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Original Article

Effect of Long-term Administration of *Ferula Gummosa* Root Extract on Serum Oxidant-antioxidant Status

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Abstract

Ferula gummosa Boiss is a good source of biologically active compounds such as monoterpene and sesquiterpene derivatives. There are also several reports on antioxidant effects of these compounds. The aim of this study was to investigate the effect of daily administration of *F. gummosa* root hydro-alcoholic extract on serum oxidant-antioxidant status. Twenty four Wistar rats were randomly divided into three groups: (1) control, (2) *F. gummosa* extract 100 mg/kg, and (3) *F. gummosa* extract 600 mg/kg. The extract was administered by orogastric gavage once daily for 28 consecutive days. The activity of catalase and superoxide dismutase (SOD) enzymes, and the level of malondialdehyde (MDA, as a marker of lipid peroxidation) and total thiol groups were evaluated in blood samples of fasting animals on day 0 and day 28. *F. gummosa* extract at both doses significantly increased the activity of catalase ($p<0.01$). The extract at dose of 600 mg/kg significantly increased the activity of SOD ($p<0.05$), and reduced the level of MDA. *F. gummosa* had no effect on content of total thiol groups. In conclusion, long-term consumption of hydro-alcoholic extract of *F. gummosa* root increases the defense of the body against oxidative stress by increasing the activity of catalase and SOD, and by reducing lipid peroxidation.

***Key words*:** Catalase, *Ferula gummosa*, Malondialdehyde, rat, root, Superoxide dismutase.

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1. Introduction

Many types of free radicals are generated in cellular metabolism and known to play a dual role as both toxic and beneficial compounds. The formation and removing of these species are kept in balance through the function of antioxidant defense system in the body. The delicate balance between proxidant and antioxidant effects is clearly an important aspect of life [1]. If this balance tends to the overproduction of reactive species, the cells start to suffer the consequences of oxidative stress [2]. The harmful effects of oxidative stress can be counteracting by highly complex antioxidant defense systems in living organisms. This system includes endogenous antioxidant produced in the body and exogenous antioxidant which obtained from diet or supplements [3]. Antioxidants compounds offer protection against oxidative stress by several mechanism including inhibiting the lipid peroxidation and scavenging the free radicals, and therefore prevent the disease progression [4].

The enzymatic human defenses against oxidative stress consist of catalase, glutathione peroxidase, and superoxide dismutase (SOD). These enzymes have a key role in free radical-removing system in human body through conversion of superoxide anion radicals to H2O2 and then catalyzing it to H2O and O2 [5]. An overproduction of oxidative stress can cause the oxidation of lipids and proteins, which is related with changes in their functions and structure [6]. Peroxidation of unsaturated membrane fatty acids produces malondialdehyde (MDA), an indication of the overall lipid peroxidation level [7]. The other targets that are attacked by free radicals are protein and non-protein thiol groups which have basic role in protection of the structure and function of intracellular and extracellular proteins. These groups are very sensitive to oxidative damages and their reduction is an important symptom of oxidative stress [8].

In the recent years, use of safe sources of antioxidants, especially of natural origin, has notably increased [9, 10]. *Ferula gummosa* Boiss is a wild medicinal plant belonging to the family of the Apiaceae and grow in Europe and Asia

particularly in the northern parts of Iran [11]. In Persian, the root and the oleoresin of *F. gummosa* called "Ghasni" and "Barijeh", respectively. In traditional medicine, people use the harvested roots or resin for teraputic purposes like tonic, emmenagogue and anti-diarrhea [12, 13]. This plant also shows several biological activities, including anticonvulsant [14], antinociceptive and anti-inflammatory [15], antiprolifrative [16, 17], cardioprotective [18], and spasmolytic effects [19]. Recent studies have revealed that *F. gummosa* is a good source of biologically active compounds such as monoterpene and sesquiterpene derivatives [20, 21]. On the other hands, there are several reports on antioxidant effects of these compounds [22, 23]. Although a previous in vitro study reported that *F. gummosa* has nitric oxide and hydrogen peroxide scavenging activities [24], no study has yet evaluated the effect of long-term administration of *F. gummosa* root extract on serum oxidant-antioxidant status. Therefore, in this study, we have examined the antioxidant effects of hydro-alcoholic extract of *F. gummosa* root when it was administered 4 weeks to rats.

2. Materials and Methods

2.1. Preparation of Hydro-alcoholic Extract of F. gummosa

The roots *F. gummosa* Boiss were collected from Hezarmasjed Mountains (Khorasan Province, Iran) and identified by Mohammadreza Joharchi, Ferdowsi University of Mashhad Herbarium (voucher specimen number 34577). The roots were dried and crushed to a powder with an electric microniser. The powdered roots (200 g) were extracted with 1000 mL 70% ethanol by maceration at 37°C for 72 h. The prepared extract was concentrated under reduced pressure (yielded 13%) and kept at -20 ºC until use [25, 26].

2.2. Animals and Treatment

Male Wistar rats (250-350 g) were obtained from Laboratory Animals Research Center of Mashhad University of Medical Sciences (Iran). The animals were kept at constant temperature (22 ± 2 °C) and standard conditions of a 12 h light/dark cycle with free access to food pellets and tap water, available *ad libitum*. All procedures were performed in accordance with the National Institutes of Health Guidelines for the Care and

Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee of Mashhad University of Medical Sciences.

Twenty four rats were randomly divided into three groups of eight animals each. Group 1 (control) was received only vehicle (distilled water), while groups 2 and 3 were administered by orogastric gavage once daily with 100 mg/kg and 600 mg/kg of *F. gummosa* extract for 28 consecutive days, respectively. These doses were chosen based on previous animal studies demonstrating pharmacological effects from these doses of *F. gummosa* extract [14, 18, 27].

For biochemical assays, at day 0 and at the end of experiments (28th day), blood samples were collected from retro-orbital sinus of fasted animals.

2.4. Determination of Catalase Activity

Catalase activity was measured according to the method of Aebi with a little modification [28, 29]. The principle of this assay is based on determination of the rate constant, k, (dimension: s-1, k) of hydrogen peroxide decomposition. Briefly, the enzyme activity was determined by measuring the decrease in absorbance at 240 nm of a reaction mixture consisting of H2O2, in phosphate buffer, pH 7.0, and requisite volume of serum sample. By measuring the decrease in absorbance at 240 nm per minute, the rate constant of the enzyme was determined. Activities were calculated and expressed as k (rate constant) per liter (as μmole/min/mg of total protein).

2.5. Determination of SOD Activity

SOD activity was measured by the method of Madesh and Balasubramanian [30]. A colorimetric assay involving generation of superoxide by pyrogallol auto-oxidation and inhibition of superoxide-dependent reduction of the tetrazolium (3-(4,5-dimethylthiazol-2-yl) 2,5-diphenyl tetrazolium) to formazan dye by SOD was measured at 570 nm. The reaction was terminated by addition of dimethyl sulfoxide (DMSO) which also helps to solubilize the formazan formed. One unit of SOD activity was defined as the amount of enzyme causing 50% inhibition in the tetrazolium reduction rate.

2.6. MDA Assay

The level of MDA was estimated by the double heating method of Draper and Hadley [31]. The method was based on spectrophotometric

measurement of the red color generated by the reaction of thiobarbituric acid (TBA) with MDA. In this method, 2.5 ml of 10% trichloroacetic acid solution was added to 0.5 ml supernatant in each tube and the tubes were boiled in water bath for 15 min. After cooling in water, the tubes were centrifuged and 2 ml of the supernatant was added to 1 ml of 0.67% TBA solution in a test tube. The tube was then placed in a boiling water bath for 15 min and then cooled in tap water and its absorbance was measured at 532 nm. The concentration of MDA was calculated by the absorbance coefficient of the MDA-TBA complex (absorbance coefficient E = 1.56 × 105 cm-1 M-1) and is expressed as μmole/μL.

2.7. Thiol Evaluation

DTNB (2, 2'-dinitro-5, 5'-dithiodibenzoic acid) reagent, which reacts with the SH group, was used to determine the total thiol groups. The produced yellow complex has a peak absorbance at 412 nm. In brief, 50 μL of serum was added to 1 ml Tris-ethylenediaminetetraacetic acid (EDTA) buffer (pH = 8.6) and the absorbance was read at 412 nm against Tris-EDTA buffer alone (A1). Then, 20 μL of 10 mM DTNB solution was mixed with the solution and it was stored in room temperature for 15 min and the absorbance was read again (A2). The absorbance of DTNB reagent was also read as blank (B). Total thiol concentration (mM) was calculated as follow equation [32].

Total thiol concentration (mM) = (A2 – A1 – B) × 1.07 / 0.05 × 13.6

2.8. Data Analysis

Statistical analyses were performed by the statistical package SPSS for Windows, Version 6.1.3 (SPSS, Chicago, IL). Analysis between experimental groups was carried out using one-way Analysis of Variance (ANOVA) followed by Tukey's post hoc test for multiple comparisons. Paired *t*-test was used for comparison of data between day 0 and day 28 within group. The results are shown as mean ± SEM and p value less than 0.05 was considered statistically significant.

3. Results and Discussion

As shown in Figure 1, daily oral administration of *F. gummosa* at the dose of 100 mg/kg significantly increased serum catalase activity from 37 ± 13 U/L (day 0) to 138 ± 24 U/L (day 28). Similarly, administration of 600 mg/kg of *F. gummosa* extract for 28 days significantly increased serum catalase activity ($p < 0.01$).

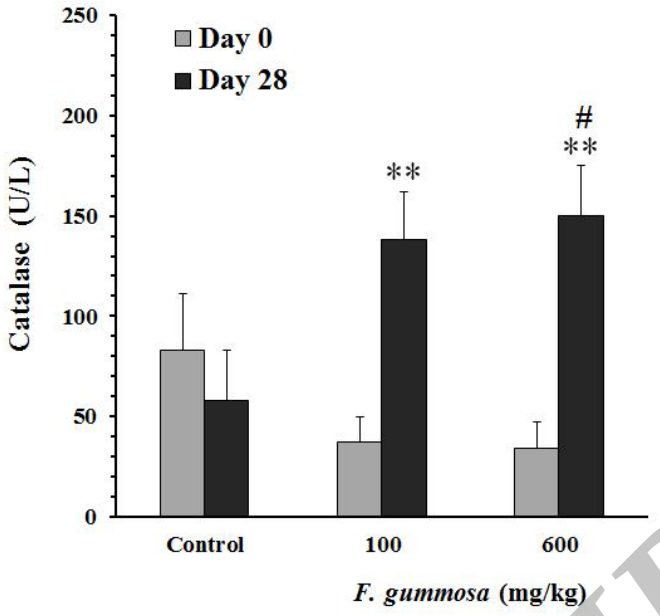

Figure 1. Effect of *F. gummosa* hydroalcoholic extract on serum catalase activity in rat. The extract was administrated by orogastric gavage once daily for 28 consecutive days. Values are expressed as mean ± SEM (n = 8). **p<0.01 *vs* day 0 in the corresponding group; #p<0.05 *vs* day 28 in control group.

Treatment of rats with 100 mg/kg of *F. gummosa* for 4 weeks caused no significant change in the activity of SOD (Figure 2). However, the activity of serum SOD was significantly higher in the animals received 600 mg/kg of *F. gummosa* extract ($p < 0.01$). Figure 3 shows that administration of 100 and 600 mg/kg of *F. gummosa* extract had no significant effect on serum thiol content. Treatment of the animals with 100 mg/kg of the extract caused no significant change in the level of serum MDA (Figure 4). However, dose of 600 mg/kg of the extract could significantly reduce serum MDA level ($p < 0.05$).

Today, the search for natural antioxidants with lesser side effects than synthetic antioxidant compounds is of great interest [4]. In general, the results of our research indicated that long-term administration of *F. gummosa* root extract lead to increase of activity of serum antioxidant enzymes catalase and SOD and to decrease of lipid peroxidation. These effects of *F. gummosa* were observed at dose of 600 mg/kg and the lower dose (100 mg/kg) had no significant effect on the activity of SOD and on the level of MDA.

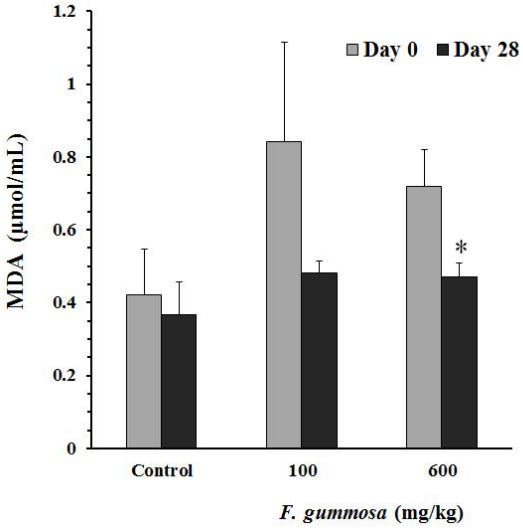

Figure 4. Effect of *F. gummosa* hydroalcoholic extract on serum malondialdehyde (MDA) level in rat. The extract was administrated by orogastric gavage once daily for 28 consecutive days. Values are expressed as mean ± SEM (*n* = 8). *p<0.05 *vs* day 0 in the corresponding group.

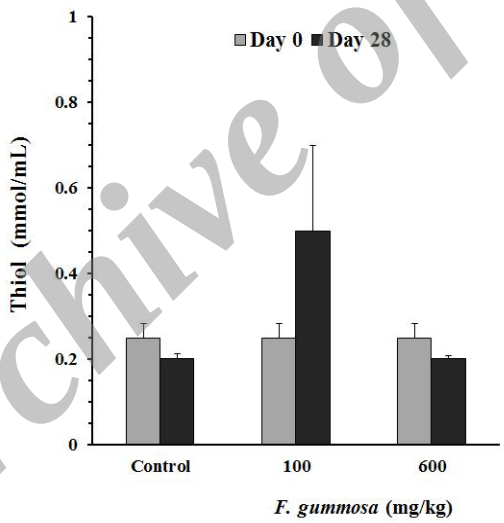

Figure 3. Effect of *F. gummosa* hydroalcoholic extract on serum thiol content in rat. The extract was administrated by orogastric gavage once daily for 28 consecutive days. Values are expressed as mean ± SEM (*n* = 8).

Studies on the molecular mechanisms of oxyradicals-induced cellular injury have revealed that OH˚ and HO2˚ lead to cellular damages through affecting on proteins, nucleic acid, and phospholipids [33]. The SOD is one of the main intracellular enzymes which neutralizes

superoxide radicals and inhibits lipid peroxidation [34]. In the present study, high dose of *F. gummosa*, but not low dose (100 mg/kg), considerably increased the activity of SOD enzyme. In consistent with our findings, Kiasalari *et al*. showed that low dose (≤ 100 mg/kg) of plant of *Ferula* family failed to change SOD activity [10]. The antioxidant action of SOD will be more effective when followed by increased catalase activity. Catalase is a member of the antioxidant defense system that cooperates with SOD against increase of reactive oxygen specious level [28]. In consistent with our results, previous studies suggests that *F. gummosa* root extract is able to scavenge H_2O_2 and this ability is attributable to phenolic and other electron-donating components of this plant [24].

Plasma has relatively low amount of thiol-based antioxidants and the level of thiols in plasma is lower than in cells [35] Although some studies on the other species of *Ferula genus* (e.g. *F. asafoetida*) reported that they can elevate the level of thiol groups in serum [36], in the present work the *F. gummosa* root extract did not have any effect on serum thiol content. This conflict can be attributed to difference in plant genus, plant habitat, the parts of plant used in extraction, method of extraction, and duration of administration.

The MDA is a mutagenic compound which can be derived from lipid peroxidation process as a byproduct [37]. In our study, MDA level reduced in the group received high dose of *F. gummosa* extract. This effect indicates that *F. gummosa* could neutralize free radicals before they can peroxide lipids. The reduced level of MDA is consistent with the increased activity of SOD, because superoxide anions can indirectly be trigger of lipid peroxidation. Therefore, increased activity of SOD prevent from increasing the level of MDA through neutralization of these anions. Results of previous studies on the other species of *Ferula* genus support our data. It has shown that *F. szovitsiana*, *F. flabelliloba*, and *F. diversivitata* extracts are able to increase activity of catalase, SOD, and to reduce liver lipid peroxidation [38, 39].

Phytochemical analysis has shown that the major components in *F. gummosa* are terpenoids (monoterpenes and sesquiterpene derivatives) and alkaloids [40-43]. There are several reports that terpenoids have antioxidant effects [44, 45]. Also, it has shown that some biological effects of *F.*

gummosa are mediated through its antioxidant property. For example, Moosavi *et al*. demonstrated that *F. gummosa* reduces oxidative stress in renal tissues of rats treated with nitric oxide synthase inhibitor [46]. Also, Gholitabar *et al*. reported that administration of *F. gummosa* to hypertensive rats led to balance in oxidant/antioxidant process and the inhibition of vascular dysfunction [18]. Considering the role of oxidative stress in the pathogenesis of several diseases such as cancer, myocardial injury, diabetes and neurodegenerative diseases [47, 48], results of present study suggest that continuous consumption of *F. gummosa* root may increase the defense of the body against oxidative stress and therefore reduce the stress-induced diseases. However, although our previous primary study showed that *F. gummosa* root is generally safe, yet it should be considered that some unwanted effects (e.g. decreased motor coordination) may appear following long-term continuous consumption of this plant [49].

4. Conclusion

In conclusion, hydro-alcoholic extract of *F. gummosa* root increases the defense of the body against oxidative stress by increasing the activity of catalase and SOD, and by reducing lipid peroxidation. These effects may increase the defense of the body against oxidative stress and therefore reduce the stress-induced diseases.

Ethical approval

All authors hereby declare that, "Principles of laboratory animal care" (NIH publication number 85-23, revised 1985) was followed, as well as specific national laws where applicable. All experiments have been examined and approved by the Ethics Committee of Mashhad University of Medical Sciences.

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