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The Hypolipidemic Effect of *Citrullus colocynthis* on Patients with Hyperlipidemia

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Abstract: *Citrullus colocynthis* is one of the medical herbs that traditionally have been used as an antidiabetic medication in tropical and subtropical countries. The aim of this study was to investigate the hypolipidemic effect of *Citrullus colocynthis* beyond the hypoglycemic impact on human. One hundred dislipidemic patients were randomly divided into two groups namely treated (n = 50) group and placebo (n = 50) group. The subjects were treated daily by powdered seeds of *Citrullus colocynthis* (300 mg) and placebo for 6 weeks. The serums, TG, Chol, LDL-C, HDL-C, SGOT and SGPT were measured with enzymatic methods at the beginning and the end of the project. The significance of differences within these groups was calculated by Paired T-test and by analysis of covariance between them. There were significant differences within and between treated and placebo groups during our treatment in TG and in Cholesterol after intervention ($p<0.05$). A daily intake of 300 mg day^{-1} of powdered seeds of *Citrullus colocynthis* can lower the triglyceride and cholesterol concentration significantly in nondiabetic hyperlipidemic patients.

Key words: Hyperlipidemia, *Citrullus colocynthis*, triglyceride, cholesterol, SGOT, SGPT

INTRODUCTION

Elevated levels of plasma low density lipoprotein cholesterol and triglyceride accompanied by reduced high-density lipoprotein levels are often associated with an increase risk of coronary heart disease (Smith *et al*., 2004; Anderson *et al*., 1991). Coronary heart disease is a leading cause of global mortality accounting for almost 12 million death annually (Smith *et al*., 2004). The intensity of the high risk status of hyperlipidemic patients and their need for more aggressive lipid lowering therapy is such immense that have been considered by both National Cholesterol Education Program and the American Diabetes Associations (2003). The search for new drugs capable to reduce or regulating serum cholesterol and triglyceride levels has gained momentum over the years, resulting in numerous reports on significant activities of natural agents (Jahromi *et al*., 1993; Abdel-Rahman *et al*., 2009; Sukandar *et al*., 2010). Among these natural products, medicinal plants provide a valuable therapeutic alternative (Reaven *et al*., 1983). *Citrullus colocynthis* is one of the medical herbs that traditionally have been used as an antidiabetic medication in tropical and subtropical countries (Diwan *et al*., 2000).

This herb is a member of the family cucurbitaciea and commonly known as the bitter apple or bitter cucumber. *Citrullus colocynthis* grows widely in the Persian, Arabian and Sahara desert and was introduced by Arabs first, in Spain and Cyprus in the middle Ages (Trease and Evans, 1970; USDA, 2006).

At the time being, this herbal preparation is used by diabetic patients in Iran especially among those who are candidates for insulin therapy and patients whose treatment were not successful (Huseini *et al*., 2006). Most studies published have shown a statistically significant decrease in blood glucose along prescription of *Citrullus colocynthis* (Huseini *et al*., 2006; Nmila *et al*., 2000; Al-Hashem *et al*., 2009) but, only one report has been published about the hypolipidemic impact of the *Citrullus colocynthis* on diabetic patients (Huseini *et al*., 2006). Huseini *et al*. (2006) reported no significant changes in serum triglyceride and cholesterol in type II diabetic patients after prescription of powdered seeds of *Citrullus colocynthis*. Whereas so far, no afford has been under taken to study the hypolipidemic effect of the fruits of *Citrullus colocynthis* in nondiabetic patients for the first time we conducted this study to investigate the effect of *Citrullus colocynthis* on lipid profile in nondiabetic patients.

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MATERIALS AND METHODS

Collection of the plant: Fresh *Citrullus colocynthis* fruit was collected from the province of Bushehr in the south of Iran. The plant was botanically authenticated and voucher specimens (2112) were deposited in the Herbarium of the medical sciences of Bushehr University (Autumn 2008). Matured black seeds were separated from the pulp of the fruits. Then the seeds were dried and powdered with a grinder (mulinex, Japan, 4234). The capsules were filled with the 100 mg seeds powder and packed in a sanitized condition.

Patients: The present study is a double blind, placebo-controlled, clinical trial over 6 weeks. Patients were recruited from the general community by media advertising. One hundred white Caucasian outpatients, 44 men and 56 women, aged 51.3±3.7 years, with hyperlipidemia (according to Criteria of the Adult Treatment Panel III) and a disease duration of 5.4±1.6 years were selected for this study. All patients fulfilled the following criteria: Body Mass Index (BMI) <30 kg m^{-2}, Serum triglycerides (TG) >150 mg dL^{-1} and cholesterol (chol) > 160 mg dL^{-1}, no previous medical history of thyroid, liver, renal or chronic inflammatory disease. No patient was on insulin or lipid lowering medication, beta-adrenergic antagonist or thiazide diuretic drugs. Subjects were excluded if they had a recent history (within 3 months) of heart disease, angina pectoris or major surgery. They were excluded also if they had a recent history [within 6 months] of myocardial infarction or stroke, significant liver or renal disease (plasma creatinine >130 μmol L^{-1}), microproteinuria, or symptomatic gastrointestinal disorders (peptic ulcer, chronic diarrhea, ulcerative colitis, irritable bowel syndrome and lastly celiac sprue). The study was approved by the Ethics Committee of the Medical Sciences of Bushehr University and the reported investigations have been carried out in accordance with the principles of the Declaration of Helsinki as revised in 2000. Also the participants in the project have given written informed consent.

The patients were randomised by the use of envelopes containing randomisation codes prepared by an independent statistician. One group received treatment with *Citrullus colocynthis* (300 mg day^{-1}, divided into 3 equal doses of 100 mg seed powder enveloped in capsules before breakfast, lunch and dinner); the other group received a corresponding placebo (starch) for 6 weeks. Used medication packets and a supplement using chart were collected at each visit to monitor compliance. The physical activities were kept constant during the study.

After an overnight fast of 12 h, blood samples were drawn at baseline and at the end of study for the evaluation of plasma Total Cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-c), Serum glutamate oxaloacetate transferase (SGOT) and Serum glutamate pyruate transferase (SGPT). Waist circumferences were measured at the umbilicus and hip circumferences at the level of maximum gluteal protuberances with a tape. The weight of the patients was measured by a calibrated scale. Three day dietary recall (2 week days and 1 weekend day) information was obtained through an interview conducted by trained dietitians at the beginning and by the end of study to control any changes in energy intake or lipid along the research. Each food and beverage was analyzed for content of energy and the other nutrients using NUNTRITIONIST III software (version 7.0; N-Squared Computing, Salem, OR), which has been designed for Iranian foods. Physical activity was completed at baseline and after the intervention period by physical activity questioner.

Laboratory assessment: Venous blood samples were taken between 8 and 9 am The blood samples were centrifuged at 3000 g for 15 min at 4°C. Immediately after centrifugation, the serum samples were frozen and stored at -80°C for a period of no more than 6 weeks.

All measurements were carried out at the research laboratory of the Persian Gulf Tropical Medicine Research Center, Bushehr University of Medical Science. TG was measured by the enzymatic techniques (Pars Azmoon-co, Iran) intra- and inter-assay coefficients of variation (CVs) were 4.0 and 3.5%, respectively. The serum concentration of cholesterol was determined by the enzymatic techniques (Pars Azmoon-Co, Iran) intra- and inter-assay coefficients of variation (CVs) were 3.5 and 3.0%, respectively The total HDL-C levels (after precipitation with magnesium chloride) were measured by enzymatic techniques (Pars Azmoon-Co, Iran); intra-and interassay CVs were 1.5 and 1.9%, respectively. The LDL-C level was calculated by using the Friedewald formula. SGPT and SGOT were measured using the sandwich Enzyme Linked Immunosorbent Assay (ELISA) method (Pars Azmoon-Co, Iran); inter-and interassay CVs were 5 and 6%, respectively).

Statistical analysis: Statistical analysis of the data was performed using SPSS statistical software version 11.0. Simple independent student t-test was used to compare

baseline data. Paired t-test was applied to test changes within groups for statistical significance. The changes were compared between the 2 groups with analysis of covariance. Two-tailed probability value of $p<0.05$ was considered as statistically significant.

RESULTS

Three patients were withdrawn from the study due to relocation, two from the placebo group and another from the *Citrullus colocynthis* group. One hundred randomly assigned subjects completed the study. The characteristics of the patients confirmed that the groups were well matched for all entry criteria (Table 1) and there were no significant differences between the groups in either the type or number of antihypertensive, medications. The antihypertensive medications taken by the subjects were angiotensin-converting enzyme inhibitors (13%), calcium channel blockers (9%), angiotensin II receptor antagonists (9%), alpha-blockers (3%) and non thiazide diuretics (4%).

There were no significant differences between the groups in total energy and macronutrient intake, body weight, number of cigarette smoking per day at baseline. No significant changes took place during the intervention (data not shown). Medication doses and physical activities were unchanged during the intervention in each group.

Mean values for baseline serum lipids and SGOT and SGOT in each group are shown in Table 1.

Fasting triglyceride concentrations at baseline were < 500 mg dL^{-1} in each of the groups, implying reliable assessment of LDL cholesterol with the use of the Friedwald formula. There were no significant differences between the groups at baseline in any of the variables Table 1.

There were significant differences within and between treated and placebo groups during our treatment in serum TG concentration (203.23±75.93 to 171.71±58.77 versus 192.70±77.23 to 193.92±82.09) and Chol (204.71±43.62 to 187.14±39.58 versus 198.41±42.32 to 193.92±47.14) ($p<0.05$). But LDL-cholesterol, HDL-cholesterol, SGOT and SGOT concentrations had no changes in *Citrullus colocynthis* group after the interventions (Table 2).

Table 1: Baseline characteristics of the patients (n = 100). Mean±SD

Characteristic	*Citrullus colocynthis* (n = 50)	Placebo (n = 50)
Age (years)	50.5±4.8	52.2±2.6
Sex (n)		
Men	24	20
Women	26	30
TG (mg dL^{-1})	203.23±75.93	192.70±77.23
Chol (mg dL^{-1})	204.71±43.62	198.41±42.32
LDL-C (mg dL^{-1})	117.42±36.28	116.76±36.43
HDL-C (mg dL^{-1})	44.51±8.37	42.27±12.13
SGOT (mg dL^{-1})	40.90±33.05	28.70±8.64
SGPT (mg dL^{-1})	19.23±9.84	20.17±17.05
BMI (kg m^{-2})	28.40±2.9	28.51±1.2
WHR	0.90±0.08	0.93±0.15

BMI: Body mass index; WHR: Waist hip ratio; TG: Triglycerides; TC: Total Cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; SGOT: Serum glutamate oxaloacetate transferase; SGPT: Serum glutamate pyruate transferase

Table 2: Mean±SD changes in variables after treatment with *Citrullus colocynthis* or placebo

	Groups (after 6 weeks)	
Characteristics	Colocynth	Placebo
TG (mg dL^{-1})	-31.52±73.98*	19.7143±49.60
TC (mg dL^{-1})	-17.57±39.55*	-6.21±33.25
HDL-C (mg dL^{-1})	2.41±5.63	-0.03±4.31
LDL-C (mg dL^{-1})	7.33±30.34	10.07±28.92
SGOT	2.95±14.11	-2.85±8.60
SGPT	-4.19±11.16	-5.28±14.20

TG: Triglycerides; TC: Total Cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; SGOT: Serum glutamate oxaloacetate transferase; SGPT: Serum glutamate pyruate transferase. *$p<0.05$ versus placebo at 6 week

DISCUSSION

The findings of our research demonstrated that the seed portion of the *Citrullus colocynthis*, exhibits a significant hypolipidemic effect at the dose of 300 mg per day in treated hyperlipidemic patients in respect to control group (Fig. 1, 2). The most hypolipidemic impact is reported by Daradka *et al.* (2007), who showed the increased cholesterol level were brought to normal by administration of *Citrullus colocynthis* about (87%) by the end of the experiment in atherogenic rabbits

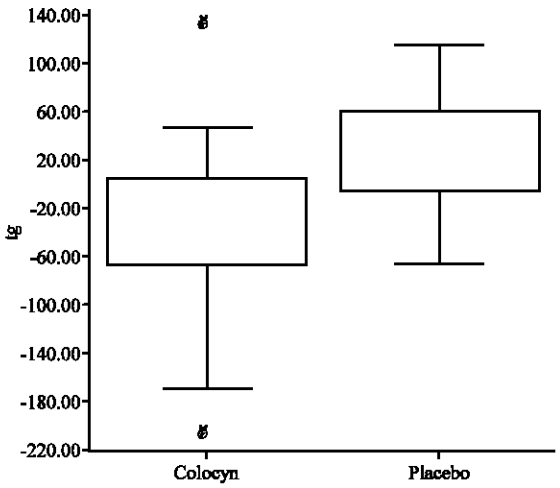

Fig. 1: Average changes in fasting plasma triglyceride (TG mg dL^{-1}). Mean±SD, differences is significant after 6 weeks ($p = 0.02$)

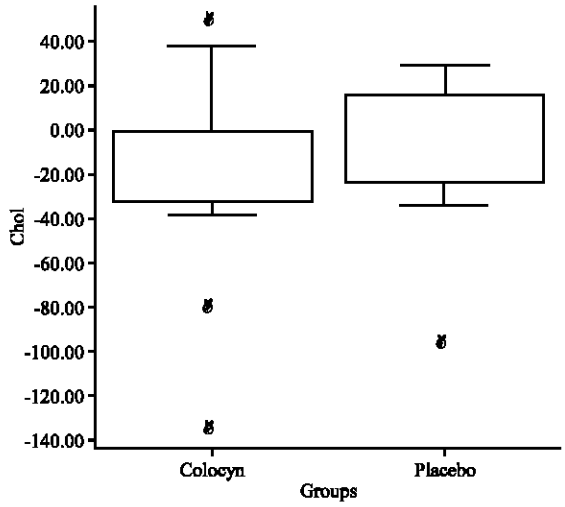

Fig. 2: Average changes in fasting plasma Cholesterol (chol mg dL^{-1}). Mean±SD, differences is significant after 6 weeks (p = 0.04)

(Daradka *et al*., 2007). The findings of our novel research in accordance to Daradka *et al.* (2007) showed significantly and consistently reduction serum cholesterol (5.3%) and triglyceride (15.7%) by prescription of *Citrullus colocynthis* seeds in hyperlipidemic patients. In contrast to our data Huseini *et al.* (2006) reported that in spite of significant reduction in fasting blood glucose, no significant changes were seen in lipid profile after ingestion of *Citrullus colocynthis* in type II diabetic patients. This discrepancy can be attributed to the number and status of the study subject. The population of our study was one hundred and nondiabetic and in fallahs studies 50 type II diabetic patients. It seems that reduction of blood glucose by glucose lowering medication is not concomitant with reduction of serum lipids in type II diabetic patients. O'Brien *et al.* (1998) have mentioned, although hypertriglyceridemia and low levels of high-density lipoprotein are the most common lipid abnormalities in patients with type 2 diabetes mellitus, but abnormalities persist even after optimal glycemic control has been achieved (O'Brien *et al*., 1998). Indeed the exact mechanism of null impact of *Citrullus colocynthis* in serum triglyceride and cholesterol in type II diabetic patients, is not yet elucidated and must be answered in the future experiments.

On the best of our knowledge, to date, a mechanism to explain the hypotriglyceridemic and hypocholesteremic effects of *Citrullus colocynthis* in human has not been clarified. Recently a few experimental studies in animal model has been developed which indicates the hypolipidemic effect of *Citrullus colocynthis* is due to enhancement of catabolism or removal of lipoproteins in liver (Brattsand, 1975) and inhibition of lysosomal lipid hydrolytic enzymes synthesis, secreted by the liver (Sherlock, 1998).

The hypolipidemic activity of the *Citrullus colocynthis* could be attributed for more extent to the presence of bioactive components. Three flavonoides glycosides, isosaponarin, isovitexin and isoorientin and two cucurbitan glucosides, 2-o-β-D-glucopyranosylcucurbitacin I, in the butanol fraction extract and two new cucurbitane-type triterpene glycosides, colocynthosides A and B in the methanolic extract of the fruit were found (Delazar *et al*., 2006; Yoshikawa *et al*., 2007). From the results has been published, on the total phenolic content, it was found that there was .074% flavonoid as gallic acids, and.013% flavonoid as catechin in fresh mass of *Citrullus colocynthis* extracts (Kumar *et al*., 2008). Abe *et al.* (2000) have proposed the selective inhibition of squalene epoxidase, a rate limiting enzyme in cholesterol biosynthesis, by the catechin in his report. Furthermore, mutsuda elucidated that the saponin is able to inhibit gastric emptying via sympatric activation or central signaling in the cerebral chemoreceptor that consequently reduces lipid absorption in the gut (Matsuda *et al*., 1999). Chan *et al.* (1999) reported that hypolipidemic effect of catechin was mediated by inhibition of dietary fat and cholesterol absorbsion (Chan *et al*., 1999). Further on enhancement of dietary fat oxidation by catechin due to increased β-oxidation in the liver was proposed by Harada *et al.* (2005).

The literature on *Citrullus colocynthis* is quiet heterogeneous, in particular, the portion of the fruit being evaluated for physiologic and toxic effects, solvent used for extraction, dosage of the lyophilized extract administered, rout of administration and acute or chronic effect of the extract. This heterogeneity through motivated by delineating the therapeutic potential of the fruit, limits comparison of various findings. Indeed the differential hypolipidemic effect of the extract from various parts of this fruit aught to be center study of investigations.

There is some evidence that ingestion of *Citrullus colocynthis* may induce side effects including: Acute colitis (Goldfain *et al*., 1989), reversible infertility (Chaturvedi *et al*., 2003) and hepatotoxicity (Barth *et al*., 2002). Present data showed no significant changes in SGOT and SGPT after prescription of *Citrullus colocynthis* at the end of the study. Dehghani and Panjehshahin (2006) studied the toxic effect of alcohol extract of *Citrullus colocynthis* on rat liver at 50, 100 and 400 mg kg^{-1} b.wt. They reported that toxic effects were

null at 50 and 100 mg kg^{-1} b.wt. and less intense at 200 and 400 mg kg^{-1} b.wt. (Dehghani and Panjehshahin, 2006). Atole *et al.* (2009) reported no significant changes in SGOT, SGPT and ALK Phosphatase after prescription of alkaloids extract of the seeds of *Citrullus colocynthis* in rats. Neither complain from gastrointestinal abnormalities nor evidence of hepatic toxicity were seen in our study which is in accordance with Fallahs report, that indicates no side effect of ingestion of *Citrullus colocynthis* in the dose of 300 mg day^{-1} in human being (Huseini *et al.*, 2006).

In conclusion, a daily intake of 300 mg day^{-1} of powdered seeds of *Citrullus colocynthis* can lower the fasting triglyceride and cholesterol concentration significantly. It is fair to mention that hypoglycemic mechanism of the *Citrullus colocynthis* on human remains obscure and an open question to be answered.

There are several limitations to this clinical trial study. First, we did not conduct the study on the pure bioactive component of the whole seeds of *Citrullus colocynthis*. These are of value in understanding the differential hypolipidemic effect of the different bioactive extracts from various parts of this fruit. Second, the data on diet were obtained by self-reported questionnaire (which could lead to possible over reporting on specific aspects of the diet, such lipid consumption)

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