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ORIGINAL ARTICLE

The therapeutic potential of aqueous extract of *Falcaria vulgaris* in the treatment of fatty liver disease: a histopathological and biochemical approach

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Abstract

The recent experiments have indicated the potential of ethno-medicinal plants on the control, prevention, and treatment of fatty liver disease. In this study, we assessed the potential of aqueous extract of *Falcaria vulgaris* in treatment of fatty liver disease by investigating the histopathological and biochemical approaches. In beginning of the research, a total of 10 Wistar male rats were selected as the negative healthy control, and 50 rats were treated with a high-fat diet for 4 months. Then, the animals were randomly divided into six subgroups, including negative healthy control group, untreated group, and four groups receiving the aqueous extract of *F. vulgaris* at 25, 50, 100, and 200-mg/kg concentrations. After 2 months, the rats were sacrificed, and blood and liver samples of them were collected to analyze the histopathological and biochemical parameters. The data were analyzed by SPSS-21 software. Different groups of *F. vulgaris* significantly ($p \leq 0.05$) decreased the increased concentrations of ALP (alkaline phosphatase), AST (aspartate transaminase), ALT (alanine aminotransferase), GGT (gamma-glutamyl transferase), cholesterol, LDL (low-density lipoprotein), triglyceride, total and conjugated bilirubin, glucose, and GR (glutathione reductase) and enhanced the concentrations of HDL (high-density lipoprotein), total protein, albumin, SOD (superoxide dismutase), CAT (catalase), and GPx (glutathione peroxidase) as compared to the untreated group. Also, *F. vulgaris* reduced the degree of hepatic steatosis as compared to the untreated group. It appears that the aqueous extract of *F. vulgaris* can treat fatty liver disease in rats. Extraction of active molecules will be the future work to peruse.

Keywords *Falcaria vulgaris* · Aqueous extract · Fatty liver disease · High-fat diet

Introduction

The liver, as one of the most important organ involved in metabolism, is exposed to many different diseases, such as fatty liver. The fatty liver disease is usually followed by extreme obesity and increased blood lipid (Day 2011; Ganz et al. 2014; Jacobs et al. 2002). Studies have revealed that a high-fat diet leads to fatty liver disease (Ganz et al. 2014; Jacobs et al. 2002). It is characterized by the accumulation of triglycerides in hepatocytes due to stratification of glycerol and free fatty acids. It is accompanied by a series of histopathologic changes varying from steatosis to cirrhosis (Flora et al. 1998; Haga et al. 2015; Shaker et al. 2010; Tamayo and Diamond 2007). In any case, it is evident now that fatty liver is dependent upon factors, such as vulnerable oxidative stress, and can

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lead to steatohepatitis, which is characterized by inflammation, necrosis, fibrosis, and cirrhosis (Bosisio et al. 1992). The possible pharmacologic treatments include insulin sensitizers, antioxidants, hepatic protectors, or lipid-reducing factors (Day 2011). Since there are numerous pharmaceutical plants with antioxidant and anti-inflammatory properties, their application can be impressive in the inhibition and treatment of steatohepatitis in high-fat diet cases (Yao et al. 2016; Moradi et al. 2018; Zangeneh et al. 2018a).

In Iranian traditional medicine, plants have been the foundation of inhibition and treatment of several diseases (Rashidi et al. 2018; Ghashghaii et al. 2017; Hagh-Nazari et al. 2017; Hamelian et al. 2018; Zhaleh et al. 2018). One of the most important herbal medicines, which are widely used in Iranian traditional medicine for the treatment of fatty liver disease, is *Falcaria vulgaris*. In Iran, people use it as food. In fact, *F. vulgaris* is a good source of low-cost food and is a perfect part of the Iranian diet (Zangeneh et al. 2018b, c). In medicine, *F. vulgaris* applied as a medicinal plant has been used for its antifungal, antiviral, antibacterial, anti-inflammatory, antioxidant, and bleeding inhibitor activities (Jivad and Bahmani 2006; Jaberian et al. 2013; Shakibaie et al. 2007). It has a long history of use in traditional medicine, but there is a little evidence to show it is useful to treat fatty liver disease. We attempted to evaluate the remedial property of *F. vulgaris* in the treatment of fatty liver disease in Wistar male rats.

Materials and methods

Animal

This experimental study was conducted on 60 Wistar male rats obtained from Razi University laboratory with the weight of 205 ± 5 g that were kept in individual cages for 10 days to adapt to the environment. All institutional and national guidelines for the care and use of laboratory animals were followed.

Plant collection and extraction

F. vulgaris was collected from Kermanshah city in the west of Iran. The leaves of the plant were dried in shadow, and after grinding, each time 300 g of the obtained powder was dissolved in 3000 cc of distilled water and put in Soxhlet extractor for 8 h. The collected extract was filtered by Whatman filter paper no. 1 and steamed into a glass container at the solvent temperature. The remaining dried extract was poured into a glass container and weighed. The powder of the obtained extract was weighed as required depending on the dose and dissolved in saline. It was then administered to the rats by the oral catheter.

In vivo design

In this study, a total of 10 rats were chosen as the negative healthy control group, and the rest of them were treated with a high-fat diet for 4 months. Then the rats with were then divided into six groups, 10 rats in each group:

I. The negative healthy control group.
II. The group received the fatty diet.
III. The group received the fatty diet plus 25 mg/kg of aqueous extract of *F. vulgaris*.
IV. The group received the fatty diet plus 50 mg/kg of aqueous extract of *F. vulgaris*.
V. The group received the fatty diet plus 100 mg/kg of aqueous extract of *F. vulgaris*.
VI. The group received the fatty diet plus 200 mg/kg of aqueous extract of *F. vulgaris*.

Different concentrations of extract were administered via gavage for 2 months. To consider gavage stress, distilled water was administered to the negative healthy control group every day. After 2 months of gavage, the rats were sacrificed, and blood and liver samples of them were collected to analyze the histopathological and biochemical parameters.

Fatty diet preparation

Rats' diet powder (28%), butter, (28%), egg yolk (19%), sucrose (14%), and egg white (11%) were mixed to prepare the fatty diet. The obtained powder was dried in 100 °C oven for 30 min and was given to the rats as the pellet. The fatty diet was prepared weekly and stored in the refrigerator.

Histopathological assay

The histopathological changes were rated based on fat accumulation in liver:

0 = no steatosis.
1 = steatosis in less than 25% of hepatocytes.
2 = steatosis in 26–50% of hepatocytes.
3 = steatosis in 51–75% of hepatocytes.
4 = steatosis in more than 75% of hepatocytes (Mohammadifar et al. 2018).

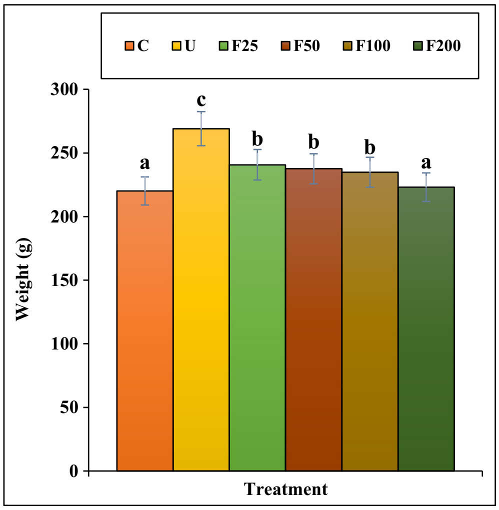

Fig. 1 The weight of the body in several groups. C: control, U: untreated, F: *Falcaria vulgaris*. Different letters represent statistical difference ($p \leq 0.05$) between tested groups of animals

Statistical analysis

To determine the normality of data, the Kolmogorov-Smirnov test was applied. To analyze the histopathological data, Kruskal-Wallis test was run.

Results

Effect of aqueous extract of *F. vulgaris* on the weights of body and liver

The weights of body and liver enhanced significantly ($p \leq 0.05$) in untreated rats as compared to the control ones (Figs. 1 and 2). Consumption of aqueous extract of *F. vulgaris* at all doses significantly ($p \leq 0.05$) reduced above weights in comparison with the untreated group. There were no meaningful changes ($p \leq 0.05$) between F200 and control groups. Administration of F25 and F50 significantly ($p \leq 0.05$) reduced the weights similar to the F100.

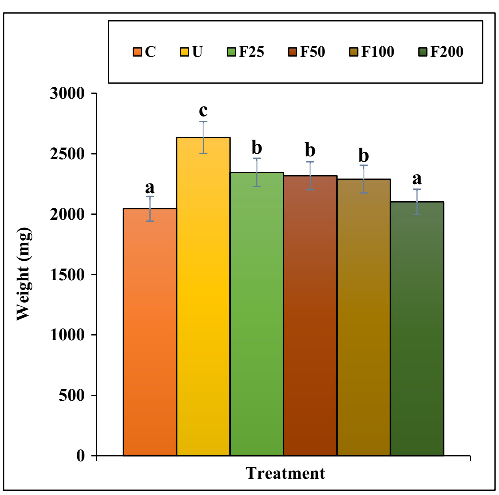

Fig. 2 The weight of the liver in several groups. C: control, U: untreated, F: *Falcaria vulgaris*. Different letters represent statistical difference ($p \leq 0.05$) between tested groups of animals

Table 1 The degrees of hepatic steatosis in several groups

Groups	The degrees of hepatic steatosis					*p*
	0	1	2	3	4	
C	10	0	0	0	0	**
U	0	3	3	1	3	*
F25	1	4	4	1	0	*, **
F50	4	4	2	0	0	*, **
F100	5	3	2	0	0	*, **
F200	7	3	0	0	0	**

C: control, U: untreated, F: *Falcaria vulgaris*

*Reveal a remarkable change between control group and other groups

**Reveal a remarkable change between untreated group and other groups

Effect of aqueous extract of *F. vulgaris* on the degree of hepatic steatosis

The degree of hepatic steatosis enhanced in untreated rats compared to the control ones. However, various doses of aqueous extract of *F. vulgaris* reduced it. There were not meaningful changes in the degree of hepatic steatosis between F200 and control groups. No meaningful changes were found among F25, F50, and F100 (Table 1).

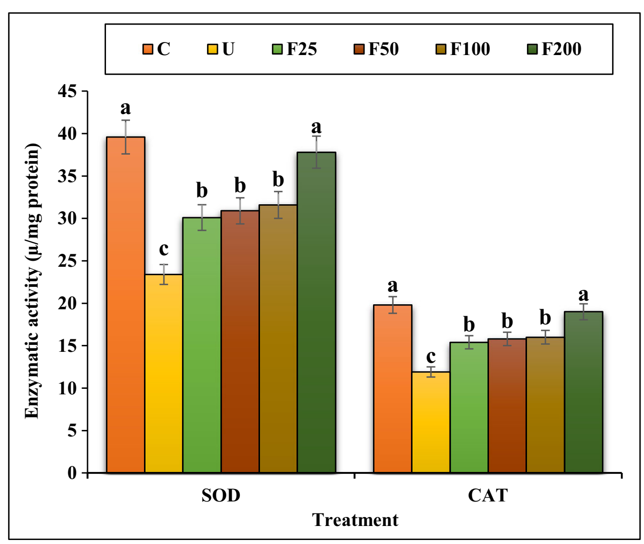

Fig. 3 The level of liver SOD and CAT in several groups C: control, U: untreated, F: *Falcaria vulgaris*, SOD: superoxide dismutase, CAT: catalase. Different letters represent statistical difference ($p \leq 0.05$) between tested groups of animals

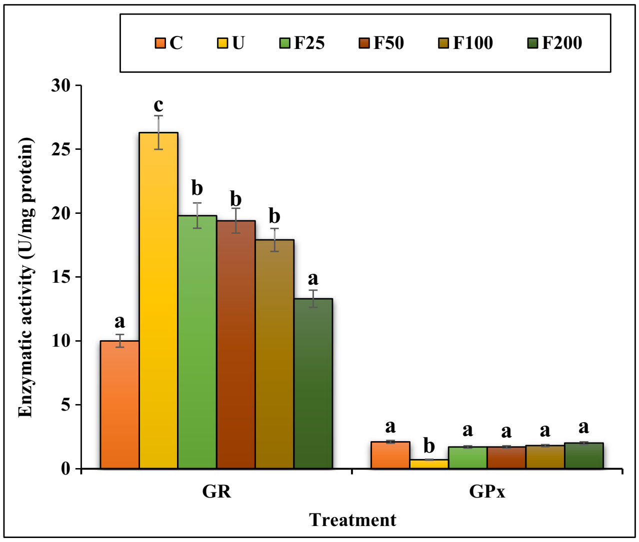

Fig. 4 The level of liver GR and GPx in several groups. C: control, U: untreated, F: *Falcaria vulgaris*, GR: glutathione reductase, GPx: glutathione peroxidase. Different letters represent statistical difference ($p \leq 0.05$) between tested groups of animals

Effect of aqueous extract of *F. vulgaris* on the concentrations of antioxidant enzymes

As shown in Figs. 3 and 4, the concentrations of SOD (superoxide dismutase), CAT (catalase), and GPx (glutathione peroxidase) enzymes were significantly ($p \leq 0.05$) reduced, and the concentration of GR (glutathione reductase) was significantly ($p \leq 0.05$) increased in the untreated group. The treatment with aqueous extract of *F. vulgaris* significantly ($p \leq 0.05$) ameliorated them. There were no meaningful changes ($p \leq 0.05$) in the concentration of GPx among several doses of *F. vulgaris* and control group. The concentrations of SOD, CAT, and GR were significantly ($p \leq 0.05$) regulated in F200 and were similar to the control group. No meaningful changes ($p \leq 0.05$) were found among F25, F50, and F100 in the concentrations of antioxidant enzymes.

Effect of aqueous extract of *F. vulgaris* on the concentrations of biochemical approaches

High-fat diet-induced fatty liver reduced significantly ($p \leq 0.05$) the levels of HDL (high-density lipoprotein), total protein, and albumin and enhanced significantly ($p \leq 0.05$) the concentrations of ALP (alkaline phosphatase), AST (aspartate transaminase), ALT (alanine aminotransferase), GGT (gamma-glutamyl transferase), cholesterol, LDL (low-density lipoprotein), triglyceride, total and conjugated bilirubin, and glucose as compared to the control group. All doses of aqueous extract of *F. vulgaris* significantly ($p \leq 0.05$) ameliorated the above parameters. There were no meaningful changes ($p \leq 0.05$) among all doses of *F. vulgaris* and control group in concentrations of GGT, and total and conjugated bilirubin. Also, administration of F100 and F200 significantly ($p \leq 0.05$) ameliorated the concentrations of ALT, triglyceride, total protein, and albumin similar to the control group. No meaningful changes ($p \leq 0.05$) were found between F200 and control groups in the concentrations of ALP, AST, LDL, and HDL (Figs. 5, 6, 7, 8, 9).

Discussion

The therapeutical properties of Iranian traditional medicine have been realized for centuries by clinical practice and experience (Farzaei et al. 2018; Sayyedrostami et al. 2018; Sherkatolabbasieh et al. 2017). They have the strong effect on the prevention, control, and treatment of every disease, such as fatty liver (Hemmati et al. 2015; Lee et al. 2010;

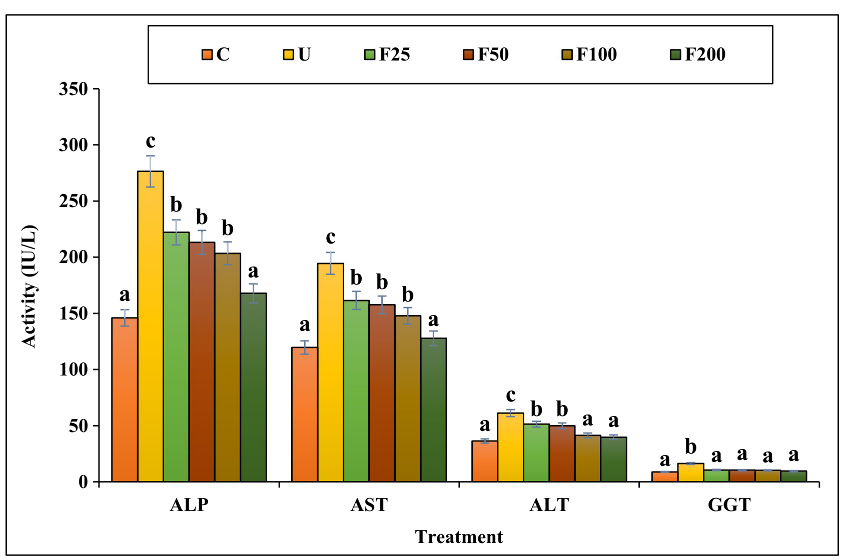

Fig. 5 The level of ALP, AST, ALT, and GGT in several groups. C: control, U: untreated, F: *Falcaria vulgaris*, ALP: alkaline phosphatase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma-glutamyl transferase. Different letters represent statistical difference ($p \leq 0.05$) between tested groups of animals

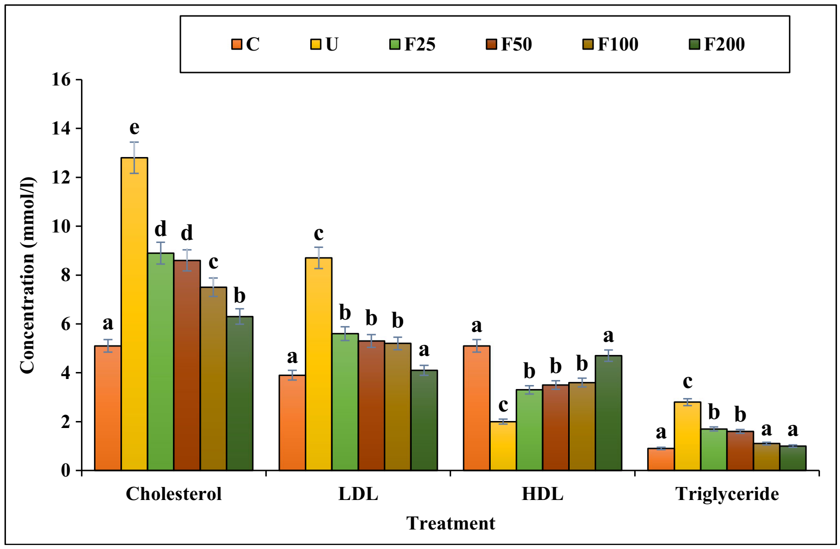

Fig. 6 The level of cholesterol, LDL, HDL, and triglyceride in several groups. C: control, U: untreated, F: *Falcaria vulgaris*, LDL: low-density lipoprotein, HDL: high-density lipoprotein. Different letters represent statistical difference ($p \leq 0.05$) between tested groups of animals

Nazni et al. 2006; Sabzghabaee et al. 2013). A list of medicinal plants used for their remedial potentials on fatty liver disease includes *Anemarrhena asphodeloides* Bunge, *Alisma orientalis* Juzep, *Alisma plantago-aquatica* Linn, *Artemisia capillaries* Thunb, *Amomum tsao-ko* Crevost et Lemaire, *Alpinia katsumadai* Hayata, *Citrus reticulata* Blanco, *Carthamus tinctorius* L, *Bupleurum scorzonerifolium* Willd, *Crataegus pinnatifida* Bunge, *Cinnamomum tamala* Nees, *Coptis chinensis* Franch, *Glycyrrhiza uralensis* Fisch, *Fructus aurantii* Immaturus, *Curcuma rcenyujin* Y, *Heteropogon contortus* P, *Gardenia jasminoides* Ellis, *Grataegus pinnati fida* Bge, *Lotus leaf* Tea, *Hypericum japonicum* Thunb, and *Panax pseudoginseng* var. notoginseng (Yao et al. 2016). In Iranian traditional medicine, people used *F. vulgaris* to treat fatty liver disease.

The obtained results from histopathological and biochemical parameters indicated that high-fat diet increased significantly ($p \leq 0.05$) the degree of hepatic steatosis and the concentrations of cholesterol, LDL, triglyceride, ALP, AST, ALT, GGT, total and conjugated bilirubin, and glucose and decreased significantly ($p \leq 0.05$) the concentrations of total protein and albumin as compared to the control group. Therefore, this diet caused severe hepatic toxicity. In spite of hepatotoxicity potential of the high-fat diet, the treatment with aqueous extract of *F. vulgaris* (especially F200) significantly ($p \leq 0.05$) improved the concentration of the above parameters. A study indicated that the aqueous extract of *F. vulgaris* at doses of 20, 40, 80, and 160 mg/kg reduced the concentration of the ALP, AST, ALT, cholesterol, and LDL and increased the

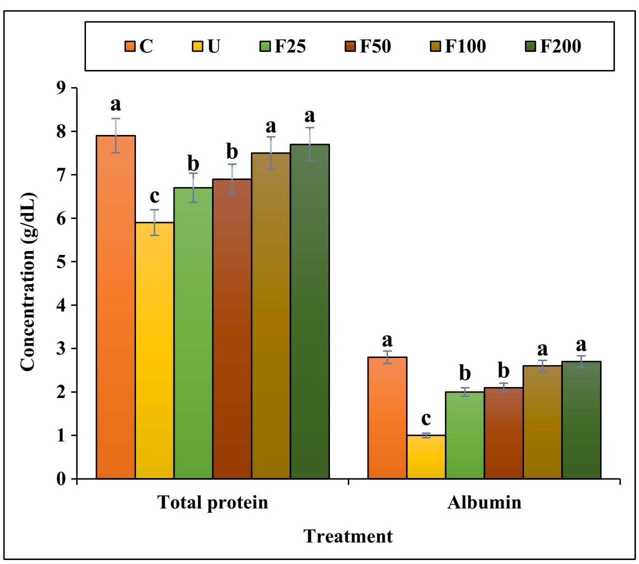

Fig. 7 The level of total protein and albumin in several groups. C: control, U: untreated, F: *Falcaria vulgaris*. Different letters represent statistical difference ($p \leq 0.05$) between tested groups of animals

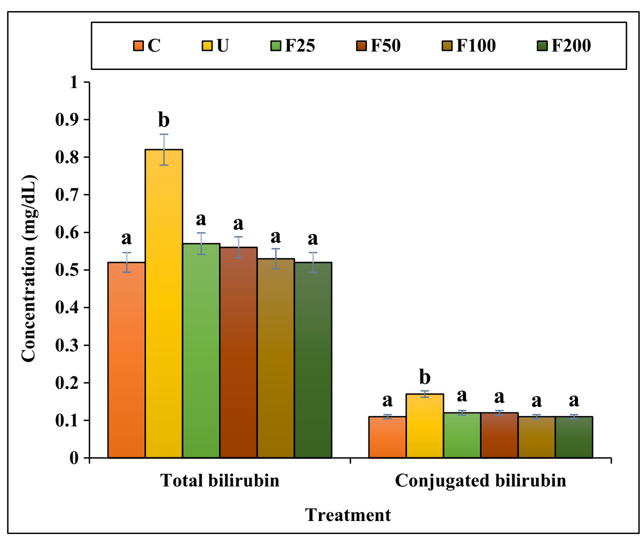

Fig. 8 The level of total and conjugated bilirubin in several groups. C: control, U: untreated, F: *Falcaria vulgaris*. Different letters represent statistical difference ($p \leq 0.05$) between tested groups of animals

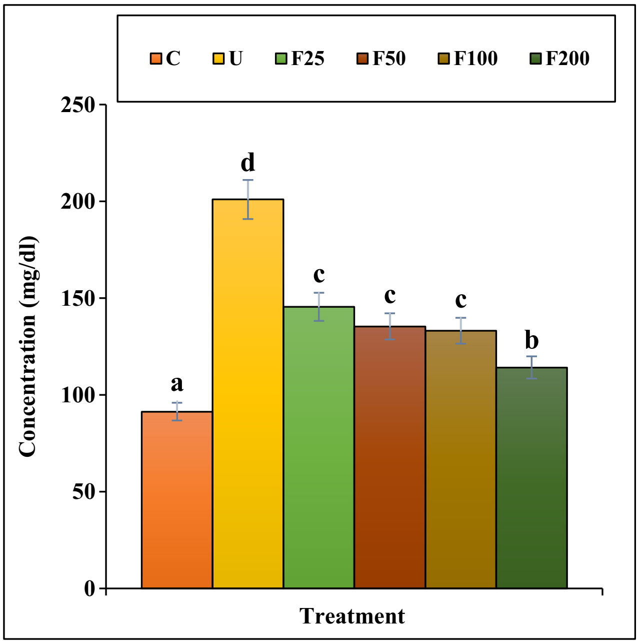

Fig. 9 The level of glucose in several groups. C: control, U: untreated, F: *Falcaria vulgaris*. Different letters represent statistical difference ($p \leq 0.05$) between tested groups of animals

concentration of HDL against carbon tetrachloride-induced acute hepatotoxicity in mice. Also, in the previous study, *F. vulgaris* decreased the volume of liver and its subcompartments, such as hepatocytes, central veins, sinusoids, portal veins, hepatic arteries, and bile ducts as compared to the CCl_4-treated group (Zangeneh et al. 2018c).

The evaluation of antioxidant enzymes of the recent study revealed that the high-fat diet significantly ($p \leq 0.05$) reduced the concentrations of SOD, CAT, and GPx and enhanced the concentration of GR. But, the treatment with all doses of aqueous extract of *F. vulgaris* significantly ($p \leq 0.05$) improved the concentrations of them. A study demonstrated that the aqueous extract of *F. vulgaris* at doses of 20, 40, 80, and 160 mg/kg, with increasing the degradation of free radicals, increased the concentrations of SOD and CAT in mice with carbon tetrachloride-induced hepatotoxicity. In the previous study, the best result was seen at a dose of 160 mg/kg and no hepatotoxicity was observed in this dose (Zangeneh et al. 2018c). There is no further information on the effect of *F. vulgaris* in increasing of antioxidant enzyme concentrations.

It is revealed that antioxidant compounds played a very necessary role in the treatment of fatty liver disease (Ferramosca et al. 2017). The study of Jaberian et al. (2013) reported that *F. vulgaris* were rich in antioxidant compounds that include anthraquinone, alkaloid, phenolic, tannin, saponin, steroids, and flavonoid. In another study, Khanahmadi and Shahrezaei (2008) indicated that spathulenol and carvacrol (antioxidant compounds) were the main compounds of *F. vulgaris*. Also, in a study, Ebrahimi Monfared et al. (2012) reported that *F. vulgaris* with phenolic compounds had good DPPH radical scavenging effect. So, it was normal in our study that *F. vulgaris* treated fatty liver disease in rats.

Conclusion

According to the findings, aqueous extract of *F. vulgaris* at all doses (especially F200) treated the fatty liver disease with improving histopathological and biochemical approaches. It is offered that clinical trials be conducted to achieve this therapeutical potential in human.

Compliance with ethical standards

Conflict of interests The authors declare that there is no conflict of interest.

Ethic approval All institutional and national guidelines for the care and use of laboratory animals were followed.

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