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Original Article

The effect of hydroalcoholic extract of *Ferula foetida* stems on blood pressure and oxidative stress in dexamethasone-induced hypertensive rats

Leila Safaeian[1,*], Alireza Ghannadi[2], Shaghayegh Haghjoo Javanmard[3], and Mohammad Hadi Vahidian[1]

[1]*Department of Pharmacology and Toxicology and Isfahan Pharmaceutical Sciences Research Center, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, I.R. Iran.*
[2]*Department of Pharmacognosy, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, I.R. Iran.*
[3]*Applied Physiology Research Center, Isfahan University of Medical Sciences, Isfahan, I.R. Iran.*

Abstract

Ferula foetida (Bunge) Regel. is one of the most widespread and important *Ferula* species with nutritional and medicinal applications. Some phytochemicals with helpful cardiovascular effects have been isolated from *Ferula* species. The present study was designed to evaluate the effects of hydroalcoholic extract of the stems of *F. foetida* in dexamethasone (Dex)-induced hypertension in rats. Hypertension was induced by subcutaneous injection of Dex (30 µg/kg) for 14 days. In a prevention study, rats received oral *F. foetida* extract (200, 400 and 800 mg/kg) for 4 days prior to Dex administration and during the test period (Days 1-18). In a treatment study, *F. foetida* extract was administered from day 8 to 14. Systolic blood pressure (SBP) was evaluated using tail-cuff method. The thymus weight was measured as an indicator of glucocorticoid activity. The hydrogen peroxide (H_2O_2) concentration and ferric reducing antioxidant power (FRAP) were measured in plasma samples. Dex-induced hypertensive rats showed significant increases in SBP and in plasma H_2O_2 and decreases in the body and thymus weights and in FRAP value (P<0.001). Administration of *F. foetida* extract significantly prevented and reversed hypertension at all doses. It also increased plasma FRAP value (P<0.001) but failed to decrease plasma H_2O_2 concentration. These results suggest antihypertensive and antioxidant effects of *F. foetida* stem extract in Dex-induced hypertension. More investigations are needed to elucidate the exact mechanism of antihypertensive effect of this traditional phytomedicine.

Keywords: *Ferula foetida*; Hypertension; Antioxidant activity; Dexamethasone

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INTRODUCTION

Hypertension or silent killer is an important risk factor for life-threatening cardiovascular diseases such as stroke, myocardial infarction, arteriosclerosis, heart failure, kidney failure, blindness, and cognitive impairment (1). The hypertension prevalence is increasing worldwide and it is predicted that 60% of the population will suffer from hypertension in 2025 (2). Management of hypertension with antihypertensive regimen could reduce the risk of cardiovascular events nevertheless their use is often associated with several side effects (3). Therefore, development of new therapeutic agents with less adverse effects and better tolerability is imperative. The results of some epidemiological studies have shown the blood pressure lowering effect of fruits and vegetables (4). Herbal medicine and natural products have been recently considered for prevention and management of hypertension and the antihypertensive effects of some of these plants have been validated (5).

The Iranian flora consists of nearly thirty species of *Ferula. Ferula foetida* (Bunge) Regel. is one of the most widespread and important Ferula species of Iran that belongs to the Umbelliferae family. The Persian name of this 1.5-2-meter-tall perennial herb is

*Corresponding author: L. Safaeian
Tel: 0098 31 37927067, Fax: 0098 31 36680011
Email: leila_safaeian@pharm.mui.ac.ir

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"Gandeh Koma" (6). *F. foetida* is used in cooking to add flavor to dishes and as pickles in some regions of Iran. Ferula species and this medicinal herb are used for the treatment of different diseases in ayurveda and traditional medicines particularly in gastrointestinal disorders, nervous disorders and respiratory problems (7). They have several pharmacological activities such as antiulcerogenic, antiflatulent, digestive (7), antibacterial, antiviral, antifungal (8), cancer chemopreventive, anti-diabetic (7,9), antispasmodic, antihaemolytic (10,11), antihelmintic, antiparasitic, antiinfertility, anti-hepatotoxic and chemoprotective in nephrotoxicity (11,12). There is also some evidence for beneficial cardiovascular properties from *F. foetida* including anticholesterolemic, anticoagulant, anti-inflammatory and antioxidant activities (11).

Phytochemical analysis of species of Ferula have shown the presence of some natural compounds like coumarins, chromones, terpenoids, phenylpropanoids, flavonoids, alkaloids, sulfur-containing compounds and ferulic acid (7,13). Ferulic acid is a natural common hydroxycinnamic acid which is found in several species of Ferula. It is antioxidant, anti-atherosclerosis, vasodilator and neuroprotective against oxidative stress-related apoptosis (14).

According to the reported activities and compounds of *F. foetida*, in this study we evaluated the hypotensive effects of the stems of this plant at various doses in dexamethasone (Dex)-induced hypertensive rats.

MATERIALS AND METHODS

Animals

Male Wistar rats weighing 200 ± 20 g were obtained from the animal house of the School of Pharmacy and Pharmaceutical Sciences (Isfahan, Iran). The animals were housed in polypropylene cages under standard laboratory conditions in a 12 h light/12 h dark cycle. The rats had free access to tap water and standard pellet diet. All animal experiments were approved by the Ethics Committee of Isfahan University of Medical Science and performed in accordance with National Institute of Health Guide for the Care and Use of Laboratory Animals.

Chemicals

Captopril was a gift from Tehran Darou Pharmaceutical Co. (Tehran, Iran). Dexamethasone was supplied by Darou Pakhsh Pharmaceutical Co. (Tehran, Iran). Folin-Ciocalteu reagent was obtained from Merck Co. (Mumbai, India). The assay kits for estimation of plasma hydroperoxides levels and ferric reducing antioxidant power (FRAP) were purchased from Hakiman Shargh Research Co. (Isfahan, Iran).

Plant material and preparation of extract

The fresh stems of *F. foetida* were collected from around the city of Sabzevar in Razavi Khorasan Province in northeastern Iran in spring 2012. The plant was authenticated by Dr. Lili Ghaemmaghami at Department of Biology in Isfahan University, Isfahan, Iran. A voucher specimen (No. 1715) of the plant is deposited in the herbarium of the School of Pharmacy and Pharmaceutical Sciences, Isfahan, Iran.

Fresh stems of the plant (3176 g) were crushed and extracted with 5.7 L 96% ethanol by percolation method at room temperature for four days. After filtartion of the extract, ethanol was evaporated by rotary evaporator under reduced pressure at 50 °C and the produced extract was freeze-dried to yied 413.7 g powder.

Determination of total phenolic content

Total phenolic content of the plant extract was measured by Folin-Ciocalteu method (15). Briefly, the plant extract samples and gallic acid (as a phenolic compound standard) were dissolved in sodium carbonate solution (20%) and mixed with diluted Folin-Ciocalteu's phenol reagent. Stock solution of gallic acid was diluted in water to give concentrations of 50, 100, 150, 250 and 500 mg/L. After preparing the blank and the reference solutions, absorbances were measured at 765 nm using a UV spectrophotometer. Total phenolic content of the plant stems was measured and the results were reported as gallic acid equivalents (GAE) per g of the plant.

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Thin-layer chromatography of the extract

For detecting the presence of ferulic acid in the plant extract, 0.1 g of the freeze-dried extract was dissolved in methanol and water (50:50 v/v) and then analyzed by thin-layer chromatography method (16). The analysis was carried out on Silica gel GF 254 precoated activated plates with 250 µm thickness (Merck, Germany) and developed in different mobile phases where chloroform-methanol-formic acid 85% (85:15:1) gave the highest resolution. Ferulic acid spot was visualized by UV illumination at 254 and 365 nm.

Experimental protocol

Hypertension was induced in animals by subcutaneous (s.c.) injection of Dex (30 µg/kg/day) for 14 days (17). The saline control group received daily injection of saline (1 ml/kg, s.c.). In a prevention study, *F. foetida* extract at 200, 400 and 800 mg/kg or captopril at 40 mg/kg (as an antihypertensive positive control), were administered orally using an intra-gastric tube 4 days before Dex administration and for 14 days afterward. In the treatment study, the animals received *F. foetida* extract or captopril from day 8 to 14. Six rats were used in each control and experimental groups. All animals were weighed on alternate days. At the end of the study, animals were sacrificed under ether anesthesia. The thymus gland was removed and weighed. The blood was collected from the neck region and plasma samples were used for further experiments.

Measurement of systolic blood pressure

Systolic blood pressure (SBP) was measured at the first day and the last day of the study by non-invasive tail-cuff method (AD Instrument PowerLab Data Acquisition System, Australia) in conscious rats restrained in heated chambers at 38 ± 1 ºC. Rats were trained with the equipment for one week before initiation of the experiment. At least 3 blood pressure values were recorded for each rat and averaged to take a mean SBP.

Measurement of thymus weight

The thymus gland weight was expressed relative to the body weight (mg/100 g of body weight) and was used as a marker of glucocorticoid activity (18).

Measurement of plasma hydroperoxides concentration

The plasma hydroperoxides concentration was assessed using commercially available kit based on the ferrous ion oxidation by xylenol orange reagent in aqueous medium with sorbitol (FOX1) (19). In brief, FOX1 reagent containing ammonium ferric sulfate was prepared in aqueous medium with sorbitol according to the manufacturer's protocol and was mixed with plasma samples. The mixture was incubated for 30 min at 37 ºC. Then absorbance was read at 540 nm against reagent blank using a microplate reader/spectrophotometer (Bio-Tek, PowerWaveXS, USA) and H_2O_2 concentration of plasma samples was estimated using a standard curve generated with different concentrations of hydrogen peroxide.

Measurement of plasma ferric reducing antioxidant power

The total antioxidant capacity of plasma samples was determined based on ferric reducing antioxidant power (FRAP) assay (20). FRAP value was estimated using commercially available kit based on the reduction of ferric tripyridyltriazine complex to ferrous form. In brief, the FRAP reagent containing tripyridyltriazine/ferric chloride/acetate buffer was prepared according to the manufacturer's protocol and was mixed with plasma samples. The mixture was incubated for 40 min at 40 °C. Then absorbance was read at 570 nm using a micro plate reader/spectrophotometer and the FRAP value of samples was assessed against the standard curve of FeSO4.7H2O concentration and expressed as micromole of Fe II equivalents per liter.

Statistical analysis

Results were reported as the mean ± SEM. Statistical analysis was performed by one-way analysis of variance (ANOVA) followed by *Tukey post-hoc* test using SPSS software version 16.0. The values of $P<0.05$ were regarded to be statistically significant.

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RESULTS

Total phenolic content

The total phenol content assay showed 23.7 ± 7.9 mg GAE/g of the fresh stem of the plant.

Thin-layer chromatography of the extract

Ferulic acid spot was visualized by UV illumination and its R_f was 0.77.

Effects of F. foetida extract on blood pressure in prevention study

Administration of Dex significantly increased the blood pressure from 110.2 ± 3.5 to 142.5 ± 6.2 mmHg (P<0.001) when compared to saline control group (109.6 ± 3.4 mmHg). Pretreatment with *F. foetida* extract (200, 400 and 800 mg/kg) and captopril (40 mg/kg) prevented the increase in SBP (P<0.001) (Fig. 1).

Effects of F. foetida extract on blood pressure in treatment study

In treatment study, administration of captopril and *F. foetida* extract at all doses significantly reduced the SBP in Dex-induced hypertensive rats (Fig. 2).

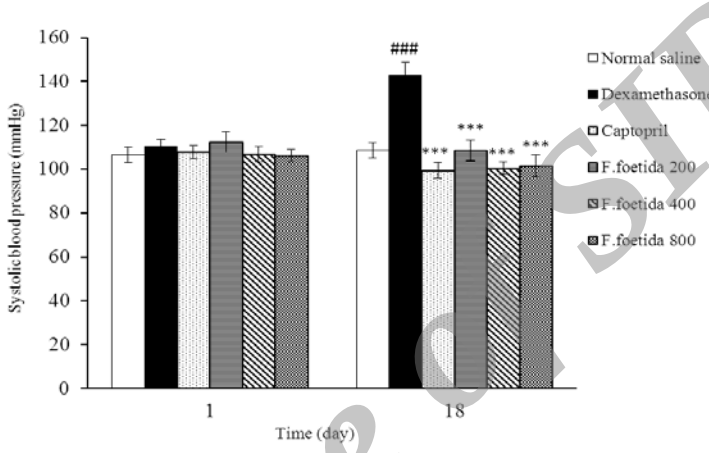

Fig. 1. Effects of *Ferula foetida* extract (200-800 mg/kg) and captopril (40 mg/kg) on systolic blood pressure in dexamethasone -induced hypertension in prevention study. Values are means ± SEM for six rats. $^{###}P$<0.001 versus saline control group, $^{***}P$<0.001 versus dexamethasone control group.

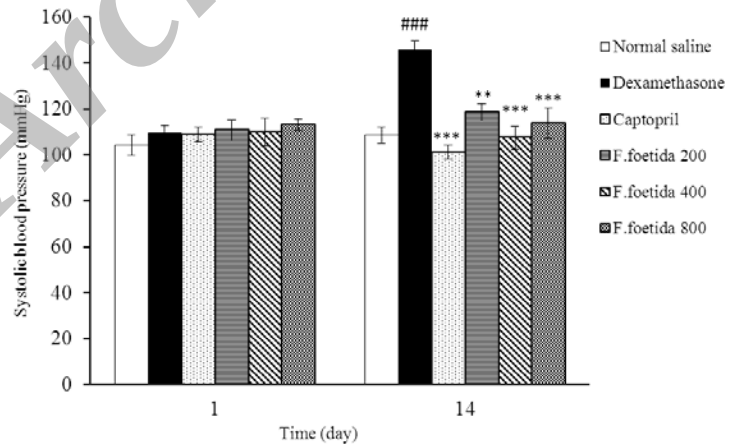

Fig. 2. Effects of *Ferula foetida* extract (200-800 mg/kg) and captopril (40 mg/kg) on systolic blood pressure in dexamethasone -induced hypertension in treatment study. Values are means ± SEM for six rats. $^{###}P$<0.001 versus saline control group, $^{**}P$<0.01 and $^{***}P$<0.001 versus dexamethasone control group.

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Effect of F. foetida extract on thymus weight

The thymus gland weight significantly decreased in Dex-induced hypertensive rats (P<0.001) however, administration of *F. foetida* extract and captopril could not prevent the thymus weight loss (Fig. 3).

Effect of F. foetida extract on body weight

There was no body weight gain in hypertensive rats during Dex injection when compared to the saline control group (P<0.001). Administration of *F. foetida* extract and captopril could not improve weight gaining in prevention and treatment studies (Fig. 4).

Effect of F. foetida extract on plasma hydroperoxides concentration

Dex treatment induced a significant increase in the plasma hydroperoxides concentration compared to saline control group (P<0.001). Oral administration of captopril significantly (P<0.001) prevented the rise in hydroperoxides concentration in prevention study and decreased the elevated plasma hydroperoxides concentration in treatment study (P<0.01). However, administration of *F. foetida* extract had no significant effect on the hydroperoxides concentration in prevention and treatment groups (Fig. 5).

Effect of F. foetida extract on plasma FRAP value

There was a significant decrease in the plasma FRAP value in Dex-induced hypertensive rats compared with saline control animals (P<0.001). Administration of *F. foetida* extract at all doses significantly increased the plasma FRAP value. Captopril had no significant effect on the FRAP value in prevention or treatment studies (Fig. 6).

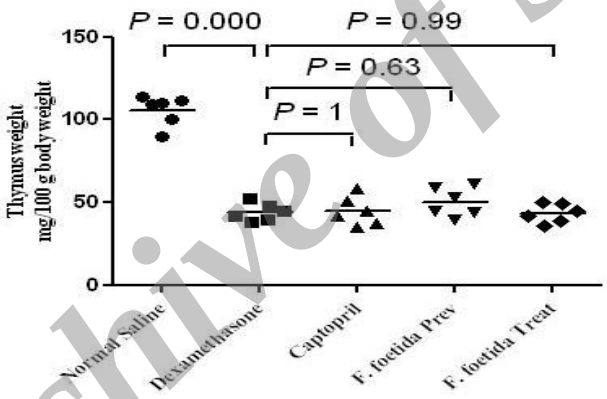

Fig. 3. Effects of administration of *Ferula foetida* (800 mg/kg) and captopril (40 mg/kg) on thymus weight in dexamethasone -induced hypertension in Prev; prevention and Treat; treatment studies. Values are means for six rats. P <0.05 is considered to be statistically significant versus dexamethasone control group.

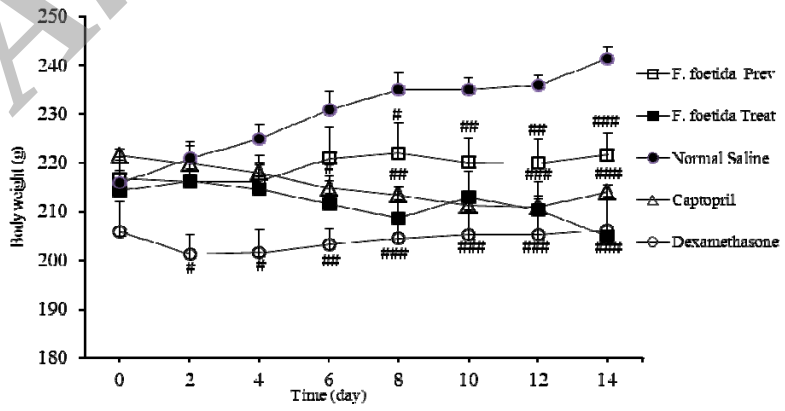

Fig. 4. Effects of *Ferula foetida* extract (800 mg/kg) and captopril (40 mg/kg) on body weight in dexamethasone - induced hypertension in Prev; prevention and Treat; treatment studies. Values are means ± SEM for six rats. $^{\#}P$<0.05, $^{\#\#}P$<0.01 and $^{\#\#\#}P$<0.001 versus saline control group.

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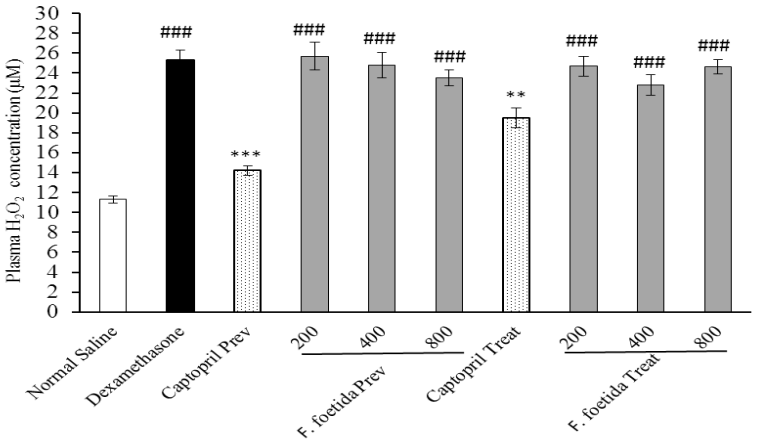

Fig. 5. Effects of *Ferula foetida* extract (200-800 mg/kg) and captopril (40 mg/kg) on plasma H_2O_2 concentration on dexamethasone -induced hypertension in Prev; prevention and Treat; treatment groups. Values are means ± SEM for six rats. $^{###}P$<0.001 versus saline control group, $^{**}P$<0.01 and $^{***}P$<0.001 versus dexamethasone control group.

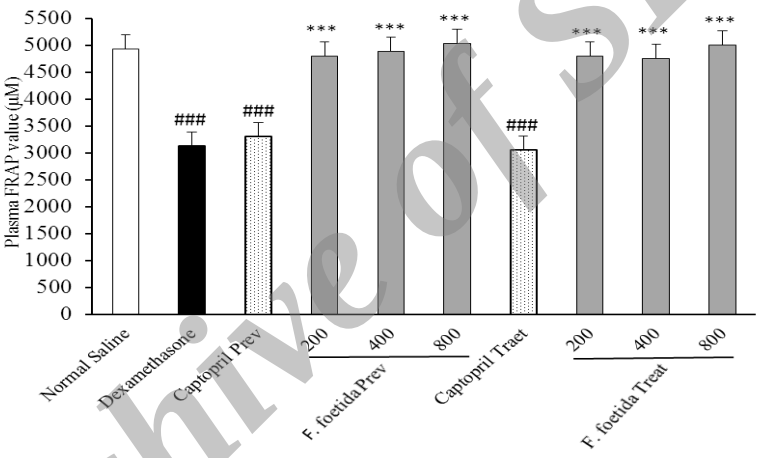

Fig. 6. Effects of *Ferula foetida* extract (200-800 mg/kg) and captopril (40 mg/kg) on plasma ferric reducing antioxidant power (FRAP) value on dexamethasone -induced hypertension in Prev; prevention and Treat; treatment groups. Values are means ± SEM for six rats. $^{###}P$<0.001 versus saline control group, $^{***}P$<0.001 versus dexamethasone control group.

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DISCUSSION

In this study, the antihypertensive effect of the stem hydroalcoholic extract of *F. foetida* was investigated in Dex-induced hypertension animals. Dex is known to cause high blood pressure, and to reduce thymus and body weight (18). Various mechanisms have been implicated in the pathogenesis of glucocorticoid-induced hypertension including increased total peripheral resistance and hemodynamic changes, increased vascular pressure responsiveness, increased sympathetic, renin-angiotensin and endothelin system activities, deficiency in vasodilator hormones and oxidative stress (21). Dex-induced hypertension is associated with increased oxidative stress and over-production of reactive oxygen species (ROS) which is predominantly generated by nicotinamide adenine dinucleotide phosphate-oxidase (NAPDH) (22). Elevated ROS production has been proposed as a major factor contributing to the tissue damage, nitric oxide (NO) deficiency, endothelial dysfunction and hypertension (23).

The findings of the present study showed the antihypertensive effects of *F. foetida* stem

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extract in Dex-induced hypertension. Administration of *F. foetida* extract significantly prevented and reversed hypertension and also improved the total antioxidant capacity of plasma at all doses. Fatehi and colleagues also reported the reducing blood pressure effect of *F. asafoetida* gum extract in anaesthetized normotensive rats (24). This hypotensive effect has been dose-related and rapid in onset and long-lasting at higher doses (24). In another study, extract from seeds and roots of *F. asafoetida* revealed potent vasodilatating property on intact rat arterial rings as an endothelial mediated effect (25).

F. foetida is an old traditional phytomedicine with nutritional and medicinal applications. Millions of people use this plant daily as a spice and its safety is established (25). A wide range of chemical compounds have been isolated from this plant. Ferulic acid (4-hydroxy-3-methoxycinnamic acid) is one of the major constituent of this herb (7). The results of investigations have shown the helpful cardiovascular effects of this phenolic acid such as antihypertensive, anti-hyperlipidemic and anti-atherogenic activities (14). Ferulic acid increases the bioavailability of NO as the main vasorelaxant factor produced by endothelial cells and improves the endothelial function (26). The structure and function of vital organs such as the heart, kidneys and liver has been improved following administration of ferulic acid in hypertensive rats. It has also enhanced the antioxidant status in the heart and kidneys by increasing superoxide dismutase and catalase activity (27). The antagonistic effect against endothelin-1 responses is another mechanism of ferulic acid in vasodilation and reducing the high blood pressure (28).

Flavonoids are other effective components of *F. foetida* which may be involved in its antioxidant and antihypertensive properties. Flavonoids are natural antioxidants with free radical scavenging activities. These polyphenolic compounds have multiple biological activities particularly beneficial cardiovascular properties such as antioxidant, anti-inflammation, anti-apoptosis, anti-hypercholesterolemia, anti-atherosclerosis, antiplatelet and antihypertensive effects which reduce the risks of coronary heart disease and stroke. Flavonoids have vascular protective effect under oxidative stress conditions and reduce hypertension through endothelium-independent vasodilation (29-31).

The antioxidant activity of *F. foetida* extract may also be accountable for its antihypertensive effects in Dex-induced hypertension. In this study, *F. foetida* extract improved the total antioxidant capacity of the plasma but failed to reduce the plasma hydroperoxides concentration. Nabavi and coworkers examined the antioxidant activities of flower, stem and leaf extracts of *F. foetida.* Their results exhibited notable antioxidant and antihemolytic activities of *F. foetida* however, different extracts revealed different levels of antioxidant activities in various experimental models. The stem extract indicated better antihaemolytic activity but similar to our results less H_2O_2 scavenging and Fe^{2+} chelating activity than the flower and leaf extract (10). It is noteworthy that although most studies have focused on antioxidant activity of ferulic acid but it has also pro-oxidant property. Ferulic acid undergoes one-electron transfer with oxidising agents and forms phenoxyl radicals which may be involved in its disability to reduce the plasma hydroperoxides concentration in this study (32).

Captopril as an angiotensin-converting enzyme inhibitor has been found to possess antioxidant activity and scavenging effects on hydroxyl radical and to protect erythrocyte membranes from lipid peroxidation (33). Although captopril has shown antioxidant property *in vitro*, but it seems that its low therapeutic plasma concentration limits its contribution to the total antioxidant capacity of plasma (34).

The role of hypothalamus–pituitary–adrenal axis in the regulation of body weight has been confirmed in various studies. The corticotropin-releasing hormone can lower the body weight set point. Administration of glucocorticoids at high doses has also lowered the body weight set point in some animal studies due to the interaction of glucocorticoids with leptin. Leptin may act as

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a signal reflecting the status of fat stores into the central nervous system and its production and secretion is stimulated by supra-physiologic levels of glucocorticoids. Furthermore, increasing the lipoprotein lipase activity and a rise in lipolysis may be participated in the animal body weight loss during administration of high doses of glucocorticoids (35,36). In the present study, administration of *F. foetida* extract could not prevent the effect of Dex on body weight loss in rats.

The thymus gland is a key organ in optimizing immune system function throughout the life and its weight loss reflects the apoptotic effects of glucocorticoids on thymocytes and lymphocytes (37). The results of investigations have shown the effect of some treatments on prevention of thymocyte apoptosis induced by Dex administration (38). However in this study, administration of *F. foetida* extract did not affect the thymus weight.

CONCLUSION

In conclusion, the results of the current study showed the antihypertensive and antioxidant effects of hydroalcoholic extract of the stems of *F. foetida* in Dex-induced hypertensive animals. These findings suggest that intake of this plant as an herbal medicine or supplementation in diet might be useful for the prevention and treatment of hypertension through attenuation of blood pressure and improvement of oxidative status. However, more investigations are still required for understanding the detailed mechanisms of antihypertensive effect of *F. foetida* extract.

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