

# 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<sup>1</sup>, Shaghayegh Haghjoo Javanmard<sup>2</sup>, Hadi Gholamzadeh

Department of Pharmacology and Toxicology, Isfahan Pharmaceutical Sciences Research Center, <sup>1</sup>Department of Pharmacognosy, School of Pharmacy and Pharmaceutical Sciences, <sup>2</sup>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<sub>2</sub>O<sub>2</sub>) 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<sub>2</sub>O<sub>2</sub> 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<sub>2</sub>O<sub>2</sub> 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

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## 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

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failure, blindness, and cognitive impairment, and also for many deaths from stroke and heart disease.<sup>[1]</sup> The prevalence of hypertension is increasing worldwide and in spite of various pharmacological treatments, hypertension remains inadequately managed.<sup>[2]</sup> 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.<sup>[3]</sup>

*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.<sup>[4-6]</sup> *K. odoratissima* is a monotypic endemic plant of Apiaceae, only growing in Iran with common name of “Karafs-e-koohi” or “keloss.”<sup>[7]</sup> The aerial parts of this plant have a unique tasty smell and are used as a popular spice.<sup>[8]</sup> In folk medicine, *K. odoratissima* is used as a sedative plant and also for treatment of hypertension, ulcer, and inflammatory conditions.<sup>[9]</sup> Some pharmacological activities including antioxidant, anti-flatulence and stomach tonic, antibacterial, analgesic, anti-inflammatory, and sedative properties have been reported for *K. odoratissima*.<sup>[9-13]</sup> 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.<sup>[14,15]</sup> 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.<sup>[16]</sup> Briefly, the plant sample was mixed with Na<sub>2</sub>CO<sub>3</sub> (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.<sup>[17]</sup> 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  $-80^{\circ}\text{C}$  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  $38 \pm 1^{\circ}\text{C}$  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 ( $\text{mg}/100\text{ g}$  of body weight).<sup>[18]</sup>

### Measurement of plasma hydrogen peroxide concentration

For measurement of plasma hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) concentration, the assay was based on the ferrous ion oxidation by xylenol orange reagent in aqueous medium with sorbitol (FOX1).<sup>[19]</sup> In brief, FOX1 reagent prepared according to the manufacturer's protocol was mixed with plasma samples. After incubation for 30 min in  $37^{\circ}\text{C}$ , the absorbance of solutions was measured at 540 nm using a microplate reader/spectrophotometer (Bio-Tek, PowerWave XS, Wincoski, USA). The  $\text{H}_2\text{O}_2$  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.<sup>[20]</sup> FRAP 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  $40^{\circ}\text{C}$ , the absorbance of colored solutions was measured at 570 nm using a microplate reader/spectrophotometer. The FRAP values of samples were estimated against the standard curve of  $\text{FeSO}_4 \times 7\text{H}_2\text{O}$  concentration and reported as micromole of  $\text{FeII}$  equivalents per liter.

### Statistical analysis

Results were expressed as the mean  $\pm$  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

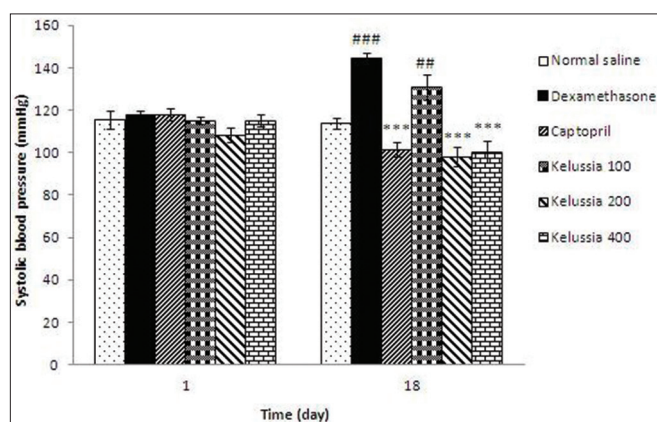
The total phenolic content assay showed  $15 \pm 0.03\text{ mg GAE/g}$  of the dried aerial parts of *K. odoratissima* extract.

### 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  $117.8 \pm 1.5$  to  $144.6 \pm 2.1\text{ mmHg}$  on day 18 in Dex-treated rats ( $P < 0.001$ ) in comparison with saline control group ( $113.7 \pm 2.5\text{ mmHg}$ ). 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

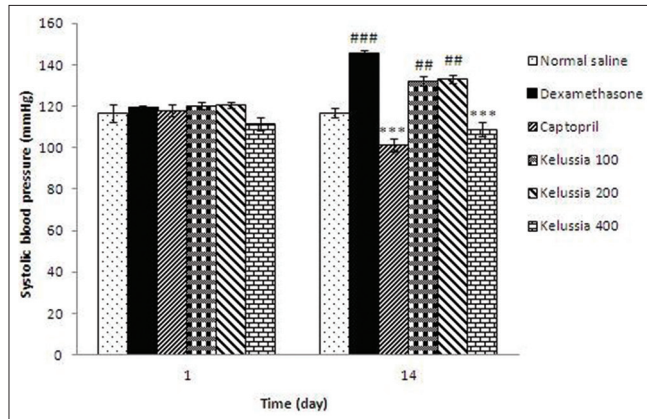
was also significantly lower than saline control group [Figure 5].

### Effect of *K. odoratissima* extract on plasma FRAP value

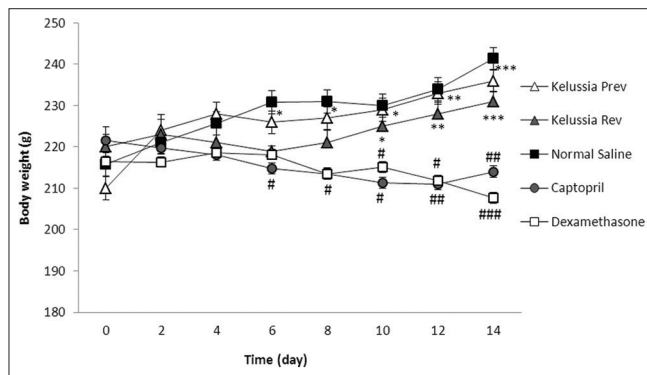
In Dex-induced hypertensive rats, the plasma FRAP value was significantly lower than saline control group ( $P < 0.001$ ). Administration of captopril and *K. odoratissima* extract had no significant effect on the FRAP value in prevention and reversal groups [Figure 6].

## DISCUSSION

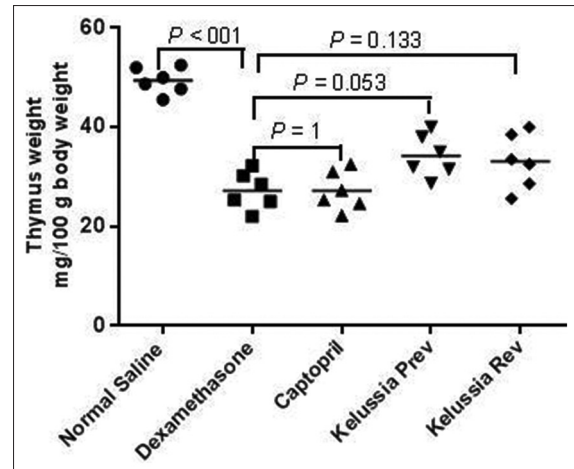
The results of the present study showed antihypertensive and antioxidant effects of *K. odoratissima* extract in Dex-induced hypertension. Administration of *K. odoratissima* extract dose-dependently prevented



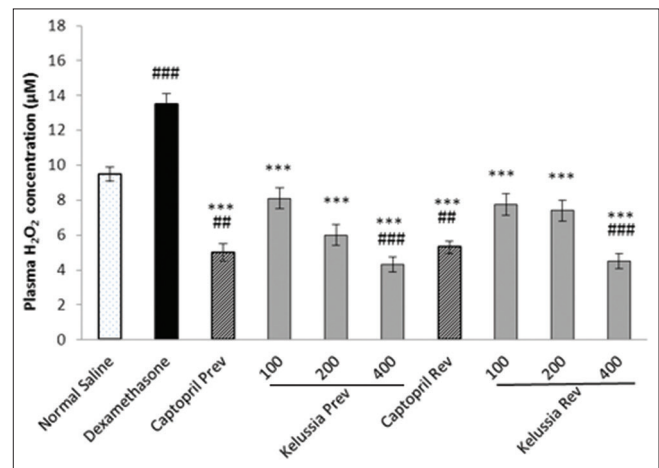
**Figure 2:** Effects of *Kelussia odoratissima* extract (100–400 mg/kg) and captopril (40 mg/kg) on systolic blood pressure in Dex-induced hypertension in reversal groups. Values are means + SEM for six rats. ##  $P < 0.01$  and ###  $P < 0.001$  versus saline control group, \*\*\*  $P < 0.001$  versus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



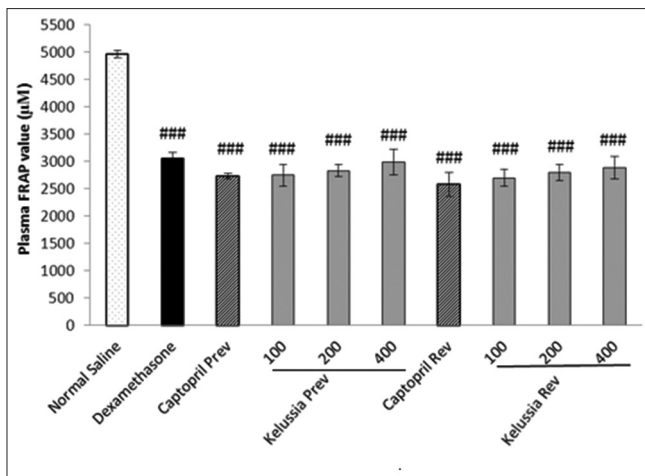
**Figure 4:** Effects of *Kelussia odoratissima* extract (400 mg/kg) and captopril (40 mg/kg) on body weight in Dex-induced hypertension. Values are means + SEM for six rats. #  $P < 0.05$ , ##  $P < 0.01$  and ###  $P < 0.001$  versus saline control group, \*  $P < 0.05$ , \*\*  $P < 0.01$  and \*\*\*  $P < 0.001$  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 FRAP 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.<sup>[21]</sup> 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.<sup>[22]</sup> Increased production of ROS in vasculature is predominantly caused through NADPH oxidase pathway in Dex-induced hypertension.<sup>[23]</sup> Some antioxidant agents have been found to prevent and attenuate hypertension from Dex.<sup>[24-25]</sup>

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.<sup>[3]</sup> *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.<sup>[8-15]</sup> 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.<sup>[13]</sup> 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.<sup>[26]</sup> 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.<sup>[27-29]</sup> Ligustilide has shown a vasodilator effect on rat abdominal aorta by inhibition of noradrenaline.<sup>[30]</sup> It has resulted in vasodilatation of rat mesenteric artery through blockade of voltage-dependent and receptor-operated calcium channels.<sup>[29]</sup> The results of investigations have also demonstrated the hypotensive and vasorelaxant effects of 3-*n*-butyl phthalide possibly through blockade of calcium channels.<sup>[31]</sup>

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.<sup>[32]</sup>

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.<sup>[33]</sup> 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.<sup>[34,35]</sup> 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.<sup>[36]</sup>

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.<sup>[9,37]</sup>

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.<sup>[38]</sup> It also possesses protective effect

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

## 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.

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