



Hepatoprotective and hematoprotective effects of *Falcaria vulgaris* aqueous extract against CCl₄-induced hepatic injury in mice

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Abstract

Medicinal plants are considered as modern resources for producing agents that could act as alternatives to chemical drugs. *Falcaria vulgaris* (FV) has been used in medicine as an antioxidant, antifungal, anti-inflammatory, and antibacterial agent. The aim of the present study was to investigate the hepatoprotective and hematoprotective effects of FV aqueous extract against CCl₄-induced hepatotoxicity in mice. Sixty male mice were divided into six groups ($n = 10$); group I served as control, received 1 mL/kg olive oil intraperitoneally and 0.5 mL distilled water through gavage. Group II served as untreated group, received 1 mg/kg CCl₄ mixed with olive oil in the ratio of 5:5 intraperitoneally and 0.5 mL distilled water orally. Groups III, IV, V, and VI received CCl₄ mixed with olive oil in the ratio of 5:5 intraperitoneally and 20, 40, 80, and 160 mg/kg of FV aqueous extract through gavage for 45 consecutive days. Different doses of FV (especially FV160) could significantly ($p \leq 0.05$) decrease the raised levels of alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, cholesterol, low-density lipoprotein, white blood cell, and platelet and increase high-density lipoprotein, superoxide dismutase, catalase, and red blood cell as compared to the untreated group. The weight and volume of the hepatic structures were decreased significantly ($p \leq 0.05$) in different doses of FV (especially FV160) compared to the untreated group. FV aqueous extract can protect hepatic tissue and regulate liver enzymes in CCl₄-induced hepatotoxicity. FV has hepatoprotective and hematoprotective properties, thereby reducing the causation of diabetes in experimental mice.

Keywords *Falcaria vulgaris* · Aqueous extract · Hepatotoxicity · Hematotoxicity · CCl₄

Introduction

Carbon tetrachloride (CCl₄) is a toxic substance for most organs of the body such as the liver, kidneys, heart, testes, brain, and blood (Alia et al. 2003). Furthermore, different documented case studies have established that CCl₄ produces hepatic disease

with a changed antioxidant status in humans (Alia et al. 2003). Findings from the screening of several ethno medicinal plants describe their antioxidant effect and demonstrate that they could protect the liver against CCl₄ by increasing the levels of antioxidant enzymes (Goodarzi et al. 2017; Sherkatolabbasieh et al. 2017). Research on hepatoprotective agents is one of the advanced fields in recent biomedical sciences. The expensive costs of modern medicines indicate that alternative strategies are need for better management of diseases and their related problems.

Ethno medicinal plants are popular remedies used by most people (Faramarzi et al. 2017; Foroughi et al. 2016; Tahvilian et al. 2017). The impression of ethno medicinal plants in prevention and treatment of diseases is irrecusable (Najafi et al. 2017). Aqueous extract is a kind of fraction of plants that includes aromatic and nonaromatic compounds (Moradi et al. 2017). This fraction could be extracted from several parts such as fruits, flowers, leaves, stems, and roots (Poorshamohammad et al. 2017). In recent years, interest in aqueous extract has been

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enhanced for pharmacological studies which claim that the aqueous extract with decreasing free radicals has useful effect for prevention and treatment of liver disease (Pooyanmehr et al. 2017; Zangeneh et al. 2017).

Falcaria vulgaris (FV) (Paghazou and Ghaziaghi in Persian) grows widely in the western parts of Iran (Ahvazi et al. 2012). The *Falcaria* genus is placed in the *Apiales* order and *Apiaceae* family (Ahvazi et al. 2012). FV have been cultivated from the earliest times and it is economically important as garden vegetable (Jaberian et al. 2013). The consumption and cooking of parts of FV are due to the large variety of flavors and textures of the species (Khazaei and Salehi 2006). FV as an eatable plant has generated a lot of interest throughout human history as a medicinal plant (Ahvazi et al. 2012). In traditional medicine, several extracts of this plant are traditionally used in treating different inflammatory, bacterial, parasitic, viral, and fungal diseases; gastric ulcer; and diabetes (Jaberian et al. 2013; Khazaei and Salehi 2006).

In the present study, we investigated the ameliorative property of the FV aqueous extract by studying the microscopic structural changes in mouse liver after CCl₄-induced hepatotoxicity using modern design-based stereological methods. Hepatic functions were also investigated by examining hematological and biochemical biomarkers.

Materials and methods

Plant collection

FV at maturity were collected from around of Kermanshah city during May 2017. The plant was identified for the first time at the herbarium of research center of Faculty of Agriculture, Razi University, Kermanshah, Iran.

Plant extraction

Leaves of the plant were shade dried for 1 week. Dried aerial parts of the plants were ground and about 150 g of the obtained powder was extracted with 450 mL of distilled water for 2 h at 40 °C with continuous shaking. The extract was left for 24 h at room temperature; then, it was filtered through Whatman paper no. 2. In a rotary evaporator, the extract was concentrated, then lyophilized.

Animals

Male Balb/c mice weighing between 38 and 40 g were procured from laboratory animal center of Kermanshah University of Medical Sciences. The animals were housed in an air-conditioned room (22 ± 2 °C) with 12-h light/dark cycle and has free access to standard pellet diet (metabolism energy 2860 kcal/kg, crude protein 21.5%, crude fiber 3.55%,

calcium 1.05%, phosphorous 0.5%, sodium 0.17%, chlorine 0.23%, methionine (digestible) 0.59%, methionine + cysteine (digestible) 0.92%, lysine (digestible) 1.2%, arginine (digestible) 1.33%, threonine (digestible) 0.82%, linoleic acid: 1.5%, dry matter 88%) and water ad libitum conditions (standard environmental and nutritional) during the study.

Experimental design

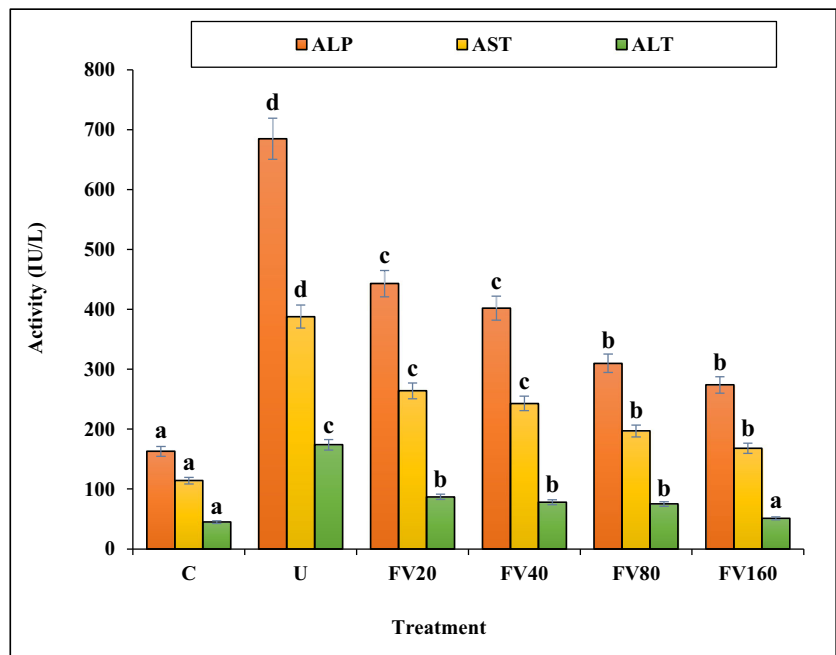
In the present study, a total of 60 mice were used. The mice were divided into six groups of ten mice each. Group I served as control, received 1 mL/kg olive oil intraperitoneally and 0.5 mL distilled water through gavage. Group II served as untreated group, received 1 mg/kg CCl₄ mixed with olive oil in the ratio of 5:5 intraperitoneally and 0.5 mL distilled water orally. Groups III, IV V, and VI received CCl₄ mixed with olive oil in the ratio of 5:5 intraperitoneally and 20, 40, 80, and 160 mg/kg of FV (FV20, FV40, FV80, and FV160) through gavage, respectively. The animals treated twice a week for 45 consecutive days. At the end of the 45-day treatment, the animals of all the groups were euthanized by xylazine (5 mg/kg) and ketamine HCl (40 mg/kg). Immediately after euthanizing, blood samples were drawn from animals' heart and inserted in serum (for determination of alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL)) and plasma (for determination of red blood cell (RBC), white blood cell (WBC), and platelet) bottles. All above parameters were measured by available commercial kits (Pars Azmun Co., Iran) according to its procedures. Also, the capacity of antioxidant enzymes was assessed by determining the activity of superoxide dismutase (SOD) and catalase (CAT) in the liver using the procedures reported by Abei (1974) and Martin et al. (1987).

Histological study

The whole liver of each group ($n = 10$) weighed and immersed in 10% neutral buffered formaldehyde. Liver volume is obtained from liver dipping method in water. After 72-h fixation, the livers were cut using orientator method. Totally, 7–10 slabs were collected from each liver. The slabs were embedded in paraffin and sections (5 µm thicknesses) were prepared and stained by hematoxylin and eosin stain.

Volume density of liver structures including hepatocytes, sinusoids, central veins, portal veins, hepatic arteries, and bile ducts was estimated with point counting rule briefly as follows: one section from each liver was used. The images of microscopical fields from each section were projected on point probe (frame 15 cm × 15 cm) by a video projector via a microscope equipped with a camera (Dinocapture ver.5, dino-lit.com 30.5 mm) attached to a computer.

Fig. 1 ALP, AST, and ALT levels in all of the experimental groups. C (control group), U (untreated group), ALP (alkaline phosphatase), AST (aspartate aminotransferase), and ALT (alanine aminotransferase). Non-identical letters demonstrate a significant difference between the groups ($p \leq 0.05$)



At total magnification of $\times 2000$, points that hit desired structures were counted and volume density was estimated using the following formula:

$$V_v := \frac{P_{\text{structure}}}{P_{\text{reference}}}$$

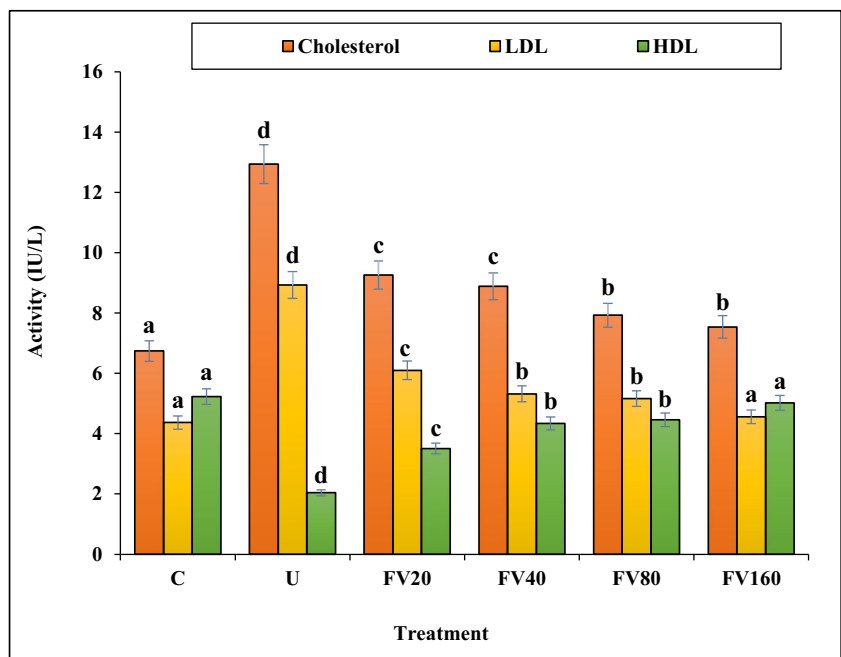
where “ $P_{\text{structure}}$ ” and “ $P_{\text{reference}}$ ” were the number of points falling on the structure’s profile and on the reference space,

respectively. Ten to 14 microscopic fields were examined in each liver (Mandarim-de-Lacerda 2003; Nyengaard 1999).

Statistical analysis

Descriptive statistics including the mean, standard error, median, minimum, and maximum were calculated for all variables. The one-way ANOVA followed by Duncan’s post hoc test was used for comparison of different parameters. The data were analyzed

Fig. 2 Cholesterol, LDL, and HDL levels in all of the experimental groups. C (control group), U (untreated group), LDL (low-density lipoprotein), and HDL (high-density lipoprotein). Non-identical letters demonstrate a significant difference between the groups ($p \leq 0.05$)



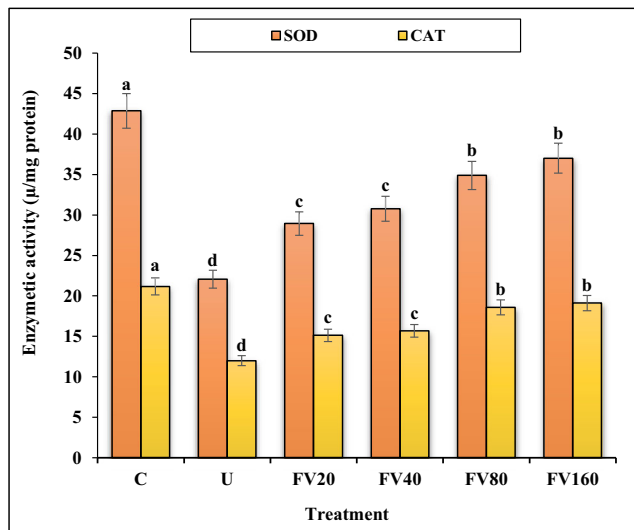


Fig. 3 The levels of SOD and CAT in the liver in all of the experimental groups. C (control group), U (untreated group), SOD (superoxide dismutase), and CAT (catalase). Non-identical letters demonstrate a significant difference between the groups ($p \leq 0.05$)

by SPSS software, version 22.0 (SPSS Inc., Chicago, IL, USA) and $p \leq 0.05$ was accepted as statistically significant.

Results

Effect of CCl_4 and FV on levels of liver biochemical parameters

The estimated values of the liver enzymes are presented in Figs. 1, 2, and 3. CCl_4 -induced toxicity increased ALP, AST, ALT, cholesterol, and LDL and decreased HDL, SOD, and CAT significantly ($p \leq 0.05$) as compared to the control group.

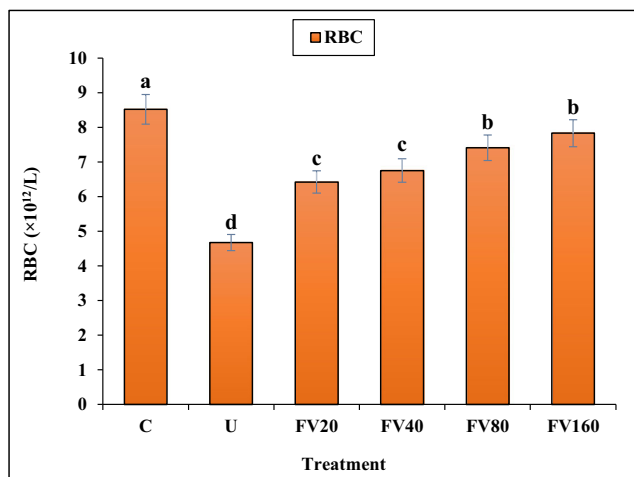


Fig. 4 RBC numbers in all of the experimental groups. C (control group), U (untreated group), and RBC (red blood cell). Non-identical letters demonstrate a significant difference between the groups ($p \leq 0.05$)

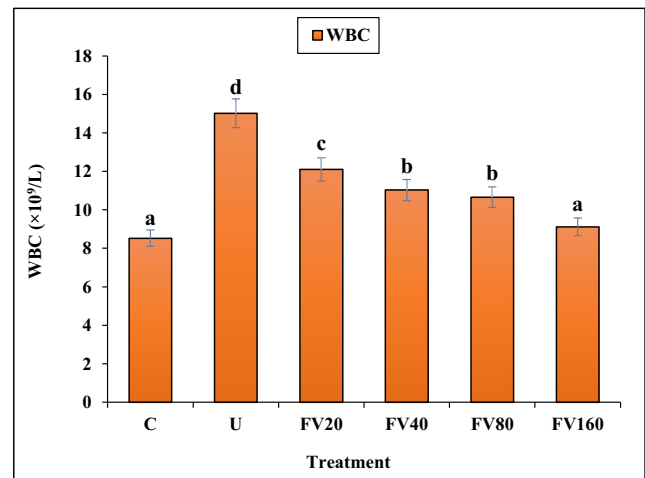


Fig. 5 WBC numbers in all of the experimental groups. C (control group), U (untreated group), and WBC (white blood cell). Non-identical letters demonstrate a significant difference between the groups ($p \leq 0.05$)

Different doses of FV could significantly ($p \leq 0.05$) decrease the raised levels of ALP, AST, ALT, cholesterol, and LDL and increase HDL, SOD, and CAT significantly ($p \leq 0.05$) as compared to the untreated group. There is no difference significant between FV160 and control in ALP, LDL, and HDL levels ($p \leq 0.05$).

Effect of FV on hematological parameters

The numbers of WBC and platelet were increased and the number of RBC decreased significantly ($p \leq 0.05$) in untreated mice. Treatment with FV significantly ($p \leq 0.05$) reduced WBC and platelet number and increased RBC number in comparison with the untreated group. Also, there is no difference significant between FV160 and control in RBC number ($p \leq 0.05$) (Figs. 4, 5, and 6).

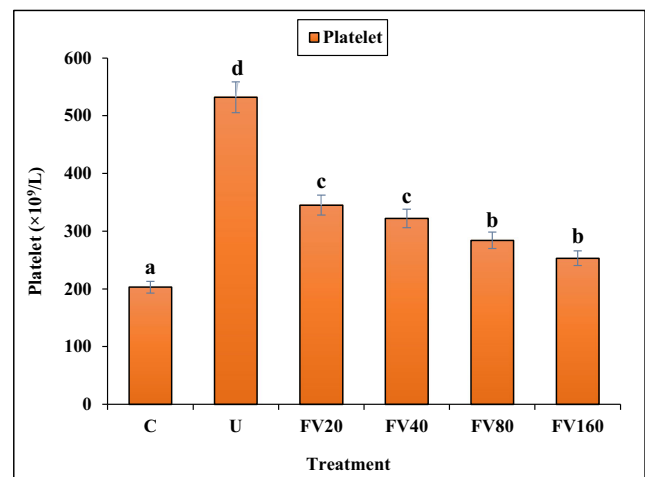


Fig. 6 Platelet numbers in all of the experimental groups. C (control group) and U (untreated group). Non-identical letters demonstrate a significant difference between the groups ($p \leq 0.05$)

Effect of FV on stereological parameters

Administration of FV at all doses could significantly ($p \leq 0.05$) improve the liver volume compared to the untreated group (Figs. 7 and 8). The volumes of hepatocytes, central veins, sinusoids, portal veins, hepatic arteries, and bile ducts were increased significantly ($p \leq 0.05$) in untreated diabetic mice compared to the control ones (Figs. 9, 10, and 11). Administration of FV at all doses could significantly ($p \leq 0.05$) decrease the volume of the above structures in comparison with the untreated group. Administration of FV160 could significantly ($p \leq 0.05$) reduce volume of central veins, portal veins, and hepatic arteries similar to the control group. FV80 could significantly ($p \leq 0.05$) decrease volumes of central veins and hepatic arteries similar to the FV160 and control groups. Also, there was no significant difference in volume of hepatic arteries ($p \leq 0.05$) among FV20, FV40, and control groups.

Discussion

Medicinal plants are popular remedies used by people. The impression of medicinal plants in prevention and treatment of diseases is irrecusable (Foroughi et al. 2017; Najafi et al. 2016). Plants have the immense potential for the management and remedy of every disease such as hepatotoxicity (Hagh-Nazari et al. 2017; Ghashghaii et al. 2017). A list of medicinal plants that are consumed for their hepatoprotective property includes *Fagonia schweinfurthii* (whole plant), *Vitex glabrata* (whole plant), *Astragalus kahiricus* (root), *Zingiber officinale* Roscoe (rhizome), *Cissus quadrangularis* (stem), *Feronia limonia* (stem bark), *Terminalia paniculata* (bark), *Melastoma malabathricum* L (leaf), *Ficus religiosa* (leaf),

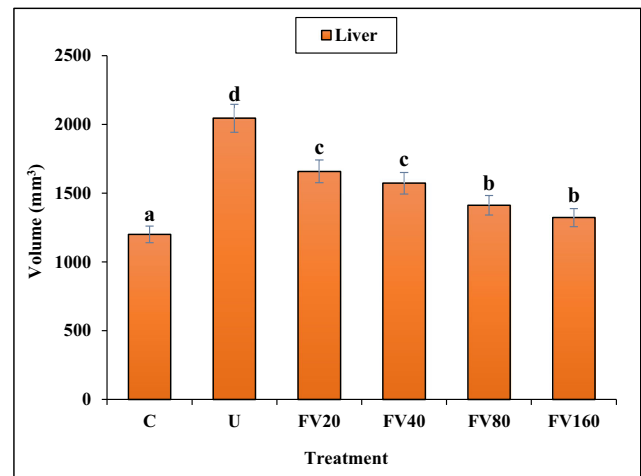


Fig. 8 Volumes of the liver in all of the experimental groups. C (control group) and U (untreated group). Non-identical letters demonstrate a significant difference between the groups ($p \leq 0.05$)

Feijoa sellowiana (fruit and peel), *Garcinia indica* (fruit rind), *Daucus carota* (seed), *Moringa oleifera* Lam (seed oil), *Abelmoschus manihot* (flower), and *Acacia nilotica* Linn (aerial parts) (Roy et al. 2014).

In this experimental study, the hepatoprotective property of FV at various doses was determined in CCl₄-induced hepatotoxicity in mouse model. But, to our knowledge, this is the first time FV with these doses has been used from experimentally induced hepatotoxicity in mice.

Hepatoprotective effect of FV

The extension of hepatic damages is assessed by the elevated serum levels of cytoplasmic enzymes as well as by histological examination (Recknagel et al. 1991; Zangar et al. 2000).

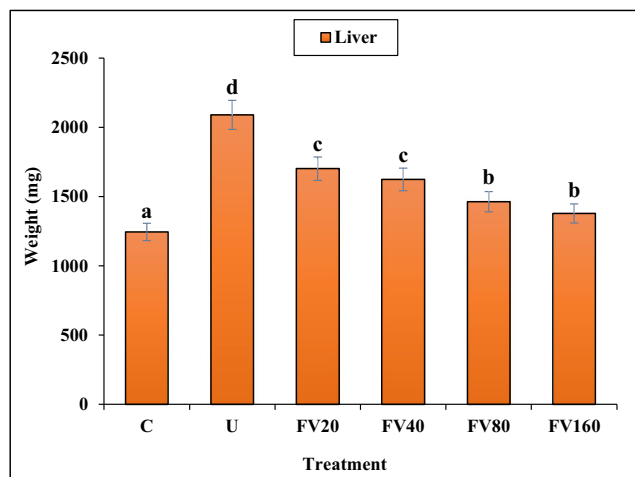


Fig. 7 Weights of the liver in all of the experimental groups. C (control group) and U (untreated group). Non-identical letters demonstrate a significant difference between the groups ($p \leq 0.05$)

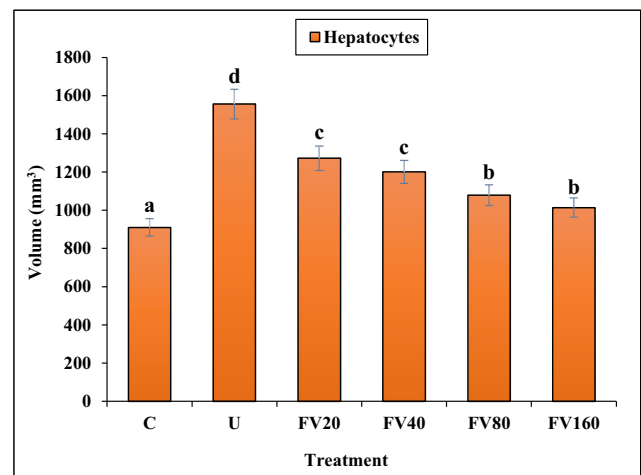
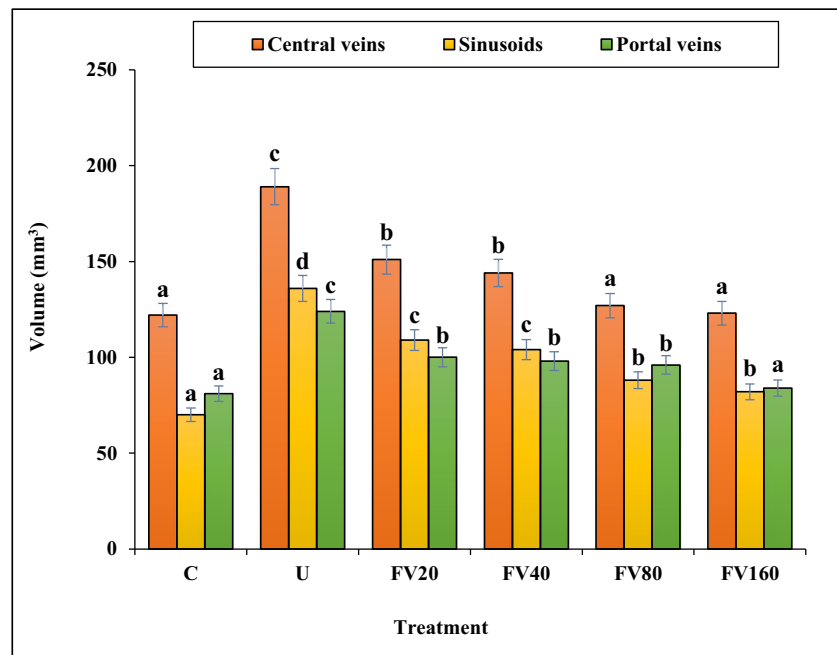


Fig. 9 Volume of hepatocytes in all of the experimental groups. C (control group) and U (untreated group). Non-identical letters demonstrate a significant difference between the groups ($p \leq 0.05$)

Fig. 10 Volume of central veins, sinusoids, and portal veins in all of the experimental groups. C (control group) and U (untreated group). Non-identical letters demonstrate a significant difference between the groups ($p \leq 0.05$)



The increased serum parameter levels such as ALP, AST, ALT, cholesterol, and LDL have been attributed to the damaged structural integrity of the liver (Recknagel et al. 1991; Zangar et al. 2000). Administration of CCl_4 produced liver damage in mice as manifested by the rise in serum parameter levels of ALP, AST, ALT, cholesterol, and LDL. The raised levels of above parameters were significantly decreased following administration of different doses of FV. Also, FV at all doses (especially 160 mg/kg) with ameliorating of liver function increased levels of HDL, SOD, and CAT. The hepatoprotective effect of FV in the present study may be partly related to its anti-inflammatory and antioxidant constituents. Previous

studies indicated that the FV is rich of spathulenol, carvacrol, alpha-pinene, and limonene (anti-inflammatory and antioxidant constituents). So FV have strong anti-inflammatory and antioxidant properties (Khanahmadi and Shahrezaei 2008; Shafaghat 2011; Jaberian et al. 2013).

Other results of this study indicated that the liver of CCl_4 -treated mice demonstrated a considerable hypertrophy which leads to increase in weight, volume, and length of the hepatic structures. These changes were alleviated significantly in all doses of FV (especially 160 mg/kg). Thus, this study suggested that FV could be used to meliorate hepatic structural changes due to CCl_4 -induced toxicity.

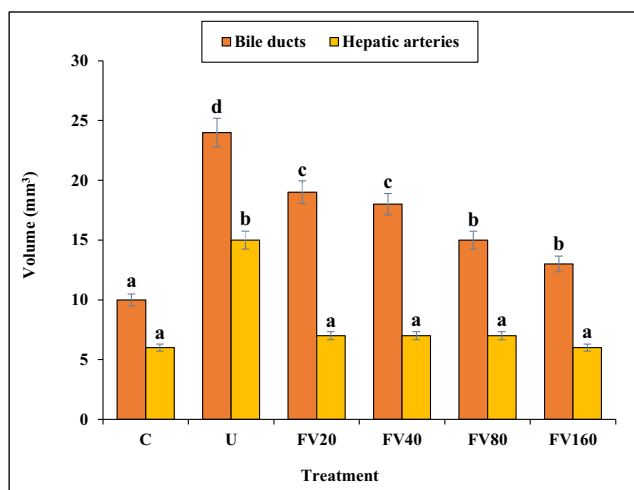


Fig. 11 Volume of hepatic arteries and bile ducts in all of the experimental groups. C (control group) and U (untreated group). Non-identical letters demonstrate a significant difference between the groups ($p \leq 0.05$)

Hematoprotective effect of FV

Alteration in the various hematological parameters and the immune system during the course of hepatotoxicity has been reported (Saba et al. 2010). Previous studies indicated that CCl_4 administration yielded microcytic hypochromic anemia by the reduction in the RBC (Saba et al. 2010; Swenson 1993). Acute stress associated with CCl_4 has been widely reported to be associated with increased white blood cell and platelet count occasioned by significant increase in the neutrophil count and the neutrophil/lymphocyte ratio (Huff et al. 2005; Larson et al. 1985). Agreeing with above reports, in our present study, the numbers of WBC and platelet were increased and number of RBC reduced significantly ($p \leq 0.05$) in untreated mice. Treatment with FV at all doses (especially FV160) significantly ($p \leq 0.05$) reduced WBC and platelet numbers and enhanced RBC numbers in comparison with untreated mice.

Conclusion

Finally, it can be concluded that FV can protect the liver against CCL₄-induced hepatocellular injuries at all dose (especially 160 mg/kg). Clinical trial studies would be needed to justify and further assess the potential of the plant as a hepatoprotective and hematoprotective agent in human.

Compliance with ethical standards

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

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

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