ORIGINAL ARTICLE

Comparison of the Effects of Cuminum Cyminuml and Sibutramine on Weight, Serum Leptin, Glucose and Lipids in Rat

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Abstract

Objectives: Diabetes is one of the most common metabolic diseases in the world. It affects 6.6% of world population and about 3 million individuals in Iran. Nowadays chemical and herbal medicines are widely prescribed to cure obesity. In Iran, cumin (Cuminum Cyminum L.) is a plant used in traditional medicine to cure obesity, and some of the new studies have suggested that cumin has a role in diabetes treatment and also in reducing the lipids level.
In this study, we investigated the cumin oil and sibutramine effect on the prevention of weight gain and the level of serum leptin, glucose, and lipids in normal Wistar rats.

Materials and methods: We divided 36 male rats of Wistar race into 3 equal groups: the control group with normal regimen, the cumin oil group with normal regimen, the sibutramine group with normal regimen. The consumed dosages of cumin oil and sibutramine were 400 µg/kg and 3mg/kg respectively which was given to the rats by gavage (tube feeding). In this study, we took samples of the hungry rats during three various periods including the first day of the study, 20th day (the beginning of the medicine usage) and 55th day (the end of the medicine usage) in order to measure their glucose and serum lipids.

Results: The results of this study showed a significant decrease in glucose, cholesterol, triglyceride, LDL ($P<0.001$) and a significant increase in serum HDL ($P=0.05$). Both drugs prevented weight gain at the end of study ($P=0.05$).

Conclusion: The findings indicate that cumin oil like sibutramine via consumption by gavage can affect the serum glucose and lipids in rats and also prevent weight gain.

Key Words: Cumin Cyminum L, sibutramine, obesity, leptin, rat

Introduction

Several spices and herbs have been shown to have hypoglycemic action in animals and humans (1). Spices increase the taste and flavors of food. Among the spices, cumin seeds (Cuminum Cyminum L.) from the family apiaceae are consumed in fairly large quantities in some counties. Cumin is widely used in Ayurvedic medicine for the treatment

of dyspepsia, diarrhea and jaundice. It also has stomachic, diuretic, carminative, and antispasmodic properties (2). Literature surveys showed that a decoction of cumin seed possesses hypoglycemic effect. Roman-Ramos in preliminary studies on the glycemic effect of antispasmodic seeds observed that they produce hypoglycemia (3).

Sibutramine is a selective inhibitor of the reuptake of monoamines, primarily serotonin and noradrenaline and, to a lesser extent, dopamine. The drug is rapidly metabolized to two active metabolites, which are 100-fold more potent than the parent compound. The half-life of the two active metabolites is 14 -16 h, with the peak concentration at 3 -4 h and a plateau from 3 to 7 h. This pharmacological profile allows for once-a day dosing, which is an advantage when appetite control is considered. Sibutramine and its metabolites are not serotonin- adrenaline- or dopamine-releasing agents and have low affinity for monoamine receptors. The dose range of sibutramine is 5 -15 mg once daily (4-5). Sibutramine has a dual mode of action. It reduces food intake and attenuates the fall in metabolic rate which occurs during weight loss. In a study in normal weight adult men, sibutramine significantly decreased the amount of food and the energy content of food that the subjects chose to consume, resulting in an average reduction of 312 kcal during the day ($P< 0.01$ vs. placebo). In non-dieting obese women, the administration of 10 mg/day sibutramine for 14 days was associated with a significant reduction in food intake ($P < 0.05$ vs. placebo) along with a reduction in total energy intake of 356 kcal per day. Weight loss with sibutramine has been reported to be attributable to enhanced satiety, as well as to decreased hunger and food consumption. In a study of the acute effects of sibutramine in energy expenditure, a single 30 mg dose of sibutramine in 11 non-obese men significantly increased basal energy expenditure compared with placebo ($P< 0.02$). Walsh et al. studied the thermogenic effects of sibutramine (15 mg/day) for 12 weeks in obese women receiving a low-calorie diet. The expected decline in resting energy expenditure usually observed with weight loss and documented in the placebo-treated patients was blunted in the sibutramine-treated patients (6).

The available reports show that very little work has been done to study the effect of cumin. In the present study its role on weight gain and glucose and lipid metabolism in normal Wistar rats is reported.

Materials and Methods

Cumin Oil was a gift of Berij Company, Kashan, IRAN. Sibutramine was purchased from RX pharma, Inc. Cholesterol was purchased from Sigma, Leptin ELISA kit from DRG. Germany, Glucose, Triglyceride, LDL, HDL and cholesterol were obtained from Grender, France. Male Wistar rats (body weight: 75–110 g) bred in the Central Animal House, faculty of medicine, Yazd University of Medical Science, were used in this study. The animals were housed in plastic cages with filter tops under controlled conditions of 12-h light/dark cycle, 50% humidity, at 28 °C.Leptin was measured by a highly sensitive direct enzyme-linked immonosorbent assay (Elisa, Biosource – leptin-Elisa-kit, Belgium-KAp2281).This assay insert reports an intra-assay coefficient of variation (CV) of 13.3% at 1.5ng/ml and 3.5% at 43.4 ng/ml and the inter-assay CV was 10.2% at 5.9 ng/ml and 12.7% at 18.9 ng/ml. Glucose, LDL, and HDL were analyzed on the EQupluse autoanalyzer, (EQupluse, Italy) using routine methods.

Experimental design

In the experiment, a total of 36 male Wistar rats were used. The rats were divided into 3 **groups as following:**

Group I: control rats with normal regimen (12 rats)

Group II: control rats given cumin oil (400µg/kg/day) in distilled water daily using gavage tube for 5 weeks (12 rats)

Group III: control rats given sibutramine (3mg/kg/day) in distilled water daily using gavage tube for 5 weeks (12 rats).

The animals were carefully monitored and weighed every day. Animals described as fasted were deprived of food for at least 12 h but allowed free access to drinking water. After 5 weeks of treatment, the rats were sacrificed by cervical dislocation. Blood was collected at the first day of the study, 20th day (the beginning of the medicine usage) and 55th day (the end of the medicine usage) in order to measure their serum leptin, glucose and serum lipids. In addition, we measured the weight of these rats during these periods. Leptin was measured by immunoassay method, and glucose and serum lipids were also measured by routine experimental methods (7).

Statistical analysis:
Results were analyzed using ANOVA, and a Scheffepost hoc test was used to compare individual means (SPSS for WINDOWS 9.05; SPSS Inc).

Results

The effect of cumin oil and sibutramine on the weight and leptin
We compared rat weight on three times in this study: Beginning of study, 20th day (start of cumin oil and sibutramine consumption) and 55th day (end of cumin oil and sibutramine consumption). The results are shown in table 1. The weights were increased until 20th day in both of groups that consumed cumin oil (205±16 g) and sibutramine (204.6±25g). At the end of our study, sibutramine and cumin oil had prevented weight gain (176±25g and 171±24g, respectively). At the end of the study the weights were different in both groups in comparison to control group (table 1). Concentrations of the blood leptin with cumin oil treatment and sibutramine are given in table 1. Levels of blood leptin were decreased in both sibutramine and Cumin treated groups as compared to their controls ($P < 0.05$) at the end of treatment.

The effect of cumin oil and sibutramine on glucose
Blood glucose at the beginning of the study, 20th day (start of cumin oil and sibutramine consumption) and 55th day (end of Cumin oil and sibutramine consumption) were measured. The results are shown in table 2 indicating that glucose increased until the 20th day in both of the groups that consumed cumin oil (106±11mg/dl) and sibutramine (115±3/6mg/dl). At the end of the study, sibutramine and cumin oil caused a decrease in blood glucose (105±18mg/dl and 80.6±15mg/dl, respectively) and also at the end of the study, the difference was significant in Cumin oil group whereas in sibutramine group was not significant (Table 2).

The effect of cumin oil and sibutramineon lipids
The Effects of administering cumin oil and sibutramine are given in table 2. TG, Chol. and LDL were significantly decreased in cumin oil and sibutramine groups as compared to their controls. Also HDL significantly increased in cumin oil and sibutramine groups compared to their control groups (Table 2).

Discussion
Obesity results from an imbalance between energy uptake and energy expenditure (8-10). Anti-obesity drugs can be classified according to their primary mechanism of action on energy balance. There are four general classes of anti-obesity drugs.

Table 1- Comparison of the effect of sibutramine and cumin oil on weight and leptin of rats in different time periods

Time	T_1			T_2			T_3		
Group	**Con**	**Cum**	**Sib**	**Con**	**Cum**	**Sib**	**Con**	**Cum**	**Sib**
WT(gr)	113	112	171	201.5	204.5	205	250	176	101
Leptin(ng/ml)	1.9	1.3	1.3	1.8	2.6	3.3	4.11	7	2.1

T_1= beginning of study, T_2= beginning of cumin oil consumption (day 20th) and T_3= end of cumin oil consumption (day 55th). Con.= control group, Sib.= sibutramine group and Cum. =cumine oil group. All the P Values are less than 0.05 significant.

Table 2- Comparison of the effect of sibutramine and cumin oil on level glucose and lipids serum in rats in different time periods

Time	T_1			T_2			T_3		
Group	**Con**	**Cum**	**Sib**	**Con**	**Cum**	**Sib**	**Con**	**Cum**	**Sib**
Glu(mg/dl)	114	113	103	109	106	115	115	80[a]	105[b]
TG(mg/dl)	107	97	12	135	128	142	165	70[a]	80[a]
Chol.(mg/dl)	85.9	84.3	85.3	95	100	92.3	106	84[a]	78[a]
LDL(mg/dl)	9.5	13.5	13	15	25	7.9	24.5	4[a]	10[a]
HDL(mg/dl)	55	51	48	52.8	55.2	45.8	48.5	66[c]	52[c]

T_1= beginning of study, T_2= beginning of cumin oil consumption (day 20th) and T_3= end of cumin oil consumption (day 55th). Con.= control group, Sib.= sibutramine group and Cum. =cumine oil group. All the PVs are less than 0.05 and significant.*:control group is common for comparison of both cumin and sibutramine groups

a: P Values Vs. Control group were significant and $p<0.01$, b: P Values Vs. control group were significant and $p\leq0.1$, c: P Values Vs. control group were significant and $p\leq0.05$

The first group comprises drugs which suppress appetite through reducing hunger perception, increasing the feeling of satiety and reducing food intake by acting on CNS. As a result, these drugs facilitate patient's compliance with caloric restriction. The second group-inhibitors of rat absorption-reduce energy intake. The third group of drugs, also acting peripherally, increase thermogenesis without planned physical activity. The last group of drugs stimulates fat mobilization acting peripherally to reduce fat mass and / or decrease triglyceride synthesis without planned increase in activity or decrease in food intake.

Sibutramine, an inhibitor of both serotonin and norepinephrine reuptake, is a derivative of ephedrine.

In this study, anti-obesity effects of cumin oil (herbal drug) and sibutramine (chemical drug) were evaluated in an animal model. Drug treatment was begun on 20th day of normal diet for 5 weeks. The results indicated that weights were increasing until 20th day in all groups. At the end of drug consumption (55days) a significantly different weight gain was observed between drug groups as compared to control ($P< 0.5$, table 1). The blood leptin level was significantly different between drug- treated group and control group ($P<005$, table 2). This study showed similar anti-obesity properties for cumin oil compared with sibutramine.

Sibutramine inhibits appetite suppression via inhibitory reuptake of serotonin and norepinephrine. Very little work has been done to study the effect of cumin oil. Thirty two compounds were identified in the essential oil of C cyminum(11) and the main components were –pinene(29.1), limonene (21.5), cineole (17.9), linalol (10.4%) -terpineole(3.17%) and linalyl acetate (4.8%).

In general, cumin aldehyde, methane derivative, c- terpinene, p-cymene and b-pinene are major components. Essential cumin oil is mainly responsive for the aroma and biological effects (12, 13).

Antibacterial effect of cumin has been wildly investigated (14). Anti-obesity effect of cumin oil to our knowledge has not been reported.

The amount of food consumption in 24 hours was measured in all groups. The results indicate no difference between consumption of food in sibutramine compared to cumin oil group (data not shown). The mechanism of cumin oil on preventing weight gain is not demonstrated. Cumin oil contains several compounds which need to be studied in future.

Administering cumin oil significantly reduced the blood glucose levels in comparison to control ($P <0.05$) whereas in sibutramine group it was not significant ($P=0.1$). The possible mechanism by which cumin oil brings about its hypoglycemic action is potentiating the insulin effect, either by increasing the pancreatic secretion of insulin from cells of islets of Langerhans or its release from bound insulin. In this context a number of other plants and plant products have also been observed to have hypoglycemic effects (14).

The results of this study show that supplementation of cumin oil for 5 weeks

prevents elevation of plasma lipid. Hypolipidemic effect of cumin oil can be explained as a result of direct reduction in the blood glucose concentration. In addition, cumin oil is known to have antioxidant properties and this may reduce the susceptibility of lipid oxidation and stabilize the membrane lipids by reducing oxidative stress. Al-shamamny et al. have observed similar results (16)

Our findings indicate that cumin oil gains anti-obesity effect lowers the blood glucose and plasma lipids as compared to control group and sibutramine group.

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