

Preventive Effect of Hydroalcoholic Extract of *Rosa damascena* on Cardiovascular Parameters in Acute Hypertensive Rats Induced by Angiotensin II

Abstract

Background: *Rosa damascena* (R.D) is an aromatic plant with numerous therapeutic effects including cardiovascular effect. The mechanism cardiovascular effect of R.D is unclear and suggested mediated through renin-angiotensin system (RAS). Therefore, in this study, the role of hydroalcoholic extract of R.D on acute hypertension induced by AngII was evaluated. **Methods:** After anesthesia, femoral artery and vein of rats were cannulated for recording cardiovascular responses and drug injection, respectively. Systolic blood pressure (SBP), mean arterial blood pressure (MAP), and heart rate (HR) were recorded continuously by power lab software. Rats were divided into saline, AngII (50 ng/kg), AngII + Losartan (10 mg/kg), and three groups of R.D extract (250, 500, and 1000 mg/kg). Losartan and AngII were administered intravenously and the other ones intraperitoneal. In the R.D groups, 30 min after injection of the extract, AngII was injected and the maximum changes in SBP, MAP, and HR were calculated and compared to that in control and AngII groups. **Results:** Results show that AngII significantly increased SBP, MAP, and decreased HR than the control group which was blocked by losartan. SBP and MAP in R.D + AngII groups were significantly lower than AngII alone ($P < 0.05$ – $P < 0.001$). Only MAP in higher dose (1000 mg/kg) was significantly lower than low dose (250 mg/kg; $P < 0.05$). Two higher doses also significantly decreased bradycardia induced by AngII ($P < 0.01$). **Conclusions:** The preventive effect of hydroalcoholic extract of R.D on cardiovascular parameters maybe is mediated by suppression of AngII activity.

Keywords: Angiotensin II, blood pressure, heart rate, renin-angiotensin system, *Rosa damascena*

Introduction

Rosa damascena mill L (R.D) is one of the important species rose families (Rosacea) that cultivated in several areas of the world including Iran, for perfume and therapeutic purposes.^[1-4] The presence several compounds such as citronellol, geraniol, kaempferol, phenylethyl alcohol, and flavonoids have been shown in this plant.^[5-7]

In traditional medicine, R.D is used in abdominal and chest pain,^[8] digestive disorder, depression, grief, nervous stress and tension,^[1] and headaches and migraine.^[9]

The R.D also has several pharmacological effects such as relaxation of tracheal,^[1] hypotensive,^[10] antioxidant,^[11] hypnotic,^[12] ileum contraction,^[13] and antidiabetic^[14] effects.

In the present time, there are a few studies about cardiovascular of R.D. In a previous study, we show that hydroalcoholic extract of R.D decreased blood pressure and heart

rate (HR) in normotensive rats.^[10] Another studies also indicated that rose oil of R.D could decrease systolic blood pressure (SBP).^[2,15] The fragrance inhalation of rose oil in humans also decreased 40% sympathetic activity and 30% adrenaline concentration.^[15] It was also indicated that R.D contains cyanidin-3-O-beta-glucoside a compound of flavonoids that decreased angiotensin converting enzyme (ACE) activity.^[7] Based on above evidence, we suggested that R.D has a beneficial effect on cardiovascular parameters through an inhibitory effect on renin-angiotensin system (RAS). Therefore, the effects of hydroalcoholic extract of R.D on blood pressure and HR in acute hypertensive rats induced by angiotensin II (AngII), the main production of RAS were evaluated.

Methods

Preparation of extract

The R.D was collected from Khorasan Province, Mashhad, Iran, and identified

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by botanists in the Herbarium (No: 254-1804-01). We used maceration method in this study. The 100 g of dried flowers, powdered then macerated in 600 cc ethanol 70% for 72 h. After that, the mixture was filtered.^[16] The solvent was evaporated by a rotary evaporator under reduced pressure at 40°C. Concentrations of the extract were prepared by adding distilled water.

Animals and surgery

Experiments were performed on 42 male Wistar rats (200–250 g). The animals were anesthetized with urethane (1.4 g/kg, intraperitoneally [i.p]). The left femoral artery was cannulated with a polyethylene catheter (PE-50) filled with heparinized saline that connected to a blood pressure transducer and SBP, mean arterial blood pressure (MAP), and HR continuously recorded by a power Lab system (ID instrument, Australia).^[17] The left femoral vein also cannulated for drug injection. Measurement, a time of 20 min, was held before the injection of any drug for stabilization of the blood pressure. The surgery and all the related procedures were approved by the Animal Research Ethics Committee of Mashhad University of Medical Sciences (approval number: 931,725).

Drugs

The drugs are included urethane, AngII, and losartan (Los; Sigma, Co; USA). All drugs dissolved in saline.

Animals

Rats were divided into six groups as follows ($n = 7$ in each group)

1. Control group; received saline through intravenous (i.v)
2. AngII group; received AngII (50 ng/kg, i.v)
3. Los group; received losartan (10 mg/kg, i.v) 30 min before injection of AngII^[18]
4. R.D 250 group; received 250 mg/kg of R.D extract (i.p) 30 min before injection of AngII
5. R.D 500 group; received 500 mg/kg of R.D extract (i.p) 30 min before injection of AngII
6. R.D 1000 group; received 1000 mg/kg of R.D extract (i.p) 30 min before injection of AngII.

Volume injection in all groups was 0.4 ml.

Experimental protocol

The AngII group received AngII (50 ng/kg) i.v, in AngII + losartan group first animal treat with Los (10 mg/kg, i.v) after 30 min AngII (50 ng/kg) injected and blood pressure was recorded. In the R.D groups, three doses of extract (250, 500, and 1000 mg/kg) administrated then after 30 min AngII (50 ng/kg, i.v) injected and changes of SBP, MAP, and HR were evaluated.^[18]

Data analysis

The changes (Δ) of SBP, MAP, and HR values were calculated and expressed as a mean \pm standard error of the mean. Statistical comparisons done by one-way ANOVA

followed by the Tukey's *post hoc* test. $P < 0.05$ was used to indicate statistical significance.

Results

Effects of saline on cardiovascular responses

Injection of saline (i.v) had no significant effects on SBP (before: 95 ± 3.4 mm Hg and after: 103.5 ± 2.17 mm Hg), MAP (before: 92 ± 3.4 mm Hg and after: 98.4 ± 2.17 mm Hg), or HR (before: 340 ± 8.22 beats/min and after: 335.18 ± 7.1 beats/min).

Effect of intravenous injection of angiotensin II alone and after pretreatment with losartan on cardiovascular responses

As shown in Figure 1a and b, injections of AngII (50 ng/kg; i.v) significantly increased maximal changes of SBP and MAP compared to control group ($P < 0.001$, $n = 7$). The maximal changes of HR also decreased than control group [$P < 0.05$; Figure 1c].

In Los + AngII group, injection of Los (10 mg/kg, i.v) 30 min before AngII (50 ng/kg; i.v) significantly attenuates increased Δ SBP ($P < 0.01$) and Δ MAP ($P < 0.001$; $n = 7$) induced by AngII. The change of HR in Los + AngII group was lower than AngII alone group, but it was not significant [Figure 1c].

Effect of pretreatment with hydroalcoholic extract of *Rosa damascena* on cardiovascular parameters in acute hypertension induced by angiotensin II

In these group rats pretreated with three doses of R.D (250, 500, and 1000 mg/kg, i.p), separately. After 30 min, AngII (50 ng/kg; i.v) slowly injected and cardiovascular parameters recorded.

In dose 250 + AngII, changes of SBP and MAP were not more significant than AngII but were significant compare to Los + AngII [$P < 0.01$; Figures 2 and 3]. The changes of HR also were not more significant than AngII alone but were more significant than Los + AngII [$P < 0.05$; Figure 4].

In dose R.D 500, Δ SBP and Δ MAP significantly reduced compared to AngII group [$P < 0.01$, Figures 2 and 3] and were not significant than Los + AngII. The changes of HR in this dose also decreased but did not significant than AngII alone and Los + AngII groups [Figure 4].

In dose R.D 1000 + AngII, Δ SBP, and Δ MAP significantly reduced compared to AngII group [$P < 0.05$, Figures 2 and 3]. However, these effects were not more significant than the Los + age group. The changes of HR did not significant than AngII alone and Los + AngII groups [Figure 4].

Discussion

In the present study, AngII significantly increased Δ SBP, Δ MAP, and Δ HR and two higher doses of hydroalcoholic

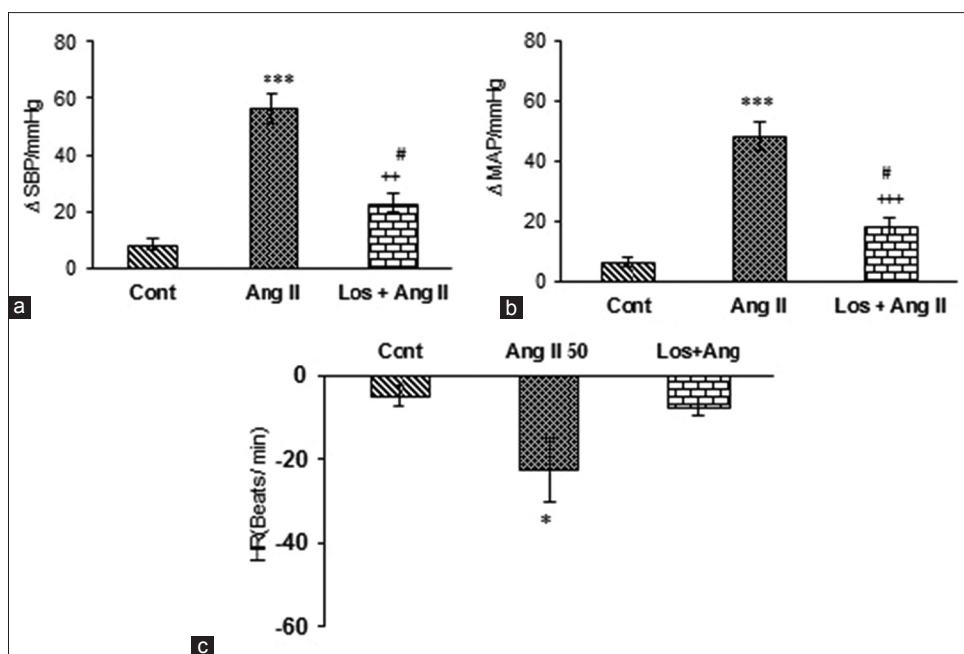


Figure 1: Effects of angiotensin II (50 ng/kg; intravenous) and angiotensin II + losartan (10mg/kg) on SBP (a) MAP (b), and HR (c) in anesthetized rats. Data were expressed as a mean \pm standard error of the mean. One-way ANOVA used for statistical analysis. ($n = 7$) *** $P < 0.001$ compare to control *** $P < 0.001$; compare to angiotensin II group #: $P < 0.05$ Los + angiotensin II compare to control SBP = systolic blood pressure, MAP: mean arterial blood pressure, HR = heart rate

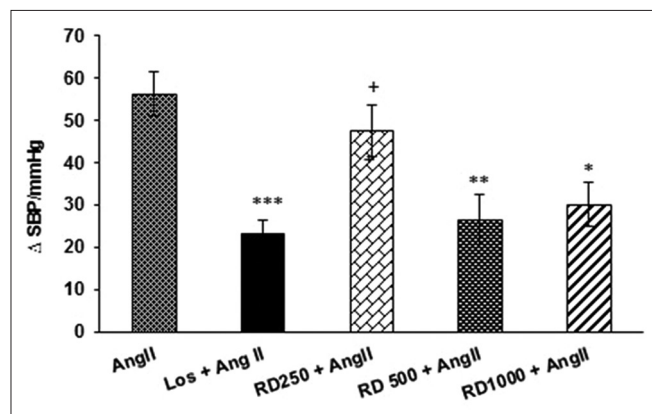


Figure 2: Effects of hydroalcoholic extract of *Rosa damascena* on changes of systolic blood pressure in anesthetized rats. Three doses of extract (250, 500, and 1000 mg/kg) injected (intraperitoneally) after 30 min angiotensin II injected and changes of systolic blood pressure determined. Data were expressed as a mean \pm standard error of the mean. One-way ANOVA used for statistical analysis ($n = 7$). *: $P < 0.01$, **: $P < 0.01$, and ***: $P < 0.001$ compared to angiotensin II +: $P < 0.01$ dose 250 compared to angiotensin II + Los

extract of R.D significantly attenuate these effects of AngII (50 ng/kg). Therefore, hypotensive effects of R.D are partly mediated by inhibition of RAS.

The RAS is one of the important systems involved in cardiovascular regulation.^[19,20] The most important product of RAS is AngII that has a complicated effect on the cardiovascular system by several mechanisms such as vasoconstriction, activation of sympathetic nervous, and increased secretion of aldosterone.^[20] The cardiovascular effect of AngII mostly mediated by its Ang II type 1 (AT1) receptor.^[20] In this study, we used losartan as an AT1

antagonist. Our results showed that the effect of AngII significantly attenuates by losartan that confirmed the role of AT1 in the cardiovascular effect of AngII. The cardiovascular effect of AT1 receptor mediated by complex intracellular signaling pathways such as activation of phospholipase C (PLC), protein kinase C, Src family kinases, tyrosine kinases, and mitogen-activated protein kinase pathways.^[21,22] Effect of this receptor on these signaling pathways is time dependent.

For example, AngII within seconds activates of PLC and increased cytosolic Ca^{++} and vascular contraction.^[21] Because in this study, acute effect of AngII decreased by R.D and AT1 also expressed in vascular smooth muscle cells;^[21] it is suggested that the ameliorating effect of R.D on AngII is mediated by inhibition short effects of AngII such as PLC pathway in smooth muscle of vessels.

The R.D has several compounds, especially flavonoids. This compound has several beneficial effects on the cardiovascular system, for example, the inhibitory effect of flavonoids on ACE has been shown in a previous study.^[23] The ACE by hydrolysis AngI to AngII plays a vital role in the regulation of blood pressure and electrolyte balance.^[23,24] The R.D contains flavonoids and its compound cyanidin-3-O-beta-glucoside has an ACE inhibitory effect.^[7] Therefore, it is possible that the R.D by inhibition of ACE decreased the production of AngII caused a hypotensive effect. Terpenes and kaempferol are other compounds of R.D that those inhibitory effects of ACE have been indicated.^[25,26] It is conceivable that the effect of R.D on AngII is mediated by these compounds. However, in this

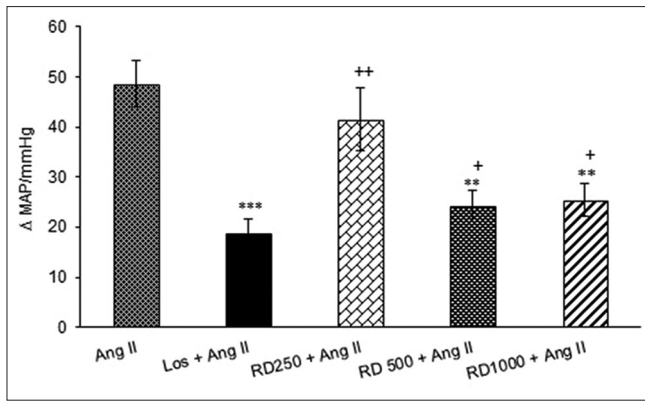


Figure 3: Effects of hydroalcoholic extract of *Rosa damascena* on changes of mean arterial blood pressure in anesthetized rats. Three doses of extract (250, 500, and 1000 mg/kg) injected (intraperitoneally) after 30 min angiotensin II injected and cardiovascular responses determined. Data were expressed as a mean \pm standard error of the mean. One-way ANOVA used for statistical analysis ($n = 7$). **: $P < 0.01$ and ***: $P < 0.001$ compare to angiotensin II + $P < 0.05$, **: $P < 0.01$ compared to angiotensin II + Los

study, the AngII was used, therefore, ACE inhibitory effect R.D was not evaluated.

The AngII by increased vascular superoxide production and decreased nitric oxide (NO) bioavailability also play an important role in AngII-induced hypertension.^[27] Hence, the NO-AngII imbalance may be an important component in the vascular pathophysiology of hypertension.^[28] It is well known that R.D has strong antioxidant properties.^[11] Therefore, extract of R.D maybe decreases the effect of AngII by antioxidant effect.

Another mechanism hypertensive effect of AngII is activation of the sympathetic system.^[29] There are evidences that the release of norepinephrine and epinephrine in presynaptic of the sympathetic system and adrenal medulla increased by AT1 receptor of AngII.^[29,30] The inhibitory effect of R.D on sympathetic system and decreased secretion of epinephrine and norepinephrine in human has been shown.^[2] Based on this evidence, it is conceivable that the cardiovascular effect of R.D mediated by attenuating effect of AngII on sympathetic system.

The depressant effect of R.D on the central nervous system and hypnotic, antianxiety, and anticonvulsant effects also has been reported.^[1,12] It is conceivable that R.D by an effect on the brain cardiovascular areas or by effect on local AngII in brain modulate the effect of AngII on the cardiovascular system. However, future studies should be performed to assess beneficial cardiovascular effects of this plant.

Conclusions

In summary, hydroalcoholic extract of R.D attenuate cardiovascular responses induced by AngII and this effect is comparable with losartan. Therefore, the effect of R.D on the cardiovascular system partly is mediated by suppression activity of RAS especially AngII.

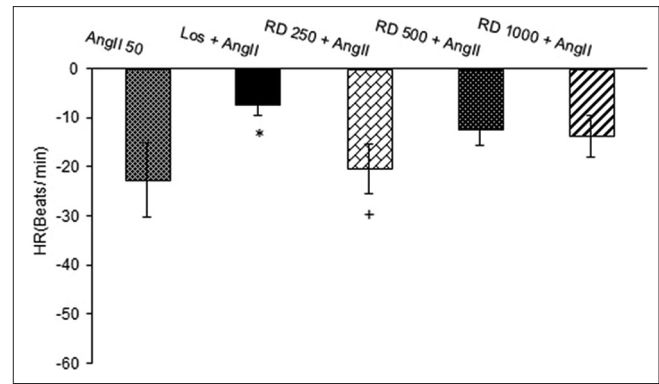


Figure 4: Effects of hydroalcoholic extract of *Rosa damascena* on changes of heart rate in anesthetized rats. Three doses of extract (250, 500, and 1000 mg/kg) injected (intraperitoneally) after 30 min angiotensin II injected and cardiovascular responses determined. Data were expressed as a mean \pm standard error of the mean. One-way ANOVA used for statistical analysis. ($n = 7$) *: $P < 0.01$ compare to angiotensin II + $P < 0.05$ compare to angiotensin II + Los

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Conflicts of interest

There are no conflicts of interest.

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