Anti-Hyperlipidemic Effect of *Fumaria officinalis* in High-Fat-Diet Induced Hyperlipidemic Rats

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ABSTRACT

The present study was designed to investigate the antihyperlipidemic effect of aqueous ethanolic extract from the aerial parts of *Fumaria officinalis* in high-fat-diet induced hyperlipidemic rats. Antihyperlipidemic drug simvastatin (10 mg/kg) was used as a standard drug. The rats were fed with high-fat-diet for the induction of hyperlipidemia for two weeks. Aqueous ethanolic extract of *Fumaria officinal* was orally administered in doses of 150, 200 and 250 mg/kg/day to rats fed with high-fat-diet. At the end of experimental period, the rats were sacrificed, and the lipid profile was examined by standard procedures and histopathology of liver sections was also performed. *Fumaria officinalis* has revealed a significant ($p<0.05$) dose dependent decrease in the levels of serum total cholesterol, triglycerides, LDL, VLDL and non-significant increase in the level of serum HDL like standard drug simvastatin. It is concluded that aqueous ethanolic extract of *F. officinalis* aerial parts possess a dose-dependent significant antihyperlipidemic activity against high-fat-diet induced hyperlipidemic rats hence it could be a potential herbal medicine for the treatment of hyperlipidemia.

Key words:

Hyperlipidemia, High-fat-diet, Simvastatin, Lipid profile, Rats, *Fumaria officinalis*.

Tob Regul Sci. ™ 2023;9(1): 3618-3629

DOI: doi.org/10.18001/TRS.9.1.253

INTRODUCTION

Hyperlipidemia is defined as the elevated levels of serum total cholesterol (TC), triglycerides (TG), LDL, IDL and VLDL. Hyperlipidemia is responsible for the progression of atherosclerosis and various complications associated with it like premature coronary heart disease, stroke, heart attack, myocardial infarction and pancreatitis (Alam *et al.,* 2018). The most potent lipid-lowering agents which are currently available are the HMG- CoA reductase inhibitors, also known as statins (Farnier and Davignon, 1998). Bile acids resins, activator of lipoprotein lipase (fibric acid derivatives), inhibitor of lipolysis and triglyceride synthesis (nicotinic acid) and fish oil supplements are other drugs which are being used for the treatment of hyperlipidemia (Dhaliya *et al.,* 2013). The consumption of synthetic hypolipidemic drugs is linked with adverse effects such as nausea, indigestion or upset stomach, dry skin, flushing of the skin, muscle inflammation, gastritis, hyperuricemia and abnormal liver function (Kanakavalli *et al.,* 2014). According to World Health Organization (WHO), approximately 80% of the world's population in developing countries relies on traditional medicines for their primary health care, which are mostly derived from plants, (Ozkan *et al.,* 2016).

Fumaria officinalis Linn. belongs to family Fumariaceae, also known as fumitory or earth smoke, is a medicinal plant which plays an important role in herbal medicines (Hentschel *et al.,* 1995). It is distributed in Pakistan (Ahmad *et al.,* 2009), Iran (Keshavarzi *et al.,* 2011), and Western part of Europe (Paltinean *et al.*, 2017). It is helpful in rheumatism, abdominal cramps, fever, conjunctivitis and diarrhea . Recent studies carried out on *Fumaria officinalis* demonstrated its pharmacological use in the treatment of hyperglycemia, hyperthermia, helminthic infections and as antibacterial agent (Sajjad *et al.,* 2015). It is hypothesized that the elevated liver enzymes and lipid profile could be reduced by Fumaria. As it has not been scientifically investigated for the hypolipidemic effects of *F. officinalis,* therefore, the current research study was conducted to explore its lipid-lowering activity.

MATERIALS AND METHODS

Chemicals and drugs: Simvastatin was received from Medpak Pharmaceuticals, Lahore, Pakistan. The cholesterol and cholic acid were purchased from Uni-Chem, USA. Coconut oil, banaspati ghee and all other chemicals used in this research study were of analytical grade.

Animals: Adult Sprague-Dawley rats of either sex (200-250g) were used in the current study. The animals were kept at the animal house of Lahore College of Pharmaceutical Sciences (LCPS), Lahore under controlled environmental conditions of room temperature (22 ± 2°C), relative humidity (50% ± 5%), and 12 h light and dark cycle. The animals were housed in the

colony cages (six rats per cage) and were provided normal pellet feed and water *ad libitum*. All the animals were acclimatized to the laboratory environment for 5 days. The animals were fasted overnight just prior to experiment but were allowed free access to water. All the experiments were carried out in accordance with the guidelines of Institutional Animal Ethnical Committee. The study was carried out after obtaining ethical committee clearance from the Institutional Animal Ethnics Committee (Desu and Saileela, 2013).

Composition of high-fat-diet: Cholesterol (2%), cholic acid (1%), banaspati ghee and coconut oil (3:2).

Plant material: Approximately 2 kg of *F.officinalis* plant was purchased from local nursery during the month of March and was authenticated by Dr. Zaheer-ud-din Khan, renowned taxonomist of Government College (GC) University, Lahore. The voucher specimen GC. Herb. Bot.3575 was deposited to Botany Department, GC for future reference.

Preparation of extract: The aerial parts of plant (2kg) were shade-dried and then it was ground into coarsely powdered form. The powdered material was macerated in aqueous ethanol (70:30) with occasional shaking for 15 days. A muslin cloth was used for the filtration of the material and then followed through Whatman qualitative grade 1 filter. This process was repeated twice for 3 days and all the filtrate was combined and dried into thick paste in rotary evaporator under reduced pressure of -760 mm Hg at the temperature of 35 to 45^{0}C. A semi-solid mass of the crude extract was obtained, and percent yield was calculated (Shah and Gilani, 2009***).*** The prepared aqueous ethanolic extract was designated as crude extract Fo. Cr.

Preliminary phytochemical analysis: Preliminary phytochemical screening of *Fumaria officinalis* was performed by diluting the extract with ethanol. Tests were performed for presence of alkaloids, glycosides, flavonoids, tannins, saponins, phenols, phytosterols and starch by following standards procedures.

Acute toxicity testing: Balb-C mice weighing 20-30 g were used in the procedure. The mice were kept fasted overnight, provided only water. The mice were divided into three groups of 9 animals and then treated with graded doses (300, 1000 and 2000 mg/kg) of the extract orally. The toxic symptoms such as behavioral changes, locomotion, convulsions, and mortality were observed in animals for 72 h after the administration of the dose. Mortality in each group was observed for 7 days (Sharma *et al.,* 2012).

High-fat-diet induced hyperlipidemic model: The cholesterol 2% w/w, cholic acid 1% w/w, banaspati ghee (dalda) and coconut oil in the ratio 3:2 w/w were mixed with powdered standard rat chow homogenously to prepare the high-fat-diet (Alamgeer *et al.,* 2014).

Experimental design: Animals were divided into six different groups with six animals in each group. Group 1 served as normal control group and this group did not receive any treatment

except a standard pellet diet. Group 2 served as negative control group. Group 3 served as positive control and was given standard drug simvastatin (10 mg/kg/b. wt) Group 4, 5 and 6 received different doses of Fo.Cr (150, 200 and 250 mg/kg) respectively (Mopuri *et al.,* 2015). Treatment period for all these groups was 14 days.

Collection of blood: At end of experimental period after overnight fasting, rats were anesthetized with chloroform and about 5ml of blood was collected in gel tubes by direct heart puncture. Then blood was left to stand for 30 minutes at room temperature for clotting (Al-Awadi *et al.,* 2013).

Bio-chemical analysis: The serum was analyzed to estimate the serum total cholesterol (TC), triglycerides (TG), high density lipoproteins (HDL), low density lipoproteins (LDL) and very low- density lipoproteins (VLDL) levels (Al- Awadi *et al.*, 2013).

Histopathological Examination: The rats were anaesthetized and executed at the end of the research period. Tissue (liver) obtained from all experimental groups were washed immediately with saline and then fixed in 10% buffered neutral formalin solution. After fixation, the tissue was processed by embedding in paraffin. Then, the tissue was sectioned and stained with hematoxylin and eosin (H&E) and examined under high power microscope (200,400X) and photomicrographs were taken (Al- Awadi *et al.*, 2013).

Statistical Analysis: Data were expressed as mean ± S.E.M. Differences among groups were evaluated by two-way ANOVA by using Graph Pad Prism. p <0.05 was selected for acceptance of statistical significance.

RESULTS

Antihyperlipidemic Activity of Ethanolic Extract of *Fumaria officinalis* in High-Fat-Diet Induced Hyperlipidemic Rats

Effect on Serum Lipid Profile: In high-fat-diet induced group, the values of TC, TG, LDL and VLDL were increased and level of HDL was reduced. In HFD induced group, there was significant (p< 0.05) increase in TC (252 ± 9.65 mg/dL), TG (172.5 ± 13.77 mg/dL), LDL (190.25 ± 9.9 mg/dL) and VLDL (34.5 ± 2.75 mg/dL) as compared to negative control group (121 ± 4.20, 84 ± 2.94 mg/dL, 65.5 ± 4.52 mg/dL and 17 ± 0.57 mg/dL respectively) and non-significant decrease in levels of HDL (27.25 ± 1.25 mg/dL) as compared to negative control group (38.5 ± 1.32 mg/dL). Crude extract of *Fumaria officinalis* (Fo.Cr) showed dose dependent hypolipidemic activity. At dose of 250 mg/kg, it significantly prevented rise in TC, TG, LDL and VLDL as compared with HFD induced group. *Fumaria officinalis* at high dose 250 mg/kg significantly (p<0.05) reduced serum TC to (152.8 ± 2.29 mg/dL) as compared to HFD induced group on 15th day (252 ± 9.65 mg/dL) and serum TG to (85.3 ± 2.63 mg/dL) in comparison to HFD induced group (172.5 ± 13.77 mg/dL). *Fumaria officinalis* also significantly reduced serum

LDL levels to (104 ± 3.49 mg/dL) in comparison with HFD induced group (190.25 ± 9.90 mg/dL), and VLDL (17.25 ± 0.48 mg/dL) as compared to HFD induced group (34.5 ± 2.75 mg/dL) and there was significant increase in serum HDL levels (31.5 ±1.44 mg/dL) as compared to HFD induced group (27.3 ± 1.25 mg/dL). HFD + simvastatin group also significantly decreased TC, TG, LDL and VLDL levels (146.25 ± 9.66 mg/dL, 71.75 ± 4.57 mg/dL, 95.75 ± 9.06 mg/dL and 14.5 ± 0.96 mg/dL) in comparison to HFD induced group (252 ± 9.65 mg/dl, 172.5 ± 13.77 mg/dL, 190.25 ± 9.90 mg/dL and 34.5 ± 2.75 mg/dl) respectively and significant increase in serum HDL levels (36 ±1.41 mg/dL) as compared to HFD induced group (27.3 ± 1.25 mg/dL) as shown in (**Table 1)**

Table 1: Effects of Ethanolic Extract of *Fumaria officinalis* and simvastatin in High-Fat-Diet Induced Hyperlipidemic Rats

SR #	PARAMETER (mg/ dL)	CONTROL	HFD	Simva 10 mg/kg	Fo. Cr 150 mg/kg	Fo. Cr 200 mg/kg	Fo. Cr 250 mg/kg
1	SERUM TC	121 ± 4.2	252 ± 9.65	146.25 ± 9.66	196 ± 5.71*	177.75 ± 8.47**	152.8 ± 2.29**
2	SERUM TG	84 ± 2.94	172.5 ± 13.77	71.75 ± 4.57	86.75 ± 4.89**	85.75 ± 11.78**	85.25 ± 2.63**
3	LDL	65.5 ± 4.52	190.25 ± 9.9	95.75 ± 9.06	149.5 ± 6.81*	129 ± 6.64*	104 ± 3.49**
4	HDL	38.5 ± 1.32	27.25 ± 1.25	36 ± 1.41	29 ± 0.91ns	31 ± 1.32ns	31.5 ± 1.44*
5	VLDL	17 ± 0.57	34.5 ± 2.75	14.5 ± 0.96	17.5 ± 0.95*	17.5 ± 2.25***	17.2 ± 0.48***

Data were expressed as mean ± S.E.M. Differences among groups were evaluated by two-way ANOVA). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, ns= non-significant difference (as compared to HFD control group).

Histopathological Evaluation of Ethanolic Extract of *Fumaria officinalis* in High-fat-diet Fed Rats: In histopathological studies of normal control group, rat liver sections showed normal hepatic architecture whereas the high-fat-diet fed rats' liver sections showed severe vacuolar degeneration of hepatocytes. Cellular swelling was also observed in few microscopic fields. There were micro-vesicles as well as macro-vesicles in the cytoplasm of hepatocytes. There were areas of hepatocytes swelling with reduced sinusoidal space. Rats liver sections treated with the highest dose of Fo. Cr (250 mg/kg) were greatly improved and hepatocytes showed mild degenerative changes. Rats liver sections treated with the medium dose of Fo. Cr (200 mg/kg) exhibited less vacuolar degeneration. Rats liver sections treated with the lowest dose of Fo. Cr (150 mg/kg) showed moderate to severe vacuolation of the cytoplasm of hepatocytes. Hepatocytes swelling was also evident in some areas. The aqueous ethanolic extract of *Fumaria officinalis* treated rats i.e. Fo. Cr 250 mg/kg and simvastatin treated rat liver sections exhibited hepatoprotective activity with less severe vacuolar degeneration as compared to high-fat-diet fed rats, as shown in **(Figure 1-6).**

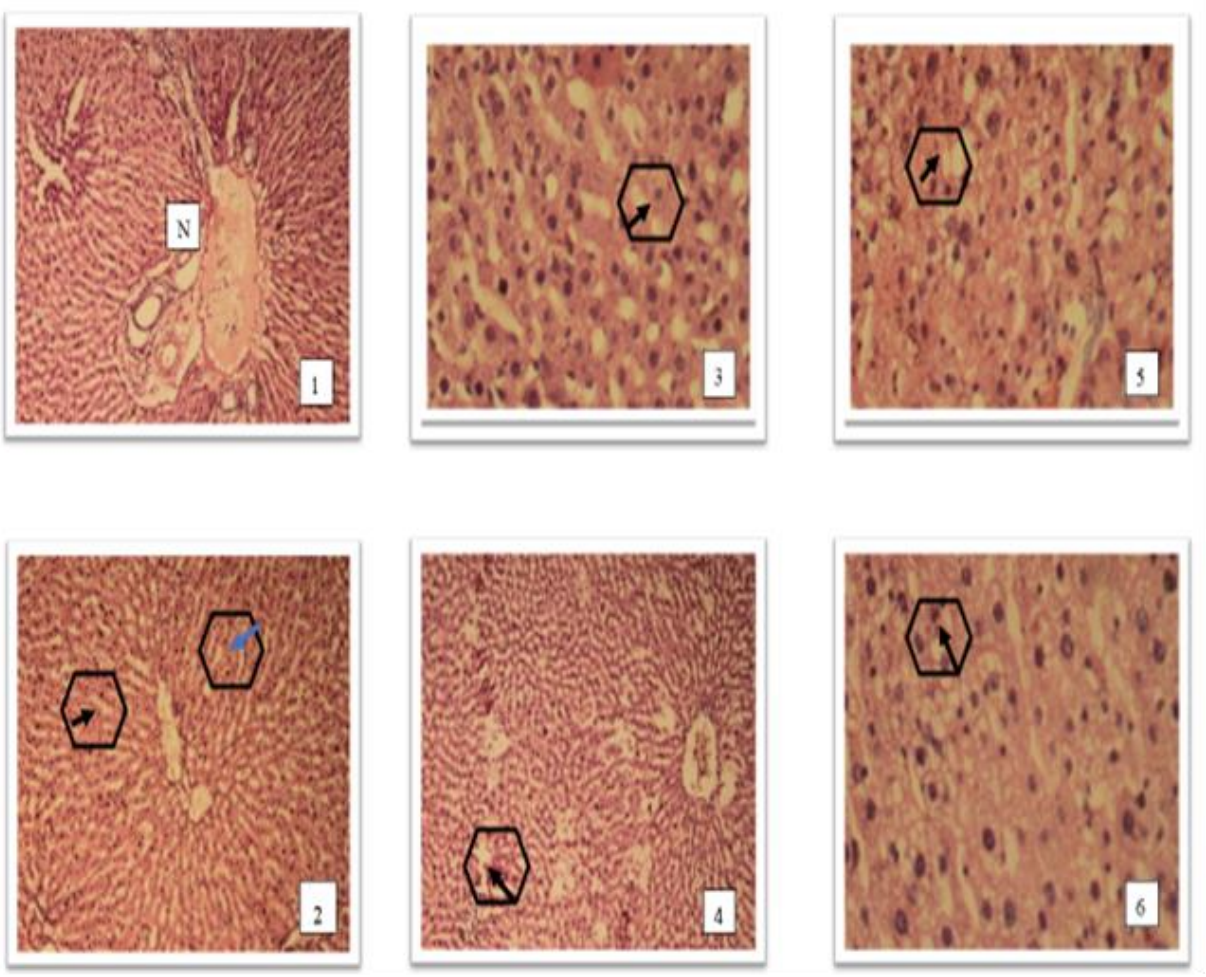

Figure (1) Liver section of normal control rat showing normal hepatic cells (N), **Figure 2** liver section of negative control rat showing macro-vesicles (black arrow) and micro-vesicles (blue arrow) in the cytoplasm of hepatocytes, **Figure 3** liver section of rat treated with simvastatin showing less severe vacuolation (black arrow), **Figure 4** liver section of rat treated with Fo. Cr (250 mg/kg) showing mild degenerative changes (black arrow), **Figure 5** liver section of rat treated with Fo. Cr (200 mg/kg) showing less vacuolar degeneration (black arrow) and **Figure 6** liver section of rat treated with Fo. Cr (150 mg/kg) showing moderate to severe vacuolation (black arrow).

Phytochemical Testing of Aqueous Ethanolic Extract of *Fumaria officinalis*: The crude extract of *Fumaria officinalis* showed the presence of alkaloids, glycosides, flavonoids tannins, phenols, phytosterols and saponins while starch was found to be absent **(Table 2).**

Table 2: Phytochemical Testing of Aqueous Ethanolic Extract of *Fumaria officinalis*

Tests	Results
Alkaloids (Dragendorff' s Reagent/ Wagner's Reagent /Mayer's Reagent)	+
Glycosides (Keller-Kiliani Test/ Legal Test)	+
Flavonoids (Alkaline Reagent Test/ Shinoda's Test)	+
Tannins (Ferric Chloride Test/ Bromine Water Test)	+
Phenols (Lead Acetate Test)	+
Phytosterols (Liebermann-Burchard's Test)	+
Saponins (Foam Test)	+
Starch (Iodine Test)	-

Acute Toxicity Studies: The crude extract of *Fumaria officinalis* was found to be safe up to the dose of 1000 mg/kg p.o. but there were observed some signs of reduced physical activity and anorexia at the dose of 2000 mg/kg p.o.

DISCUSSION

Present study has evaluated the antihyperlipidemic effect of aqueous ethanolic extract of *F. officinalis*. *F. officinalis* is a good source of phytoconstituents. The ethanolic extract contains carbohydrates, saponins, flavonoids, phytosterols, tannins and phenolic compounds (Sharma *et al.,* 2014). Phytochemical testing of *F. officinalis* also showed the presence of isoquinoline alkaloids and polyphenols. The flavonoid glycosides isovitexin, rutin, isoquercitrin and quercitrin are also reported in aerial parts of *Fumaria officinalis* (Paltinean *et al.,* 2016). In the current study, alkaloids, glycosides, flavonoids tannins, phenols, phytosterols and saponins were detected in aqueous ethanolic extract of *Fumaria officinalis* **(Table 2).** Alkaloid has multi pharmacological

effects. Hypolipidemic potential, anti- inflammatory, anti- oxidative, and anti-atherosclerotic properties are the multi therapeutic effects exhibited by alkaloids. The number of experiments and researches have carried out on hyperlipidemia induced animals and the favorable outcome of alkaloid are supported by the results of these studies showing progression of atherosclerosis can be delayed from the use of alkaloids. The isoquinolone alkaloids are considered the most important alkaloids. Isoquinoline alkaloids has a direct anti-atherosclerotic effect (Zhang *et al.,* 2018). Furthermore, (Duke, 2002) also reported the folklore use of *Fumaria officinalis* in atherosclerosis.

Researches have proved that polyphenols are involved in the prevention of hypercholesterolemia. The oxidative change in low density lipoproteins is inhibited by polyphenols, and this is the fundamental component in endothelial lesions occurring in atherosclerosis (Abbas *et al.,* 2017).

Rutin is a natural flavonoid glycoside (vitamin p) which is known to have anti-oxidative properties. TGF-β/Smad signaling pathway is involved in HFD-induced hepatotoxicity and rutin inhibits the hepatotoxicity via suppressing this pathway. Therefore, rutin might be considered as well as a protective agent for hepatotoxicity and responsible for the hypolipidemic activity of *F. officinalis* (AlSharari *et al.,* 2016). Studies report that saponins change the rate of fatty acids oxidation in the liver and reduce the rate of triglycerides biosynthesis so saponins possess hypolipidemic activity (Elekofehinti *et al.,* 2012).

The metabolic power station of mammalians is the liver and is the principal site for cholesterol homeostasis maintenance carried out in many mechanisms. The overall rate of hepatic cholesterol biosynthesis is regulated by HMG-CoA reductase enzyme activity (Trapani *et al.,* 2012).

In current investigation, aqueous ethanolic extract of *Fumaria officinalis* was used to evaluate anti-hyperlipidemic activity in high-fat-diet induced hyperlipidemia in rats. In the present study, the feeding of high-fat-diet (HFD) for successive 14 days significantly elevated serum levels of TG, TC, LDL and VLDL as compared to negative control rats. The extreme burden of cholesterol to the liver was the reason. The liver was unable to metabolize the lipids, so lipid level crossed the normal physiological cholesterol levels. As a result of which, there was elevated levels of cholesterol in the blood circulation (Daradka *et al.,* 2017). The administration of cholesterol in diet increases considerably the hepatic concentrations of the TG and TC in rats indicating hepatic lipid metabolism disturbance. The level of hepatic TG is predominantly controlled by ß-oxidation, secretion and TG synthesis in the lipoproteins form. The accumulation of hepatic TG by high dietary cholesterol is participated in the TG synthesis and fatty acid stimulation in rats (Daradka *et al.,* 2017). HFD intends to increase the oxidative lipid peroxidation was also stimulated by cholesterol present in high-fat-diet (AlSharari *et al.,* 2016; Alamgeer *et al.,* 2014). Fo.Cr significantly decreased the levels of serum cholesterol, TG, LDL and VLDL which are comparable to simvastatin group at dose 250 mg/kg and non-significantly increased HDL levels.

The hypolipidemic activity of Fo.Cr might be due to the presence of some constituents responsible for imbalance in lipid metabolism, inhibition of enzyme. Our findings agree with previous study (Alamgeer *et al.*, 2014).

In the current research, histopathological studies of isolated rat liver sections were also carried out to assess the hepatoprotective activity of the plant. The results revealed that high-fat-diet administration showed severe vacuolar degeneration of hepatocytes and presence of micro-vesicles and macro-vesicles in the cytoplasm of hepatocytes which might be because of increased hepatic cholesterol synthesis in liver with increased hepatic HMG-CoA reductase activity. The plant extract showed hepatoprotective activity and hepatocytes showed mild degenerative changes with aqueous ethanolic extract of *F. officinalis* at the dose of 250 mg/kg. Previously hepatoprotective activity of *F. officinalis* of ethanolic extract was reported in carbon tetrachloride (CCl_4) induced liver damage in rats. The extract significantly reduced the levels of serum marker enzymes like SGPT, SGOT, ALP, bilirubin, cholesterol and triglycerides (Sharma *et al.,* 2012). These results of previous study also support our findings that ethanolic extract of *F. officinalis* has protective effect on hepatocytes.

Conclusion: The results obtained have led to the conclusion that aqueous ethanolic extract of *F. officinalis* produced significant hypolipidemic activity in high-fat-diet induced rats. The lipid lowering activity of *Fumaria officinalis* might be due to the presence of active phytochemicals such as alkaloids, glycosides, flavonoids, phenols and saponins. This study validates traditional use of *F. officinalis*. Further investigations are needed to study other underlying antihyperlipidemic pathways. The clinical relevance of *Fumaria officinalis* on hypolipidemic activity should also be further determined.

Acknowledgement: The authors would like to director and management of Lahore College of Pharmaceutical Sciences, Lahore, Pakistan, for their efforts and facilitations to complete this study.

Authors contribution: The manuscript is based on M. Phil thesis of first author (RS). RS and AA designed the study and performed the experiments. RS conducted this study as a principle investigator. SK: Supervised the study and contributed in data analysis. MNM: Contributed in the write up of the manuscript and technical assistance. RS: Contributed in the data analysis and write up.

GC-MS analysis of *Fumaria officinalis*

	Compounds	Amino acids
1	Palmitic acid	L-Valine

2	Stearic acid	L-Isoleucine
3	Oleic acid	L-Proline
4	Linolenic acid	L-Glycine
5	1-Palmitoyl-glycerol	L-Serine
6	1-Stearoyl-glycerol	L-Threonine
7	Octadecanol	L-Glutamic acid
8	Octacosanol	L-Phenylalanie

Statement of Novelty

It is claimed that the aerial parts of *Fumaria officinalis* possess hypolipidemic activity. However, this is not proved scientifically. To confirm if there is present any antihyperlipidemic potential of *Fumaria officinalis,* we performed the current study to validate hyperlipidemia on rats with high-fat-diet for 14 days, investigated and compared with the standard drug Simvastatin. The results showed significant hyperlipidemic activity. Therefore, first time, we scientifically prove that this plant possesses antihyperlipidemic activity

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