Original Article

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Study the Effect of Hydro-Alcoholic Extract of Achillea Eriophora on Cardiovascular System of Male Rats

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ABSTRACT

BACKGROUND AND OBJECTIVE: *Achillea eriophora* has been used in traditional medicine for treatment of gastrointestinal disorders and cardiovascular disease. This study was performed to determine its cardiovascular effects and its interaction with adrenergic system.

METHODS: In this study, 15 male wistar rats (weighed 220-250 g) were divided randomly into 3 groups. The first group received distilled water (Epinephrine solvent), epinephrine (0.04 mg/kg) and epinephrine plus extract solvent (ethanol 70%), respectively. The second group received distilled water, epinephrine and epinephrine plus extract (60 mg/kg), respectively. The third group received extract and after the onset of the extract effects, epinephrine were injected. In different groups, blood pressure and heart rate were recorded via arterial cannula linked to pressure transducer and A-D instrument powerlab.

FINDINGS: Extract significantly reduced mean arterial blood pressure (67±8, 65±3, 67±8), compared to the base stage (86±5, 84±6, 86±5) ($p<0.05$). In addition, a significant reduction was observed in the diastolic pressure in the presence of the epinephrine plus extract (76±7) in comparison with the stage that epinephrine injected (85±6) ($p<0.05$).

CONCLUSION: Result of the study showed that *A. eriophora* extract reduces diastolic pressure in the presence of the epinephrine. It can be concluded that *A. eriophora* has a hypotensive effect that this effect seems at least in part, related to vascular factors.

KEY WORDS: *Achillea eriophora*, *Adrenergic System*, *Blood pressure*, *Rat*.

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Introduction

Achillea eriophora is one of the native species in Iran, and its distribution is in the southern provinces at an altitude of 700-3000 meters (1). Phytochemical research on various species of Achillea eriophora has been shown the existence of bioactive compounds such as flavonoids, terinoids, lignans, amino acids derivatives, fatty acids and alkamines in this plant (3, 2). In Iran, Achillea is used more as a herbal medicine for digestive disorders. This plant has been effective for the treatment of feeling cramps and pain in the heart area, as well as renal stone excretion due to its diuretic effect on urinary volume (5, 4).

In previous studies, the effect of A. millefolium and A. wilhelmsii species of Achillea eriophora on blood pressure has been investigated (9-6). Also, in clinical and laboratory studies, the beneficial effects of Achillea eriophora in the treatment of respiratory diseases (8), the reduction of vascular inflammation (10), the antispasmodic effect (11), the reduction of triglycerides and LDL (6), the protection of the mucosal layer of the stomach and the reduction of acid secretion (12), anti-inflammatory effect (13), immune system stimulation (14), therapeutic effects on the liver (16,15), and its diuretic (17) effects have been determined. In some studies, the ester compounds of Achillea eriophora were isolated and its antimicrobial effects were investigated on a number of microbial agents (18).

In other studies, the anti-hypertensive effects of Achillea eriophora and its interaction with cholinergic and nitronergic systems have been investigated (5). Because Achillea eriophora is a native plant in Iran and had an extensive use in traditional medicine for heart and vascular disorders and because many studies on the effect of intravenous injection of this plant has not been done so far, therefore in this study, the effect of aqueous-alcoholic extract of Achillea eriophora leaf and flower on the cardiovascular system of male rats and its interference with adrenergic system have been investigated.

Methods

Plant extraction method: The Achillea eriophora plant was identified by a botanical specialist after collection (Voucher no 25049). Then the plant was dried and extracted by percolator method. In this method, the flowers and leaves were separated and, after pouring, enough 70% ethanol (73 ml of 96% ethanol and 27 ml of distilled water) was added to fill the space between the powders and completely to place solvent on the powder. Upon penetration of the solvent into the powder, a portion of 70% ethanol was again used. The percolator funnel was covered with aluminum foil and underneath the funnel there was a dark container to collect the extract, which darkened the color of the container to prevent the harmful effect of light on the extract.

During this time, with the solvent level lowered, enough 70% ethanol was added. After that, the dilute extract was concentrated by a rotary device. Due to the lack of complete evaporation of the solvent, according to the pharmacology specialist comments, the condensation process of the extract was stopped by rotary evacuation and the freeze dryer was continued. The extract was turned into powdery condition by freeze dryer at 49 °C.

Maintenance of laboratory animals: 15 adult male Wistar rats weighing 250-220 g were kept under controlled light conditions (12 hours of light and 12 hours of darkness) and temperatures of 22 ° C for one week. During the maintenance period, they were given enough food and water. Ethical issues related to working with laboratory animals such as anesthesia and surgery were conducted under the Biological Bioethics Committee with code 9130527BBC-DBSU.

Experimental methods: After one week and ensuring animal health, the rats were anesthetized by intraperitoneal urethane (1 g/kg dose) and then tracheostomy was performed to prevent aspiration and choking during anesthesia. The animal's cane was conveyed. The femoral artery and vein of the animal were also cannulated, which was used to carry out injections during the test, and the arterial cannula was connected to a pressure transducer connected to the PowerLab system via the Bridge Amplifier. The changes in arterial pressure, systolic pressure, diastolic pressure and heart rate were observed and recorded on the monitor. During the whole time of the experiment, physiological serum was injected to the animal in an amount of 0.1 cc per minute for ten minutes and the body temperature of the animal was controlled at 37 ° C. After 60 minutes and to balance the animal's arrival with surgical conditions, blood pressure and normal heart rate were recorded at baseline.

Considering the effects of doses of 40, 50, 60, 80 mg/kg from extract, dose of 60 mg/kg was selected as the effective dose of the extract (5). After normal recording in different groups, the interaction of the effective dose of the extract with the adrenergic system was investigated using epinephrine (manufactured by Iran Pharmaceuticals Company).

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Animals group: In this study, the rats were randomly divided into five groups. The control group was injected with epinephrine and solvent volume (70% ethanol). In this group, the basal state was a condition in which the mice received only a physiological serum. After thirty minutes of normal registration, animals were injected with distilled water as a solvent of epinephrine and parameters were recorded for ten minutes. After this stage, the animal was injected with epinephrine and the effects of blood pressure and heart rate were recorded and allowed the parameters to return to normal normalization.

At the last stage, epinephrine and then ethanol 70% were injected and parameters were recorded. The second group was injected as a test group, to which the epinephrine and the extract were injected. In this group, the basal state was a condition in which the mice received only a physiological serum.

After thirty minutes of normal administration, the animals were administrated with distilled water as solvent of epinephrine and parameters were recorded for ten minutes. After this stage, the animal was injected with epinephrine and the parameters were recorded. After returning the blood pressure and heart rate to normal state, at the end stage, the epinephrine and then the extract was injected. In the third group, the experimental stages were different from two previous ones, after the normal recording, the extract was injected and the mean blood pressure and heart rate data were recorded and allowed the pressure and heart rate to return to normal level. At the last stage, firstly extract was injected and after initiating the effects of lowering blood pressure, the epinephrine was injected and the data were recorded.

Data analysis: The recorded graphs were converted to numbers by using the Labchart software for the Power Lab system, and these numbers were analyzed by SPSS software using Repeated Measure test for intra-group statistical analysis and for statistical analysis between groups, the Independent T-test was used and $p<0.05$ was considered significant.

Results

The findings showed that the mean arterial pressure in the basal state and drug control mode (distilled water injection) did not change significantly in the control and experimental groups compared to each other (Fig. 1). These data indicated that the control and treated groups had no significant difference in blood pressure before the injection of the drug, the extract solvent or the extract.

Systolic pressure was significantly increased in epinephrine injections compared to drug control ($p<0.05$). Systolic pressure in the control group was not significantly different from the epinephrine injection with the injection of solvent of the extract with epinephrine and also in the experimental group by injection of the extract with epinephrine (Fig 2). The diastolic pressure had a significant decrease in the injection of Achillea eriophora extract along with epinephrine (76±7) than injection of epinephrine (85±6) ($p<0.05$).

However, diastolic pressure in the control group did not show a significant difference in the solvent injection of the extract with epinephrine compared to the epinephrine injection (Fig 3).

The heart rate in both control and experimental groups was significantly increased in injection of epinephrine compared to drug control (distilled water injection) ($p<0.05$). While in the injection of the Achillea eriophora extract with epinephrine in the control group as well as in the injection of Achillea eriophora extract along with epinephrine in the experimental group were observed no significant changes compared with epinephrine injection lonely (Fig 4).

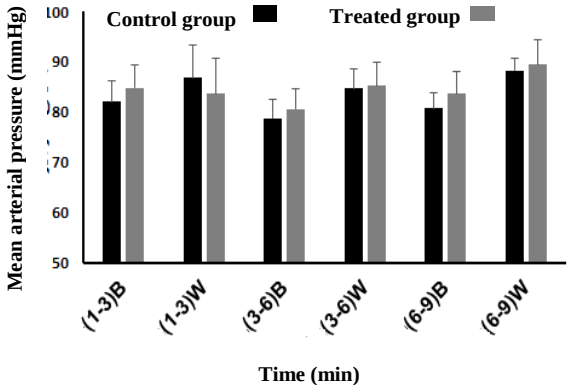

Figure 1. Comparison of mean arterial pressure changes in baseline (B) and control mode of epinephrine (distilled water injection) in both control and experimental groups.

The mean arterial pressure at baseline and drug control status in the same time interval was not significantly different in the control and experimental groups compared to each other. The mean arterial pressure values were calculated as the average mean arterial pressure at the same time interval of three minutes, and the statistical analysis was performed between the same minutes and the same conditions in the control and experimental groups.

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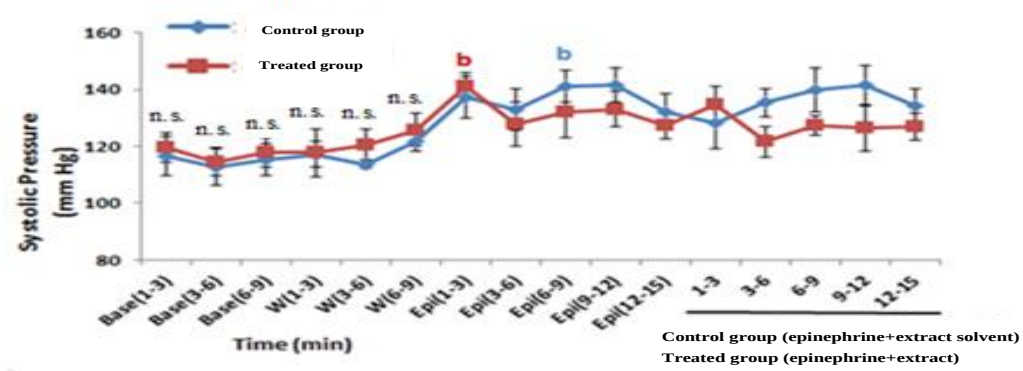

Figure 2. Systolic pressure changes in baseline and in the presence of epinephrine solvent (distilled water) and epinephrine (Epi) and solvent of extract+epinephrine in the control group. Systolic pressure changes in baseline and in the presence of epinephrine solvent (distilled water W) and epinephrine (Epi) and extract+epinephrine in the experimental group.

N.s: Not significant: There was no significant difference between the same minutes and the same conditions in both control and experimental groups. B: Significant difference in epinephrine injection with drug control (distilled water injection, W) $p<0.05$, systolic pressure numbers were considered as mean systolic pressure at the same time interval of three minutes, and statistical analysis between the same minutes were done in different modes.

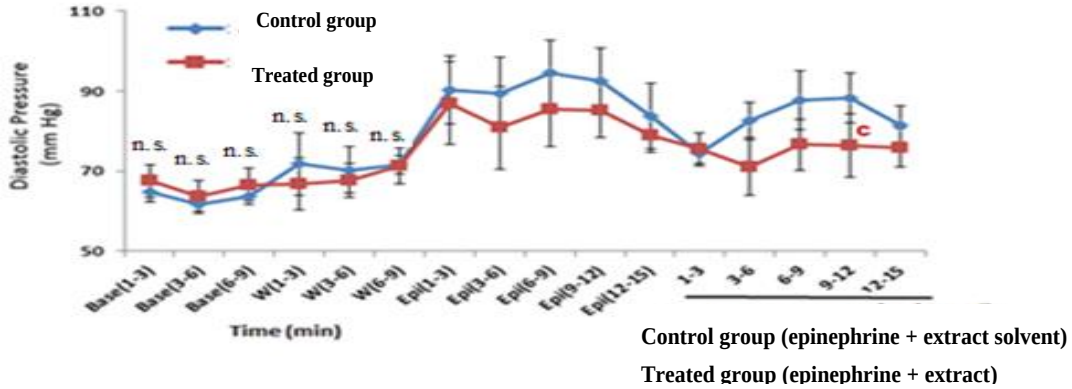

Figure 3. Diastolic pressure changes in baseline and in the presence of epinephrine solvent (distilled water W) and epinephrine (Epi) and solvent of extract+epinephrine in the control group. Diastolic pressure changes in baseline and in the presence of epinephrine solvent (distilled water W) and epinephrine (Epi) and extract+epinephrine in the experimental group.

N.s. Not significant: There was no significant difference between the same minutes and the same states in the control and experimental groups. C: Significant difference between extract+epinephrine compared with epinephrine (Epi) $p<0.05$. Diastolic pressure numbers were considered as mean diastolic pressure at the same time interval of three minutes, and statistical analysis was performed between the same minutes in different modes.

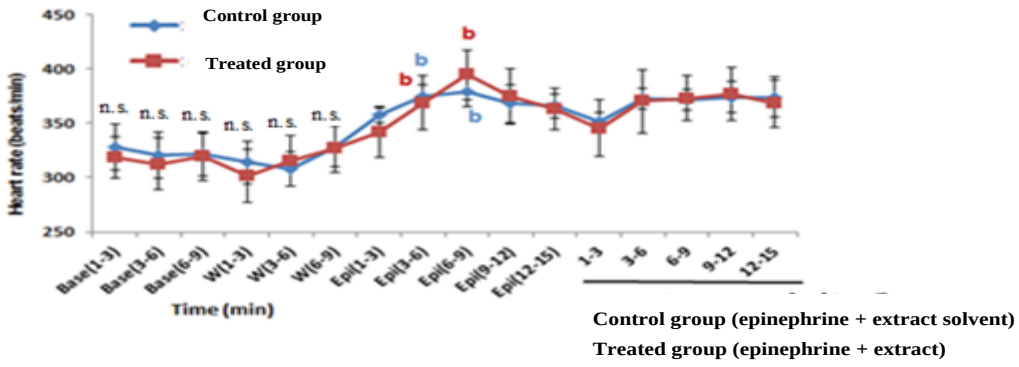

Figure 4. Changes in heart rate in baseline and in the presence of epinephrine solvent (distilled water W) and epinephrine (Epi) and solvent of extract + epinephrine in the control group. Heart rate changes in baseline and in the presence of epinephrine (distilled water W) and epinephrine (Epi) and extract+epinephrine in the experimental group

N.s. No significant: There was no significant difference between the same minutes and the same states in the control and experimental groups: B Significant difference in epinephrine (Epi) with drug control (W) $p<0.05$. Heart rate numbers were considered as the mean heart rate for the same three-minute time interval and statistical analysis was performed between the same minutes in different modes

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According to Table 1, mean of mean arterial pressure in baseline in minutes 3-6, 9-12 and 12-15 was 86+5, 84+6, and 86+5, respectively, which a significant decrease was observed in mean arterial pressure with the injection of extract in these moments (67+8, 65+3, 67+8 respectively) ($p<0.05$). With the injection of epinephrine at the onset of the hypotensive effects of the extract, the mean arterial pressure increased significantly in the 3rd and 6th minutes (92+3 and 92+8), respectively ($p<0.05$). Over time, the effects of lowering blood pressure were observed and the mean pressure values were close to those of the mean pressure in the infusion of the extract (Table 1). Injection of Achillea eriophora extract showed no significant changes in heart rate compared to baseline, while epinephrine injection caused a significant increase in heart rate at the same time of reducing blood pressure by extract, and heart rate in the 9-12 and 12-15 minutes showed a decreased trend and the number of beats was close to the level seen in the extract injection (Table 2).

Table 1. Changes in mean arterial pressure in the baseline, extract injection mode and epinephrine injection at the same time with effects of reducing blood pressure of the extract

Time	Baseline	Extract injection	Epinephrine injection
Minutes1-3	88±2	80±2	91±2
Minutes3-6	86±5	67±8 a	92±3 b
Minutes6-9	85±6	73±4	92±8 b
Minutes9-12	84±6	65±3 a	68±3
Minutes12-15	86±5	67±8 a	69±5

a: Significant difference in injection of extract with baseline, b: Significant difference in injection of epinephrine after extract with extract injection ($p<0.05$). The mean arterial pressure numbers were considered as the average of mean arterial pressure at the same time interval of three minutes, and statistical analysis was performed between the same minutes in different modes.

Table 2. Heart rate changes in baseline, extract injection mode and epinephrine injection at the same time with the effects of reducing blood pressure of the extract

Time	Baseline	Extract injection	Epinephrine injection
Minutes1-3	320±16	327±14	377±26 b
Minutes3-6	323±19	336±16	390±19 b
Minutes6-9	318±18	328±18	381±24 b
Minutes9-12	311±21	334±14	354±15
Minutes12-15	316±14	329±16	338±18

b: Significant difference in epinephrine injection after extract with extract injection ($p<0.05$). Heart rate numbers were considered as mean heart rate for the same three-minute time interval and statistical analysis was performed between the same minutes in different states.

Discussion

The results of this study showed that intravenous injection of aqueous-alcoholic extract of Leaf and Flower of Achillea eriophora caused a decrease in blood pressure (arterial pressure) in normal blood pressure rats and also, Achillea eriophora reduced diastolic pressure in mice injected with epinephrine. The effects of different species of Achillea eriophora on blood pressure have been investigated in several studies. Study of De Souza et al. showed that Achillea eriophora with effect on vascular mechanisms decreases arterial pressure in rats (7).

Asgari et al., in a clinical study, showed that oral administration of Achillea extract in a six-month period in 120 men and women aged between 60-40 years reduced systolic pressure and diastolic pressure (6). In the research by Niazmand et al., The aqueous-alcoholic extract of the Achillea eriophora reduced the blood pressure of the rabbit (9).

In a study by Khan et al., effect of Achillea eriophora extract on reducing blood pressure can be used to treat high blood pressure (8). The results of this research can confirm the findings of this research. The effect of reducing the blood pressure of the Achillea eriophora may be due to the presence of useful drug compounds such as flavonoids, which have been studied in some investigations. In the study of DeSouza et al., the artemetin flavonoid contained in Achillea eriophora reduced the blood pressure of rats, the findings of this study showed that this flavonoid may have been associated with a decrease in blood pressure by inhibiting the ACE activity and, consequently, reducing the production of angiotensin II. (7). In previous studies, it has been shown that the extract of Achillea eriophora with its effect on vascular mechanisms and reduction of cardiac output decreases blood pressure, which is consistent with the cholinergic system and is independent of the nitronergic system (5).

In this study, epinephrine as an adrenergic (sympathetic) adjunct system was used to investigate the possible mechanism of decreasing blood pressure of the hydro-alcoholic extract of Achillea eriophora and its interference with the adrenergic system. According to the findings of this study, the prescription of Achillea eriophora extract reduced the mean arterial pressure, but had no significant effect on heart rate. These findings are consistent with results of previous research (5). As indicated in the results, intravenous injection of epinephrine increased systolic pressure and pulse rate, while epinephrine and extract injections did not

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significantly change systolic pressure and heart rate compared to epinephrine injection. Also, according to the results, epinephrine injection along with Achillea eriophora extract, diastolic blood pressure decreased in minutes as compared to epinephrine injection. This indicates that the extract has somehow reduced the effects of epinephrine on vascular contraction. In a study by Harandizadeh et al. (4), Achillea eriophora extract has shown the effects of endothelial non-dependent vascular relaxation. In the results of this study, it has been argued that a significant part of this effect is likely to be applied through inhibition of receptor-dependent calcium input and also dependent on voltage-dependent calcium channels.

The results of previous studies show that some compounds of Achillea eriophora extract such as cineol (19), luteolin (20) and carvacrol (21) have a relaxing effect on smooth muscle. Therefore, the observed effects could be due to the presence of these compounds in the Achillea eriophora extract. The results showed that when the epinephrine was injected with the extract after the onset of the effects of lowering blood pressure, it increased blood pressure and heart rate.

The above results indicate the effect of extract on the vessels, and the adrenergic system does not seem to affect the effects of lowering blood pressure of the Achillea eriophora extract. Regarding the role of various alpha and beta receptors of the adrenergic system in the regulation of cardiovascular system function, the use of agonists and antagonists of various adrenergic receptors in the determination of the precise mechanism of reduction of blood pressure in Achillea eriophora is essential in future researches. In the system of herbs, the Achillea eriophora genus has a variety of useful drug compounds, including flavonoids (23, 22, 3), which the interaction of these compounds with the adrenergic system in the arteries have been investigated in several studies. In a study by Ajay et al., flavonoid quercetin reduced the contractile responses of phenylephrine in isolated diabetic rats expressed as part of this effect due to an increase in nitric oxide in the endothelial vasculature (24). In the results of a study on the effects of several flavonoids on the mechanical activity of isolated aorta in rats, flavonoids also cause vasodilatation after the use of compounds such as noradrenaline and KCl. In this study, flavonoids had no effect on adrenergic system (25). In a study by flavonoid Galanjin reduced the effects of phenylephrine on contraction. The results of this study suggest that this flavonoid is dependent on the endothelium (nitric oxide release) and an endothelium independent pathway (preventing the passage of calcium ions from the membrane cells) has caused such a trace (26). In a study, flavonoid Flavone reduced the effects of phenylephrine on contraction, probably due to the increased release of nitric oxide from endothelial cells (27).

Mentioned research was performed on isolated vessels that are different from the present research, but the reduction of diastolic pressure at the injection phase of the extract and epinephrine is consistent with the results of this study. Considering the fact that in this study, the aqueous-alcoholic extract of Achillea eriophora leaves and flowers was used and this extract is a combination of different pharmacological elements, and also the amount of each of these compounds is different, more researches are needed to predict which specific compound causes such effects on the cardiovascular system.

In general, according to the results obtained from this study, the hydroalcoholic extract of Achillea eriophora leaves and flowers can reduce blood pressure and possibly some part of this effects of the Achillea eriophora extract is through effects on vessels and independent of the adrenergic system. However, more researches are needed to determine the exact mechanism of the effect of this plant on male rat cardiovascular system.

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