1C levels in two patients with herbal medicine consumption were2.6 and 1.6 % and in two cases with placebo were 1.5 and 0.9%. The mean HOMA IR index, after two months intervention with herbal medicine and placebo, was 2.9±1.95 and 3.9±1.97 respectively (*P*-value=0.05).HbA1C and HOMA IR differences were not significantly different in herbal medicine or placebo groups. (Table 2)

Discussion

In the present study, the combination of low dose of five lowering blood glucose herbal medicine, P.harmala, Q.i, V.myrtillus, C.colocynthis, S.s did not have significant effect on blood glucose.

V.myrtillus (bilberry) is a member of Ericaceaefamily, its leave decoction had been used to lower blood glucose in diabetes even in the presence of concurrently injected glucose (8-9).This effect is attributed to the myrtillinantocyanoside, the most active hypoglycemic component. V.myrtillus

Table 1. Basic information of patients

Variable	Placebo mean±SD*	Herbal medicine mean± SD	*P*-value
Fasting blood glucose(mg/dl)	133±20.8	133±22.1	0.85
Postprandial blood glucose (mg/dl)	160±36.6	158±44.8	0.89
HbA1C	6.4±0.83	6.5±0.78	0.59
Body mass index(kg/m2)	30.1±6.51	30.5±6.37	0.25
Cholesterol(mg/dl)	192±30.6	193±29.1	0.92
Triglyceride(mg/dl)	164±80.9	157±90.7	0.63
HDL Cholesterol(mg/dl)	59±12.3	59±9.1	0.92
LDL Cholesterol(mg/dl)	106±16.1	92±17.8	0.05
Systolic blood pressure(mm/hg)	110±14.6	105±13.2	0.34
Diastolic blood pressure(mm/hg)	76±5.5	74±5.5	0.23

*: Standard Deviation

enhances collagen integrity, stabilizes capillary Permeability and inhibits sorbitol accumulation, thus providing protection against vascular and neurological sequel of diabetes (10).Another significant property of myrtillin is the protective capacity against LDL particle during copper- mediated oxidation with only the trace amounts of V.myrtillus (15-20 mcq/ml) (11). It has also antinociceptive effect on diabetic rats (12). The hypoglycemic effect of bilberry may be because of α-glucosidase activity (13), insulin secretion (14) and also glucose transport (15). The antilipidemic effect and lowering blood glucose of this plant was shown in several animal studies (16-18). Bilberry consumption is very safe and a dosage up to 400 mg/kg have been administered to rats without toxicity and also no toxic effects were seen with long-term oral consumption equivalent to 180 mg/kg anthocyanosides per day for six months in human (10).The dosage of this herbal drug in our study was 250 mg/d which was lower than the other studies.

In several experimental studies, the anti-diabetic effect of C.colocynthis was shown individually or in combination with P.harmala (19-26).The underlying mechanism of glucose lowering effect of C. colocynthis is not exactly clear. C. colocynthis contains a wide number of active constituents that may interact with several metabolic pathways of the human body which can directly or indirectly influence glucose or insulin metabolism. In type II diabetes mellitus, the elevation of plasma glucose and free fatty acid levels lead to the generation of reactive oxygen species and oxidative stress markers (27). These metabolic abnormalities did not only induce diabetic complications but also lead to insulin resistance, ß-cell dysfunction and impaired insulin secretion (28) C. colocynthis with its antioxidant properties inhibit lipoperoxidation (29-30)and is active against oxidative stress and may induce a positive effect on diabetic metabolic abnormalities. Nmilaand et al. showed the significant immediate stimulated insulin secretion with different kinds of C.colocynthis extract after 0.1 mg/ml perfusion for 2 minutes through the insulin tropic effect of C. colocynthison isolated pancreatic islets too (22). C. colocynthis in another study inhibited the toxic effect of streptozotocin on pancreatic cells in rats (26, 31).The toxicity of large doses of C. colocynthis has been reported in experimental studies on both animals and human (32-34). However, in experimental studies, the aqueous extract of the C. colocynthis at lower doses can ameliorate some of the toxic effects of streptozotocin (26,29). Fallah Hoseini et al. have shown 300 mg/d of Citrulloscolocyn significantly decreases HbA1C and fasting blood glucose comparing to placebo without any notable gastrointestinal side effect and this dosage of drug was effective and safe after two months (20).In the present study, 125 mg/d of Citrulloscolocyn was used in combination to four other plants.

Some other plants such as P.harmala have antidiabetic activity. Nafisiand et al. in one study on streptozocine induced mouse showed the antidiabetic activity of P.harmala (270 mg/kg of oral form) (35). Singhand et al.

Table 2. Comparison of variables after intervention in diabetic patients receiving herbal medicine and placebo

Variable	Placebo mean±SD	Herbal medicine mean± SD	*P*-value
Cholesterol(mg/dl)	195±41.9	1973±9.0	0.77
Triglyceride(mg/dl)	154±88.7	177±84.4	0.15
HDL Cholesterol(mg/dl)	60±16.3	53±12.8	0.28
LDL Cholesterol(mg/dl)	92±20.9	109±21.9	0.02
Hemoglobin(mg/dl)	14.1±1.39	15.1±1.60	0.10
Creatinine (mg/dl)	0.8±0.12	0.8±0.19	0.38
Systolic blood pressure(mm Hg)	112±18.6	112±20.2	0.84
Diastolic blood pressure(mm Hg)	73±15.3	77±5.8	0.68
HbA1C (%)differences	0.05±0.7	0.17±-0.9	0.52
HOMA IR differences	0.8±1.6	-0.13±3.2	0.39

showed that the ethanolicextract of P.harmala seed (150 and 250 mg/d) significantly lower blood glucose level in normal and diabetic rats, that was comparable with metformin effect (36). in another study on db/db mice, Singh also showed that the P.harmala (50 mg/kg hydroxyl pipecolicacid isolated from feeds can cause the significant reduction in fasting blood glucose ,plasma triglyceride , cholesterol ,free fatty acid and low density lipoprotein cholesterol and significant increase in high density lipoprotein cholesterol level (37). Zakir Hussain et al reported in 2004 (38) that P.harmala has no insulin secretion activity and its hypoglycemic effect maybe according to glucose absorption. Some study must be conducted to find out the mechanism of action. In our study, we used 125 mg/d of P.harmala seeds powder.

Q.i is another glucose lowering plant that its alpha- glycosidase inhibitory activity has been shown in Hwang's study (39).In addition to hypoglycemic effect, S.s (L.) seeds have different activities such as antiepileptic, marked chronotropic, diuretic and hypokalemic effects (40-42). Phytochemical analysis has shown that the S. securidaca (L.) seed extracts are rich in flavonoids and so they have antioxidant properties (42).In Minaiyan and et al.'s study, different oral dosages (200,400,800 mg/kg) hydroalcoholic extract of S.s seeds were not effective to reduce blood glucose (43). Pouramirand et al.

Showed the protective effect of S.s suspension against all oxan induced hyperglycemia and oxidative stress in rats (44). In Zahedi Asles' study, oral form of chloroformic seeds extract of S.s (3 mg/kg) lowered blood glucose. It can be because of insulin release effect or insulin like activity of this plant but its hydroalcoholic extract did not have anti hyperglycemic effect (45).In our research, we used 250 mg /d of S.s seeds powder. The limitations of our study were finding of eligible patients that accept and sign the entrance to study and also begining of antidiabetic agents by other physicians during the treatment.

Conclusion

According to several studies about the effect of herbal drug on blood glucose, we prepared low dose combination of P.harmala, Q.i, V.myrtillus, C.colocynthis, S.s (125mg V.myrtillus, S.s and Mazoj and 62.5mg C.colocynthis, P.harmala), the combination witch is used in our region for

lowering blood sugar . We did not find the significant effect on blood glucose, HbA1C and HOMA IR with combination of low dose this herbal drugs The use of low dose of these plants may be the cause of this combination drug ineffectiveness .More research with higher dose of this combined extract and more sample size are recommended for defining blood sugar change.

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