Original Article

Antihypertensive and antioxidant effects of hydroalcoholic extract from the aerial parts of *Kelussia odoratissima* Mozaff. in dexamethasone-induced hypertensive rats

Leila Safaeian, Seyed Ebrahim Sajjadi[1], Shaghayegh Haghjoo Javanmard[2], Hadi Gholamzadeh

Department of Pharmacology and Toxicology, Isfahan Pharmaceutical Sciences Research Center, [1]Department of Pharmacognosy, School of Pharmacy and Pharmaceutical Sciences, [2]Department of Physiology, Applied Physiology Research Center, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: *Kelussia odoratissima* Mozaff. is a monotypic endemic plant of Apiaceae growing wild in Iran. The aerial parts of this plant are used for treatment of hypertension, ulcer, and inflammatory conditions in folk medicine. In this study, the effects of hydroalcoholic extract of the aerial parts of *K. odoratissima* were evaluated in dexamethasone (Dex)-induced hypertension in male Wistar rats.

Materials and Methods: For induction of hypertension, Dex (30 μg/kg/day) was administered subcutaneously for 14 days. In a prevention study, rats received oral *K. odoratissima* extract (100, 200, and 400 mg/kg) from 4 days before Dex administration and during the test period (days 1–18). In a reversal study, *K. odoratissima* extract was administered orally from day 8 to 14. Systolic blood pressure (SBP) was evaluated using tail-cuff method. The hydrogen peroxide (H_2O_2) concentration and ferric-reducing antioxidant power (FRAP) were measured in plasma samples.

Results: Administrations of Dex significantly induced an increase in SBP and in plasma H_2O_2 and a decrease in body and thymus weights, and in FRAP value ($P < 0.001$). *K. odoratissima* extract dose-dependently prevented and reversed hypertension ($P < 0.001$). It also prevented and reduced the plasma H_2O_2 concentration and prevented the body weight loss upon Dex administration at all doses (100–400 mg/kg, $P < 0.001$) but failed to improve FRAP value.

Conclusions: These results suggest antihypertensive and antioxidant effects of *K. odoratissima* extract in Dex-induced hypertension. Further studies are needed to elucidate the exact mechanism of the antihypertensive effect of this herbal medicine.

Key Words: Antioxidant activity, dexamethasone, hypertension, *Kelussia odoratissima* Mozaff

Address for correspondence:
Dr. Leila Safaeian, Department of Pharmacology and Toxicology, Isfahan Pharmaceutical Sciences Research Center, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: leila_safaeian@pharm.mui.ac.ir
Received: 23.07.2014, **Accepted:** 20.08.2014

Access this article online	
Quick Response Code:	Website: www.advbiores.net
	DOI: 10.4103/2277-9175.176342

INTRODUCTION

Hypertension is one of the most common cardiovascular risk factor and a main public health issue, which accounts for developing critical damage in major end-organs. The sustained high blood pressure is considered responsible for many serious medical conditions such as arteriosclerosis, heart failure, kidney

How to cite this article: Safaeian L, Sajjadi SE, Javanmard SH, Gholamzadeh H. Antihypertensive and antioxidant effects of hydroalcoholic extract from the aerial parts of *Kelussia odoratissima* Mozaff. in dexamethasone-induced hypertensive rats. Adv Biomed Res 2016;5:25.

failure, blindness, and cognitive impairment, and also for many deaths from stroke and heart disease.[1] The prevalence of hypertension is increasing worldwide and in spite of various pharmacological treatments, hypertension remains inadequately managed.[2] Moreover, the use of conventional antihypertensive drugs is often limited because of many side effects. Therefore, recent efforts have focused on herbal medicines for treatment of hypertension.[3]

Kelussia odoratissima Mozaff., also named *Amirkabiria odoratissima*, belongs to the Apiaceae family whose species are considered as the well-known sources for functional foods and natural medicines. This family possesses mostly aromatic plants with important chemical constituents including essential oils, coumarins, polyacetylenes, flavonoids, sesquiterpenes, and phthalides.[4-6] *K. odoratissima* is a monotypic endemic plant of Apiaceae, only growing in Iran with common name of "Karafs-e-koohi" or "keloss."[7] The aerial parts of this plant have a unique tasty smell and are used as a popular spice.[8] In folk medicine, *K. odoratissima* is used as a sedative plant and also for treatment of hypertension, ulcer, and inflammatory conditions.[9] Some pharmacological activities including antioxidant, anti-flatulence and stomach tonic, antibacterial, analgesic, anti-inflammatory, and sedative properties have been reported for *K. odoratissima*.[9-13] This plant also possesses beneficial cardiovascular properties such as anti-atherosclerotic effects because of fibrinolytic activity and its ability to inhibit lipid oxidation and to reduce total and low-density lipoprotein (LDL) cholesterol levels and C-reactive protein levels.[14,15] Because there is no pharmacological study on anti-hypertensive activity of *K. odoratissima*, the present study was designed to evaluate the effects of chronic administration of *K. odoratissima* on hypertension and oxidative status in dexamethasone (Dex)-induced hypertensive rats.

MATERIALS AND METHODS

Animals

Male Wistar rats (200 ± 20 g) were obtained from the animal house of the School of Pharmacy and Pharmaceutical Sciences (Isfahan, Iran). The animals were housed under standard laboratory conditions with a 12 h light/12 h dark cycle. They had free access to tap water and standard pellet diet. The whole experiments were according to the international guidelines for laboratory animal use and care.

Chemicals

Dexamethasone was purchased from Darou Pakhsh Pharmaceutical Co. (Tehran, Iran) and captopril was obtained from Tehran Darou Pharmaceutical Co. (Tehran, Iran). Folin–Ciocalteu reagents were obtained from Merck Co. (Mumbai, India). The standard assay kits (Hakiman Shargh Research Co., Isfahan, Iran) were used for measurement of plasma hydroperoxides and ferric-reducing antioxidant power (FRAP) assay.

Plant material and preparation of extract

The aerial parts of *K. odoratissima* were collected from the central Zagros Mountain, Charmahal Bakhtiari province, in west of Iran, during March 2013. After verification of plant identity, a voucher specimen (No. 2022) was deposited at the Herbarium of the School of Pharmacy and Pharmaceutical Sciences, Isfahan, Iran. For preparation of hydroalcoholic extract, the air-dried aerial parts of the plant were powdered and extracted with ethanol (70%), using maceration method for 72 h, three times at room temperature. The solvent was removed by a rotary evaporator (Bibby RE200, UK) under pressure at 50°C to yield a viscous residue. Then the extract was freeze-dried and stored at – 20°C. The yield of the plant extract was 13.3% (w/w). Different concentrations of the extract were prepared in normal saline and 0.5% Tween 80 and desirable doses were administered orally in a volume of 0.1 ml/10 g body weight of rats.

Determination of total phenolic content

The phenolic compounds have an important role in the quality and nutritional value and also in antioxidant activity of plants. The total phenol content of the plant extract was measured colorimetrically using the Folin–Ciocalteu method.[16] Briefly, the plant sample was mixed with Na_2CO_3 (20%) and treated with diluted Folin–Ciocalteu's phenol reagent and the absorbance was measured at 765 nm using a UV spectrophotometer. The total phenol content was estimated by comparison with a standard curve generated from different concentrations of gallic acid and was expressed as gallic acid equivalents (GAE) per gram of the plant.

Experimental protocol

To induce hypertension, rats received subcutaneously (s.c.) injection of Dex (30 μg/kg/day) for 14 days.[17] In the saline control group, animals received daily injection of saline (1 mL/kg, s.c.). In a prevention study, rats received oral *K. odoratissima* extract (100, 200, and 400 mg/kg) or captopril (40 mg/kg, as an antihypertensive positive control) using an intragastric tube from 4 days before Dex administration and during the test period (days 1–18). In the reversal study, *K. odoratissima* extract or captopril was administered from day 8 to 14.

Six animals were used in each control and experimental groups. All rats were weighed on

alternate days. Animals were sacrificed at the end of the experiment under ether anesthesia. The thymus gland was removed and weighed. Blood was collected and plasma samples were stored at –80°C for further experiments.

Measurement of systolic blood pressure

The systolic blood pressure (SBP) was measured by noninvasive tail-cuff method (AD Instrument PowerLab Data Acquisition System, Sydney, Australia) at the first day and the last day of the experiment (days 1 and 18) in conscious rats. The animals were restrained in heated chambers at 38 ± 1°C for 10 min. Rats were trained with blood pressure measuring equipment for one week before initiation of the experiment. Blood pressure was recorded at least three times for each rat and averaged to obtain a mean SBP.

Measurement of thymus weight

The thymus gland weight, as a marker of glucocorticoid activity was expressed relative to body weight (mg/100 g of body weight).[18]

Measurement of plasma hydrogen peroxide concentration

For measurement of plasma hydrogen peroxide (H_2O_2) concentration, the assay was based on the ferrous ion oxidation by xylenol orange reagent in aqueous medium with sorbitol (FOX1).[19] In brief, FOX1 reagent prepared according to the manufacturer's protocol was mixed with plasma samples. After incubation for 30 min in 37°C, the absorbance of solutions was measured at 540 nm using a microplate reader/spectrophotometer (Bio-Tek, PowerWave XS, Wincoski, USA). The H_2O_2 concentration of plasma samples was estimated using a standard curve generated from different concentrations of hydrogen peroxide.

Measurement of plasma ferric-reducing antioxidant power

The total antioxidant capacity of plasma samples was determined based on FRAP assay.[20] FRA*P* values were evaluated based on the reduction of ferric–tripyridyltriazine complex to ferrous form. In brief, the FRAP reagent prepared according to the manufacturer's protocol was added to plasma samples. After incubation for 40 min in 40°C, the absorbance of colored solutions was measured at 570 nm using a microplate reader/spectrophotometer. The FRA*P* values of samples were estimated against the standard curve of $FeSO_4 \times 7H_2O$ concentration and reported as micromole of FeII equivalents per liter.

Statistical analysis

Results were expressed as the mean ± standard error of mean. Statistical analysis was done by one-way analysis of variance followed by Tukey *post hoc* test using SPSS software version 16.0. The graph of thymus weight data were drawn using GraphPad-Prism software version 5. *P* values < 0.05 were used as the criteria for significant differences.

RESULTS

Total phenolic content

The total phenolic content assay showed 15 ± 0.03 mg GAE/g of the dried aerial parts of *K. odoratissima* extract.

Effect of *K. odoratissima* extract on blood pressure

Figure 1 shows the effect of pretreatment with *K. odoratissima* extract (100, 200, and 400 mg/kg) and captopril (40 mg/kg) on SBP in Dex-induced hypertension. The blood pressure significantly increased from 117.8 ± 1.5 to 144.6 ± 2.1 mmHg on day 18 in Dex-treated rats ($P < 0.001$) in comparison with saline control group (113.7 ± 2.5 mmHg). Pretreatment with captopril and *K. odoratissima* extract at doses of 200 and 400 mg/kg significantly prevented the increase in SBP ($P < 0.001$) [Figure 1]. In reversal study, administration of *K. odoratissima* extract at dose of 400 mg/kg lowered the SBP in Dex-induced hypertensive rats ($P < 0.001$) [Figure 2].

Effect of *K. odoratissima* extract on thymus weight

After Dex injection, the thymus gland weight significantly decreased in hypertensive rats ($P < 0.001$) but administration of *K. odoratissima* extract and captopril could not prevent the thymus weight decrease [Figure 3].

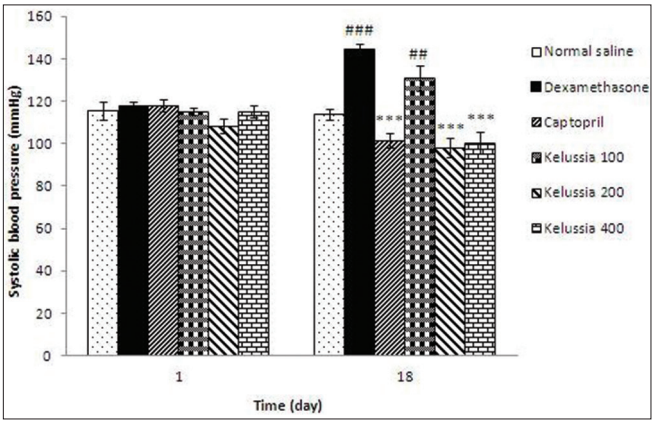

Figure 1: Effects of *Kelussia odoratissima* extract (100–400 mg/kg) and captopril (40 mg/kg) on systolic blood pressure in Dex-induced hypertension in prevention groups. Values are means + SEM for six rats. $^{##}P < 0.01$ and $^{###}P < 0.001$ versus saline control group, $^{***}P < 0.001$ versus Dex control group

Effect of *K. odoratissima* extract on body weight

The body weight significantly decreased during Dex injection in hypertensive rats when compared with saline control group ($P < 0.001$). Administration of *K. odoratissima* extract at all doses improved weight gaining in rats but captopril could not prevent weight loss induced by dexamethasone [Figure 4].

Effect of *K. odoratissima* extract on plasma H_2O_2 concentration

In Dex-treated group, the level of plasma H_2O_2 was significantly higher than saline control group ($P < 0.001$). Administration of captopril and *K. odoratissima* extract at all doses significantly ($P < 0.001$) prevented the rise in H_2O_2 concentration in prevention study and reduced the elevated plasma H_2O_2 concentration in reversal study ($P < 0.001$). At a dose of 400 mg/kg of *K. odoratissima*, the plasma H_2O_2 concentration was also significantly lower than saline control group [Figure 5].

Effect of *K. odoratissima* extract on plasma FRA*P* value

In Dex-induced hypertensive rats, the plasma FRA *P* value was significantly lower than saline control group ($P < 0.001$). Administration of captopril and *K. odoratissima* extract had no significant effect on the FRA*P* value in prevention and reversal groups [Figure 6].

DISCUSSION

The results of the present study showed antihypertensive and antioxidant effects of *K. odoratissima* extract in Dex-induced hypertension. Administration of *K. odoratissima* extract dose-dependently prevented

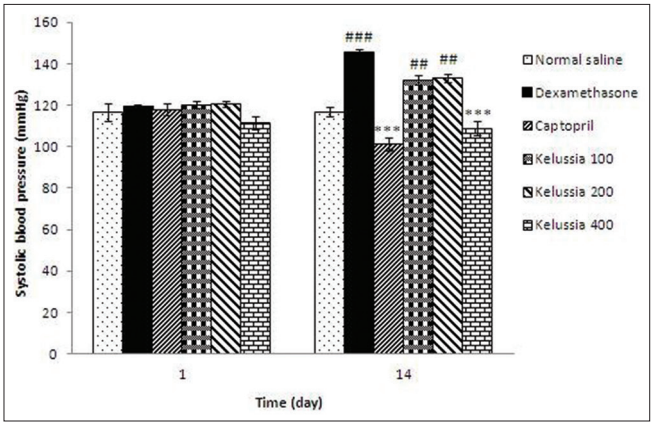

Figure 2: Effects of *Kelussia odoratissima* extract (100–400 mg/kg) and captopril (40 mg/kg) on systolic blood pressure in Dex-induced hypertension in reversal groups. Values are means + SEM for six rats. $^{\#\#}P < 0.01$ and $^{\#\#\#}P < 0.001$ versus saline control group, $^{***}P < 0.001$ versus Dex control group

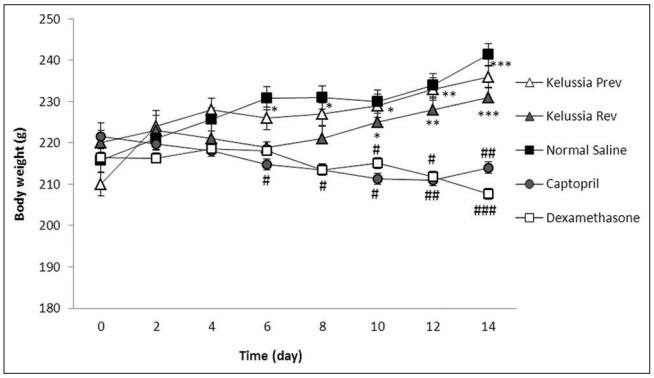

Figure 4: Effects of *Kelussia odoratissima* extract (400 mg/kg) and captopril (40 mg/kg) on body weight in Dex-induced hypertension. Values are means + SEM for six rats. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ and $^{\#\#\#}P < 0.001$ versus saline control group, $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$ versus Dex control group

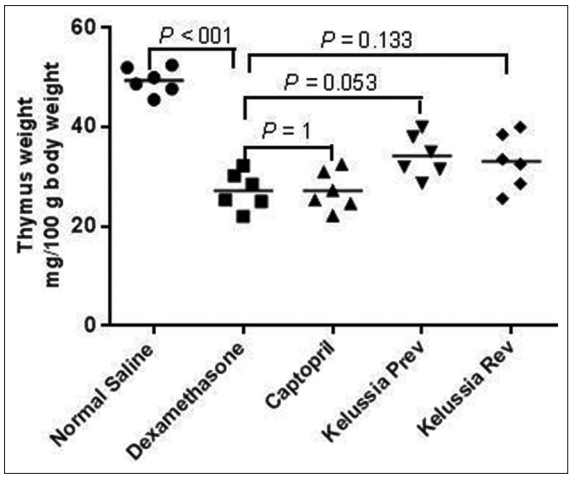

Figure 3: Effects of administration of *Kelussia odoratissima* (400 mg/kg) and captopril (40 mg/kg) on thymus weight in Dex-induced hypertension in prevention (Prev) and reversal (Rev) groups. Values are means for six rats

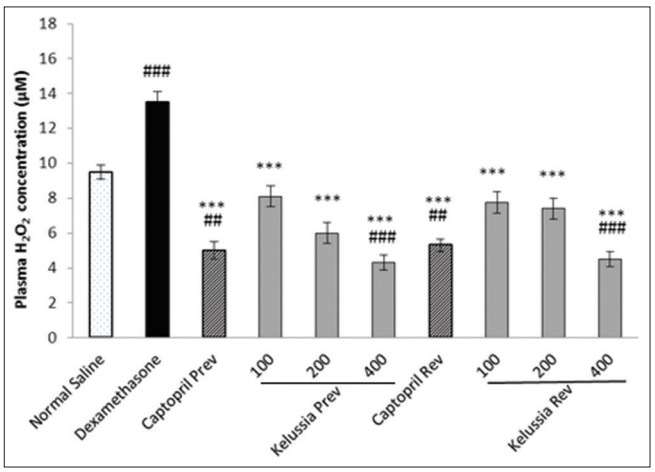

Figure 5: Effects of *Kelussia odoratissima* extract (100–400 mg/kg) and captopril (40 mg/kg) on plasma H_2O_2 concentration on Dex-induced hypertension in prevention (Prev) and reversal (Rev) groups. Values are means + SEM for six rats. $^{\#\#}P < 0.01$ and $^{\#\#\#}P < 0.001$ versus saline control group, $^{***}P < 0.001$ versus Dex control group

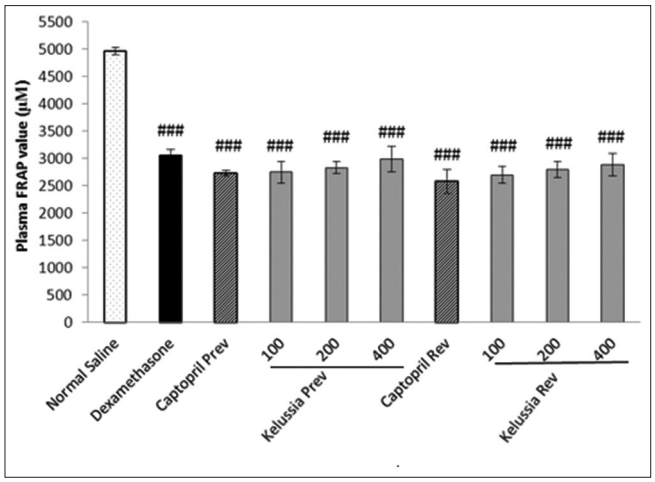

Figure 6: Effects of *Kelussia odoratissima* extract (100–400 mg/kg) and captopril (40 mg/kg) on plasma FRA*P* value on Dex-induced hypertension in prevention (Prev) and reversal (Rev) groups. Values are means + SEM for six rats. $^{###}P < 0.001$ versus saline control group

and reversed a rise in SBP and also reduced the plasma H_2O_2 concentration and prevented the body weight loss upon Dex administration.

During chronic use of glucocorticoids such as dexamethasone, hypertension develops as a result of increased activity of renin–angiotensin, endothelin and sympathetic systems, and hemodynamic alterations.[21] Glucocorticoid-induced hypertension is also associated with increased oxidative stress and overproduction of reactive oxygen species (ROS), which interacts with NO and contributes to NO deficiency and vasoconstriction.[22] Increased production of ROS in vasculature is predominantly caused through NAPDH oxidase pathway in Dex-induced hypertension.[23] Some antioxidant agents have been found to prevent and attenuate hypertension from Dex.[24-25]

The beneficial effects of some traditional herbal medicine have been also reported for the management of hypertension; however, their usage needs scientific confirmation and validation.[3] *K. odoratissima* Mozaff. is a plant with nutritional and medicinal applications. Phytochemical analysis of *K. odoratissima* extract has shown the presence of flavonols, caffeic acid, rutin, ferulic acid, and phthalides.[8-15] The major constituent of the volatile oils of this herb is 3-butylidene-4,5-dihydrophthalide (z-ligustilide), and also other phthalides including *cis*-3-butylidene phthalide and 3-*n*-butyl phthalide.[13] The presence of these effective components may be involved in the antioxidant and antihypertensive properties of *K. odoratissima*.

Phthalides are known as the bioactive phytochemicals occurring in some species of Apiaceae family.[26] Various biological activities have been established for ligustilide such as antioxidant, vascular smooth muscle relaxation, improved microcirculation actions, or effects on central noradrenergic and/or GABA systems.[27-29] Ligustilide has shown a vasodilator effect on rat abdominal aorta by inhibition of noradrenaline.[30] It has resulted in vasodilatation of rat mesenteric artery through blockade of voltage-dependent and receptor-operated calcium channels.[29] The results of investigations have also demonstrated the hypotensive and vasorelaxant effects of 3-*n*-butyl phthalide possibly through blockade of calcium channels.[31]

Flavonols are polyphenolic antioxidant compounds, which are widely distributed in plants and have beneficial cardiovascular effects. Some flavonols produce an antihypertensive effect through endothelium-independent vasodilation action and have vascular protective effect under oxidative stress conditions.[32]

Other constituents of *K. odoratissima* extract are cinnamic acid compounds including caffeic acid and ferulic acid. Caffeic acid is a phenolic acid with ability to reduce the risk of cardiovascular disorders. It has been found that caffeic acid reduces the proliferative reaction of vascular smooth muscle cell to angiotensin II in hypertensive rats by inhibiting the production of ROS and blocking the JAK/STAT signaling cascade and the Ras/Raf-1/ERK1/2 cascade.[33] Ferulic acid is a phenolic compound with antihypertensive effects, which induces NO-mediated vasodilation and improvement of structure and function and antioxidant status of the heart, blood vessels, liver, and kidneys in hypertensive rats.[34,35] Both of caffeic acid and ferulic acid also possess antagonist effects against endothelin-1 responses. They could blunt the blood pressure elevation and dilate the vasoconstriction of isolated aortic rings induced by endothelin-1.[36]

The antioxidant effect of *K. odoratissima* extract may also account for its antihypertensive effects in Dex-induced hypertension. In this study, *K. odoratissima* extract reduced the plasma H_2O_2 concentration nevertheless failed to improve the total antioxidant capacity of the plasma. *K. odoratissima* has been introduced as a potential herbal source for preparing the effective medicines in oxidant-related diseases regarding its antioxidant activity and ability to reduce lipid peroxidation.[9,37]

The results of several studies have also indicated the antioxidant effect of captopril. Captopril as an angiotensin-converting enzyme inhibitor was found to possess scavenging effects on hydroxyl radical and to protect erythrocyte membranes from lipid peroxidation.[38] It also possesses protective effect

on tissues from oxidative damage by increasing enzymatic and nonenzymatic antioxidant defenses.[39]

CONCLUSION

In conclusion, this study showed the antihypertensive and antioxidant effects of hydroalcoholic extract of the aerial parts of *K. odoratissima* in Dex-induced hypertension. These findings provide validation and support for the use of this plant as folk medicine for the treatment of hypertension in Iran. Further investigations are still required for understanding the detailed mechanisms of antihypertensive effect of *K. odoratissima* extract.

ACKNOWLEDGMENTS

This study was financially supported by research project No. 391397 from Isfahan University of Medical Sciences.

REFERENCES

1. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, *et al*. General cardiovascular risk profile for use in primary care: The Framingham Heart Study. Circulation 2008;117:743-53.
2. Whitworth JA; World Health Organization, International Society of Hypertension Writing Group. 2003 World Health Organization (WHO)/ International Society of Hypertension (ISH) statement on management of hypertension. J Hypertens 2003;11:1983-92.
3. Tabassum N, Ahmad F. Role of natural herbs in the treatment of hypertension. Pharmacogn Rev 2011;5:30-40.
4. Christensen LP, Brandt K. Bioactive polyacetylenes in food plants of the Apiaceae family: Occurrence, bioactivity and analysis. J Pharm Biomed Anal 2006;41:683-93.
5. Harborne JB. Flavonoid and phenylpropanoid patterns in the Umbelliferae. In: Heywood VH, editor. The Biology and Chemistry of the Umbelliferae. London: Academic Press; 1971. p. 1-8.
6. Sajjadi SE, Zeinvand H, Shokoohinia Y. Isolation and identification of osthol from the fruits and essential oil composition of the leaves of *Prangos asperula* Boiss. Res Pharm Sci 2009;4:19-23.
7. Mozaffarian V. Two new genera of Iranian umbelliferae. Bot Zhurn (Leningrad) 2003;88:88-94.
8. Sajjadi SE, Shokoohinia Y, Moayedi NS. Isolation and identification of ferulic acid from aerial parts of *Kelussia odoratissima* Mozaff. Jundishapur J Nat Pharm Prod 2012;7:159-62.
9. Ahmadi F, Kadivar M, Shahedi M. Antioxidant activity of *Kelussia odoratissima* Mozaff. in model and food systems. Food Chem 2007;105:57-64.
10. Shahrani M, Rafieian M, Pilevarian AA, Shirzad H, Hashemzadeh M, Yousefi H, *et al*. The effect of *Amirkabiria odoratissima* M extract on gastric acid and pepsin secretion level in rat. J Shahrekord Univ Med Sci 2007;8:88-95.
11. Pirbalouti AG, Malekpoor F, Enteshari SH, Yousefi M, Momtaz H, Hamedi B. Antibacterial activity of some folklore medicinal plants used by Bakhtiari Tribal in southwest Iran. Int J Biol 2010;2:55-63.
12. Haj Hashemi VA, Ghannadi A, Soltani L. Analgesic and anti-inflammatory effects of *Amirkabiria odoratissima*. J Res Med Sci 2003;7:121-5.
13. Rabbani M, Sajjadi SE, Sadeghi M. Chemical composition of the essential oil from *Kelussia odoratissima* Mozaff. and the evaluation of its sedative and anxiolytic effects in mice. Clinics (Sao Paulo) 2011;66:843-8.
14. Asgary S, Naderi G, Dashti GH, Paknahad Z. Effect of *Amirkabiria odorastissima Mozaffarian* on the development and progression of fatty streaks in hypercholesterolemic rabbits. Phytother Res 2004;18:370-2.
15. Asgari S, Naderi G, Jafarian-Dehkordi A, Askary N, Behagh AR. Fibrinolytic activity of *Amirkabiria odoratissima* Mozaffarian. J Med Plants 2005;13:50-9.
16. Yoo KM, Lee CH, Lee H, Moon B, Lee CY. Relative antioxidant and cytoprotective activities of common herbs. Food Chem 2008;106:929-36.
17. Zhang Y, Wu JH, Vickers JJ, Ong SL, Temple SE, Mori TA, *et al*. The role of 20-hydroxyeicosatetraenoic acid in adrenocorticotrophic hormone and dexamethasone-induced hypertension. J Hypertens 2009;27:1609-16.
18. Ong SL, Vickers JJ, Zhang Y, McKenzie KU, Walsh CE, Whitworth JA. Role of xanthine oxidase in dexamethasone-induced hypertension in rats. Clin Exp Pharmacol Physiol 2007;34:517-9.
19. Wolff SP. Ferrous ion oxidation in presence of ferric ion indicator xylenol orange for measurement of hydroperoxides. Methods Enzymol 1994;233C: 182-9.
20. Benzie IF, Strain JJ. The ferric reducing ability of plasma (FRAP) as a measure of "antioxidant power": The FRAP assay. Anal Biochem 1996;239:70-6.
21. Ong SL, Zhang Y, Whitworth JA. Mechanisms of dexamethasone-induced hypertension. Curr Hypertens Rev 2009;5:61-74.
22. Safaeian L, Zabolian H. Antioxidant effects of bovine lactoferrin on dexamethasone-induced hypertension in rat. ISRN Pharmacol 2014;2014:943523.
23. Zhang Y, Croft KD, Mori TA, Schyvens CG, McKenzie KU, Whitworth JA. The antioxidant tempol prevents and partially reverses dexamethasone-induced hypertension in the rat. Am J Hypertens 2004;17:260-5.
24. Bachhav SS, Pati SD, Bhutada MS, Surana SJ. Oleanolic acid prevents glucocorticoid-induced hypertension in rats. J Phytother Res 2011;10:1435-9.
25. Safaeian L, Zabolian H. Antihypertensive effect of lactoferrin on dexamethasone-induced hypertension in rat. J Isfahan Med Sch 2013;31:1096-104.
26. Beck JJ, Chou SC. The structural diversity of phthalides from the Apiaceae. J Nat Prod 2007;70:891-900.
27. Yu Y, Du JR, Wang CY, Qian ZM. Protection against hydrogen peroxide-induced injury by Z-ligustilide in PC12 cells. Exp Brain Res 2008;184:307-12.
28. Yan S, Qiao GF. Effect of the oil of *Angelica sinensis* on contractial function of isolated uterine smooth muscle of mice. Chin Tradit Herb Drugs 2000;31:604-6.
29. Cao YX, Zhang W, He JY, He LC, Xu CB. Ligustilide induces vasodilatation via inhibiting voltage dependent calcium channel and receptor-mediated Ca2+ influx and release. Vascul Pharmacol 2006;45:171-6.
30. Liang MJ, He LC, Yang GD. Screening, analysis and *in vitro* vasodilation of effective components from *Ligusticum chuanxiong*. Life Sci 2005;78:128-33.
31. Tsi D, Tan BK. Cardiovascular pharmacology of 3-*n* -butylphthalide in spontaneously hypertensive rats. Phyhother Res 1997;11:576-82.
32. Perez-Vizcaino F, Duarte J. Flavonols and cardiovascular disease. Mol Aspects Med 2010;31:478-94.
33. Li PG, Xu JW, Ikeda K, Kobayakawa A, Kayano Y, Mitani T, *et al*. Caffeic acid inhibits vascular smooth muscle cell proliferation induced by angiotensin II in stroke-prone spontaneously hypertensive rats. Hypertens Res 2005;28:369-77.
34. Suzuki A, Yamamoto M, Jokura H, Fujii A, Tokimitsu I, Hase T, *et al*. Ferulic acid restores endothelium-dependent vasodilation in aortas of spontaneously hypertensive rats. Am J Hypertens 2007;20:508-13.
35. Alam MA, Sernia C, Brown L. Ferulic acid improves cardiovascular and kidney structure and function in hypertensive rats. J Cardiovasc Pharmacol 2013;61:240-9.
36. Feng W, Min L, Lianchun Y, Jingyuan W, Min L, Fei L. A new kind of non-peptide endothelin antagonist Caffeic acid ferulic acid. Yaoxue Xuebao 1999;34:898-901.
37. Hasani-Ranjbar S, Larijani B, Abdollahi M. A systematic review of the potential herbal sources of future drugs effective in oxidant-related diseases. Inflamm Allergy Drug Targets 2009;8:2-10.
38. Bartosz M, Kedziora J, Bartosz G. Antioxidant and prooxidant properties of captopril and enalapril. Free Radic Biol Med 1997;23:729-35.
39. de Cavanagh EM, Fraga CG, Ferder L, Inserra F. Enalapril and captopril enhance antioxidant defenses in mouse tissues. Am J Physiol 1997;272:R514-8.

Source of Support: Nil, **Conflict of Interest:** None declared.