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Original Article

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

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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

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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]

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