

Cardiovascular effects of *Teucrium polium* L. extract in rabbit

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ABSTRACT

Background: *Teucrium polium* L. (TP) have been used in herbal medicine for different purposes such as antispasmodic, antidiabetic and lowering blood lipid. In the present study, the impact of aqueous-ethanol extract of TP on blood pressure, heart rate and intraventricular pressure was investigated in rabbit. **Materials and Methods:** Twenty-four NWZ rabbits weighed (2-3 kg) were randomly divided into four groups. In each experiment, two groups of six rabbits received jugular injection of either TP extract (20, 40 and 80 mg/kg) or normal saline for blood pressure effects and two groups for intraventricular pressure. Then, blood pressure, heart rate and intraventricular pressure were measured via carotid cannula using pressure transducer connected to a power lab system, and the data were pooled from independent, single-blinded experiments for each group. **Results:** Treatment with 80 mg/kg of TP extract significantly depressed the mean arterial blood pressure (12.5%, $P < 0.05$). However, there was no significant decrease in the 20 or 40 mg/kg dose or normal saline treatment group. Moreover, the extract increased (dp/dt)_{max} ($P < 0.05$), maximum left ventricular pressure (LVP_{max}) ($P < 0.05$) and decreased (dp/dt)_{min} significantly ($P < 0.05$), there was no meaningful effect on left ventricular end-diastolic pressure (LVEDP). **Conclusion:** The present results demonstrated the extract had no effect on the heart rate, but showed a positive inotropic on the heart and hypotensive effects. These data suggested that hypotensive effect may counterbalance by the inotropic effect of the extract.

Key words: Blood pressure, intraventricular pressure, heart rate, Rabbit, *Teucrium polium* L.

INTRODUCTION

The prevalence of cardiovascular diseases is very high and increases dramatically worldwide. Hypertension is a very important risk factor for development of other cardiovascular diseases such as myocardial infarction and heart failure.^[1] These conditions are the most important causes of hospital admissions which are responsible for high mortality rates, disabilities and costs. Therefore, heart failure treatment, particularly, lowering blood pressure by pharmacological treatment is an essential step for preventing cardiovascular diseases. In the recent years, using herbal medicine for the prophylaxis and treatment of cardiovascular diseases has been increased and scientists

have been paying more attention to investigate the cardiovascular effects of herbs.^[2]

Lamiaceae or Labiatae which also known as the Mint family comprises about 210 genera and 3,500 species. One of the most popular species of this family native to the Mediterranean region and the Middle East is *Teucrium polium* L. (TP) which has been used for over 2000 years in traditional medicine mainly for its antidiabetic, antipyretic, anti-inflammatory and antispasmodic properties. In some parts of Iran it is traditionally used for treatment of heart failure. TP contains chemical compositions such as salvigenin, cirsiolol,^[3] α - and β -pinen, sabinene, myrcene, germacrene D, limonene, β -caryophyllene and spathulenol.^[4-6] Previous studies have demonstrated some of the pharmacological effects of TP such as antibacterial,^[7] anti-inflammatory,^[8] antioxidant,^[9,10] antiulcerogenic,^[11,12] antinociceptive,^[13,14] antidiabetic^[15,16] and antispasmodic.^[17-19] In addition, lowering blood lipid,^[20,21] induction of vascular relaxation,^[18] positive

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inotropic and chronotropic^[22] and decreasing of blood pressure^[23] has been reported to be affected by this plant. However, there is no a comprehensive study to specify the pharmacological activities of TP extract on cardiovascular system. Therefore, the present study was conducted to investigate the possible inotropic, chronotropic and blood pressure effects of the aqueous-ethanol extract of TP *in vivo*.

MATERIALS AND METHODS

Plant material

Aerial part of TP was collected from hills around Ferdows city (south Khorasan province, Iran) and identified by botanists in Herbarium of Pharmacy School, Mashhad University of Medical Sciences (voucher No. 152-2016-4) and then dried at room temperature.

Extraction method

Two hundred grams of aerial parts of TP were macerated with ethanol (50%) at 30°C for 24 hours and shaken intermittently. The solution was then filtered and dried by oven at 40°C. The average w/w yield was 12.5%. The dried extract was dissolved in the distilled water to make 20, 40 and 80 mg/kg doses. The extract doses were chosen after a pilot study. *Teucrium polium* L. showed no cytotoxic effect^[24] and on the base of previous studies^[14,20] the used acute doses of TP extract in this study were not toxic.

Experimental procedure

Twenty-four NWZ rabbits weighed (2-3 kg) were randomly divided into four groups. In each experiment, two groups of six rabbits received jugular injection of either TP extract (20, 40 and 80 mg/kg) or normal saline for blood pressure effects and two groups for intraventricular pressure which received jugular injection of either TP extract (20, 40 and 80 mg/kg) or normal saline.

In control groups, normal saline (37°C) with similar volumes of extracts used to rule out the effects of blood volume changes on cardiovascular parameters. The rabbits were kept in standard conditions at 22 ± 2°C and fed with standard diet. The study was permitted by the Institutional Animal Ethics Committee of Mashhad University of Medical sciences (MUMS).

Animals were anesthetized using sodium thiopental (50 mg/kg, ip) and then jugular vein and carotid artery were cannulated. TP extracts were introduced through the jugular vein. The carotid cannula with a pressure transducer connected to a power lab machine (AD Instruments, Australia) was used for blood pressure, heart rate and LVP measurement. The data were pooled from independent, single-blinded experiments for each group.

Data analysis

The changes in blood pressure and intraventricular pressure before and after injections were analyzed, using the Wilcoxon signed rank test. The results represent mean ± SEM and the differences were considered significant if $P < 0.05$.

RESULTS

Effects on blood pressure

Treatment with TP extract at 80 mg/kg reduced the mean arterial blood pressure (79.6 vs 68.6 mmHg), significantly [Figure 1]. However, in the 20 and 40 mg/kg doses of TP extracts the mean blood pressure reduced, the changes were not reaching a significant value [Figure 1]. As expected, there was no significant differences in the normal saline treatment groups for mean arterial blood pressure, heart rate, LVP_{max} (maximum left ventricular pressure), LVEDP (left ventricular end diastolic pressure), (dp/dt)_{max} (maximum rate of rise of left ventricular pressure during ventricular contraction) and (dp/dt)_{min} (maximum rate of fall of LVP during left ventricular relaxation) [Table 1].

Effects on intraventricular pressure

TP extract injection increased the mean of (dp/dt)_{max} (1288 vs 1508 mmHg s⁻¹ for 20 mg/kg and 1540 mmHg s⁻¹ for 40 mg/kg and 1561 mmHg s⁻¹ for 80 mg/kg, $P < 0.05$) [Figure 2a]. The extract also increased the mean of LVP_{max} (95 vs 112 and 110 mmHg for 40 and 80 mg/kg, respectively $P < 0.05$), significantly [Figure 3a]. Furthermore, the mean of (dp/dt)_{min}, decreased after TP injection which was statistically meaningful (-1143 vs -1456 and -1449 mmHg s⁻¹ for 40 and 80 mg/kg respectively, $P < 0.05$) [Figure 2b]; however, there was no significant effect of TP injection on LVEDP [Figure 3b].

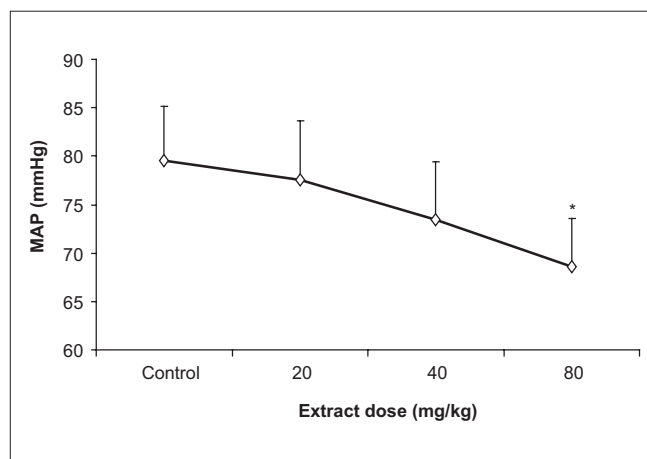
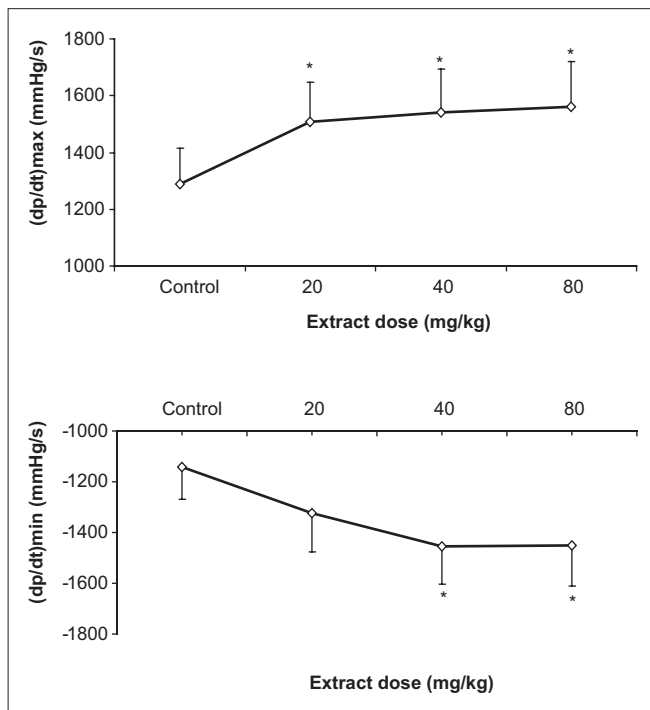
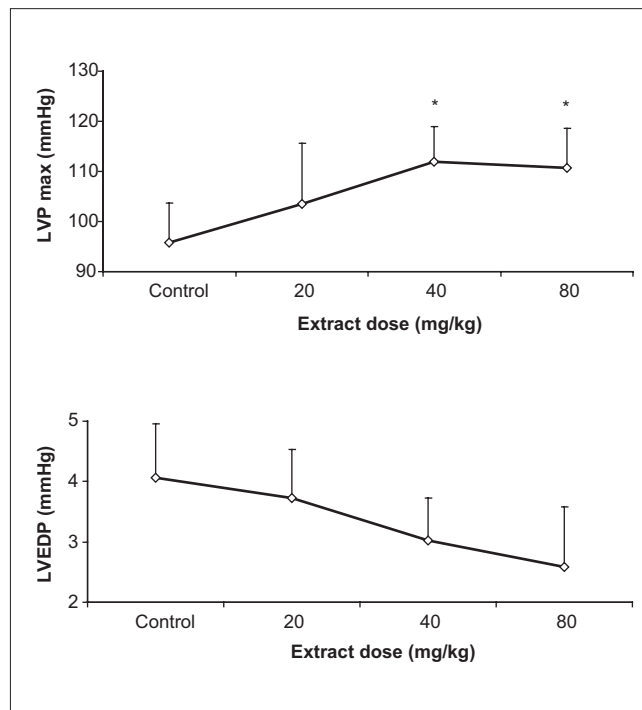


Figure 1: Effect of *Teucrium polium* L. extract on mean arterial pressure (n=6, * $P < 0.05$).

Table 1: Effect of normal saline injection by the same volume of *Teucrium polium* L. extract on intraventricular pressure, mean arterial pressure and heart rate. (n=6 for intraventricular pressure control group, n=6 for mean arterial pressure control group)

Parameters	Before injection of normal saline	After injection of normal saline	P value
$(dp/dt)_{max}$ (mmHg s ⁻¹)	2197.56±120.53	2144.14±140.54	0.41
$(dp/dt)_{min}$ (mmHg s ⁻¹)	-1151.33±137.4	-1186±143.2	0.65
LVP _{max} (mmHg)	97.3±6.5	96.9±7.1	0.75
LVEDP (mmHg)	3.8±1.4	3.5±1.8	0.88
MAP (mmHg)	77.75±5.9	78±6.1	0.79
H.R (beat/min)	217±24.9	219±22.1	0.51

**Figure 2:** Effect of *Teucrium polium* L. extract on maximum rate of rise of left ventricular pressure during ventricular contraction [(dp/dt)max] (a) and maximum rate of fall of left ventricular pressure during left ventricular relaxation [(dp/dt)min] (b) (n=6, *P<0.05).**Figure 3:** Effect of *Teucrium polium* L. extract on LVP_{max} (maximum left ventricular pressure) (a) and left ventricular end diastolic pressure (b) (n=6)

DISCUSSION

In the present study the injection of normal saline with the same volume of TP extract in blood pressure and intraventricular pressure control groups had not significant effects on heart functions, thus the results of control groups could be attributed to TP extract groups. The TP extract (80 mg/kg) significantly reduced mean arterial blood pressure (14%) in normotensive condition which indicated a relaxation effect on vascular smooth muscles. Previous studies have also demonstrated that TP extract had relaxation effects on ileum^[17] and vascular smooth muscles.^[18] Moreover, TP contains important ingredients such as salvigenin, cirsiolol, pinen- α and β , Sabinene, myrcene, germacrene D, limonene, β -caryophyllene,

spathulenol which can influence on vascular smooth muscle tone. For instance, in many studies the antispasmodic effect of some components such as α - and β -pinen,^[25,26] cirsiolol,^[27,28] spathulenol,^[29] limonene^[30] and salvigenin^[31] from other members of Lamiaceae family have been demonstrated. Taking together, it seems that the TP ingredients can induce the hypotensive effects in rabbits.

Blood pressure is not determined by vascular factors alone and cardiac interaction is also important for determining the final arterial blood pressure value. We recently demonstrated positive inotropic effects of TP extract on isolated Guinea pig heart.^[22] This effect may counterbalance the relaxant effect of lower doses of TP extracts on vascular smooth muscle; consequently, in such situation,

the blood pressure could not be reduced significantly. In other words, the positive inotropic effect of TP extract may suppress its relaxant properties *in vivo*.

However, in several studies the relaxation effect of TP extract has been observed in contracted smooth muscle *in vitro*,^[17,18] in the present study this effect has been investigated in normotensive condition *in vivo* which may differ in methodology.

Although, different TP extract doses had not any significant effect on heart rate in this study. In the pervious study,^[22] we demonstrated that the TP extract had a positive chronotropic effect. The logical reason for these differences between such studies could be explained by different methodological approaches. There are many factors such as cardiac, vascular, hormonal and neural that can influence the heart rate *in vivo*. Therefore, further studies needed to be conducted to evaluate the influences of such factors on heart rate in TP-treated animals.

Furthermore, in the present study, the effects of TP extracts on cardiac parameters such as (dp/dt)_{max}, (dp/dt)_{min}, LVP_{max} and LVEDP were investigated. The data shows that (dp/dt)_{max} was significantly increased by TP extract treatment (17.1%, 19.5% and 21.1% for 20, 40 and 80 mg/kg dosages, respectively). This parameter is an indicator for maximum rate of rise of LVP during ventricular contraction and it is a valid criterion for inotropic effect of a substance. We have seen the inotropic effect of TP extract *in vitro* and *in vivo*. However, these findings are in contrast with other findings that demonstrated a relaxant effect on vascular smooth muscle, thus it can be concluded that the mechanism of TP activity on smooth and cardiac striated muscles are different. TP extract also significantly decreases (dp/dt)_{min} (27.4% and 26.7% for 40 and 80 mg/kg dosages, respectively). This parameter is an indicator for maximum rate of fall of LVP during left ventricular relaxation and its reduction indicates the rapidity of ventricular relaxation, ventricular efficiency and positive inotropic effect. Therefore, the positive effect of the extract on (dp/dt)_{max} and negative effect on (dp/dt)_{min} after injection shows an enhancement of cardiac performance and indicates a positive inotropic effect.

LVP_{max} is significantly increased by TP extract (16.2% and 11.4% for 40 and 80 mg/kg dosages respectively) which also indicates the positive inotropic effect. Taking together our findings in the present and the previous study,^[22] reveal that TP extract may has a significant positive inotropic effect. More interestingly, in Iranian traditional medicine, TP is used for treatment of CHF, therefore it seems that the results of the present study can strengthen such applications. In conclusion, for better understanding of the

effects of TP extract and the mechanism/s of actions on the cardiovascular system, particularly on blood pressure in hypertension status, further studies are needed to be conducted.

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