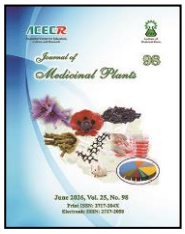
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Research Article

Effects of essential oil and hydroalcoholic extract of *Dracocephalum kotschyi* on blood pressure in rats

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ABSTRACT

Background: *Dracocephalum kotschyi* is a medicinal plant with well-documented anti-spasmodic and anti-inflammatory properties. However, its potential effects on blood pressure have not been previously investigated. **Objective:** This study aimed to evaluate the pharmacological effects of *D. kotschyi* essential oils and its hydroalcoholic extract on blood pressure in rats. **Methods:** Male Wistar rats were divided into four groups (n = 6/group): vehicle, Nifedipine, *D. kotschyi* hydroalcoholic extract, and *D. kotschyi* essential oil. The hydroalcoholic extract and essential oil were prepared by maceration and hydrodistillation, respectively. Under anesthesia, the jugular vein and carotid artery were cannulated, and the carotid cannula was connected to a pressure transducer for continuous blood pressure recording. The effects of intravenous administration of the vehicle, Nifedipine (50-500 µg/kg), the hydroalcoholic extract (20-200 mg/kg), and the essential oil (2-20 mg/kg) on blood pressure were assessed. **Results:** Intravenous administration of *D. kotschyi* essential oil significantly reduced blood pressure at 8 mg/kg ($P < 0.05$) and at 12 and 20 mg/kg ($P < 0.01$) compared with the vehicle-treated group. In contrast, the hydroalcoholic extract did not significantly affect blood pressure at any of the tested dose. As expected, Nifedipine significantly reduced blood pressure compared with the vehicle-treated group ($P < 0.01$). **Conclusion:** The *D. kotschyi* essential oil contains vasoactive constituents capable of lowering blood pressure. Conversely, the inactivity of the hydroalcoholic extract suggests that its volatile hypotensive constituents were largely lost during rotary evaporation.

1. Introduction

High blood pressure (hypertension) is an important global public health problem and one of the leading risk factors for cardiovascular morbidity and mortality [1]. It substantially increases the risk of myocardial infarction, stroke, heart failure, chronic kidney disease, and premature death [2]. Blood pressure which means the force exerted by circulating blood against the arterial walls, is determined by

Abbreviations: HP, Heart rate; BP, Blood pressure; IV, Intravenous; SEM, Standard error of mean; ANOVA, Analysis of variance

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cardiac output and peripheral vascular resistance [3]. Hypertension develops through a complex, multifactorial pathophysiology involving dysregulation of the renin–angiotensin–aldosterone system, endothelial impairment, oxidative stress, vascular inflammation, increased sympathetic nervous system activity, and impaired nitric oxide (NO) bioavailability, all of which contribute to increased vascular resistance and sustained elevation of blood pressure [4]. Despite the availability of several modern drugs for the treatment of hypertension, these drugs are associated with adverse effects [5-7]. The use of herbal medications with putative antihypertensive properties and fewer adverse effects would therefore provide a good therapeutic alternative to conventional drugs [8, 9], particularly when supplemented with lifestyle modifications and mild physical exercises [10, 11].

Zaringiah (*Dracocephalum kotschyi* Boiss.) (*D. kotschyi*), a medicinal plant belonging to the Lamiaceae family and widely distributed in Iran, is rich in bioactive constituents, including flavonoids, phenolic acids, terpenoids, and methoxylated flavones. These phytochemicals have been reported to possess antioxidant, anti-inflammatory, antispasmodic, and vasorelaxant properties [12-14]. It has been used as a natural remedy for gastrointestinal disorders, bronchitis, rheumatism, and other ailments. Local populations have used boiled extracts of Zaringiah to alleviate shortness of breath [15].

Preclinical studies have illustrated that the hydroalcoholic extract of *D. kotschyi* can prevent pulmonary inflammation and fibrosis in animal models [16]. Its anti-inflammatory effects have also been observed in conditions such as colic ulcers, peptic ulcers, and other inflammation-induced models [17, 18]. Additionally, *D. kotschyi* extract and its active components, apigenin and luteolin, exhibit direct antispasmodic effects on bronchial smooth muscles [19]. This spasmolytic effect extends beyond the airway smooth muscle, as the extract inhibits intestinal contractions induced by various spasmogens, including acetylcholine, histamine, serotonin, potassium chloride, neuronal stimulation, and spontaneous contraction [12-15]. At different concentrations, *D. kotschyi* extract has shown relaxant effects on other smooth muscles, such as those in the bladder and uterus [20]. However, its effects on blood pressure have not been previously reported. Given that drugs with antispasmodic activity can affect vascular smooth muscle contraction and that another *Dracocephalum* species has antihypertensive properties [21], this study aimed to investigate the effects of *D. kotschyi* on blood pressure in anesthetized rats.

2. Materials and methods

2.1. Extraction procedure

Zaringiah was purchased from a cultivated farm (Pertican Kesht) in Shahankoh (Fareydunshahr, Isfahan Province, Iran). The plant was identified as *D. kotschyi* by a botanist from the Department of Natural Resources, Isfahan Province. An authenticated voucher specimen (1519) is stored in the herbarium of the Department of Pharmacognosy at the School of Pharmacy and Pharmaceutical Sciences, Isfahan, Iran. Dried leafy branches were collected during the flowering season and dried in the shade. In the laboratory, the plant material was ground into a fine powder for extraction.

The hydroalcoholic extract was prepared by the maceration method as previously described [22]. Briefly, the dried powdered plant material was first moistened with 70 % ethanol and allowed to stand for 2 h. The material was then transferred to a percolator, gently compressed,

and 70 % ethanol was added at a plant-to-solvent ratio of 1:8 (w/v), ensuring that the plant material was completely immersed. The mixture was macerated for 72 h (3 days) at room temperature. After the maceration period, the extract was collected by opening the percolator valve, the plant material was replenished with fresh 70 % ethanol, and the extraction procedure was repeated three additional times. The combined filtrates were concentrated under reduced pressure at 50 °C using a rotary evaporator (Heidolph, Germany), and the concentrated extract was stored at 4 °C until use [23].

The essential oil was obtained by hydrodistillation as previously described [24] and was stored at 4 °C until use.

2.2. Phytochemical analysis of the Hydroalcoholic extract and essential oil

The volatile constituents of the essential oil were characterized using gas chromatography coupled with mass spectrometry (GC–MS). The analysis was carried out on an Agilent 7890A gas chromatograph interfaced with an Agilent 5975C mass spectrometer equipped with an electron ionization source operated at 70 eV. Chromatographic separation was performed using an HP-5 capillary column (30 m × 0.25 mm internal diameter; 0.25 μm film thickness), with helium serving as the carrier gas at a constant flow rate of 2 ml/min. The oven program started at 50 °C, which was held for 2 min, followed by heating to 250 °C at 8 °C/min and subsequently to 330°C at 3 °C/min. The injector and detector were both set at 280 °C. Mass spectra were acquired within the m/z 50-700 range. Identification of individual compounds was based on comparison of their mass spectral profiles and retention indices with reference data in the NIST mass spectral library and previously published reports [25].

The total phenolic content of the hydroalcoholic extract was determined using the Folin–Ciocalteu colorimetric assay. Gallic acid was used as the reference standard, and the total phenolic content was expressed as milligrams of gallic acid equivalents (GAE) per gram of dry extract.

2.3. Materials and Solutions

The instruments used included Harvard Universal Oscillographs equipped with pressure transducers, a sphygmomanometer, and standard surgical instruments. The cannula consisted of a sterile cutdown tube (4FR, Wellstone) and polyethylene tubing with an internal diameter of 0.5 mm and an outer diameter of 0.9 mm (AD Instruments). A three-way stopcock (Discofix-3) was attached to the end of the catheter lines for infusion and pressure monitoring. A syringe filled with normal saline was used to flush the catheter lines, remove air bubbles, and ensure patency.

The effects of intravenous (IV) administration of nifedipine (Sigma), *D. kotschyi* essential oil, the hydroalcoholic extract, and the vehicle on blood pressure were assessed. A hydroalcoholic extract stock solution (50 mg/mL) was prepared in 50 % (v/v) ethanol. A stock solution of the essential oil (50 mg/ml) was also prepared in 50 % (v/v) ethanol. The vehicle consisted of 50 % (v/v) ethanol in distilled water, and the corresponding vehicle was administered to the control group at the same injection volumes as the treatment groups. All solutions were filtered with a 0.2 μm pore syringe filter (Schleicher & Schuell, FP 30/0.2 CA-S) before drug administration. Other agents used included ketamine (Bremer Pharma GmbH, Germany), xylazine (Kela N.V., Belgium), and heparin sodium (Daropakhsh, Iran).

2.4. Surgical Procedure

Healthy adult male Wistar rats (200-240 g) were used for the experiment. The handling and procedures were approved by the university animal ethics committee. To comply with the principles of the international Animal Scientific Procedure Act and the 3Rs (Replacement, Reduction, and Refinement), all investigators underwent practical training in the required surgical techniques using dead animals before the commencement of the study. This training minimized unnecessary animal use and ensured surgical proficiency [26]. To ensure reliable vascular access, cannulation of the jugular vein and carotid artery was performed by experienced staff under the supervision of a trained demonstrator, in fully anesthetized rats. The male Wistar rats were divided into four groups (n = 6 rats/group): vehicle, nifedipine, *D. kotschyi* hydroalcoholic extract, and *D. kotschyi* essential oil. The combination of ketamine and xylazine provided sustainable anesthesia during the surgery and experimental periods without the need for a ventilator. Ketamine, in combination with xylazine, was used effectively as an anesthetic without causing significant respiratory depression [27]. While anesthesia can affect blood pressure [28], all measurements were taken under consistent conditions. Therefore, the rats were anesthetized with ketamine (120 mg/kg, IP) and xylazine (8 mg/kg, IP). After confirming the absence of reflexes, the animal was placed on a flat, movable surface. The animal was monitored throughout the procedure, and additional ketamine was administered subcutaneously as required. Special care was taken to maintain body temperature during the experiment. With the rat on its back, a small incision was made in the neck to expose the external jugular vein (Fig. 1). The vein, which appeared dark red, was separated from underlying tissues using curved forceps. The upper part of the vein was tied with thread, a small cut was made, and a cutdown tube was inserted towards the heart. The cannulated vein was secured with threads, and the other end of the tube was connected to a three-way tap filled with saline. Drug or extract solutions were administered through the jugular vein. The carotid artery, which appeared bright red, was separated from adjacent connective tissue and cleaned carefully. The cephalic end of the artery was tied, and the cardiac end was clamped. The artery was cannulated using a heparinized (25 IU/ml) normal saline-filled cannula attached to a three-way tap. The cannulation site was secured with ligatures without obstructing blood flow. The three-way tap was connected to a pressure transducer and a syringe filled with heparinized saline. The clamp was released, and the incision area was covered with saline-soaked gauze. The pressure transducer was connected to a calibrated Harvard Oscillograph to record arterial blood pressure [29, 30].



Fig. 1. The surgical procedure.

2.5. Blood Pressure Monitoring

After completing the surgical and cannulation procedures and removing the artery clamp, blood pressure waveforms were observed, and arterial pressure was continuously recorded from the anesthetized rats. The maximum pressure represented systolic pressure, while the minimum pressure represented diastolic pressure. Baseline blood pressure recordings were relatively stable during the control period, with systolic pressures ranging from 90 to 120 mmHg and diastolic pressures from 70 to 95 mmHg. Following IV administration of 0.1, 0.2, 0.4 ml saline solution via the jugular vein, a brief disturbance in blood pressure was observed during the injection period. These transient disturbances were considered injection artifacts and were excluded from data analysis. Although slight blood pressure fluctuations were observed, no significant changes were observed in the control groups. To minimize injection artifacts, all drugs, extracts, essential oil, and vehicle solutions were administered slowly over a fixed period of 3 min, with an injection volume not exceeding 0.2 ml.

Initially, a stable baseline blood pressure was recorded for at least 10 min, followed by IV administration of normal saline while blood pressure recording continued. Nifedipine (50 µg/kg, IV) was then administered via the jugular vein to reduce blood pressure, and increasing doses (50, 100, 200, 300, and 500 µg/kg) were subsequently administered at 10-min intervals. The same protocol was used to evaluate the effects of IV administration of the hydroalcoholic extract (20, 40, 80, 120, and 200 mg/kg) or the essential oil (2, 4, 8, 12, and 20 mg/kg) on blood pressure. The effect of the vehicle (50 % ethanol in distilled water) was also evaluated.

At the end of the experimental period, all rats were humanely euthanized in accordance with institutional ethical guidelines and internationally accepted recommendations for the care and use of laboratory animals. Euthanasia was performed by carbon dioxide (CO_2) inhalation using a gradual-fill method in a dedicated euthanasia chamber. CO_2 was introduced gradually to minimize pain and distress until the animals lost consciousness, followed by respiratory and cardiac arrest. Death was confirmed by the absence of respiration, heartbeat, and corneal and pedal withdrawal reflexes [31].

2.6. Data and statistical analysis

The pressure recording system was calibrated against a standard sphygmomanometer. For this purpose, the cuff was detached from the sphygmomanometer and coupled to the pressure transducer of the Harvard Oscillograph. Calibration was carried out by inflating the cuff to predetermined pressure values, allowing the recording system to be standardized across a pressure range of 50–150 mmHg. Systolic and diastolic blood pressure values were subsequently recorded in mmHg throughout the experimental period. The results were expressed as mean ± standard error of the mean (SEM). Statistical analyses were conducted using GraphPad Prism software, version 8.4.3. Differences among groups were evaluated by two-way analysis of variance (ANOVA), with time considered the repeated-measures factor and drug dose treated as the between-subject factor. When significant differences were detected, Tukey's multiple-comparisons post hoc test was applied. A $P < 0.05$ was considered statistically significant.

3. Results

3.1. Phytochemical analysis of the Hydroalcoholic extract and essential oil

GC–MS analysis identified more than 49 volatile constituents in the essential oil of *D. kotschyi*. The compounds representing more than 1 % of the total essential oil composition are presented in Table 1. The major constituents were geranial (12.49 %), neral (10.72 %), geraniol acetate (10.01 %), geraniol (10.01 %), α-pinene (9.96 %), and limonene (8.97 %). Other constituents detected in lower amounts included cyclononadiene (3.94 %), *β*-campholenal (1.71 %), terpinene-4-ol (1.68 %), linalool (1.67 %), carveol (1.44 %), myrcene (1.41 %), germacrene D (1.19 %), isopinocarveol (1.08 %), and α-terpineol (1.07 %) (Table 1).

The total phenolic content of the hydroalcoholic extract, determined using the Folin–Ciocalteu assay, was 57.9 mg gallic acid equivalents (GAE)/g dry extract.

Table 1. Main components of *D. kotschyi* essential oil

NO	Compound	Percent %	RT
1	Germacrene-D	1.19	19.25
2	Geraniol acetate	10.01	16.56
3	Geranial	12.49	13.16
4	Geraniol	10.01	12.73
5	Neral	10.72	12.13
6	Carveol	1.44	11.35
7	Cyclononadiene	3.94	10.84
8	*α*-Terpineol	1.07	10.38
9	Terpinene-4-ol	1.68	9.94
10	*β*-Campholene aldehyde	1.71	8.42
11	Isopinocarveol	1.08	8.77
12	Linalool	1.67	7.68
13	Limonene	8.97	5.87
14	Myrcene	1.41	4.92
15	*α*-Pinene	9.96	3.9

3.2. Effect of Nifedipine on blood pressure

As expected, IV administration of nifedipine significantly reduced both systolic and diastolic blood pressure (Fig. 2). Nifedipine at doses of 300 µg/kg ($P < 0.05$) and 500 µg/kg ($P < 0.01$) significantly decreased systolic blood pressure compared with the vehicle-treated group (Fig. 2). Furthermore, nifedipine at doses of 300 µg/kg ($P < 0.01$) and 500 µg/kg ($P < 0.05$) significantly decreased diastolic blood pressure

compared with the vehicle-treated group (Fig. 2). For the measured parameters, the corresponding F-values and P-values obtained from the two-way ANOVA were as follows: time, F(2.304, 46.08) =17.56, P < 0.0001; dose, F(3, 20) = 7.656, P = 0.0013; time × dose, F(18, 120) = 5.778, P < 0.0001.

3.3. Effect of Hydroalcoholic extract of D. kotschyi on blood pressure

In contrast, IV administration of the hydroalcoholic extract of *D. kotschyi* at doses up to 200 mg/kg did not significantly reduce blood pressure compared with the vehicle-treated group (Fig. 3). Although slight fluctuations in blood pressure were observed during the injection period, no significant changes in either systolic or diastolic blood pressure were detected throughout the study (Fig. 3). For the measured parameters, the corresponding F-values and P-values obtained from the two-way ANOVA were as follows: time, F(3.759, 75.18) = 2.855, P = 0.0320; dose, F(3, 20) =6.798, P = 0.0024; time × dose, F(18, 120) = 1.742, P = 0.0410.

3.4. Effect of D. kotschyi essential oil on blood pressure

In contrast to the hydroalcoholic extract, IV administration of the *D. kotschyi* essential oil at doses of 8 mg/kg (P < 0.05), 12 mg/kg (P < 0.01), and 20 mg/kg (P < 0.01) significantly decreased both systolic and diastolic blood pressure compared with the vehicle-treated group (Fig. 4). For the measured parameters, the corresponding F-values and P-values obtained from the two-way ANOVA were as follows: time, F(2.868, 57.37) = 12.83, P < 0.0001; dose, F(3, 20) = 15.11, P < 0.0001; time × dose, F(18, 120) = 4.222, P < 0.0001.

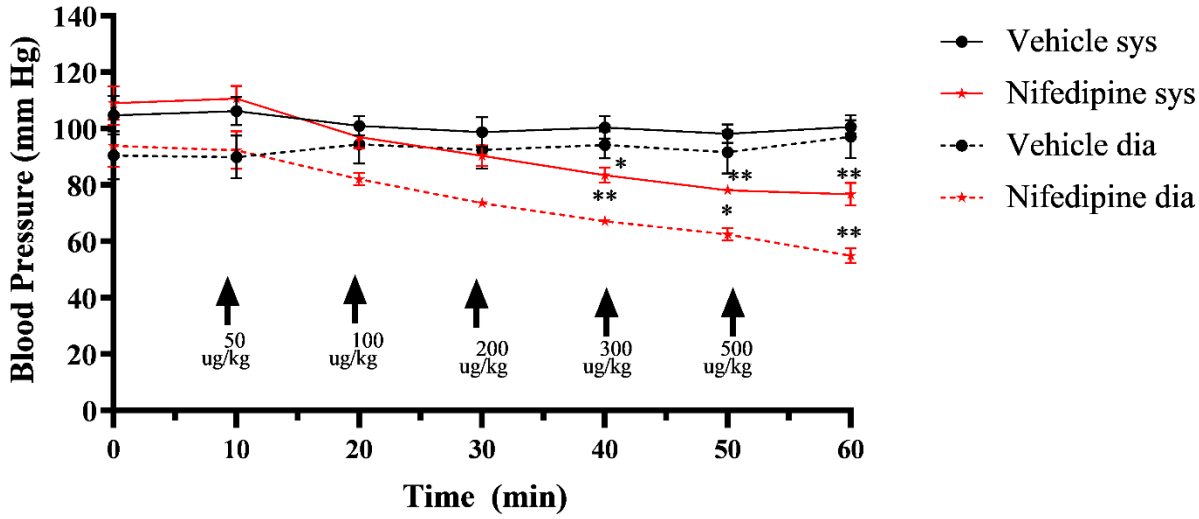


Fig. 2. Time course of systolic and diastolic blood pressure (BP) in anesthetized rats following successive intravenous administration of nifedipine compared with the vehicle-treated group. Nifedipine was administered intravenously at cumulative doses of 50, 100, 200, 300, and 500 µg/kg, with a maximum injection volume of 0.2 ml. The vehicle consisted of 50 % (v/v) ethanol in distilled water. Blood pressure was recorded at 10-minute intervals for 60 minutes, and arrows indicate the timing of nifedipine administration. Data are presented as mean ± SEM (n = 6). Statistical analysis was performed using two-way repeated-measures ANOVA (time as the within-subject factor and treatment as the between-subject factor), followed by Tukey's post hoc test. Significant differences compared with the vehicle-treated group are indicated as *P < 0.05 and **P < 0.01.

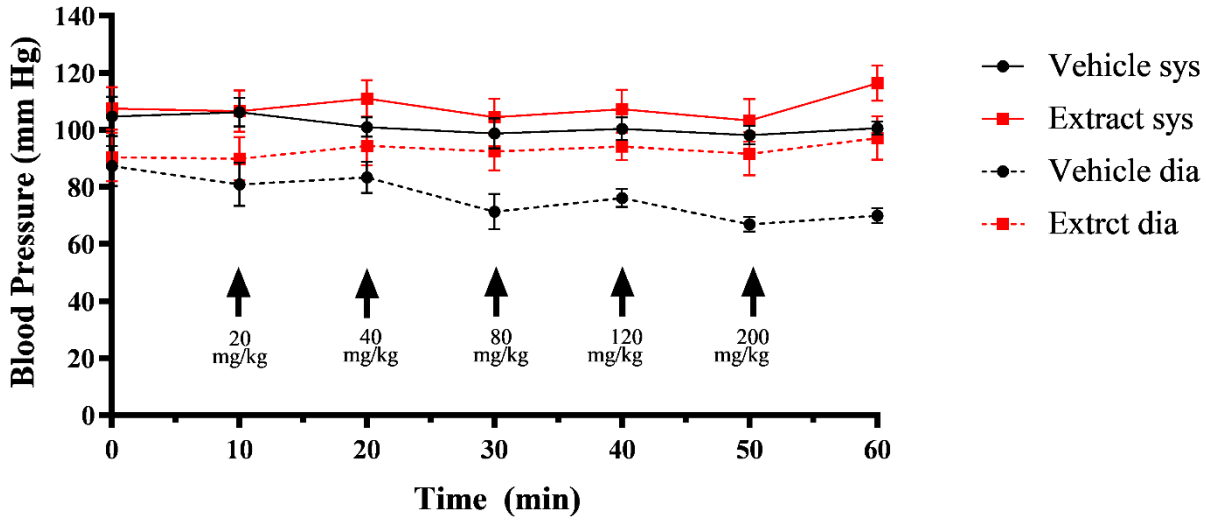


Fig. 3. Time course of systolic and diastolic blood pressure (BP) in anesthetized rats following successive intravenous administration of the hydroalcoholic extract of *D. kotschyi* compared with the vehicle-treated group. The hydroalcoholic extract was administered intravenously at cumulative doses of 20, 40, 80, 120, and 200 mg/kg, with a maximum injection volume of 0.2 ml. The vehicle consisted of 50 % (v/v) ethanol in distilled water. Blood pressure was recorded at 10-minute intervals for 60 minutes, and arrows indicate the timing of extract administration. Data are presented as mean ± SEM (n = 6). Statistical analysis was performed using two-way repeated-measures ANOVA (time as the within-subject factor and treatment as the between-subject factor), followed by Tukey's post hoc test. No statistically significant differences in either systolic or diastolic blood pressure were observed between the hydroalcoholic extract-treated and vehicle-treated groups throughout the experimental period.

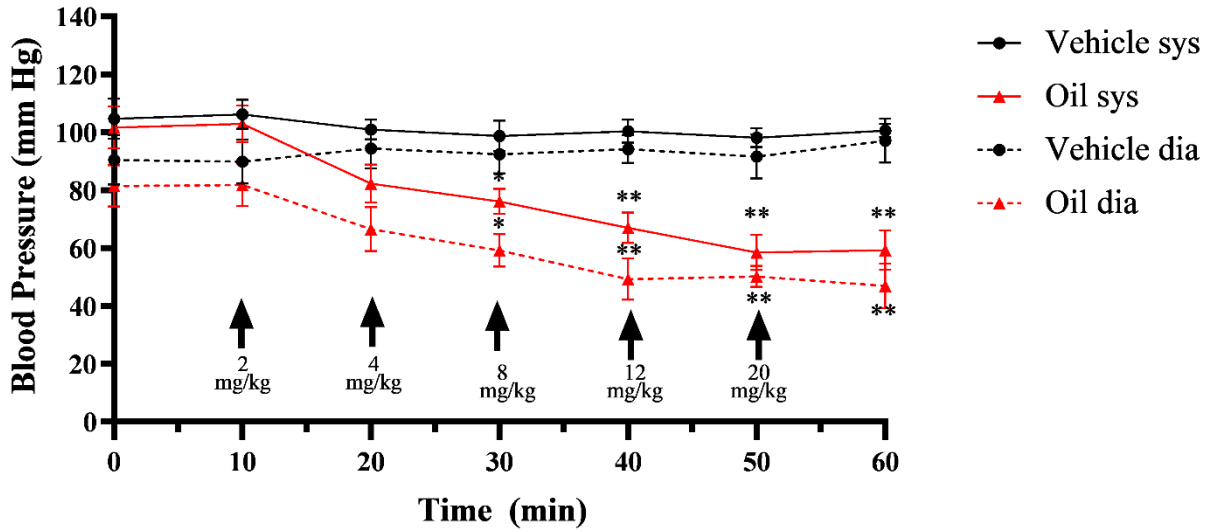


Fig. 4. Time course of systolic and diastolic blood pressure (BP) in anesthetized rats following successive intravenous administration of the essential oil of *D. kotschyi* compared with the vehicle-treated group. The essential oil was administered intravenously at cumulative doses of 2, 4, 8, 12, and 20 mg/kg, with a maximum injection volume of 0.2 mL. The vehicle consisted of 50 % (v/v) ethanol in distilled water. Blood pressure was recorded at 10-minute intervals for 60 minutes, and arrows indicate the timing of essential oil administration. Data are presented as mean ± SEM (n = 6). Statistical analysis was performed using two-way repeated-measures ANOVA (time as the within-subject factor and treatment as the between-subject factor), followed by Tukey's post hoc test. The essential oil produced a significant reduction in both systolic and diastolic blood pressure compared with the vehicle-treated group. Significant differences are indicated as *P<0.05 and **P<0.01 versus the vehicle-treated group.

4. Discussion

Hypertension is one of the major causes of morbidity and mortality [32]. Several cardioprotective agents have been recommended for the management of hypertension; however, most of them are associated with adverse effects and toxicity [33]. One of the alternative, safe, and effective approaches of managing these complications is the use of natural products [34]. In the present study, we investigated the effects of *D. kotschyi* extract and essential oil on blood pressure in anesthetized rats. As expected, nifedipine, a calcium channel blocker, effectively reduced blood pressure by decreasing peripheral vascular resistance [35, 36]. Consistent with its established pharmacological action, IV administration of nifedipine significantly reduced both systolic and diastolic blood pressure at doses of 300 and 500 µg/kg. In addition, our results showed that the *D. kotschyi* essential oil at doses of 8, 12, and 20 mg/kg significantly decreased both systolic and diastolic blood pressure. In contrast, IV injection of the hydroalcoholic extract of *D. kotschyi* had no significant effect on blood pressure. The different effects observed between the hydroalcoholic extract and the essential oil suggest that the hypotensive activity of *D. kotschyi* is mainly attributable to its volatile constituents rather than the polar constituents. This difference may be explained by variations in phytochemical composition between the two preparations. Since essential oils are volatile substances, it is likely that some of these constituents were lost during the rotary evaporation process used in preparing the hydroalcoholic extract, thereby reducing its hypotensive activity. In addition, hydroalcoholic extraction primarily yields polar phytochemicals, whereas the essential oil is enriched with volatile monoterpenes and oxygenated terpenoids with vasorelaxant properties. Therefore, the essential oil of *D. kotschyi* contains the components responsible for reducing blood pressure. In addition, it has spasmolytic activity on ileal smooth muscle [37], supporting our findings that the essential oil possesses biological activities capable of reducing vascular tone. Among the major constituents of the essential oil, limonene, α-terpinen-4-ol, α-terpineol, and linalool have been reported to reduce blood pressure and induce vasorelaxation [38, 39]. These constituents are therefore likely to contribute, either individually or synergistically, to the antihypertensive effect observed in the present study. Most research suggests that the spasmolytic effects of essential oils are primarily due to inhibition of voltage-operated calcium channels [40]. However, other mechanisms, including modulation of intracellular cyclic AMP (cAMP) signaling and potassium channels, have also been indicated for some constituents of essential oils [41]. Study has demonstrated that α-terpineol has vasorelaxant effects and decreases mean arterial pressure in normotensive and hypertensive animal models [38]. Previous studies have shown that *α*-terpineol produces vasorelaxation and decreases mean arterial pressure through endothelium-dependent NO release and inhibition of calcium influx into vascular smooth muscle cells [38]. These pharmacological actions may collectively explain the blood pressure-lowering effects of the *D. kotschyi* essential oil observed in the present study. Research shows that linalool can cause hypotension and vasorelaxation, which may affect calcium mobilization in vascular smooth muscle and activate NO mechanisms [38]. Previous studies have also reported anti-spasmodic and anti-inflammatory properties of the *D. kotschyi* extract [14, 18]. In another study, the effects of the hydroalcoholic extract and essential oil of *D. kotschyi* were evaluated on the contractions of rat isolated heart and aortic artery *in vitro* [23]. The essential oil exerted potent vasodilatory and negative inotropic effects, whereas the hydroalcoholic

extract had minimal effects on cardiac contractions at antispasmodic concentrations but produced positive inotropic activity at higher concentrations while also inhibiting aortic contractions. Furthermore, the hydroalcoholic extract at concentrations that inhibited ileum smooth muscle contractions did not significantly affect myocardial contractions [23], whereas concentrations above 400 µg/ml potentiated myocardial contractions in the isolated heart preparation [23]. Although the extract exhibited a positive inotropic effect, it showed only a weak relaxant effect on the isolated rat aorta [23]. These findings are in agreement with our results and further support the conclusion that the hypotensive effect of *D. kotschyi* is primarily attributable to its essential oil rather than its hydroalcoholic extract. Therefore, it can be concluded that any hypotensive effects of Zaringiah are attributable to its essential oil constituents rather than the extract itself.

5. Conclusion

The present study demonstrated that the essential oil of *D. kotschyi* has the potential to induce hypotension, whereas the hydroalcoholic extract did not produce significant antihypertensive effects. Further studies are needed to determine the safety profile and therapeutic margin of the essential oil.

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Authors' Contributions

MSI conducted the statistical analysis and prepared the initial draft of the manuscript. ZK contributed to the experimental procedures and data analysis. AY supervised the preparation of the plant extract. HS developed the study concept and provided overall supervision of the research. HS also coordinated and contributed substantially to the preparation of the manuscript. All authors reviewed and approved the final manuscript for publication.

Conflict of Interest

The authors declare that there are no conflicts of interest.

Ethical Considerations

Animal care and experiments were conducted in accordance with the guidelines for the care and use of laboratory animals set forth by Isfahan University of Medical Sciences. The project received approval from the university's ethical committee (IR.MUI.RESEARCH.REC.1400.541).

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