



# Antihypertensive and Hypocholesterolemic Activity of a Novel Herbal Formulation of Fenugreek, Cumin and Ajowan in Rats

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## Abstract

**Aims:** To elucidate the antihypertensive and hypocholesterolemic effects of fenugreek, cumin, ajowan and their combined extracts along with enalapril maleate and fenofibrate in conscious 1K-1C hypertensive and hypercholesterolemic rats respectively.

**Materials and methods:** Male Sprague-Dawley hypertensive rats were administered fenugreek, cumin, ajowan and their combined alcoholic extracts, which were compared with enalapril maleate (per oral). Blood pressure readings were taken on each of 3 days prior to drug treatment. Rats were divided into groups of six animals per dose, and each animal was used as its own control. Pre-drug and 2 hours post-drug blood pressure readings were recorded using the tail-cuff method. The antihypercholesterolemic study was carried out for 28 days. At the end of the treatment, the animals were fasted for 24 hours prior to the collection of blood samples. Blood was collected on the 8th, 15th and 29th days for measurement of plasma cholesterol, triglycerides and high density lipoprotein-cholesterol estimations using standard kits. The results were analyzed statistically using either paired *t*-test or ANOVA, followed by Dunnett's test;  $p < 0.05$  was considered to be significant.

**Results:** The seeds' of alcoholic extracts and their combination exhibited significant antihypertensive and antihypercholesterolemic effects at 300 and 500 mg (*per os*) in conscious 1K-1C hypertensive and hypercholesterolemic rats, at  $p < 0.05$  when compared to enalapril maleate and fenofibrate respectively.

**Conclusions:** The study reveals the antihypertensive and antihypercholesterolemic activity of fenugreek, cumin, ajowan and their combined extracts in hypertensive and hypercholesterolemic rats. The combined extract seems to be promising for the development of a phytomedicine for hypertension and atherosclerosis.

## Introduction

Hypertension and atherosclerosis are the major causes of morbidity and mortality in industrialized societies, with hypertension being an atherosclerosis factor linked to cardiovascular risk.<sup>1,2</sup> Myocar-

dial infarction and cerebral ischemia are the major manifestations of circulatory diseases, such as hypertension and atherosclerotic vascular disease, which continue to be important public health risk factors in developed nation.<sup>3,4</sup> The classic manifestations of hypertensive end-organ damage include vascular and hemorrhagic stroke, retinopathy, coronary heart disease/myocardial infarction and heart failure, proteinuria and renal failure, and in the vasculature, atherosclerotic changes, including the development of stenoses and aneurysms,<sup>5</sup> result from prolonged rises in blood pressure.<sup>6</sup>

Hyperlipidemia (hypercholesterolemia) is a major cause of atherosclerosis- and atherosclerosis-associated conditions, such as coronary heart disease, ischemic cerebrovascular disease, and peripheral vascular disease.<sup>3-5</sup> Animal and human studies have established the role of cholesterol in the development and progression of atherosclerosis. Low density lipoprotein (LDL)-cholesterol constitutes approximately 60–70% of total serum cholesterol. Epi-

**Keywords:** Hypertension; Hypolipidemic; Fenugreek; Cumin; Ajowan; Atherosclerosis.

**Abbreviations:** HDL, high density lipoprotein; LDL, low density lipoprotein; VLDL, very low density lipoprotein.

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demioleological studies directly implicated LDL-cholesterol in the development of atherosclerosis and coronary heart disease. Atherosclerosis is three times more common in patients with hypertension,<sup>7,8</sup> and there is a positive although not linear correlation between high blood pressure and atherosclerosis.<sup>9</sup> Atherosclerosis is a complex multifactorial inflammatory disease, characterized by the presence of lesions due to the accumulation of lipids in the walls of large- and medium-sized arteries.

The clinical manifestation of atherosclerotic plaque formation is acute vascular occlusion due to the formation of a thrombus or clot, which can lead to ischemia of vital organs, such as heart causing myocardial infarction, brain resulting in strokes, and lower extremities causing peripheral artery disease.<sup>10,11</sup> Clinically, many antihypertensive drugs are effective in reducing morbidity and mortality from atherosclerotic-mediated cardiovascular events. Since hypertension is a long-term disorder, the most perplexing problems in the management of hypertension are the adverse effects of antihypertensive drugs or their metabolites on the cardiovascular system.<sup>12</sup> Today, use of herbal medicinal products and supplements has increased tremendously from the past three decades previous, with not less than 80% of people worldwide relying on them.<sup>13</sup> Medicinal plants represent a great deal of untapped reservoir of drugs and the structural diversity of their component molecules makes a valuable source of novel lead compounds.<sup>14,15</sup>

*Trigonella foenum-graecum* L (Leguminosae), commonly known as fenugreek, possess laxative, expectorant, hypocholesterolemic and hypoglycemic activities.<sup>16,17</sup> Cumin (*Cuminum cyminum*), belonging to the family Umbelliferae, is a small slender annual herb about one foot in height, with grayish fruits, tapering towards both ends, and being compressed laterally.<sup>18</sup> Fruits of cumin possess antimicrobial, mutagenic and estrogenic effects and also influence blood clotting.<sup>17</sup> Ajowan (*Trachyspermum ammi*), belonging to the family Umbelliferae, is largely cultivated in Eastern India. The fruits are used as anthelmintic and hypotensive agents.<sup>18,19</sup> The drug also intensifies coronary and myocardial circulation, acting as a mild positive inotrope. Fenugreek seeds have been shown to possess antihypertensive and hypolipidemic activity.<sup>20</sup>

Although the complementary and alternative medicine literature reported several studies with scientific evidence involving each herb towards the treatment of hypertension and atherosclerosis, no scientific study has been reported so far that evaluated the antihypertensive and hypolipidemic activity in their combinations as herbal formulations containing combined alcoholic extracts of fenugreek, cumin and ajowan. Therefore, the present study was designed to explore the effects of combined extracts of fenugreek, cumin and ajowan on blood pressure and the lipid profile in albino Wistar and Sprague-Dawley rats.

## Materials and methods

### Animals

Albino rats of either sex (180–230 g) were used for the hypocholesterolemic study, whereas male Sprague-Dawley rats (250–300 g) were used for the antihypertensive study. Rats were procured from Venkatesh Enterprises, Bangalore, India. They were housed in groups of six in clean acrylic cages. The animals were maintained under natural day and night cycle. They were acclimatized for 1 week to the laboratory condition before starting the experiment. They were given the diet of standard pellet (Mahaveer Enterprises, Hyderabad, India) and allowed free access to food and

water. All the animal studies were conducted in accordance with the guidelines for animal care. The study obtained prior approval from the Institutional Animal Ethical Committee, Hyderabad, with CPCSEA registration number 1015/PO/Re/S/06/CPCSEA, New Delhi (India).

### Preparation of extracts

The Methi (fenugreek), Zeera (cumin) and Ajmud (ajowan) seeds were procured from the local market of Hyderabad, Telangana (India). The seeds were authenticated from the Botanical Survey of India, Pune (Maharashtra) (Voucher specimen no. 557). About 150 g of powdered seeds of fenugreek, cumin, and ajowan were packed separately in the thimble of a soxhlet extractor and powders were subjected to extraction with 95% alcohol. The procedure was continued for about 20 cycles for each drug, one after another. The temperature was maintained around 60°C on an electric heating mantle with thermostat control. The extracts obtained were then distilled and the concentrated extracts were evaporated using a water bath to obtain a thicker mass.

### Drugs used

Alcoholic extracts of fenugreek, cumin, ajowan and their combination in the proportion of 75:25:25 for fenugreek:cumin:ajowan respectively. Standard drugs like enalapril maleate (Evans, 10 mg; Cadila Health Care Ltd, Ahmedabad, India) and marketed preparation of fenofibrate (200 mg/kg oral) were used. The test drugs (300 mg/kg body weight) and combined extracts (300 and 500 mg/kg body weight) were administered orally as a suspension made using 1% gum acacia. The standard drug was administered as a suspension in distilled water at 3 mg/kg body weight (*per os*). The oral drug administration was carried out making use of a pediatric oral feeding catheter and mouth gag, taking care to avoid intubation of the trachea. The doses of alcohol extracts were selected after performing acute toxicity studies according to the OECD Guidelines.

## Methods

### Antihypertensive activity

#### Induction of experimental hypertension

Animals were starved for 24 h prior to performing the surgical procedure, with free access to water. Sprague-Dawley rats weighing 250–300 g were anesthetized. The fur on the back was shaved and the skin disinfected. In the left lumbar area of the flank, an incision was made parallel to a long axis of the rat. The renal pedicle was exposed, with the kidney retracted to the abdomen. The renal artery was traced out and a U-shaped silver clip was clipped around it, near the aorta. Using a special forceps, the size of the clip was adjusted so that the internal gap ranged from 0.25–0.38 mm. The right kidney was removed after tying of the renal pedicle.

The skin incisions were closed and appropriate treatment was given to prevent infection to the wounds. Four to five weeks after clipping, blood pressure was measured and rats with values higher than 150 mmHg were selected for the experiments. Blood pressure readings were taken on each of 3 days prior to drug treatment. Rats

**Table 1. Comparison of the effects of alcoholic extracts**

Group	Before treatment	After treatment	Percentage inhibition
Fenugreek, 300 mg/kg	176.1 ± 5.23	160.5 ± 4.64	9.71
Cumin, 300 mg/kg	178.7 ± 3.04	161.7 ± 7.03	10.5
Ajowan, 300 mg/kg	160.9 ± 3.81	149.7 ± 3.25	7.48
Combined extract, 300 mg/kg	172.7 ± 9.96	139.4 ± 7.16*	23.8
Combined extract, 500 mg/kg	169.8 ± 7.74	139.7 ± 5.67*	21.5
Enalapril maleate, 3 mg/kg	162.2 ± 5.26	81.86 ± 5.28**	98.1

Before and after treatment on blood pressure (mmHg) in 1K-1C Goldblatt hypertensive rats. Each value represents mean ± standard error of the mean for groups of  $n = 6$ . \* $p < 0.05$ , \*\* $p < 0.01$ .

were divided into groups of six animals per dose and each animal was used as its own control. Pre-drug and 2-h post-drug pressure readings were taken.

#### Measurement of systolic blood pressure

The systolic blood pressure was measured by the tail-cuff method using a Harvard noninvasive blood pressure apparatus. The acquisition of the data was made by the Biopack Data acquisition system and visualized on the computer screen. The tail-cuff was inflated and then deflated. Pulsations disappeared when the cuff was inflated. When the cuff started deflating, pulsation started appearing when pressure in the cuff equaled systolic pressure. The cuff was attached to the Harvard noninvasive blood pressure monitor and the blood pressure was recorded.

#### Hypocholesterolemic activity

Albino rats of either sex, weighing 200–250 g, were maintained under controlled conditions [24 ± 1 °C; 30–70%; light-dark (10/14h) cycle] with free access to food and water.

#### Collection of blood samples

The animal was secured by tying in the supine position on a small operation table after anesthetizing with anesthetic ether. A 23-g hypodermic needle attached to a 2-mL syringe was introduced into the heart, with the guidance of cardiac pulse. About 1 mL of blood was withdrawn at a time. Throughout the procedure, the animal was maintained under ether anesthesia. After the procedure, about 1.0 mL of normal saline was injected intraperitoneally into the animal. The animal was placed back in their respective cage after complete recovery from the anesthesia.

The study was carried for 28 days. Hyperlipidemia was induced in rats by administering cholesterol in coconut oil (15 mg/kg, p.o.) for 7, 14 and 28 days. Concomitantly, the alcoholic extracts of fenugreek, cumin, and ajowan were administered at the dose of 300 mg/kg *per os*, whereas their combined alcoholic extracts were administered at the two different doses of 300 mg/kg and 500 mg/kg *per os* respectively. The standard drug, fenofibrate, was administered at the dose of 200 mg/kg *per os*. The control animals received the appropriate amount of vehicle. At the end of the treatment, the animals were fasted for 24 h prior to the collection of blood samples. The blood was collected by cardiac puncture on the 8th, 15th and 29th days for measurement of plasma cholesterol, triglycerides and high density lipoprotein (HDL)-cholesterol estimations using

standard kits.

## Results

### Antihypertensive activity

Effect on blood pressure in conscious 1K-1C Goldblatt hypertensive rats

Half an hour after oral administration of the alcoholic extracts of fenugreek, cumin and ajowan and their combined extracts at the dose of 300 mg/kg or 500 mg/kg body weight, the systolic blood pressure was measured by the tail-cuff method. The blood pressure gradually decreased and reached a minimum level after 30 min of drugs' administration in the 1K1C Goldblatt hypertensive rats (Table 1).

In extracts-treated groups of fenugreek, cumin, and ajowan, the systolic blood pressure reduced significantly ( $p < 0.05$ ) from 176.1 ± 5.226 mmHg to 160.5 ± 4.635 mmHg, 178.7 ± 3.042 mmHg to 161.7 ± 7.032 mmHg and 160.9 ± 3.813 mmHg to 149.7 ± 3.248 mmHg respectively. In groups treated with combined alcoholic extract of fenugreek, cumin and ajowan, the systolic blood pressure significantly ( $p < 0.05$ ) reduced from 172.7 ± 9.96 mmHg to 139.4 ± 7.155 mmHg and from 169.8 ± 7.735 mmHg to 139.7 ± 5.67 mmHg at 300 mg/kg and 500 mg/kg respectively, in the same ratio. In the same way, enalapril maleate was given at the dose of 3 mg/kg orally and after 1 h of treatment, a drastic reduction in blood pressure was observed, with the mean systolic blood pressure reduced from 162.2 ± 5.26 mmHg to 81.86 ± 5.28 mmHg; as well, the hypotensive effect was long lasting, with  $p < 0.01$  (Fig. 1). The combined alcoholic extracts of fenugreek, cumin and ajowan elicited a significant decrease in systolic blood pressure in a dose-dependent manner compared to the individual alcoholic extracts. However, the mean systolic blood pressure reduction in enalapril treated group was more than the combined extract-treated group.

### Hypocholesterolemic activity

Total cholesterol estimations (mg %)

The mean values 83.52 ± 2.26, 107.4 ± 3.372, 103.2 ± 5.612, 98.4 ± 4.472, and 91.6 ± 2.493 of fenofibrate, fenugreek, cumin, and combined extract at a dose of 300 mg/kg- or 500mg/kg-treated groups respectively showed significant ( $p < 0.01$ ) decrease in total cholesterol compared to the control with mean value of 157.9 ± 4.634. Similarly, the mean value 140.1 ± 4.794 of ajowan showed

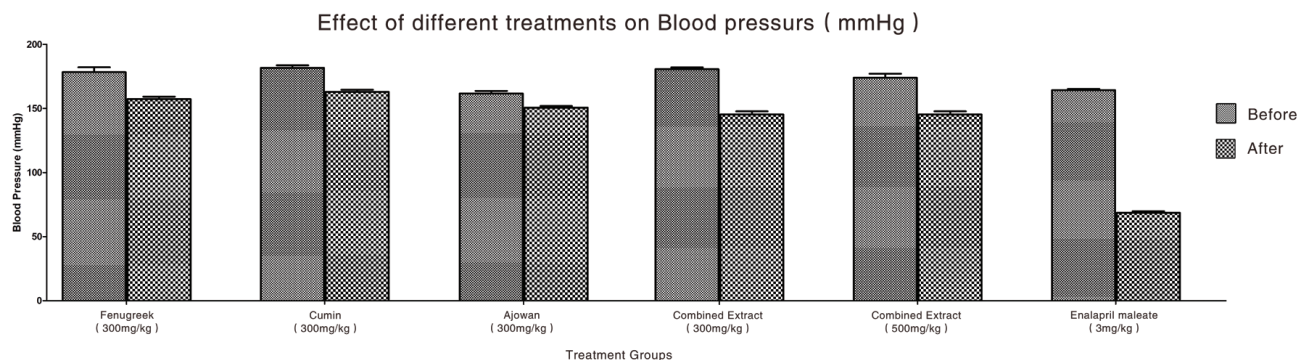


Fig. 1. Effect of different treatments on blood pressures (mmHg).

Table 2. Comparison of the effects of alcoholic extracts on hypocholesterolemic parameters in rats

Treatment group	Total cholesterol, mg %	Triglycerides, mg %	HDL, mg %	LDL, mg %	VLDL, mg %	LDL/HDL, mg %
Vehicle (control)	157.9 ± 4.63	88.83 ± 1.716	12.9 ± 1.18	127.2 ± 4.42	17.75 ± 0.34	10.29 ± 1.04
Fenofibrate (10 mg)	83.52 ± 2.26**	47.4 ± 0.94**	30.25 ± 1.72**	43.79 ± 3.32**	9.38 ± 0.16**	1.49 ± 0.19**
Fenugreek (300 mg)	107.4 ± 3.37**	74.63 ± 3.51**	25.93 ± 1.57**	66.93 ± 2.22**	14.23 ± 0.81**	2.63 ± 0.14**
Cumin (300 mg)	103.2 ± 5.61**	73.63 ± 3.62**	26.73 ± 1.25**	61.93 ± 6.54**	14.7 ± 0.73**	2.38 ± 0.32**
Ajowan (300 mg)	140.1 ± 4.79*	80.15 ± 1.10*	19.45 ± 1.03*	108.5 ± 3.09*	16.0 ± 0.19*	5.47 ± 0.35**
Combined extract (300 mg)	98.4 ± 4.47**	52.85 ± 1.27**	22.63 ± 2.10**	65.58 ± 4.22**	10.52 ± 0.25**	3.03 ± 0.34**
Combined extract (500 mg)	91.6 ± 2.49**	52.2 ± 0.73**	28.78 ± 1.31**	54.13 ± 4.50**	10.51 ± 0.14**	1.93 ± 0.23**

Each value represents mean ± standard error of the mean for groups of  $n = 6$ . \* $p < 0.05$ , \*\* $p < 0.01$  vs. control group.

significant ( $p < 0.05$ ) decrease in total cholesterol compared to the control with mean value of  $157.9 \pm 4.634$  (Table 2, Fig. 2).

Triglycerides' estimations (mg %)

The groups treated with fenofibrate, fenugreek, cumin, and com-

binated extract at a dose of 300 mg/kg or 500 mg/kg with mean values of  $47.4 \pm 0.942$ ,  $74.63 \pm 3.509$ ,  $73.63 \pm 3.616$ ,  $52.85 \pm 1.271$ , and  $52.2 \pm 0.7262$  respectively showed significantly ( $p < 0.01$ ) decreased triglycerides compared to the control group with a mean value of  $88.83 \pm 1.716$ . Similarly, the mean value  $47.4 \pm 0.942$  of ajowan showed significant ( $p < 0.05$ ) decrease in HDL-cholesterol compared to control (Table 2, Fig. 3).

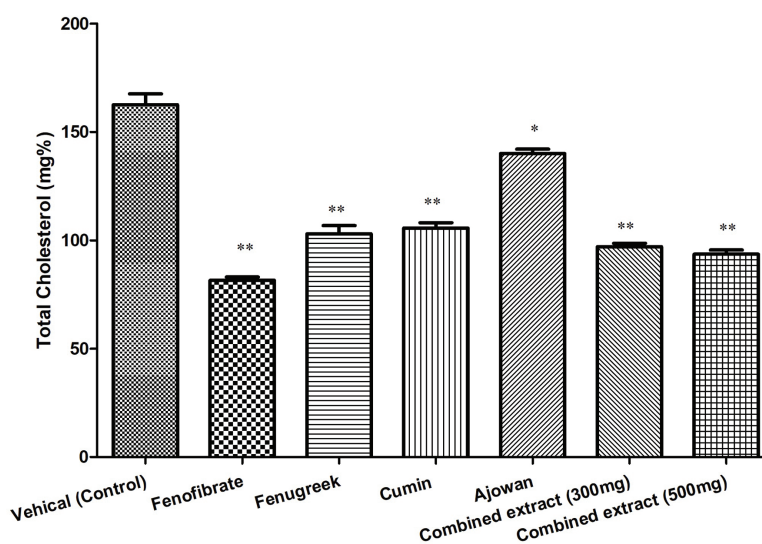


Fig. 2. Total cholesterol (mg%) in various treated hypercholesterolemic animals. \* $p < 0.05$ ; \*\* $p < 0.01$ .



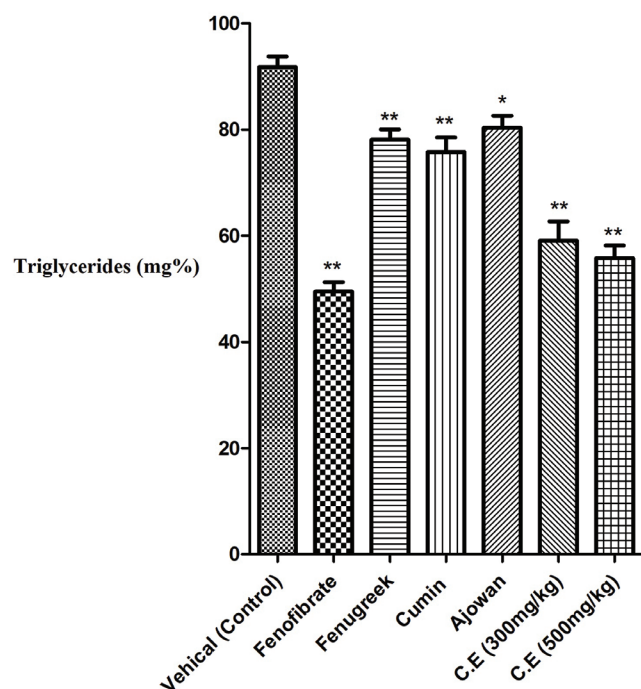


Fig. 3. Triglycerides (mg%) in various treated hypercholesterolemic rats. \* $P < 0.05$ ; \*\* $P < 0.01$ .

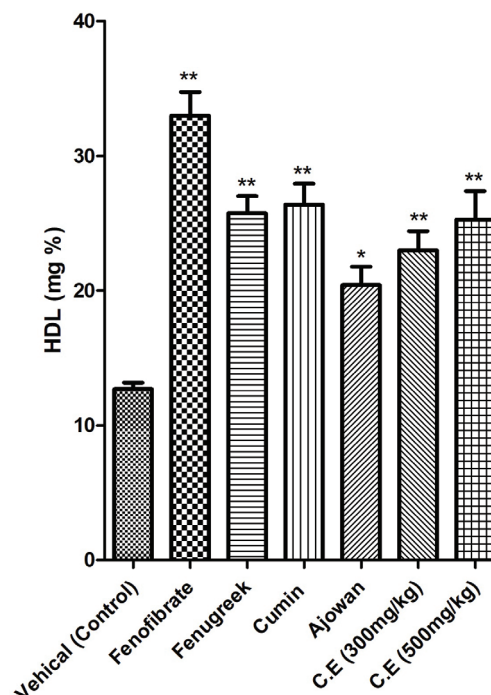


Fig. 4. HDL (mg%) in various treated hypercholesterolemic rats. \* $P < 0.05$ ; \*\* $P < 0.01$ .

#### HDL-cholesterol estimations (mg %)

The mean values  $30.25 \pm 1.715$ ,  $25.93 \pm 1.574$ ,  $26.73 \pm 1.245$ ,  $22.63 \pm 2.095$ , and  $28.78 \pm 1.305$  of fenofibrate, fenugreek, cumin, and combined extract at a dose of 300 mg/kg- or 500 mg/kg-treated groups respectively showed significant ( $p < 0.01$ ) decrease in HDL-cholesterol compared to the control with mean value of  $157.9 \pm 4.634$ . Similarly, the mean value  $19.45 \pm 1.034$  of ajowan showed significant ( $p < 0.05$ ) decrease in HDL-cholesterol compared to the control with  $157.9 \pm 4.634$  (Table 2, Fig. 4).

#### LDL-cholesterol estimations (mg %)

Fenofibrate, fenugreek, cumin, and combined extract-treated groups with mean values of  $43.79 \pm 3.319$ ,  $66.93 \pm 2.217$ ,  $61.93 \pm 6.535$ ,  $65.58 \pm 4.224$  and  $54.13 \pm 4.495$  respectively showed significant ( $p < 0.01$ ) change in LDL-cholesterol compared to that of the control group with a mean value of  $127.2 \pm 4.419$ . Similarly, the mean value  $108.5 \pm 3.085$  of ajowan showed significant ( $p < 0.05$ ) decrease in LDL-cholesterol compared to control (Table 2, Fig. 5).

#### VLDL-cholesterol estimations (mg %)

The mean values  $9.38 \pm 0.1622$ ,  $14.23 \pm 0.811$ ,  $14.7 \pm 0.733$ ,  $10.52 \pm 0.2496$ , and  $10.51 \pm 0.1367$  of fenofibrate, fenugreek, cumin, and combined extract at a dose of 300 mg/kg- or 500mg/kg-treated groups respectively showed significant ( $p < 0.01$ ) decrease in very VLDL-cholesterol compared to the control with mean value of  $17.75 \pm 0.3364$ . Similarly, the mean value  $16 \pm 0.1915$  of ajowan showed significant ( $p < 0.05$ ) decrease in VLDL-cholesterol compared to the control (Table 2, Fig. 6).

#### LDL/HDL ratio (mg %)

Fenofibrate, fenugreek, cumin, ajowan, and combined extract-treated groups with mean values of  $1.492 \pm 0.189$ ,  $2.625 \pm 0.1418$ ,  $2.375 \pm 0.3185$ ,  $3.033 \pm 0.3355$ , and  $1.925 \pm 0.2295$  respectively showed significant ( $p < 0.01$ ) change in LDL-cholesterol compared to that of the control group with a mean value of  $10.29 \pm 1.036$  (Table 2, Fig. 7).

## Discussion

In the present study, antihypertensive and hypocholesterolemic activity of fenugreek, cumin and ajowan extracts individually as well as in combination were investigated, both in conscious 1K-1C Goldblatt hypertensive and hypercholesterolemic rats. The pharmacological data from the present study showed that there was decrease in the blood pressure levels in conscious 1K-1C Goldblatt hypertensive rats when treated with oral administration for alcoholic extracts of fenugreek, cumin and ajowan, but the significant decrease was found with combined extract of fenugreek, cumin and ajowan at two different doses (*i.e.* 300 mg/kg and 500 mg/kg *per os* and enalapril maleate at a dose of 3 mg/kg *per os*). However, the reduction in blood pressure was not as long lasting as that of enalapril at 3 mg/kg. The reduction was statistically significant with the combined extracts at the two different doses levels (*i.e.* 300 mg/kg and 500 mg/kg), thus showing good antihypertensive activity in 1K-1C Goldblatt hypertensive rats.

Several fibric acid derivatives (fibrates) are available, including bezafibrate, ciprofibrate, clofibrate, and fenofibrate. But, these fibrates, in addition to their effects on LDL, can cause increased lithogenicity of bile and increased gallstone incidences, decreased libido, muscle pain, and abdominal discomfort. These effects pro-

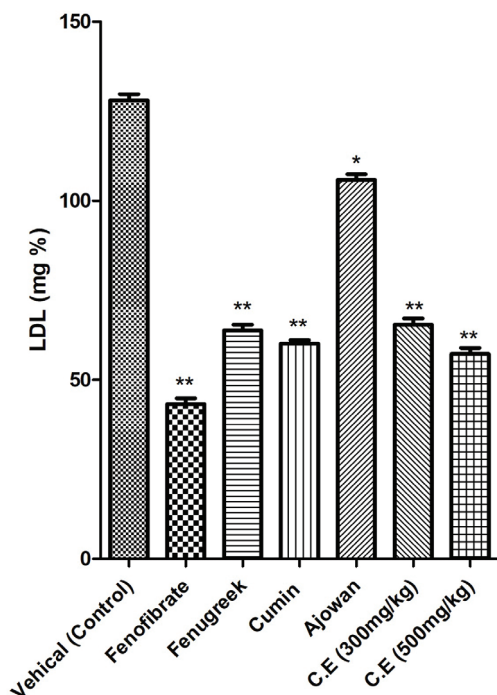


Fig. 5. LDL (mg%) in various treated hypercholesterolemic rats. \* $P < 0.05$ ; \*\* $P < 0.01$ .

mote the need to invent better and safer drugs for long-term use. Keeping this in view, the hypocholesterolemic properties of an ethanol extract from defatted fenugreek (*Trigonella foenum graecum*) seeds were investigated. Reduction in plasma cholesterol levels

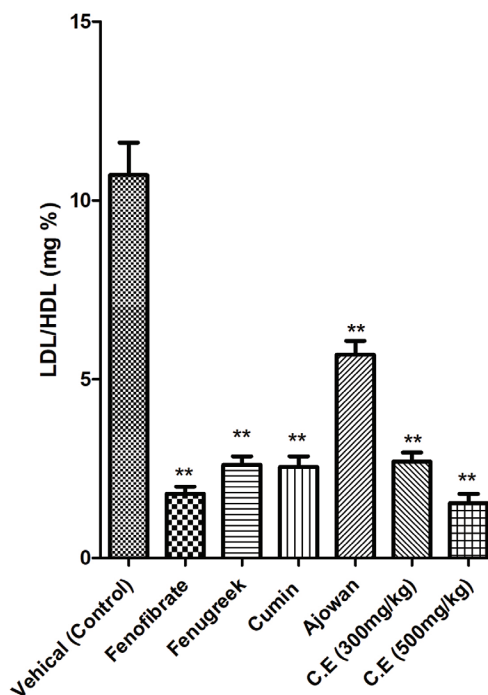


Fig. 7. LDL/HDL (mg%) in various treated hypercholesterolemic rats. \*\* $P < 0.01$ .

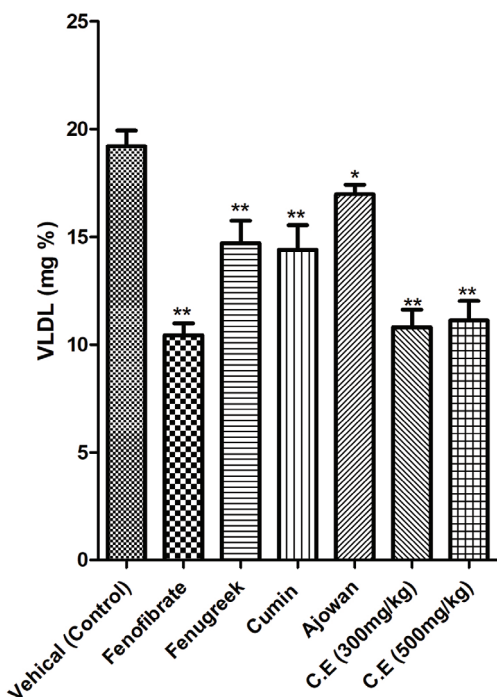


Fig. 6. VLDL (mg%) in various treated hypercholesterolemic rats. \* $P < 0.05$ ; \*\* $P < 0.01$ .

ranged from 18–20% and a tendency for lower concentrations of liver cholesterol was observed. These results indicated that the ethanol extract from fenugreek seeds contained hypocholesterolemic components, which appear to be saponins that interact with bile salts in the digestive tract. Cumin (*Cuminum cyminum*) has been reported to produce significant decreases in plasma and tissue cholesterol, phospholipids, free fatty acids, and triglycerides. However, there are no such reports which are known to claim that ajowan (*Trachyspermum ammi*) possess antihyperlipidemic properties.

The pharmacological data of the present study indicate that alcoholic extracts of fenugreek, cumin, ajowan, and their combination are more potent antihypertensives and are equally effective in lowering total cholesterol, LDL, VLDL, triglycerides, and LDL/HDL ratio, and work by significantly increasing HDL. The significant antihypertensive and antihypercholesterolemic effect by treatment with the combined extract at two different doses 300 mg/kg and 500 mg/kg indicate synergistic interaction between these agents. No such interactions have been reported in the literature. The mechanism, though, appears to be pharmacodynamic in nature. The contribution of pharmacokinetic components cannot be ruled out. Hence, it is very difficult to comment on the mechanism of antihypertensive and antihypercholesterolemic effects of alcoholic extracts. However, considering the rich content of saponins, flavonoids, terpenes and glycosides, and the reported pharmacological effects of the extracts, the observed antihypertensive and antihypercholesterolemic activity in the present study could be attributed to the saponins, flavonoids, terpenes, and glycosides, a theory which is substantiated by earlier reports.

## Conclusions

The combination of alcoholic extracts of fenugreek, cumin and

ajowan (300 mg/kg and 500 mg/kg) were found to be more effective for antihypertensive and antihypercholesterolemic activities than the individual extracts. As all the three drugs are widely used in Indian foods and traditional medicine, they are known to be absolutely nontoxic to human beings. Hence, further studies are required to find out the clinical implication of these drugs in combination.

### Future research directions/prospective/prediction

The further studies are being planned to confirm the mechanism of action of these drugs in various animal models and to determine the typical dosage regimens necessary to assess their pharmaceutical avenues.

### Funding

The study did not receive any funding or grants, and was carried out without any financial support.

### Conflict of interest

The author has no conflict of interest related to this publication.

### Author contributions

All works are done by (SG) as a part of patent work.

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