Experimental Research

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The therapeutic effect of alcoholic extract of *Fumaria parviflora* on high-fat diet-induced nonalcoholic fatty liver in rats: an animal experiment

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Background and purpose: Nonalcoholic fatty liver disease (NAFLD) is a growing problem with a significant burden. Lifestyle modification is the recommended treatment, but researchers are exploring other options. This study focused on the effects of *Fumaria parviflora* (FP) extracts on NAFLD induced by a high-fat diet in rats.

Experimental approach: Thirty-five 10-week-old male Wister-Albino rats were divided into seven groups: normal diet control, high fat diet control, high fat diet with oral normal saline gavage, high fat diet with oral Atorvastatin gavage, and three groups receiving high fat diet with FP extract in 200 mg/kg, 400 mg/kg, and 700 mg/kg. Blood samples of rats were used for the measurement of total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP). 1 × 1 cm Liver biopsies were taken, stained with Trichrome Stain (Masson) and Hematoxylin and eosin (H&E) stain for evaluation by a pathologist.

Findings/results: Lab results showed that FP extract inhibits weight gain, has positive effects on triglyceride and alkaline phosphatase levels, and reduces hepatocyte ballooning and inflammation in rats.

Conclusion: FP extract may lower liver enzymes and have a positive impact on triglyceride, LDL, and HDL levels in rats with NAFLD.

Keywords: fumaria parviflora, histopathology, lipid profile, liver function test, nonalcoholic fatty liver disease

Introduction

During the last decade, there was a growing demand for natural plants having diverse activities towards diseases especially chronic ones that need long term managements[1].

Fumaria parviflora, family Papaveraceae (Fumariaceae), also named 'smoke of the earth' is a small plant that grows in many Eastern-Mediterranean countries. The genus Fumaria (Fumariaceae) consists of 60 species widely distributed all over the world and especially in Mediterranean region. It has been utilized in the Asian medical societies in many inflammatory and painful conditions like conjunctivitis and rheumatism[2,3]. In Persian medicine, *Fumaria spp*. (named Shahtareh) used for liver disease[4,5].

Traditionally Extracts of *Fumaria spp*. have been widely utilized for the treatment of various skin problems such as rashes or conjunctivitis. They have also been used for rheumatic diseases, stomach ache, abdominal cramps, fever, diarrhea, syphilis, leprosy, and as a remedy against hepatic and gallbladder diseases. In northern Portugal, these extracts were commonly consumed as tea[6].

In addition, some species of Fumaria, such as *F. parviflora* and *F. officinalis* have been reported to have strong antioxidant activities, likely due to their high phenolic contents[7].

HIGHLIGHTS

- Nonalcoholic fatty liver disease (NAFLD) is a growing problem with a significant burden.
- *Fumaria parviflora* (FP) is a small plant that grows in many Eastern-Mediterranean countries.
- Traditionally extracts of Fumaria spp. have been widely utilized for the treatment of various liver problems such as rashes or conjunctivitis.
- To study the effects of a purified extract of FP on NAFLD induced by a high-fat diet, scientific methods and approaches are necessary.
- FP extract may lower liver enzymes and have a positive impact on triglyceride, low-density lipoprotein, and high-density lipoprotein levels in rats with NAFLD.

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Nonalcoholic fatty liver disease (NAFLD) occurs when over 5% of hepatocytes exhibit steatosis, which is primarily caused by a high-fat diet rather than alcohol consumption, medications, or toxins. It is predicted that by 2030, NAFLD will also become the most common indication for liver transplantation[8].

NAFLD encompasses a wide spectrum of conditions, including nonalcoholic fatty liver (NAFL), which progresses to nonalcoholic steatohepatitis (NASH) in around 10% of patients. NASH is a more severe form characterized by steatosis, hepatocellular ballooning, lobular inflammation, and fibrosis. In 30–50% of cases, NASH could lead to cirrhosis[9], an end-stage liver disease that can only be treated through liver transplantation. Cirrhosis is also a major risk factor for life-threatening conditions such as hepatocellular carcinoma[10].

The prevalence of NAFLD is reported to be between 6 and 35% worldwide, with a specific rate of 32% in the Middle East[11] and since NAFLD can lead to serious conditions, as insulin resistance, type 2 diabetes mellitus, dyslipidemia, and cardiovascular diseases, it requires special attention in public health[12].

Even though no medication is currently approved by the FDA for NAFLD, vitamin E, pentoxifylline, and insulin sensitizers such as glitazones, pioglitazone, and metformin in diabetic patients may be effective[13] since all these medications have side effects and drug interactions, more attention has recently been focused on the benefits of herbal remedies in the treatment of NAFLD and the utilization of traditional herbal medications has increased in many countries in Asia, America, and Europe[14–16].

So far, studies have focused on the effect of *F. parviflora* on improving liver damage and inflammatory and oxidative markers, as well as the lipid profile in diabetic rats[17]. Due to the traditional use of Fumaria in Persian medicine for liver diseases, in this study, we investigated the therapeutic effect of the alcoholic extract of FP on NAFLD induced by a high-fat diet in rats.

Material and methods

Preparation of extract

The dried aerial parts of the *F. parviflora* were powdered, and the hydroalcoholic extract (70:30 ethanol and water ratio) was prepared using the maceration method. This process was repeated three times, each time for 3 days. The extract was then concentrated using a rotary evaporator. The prepared dried hydroalcoholic extract was used to induce nonalcoholic fatty livers in the rats.

Preparation of fatty diet

Fatty liver was induced by a high-fat diet including the following ingredients: (per 100 g) 15 g of rat pellet, 15 grams of dried milk (Nestle), 15 g of plain flour, 5 g of solid oil from animal source, 15 grams of fructose, 6 g of sucrose, 8 g of liquid oil from corn, 6 g of yolk, 15 g of high-fat milk.

The product was flattened on a metallic tray and kept at 3°C for 8 h before being fed to the rats.

Experimental animal procedures

Thirty-five 10-week-old male Wister-Albino rats (255–326 g) were obtained, and kept at a room temperature of 26°C with a 12:12 h light-dark cycle, and had ad libitum access to food and water.

The animals were divided into seven groups, each containing five rats. Group 1 received a standard pellet diet as the normal diet control group. Group 2 received only a high fat diet as the high fat diet control group. Group 3 received a high fat diet and oral normal saline gavage. Group 4 received a high fat diet and oral 40 mg/kg of Atorvastatin gavage. Group 5–7 received a high fat diet and oral gavage of FP Extract at doses 200, 400, 700 mg/kg, respectively. All animals had access to clean water ad libitum.

The first and second groups received their specific diet for 14 weeks, while the remaining groups received a high fat diet without the described intervention for 8 weeks. After this period, they receiving the high fat diet and oral gavage for another 6 weeks. All rats were weighed on a weekly basis.

After 14 weeks from the beginning, blood samples were collected directly from the beating heart of sacrificed rats. These samples were then centrifuged for 15 min at 3000 g, and the resulting serums were used to measure total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) levels.

Additionally, liver biopsies measuring 1×1 cm were taken from the left lobes of the rats' livers and stored in 10% formalin. The samples were then stained with Trichrome Stain (Masson) and Hematoxylin and eosin (H&E) stain. All liver biopsies were evaluated by a blinded pathologist and scored using histological scoring system for nonalcoholic fatty liver disease as a grading tool.

Statistical analysis

Statistical analyses were performed by SPSS version 18 software for windows. Data was tested by one-way Anova and Tukey's post-hoc test. Due to the normal distribution of the study's variable the mode and mean were used as measures of central tendency. As measures of dispersion, we utilized SD, range, and interquartile range. *P*-values lower than 0.05 was considered as significant.

This work has been reported in line with the ARRIVE criteria[18].

Results

All rats were weighed on a weekly basis, and as depicted in Figure 1, all groups showed weight gain. The group that received only the fatty diet (G) exhibited the highest weight gain, while the group that consumed pellet food without any additional gavage intervention (F) experienced the least amount of weight gain.

The measurement of lipid profile, including triglyceride (A), cholesterol (B), LDL(C), and HDL (D), revealed that rats treated with atorvastatin exhibited the lowest level of triglyceride (Fig. 2A). Groups treated with 700 mg/kg and 400 mg/kg of FP extract were the second and third groups with lower triglyceride level. Conversely, the groups treated with 200 mg/kg of FP extract, the group that only received pellet food and the group that received high-fat diet with normal saline showed significantly higher levels of triglycerides. Notably, the group that only received a high fat diet without any intervention via the gavage needle displayed the highest level of triglycerides.

Cholesterol level is shown in Figure 2B, the lowest level of cholesterol was seen in rats receiving atorvastatin and the highest level was seen in rats receiving high fat diet and normal saline via gavage; although rats receiving FP extract have lower level of

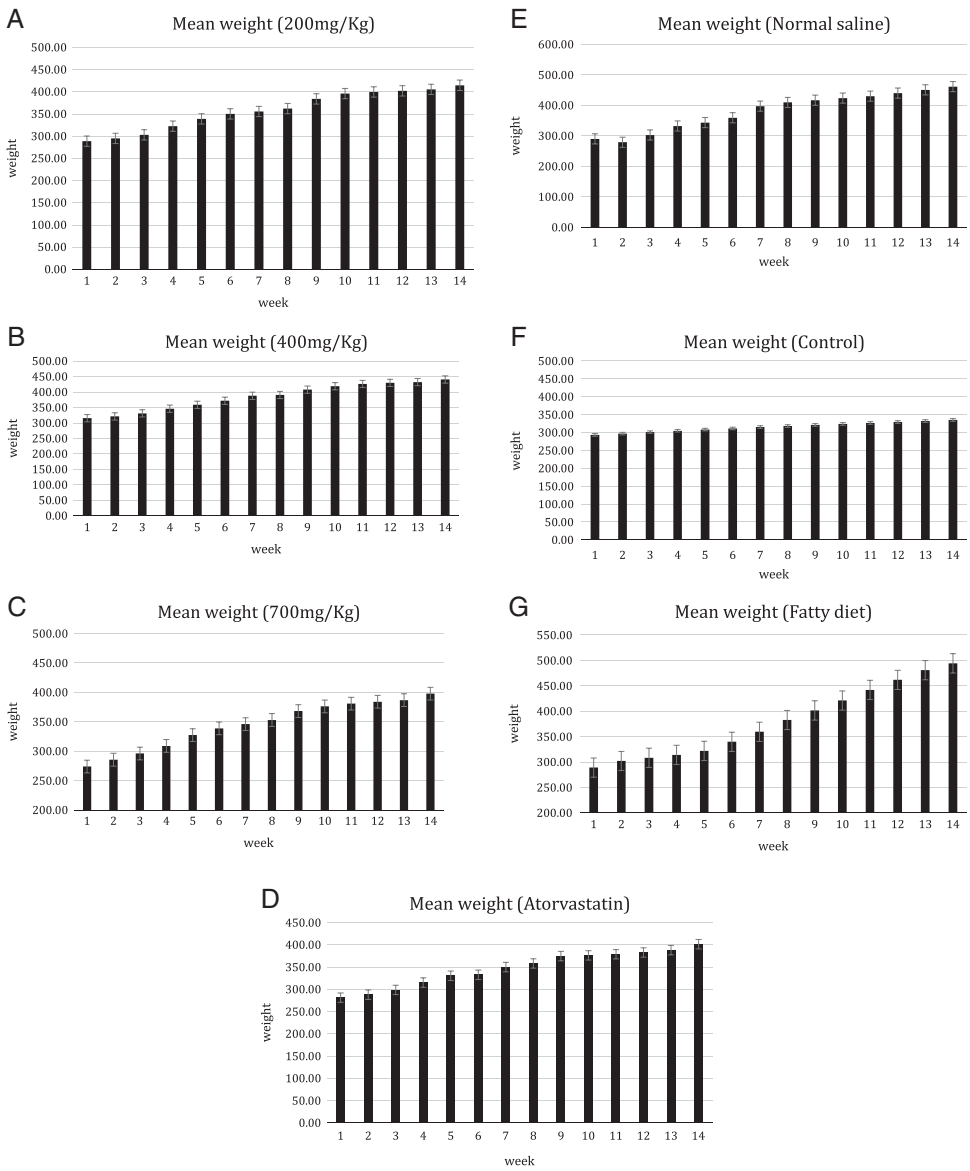

Figure 1. Mean weight of rats (A) consuming fatty diet for 14 weeks and 200 mg/kg of fumaria extract from week 9 to 14 by the gavage needle (B) rats consuming fatty diet for 14 weeks and 400 mg/kg of fumaria extract from week 9 to 14 by the gavage needle (C) rats consuming fatty diet for 14 weeks and 700 mg/kg of fumaria extract from week 9 to 14 by the gavage needle (D) rats consuming fatty diet for 14 weeks and 40 mg/kg of Atorvastatin from week 9 to 14 by the gavage needle (E) rats consuming fatty diet for 14 weeks and normal saline from week 9 to 14 by the gavage needle (F) rats consuming mice pellets as usual food for 14 weeks and nothing by the gavage needle (G) rats consuming fatty diet for 14 weeks and nothing by the gavage needle.

cholesterol than the high fat plus normal saline group but this difference was not statistically significant.

LDL level is depicted in Figure 2C. The lowest level was observed in rats received atorvastatin, whereas the highest level was observed in rats received the high-fat diet and normal saline. Rats treated with 400 mg/kg of FP extract did not show a significant difference compared to the high fat plus normal saline group. However, rats treated with 700 mg/kg of FP extract exhibited a significantly lower LDL level compared to the high-fat plus normal saline group.

The HDL level is illustrated in Figure 2D. The lowest level of HDL was observed in rats that only received the high-fat diet, while the highest HDL level was observed in rats treated with atorvastatin. Furthermore, rats treated with FP extracts demonstrated significantly higher HDL level compared to the high fat group.

The measurement of liver enzymes is depicted in Figure 3. The highest level of alanine transaminase (Fig. 3A) was observed in rats that received the high-fat diet plus normal saline. However, this difference was not significantly higher compared to the other groups.

The measurement of Aspartate aminotransferase (AST) is illustrated in Figure 3-B. Although the highest level of AST was observed in rats treated with atorvastatin and the lowest level was seen in rats treated with 200 mg/kg of FP extract, the difference between all groups was not significant.

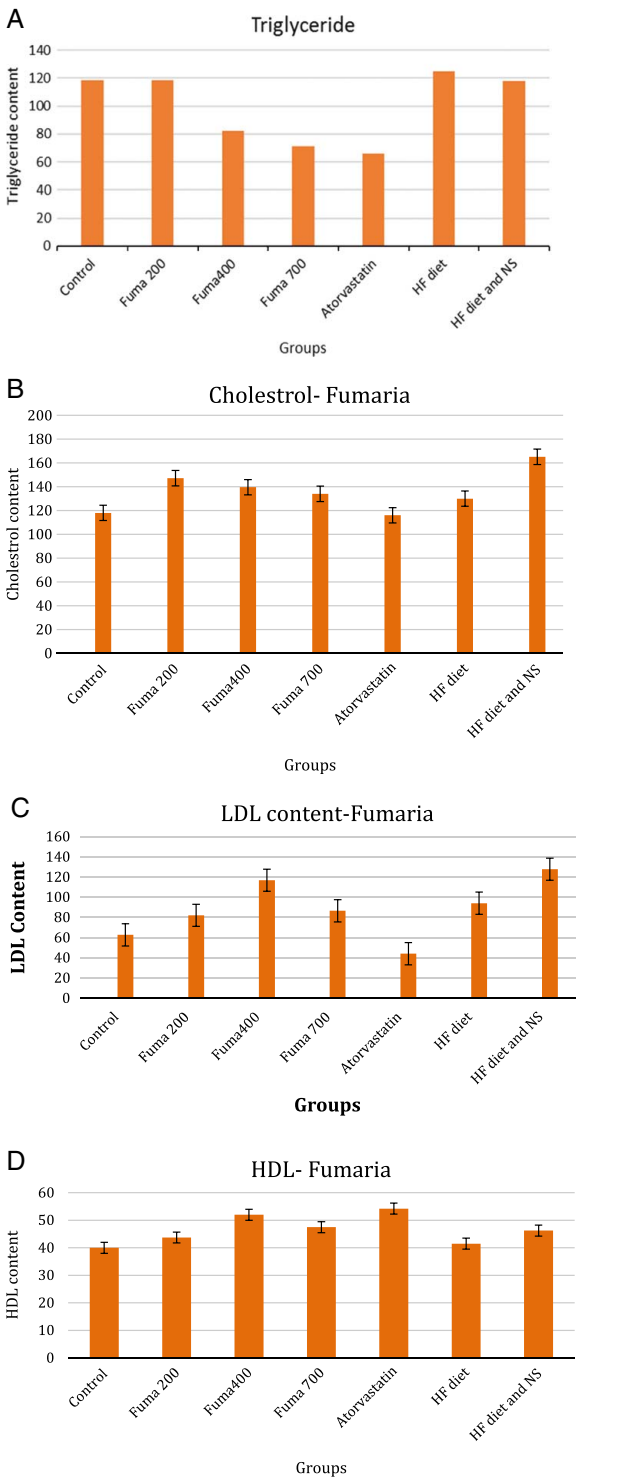

Figure 2. Graph showing changes in blood (A) Triglyceride (B) Cholesterol (C) LDL (D) HDL content in different groups. Fuma, Fumaria officinalis; HF, high fat regimen; NS, normal saline.

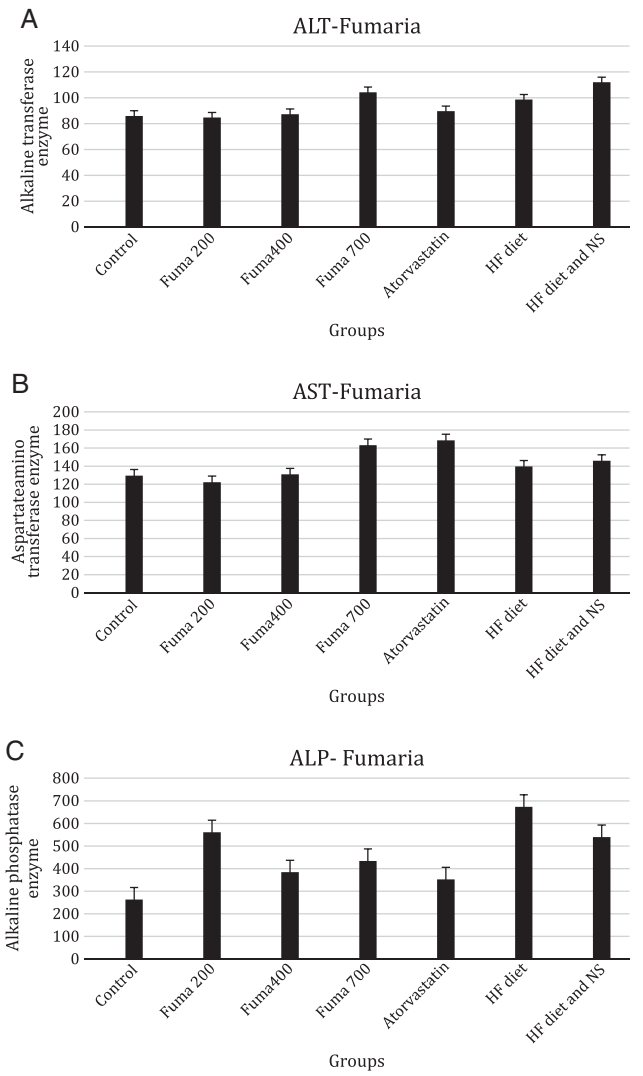

Figure 3. Graph showing changes in blood (A) ALT (B) AST (C) alkaline phosphatase content in different groups. Fuma, Fumaria officinalis; HF, high fat regimen; NS, normal saline.

Alkaline phosphatase (ALP) level is demonstrated in Figure 3-C. The highest level of ALP was observed in rats that only received the high-fat diet, while the lowest level was observed in rats that only received pellets as food. On the other hand, rats treated with 400 and 700 mg/kg of FP extracts also exhibited significantly lower ALP levels compared to rats that only received the high-fat diets.

Pathology findings have shown that rats consumed the high-fat diet for 14 weeks and 200 mg/kg of FP extract from week 9 to 14 via gavage needle exhibited 30–40% ballooning of hepatocytes (Fig. 4A-1), which is a relative indication of fatty liver. Additionally, there was 5% necrosis of hepatocytes (Fig. 4B-2) and no evidence of lobular inflammation.

Rats consumed the high-fat diet for 14 weeks and received 400 mg/kg of FP extract from week 9 to 14 via gavage needle displayed 25–30% ballooning of hepatocytes (Fig. 5A-1), with no sign of inflammation or necrosis.

Rats consumed the high-fat diet for 14 weeks and received 700 mg/kg of FP extract from week 9 to 14 via gavage needle displayed 15% ballooning of hepatocytes (Fig. 6A-1), without any sign of significant inflammation, necrosis or fibrosis.

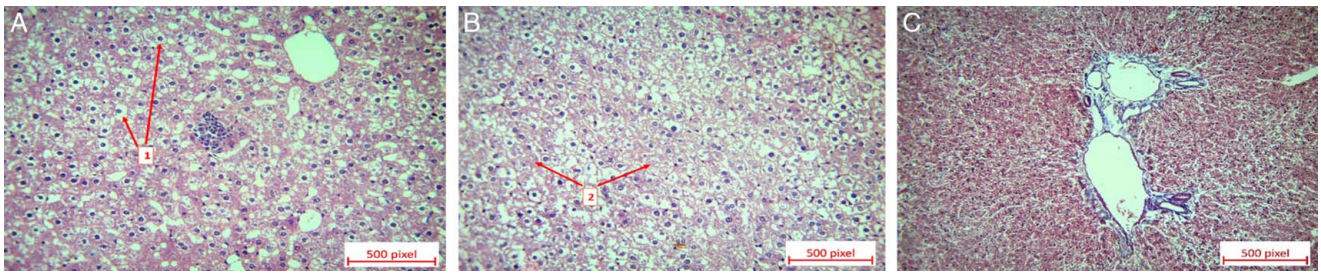

Figure 4. Histology of the dissected left lobe of liver of rats consuming fatty diet for 14 weeks and 200mg/kg of fumaria extract from week 9 to 14 by gavage needle, trichrome stain. Ballooning of hepatocytes in about 30-40% of hepatocytes (A) and necrosis in about 5% of hepatocytes(B) with no sign of lobular inflammation nor fibrosis (C).

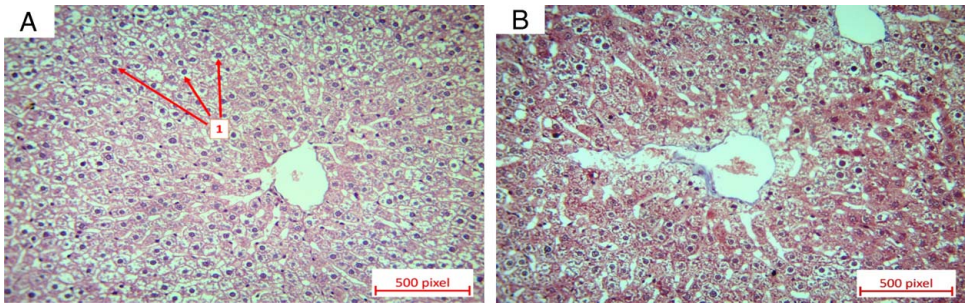

Figure 5. Histology of the dissected left lobe of liver of rats consuming fatty diet for 14 weeks and 400mg/kg of fumaria extract from week 9 to 14 by gavage needle, trichrome stain. Ballooning of hepatocytes in about 25-30% of hepatocytes (A) with no sign of necrosis, no sign of lobular inflammation nor fibrosis (B).

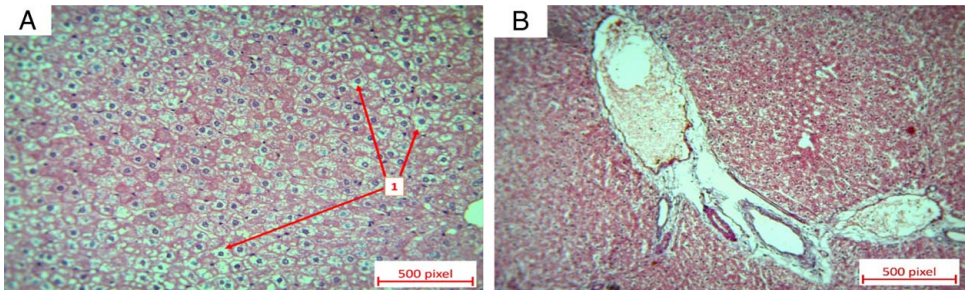

Figure 6. Histology of the dissected left lobe of liver of rats consuming fatty diet and 700mg/kg of fumaria extract by gavage needle, trichrome stain. Ballooning of hepatocytes in about 15% of hepatocytes (A). No sign of significant necrosis, no sign of lobular inflammation nor fibrosis (B).

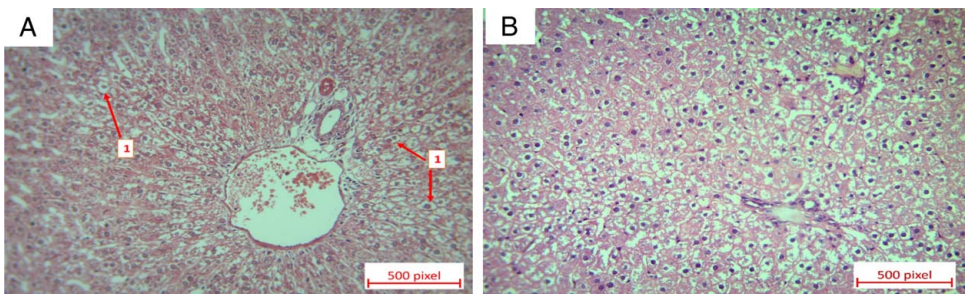

Figure 7. Histology of the dissected left lobe of liver of rats consuming fatty diet for 14 weeks and 40mg/kg of Atorvastatin from week 9 to 14 by gavage needle, trichrome stain. Ballooning of hepatocytes in about 10-25% of hepatocytes (A). No sign of significant necrosis, no sign of lobular inflammation nor fibrosis (B).

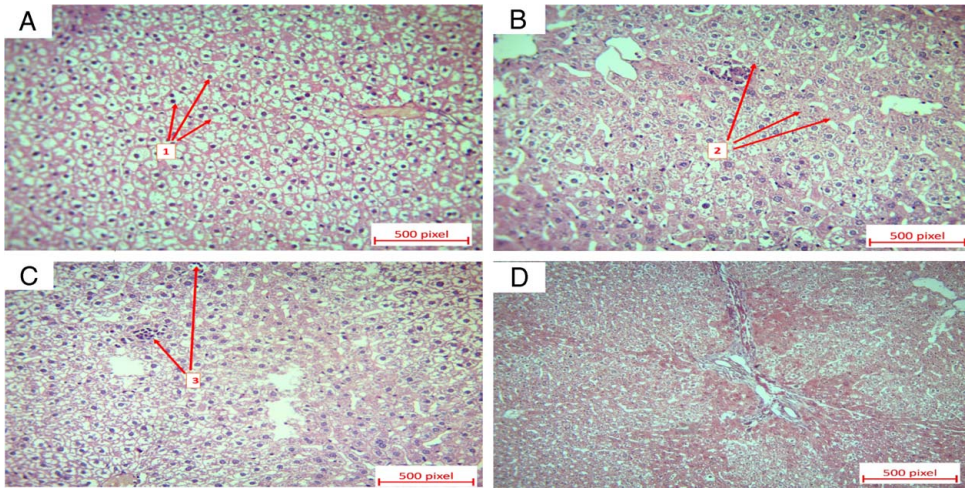

Figure 8. Histology of the dissected left lobe of liver of rats consuming fatty diet for 14 weeks and normal saline from week 9 to 14 by gavage needle, trichrome stain. Ballooning of hepatocytes in about 75-80% of hepatocytes(A), necrosis in about 10% of hepatocytes(B). lobular inflammation about 2/x10 objectives (C), no sign of fibrosis (D).

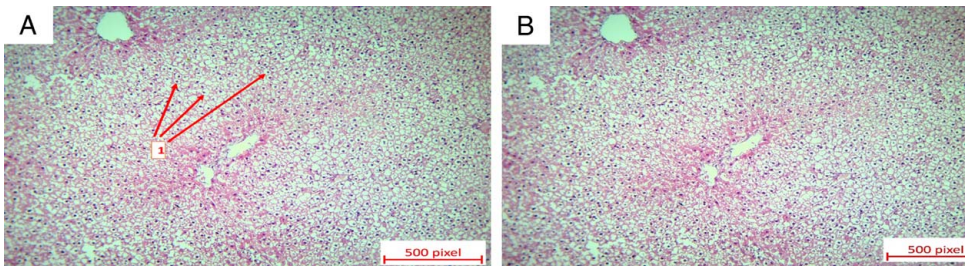

Figure 9. Histology of the dissected left lobe of liver of rats consuming fatty diet for 14 weeks and nothing by gavage needle, trichrome stain. Ballooning of hepatocytes in about 80% of hepatocytes(A), no sign of necrosis, no sign of lobular inflammation nor fibrosis (B).

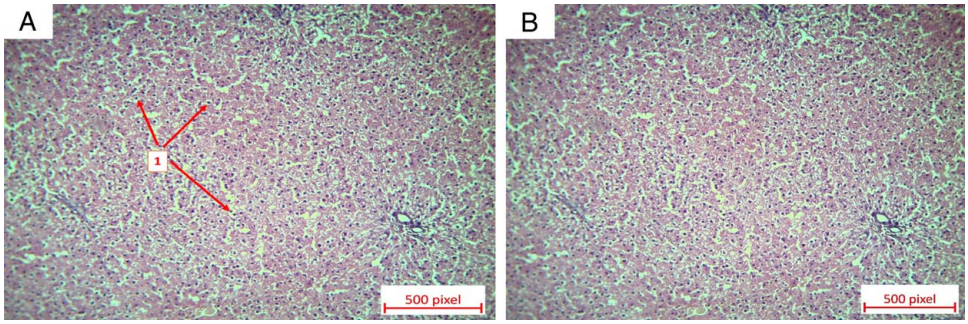

Figure 10. Histology of the dissected left lobe of liver of rats consuming rat pellets as usual diet for 14 weeks and nothing by gavage needle, trichrome stain. Ballooning of hepatocytes in about 5% of hepatocytes(A), no sign of necrosis, no sign of lobular inflammation nor fibrosis (B).

On the other hand, pathology findings of rats treated with the high-fat diet for 14 weeks in addition to 40 mg/kg of Atorvastatin from week 9 to 14 via the gavage needle showed 10–25% of hepatocytes ballooning (Fig. 7A-1) with no sign of significant inflammation, necrosis or fibrosis.

The histology of the dissected left lobe of the rat's that consumed the high-fat diet for 14 weeks and received normal saline from week 9 to 14 via gavage needle has shown 75–80% of hepatocyte ballooning (Fig. 8A-1), necrosis in 10% of hepatocytes (Fig. 8B-2), lobular inflammation observed at ~2/×10 objectives (Fig. 8C-3) and no sign of necrosis.

Rats consumed the high fat-diet for 14 weeks without any additional treatment via gavage needle showed hepatocytes ballooning in ~80% of hepatocytes (Fig. 9A-1), with no sign of necrosis, lobular inflammation, or fibrosis (Fig. 9B). On the other hand, rats consumed their usual diet of rat pellets for 14 weeks

without any treatment via gavage needle displayed 5% hepatocyte ballooning (Fig. 10A-1) without any sign of necrosis, lobular inflammation, or fibrosis.

Discussion

Despite efforts to achieve the primary objectives of lowering lipid profile, liver enzymes, and histologic repair of the liver in the treatment of NAFLD, the search for an ideal and effective agent with minimal side effects remains elusive[19].

Long-term use of chemical drugs for treating fatty liver is not very effective and often leads to side effects like cold-like symptoms, fatigue, and flatulence[20]. On the other hand, medical plants with antioxidative properties are gaining popularity for treating different diseases due to their fewer side effects[21]. It is important to mention that the WHO endorses the use of medical plants[22].

This study aims to evaluate the effect of *F. parviflora* (FP) extract on nonalcoholic fatty liver disease, lipid profile, and liver enzymes in rats after consuming a fatty diet. The study has shown that the use of FP extract had a positive influence on the grade of fatty liver.

The highest amount of weight gain was observed in rats that consumed only the high-fat diet. The use of 400 and 700 mg/kg of FP extract showed protective effects on weight gain, which were significant in compared with the group treated with atorvastatin; Additionally, the use of FP extract had a significantly positive effect on triglyceride, LDL, and HDL level and this effect was dose-dependent. However, the effect of the extract on cholesterol levels was not found to be significant.

Although rats treated with FP extract had a significantly lower level of ALP, the effect on ALT and AST was not significant; this lack of significance may be due to the timing of laboratory tests and we suggest the future studies to evaluate the liver enzymes right after the end of the fatty diets period.

In a study conducted by Kooshki *et al*., the efficacy of *F. parviflora* extract on liver damage and lipid profile was evaluated. The findings of this study revealed that the serum HDL level increased in the Fumaria group, which supports our own findings. Additionally, the study found that treatment with the FP extract led to a decrease in serum LDL, TG, and cholesterol levels, as well as AST and ALT levels. These findings are consistent with the results of our study[23].

Furthermore, the hepatoprotective effect of FP extract was demonstrated on CCL4-induced hepatotoxicity. The results revealed that doses of 200 and 300 mg/kg of FP extract effectively prevented liver damage caused by CCL4[24]. In a similar study, it was shown that pretreatment of rats with FP extract (500 mg/kg, orally twice daily for 2 days) prevented the rise in ALP and transaminases (GOT and GPT), which was induced by paracetamol. Additionally, post-treatment with three successive doses of the extract (500 mg/kg, four times a day) also limited the hepatic damage induced by paracetamol[25].

Our pathology findings indicate a reduction in hepatocytes ballooning in rats consuming higher dosage of FP extract, which was significantly different when compared to both the control group and the groups only consuming high-fat diet. However, consuming higher dosage of FP extract did not show any signs of lobular inflammation or fibrosis.

Previous research studies have also reported similar findings that align with our study. In 2010, Tirpathi *et al*.[26] reported on the antioxidant function of Fumaria extract and its positive effect on liver repair. Additionally, in 2017, Rizvi *et al*. demonstrated the positive effect of fumaria extract on hepatocytes[27,28].

This study had several limitations. Firstly, due to practical constraints, we had to house five rats in each container and the distributed food of each container was weighed daily and divided by five. However, there was no convenient method to accurately determine the individual amount of food consumed by each rat. Therefore, it is possible that some rats may have consumed more food than others within each container. To address this, we recommend that future studies consider housing each rat in an individual container.

Secondly, The FP extract was made using a hydroalcoholic solution, and the complete effect of this compound on lipid profile or liver function is not fully understood. To gain better understanding, we suggest that future studies further investigate the effect of this compound.

Thirdly, although our study demonstrated the effect of FP extract has a beneficial impact on lipid profile and liver function, the cellular and molecular mechanisms responsible for this effect are still not well understood. Hence, it is imperative for future studies to prioritize the investigation and comprehensive understanding of this pathway.

On the other hand, this study had multiple strength as well. Firstly, we investigated multiple arms of treatments, including three different dosages of FP extract, atorvastatin, and the potential impact of the stress induced by the gavage needle. Secondly, we conducted this study using a substantial number of samples and over an extended period of time, which surpasses the duration of previous studies. In addition, we examined three aspect of lipid profile, liver function test, and histopathological changes to comprehensively investigate the effect of the extract.

Conclusion

According to the findings of the present study, *F. parviflora* extract was found to reduce liver enzymes and had a significantly positive effect on triglyceride, LDL and HDL level in rats with NAFLD. These data provide support for the traditional use of Fumaria species in treating liver disease.

Ethical approval

Ethical approval for this study (Ethical code- IR.IUMS.FMD.REC.1399.081) was provided by the Ethical Committee of research deputy of Iran University of Medical Sciences, Tehran, Iran on 13 September 2020.

Consent

We confirm that (a) the present study followed international, national, and/or institutional guidelines for humane animal treatment and complied with relevant legislation. Also we confirm the present study involved client-owned animals and demonstrated a high standard (best practice) of veterinary care and involved informed client consent.

Sources of funding

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Author contribution

S.E. and M.M.: designed the study; S.E. and F.A.: performed the study; A.S.: provided the data regarding the extract and purified the product; M.A.: prepared the pathological slides and reported the pathological findings; S.E. and M.M.: wrote the first draft. All authors contributed in writing the manuscript and approved the final version.

Conflicts of interest disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Research registration unique identifying number (UIN)

This is an animal study.

Guarantor

Manijeh Motevalian.

Data availability statement

Full data is available upon for review by the Editor-in-Chief of this journal on request.

Provenance and peer review

The paper was not invited.

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