

Evaluation of the effectiveness of cinnamon, fenugreek and their combination on patients with type 2 diabetes in Basrah

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ABSTRACT

Background: People often seek care from multiple sources outside the formal traditional health care system. One of these sources is the use of Complementary and Alternative Medicine (CAM) including herbal medications. Diabetic patients are found 1.6 times more likely to use CAM than non diabetic patients.

Aim: To investigate the effectiveness of cinnamon, fenugreek and their combination in type 2 diabetic patients not well controlled by oral antidiabetic drugs.

Methodology: Fifty four diabetic patients who were on oral hypoglycemic drugs were randomly divided into 4 groups. Group 1, 2, 3 and 4 were treated with bran, cinnamon (3 gm), fenugreek (15 gm), and the combination of fenugreek and cinnamon. HbA1C and 2 h postprandial glucose (PPG) were measured at baseline and 40 days of treatment. **Results:** HbA1C level and 2 h (PPG) were significantly declined from baseline with 40 days placebo treatment. Significant reduction in HbA1C was noticed with 40 days cinnamon treatment ($9.37 \pm 2.1\%$ to $8.76 \pm 1.9\%$). This effect was paralleled with reduction of 2 h-PPG from 291 ± 99 mg/100ml at baseline to 233 ± 61 mg/100ml after 40 days treatment. The same changes in HbA1C and 2 h PPG were noticed with fenugreek and even more with the combination of fenugreek and cinnamon.

Conclusions: daily supplementation with cinnamon, fenugreek or their combination to patients not achieving glycemic control with oral antidiabetic medications and diet is effective in lowering HbA1C and 2 h PPG in type 2 diabetic patients.

Key words: Cinnamon, Fenugreek, type 2 diabetes mellitus, 2 h-PPG, HbA1C.

تقييم فعالية نبات القرفة (دارسين)، الحلبة و كليهما في مرضى السكري من النوع الثاني في البصرة

خلفية الدراسة: يسعى الكثير من المرضى الحصول على الرعاية الصحية من مصادر متعددة خارج نظام الرعاية الصحية التقليدية. وأحد هذه المصادر هو استخدام الطب التكميلي والبديل (CAM) ومنها استعمال المستخلصات العشبية. ولقد وجدت الدراسات إن مرضى السكري أكثر استعمالاً للطب المتمم أو البديل (CAM) ويحدود 1.6 مرة من غير مرضى السكري.

الهدف: دراسة فعالية القرفة والحلبة وإعطائهما معاً في النوع الثاني من مرضى السكري والذين لم يتم السيطرة على نسبة السكر في الدم لديهم باستخدام الأدوية التقليدية للمرض.

المنهجية: تم تقسيم أربع وخمسون مريضاً من المستمرين على أدوية مرض السكري عن طريق الفم إلى أربعة مجاميع، وتمت معالجة المجموعة 1، 2، 3 و 4 بالنخالة، والقرفة (3 غرام) والحلبة (15 غرام) وخليطهما عن طريق الفم. وتم قياس الهيموجلوبين السكري (HbA1c) وكغلوكونز البلازما بعد الأكل بساعتين (2h-PPG) قبل البدء بالتجربة وبعد 40 يوماً من العلاج.

النتائج: انخفض مستوى نسبة (HbA1c) و (2h-PPG) بشكل ملحوظ في المجموعة الضابطة بعد 40 يوماً من العلاج بالنخالة. وانخفضت نسبة (HbA1c) بشكل ملحوظ بعد العلاج بالقرفة لنفس الفترة من $9.37 \pm 2.1\%$ إلى $8.76 \pm 1.9\%$. ورافق هذا التأثير انخفاض في (2h-PPG) من 291 ± 99 ملغم/100 مللتر قبل المعالجة إلى 233 ± 61 ملغم/100 مللتر بعد 40 يوماً من العلاج. وقد لوحظت نفس التغيرات في نسبة (HbA1c) و (2h-PPG) مع الحلبة وكان الانخفاض أكثر باستعمال الحلبة والقرفة معاً.

الاستنتاج: يؤدي استعمال 3 غرام من القرفة، أو 15 غرام من الحلبة أو الجمع بينهما في المرضى الذين لا يتحكمون بصورة جيدة بنسبة السكر في الدم على الرغم من استخدامهم أدوية السكري والحمية الغذائية، إلى خفض نسبة (HbA1c) و (2h-PPG) في مرضى السكري من النوع الثاني.

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INTRODUCTION

Between 1995 and 2025, diabetes is predicted to increase by 27% in developed countries and 48% in the developing countries.^[1] It is the seventh leading cause of death and may cause significant health complications, such as kidney failure, heart disease, macro-and micro vascular dysfunctions, and blindness.^[2] Complementary and alternative medicine (CAM) is defined as a wide range of clinical practice which is not part of conventional medicine.^[3] In general, the use of CAM has increased significantly over the last two decades.^[4-7] The commonly used CAMs are herbal therapies, multivitamins, prayer, acupuncture, yoga and aromatherapy.^[5,8,9,10] Among widely used herbs by diabetic patients is fenugreek (*Trigonella foenum graecum*). The seeds were commonly used as a spice in Middle Eastern countries and widely used in South Asia and Europe and has been shown in animals to have anti-diabetic properties.^[11,12] Second most commonly used herb in diabetes is cinnamon (*Cinnamomum zeylanicum*) for which many clinical trials in diabetic patients confirmed its hypoglycemic effects. The problem with herb use in diabetes, the doses and the way of intake are not well documented. Moreover, most patients used mixture of herbs either alone or in combination with antidiabetic treatments which has not yet been evaluated. The aim of the present study therefore, was to evaluate the effect of specified doses and dosage form of cinnamon, fenugreek and their combination on patients with type 2 diabetes on antidiabetic treatments not achieving accepted glycemic control.

PATIENTS AND METHODS

The study protocol was approved by Basrah College of Medicine ethical committee. Sixty four patients with type 2 diabetes were enrolled for the study. The patients were selected during their visit to Al-Faiha Diabetes Endocrine and Metabolism Center (FDEMC) in Basrah during

the period, September 2013 to November 2013. The protocol of the study was explained to the patients and verbal consents were obtained from all patients. The Patients were recruited for the study after meeting a set of inclusion criteria; these are: Type 2 diabetes mellitus patients (male and female) not controlled by conventional antidiabetic drugs and not on insulin, age ≥ 20 years, HbA1C $\geq 7\%$, 2 h-PPG ≥ 200 mg/dl (11.1 mmol/l). Patients were excluded from the study if they were type 1 diabetic or previously on herbs for the last 3 months. Pregnancy or planning for pregnancy, current or scheduled treatment liable to influence plasma glucose levels, such as glucocorticosteroid, current or recent hospitalization < 3 months, diabetes related problems, type 2 diabetic patients on insulin. Eight patients refused to take herbs because they were not convinced with their benefit, two patients started intake then discontinued them few days later, because of severe diarrhea in one patient on cinnamon, and the other patient on the combination treatment because the effect of herbs was not up to patient's expectation. Fifty four patients completed the study (response rate 87%). Seventeen were males and 37 were females.

Preparation of herbs

The herbs were purchased from a local market in Basrah, authenticated by a herbalist and a voucher specimen of the seeds was kept in the Department of Pharmacology for future reference. The placebo labeled capsules (size 0) was filled with bran as an inert substance, packed in plastic bags of 100 capsules. Cinnamon fine powder was obtained by grinding cinnamon peel by mechanical grinder, filled in the same capsules size. Each capsule was filled with 500 mg of the fine powder of cinnamon. The capsules were packed in plastic bags of 100 capsules. Fenugreek was prepared as a drink. The patient was given a plastic bag

containing 240 gm of fenugreek seeds and instructed to prepare a Fenugreek drink by boiling the whole content of the plastic bag in 1000ml of drinking water. The extract was then obtained by filtration using a household mesh filter. The liquid then transferred into 500 ml bottle. The patient was instructed to take a dose of 15 gm / 30 ml which is approximately one small cupful of the liquid once daily after breakfast. Clear instructions were printed on a piece of paper and inserted in each pack.

Study design:

The patients were divided by simple random selection in to 4 groups. The number of patients in each group ranged from 12-15 patients. Sample size calculation were based on recruiting patients for the study to achieve 80% power to detect 20% difference in HbA1c and 2h-PPG using a formula for one-tailed unpaired t-test.^[13] Recalculation of the sample size was attempted after exclusion of patients. The patients were blinded for the treatment at least for the placebo and cinnamon treatments. Group 1: control group (12 diabetic patients) received two placebo capsules three times daily; group 2:(13 patients) received cinnamon two capsules, 500 mg three times daily; group 3:(14 patients) received fenugreek seeds (boiled filtered liquid) 15 g/30 ml once daily, and group 4:(15 patients) received combination of fenugreek and cinnamon at the same above mentioned doses. All herbal medications were given after meal with a glass of water. The patients were instructed to continue using their antidiabetic treatment (metformin 850 mg once or twice daily+glibenclamide 5 mg twice daily) and to adhere to diet program in addition to herbal treatment. The study was continued for 40 days.

Laboratory investigations:

HbA1C and 2 h-PPG were measured for each participant before and 40 days after herbal administration. HbA1C was measured by D-10 Dual Program Bio-Rad Laboratories, Inc.,

Hercules, CA 94547, 220-020, California; USA. D-10 Dual Program is based on chromatographic separation of the analytes by ion-exchange (HPLC). Plasma glucose was measured by Glucometer Accu-Chek Go, Roche Diagnostic GmbH, and Germany.

Follow up of patients:

During the 40 days study period, the patients were approached by telephone every week to ensure compliance with herbs intake and adherence to proper diabetic diet regimen and oral antidiabetic drugs. Adverse effects of herbs, appearance of new symptoms were also looked for. They were also asked to report any changes in their medication or lifestyle throughout the study. Compliance of the patients was monitored by capsules count.

Statistical analysis:

SPSS version 15 was used for statistical analysis. One sample t-test was used for comparison of the mean at baseline and 40 days after treatment with herbs. Two sample t-test was used for the comparison between reduction in HbA1C and 2h-PPG obtained with herbs compared with placebo. The data are presented as mean \pm SD, P value $<$ 0.05 is considered significant.

RESULTS

Fifty four patients completed the study, their characteristic are listed in (Table-1). In the control group, HbA1C level slightly but significantly declined from $9.25\% \pm 1.63$ at baseline to $9.05\% \pm 1.74$ after 40 days of treatment with placebo, $P < 0.01$. In the same group, 2 h-PPG was also significantly reduced from 266 ± 64 mg/100ml to 240 ± 75 mg/100ml, $P < 0.01$. Treatment with cinnamon for 40 days has resulted in more reduction in HbA1C than the control group, in which the level of HbA1C significantly declined from a baseline value of $9.37\% \pm 2.1$ to $8.76\% \pm 1.9$, $P < 0.01$, and 2 h-PPG was reduced from 291 ± 99 mg/100ml at

baseline to 233 ± 61 mg/100ml after 40 days treatment. The same changes in HbA1C and 2 h-PPG were noticed with fenugreek and even

more reduction was noticed with the combination of fenugreek and cinnamon (Table2).

Table 1. Patient characteristics*

Variable	Control group n = 12	Cinnamon group n = 13	Fenugreek group n = 14	Combination group n = 15
Age (years)	49.33 ± 3.36	48.53 ± 10.07	52.13 ± 7.92	52.13 ± 7.92
Men (%)	(33.3%), n = 4	(30.8%), n = 4	(35.7%), n = 5	(20%), n = 3
Women (%)	(66.7%), n = 8	(69.2%), n = 9	(64.3%), n = 9	(80%), n = 12
Body weight (kg)	80.83 ± 12.22	82.23 ± 25.36	83.57 ± 13.28	79.13 ± 14.9
Time since diagnosis (years)	3.08 ± 1.78	3.33 ± 3.08	3.50 ± 2.90	2.58 ± 1.44

[*] Statistical analysis of patient's characteristics in cinnamon, fenugreek and the combination groups compared with the control group revealed no significant differences.

Since HbA1C and 2 h-PPG were significantly reduced with placebo (Table-2), attempt was made to evaluate the net effect attributed to herbal treatments. The data were rearranged and presented in (table-2) as a change from baseline values. Comparison was then made between changes in the control group with that of the treated groups using independent t-test. The reduction in HbA1C after 40 days treatment with cinnamon was (-0.6 ± 0.5) which was significantly greater than the reduction with the control group (-0.2 ± 0.37) , $P < 0.05$. The reduction in HbA1C with fenugreek treatment for 40 days was more than the control group but less than with cinnamon, and significant difference from the control group was not achieved. Maximum reduction in HbA1C was

obtained with the combination, cinnamon and fenugreek for which a reduction of (-0.8 ± 1) was obtained which is significantly different from the control group, $P < 0.05$. The effect of treatments on 2h-PPG was also presented as a change from baseline and comparisons were made between treatments. In the control group, 2 h-PPG after 40 days treatment with placebo was reduced from baseline by $(-26 \pm 48$ mg/100ml), and the reduction was $(-58 \pm 55$ mg/100ml), $(-57 \pm 76$ mg/100 ml), and $(-75 \pm 71$ mg/100ml) for cinnamon, fenugreek and cinnamon fenugreek combination respectively. Statistical significance was obtained between the combination and the control, $P < 0.05$ (Table-2).

Table 2. The effect of treatment with cinnamon, fenugreek and their combination on HbA1C and 2h-PPG before and after 40 days treatment

Treatment	HBA1C%			2 h – PPG mg/100ML		
	Baseline	After 40 days	Difference	Baseline	After 40 days	difference
Control	9.25 ± 1.63	$9.05 \pm 1.74^*$	$- 0.2 \pm 0.37$	266 ± 64	$240 \pm 75^*$	$- 26 \pm 48$
Cinnamon	9.37 ± 2.1	$8.76 \pm 1.9^*$	$- 0.6 \pm 0.5 \text{ ¥}$	291 ± 99	$233 \pm 61^*$	$- 58 \pm 55$
Fenugreek	9.38 ± 1.45	$8.87 \pm 1.3^*$	$- 0.5 \pm 0.4$	272 ± 88	$215 \pm 61^*$	$- 57 \pm 76$
Cinnamone+ Fenugreek	10.4 ± 1.7	$9.58 \pm 1.21^*$	$- 0.8 \pm 1 \text{ ¥}$	303 ± 74	$228 \pm 58^*$	$- 75 \pm 71 \text{ ¥}$

*Significantly different from the corresponding baseline value, $P < 0.01$

¥ Significantly different from the corresponding value of the control

DISCUSSION

The study was designed to evaluate the effect of commonly used herbal medications by diabetic patients in Basrah. Recently, an epidemiological study completed by our team (under publication), had found that cinnamon (which is known in Arabic as darcien, Kerfah) and fenugreek (Helba) were among the most commonly used herbs by diabetic patients. This finding stimulated interest to pursue with the present study with a primary aim to evaluate, in a randomised placebo controlled clinical trial, the effect of these herbs on HbA1c and 2 h-PPG in patients with type 2 diabetes not well controlled with a full dose of oral antidiabetic drugs, and to compare that with diabetic patients treated with placebo capsules filled with bran. The striking finding was a significant reduction in both HbA1C and 2 h-PPG from their baseline values in patients treated with the placebo capsules. This, though small reduction, may in part be explained by closely following the patients up through a weekly telephone calls to ensure compliance with treatments, and by the way educating the patients and attracting their attention towards treatments and importance of diet restriction in controlling the disease. Treatment for 40 days with cinnamon, fenugreek, and their combination significantly reduced HbA1C and 2 h plasma glucose compared with their corresponding baseline values. The reduction from baseline in HbA1C and 2 h-PPG obtained with 40 days treatment with placebo or herbs was compared with placebo. The reduction in HbA1C and 2h-PPG was greater with cinnamon compared with placebo and even greater reduction with the combination of cinnamon and fenugreek suggesting an additive effect of the combination on HbA1C and 2 h-PPG. Improvement in parameters of glycemic control in the present study is in agreement with many other studies in type 2 diabetic patients which demonstrated similar improvement with cinnamon supplementation. In one study, type 2 diabetic

patients with HbA1C > 7% supplemented with 1gm of cinnamon per day for 90 days had achieved a reduction in HbA1C of 0.8%.^[14] In a series of randomized placebo controlled clinical trials performed on patients with type 2 diabetes treated with cinnamon as a fine powder capsules or as aqueous extract of crude powder at doses:1, 3 and 6 gm for 90 days, significant reduction in fasting blood sugar (18-29%) was observed with no significant changes in the placebo groups.^[15] A reduction in postprandial blood glucose levels^[16] and HbA1C has been reported also.^[14,17] Cinnamon, in addition, has an effect on serum lipid through reducing low density lipoprotein (LDL), and insulin resistance.^[18,19,20] In a randomized, controlled crossover trial, fenugreek was studied on ten patients with type 2 diabetes at a relatively high dose (25 gm) daily for 15 days. Fenugreek in this study significantly reduced the area under the plasma glucose curve and improved glucose tolerance.^[21] In another placebo controlled study in which fenugreek was used at relatively high dose (18 pills, each 500 mg) given orally to 69 patients with type 2 diabetes who were not achieving glycemic control with oral sulfonylureas. The patients in this study were treated for 12 weeks with fenugreek while still receiving sulphonylureas. Supplementation with fenugreek pills in the treatment group significantly decreased FPG, postprandial plasma glucose and HbA1C levels, with improvement of clinical symptoms.^[22] Other studies with fenugreek have shown the same effect on FBS or HbA1c.^[23,24] The results of the present study are in agreement with these studies. The mechanism of hypoglycemic effect of fenugreek is not well understood, however, in an animal study it was found to have efficacy in restoring kidney function of diabetic rats via its antioxidant and anti-inflammatory activities.^[25] In another study, it was found that the seeds of fenugreek contain an unusual amino acid (2S, 3R, 4S) 4-hydroxyisoleucine (4HO-Ile), which

is found only in fenugreek and has antidiabetic properties of enhancing insulin secretion under hyperglycaemic conditions, and increasing insulin sensitivity.^[26] Cinnamon was reported to reduce blood sugar through more than one mechanism; first, regulation of enzymes of carbohydrate metabolism, glycolysis and gluconeogenesis^[27]; second, stimulation of cellular glucose uptake^[28]; third, stimulation of insulin release and insulin receptor signaling.^[29] It is worth mentioning that the dose is an important determinant of the effect, and in the present study, for safety reasons, a dose of 3 gm daily of cinnamon was used while in a similar study a range of doses of 3, and 6 gm was used.^[15] For fenugreek, the dose used in the present study was 15 gm while in other studies 5 gm^[30], 15 gm,^[31] and up to 100 gm^[32] were used. Cinnamon or fenugreek is safe apart from one patient on cinnamon complained from gastric discomfort, and two participants in fenugreek group had diarrhea for two days. We have to admit that 40 days treatment with herbs may be short to obtain a maximum effect on HbA1C. In some studies, eight weeks treatment was tried to produce effect on HbA1C^[22], in another study 12 weeks were used.^[23] However, a decision to treat for 40 days was taken firstly; to minimize noncompliance if treatment is extended for longer period of time, secondly, there is some evidence that a 50% change in HbA1C could be achieved with treatment for 30 days. In fact most of the changes in HbA1C occur during the first 30 days and the rest may take place during the next 90 - 120 days.^[33] It can be concluded that cinnamon and fenugreek are effective in lowering HbA1C and 2 h-PPG in type 2 diabetic patients and demonstrated acceptable level of safety and may be used in conjunction with oral antidiabetic drugs for treatment of diabetes.

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