Evaluation of the Effects of *Cucumis sativus* Seed Extract on Serum Lipids in Adult Hyperlipidemic Patients: A Randomized Double-Blind Placebo-Controlled Clinical Trial

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Abstract: Hyperlipidemia is associated with increased risk of atherosclerosis; therefore, control of this risk factor is very important in preventing atherosclerosis. Cucumber (*Cucumis sativus*) seed is used traditionally as a lipid-lowering nutritional supplement. The aim of this study was to evaluate the effect of cucumber seed extract on serum lipid profile in adult patients with mild hyperlipidemia. In a randomized double-blind placebo-controlled clinical trial, hyperlipidemic patients with inclusion criteria were randomly and equally assigned to either Cucumis or placebo groups and used one medicinal or placebo capsule, respectively, once daily with food for 6 wk. Body mass index (BMI) as well as fasting serum levels of total cholesterol, triglycerides (TG), low-density lipoprotein (LDL-C), and high-density lipoprotein (HDL-C) were measured for all patients pre- and post-intervention and finally the changes were compared between the groups. Twenty-four patients in Cucumis group and 23 patients in placebo group completed the study. Cucumis seed extract resulted in significant reduction of total cholesterol ($P = 0.016$), LDL-C ($P < 0.001$), TG ($P < 0.001$), and BMI ($P < 0.001$) as well as significant increase of HDL-C ($P = 0.012$) compared to placebo. In conclusion, the consumption of *C. sativus* seed extract with daily dose of 500 mg results in desirable effects on serum lipid profile in adult hyperlipidemic patients. Therefore, cucumber seed could be considered as a food supplement for treatment of dyslipidemia.

Keywords: body mass index, clinical trial, *Cucumis sativus* seed, hyperlipidemia

Practical Application: According to the results of this work, cucumber seed extract has the potential application for adjunctive treatment of dyslipidemia or treatment of mild dyslipidemia so that lower doses of antihyperlipidemic drugs could be used resulting in lower incidence of adverse drug reactions.

Introduction

Rapid changes in lifestyle, particularly in the areas of nutrition and physical activity, leads to change in the pattern of noncommunicable diseases and increased risk of diseases such as diabetes, osteoporosis, cardiovascular disease, and obesity (Reddy 2002). The role of prevention of risk factors for these disorders is highlighted. Coronary artery atherosclerosis is the main cause of death and disability in western societies. On the other hand, 47.3% of deaths rate in Iran is due to cardiovascular diseases (Rother and Collard 2001; Sarrafzadegan and others 2006). The prevalence of hyperlipidemia in 25- to 64-year-old age Iranian people is 42.9% (Esteghamati and others 2009). High serum levels of total cholesterol (TC), low density lipoprotein cholesterol (LDL), and triglycerides (TG) are the independent risk factors for coronary heart disease (CHD) (Henderson and others 2005; Jain and others 2007). Since hyperlipidemia, especially hypercholesterolemia, is associated with increased risk of atherosclerosis, control of this risk factor is very important in preventing atherosclerosis.

Nowadays, hyperlipidemia could be treated or prevented by using different synthetic and herbal types of medications. Statins and fibrates are the most common and favorable medicines used to treat serum lipid disorders; however, concerns about their side effects like elevation of liver enzymes, gastrointestinal symptoms, predisposition to cholelithiasis, myopathy and rhabdomyolysis, as well as the lack of general agreement about their use in children and adolescents have persuaded the scientists to find an appropriate substitution for them (Cybulsky and others 2001; Massberg and others 2002; Miller and others 2003; Hansson 2005).

Several studies have demonstrated the efficacy of some herbal drugs in the treatment of dyslipidemia due to their components such as dietary fibers, vitamins, flavonoids, polyphenols, and antioxidant compounds (Kannar and others 2001; Durak and others 2004; Sabzghabaee and others 2013; Guo and others 2014; Soltani and others 2014). So, it has been concluded that the combinations of nutraceuticals with different lipid-lowering activities should provide an alternative to drug treatment for patients in primary cardiovascular disease prevention and in some statin-intolerant patients (Cicero and Colletti 2016).

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Cucumis sativus is a plant belonging to the Cucurbitaceae family and is widely cultivated in the tropical areas (Trease and Evans 2002; Minaiyan and others 2011).

C. sativus seed has been previously analyzed by Abou-Zaid and coworkers by phytochemical analysis (Abou-Zaid and others 2001). It contains 24-ethyl-Δ^7-phytosterols like 24-ethylcholesta-7,22-dien-3-ol and 4-ethylcholesta-7-en-3-ol and small amounts of Δ^5 sterols like 24-ethyl- cholest-5-en-3-ol with cholesterol related structures. Other chemical constituents of *C. sativus* seed include volatile and fixed oils, saponins, steroids, carotenes, flavones, flavonoids, alkaloids, amino acids, resins, and tannins (Roman-Ramos and others 1995; Abou-Zaid and others 2001; Han and others 2008; Minaiyan and others 2011).

Cucumber seed is also rich in monounsaturated (oleic acid, 7%) and polyunsaturated (linoleic acid, 71%) fatty acids (Matsson and Volpenhein 1963; Rayees and others 2013) justifying its potential use for treatment of hyperlipidemia. Although cucumber seed is used traditionally as a lipid-lowering nutritional supplement, there is no clinical study confirming this effect. The aim of this study was to evaluate the effect of *C. sativus* seed extract on serum lipid profile in adult patients with mild hyperlipidemia.

Materials and Methods

Seed preparation and extraction

Seed preparation and extraction was performed in pharmacognosy laboratory of faculty of pharmacy, Isfahan University of Medical Sciences. Once purchased, the cucumber seeds were identified and confirmed by a botanist. Then the seeds were powdered by electric mixer (Moulinex, France) and extracted by maceration method using ethanol 70% (Stalk, Iran). The extract was then filtrated, concentrated under vacuum, and finally dried using freeze dryer (Christ, Germany).

Preparation of medicinal and placebo capsules

Each medicinal capsule was filled with 500 mg of dried extract. The placebo capsules with shape, size, and color similar to medicinal ones were filled only with dried granulated tribasic calcium phosphate (Merck, Germany).

Patient selection

Patients were selected from those who referred to Farhangian clinic of Isfahan. Those who met the following inclusion criteria,

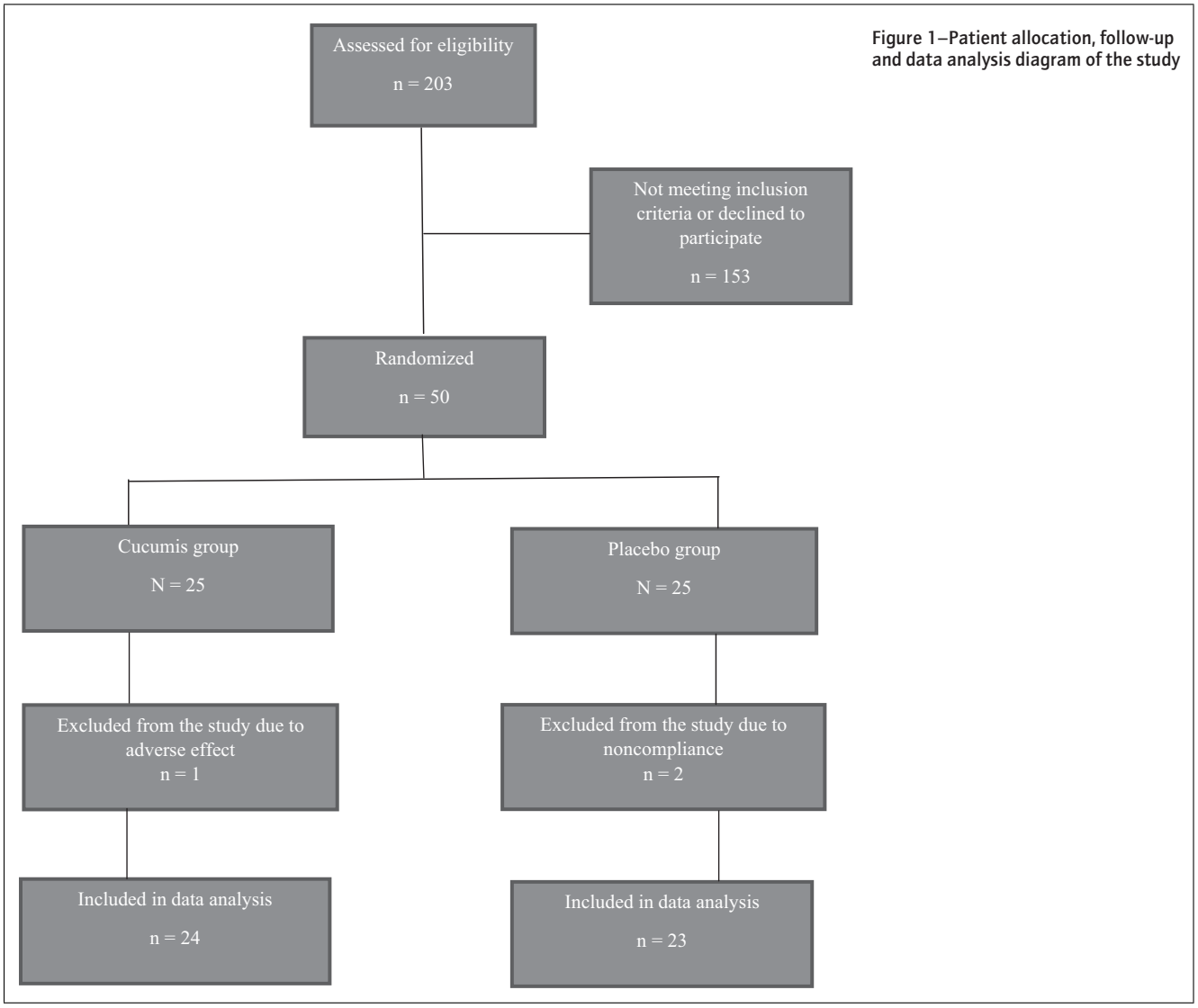

Figure 1–Patient allocation, follow-up and data analysis diagram of the study

were recruited to the study: (1) age ≥ 18 y; (2) serum levels of total cholesterol 200 to 239 mg/dL and/or triglyceride (TG) 150 to 199 mg/dL and/or low-density lipoprotein cholesterol (LDL-C) 130 to 160 mg/dL; (3) having <2 cardiovascular risk factors including age ≥45 y for men and ≥45 y for women, family history of a premature coronary heart disease (definite myocardial infarction or sudden death before 55 y in father or other male first-degree relative or before 65 y in mother or other female first-degree relative), current cigarette smoking, hypertension (≥140/90 mm Hg) or use of antihypertensive drugs), and serum HDL-C <40 mg/dL (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001); (4) not using alcohol and/or other substances of abuse; (5) free of diseases affecting serum lipids (for example, diabetes, thyroid disorders, and pancreatitis); (6) not using drugs or supplements affecting serum lipids (for example, statins, fibrate derivatives, estrogens, progestins, beta-blockers, thiazide diuretics, and fish oil) within the last 2 months; (7) free of liver or kidney disease; and (8) being nonpregnant and nonlactating (women).

Irregular use of capsules and allergic reaction to the extract or any component of the capsules were considered as the exclusion criteria.

Study design and interventions

This was a randomized double-blind placebo-controlled clinical trial performed in Farhangian Clinic of Isfahan, Iran, from June 2014 to September 2015. Informed consent was obtained from all participants and the study protocol was approved by the ethical committee of Isfahan University of Medical Sciences. Patients with inclusion criteria were randomly and equally assigned to either study drug (Cucumis seed extract) or placebo groups. Before intervention, the demographic characteristics (including BMI) and fasting serum levels of total cholesterol, TG, LDL-C, and HDL-C were measured for all patients. Also, to detect any possible side effects of the extract on the liver and kidney, the serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), BUN, and creatinine were measured. All venous blood samples were taken in the morning between 7:00 am and 9:00 am after 8 h of fasting and blood samples were frozen for a maximum of 2 wk and stored at −70 °C until the time of biochemical assay. The serum levels were measured by enzymatic colorimetric methods using commercial kits obtained from Pars Azmoon company (Karaj, Iran).

The patients of Cucumis and placebo groups were instructed to use one medicinal or placebo capsule, respectively, once daily with food for 6 wk. All patients were instructed to maintain their usual diet and physical activity and report any adverse effect during the study. The patients compliance was evaluated by counting their capsules at the end of use and their results were included in data analysis if they used more than 80% of their capsules. At the end of 6 wk, all above-mentioned parameters were again measured and compared to baseline values. All participants, the prescriber, and laboratory personnel were blind to intervention type.

Statistical analysis

Kolmogorov–Smirnov test was performed to assess normal distribution of obtained data. Independent samples *t*-test was used to verify differences between baseline values. Chi-square test was done to compare gender distribution between the groups. Paired-samples *t*-test was used to compare values before and after the study in each group. Analysis of covariance (ANCOVA) was used for comparing parameters between drug and placebo groups with statistical control of baseline values. The level of significance was considered as $P < 0.05$.

Table 1–The effects of interventions on tested parameters after 6 wk in the study subjects in each group. The values are presented as mean (SD).

Parameter (Unit)	Cucumis ($n = 24$)	Placebo ($n = 23$)
BMI (kg/m^2)		
Baseline	27.81 (3.68)	27.60 (5.35)
End	28.49 (3.81)	27.75 (5.67)
P-value[a]	0.041	0.371
Total cholesterol (mg/dL)		
Baseline	217.08 (30.71)	223.91 (32.18)
End	201.21 (38.15)	213.17 (43.07)
P-value	0.015[b]	0.336[a]
LDL-C (mg/dL)		
Baseline	133.05 (35.56)	145.40 (32.68)
End	96.50 (17.68)	140.95 (29.83)
P-value[b]	0.000	0.317
TG (mg/dL)		
Baseline	230.66 (140.19)	199.43 (126.26)
End	156.83 (78.43)	177.48 (104.50)
P-value[a]	0.000	0.260
HDL-C (mg/dL)		
Baseline	45.54 (7.52)	56.26 (11.61)
End	53.00 (12.39)	52.48 (14.97)
P-value[b]	0.001	0.708

BMI, body mass index; LDL, low-density lipoprotein; TG, triglycerides; HDL, high-density lipoprotein.
[a]Wilcoxon Signed-Rank test.
[b]Paired-Samples *t*-test.

Table 2–Mean changes of tested parameters from baseline after 6 wk in study patients. The values are presented as mean (SD).

Parameter (unit)	Cucumis ($n = 24$)	Placebo ($n = 23$)	*P*-Value[a]
BMI (kg/m^2)	−0.23 (0.52)	0.15 (0.77)	0.000
Total cholesterol (mg/dL)	−15.88 (29.65)	−10.74 (52.41)	0.016
LDL-C (mg/dL)	−36.55 (30.85)	−4.47 (5.70)	0.000
TG (mg/dL)	−73.83 (79.50)	−21.96 (90.98)	0.000
HDL-C (mg/dL)	7.46 (9.67)	−4.15 (9.91)	0.012

BMI, body mass index; LDL, low-density lipoprotein; TG, triglycerides; HDL, high-density lipoprotein.
[a]ANCOVA test.

Results and Discussion

During the study, a total of 203 patients were evaluated for eligibility that 65 of them met the inclusion criteria and 50 patients participated in the study. However, 2 participants dropped out from placebo group due to irregular consumption of capsules and changing usual diet and 1 case was excluded from drug group because of side effect (Figure 1).

Regarding gender distribution, 52.5% ($n = 21$) and 47.5% ($n = 19$), respectively, of patients in Cucumis and placebo groups were male ($P = 701$). The mean (± SD) age of patients in Cucumis and placebo groups was 36.91 (± 6.47) and 39.86 (± 9.06), respectively ($P = 0.200$).

The effects of interventions on evaluated parameters are depicted in Table 1. As seen, the data showed significant decrease in BMI and serum total cholesterol, LDL-C, and TG as well as significant increase in HDL-C level in Cucumis group, while no significant change was observed in placebo group.

Table 2 shows the mean changes of evaluated parameters in Cucumis group compared to placebo group. As shown, Cucumis seed extract resulted in significant reduction of total cholesterol,

Table 3–The effects of interventions on the liver and kidney function tests of the study subjects after 6 wk. The values are presented as mean ± SD.

	Cucumis (n = 24)			Placebo (n = 23)			
Parameter (Unit)	Baseline	Week 4	P-value	Baseline	Week 4	P-value	P-value[a] (between groups)
ALT (U/L)	34.41 (10.95)	32.25 (12.40)	0.080[b]	31.69 (7.90)	30.40 (8.08)	0.054[c]	0.610
AST (U/L)	26.80 (10.24)	24.21 (11.41)	0.091[c]	26.47 (3.90)	23.17 (4.65)	0.070[b]	0.076
BUN (mg/dL)	15.87 (1.51)	15.42 (2.43)	0.469[c]	15.78 (2.28)	15.35 (2.53)	0.494[c]	0.645
Creatinine (mg/dL)	0.99 (0.13)	1.10 (0.16)	0.061[b]	0.94 (0.88)	1.07 (0.18)	0.057[c]	0.093

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen.
[a]ANCOVA test.
[b]Wilcoxon Signed-Rank test.
[c]Paired-Samples t-test.

LDL-C, TG, and BMI as well as significant increase of HDL-C compared to placebo.

Table 3 shows the effects of Cucumis and placebo on laboratory markers of liver and kidney function after 6 wk of use. As seen, no significant changes were detected in these values during the study. Also, no complication or adverse effect was reported by patients of both groups at the end of study; however, hair loss was reported by a male patient in Cucumis group excluded from the study.

Based on our searches, this was the first clinical study on the effects of cucumber seed. Animal studies on this herb were also very limited. In an animal study, the effect of hydroalcoholic and butanolic extract of cucumber seed on blood glucose levels in streptozocin-induced diabetic and normal rats was evaluated. The results showed that the extracts were not effective on reducing blood glucose levels in normal and diabetic rats for initial phase of treatments; however, both hydroalcoholic (22.5% to 33.8%) and butanolic (26.6% to 45.0%) extracts were effective in reduction of blood glucose in diabetic rats compared to controls after 9 d of continued daily therapy (Minaiyan and others 2011).

It seems that the observed lipid-lowering effects in this study is due to linoleic acid and resin content of the seeds. The anti-hyperlipidemic effects of linoleic acid have been shown in several studies. In a study, replacement of 10% of energy from saturated fatty acids with linoleic acid instead of carbohydrates led to more reduction of LDL-C levels (Mensink and Katan 1992). Also, the lipid-lowering effects of some plants with large amounts of unsaturated fatty acids including linoleic acid have been shown. In the study of Fu and others (2012), the hypolipidemic effects of *Cornus wilsoniana* fruit oil were studied in rats. The results showed that the oil could significantly reduce the serum total cholesterol, TG, and LDL. The analysis of oil chemical constituents demonstrated large amounts of unsaturated fatty acids (69.12%) including linoleic acid and γ-linolenic acid. In a clinical study, consumption of pomegranate seed oil (containing 6% to 7% linoleic acid) at a dose of 400 mg twice daily was associated with a favorable effect on HDL and TG (Mirmiran and others 2010). Another study conducted by Berrougui and others (2003) to assess the effect of *Argania spinosa* oil (containing oleic acid and linoleic acid) on serum lipids, reduction of serum cholesterol, TG, and LDL was observed. Furthermore, consumption of this herbal oil was also associated with a significant reduction in body weight, an effect consistent with the results of our study. Indeed, a desirable effect observed in our study distinguishing it from many other plants, is significant effect in increasing HDL levels, since most herbal oils have little effect on this lipoprotein (Berrougui and others 2003).

The hypolipidemic effects of linoleic acid and other fatty acids could be due to their binding to peroxisome proliferator-activated receptors (PPARs) (Wolfrum and others 2001). These nuclear receptors have a substantial role in regulation of the expression of several genes resulting in lipid homeostasis in hepatocytes (Wolfrum and others 2001).

Cucumber seed extract resins may also have a role in reducing blood lipids. In a double-blind study conducted by Azadmehr and others (2014) on 71 patients for 12 wk, the effect of Olibanum gum in reduction of serum LDL and TG was in type 2 diabetic patients was shown. It seems that this effect was mediated by the gum resins. Another study showed the antidyslipidemic effects of *Commiphora mukul* gum resin extract in fructose-fed diabetic rats (Ramesh and Saralakumari 2012).

The phytosterols present in Cucumis seed extract may also be responsible for its hypolipidemic effects. Absorption of cholesterol because of its hydrophobic structure is low in water and is dependent to emulsifying properties of bile salts to incorporate it into small micelles. Phytosterols with cholesterol related structures have low enteric absorption and can compete with cholesterol in a way that a portion of cholesterol is not transported and excreted via feces (Kelishadi and others 2016). The lowering effects of plant sterols were reported in different types of hypercholesterolemia including familial hypercholesterolemia, familial combined hypercholesterolemia and undefined hypercholesterolemia (Garaiova and others 2013).

The significant effect of cucumber seed in reduction of BMI observed in our study, suggests that this plant can be used as a nutritional supplement for weight loss in overweight and obese patients. However, given insubstantial reduction of BMI, another separate study to determine the effects of cucumber seeds on the weight and other relevant parameters (for example, waist circumference) with a longer duration and larger sample size is suggested.

Several limitations of the present study include small sample size, short duration of intervention, and no chemical analysis of the herbal extract. Therefore, more studies are needed to better define antihyperlipidemic and anti-obesity effects of cucumber seed extract and detect its active ingredients.

Conclusion

The consumption of *C. sativus* seed extract with daily dose of 500 mg results in significant reduction of serum total cholesterol, LDL-C, and TG as well as significant increase of serum HDL-C in adult hyperlipidemic patients. Therefore, cucumber seed could be considered as a food supplement for treatment of dyslipidemia.

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Author Contributions

R. Soltani analyzed and interpreted the data and drafted the manuscript. M. Hashemi and K. Heshmat selected the patients according to the inclusion criteria and interpreted the results. A. Farazmand performed the extraction of herbal material and collected the data. Gh. Asghari and S.M. Ghanadian assisted for the identification and extraction of herbal material.

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