Journal of Traditional and Complementary Medicine 7 (2017) 508–514

Contents lists available at ScienceDirect

Journal of Traditional and Complementary Medicine

journal homepage: http://www.elsevier.com/locate/jtcme

Original Article

Promising effect of *Rosa damascena* extract on high-fat diet-induced nonalcoholic fatty liver

Ida Davoodi [a], Roja Rahimi [b], Mohammad Abdollahi [c], Fatemeh Farzaei [d], Mohammad Hosein Farzaei [e, f, *], Zahra Memariani [g], Fariba Najafi [h]

[a] Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[b] Department of Traditional Pharmacy, School of Traditional Medicine, Tehran University of Medical Sciences, Tehran, Iran
[c] Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran
[d] Medical Biology Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran
[e] Pharmaceutical Sciences Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran
[f] PhytoPharmacology Interest Group (PPIG), Universal Scientific Education and Research Network (USERN), Kermanshah, Iran
[g] School of Iranian Traditional Medicine, Traditional Medicine and History of Medical Sciences Research Center, Babol University of Medical Sciences, Babol, Iran
[h] Kermanshah University of Medical Sciences, Kermanshah, Iran

ARTICLE INFO

Article history:
Received 3 September 2016
Received in revised form
13 January 2017
Accepted 16 January 2017
Available online 13 February 2017

Keywords:
Fatty liver
Oxidative stress
Rosa damascena
Dietary supplement
Medicinal plant

ABSTRACT

NAFLD is a chronic liver disease that affects a high proportion of the world's population which causes metabolic and hepatic damages. *Rosa damascena* Mill is traditionally used as a dietary supplement for liver disorders. This study was carried out to determine the beneficial effect of standardized extract of *R. damascena* on animal model of nonalcoholic fatty liver disease (NAFLD). NAFLD was induced by high-fat diet (HFD) in Wistar rats. HFD rats showed an increase ($p < 0.05$) in the plasma lipid levels of total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), and reduced the high-density lipoprotein (HDL) levels. *R. damascena* significantly reduced the elevation of final body weight, liver fat accumulation, TG, TC, LDL-C concentrations and hepatic enzymes ($p < 0.05$). Histopathological examination of hepatic tissue confirmed the therapeutic effect of *R. damascena.* Improvement of total antioxidant power activity, total thiol content, MPO enzyme activity, and also lipid peroxidation were also considered in treated animals ($p < 0.05$). HPLC analysis showed that phenolic compounds including gallic acid, quercetin and syringic acid are the main bioactive compounds of *R. damascena* hydroalcoholic extract. In conclusion, *R. damascena* dietary supplementation has a therapeutic effect in NAFLD. Improvement of oxidative stress associated damage in liver tissue is among the main pharmacological mechanisms involved in therapeutic activity of the plant.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is defined as accumulation of fat in the hepatic tissue which exceeds 5%–10% of its weight in the absence of substantial ethanol consumption and refers to a range of related disorders from simple hepatic steatosis to steatohepatitis, advanced fibrosis, as well as cirrhosis.[1] Fatty liver and hepatic triglyceride accumulation possess a key role in the progression of different metabolic disorders like diabetes mellitus, obesity, insulin resistance, hypertension, as well as dyslipidemia indicating the pivotal contribution of management of NAFLD in health promotion.[2] Recent evidence has fuelled concerns that NAFLD may be a new risk factor for extra-hepatic cancers.[3] Currently, due to alterations in human's dietary regimen and life style, the incidence of NAFLD has been raised resulting in making this disease as one of the most common chronic diseases.[4]

Limitations of conventional drugs have been considered useful in the management of NAFLD, including serious adverse effects, disease recurrence, and drug interaction lead to an extensive trend

* Corresponding author. Faculty of Pharmacy, Kermanshah University of Medical Sciences, Kermanshah, 6734667149, Iran. Fax: +98 8338250271.
E-mail address: mh.farzaei@gmail.com (M.H. Farzaei).
Peer review under responsibility of The Center for Food and Biomolecules, National Taiwan University.

http://dx.doi.org/10.1016/j.jtcme.2017.01.008

to novel resources of treatments. Natural drugs possess a long history of efficacious and safe usage in the traditional medicine of different nations. Recent investigations on nutritional aspects of fatty liver pathogenesis have focused on evaluating potential effects of herbal extracts and supplements as functional food ingredients in preventing hepatic lipid accumulation.[5]

Rosa damascena Mill. from the family Rosaceae is commonly known as Damask rose. It has been found that more than 200 rose species and approximately 18000 cultivars of this herb have been identified.[6] *R. damascena* is a perennial bushy shrub with cylindrical branches. The flowers are composite, colorful and showy. Its height is between 1 and 2 m. It has imparipinnate and compound leaf with 5–7 leaflets. Nowadays, this plant is widely cultivated across the world including Europe and Middle East countries, particularly in Iran and Turkey, because of its scent and visual beauty. *R. damascena* flowers have been widely used in perfume, medicine and food industries. In the context of traditional medicinal approaches, the flowers of *R. damascena* is worthy of attention due to its safe and efficacious history of administration in Persian medicine. *R. damascena* is a well-known medicinal plant regarding the beneficial effects in various diseases including gastrointestinal disease, cardiovascular disorders, wound healing and skin health, inflammatory diseases, menstrual bleeding, pregnancy-related disorders, as well as mental disorders particularly depression, nervous stress and tension.[7–10] The flower of *R. damascena* has been claimed to be useful for liver dysfunction and have liver tonic properties in the literatures of Persian medicine.[11]

A wide range of phytochemical ingredients were isolated from hips, petals and flowers of *R. damascena* containing flavonoids, glycosides, terpenes, and anthocyanins. The major active constituent of *R. damascena* is phenolic compounds including kaempferol, quercetin, gallic acid, cyanidin 3, 5, D-glycoside.[12] β-citronellol, nonadecane, geraniol, nerol, and kaempferol are the main chemical constituents of volatile oil of *R. damascena* flower.[13] Galactoside, xyloside, galactoside, rutinoside, and arabinoside are among glycoside component of this plant.[12] In addition, carboxylic acid, myrcene, azlyn, linalool, geraniol, and vitamin C are other identified compounds of *R. damascena*.[9,14] The present study was conducted to investigate the efficacy of standardized extract of *R. damascena* in experimental model of NAFLD and revealing the potential mechanisms.

2. Material and method

2.1. Chemical and reagents

Reagent kits for triglyceride (TG), cholesterol (Chol), high-density lipoprotein (HDL), low-density lipoprotein (LDL), alanine aminotransferase (ALT), and aspartate transaminase (AST) were supplied from (Sigma-Aldrich, Steinheim, Germany). We obtained other chemicals, unless otherwise stated, from Sigma Chemicals Co. (St. Louis, MO, USA).

2.2. Plant material and extraction

R. damascena flowers were collected in July 2015 from local herbal store of Tehran and authenticated and a voucher specimen [No: PMP-507] was deposited in the herbarium of Faculty of Pharmacy, Tehran University of Medical Sciences. The flowers were shade-dried at room temperature and ground into coarse particles. To prepare hydroalcoholic extract, 700 g of the plant powder were extracted three times with 70% ethanol. Each extracted solution was filtered and evaporated to dryness at 40 °C to yield residues about 19.65%. *R. damascena* hydroalcoholic extract (RHE) was standardized based on three polyphenols (syringic acid, gallic acid and quercetin) using HPLC method as previously described.[15]

2.3. Animal models and experimental design

Male 10-weeks-old Wistar-albino rats, weighing (300–350 g) were accommodated under standard conditions of temperature (20–25 °C), 12 h light/dark cycle, and relative humidity (55± 10%), enough attainment to food (standard pellet) and water *ad libitum*. All animal practices were carried out base on the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health which were approbated by ethical committee of Tehran University of Medical Sciences.

42 rats were randomly separated to seven groups of six per each. One group received routine diet as normal. Other groups were fed with high fat diet (HFD) containing 83% of basal fodder, 10% of lard, 5% egg yolk powder, and 2% of cholesterol for a period of 8 weeks. After two weeks of study, HFD groups were planned to receive vehicle (distilled water), simvastatin (as positive control) as well as 25, 50, 100 and 200 mg kg^{-1} day^{-1} of RHE. Orally treatment was administered every 24 h for 6 weeks. We measured body weights every week. The last day of the study, blood samples of sacrificed rats collected from abdominal aorta for the measurement of TC, LDL, HDL, TG, ALT, and AST.

2.4. Evaluation of oxidative stress biomarkers

Blood samples were collected into tubes containing EDTA and were centrifuged at 3000 *g* for 15 min for evaluating oxidative stress biomarkers. For determining the following biomarkers, separated plasma was kept at −80 °C.

2.5. Myeloperoxidase (MPO)

Defrosted plasma and 50 mM phosphate buffer containing 0.167 mg/ml o-dianisidine hydrochloride and 0.0005% H_2O_2 was mixed. Afterward, we recorded the absorbance at 460 nm for 3 min using a UV-visible spectrophotometer (GBC, Cintra 40). The definition of one unit of MPO activity is the change in absorbance per min at room temperature, in the final reaction.

2.6. Lipid peroxidation (LPO)

LPO was evaluated using thiobarbituric acid reactive substances assay. Trichloroacetic acid (20%) was reacted with blood samples and the residual was mixed with a solution of 0.05 M H_2SO_4. Then, in a boiling water bath, 2-thiobarbituric acid was added followed by 30 min incubation. *n*-butanol was used to extract the mixture and absorbance was recorded at 532 nm (ELISA reader, Biotek, Germany).[16]

2.7. Total thiol molecule (TTM)

In order to assess levels of plasma TTM, 5′5′ dithiobisnitrobenzoic acid (DTNB) was reacted with blood samples to create a yellow complex. The absorbance was measured by spectrophotometry at 412 nm.[17]

2.8. Ferric reducing ability of plasma (FRAP)

We measured FRAP by using fresh FRAP reagent (25 mL of 0.3 M acetate buffer, 2.5 mL of TPTZ solution, and 2.5 mL of $FeCl_3 \cdot 6H2O$ solution) mixed with defrosted plasma samples and absorbance was recorded at 593 nm.[18]

Table 1
Effect of *R. damascena* extract on body weights of rats with fatty liver induced by HFD.

Groups	Body weight (g)
Normal	326.5 ± 16.03
HFD-fed + V	367.33 ± 12.41[a]
HFD-fed + Simvastatin (20 mg/kg)	337.16 ± 16.75[b]
HFD-fed + RHE 25 mg kg^{-1} day^{-1}	350.33 ± 22.50[a]
HFD-fed + RHE 50 mg kg^{-1} day^{-1}	348.33 ± 18.59[a,b]
HFD-fed + RHE 100 mg kg^{-1} day^{-1}	342.83 ± 17.21[b]
HFD-fed + RHE 200 mg kg^{-1} day^{-1}	335.83 ± 13.79[b]

Values are mean ± SEM. HFD: high fat diet; RHE: *R. damascena* hydroalcoholic extract; V: vehicle.
[a] Significantly different from the normal group at $p < 0.05$.
[b] Significantly different from the HFD-fed + V at $p < 0.05$.

2.9. Histopathological analysis

For evaluating the histopathological analysis, the fixed segments in formalin 10% were embedded in paraffin and stained with hematoxylin and eosin to detect hepatic steatosis, inflammation and necrosis. A blind pathologist performed the histological evaluation.

2.10. Statistical analysis

Data were analyzed by SPSS (SPSS Inc., Chicago, Ill., USA). We used One-way ANOVA followed by Newman–Keul's post hoc test for multiple comparisons. The p values less than 0.05 were considered significant. Results are expressed as mean ± standard error of the mean (SEM).

3. Results

3.1. Effect of RHE on weight gain and lipid profile

HFD fed animals had significantly higher weight gain compared with normal diet group. Weight gain was reduced by all doses of RHE as well as simvastatin in comparison with rats treated with HFD plus vehicle ($p < 0.05$, Table 1).

Table 2 demonstrates lipid profile changes in different groups of animals. TG, TC and LDL-C plasma levels were significantly lower in normal animals compared with HFD diet rats; however, HDL-C was significantly higher in normal rats. TG level was significantly reduced compared to vehicle treated HFD animals by using different doses of RHE as well as simvastatin ($p < 0.05$). In addition, all doses of RHE treatment reduced TC and LDL-C plasma levels compared to negative control. Higher doses of RHE demonstrated numerically better activity in regulation of lipid profile parameters. Regarding HDL-C levels, all doses of RHE except 25 mg/kg were able to induce a significant increase compared to vehicle treated animals.

3.2. Effect of RHE on hepatic enzymes

As shown in Fig. 1, HFD group treated with vehicle had significant elevation of ALT and AST plasma levels; but, these levels were reduced by using simvastatin and different doses of RHE in dose dependent manner ($p < 0.05$).

3.3. Effect of RHE on biomarkers of oxidative damage

As demonstrated in Figs. 2–4, HFD resulted in remarkable oxidative damage in animal with NAFLD treated with vehicle. Oxidative stress-associated parameters were apparently modulated by utilizing different doses of RHE. MPO activity was significantly suppressed by applying RHE in a dose dependent manner (Fig. 2). Likewise, all doses of RHE reduced the elevated level of LPO (Fig. 3). Treatment with 200 mg/kg dose of RHE showed significantly the

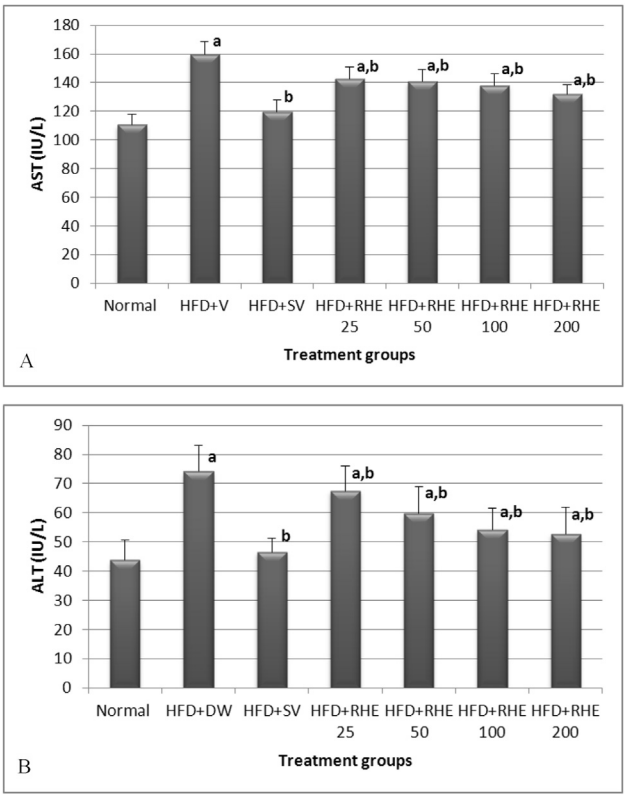

Fig. 1. AST and ALT values in animals with fatty liver induced by HFD. Values are mean ± SEM. V: vehicle (distilled water); DW: distilled water; HFD: high fat diet; RHE: *R. damascena* hydroalcoholic extract; SV: simvastatin. [a]Significantly different from the normal group at $p < 0.05$. [b]Significantly different from the HFD-fed + V group at $p < 0.05$.

Table 2
Alterations on the plasma lipid parameters in HFD-fed rats treated with *R. damascena* extract for 8 weeks.

Groups	TG ($mg.dl^{-1}$)	Chol ($mg.dl^{-1}$)	LDL ($mg.dl^{-1}$)	HDL ($mg.dl^{-1}$)
Normal	79.5 ± 5.31	93.5 ± 6.71	47.95 ± 6.35	50.5 ± 4.88
HFD-fed + V	132.5 ± 9.71[a]	164.5 ± 8.5[a]	126.26 ± 7.18[a]	35.83 ± 5.49[a]
HFD-fed + Simvastatin (20 mg/kg)	82.66 ± 4.17[b]	102.83 ± 8.86[b]	52.53 ± 6.48[b]	46.83 ± 5.03[b]
HFD-fed + RHE 25 mg kg^{-1} day^{-1}	97.83 ± 5.41[a,b]	138.16 ± 4.49[a,b]	84.56 ± 7.08[a,b]	39.83 ± 6.61[a]
HFD-fed + RHE 50 mg kg^{-1} day^{-1}	92.16 ± 7.73[a,b]	135.33 ± 8.16[a,b]	79.21 ± 5.52[a,b]	41.66 ± 6.25[a,b]
HFD-fed + RHE 100 mg kg^{-1} day^{-1}	90.66 ± 7.61[a,b]	130.16 ± 8.95[a,b]	66.65 ± 4.46[a,b]	42.83 ± 3.76[a,b]
HFD-fed + RHE 200 mg kg^{-1} day^{-1}	87.66 ± 7.11[a,b]	125.5 ± 9.33[a,b]	57.48 ± 7.85[a,b]	44.5 ± 5.89[a,b]

Values are mean ± SEM. V: vehicle; HFD: high fat diet; RHE: *R. damascena* hydroalcoholic extract.
[a] Significantly different from the normal group at $p < 0.05$.
[b] Significantly different from the HFD-fed + V group at $p < 0.05$.

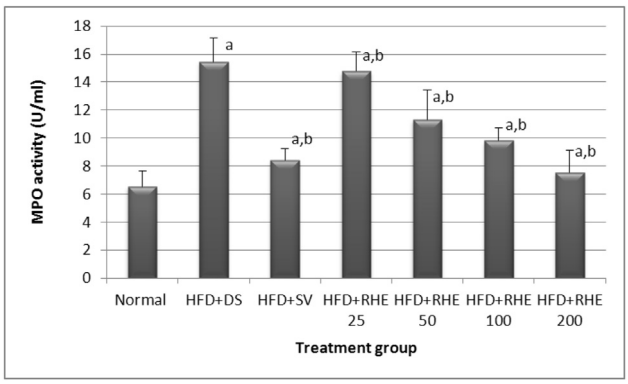

Fig. 2. MPO (myeloperoxidase) values in animals with fatty liver induced by HFD. Values are mean ± SEM. DS: Distilled water; HFD: high fat diet; RHE: *Rosa damascena* extract; SV: simvastatin. [a]Significantly different from the normal group at $p < 0.05$. [b]Significantly different from the HFD-fed + DS group at $p < 0.05$.

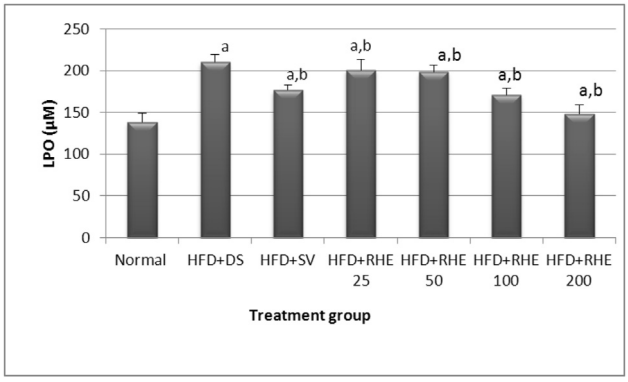

Fig. 3. LPO (lipid peroxidation) values in animals with fatty liver induced by HFD. Values are mean ± SEM. DS: Distilled water; HFD: high fat diet; RHE: *Rosa damascena* extract; SV: simvastatin. [a]Significantly different from the normal group at $p < 0.05$. [b]Significantly different from the HFD-fed + DS group at $p < 0.05$.

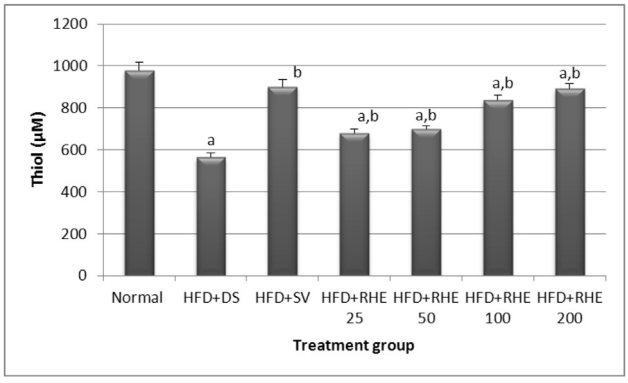

Fig. 4. Total thiol values in animals with fatty liver induced by HFD. Values are mean ± SEM. DS: Distilled water; HFD: high fat diet; RHE: *Rosa damascena* extract; SV: simvastatin. [a]Significantly different from the normal group at $p < 0.05$. [b]Significantly different from the HFD-fed + DS group at $p < 0.05$.

best effect on TIM (Fig. 4). In addition, all doses of RHE could remarkably increase FRAP value (Fig. 5).

3.4. Effect of RHE on liver histology

Liver sections evaluated histologically in order to confirm the efficacy of RHE on hepatic steatosis. Fig. 6A demonstrates liver

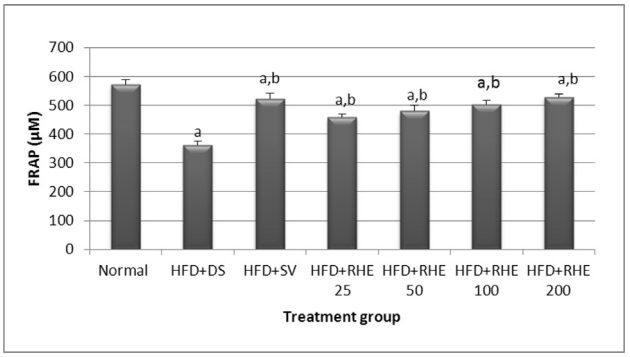

Fig. 5. FRAP (Ferric reducing ability of plasma) values in animals with fatty liver induced by HFD. Values are mean ± SEM. DS: Distilled water; HFD: high fat diet; RHE: *Rosa damascena* extract; SV: simvastatin. [a]Significantly different from the normal group at $p < 0.05$. [b]Significantly different from the HFD-fed + DS group at $p < 0.05$.

tissue of a normal rat in which large, round and fairly euchromatic and nuclei with no inflammatory cells were appeared. A higher level of steatosis was seen in animals fed with HFD for 8 weeks (Fig. 6C). Liver steatosis was determined by staining (hematoxylin-eosin) of the liver tissue. Severe fat vacuoles accumulation in the cytoplasmic of hepatocytes, steatohepatitis and pericentral necrosis as well as scattered inflammatory cell infiltration was represented in animals fed with HFD (Fig. 6C). As represented in Fig. 6B, limited symptoms of fatty change in liver cells of the simvastatin group indicate that the drug prevents the accumulation of triglycerides within hepatocytes. Steatohepatitis and necrosis were obviously suppressed by applying RHE treatment (Fig. 6D).

4. Discussion

Non-alcoholic fatty liver disease (NAFLD) is a common cause of chronic liver disease and its prevalence has approximately doubled in the past decade with the growing epidemic of obesity.[19] NAFLD is highly correlated with the so-called metabolic syndrome, along with diabetes, hypertension, atherosclerosis, hypertriglyceridemia and obesity. Unhealthy dietary habits and high calorie diets are among the most important risk factors. On the other hand, several studies showed that Mediterranean diet, applying various herbs and taking unsaturated fatty acids, reduce prevalence and/or severity of liver diseases including NAFLD.[20] NAFLD is associated with insulin resistance and hyperinsulinemia leading to a resistance in the antilipolytic effect of insulin in the adipose tissue with an increase of free fatty acids.[21,22]

There are limited conventional drugs for NAFLD which have different adverse effects; therefore, herbal remedies with lipid-lowering and antioxidant as well as anti-inflammatory activities can play a beneficial role for the management of the disease.[23]

R. damascena has been traditionally used in various diseases including gastrointestinal disease.[9] The fresh juice of *R. damascena* exhibited antioxidant potential effects in vitro.[24] Current study confirmed the efficacy of RHE in animal model of NAFLD. In this study, NAFLD was induced by a high fat diet and the outcome of treatment with RHE on gaining weight as well as lipid profile in treated animals was evaluated. All doses of RHE could moderate lipid plasma levels in rats under HFD diet compared with vehicle treated animals. RHE and simvastatin treatment could suppress AST and ALT levels. Beneficial effects of RHE treatment in NAFLD is also evaluated in histopathological studies.

An important risk factor in pathogenesis of NAFLD is oxidative stress. It has been shown that oxidation of cytotoxic free fatty acids cause by chronic oxidative stress, may lead to up regulation of

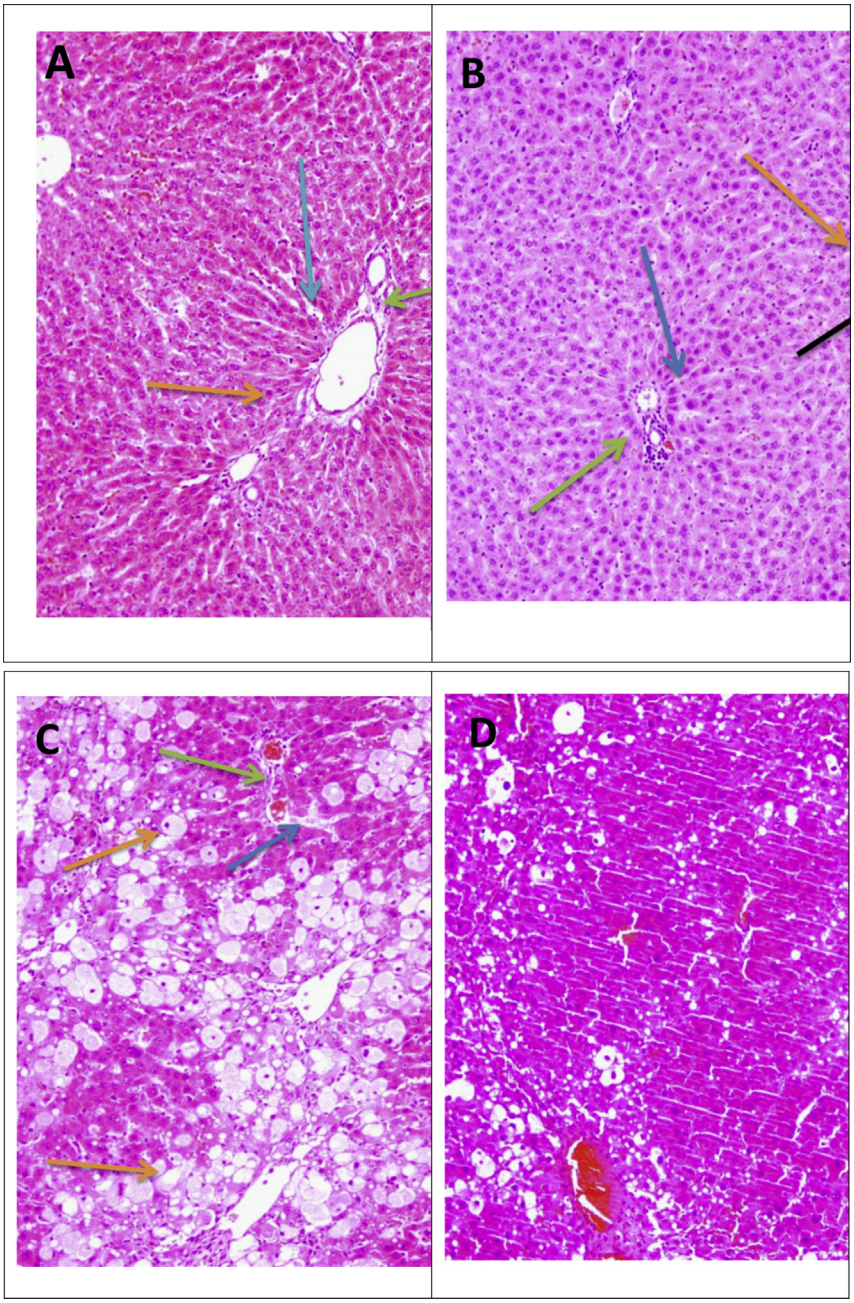

Fig. 6. Histological images of liver tissues obtained from animal groups. The liver sections were stained with hematoxylin and eosin (H & E), and the magnification is 40. A: Microscopic evaluation of normal group show large, round and fairly euchromatic and nuclei with no inflammatory cells. Black arrow shows normal centrilobular vein. Normal sinusoids are shown by blue arrows. Green arrow shows portal triad. Orange arrow shows normal hepatocyte. B: Histological images of liver tissues obtained from HFD-fed simvastatin group, no signs of fatty change in liver cells indicating that the drug prevents the accumulation of triglycerides within hepatocytes, inspite of heavy lipids fed. Hepatocytes have large, round and fairly euchromatic and nuclei with acidophilic cytoplasm. Some cells are degenerated or without nuclei. Kupffer cells count is more than normal. Black arrow shows normal centrilobular vein. Normal sinusoids are shown by blue arrows. Green arrow shows portal triad. Orange arrow shows hepatocyte. C: Microscopic evaluation of the HFD-fed control group showed intense hepatic steatosis, pericentral necrosis and abundant inflammatory cells. Severe fat vacuoles accumulation in the cytoplasmic of hepatocytes and vacuolar hepatocyte degeneration as well as numerous kupffer cells infiltration are seen. Sinusoids and centrilobular veins are dilated. . Black arrow shows dilated centrilobular vein. Dilated sinusoids are shown by blue arrows. Green arrow shows portal triad. Orange arrows show hepatocyte. D: Histological examination of liver tissues obtained from HFD-fed RHE (200 mg/kg) treated group, lipid accumulation within cytoplasm of hepatocytes were considerably diminished comparing to untreated group. Black arrow shows dilated centrilobular vein. Normal sinusoids are shown by blue arrows. Green arrow shows portal triad.

cytokine and depletion of hepatic antioxidant levels.[25] Free radicals are nowadays known as one of the prime suspects of inflammation and tissue damage in many chronic disorders, including liver diseases.[26,27] Products of lipid peroxidation such as malondialdehyde, GGT and oxidized LDL which are increased in NAFLD patients may be related to decreased antioxidants.[28] Therefore, applying antioxidant supplementations may play an important role and one of the current pharmacological treatments for NAFLD. Previous study by Memariani et al for the determination of phenolic components from flowers of *R. damascena* using HPLC analysis resulted in detection and quantification of three phenolic compounds including gallic acid (118.213 ± 0.12 mg/g dried extract), quercetin

(12.86 ± 0.31 mg/g dried extract), and syringic acid (3.48 ± 0.19 mg/g dried extract).[15] Determination of these polyphenols with HPLC analysis was executed for standardization of RHE.

Evaluation of biomarkers of oxidative damage in NAFLD animals treated with RHE extract showed significant suppression in MPO and LPO levels. In addition, TTM and FRAP value were remarkably higher in animals treated with the extract. Another species of the same genus, *Rosa laevigata* Michx showed hepatoprotective effects in rat model of CCl4-induced liver fibrosis through modulating inflammatory process and suppressing oxidative mediated by regulating TGF-β/Smad and mitogen-activated protein kinases (MAPK) signaling. Likewise, down-regulation of TNF-α level has a significant role in the hepatoprotective activity of total flavonoid extract from fruit of *R. laevigata* Michx.[29,30] High amount of phenolic compounds possess a pivotal contribution in therapeutic potential of this natural preparation in NAFLD animals. Phenolic compounds identified in standardized extract of RHE are well-known antioxidant agents which have demonstrated beneficial effects in several pathologic conditions, including hepatic injuries.[31–33] A wide range of experimental studies confirm the efficacy of phenolic compounds in the treatment of NAFLD via numerous biological mechanisms including ant-oxidative stress activity, inhibition of pro-inflammatory cytokines, and modulatory effect on inflammatory signaling pathways.[31] In addition, investigations revealed the beneficial effects of gallic acid – one of the main phenolics of RHE – in paracetamol induced hepatotoxicity through suppression of lipid peroxidation and anti-inflammatory activity via decreasing TNF-α.[34] Moreover, Oxygen radical absorbance capacity of plasma and the level of phenol sulfotransferase were significantly increased in rats treated with gallic acid and *p*-coumaric acid.[35] Gallic acid also attenuated steatohepatitis, hypercholesterolemia, weight gain, as well as insulin resistance via modulation of glycolysis, gluconeogenesis and metabolism of amino acids and choline in mice with NAFLD induced by high fat diet.[36] Chronic dietary intake of quercetin could suppress cholesterol and liver fat accumulation and improved systemic parameters related to metabolic syndrome, probably mainly through decreasing oxidative stress, by suppressing TNFα, hepatic thiobarbituric acid-reactive as well as peroxisome proliferator-activated receptor (PPAR)-α expression[37]. The beneficial effects of RHE in experimental NAFLD could be explained by considering the presence of these phenolic compounds with obvious antioxidant and hepatoprotective properties.

5. Conclusion

R. damascena from the family Rosaceace is a traditionally used medicinal plant which has demonstrated beneficial effects in several gastrointestinal complications. Current study demonstrated positive effects of *R. damascena* as a dietary supplement and an alternative medicine in the management of NAFLD. *R. damascena* significantly reduced the elevations of serum TG, cholesterol, LDL, and hepatic enzymes. Improvement of antioxidant status as well as hepatoprotective activity mediated by phenolic ingredients are among the main potential mechanisms of action of this natural remedy. Since this plant is well-known and safe so could be a candidate as an adjuvant therapy along with conventional pharmacological treatments for future human studies in patients suffering from NAFLD.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

This study is supported by Tehran University of Medical Sciences, Tehran, Iran.

References

1. Cohen JC, Horton JD, Hobbs HH. Human fatty liver disease: old questions and new insights. *Science*. 2011;332:1519–1523.
2. Moore JB. Non-alcoholic fatty liver disease: the hepatic consequence of obesity and the metabolic syndrome. *Proc Nutr Soc*. 2010;69(02):211–220.
3. Sanna C, Rosso C, Marietti M, Bugianesi E. Non-alcoholic fatty liver disease and extra-hepatic cancers. *Int J Mol Biol*. 2016;17(5):717.
4. Fan JG. Epidemiological studies of nonalcoholic fatty liver disease in China. *Chin J Postgrad Med (Chin)*. 2010;33:4–6.
5. Farzaei MH, Rahimi R, Farzaei F, Abdollahi M. Traditional medicinal herbs for the management of diabetes and its complications: an evidence-based review. *Int J Pharmacol*. 2015;11(7):874–887.
6. Gudin S. Rose: genetics and breeding. *J Plant Breed*. 2000;17:159–189.
7. Farzaei MH, Abbasabadi Z, Sahms-Ardekani MR, Abdollahi M, Rahimi R. A comprehensive review of plants and their active constituents with wound healing activity in traditional Iranian medicine. *Wounds*. 2014;26(7):197–206.
8. Bahramsoltani R, Farzaei MH, Farahani MS, Rahimi R. Phytochemical constituents as future antidepressants: a comprehensive review. *Rev Neurosci*. 2015;26(6):699–719.
9. Boskabady MH, Shafei MN, Saberi Z, Amini S. Pharmacological effects of rosa damascena. *Iran J Basic Med Sci*. 2011;14(4):295–307.
10. Shirazi M, Mohebitabar S, Bioos S, et al. The effect of topical *Rosa damascena* (rose) oil on pregnancy-related low back pain: a randomized controlled clinical trial. *J Evid Based Complement Altern Med*. 2017;22(1):120–126.
11. Farzaei MH, Rahimi R, Abbasabadi Z, Abdollahi M. An evidence-based review on medicinal plants used for the treatment of peptic ulcer in traditional Iranian medicine. *Int J Pharmacol*. 2013;9(2):108–124.
12. Schiber A, Mihalev K, Berardini N, Mollov P, Carle R. Flavonol glycosides from distilled petals of *Rosa damascena* Mill. *Z Naturforsch C*. 2005;60(5–6):379–384.
13. Loghmani-Khouzani H, Sabzi-Fini O, Safari J. Essential oil composition of *Rosa damascena* Mill cultivated in central Iran. *Sci Iran*. 2007;14:316–319.
14. Sedighi. In vitro impact of hydroalcoholic extract of *Rosa damascena* Mill. On rat ileum contractions and the mechanisms involved. *Int J Prev Med*. 2014;5(6):767–775.
15. Memariani Z, Amin G, Moghaddam G, Hajimahmoodi M. Comparative analysis of phenolic compounds in two samples of *Rosa damascena* by HPLC. *Int J Biosci (IJB)*. 2015;7(1):112–118.
16. Rahimi R, Baghaei A, Baeeri M, et al. Promising effect of *Magliasa*, a traditional Iranian formula, on experimental colitis on the basis of biochemical and cellular findings. *World J Gastroenterol*. 2013 Mar 28;19(12):1901.
17. Soleimani H, Ranjbar A, Baeeri M, et al. Protection by *Nigella sativa* L. of CCL 4-induced toxic nitrosative stress in rats. *Toxicol Lett*. 2008;180:S39.
18. Navaei-Nigjeh M, Rahimifard M, Pourkhalili N, et al. Multi-organ protective effects of cerium oxide nanoparticle/selenium in diabetic rats: evidence for more efficiency of nanocerium in comparison to metal form of cerium. *Asian J Anim Vet Adv*. 2012;7(7):605–612.
19. Bugianesi E, McCullough AJ, Marchesini G. Insulin resistance: a metabolic pathway to chronic liver disease. *Hepatology*. 2005;42:987–1000.
20. Nseir W, Hellou E, Assy N. Role of diet and lifestyle changes in nonalcoholic fatty liver. *World J Gastroenterol*. 2014;20(28):9338–9344.
21. Marchesini G, Brizi M, Morselli-Labate AM, et al. Association of nonalcoholic fatty liver disease with insulin resistance. *Am J Med*. 1999;107(5):450–455.
22. Gaggini M, Morelli M, Buzzigoli E, DeFronzo RA, Bugianesi E, Gastaldelli A. Non-alcoholic fatty liver disease (NAFLD) and its connection with insulin resistance, dyslipidemia, atherosclerosis and coronary heart disease. *Nutrients*. 2013;5(5):1544–1560.
23. Pisonero-Vaquero S, González-Gallego J, Sánchez-Campos S, García-Mediavilla MV. Flavonoids and related compounds in non-alcoholic fatty liver disease therapy. *Curr Med Chem*. 2015;22(25):2991–3012.
24. Achuthan CR, Babu BH, Padikkala J. Antioxidant and hepatoprotective effects of *Rosa damascena*. *Pharm Biol*. 2003;41(5):357–361.
25. Garcia-Ruiz C, Colell A, Morales A, Kaplowitz N, Fernandez Checa JC. Role of oxidative stress generated form the mitochondrial electron transport chain and mitochondrial glutathione status in loss of mitochondrial function and activation of transcription factor nuclear factor-kappa B: studies with isolated mitochondria and rat hepatocytes. *Mol Pharmacol*. 1995;48:825–834.
26. Yesilova Z, Yaman H, Oktenli C, et al. Systemic markers of lipid peroxidation and antioxidants in patients with nonalcoholic fatty liver disease. *Am J Gastroenterol*. 2005;100:850–855.
27. Shokoohinia Y, Rashidi M, Hosseinzadeh L, Jelodarian Z. Quercetin-3-O-β-d-glucopyranoside, a dietary flavonoid, protects PC12 cells from H 2 O 2-induced cytotoxicity through inhibition of reactive oxygen species. *Food Chem*. 2015;167:162–167.
28. Del Ben M, Polimeni L, Baratta F, Pastori D, Angelico F. The role of nutraceuticals for the treatment of non-alcoholic fatty liver disease. *Brit J Clin Pharm*. 2017;83(1):88–95.

29. Liu YT, Lu BN, Peng JY. Hepatoprotective activity of the total flavonoids from *Rosa laevigata Michx* fruit in mice treated by paracetamol. *Food Chem*. 2011;125(2):719–725.
30. Dong D, Zhang S, Yin L, et al. Protective effects of the total saponins from *Rosa laevigata Michx* fruit against carbon tetrachloride-induced acute liver injury in mice. *Food Chem Toxicol*. 2013;62:120–130.
31. Akhlaghi M. Non-alcoholic fatty liver disease: beneficial effects of flavonoids. *Phytother Res*. 2016;30(10):1559–1571.
32. Farzaei MH, Abdollahi M, Rahimi R. Role of dietary polyphenols in the management of peptic ulcer. *World J Gastroenterol*. 2015;21(21):6499–6517.
33. Farzaei MH, Khanavi M, Moghaddam G, et al. Standardization of *Tragopogon graminifolius* DC. Extract based on phenolic compounds and antioxidant activity. *J Chem*. 2014:2014.
34. Rasool MK, Sabina EP, Ramya SR, et al. Hepatoprotective and antioxidant effects of gallic acid in paracetamol-induced liver damage in mice. *J Pharm Pharm*. 2010;62(5):638–643.
35. Yeh CT, Yen GC. Modulation of hepatic phase II phenol sulfotransferase and antioxidant status by phenolic acids in rats. *J Nutr Biochem*. 2006;17(8):561.
36. Chao J, Huo TI, Cheng HY, et al. Gallic acid ameliorated impaired glucose and lipid homeostasis in high fat diet-induced NAFLD mice. *PloS One*. 2014;9(6):e96969.
37. Kobori M, Masumoto S, Akimoto Y, Oike H. Chronic dietary intake of quercetin alleviates hepatic fat accumulation associated with consumption of a Western-style diet in C57/BL6J mice. *Mol Nutr Food Res*. 2011;55(4):530–540.