PHYTOTHERAPY RESEARCH
*Phytother. Res.* **23**, 1186–1189 (2009)
Published online 23 January 2009 in Wiley InterScience
(www.interscience.wiley.com) **DOI**: 10.1002/ptr.2754

*SHORT COMMUNICATION*

# The Clinical Investigation of *Citrullus colocynthis* (L.) Schrad Fruit in Treatment of Type II Diabetic Patients: A Randomized, Double Blind, Placebo-controlled Clinical Trial

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***Citrullus colocynthis* (L.) Schrad fruit is an herbal medicine used by traditional herbalists for the treatment of diabetes in Iran. To determine its efficacy and toxicity, a 2 month clinical trial was conducted in 50 type II diabetic patients. Two groups of 25 each under standard antidiabetic therapy, received 100 mg *C. colocynthis* fruit capsules or placebos three times a day, respectively. The patients were visited monthly and glycosylated hemoglobin (HbA1c), fasting blood glucose, total cholesterol, LDL, HDL, triglyceride, aspartate transaminase, alanine transaminase, alkaline phosphatase, urea and creatinine levels were determined at the beginning and after 2 months. The results showed a significant decrease in HbA1c and fasting blood glucose levels in *C. colocynthis* treated patients. Other serological parameters levels in both the groups did not change significantly. No notable gastrointestinal side effect was observed in either group. In conclusion, *C. colocynthis* fruit treatment had a beneficial effect on improving the glycemic profile without severe adverse effects in type II diabetic patients. Further clinical studies are recommended to evaluate the long-term efficacy and toxicity of *C. colocynthis* in diabetic patients. Copyright © 2009 John Wiley & Sons, Ltd.**

*Keywords: Citrullus colocynthis*; herbal medicine; diabetes; HbA1c.

## INTRODUCTION

Diabetes mellitus is one of the most common endocrine diseases. Apart from conventional antidiabetic therapy, several studies have shown that some medicinal plants used in traditional systems of medicine have beneficial effects and can reduce blood glucose in diabetic patients (Bradley *et al.*, 2007; Triggiani *et al.*, 2006). *C. colocynthis* (L.) Schrad is a member of the Cucurbitaceae family and is used traditionally as an antidiabetic medication. It is also used as a natural laxative in several Asian countries (Ziyyat *et al.*, 1997).

*C. colocynthis* grows widely in Asia, especially East Asian countries. The plant fruits are a potent and drastic hydragogue and catharsis producer in humans, when more than 2 g dry fruit pulp is eaten daily (Haji Sharifi, 2003). The prominent clinical feature is dysenteric diarrhea with colonic congestion and hyperemia of the mucosa with abundant exudates (Goldfain *et al.*, 1989; Al Faraj, 1995). Its toxicity in experimental animals has been reported in several studies (Al-Yahya *et al.*, 2000; Diwan *et al.*, 2000; Bakhiet and Adam, 1995; Elawad *et al.*, 1984). A saponin extract of *C. colocynthis* fruit at acute lethal doses of 200 mg/kg (2000 mg/kg aqueous fruit extract), produced histological changes in the small intestine, liver and kidney (Diwan *et al.*, 2000). However, *C. colocynthis* aqueous extract at a dosage of 200 mg/kg ameliorated some of the toxic effects of streptozotocin on rats (Zaree *et al.*, 2007). The pulp contains the bitter substances colocynthin and colocynthetin as well as several other substances such as phytosterol glycoside, gum, pectins and albuminoids (Wasfi, 1994; Afifia *et al.*, 1973; Darwish *et al.*, 1974).

*C. colocynthis* is prescribed for diabetes in several cities of Iran by traditional healers in a different range of doses from 300 to 800 mg/day dry fruit. There is no monitoring of the patients after treatment for its efficacy and toxicity. Although experimental studies confirm the blood glucose lowering properties of *C. colocynthis* (Abdel-Hassan *et al.*, 2000; Nmila *et al.*, 2000), to our knowledge no clinical studies have been undertaken so far to determine its antidiabetic properties as well as its toxicity at therapeutic doses. The present study was designed to investigate the antidiabetic efficacy and toxicity of *C. colocynthis* fruit at traditionally prescribed doses in type II diabetic patients.

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Contract/grant sponsor: Endocrinology and Metabolism Research Center, Tehran University of Medical Sciences, Tehran, Iran; contract/grant number: 207-Q-1/8/1383.

*Received 2 October 2007*
*Revised 3 November 2008*
*Accepted 7 November 2008*

## MATERIALS AND METHODS

A total of 50 type II diabetic patients (aged 40–65 years), registered at the Diabetic Clinic registry of Shariati Hospital, were selected and enrolled in this study. The patients were admitted by investigators and informed about the rationale and main aims of the study. A written informed consent was obtained from each patient in the presence of a member of the ethics committee of the Tehran University of Medical Sciences.

All the patients who participated (12 males and 38 females) had a confirmed diabetes type II diagnosis according to ADA criteria (ADAS, 2003) and had been on treatment for at least 2 months with a diabetic food regimen and had not taken any herbal medicine during the past 2 months. Inclusion criteria were: type II diabetes with a fasting blood glucose of less than 200 mg/dL and with a disease duration of 2–8 years, body weight between 55 and 75 kg, normal blood pressure and lipid levels, taking only one type and not more than four antidiabetic drugs. The exclusion criteria were insulin therapy, cardiovascular disease, infectious diseases, pregnancy and breast-feeding.

*C. colocynthis* (100 mg whole dried fruit powder per capsule) and placebo capsules in the same shape and color were prepared in the Institute of Medicinal Plants (Tehran, Iran). The selected 300 mg (5 mg/kg for average of 60 kg body weight/day) dried fruit powder in three divided doses was the lowest of doses of *C. colocynthis* prescribed by 10 herbalists (range of doses 300–800 mg/day) with no gastrointestinal disturbance. A total of 90 capsules from placebo or *C. colocynthis* were packed in boxes and marked A or B. The same number of both A and B boxes were placed in closed big boxes. The patients selected by physician for the study were allowed to take either box A or B of their own choice from the nursing staff. Nurses were instructed to keep a written record of patients that selected boxes A or B. The patients were then given the same A or B box the next month by the nursing staff. The patients and the investigators who carried out clinical and paraclinical assessments were unaware of treatment groups and type of medication. The patients in both groups took similarly 100 mg capsules three times a day before meals. The conventional oral hypoglycemic agent treatment continued in two groups. The compliance was assessed indirectly using a pill count method.

The fasting blood glucose, glycosylated hemoglobin, total cholesterol, LDL, HDL, triglyceride, aspartate transaminase, alanine transaminase, alkaline phosphatase, urea and creatinine levels were determined at the beginning and after 2 months of the study in both groups.

Blood samples were drawn after an overnight (12 h) fasting. Fasting glucose levels were determined by the glucose-oxidase method using a Beckman Glucose-2 Analyser immediately after blood sampling at the Endocrine Research Center Laboratory. Glycosylated hemoglobin levels were determined by D-10 Hemoglobin testing system (Bio-Rad Laboratories, Inc. Germany). All other blood sample parameters were measured by auto analyser Hitachi 902 using commercially available kits (Pars Azmon).

Patients were in contact with the department for any gastrointestinal adverse effects and visited every month to assess the efficacy of treatment and for the determination of fasting blood glucose level.

**Statistical analysis.** The statistical analysis of the recorded data at the start and after 2 months was performed using independent and paired Student's *t*-tests of SPSS statistical software for quantitative variables. A value of $p < 0.05$ was considered as statistically significant.

## RESULTS

All the patients completed 2 months therapy. The demographic and paraclinical characteristics of two groups at the beginning of the study are summarized in Table 1. Most of the patients in the *C. colocynthis* treated group were satisfied with the therapy, having apparently good gastrointestinal status. The average finding of patient's blood parameters in the two groups at the beginning and after 2 months of the study are summarized in Table 2.

### Blood biochemical studies

**Glucose.** The average fasting blood glucose level in the *C. colocynthis* group at the beginning of the study was 189.2 ± 27 mg/dL and significantly decreased to 174.0 ± 34 mg/dL ($p < 0.015$) at the end of the study. The average fasting blood glucose levels in the placebo group at

**Table 1. The demographic and some of the paraclinical characteristics of placebo and *C. colocynthis* treated groups at beginning of the study**

| | Group | | |
|---|---|---|---|
| | *C. colocynthis* ($n$ = 25) (mean ± SD) | Placebo ($n$ = 25) (mean ± SD) | $p$ value |
| Age (year) | 53.3 ± 5.6 | 55.1 ± 5.4 | 0.623 |
| Duration of disease (year) | 4.7 ± 2.4 | 5.1 ± 3.7 | 0.381 |
| Weight (kg) | 66.2 ± 5.4 | 67.1 ± 4.9 | 0.801 |
| Glucose (mg/dL) | 189.2 ± 27 | 172.0 ± 24 | 0.240 |
| HbA1c (%) | 10.4 ± 1.9 | 9.1 ± 1.9 | 0.032 |
| Total cholesterol (mg/dL) | 211.9 ± 37 | 194.7 ± 43 | 0.051 |
| Triglyceride (mg/dL) | 171.5 ± 74 | 192.7 ± 83 | 0.373 |



DOI: 10.1002/ptr

**Table 2. The average serological parameters at beginning and after 2 months of the study in placebo and *C. colocynthis* treated groups**

| | Group ($n$ = 25) | | | |
|---|---|---|---|---|
| | *C. colocynthis* (mean ± SD) | | Placebo (mean ± SD) | |
| | Beginning | After 2 months | Beginning | After 2 months |
| Glucose (mg/dL)[a] | 189.2 ± 27 | 173.9 ± 34 | 172.0 ± 24 | 176.6 ± 32 |
| HbA1c (%)[a] | 10.4 ± 1.9 | 9.0 ± 2.4 | 9.1 ± 1.9 | 9.1 ± 1.6 |
| Total cholesterol (mg/dL) | 211.9 ± 37 | 204.8 ± 40 | 194.7 ± 43 | 202.6 ± 36 |
| LDL cholesterol (mg/dL) | 126.2 ± 28 | 118.0 ± 46 | 108.7 ± 24 | 115.0 ± 31 |
| HDL cholesterol (mg/dL) | 69.3 ± 20 | 62.5 ± 17 | 65.6 ± 21 | 55.6 ± 18 |
| Triglyceride (mg/dL) | 171.5 ± 74 | 170.2 ± 40 | 192.7 ± 83 | 215.5 ± 97 |
| Urea (mg/dL) | 13.9 ± 3.1 | 15.7 ± 4.7 | 15.0 ± 3.8 | 14.7 ± 3.5 |
| Creatinine (mg/dL) | 0.91 ± 0.1 | 0.92 ± 0.1 | 0.87 ± 0.0 | 0.94 ± 2.5 |
| Aspartate transaminase (U/L) | 25.8 ± 8.2 | 28.4 ± 7.1 | 27.6 ± 6.0 | 28.7 ± 5.1 |
| Alanine transaminase (U/L) | 34.9 ± 7.1 | 31.3 ± 1.1 | 33.0 ± 12 | 32.5 ± 8.1 |
| Alkaline phosphatase (IU/L) | 182.8 ± 52 | 171.5 ± 43 | 165.0 ± 62 | 175.0 ± 60 |

[a] Fasting blood glucose and glycosylated hemoglobin (HbA1C) levels significantly decreased in the *C. colocynthis* treated group compared with the beginning of the study (0.015 and 0.003, respectively) and compared with the placebo group (0.029 and 0.023, respectively).

the beginning and end of the study were 172.0 ± 24 mg/dL and 177.7 ± 32 mg/dL, respectively.

**Glycosylated hemoglobin.** The average glycosylated hemoglobin (HbA1c) level in the *C. colocynthis* group at the beginning of the study was 10.4 ± 1.9% and significantly decreased to 9.0 ± 2.4% ($p < 0.003$) at the end of the study. The average blood HbA1c level in the placebo group at the beginning and end of the study were 9.1 ± 1.9% and 9.1 ± 1.6%, respectively.

**Other blood biochemical values.** The average fasting blood levels of total cholesterol, LDL, HDL, triglyceride, aspartate transaminase, alanine transaminase, alkaline phosphatase, urea and creatinine levels in both the groups did not change significantly at the end of the study compared with the beginning of the study (Table 2).

In addition, only three patients (12%) reported mild diarrhea at the beginning of the study and no significant gastrointestinal adverse effects or any notable change in weight, systolic and diastolic blood pressure were found in any patient from the two groups.

## DISCUSSION

The present study showed the beneficial effect of *C. colocynthis* on the glucose profile in patients with type II diabetes. The *C. colocynthis* treatment significantly lowered the glycosylated hemoglobin and fasting blood glucose levels in diabetic patients.

Although the hypoglycemic effect of *C. colocynthis* fruit has also been reported in experimental studies (Abdel-Hassan *et al.*, 2000; Al-Ghaithi *et al.*, 2004), the mechanism underlying the glucose lowering effect of *C. colocynthis* is not clear. One study indicated that *C. colocynthis* had an insulin tropic effect on isolated pancreatic islets (Nmila *et al.*, 2000). Another study showed that *C. colocynthis* inhibited the toxic effect of streptozotocin on pancreatic cells in rats (Ramachandran *et al.*, 2004; Al-Ghaithi *et al.*, 2004). These two effects may suggest a role in the production and protection of pancreatic cells in rats from harmful metabolic products produced during hyperglycemic conditions.

*C. colocynthis* is an herbal medicine and 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, the elevation of glucose and free fatty acid levels leads to the generation of reactive oxygen species and oxidative stress (McGarry, 2002). These metabolic abnormalities not only induce late diabetic complications but also lead to insulin resistance, ß-cell dysfunction and impaired insulin secretion (Boden, 1997; Rosen *et al.*, 2001; Paolisso and Giugliano, 1996). *C. colocynthis* with its antioxidant properties and inhibition of lipoperoxidation (Zaree *et al.*, 2007; Barth *et al.*, 2002; Gebhardt, 2003) is active against oxidative stress and may induce a positive effect on diabetic metabolic abnormalities. The favorable effect of substances with antioxidant properties on oxidative metabolic derangement caused by hyperglycemia has been reported in other studies (Huseini *et al.*, 2006; Soto *et al.*, 1998).

The toxicity of large doses of *C. colocynthis* has been reported in experimental studies with both animals and humans (Goldfain *et al.*, 1989; Bakhiet and Adam, 1995; Elawad *et al.*, 1984). However, in experimental studies the aqueous extract of the *C. colocynthis* at lower doses can ameliorate some of the toxic effects of streptozotocin (Zaree *et al.*, 2007; Al-Ghaithi *et al.*, 2004). The absence of any significant changes in aspartate transaminase, alanine transaminase and alkaline phosphatase activity, and in levels of urea and creatinine, indicate that at the doses given, the extracts did not cause any damage to liver or kidney function. Furthermore, the absence of significant gastrointestinal disturbances observed in the present study following *C. colocynthis* administration, indicates that *C. colocynthis* is safe at a dose of 300 mg/day treatment to diabetic patients for 2 months.

In conclusion, the results showed that the *C. colocynthis* fruit treatment has a beneficial effect on reducing the



DOI: 10.1002/ptr

glycemic state in type II diabetic patients. The use of this herbal medicine at a dose of 300 mg/day in three divided doses showed no adverse gastrointestinal symptoms or liver and kidney abnormalities during 2 months of therapy. Large-scale clinical trials studies are needed to evaluate the long-term efficacy and toxicity of *C. colocynthis* in diabetic patients.

## Acknowledgements

This study was supported by a research grant 207-Q-1/8/1383 from the Endocrinology and Metabolism Research Center, Tehran University of Medical Sciences, Tehran, Iran. We thank the administration of the Institute of Medicinal Plants and the Medical and Nursing staff of the Diabetic Center of Shariati Hospital for their support in providing the necessary facilities for conducting this study.

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