Original Article

Effects of cumin on nonalcoholic steatohepatitis: A double blind, randomised, controlled trial

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Abstract

Background: This study was designed to evaluate the effect of cumin on nonalcoholic steatohepatitis (NASH) in compare to placebo.

Materials and Methods: One hundred patients with histopathological diagnosis NASH in two groups of case and control received oral cumin capsule or placebo thrice daily for 6 months. Clinical and laboratory data were body mass index (BMI), serum triglyceride, serum total cholesterol, alanine aminotransferase (ALT), aspartate aminotransferase (AST), high-density lipoprotein (HDL), low-density lipoprotein (LDL), fasting blood sugar (FBS), steatosis grade, and side-effects and were measured at baseline and after treatment period using standard clinical chemistry techniques. The grade of steatosis was assessed by liver sonography in 3 stages (mild, moderate and severe).

Results: Of 100 eligible patients during follow-up 10/50 cases and 9/50 controls were excluded. At baseline and after treatment BMI, triglyceride, cholesterol, ALT, AST, HDL, LDL, and FBS were not statistically significant between groups ($P \geq 0.5$). BMI, triglyceride, cholesterol, ALT, AST, LDL, and FBS after treatment decreased compare to baseline but were not statistically significant ($P \geq 0.5$). The mean of changes in the level of BMI, triglyceride, cholesterol, ALT, LDL and FBS were not statistically significant ($P \geq 0.5$). The mean of changes in AST and HDL between groups was significant ($P < 0.05$). The grade of steatosis before and after treatment between studied groups was not statistically significant ($P \geq 0.5$). Side-effects were not statistically significant among the two groups.

Conclusion: Findings show that there the effect of cumin in in the treatment of NASH was not significantly different in compare to placebo.

Key Words: Cumin, herbal medicines, nonalcoholic steatohepatitis

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) as a condition that defined by excessive fat accumulation in the form of triglycerides in the liver is increasingly diagnosed worldwide over the past couple of decades, and in both developed and developing countries is now the number one cause of abnormal liver function tests and chronic liver disease.[1-3] During last 20 years, the prevalence of NAFLD has doubled whereas the prevalence of other chronic liver diseases decreased or has remained stable.[4]

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Nonalcoholic steatohepatitis (NASH) forms part of a histological spectrum of NAFLD, which includes fatty liver in the absence of liver injury or inflammation.[5] Dramatically, NASH increases the risks of cirrhosis, liver failure, and hepatocellular carcinoma and an increasingly frequent reason for liver transplantation is cirrhosis due to NASH.[6] The exact cause of NASH has not been elucidated, and it is almost certainly not the same in every patient. NASH is most commonly associated with underlying insulin resistance and thus is frequently present in patients who are overweight or obese, or who have type 2 diabetes mellitus.[7] At present there is a worldwide epidemic of diabetes and obesity. Obesity is the most common risk factor for NASH and in the obese population, the median prevalence of NASH is 33%, ranging from 10% to 56%.[8,9]

Increasing in the numbers of NASH, indicated that, in both rich and poor countries, it will become an increasingly common liver problem, affecting public health and health-care costs globally and raising the global burden of liver disease.[10] Demand for medical therapy is rising after the increasing prevalence of NASH.[11] Reduce the histologic features and improve insulin resistance and liver enzyme levels are the goals of treatment for NASH. And no pharmacological therapy has been proven effective in long-term use.[12] Thiazolidinediones and metformin are the most widely studied pharmacological therapy but the results are inconsistent and in practice, weight gain and bone loss are the most challenging side-effect of thiazolidinediones therapy.[13] Therefore, the management of NASH focuses on associated conditions in the absence of a treatment that would represent a standard of care. Currently, both exercise and healthy weight loss, either separately or in combination therapy are recommended by the American Gastroenterology Association as interventions for NASH.[14,15] This current standard of care is difficult for many patients to achieve. Bariatric surgery as another option for weight loss, offers durable weight loss and histological improvement, but is associated with significant morbidity. In general, all drugs that induce weight loss might be beneficial against NASH.[16]

Herbal medicines are gaining increasing popularity and recognition in the management of hyperlipidemia and obesity because of their multiple modes of action and their minimal side-effects. There are some reports on of the utility of herbal medicines in NASH.[17]

Cumin (cuminum cyminum) is one of the most commonly used spice condiment in food preparations in Asia.[18] Iran is one of the major lands in the world known for the production of cumin. All the cumin varieties are used in traditional and veterinary medicine. In Iranian traditional medicine, cumin is considered stimulant, carminative and astringent and its therapeutic effects have been described on gastrointestinal, gynecological and respiratory disorders. For centuries, cumin has been used to reduce appetite.[19] Also, cumin was reported to reduce raised blood sugar, improve glucose utilization, and promote digestion by stimulating gastrointestinal mucosa and pancreatic digestive enzymes.[20,21]

As highlighted above, there is no approved therapy for NASH, and data on treatment options for NASH are limited with different findings. Also, to the best of our knowledge, the cumin powder has not yet been undertaken in patients with NASH. So, the present study was conducted to evaluate the efficacy of cumin powder in the treatment of NASH.

MATERIALS AND METHODS

This double blind, randomised, controlled trial was conducted between October 2013 and March 2014, on 100 patients with NASH who referred to Al-Zahra Hospital in Isfahan, Iran, after that the Ethics Committee of Isfahan University of Medical Sciences approved the study. The diagnosis of NASH was based on both clinical and pathological findings in the liver and appropriate exclusion of other liver diseases such as alcoholic liver disease, viral hepatitis, autoimmune hepatitis, drug-induced liver disease, primary biliary cirrhosis, primary sclerosing cholangitis, biliary obstruction and metabolic liver diseases. Other eligible criteria were age between 18 and 60 years, morbid obesity (represented by a body mass index [BMI] 30–35 kg/m^2) and HbA1c level ≤7 in presence of diabetes. Exclusion criteria were use of drugs known to produce fatty liver disease, weight loss more than 10% from baseline in the previous 6 months (based on self-reported by studied patients), evidence of viral or autoimmune hepatitis, increase in the level of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) 3 times from baseline, the level of total bilirubin more than 3 mg/dL, primary biliary cirrhosis, biliary obstruction, Wilson's disease, hemochromatosis and decompensated cirrhosis, and allergy to cumin.

Eligible patients after given written informed consent were randomly divided into two 50-member groups using random-maker software "random allocation." Case group included 50 patients who received oral cumin capsule (Barij Esance Co., Iran, contain 25 mg saponin) thrice before main meals daily for 6 months. Control group included 50 patients who received placebo (formally, manufactured as the same as cumin

capsule, in Isfahan University, Faculty of Pharmacy) thrice daily for 3 months. Patients in both groups were suggested to have same diet and exercise regimen.

Clinical and laboratory data were collected after randomization and 6 months treatment period. Collected data included age, BMI, serum triglyceride, serum total cholesterol, ALT, AST, high-density lipoprotein (HDL), low-density lipoprotein (LDL), fasting blood sugar (FBS), steatosis grade, and side-effects. BMI was calculated as weight in kilograms/(height in meters^2). Laboratory evaluations were measured using standard clinical chemistry techniques. Serum AST and ALT level and lipid parameters were determined via an automatic biochemistry analyzer (Aerosets, Wiesbaden, Germany) using commercially available assay kits. The grade of steatosis was assessed by liver sonography based on the following scale of 1–3: (1) Mild (affecting 10–29% of hepatocytes); (2) moderate (affecting 30–69% of hepatocytes); and (3) severe (affecting >70% of hepatocytes).[22]

To maintain blinding, patients, personnel, and outcome assessors were unaware of the treatment allocation. The sealed white envelope containing patient allocation and treatment capsule were given to a previously trained nurse who was not involved in the study.

The sample size was calculated using the comparison of means formula with two-sided log-rank test, α =0.05, and 80% power. All statistical analyses were done using SPSS software for windows, version 20 (SPSS Inc; Chicago, IL, USA). Descriptive data are reported as mean ± standard deviation (SD) or number (%) as appropriate. To comparing all studied variables between groups Independent sample *t*-test for quantitative data and Chi-square test for qualitative data were used. Also, repeated measurement of ANOVA was used to assess changes in the level of laboratory data after treatment compare to baseline between groups. $P < 0.05$ were considered statistically significant.

RESULTS

Figure 1 shows the flowchart of the study, seven of 107 reviewed patients did not enter to the study (four did not eligible and three refused informed consent). One hundred eligible patients were assigned to case and control groups, received treatment and followed for 6 months. During follow-up 10 patients in case group and nine patients in control group were excluded from the study. Finally, 81 patients (40 in case group and 41 in control group) completed the study and analyzed.

The mean age of the studied patients was 38.6 ± 9.9 years old. Table 1 shows baseline characteristics of patients between studied groups. No significant differences were noted between groups for mean of age, BMI, triglyceride, cholesterol, ALT, AST, HDL, LDL, and FBS ($P \geq 0.5$).

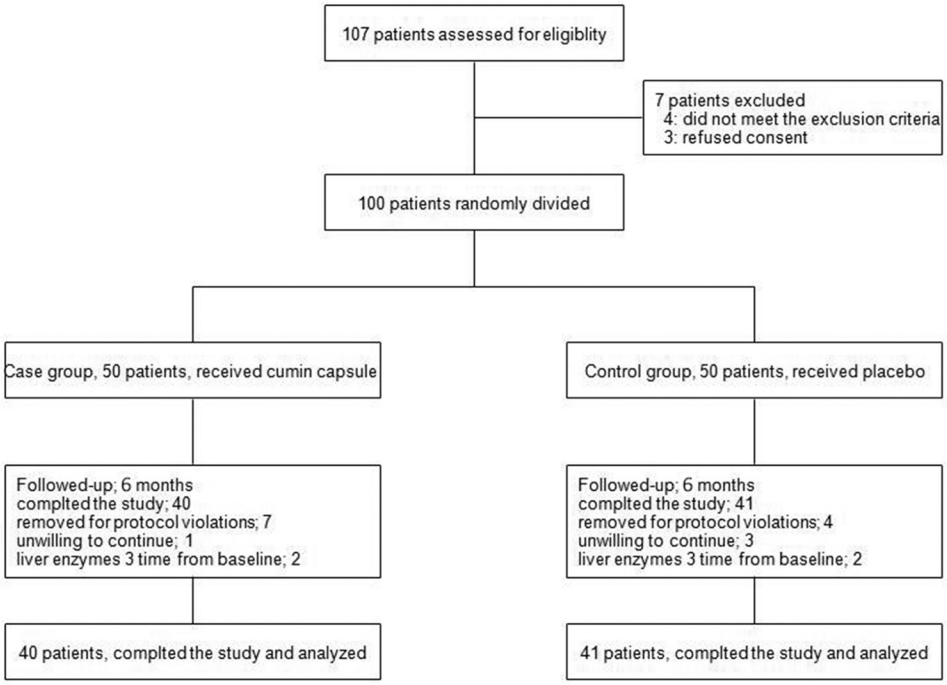

Figure 1: Patients who entered to the study, divided into the study groups and analyzed

Table 2 shows the comparison of BMI and laboratory data after 6 months treatment between studied groups. As shown after 6 months treatment the differences in the mean of BMI, triglyceride, cholesterol, ALT, AST, HDL, LDL, FBS between groups were not statistically significant ($P \geq 0.5$). All studied variables in both case and control groups after treatment decreased compare to baseline, HDL level in both groups after treatment increased compare to baseline, but results of repeated measurements of ANOVA show that changes in the level of studied variables after treatment compare to baseline were not statistically significant [$P \geq 0.5$, Table 2].

The mean of decrease in BMI and laboratory data after 6 months treatment compare to baseline between groups were assessed by independent sample *t*-test and results showed that mean of changes in the level of BMI, triglyceride, cholesterol, ALT, LDL and FBS were not statistically significant [$P \geq 0.5$, Table 3]. The mean of decrease in AST in cases was significantly more than in controls [33.6 and 20.9 respectively, $P = 0.031$, Table 3]. The level of HDL in cases was increased significantly more than in controls [−6.9 and −1.8 respectively, $P = 0.0001$, Table 3].

The grade of steatosis before treatment between studied groups was not statistically significant [$P \geq 0.5$, Table 4]. Before treatment most of studied patients in both groups had moderate steatosis but after treatment most of them had mild steatosis. After treatment, steatosis was proved in 29 patients of cases and 27 patients of controls. Of cases, 13 patients had no evidence of steatosis and of controls nine patients had no evidence of steatosis. As shown in Table 4, after treatment the differences in the frequency of steatosis grade between groups was not statistically significant ($P \geq 0.5$).

No serious side-effects were observed in patients in both groups and the rates of other side-effects were similar among the two groups. Nausea was reported in six of cases and two of controls. Vomiting was reported in two of cases. Mild weakness was reported in five of cases and three of controls.

DISCUSSION

Several treatments have been tried for NASH, including diet, antioxidants and improvement of insulin resistance, but no commonly accepted therapeutic protocol has yet been established.[23] Slow weight reduction is effective in many obese patients, but education and sticking to a diet are difficult, and maintaining a suitable body weight is even more difficult. Therefore, effective drug therapy for NASH would be very useful.[24]

Table 1: Baseline characteristics in 81 patients with nonalcoholic steatohepatitis by groups

Variables	Case group (*n*=40)	Control group (*n*=41)	*P*
Age (year)	38.6±10	38.5±9.9	NS
Sex, male/female	20 (50)/20 (50)	12 (29.3)/29 (70.7)	NS
BMI, kg/m^2	30.8±5.9	30.9±4.4	NS
Triglyceride	225.6±77.3	237.3±94.1	NS
Cholesterol	227.3±52.2	239.7±51.1	NS
ALT	74.3±29.3	77.2±33.1	NS
AST	75.6±31.1	72.9±33.1	NS
HDL	41.3±5.3	43.8±7.1	NS
LDL	140.9±42.8	151.1±42.9	NS
FBS	94.3±28.9	97.4±19.7	NS

Data expressed as mean±SD or number (%). BMI: Body mass index, NS: No significant, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, FBS: Fasting blood sugar, SD: Standard deviation. Case group: Patients who received oral cumin capsule, Control group: Patients who received placebo. *P* values calculated by independent sample *t*-test, and Chi-square test

Table 2: Comparison of BMI and laboratory data of 81 patients with nonalcoholic steatohepatitis after 6 months treatment

Variable	Case group (*n*=40)	Control group (*n*=41)	*P**	*P***
BMI, kg/m^2				
Before	30.8±5.9	30.9±4.4	-	NS
After	27.9±5.2	28.7±4.3	NS	
Triglyceride (mg/dL)				
Before	225.6±77.3	237.3±94.1	-	NS
After	180.1±49.6	184.5±50.2	NS	
Cholesterol (mg/dL)				
Before	227.3±52.2	239.7±51.1	-	NS
After	196.2±34.4	205.2±42.9	NS	
ALT (U/L)				
Before	74.3±29.3	77.2±33.1	-	NS
After	44.3±17.8	54±29.6	NS	
AST (U/L)				
Before	75.6±31.1	72.9±33.1	-	NS
After	43.2±20.6	52±28.7	NS	
HDL (mg/dL)				
Before	41.3±5.3	43.8±7.1	-	NS
After	48.2±5.5	45.5±7.2	NS	
LDL (mg/dL)				
Before	140.9±42.8	151.1±42.9	-	NS
After	112±32.6	123.3±37.3	NS	
FBS (mg/dL)				
Before	94.3±28.9	97.4±19.7	-	NS
After	81.4±18.4	87±16.9	NS	

Data expressed as mean±SD. BMI: Body mass index, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, FBS: Fasting blood sugar, SD: Standard deviation, NS: No significant. Case group: Patients who received oral cumin capsule, Control group: Patients who received placebo. *P* values calculated by *Independent sample *t*-test, **Repeated measurements of ANOVA

In the present study cumin as a therapeutic plant in traditional medicine was used in the treatment of NASH in compare to placebo, and our results showed that 6 months treatment with cumin capsule was

Table 3: Comparison of mean of change in BMI and laboratory data of 81 patients with nonalcoholic steatohepatitis after 6 months treatment

Variables	Case group (*n*=40)	Control group (*n*=41)	*P*
BMI, kg/m^2	2.9±2.1	2.2±1.8	NS
Triglyceride	41.5±47.6	49.5±69.4	NS
Cholesterol	30.7±30.9	33.5±30.1	NS
ALT	30.9±24.7	23.1±23.9	NS
AST	33.6±28.5	20.9±22.3	0.031
HDL	−6.9±5.7	−1.8±6.5	0.0001
LDL	29.3±25.2	27.7±30.4	NS
FBS	12.9±17.6	10.7±10.5	NS

Data expressed as mean±SD. BMI: Body mass index, SD: Standard deviation, NS: No significant, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, FBS: Fasting blood sugar. Case group: Patients who received oral cumin capsule, Control group: Patients who received placebo. *P* values calculated by independent sample *t*-test

Table 4: The grade of steatosis before and after treatment between studied groups

Variables	Case group (*n*=40)	Control group (*n*=41)	*P*
Baseline			
Mild	15 (37.5)	11 (26.8)	NS
Moderate	22 (55)	22 (53.7)	
Severe	3 (7.5)	8 (19.5)	
After treatment			
No	13 (32.5)	9 (21.9)	NS
Mild	21 (52.5)	23 (53.6)	
Moderate	5 (12.5)	6 (14.6)	
Severe	1 (2.5)	3 (7.3)	

Data expressed as number (%). NS: No significant, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, FBS: Fasting blood sugar. Case group: Patients who received oral cumin capsule, Control group: Patients who received placebo. *P* values calculated by independent sample *t*-test, and Chi-square test

not significantly different from placebo effect. BMI and liver enzymes were decreased in patients after use of cumin capsule more than placebo group but were not statistically significant. In our study only the mean of decreased value in AST and HDL in case group were significantly higher than decreased value in control group. Also, during study period no serious side-effects were noted in all patients in both case and control groups. In addition to the anti-overweight effects of cumin our results did not show significant effect of cumin on BMI compare to placebo. This can be explain by duration and doses of treatment regimen and probable differences in diet regimen and lifestyle however all patients suggested to have same diet and exercise regimen. To the best of our knowledge, the cumin has not yet been undertaken in patients with NASH, so further prospective studies with a longer treatment period and follow-up duration and larger cohort of patients are warranted to determine the effects of cumin in patients with NASH.

There is no strong evidence supporting any effective therapeutic agents for reducing inflammation and fibrosis or preventing the progression of NASH.[25] Thiazolidinediones are the most widely studied pharmacological therapy, in a systematic review and meta-analysis, randomized trials of people with NASH receiving thiazolidinediones, compared with placebo or other treatments were reviewed and showed improvement in fibrosis and steatosis with some controversy in trials results. Authors in this study suggested that thiazolidinediones may confer modest histological improvement in people with NASH but at the cost of significant weight gain and other adverse events. And also, they offered future randomized trials to more comprehensively inform clinical care.[13]

Traditional Chinese medicine for NASH using Yinchenhao Decoction (a Chinese herbal compound preparation) in animal model is evaluated by Shao-dong *et al*. In this study the effects of Yinchenhao Decoction on 18 male SD rats was assessed and results show a good therapeutic effects of Yinchenhao Decoction, protecting the liver function and reducing the fatty deposition in liver.[15] Other animal model studies show the effect of some traditional medicines such as coffee, curcumin, and green tea in the management an experimental model of NASH.[26-30] Also, some limited studies reported effect of some traditional medicines on patients with NASH.[31-33]

Another finding of this study was that treatment with cumin in patients with NAFLD was safe and well tolerated and patient compliance with medication was good in all patients completed the study. Cumin has a variety of health-promoting actions and low toxicity, warranting their consideration as potential therapeutic agents. Given the associations between obesity and metabolic syndrome, black cumin should be considered as a complementary treatment.

One of the limitations of our study was that diet regimen and lifestyle in studied patients did not assesse and we were not able to compare and evaluate the effect of these variables. Other limitation was the number of excluded patients in studied groups whereas 19 were losing during follow-up and data of these patients did not collected.

CONCLUSION

The findings of this study show that there were no significant differences between cumin and placebo in the treatment of NASH but suggest that cumin may confer modest histological improvement in people with NASH with tolerable side-effects. But NASH, as

this silent fast developing debilitating disorder needs serious and immediate attention, especially in the context of modern life style.

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Conflicts of interest
There are no conflicts of interest.

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