Antihypertensive Effects of Standardized Asafoetida: Effect on Hypertension Induced by Angiotensin II

Abstract

Background: Asafoetida is an oleo-gum-resin obtained from the rhizome of Ferula assa-foetida plant that its effects on hypertension have been reported. This study examines the effect of aqueous extract of asafoetida on the cardiovascular parameters in acute hypertension induced by angiotensin II (AngII). Materials and Methods: Thirty-six male rats were divided into six groups including Group 1: control; Group 2: AngII (50 ng/kg, intravenous); Group 3: losartan (Los; 10 mg/kg, i. p) + AngII; and Groups 4, 5, and 6 that received three doses of asafoetida (10, 30, and 60 mg/kg, i. p), separately. Los and extract were injected 30 min before hypertension induced by AngII. The femoral artery was cannulated and was connected to a pressure transducer, and cardiovascular parameters (systolic blood pressure [SBP], mean arterial pressure [MAP], and heart rate [HR]) were continuously recorded by a Power Lab system. The changes (Δ) of parameters were calculated and used for statistical analysis. Results: AngII significantly increased the value of Δ SBP and Δ MAP compared to the control and significantly decreased Δ HR value. Injection of Los attenuated increased cardiovascular responses by AngII. Three doses of asafoetida ameliorated cardiovascular responses by AngII. Three doses of asafoetida decreased the Δ HR non significantly compared to AngII. Conclusion: Our results indicated that aqueous extract of asafoetida ameliorated cardiovascular responses in acute hypertension induced by AngII. This effect in a lower dose was more effective and comparable with Los. Therefore, a part of antihypertensive effect of asafoetida is mediated through inhibition of the AngII receptor type 1 receptor of AngII.

Keywords: Angiotensin II type 2 receptor blockers, asafoetida, blood pressure, cardiovascular system

Introduction

Hypertension, that also known as high blood pressure is a serious disorder in the worldwide and it is often called ‘the silent killer ’because this disease can lead to serious complications to vital organs however, due to the lack of specific symptoms, the patient may not be aware of his disease.[1] Hypertension is one of the most important risk factors for cardiovascular diseases including stroke, myocardial infarction, arteriosclerosis, heart failure, kidney failure, blindness, and cognitive impairment.[2] Its prevalence is increasing, and based on the statistical data, it is predicted that 60% of adults will have hypertension until the 2025 year.[3] According to a guideline published by the American College of Cardiology in 2017, Stage 1 of hypertension is when systolic blood pressure (SBP) is 130–139 mmHg and diastolic blood pressure (DBP) is 80–89 mmHg and Stage 2 of hypertension is when SBP ≥140 mmHg and DBP ≥90 mmHg.[4] The exact mechanism (s) of hypertension have not been fully understood, but there are several possible mechanisms in this regard such as role of autonomic nervous activity, circulating hormones, and local autoregulation.[5] The most well-known system is renin–angiotensin system (RAS) that its main product is angiotensin II (AngII) with vasoconstriction effect and stimulatory effect on proliferation of vascular smooth muscle.[6] AngII is formed in two stages and under the influence of two main enzymes. In the first stage, angiotensinogen is converted to AngI by renin enzyme, and in the second stage, AngI is converted to AngII by angiotensin-converting enzyme (ACE).[7] Hyperactivity in the renin–angiotensin system (RAS) lead to hypertension, and as a result, the drugs have an inhibitory effect on the performance...
of this system, they can be used to treat hypertension. Losartan (Los) as a blocker of AngII receptor type 1 (AT₁) and captopril as an inhibitor of ACE are common drugs in the treatment of hypertension. In addition to the use of chemical drugs to treat hypertension, the use of herbal medicines is also increasing worldwide due to lesser side effects, availability, and lower cost. So far, various plants with antihypertensive effect have been identified that one of them is Ferula asa-foetida L. (FA). This herb is herbaceous and monocarpic of the Apiaceae family. The main source of this herb is the steppes of Iran and Afghanistan. The asafoetida is an oleo-gum-resin that obtained from the exudates of the roots and rhizome of some species of Ferula (Ferula rubricaulis, Ferula rigidula, Ferula alliacea but Ferula asa-foetida L. is the main source of asafoetida. The asafoetida is also called “Anghouzeh,” “Khorakoma,” and “Anguzakoma” in Iran. The various effects of the asafoetida are known including antispasmodic, antifungal, antioxidant, antiviral, anticancer, and antidiabetic and antihypertensive effects. The asafoetida is consists of three main fractions, including resin (40%–64%), gum (25%), and essential oil (volatile fraction) (10%–17%). The resin fraction is containing ferulic acid and its esters, coumarins, sesquiterpene coumarins, and other terpenoids. The gum includes glucose, galactose, L-arabinose, rhamnose, glucuronic acid, polysaccharides, and glycoproteins, and volatile fraction contains sulfur-containing compounds, monoterpenes, and other volatile terpenoids. Few studies have been performed on the antihypertensive effect of asafoetida, so we designed this study to investigate the possible mechanisms of this OLGR in relation to its effects on the cardiovascular system. Fatehi et al. reported that FA gum extract (0.3–2.2 mg/100 g, body weight) significantly reduced the mean arterial pressure (MAP) in anesthetized rats. Furthermore, Esmaeili et al. demonstrated that FA essential oil has a potent vasodilatory effect. Therefore, in this study, we aimed to investigate the possible cardiovascular mechanism(s) of asafoetida. The effect of its aqueous extract on the cardiovascular parameters in acute hypertension induced by AngII was evaluated.

Materials and Methods

Extract preparation

The asafoetida was provided from a medicinal plant shop in Birjand, South Khorasan, Iran. It was identified by a botanist at Pharmacological Research Center of Medicinal Plants, Mashhad University of Medical Sciences, Mashhad, Iran. According to required doses, one hundred grams of asafoetida was soaked in 600 ml distilled water for 72 h at room temperature. Then, the extract was filtered and dried at 40°C using a rotary evaporator. The weight of the material was achieved and was calculated and subtracted from initial total weight for reaching to exact dose.

Extract standardization

The polyphenol content of the asafoetida was evaluated based on the Folin–Ciocalteu method in which asafoetida has 20.7 mg gallic acid/g crude extract. Furthermore, the flavonoid content of the asafoetida was estimated based on the aluminum chloride colorimetric assay in which asafoetida has 16.8 mg quercetin/g crude extract. Finally, the anthocyanin content of the asafoetida was evaluated based on the pH-differential method described by Rodriguez-Saona in which asafoetida has 1.9 mg/g crude extract. The line equations for standard curves of gallic acid and quercetin were

\[ Y = 0.0669 X + 0.0116 \]

\[ Y = 0.06632 X − 0.01448 \]

respectively.

Animals

Thirty-six male Wistar rats weighting 250 ± 20 g were obtained from Animal House, Mashhad University of Medical Sciences, Mashhad, Iran. Animals were kept under standard conditions including free access to water and food, 12:12 light-dark cycle, temperature 21°C ± 4°C, humidity 25%–35%, and quiet and stress-free environment.

Surgery

The animals were anesthetized with sodium thiopental (60 mg/kg, i. p.) After confirming the anesthesia, the femoral artery was cannulated with a heparinized blue Angiocath. It was connected to a pressure transducer, and cardiovascular parameters were continuously recorded by a PowerLab system (ID instrument, Australia). After a stabilization time (15 min), drugs and extract were administrated.

Drug and animal groups

AngII and Los were purchased from Sigma, USA, and sodium thiopental was provided from Kavosh Gostar Darou Company, Iran.

Animals were divided into six groups (n = 6 for each group) as described below:

1. Control group: Saline was injected
2. AngII group: AngII (50 ng/kg, intravenous) was perfused at 30 min after saline administration
3. Los group: Los (10 mg/kg, intraperitoneal [i. p]) received at 30 min before AngII injection
4. Asafoetida with dose 10 mg/kg (A10) + AngII group: 10 mg of asafoetida extract was injected (i. p) 30 min before AngII
5. Asafoetida with dose 30 mg/kg (A30) + AngII group: 30 mg of asafoetida extract was injected (i. p) 30 min before AngII
6. Asafoetida with dose 60 mg/kg (A60) + AngII group: 60 mg of asafoetida extract was injected (i. p) 30 min before AngII.
Data analysis

The changes (Δ) of the cardiovascular parameters (MAP, SBP, and heart rate [HR]) were calculated and demonstrated as mean ± standard error of the mean statistical analysis performed by one-way ANOVA followed by the Tukey’s post hoc test. Instant software was used for analysis. \( P < 0.05 \) was considered as statistically significant.

Results

In the control group, after 15 min, saline was injected ip and then cardiovascular responses were recorded. Saline had no significant effect on cardiovascular parameters (before injection, SBP: 106.47 ± 2 mmHg, MAP: 92.51 ± 1.1 mmHg, and HR: 477 ± 14.7 beats/min and after injection: SBP: 108.88 ± 1.8 mmHg, MAP: 94.91 ± 0.9 mmHg, and HR: 478.24 ± 14.4 beats/min).

In the AngII group, AngII was slowly perfused, and after recording the cardiovascular responses, those changes (Δ) were recorded and compared to the control group. The AngII significantly increased the Δ SBP (AngII group: 39.6 ± 3.3 mmHg vs. control: 2.4 ± 0.3 mmHg) and Δ MAP (AngII group: 30.8 ± 4 mmHg vs. control: 2.4 ± 0.25 mmHg; \( P < 0.001 \)). AngII also significantly decreased Δ HR (AngII group: −2.6 ± −5.2 beats/min vs. control: 1.2 ± 1.9 beats/min; \( P < 0.001 \) [Figure 1a-c]).

In the Los + AngII group, Los was injected 30 min before perfusion of AngII. The result indicated that pretreatment of Los significantly ameliorated cardiovascular responses evoked by AngII (ΔSBP in the Los + AngII group: 16.3 ± 1.6 mmHg vs. AngII alone: 39.6 ± 3.3 mmHg; \( P < 0.001 \)). The Δ MAP (Los + AngII: 14.9 ± 2 mmHg vs AngII: 30.8 ± 4 mmHg; \( P < 0.001 \)). The Δ HR in Los + AngII was −13.2 ± −2.4 Beat/min that was significantly respect to the AngII group: −26 ± −5.2 Beat/min [Figure 1a]. The Δ SBP and ΔMAP, in the Los + AngII group also were significant compared to the control group [\( P < 0.01 \) to \( P < 0.05 \), Figure 1b-c].

In the asafoetida groups, three doses of extract (10, 30, and 60 mg/kg, i. p) were injected (i. p), and after 30 min, AngII was slowly perfused and cardiovascular responses were recorded. ΔSBP and Δ MAP in the A10 + AngII group were significantly reduced compared to the AngII group (ΔSBP: A10 + AngII: 14 ± 4.8 vs. AngII group: 39.6 ± 3.3 mmHg vs. AngII group: 30.8 ± 4 mmHg; \( P < 0.001 \)). The Δ HR in Los + AngII was −26 ± −5.2 Beat/min compared to the Los + AngII group: −22 ± −5.2 Beat/min. In addition, the effect of dose 30 extract on all parameters was not significant compared to the Los + AngII group (A30 + AngII: −22 ± −5.2 Beat/min vs. AngII: −26 ± −5.2 Beat/min). In addition, the effect of dose 30 extract on all parameters was not significant compared to the Los + AngII group (A30 + AngII: −22 ± −5.2 Beat/min vs. Los + AngII: −26 ± −5.2 Beat/min; \( P < 0.001 \), \( P < 0.01 \)). The A30 extract doses could not significantly improve AngII-induced bradycardia (ΔHR in the A30 + AngII group: −22 ± −2.5 Beat/min vs. AngII: −26 ± −5.2 Beat/min). In addition, the effect of dose 30 extract on all parameters was not significant compared to the Los + AngII group (A30 + AngII: ΔSBP: 15.2 ± 2.3 mmHg, ΔMAP: 14.7 ± 2.9 mmHg, and Δ HR: −22 ± −2.5 Beat/min compared to the Los + AngII group: ΔSBP: 16.3 ± 1.6, ΔMAP: 14.9 ± 2, and Δ HR: −13.2 ± −2.4 Beat/min) [Figure 2-4].

Results in the A60 + AngII indicate that Δ SBP and Δ MAP were reduced significantly vs AngII group (A60 + AngII: ΔSBP: 22.4 ± 3.4 mmHg, ΔMAP: 15.6 ± 2.8 mmHg vs. ΔSPB of AngII: 39.6 ± 3.3 mmHg, ΔMAP: 30.8 ± 4 mmHg, \( P < 0.01 \), for both parameters). Effects of A60 on Δ HR were not significant (ΔHR: −23.4 ± −10.8 Beat/min vs. AngII: −26 ± −5.2 Beat/min). In addition, the effect of dose 60 extract on all parameters was not significant compared to the Los + AngII group (A60 + AngII: ΔSBP: 22.4 ± 3.4 mmHg, ΔMAP: 15.6 ± 2.8 mmHg, and Δ HR: −23.4 ± −10.8 Beat/min compared to the Los + AngII group: ΔSBP: 16.3 ± 1.6, ΔMAP: 14.9 ± 2, and Δ HR: −13.2 ± −2.4) [Figures 2 - 4].

Discussion

In the present study, we investigated the effects of aqueous extract of asafoetida gum on cardiovascular parameters in acute hypertension induced by AngII. Injection of AngII leads to significantly increased SBP, MAP, and reduced HR respect to the control group. Three doses of aqueous extract of asafoetida (10, 30, and 60 mg/kg) decreased the value of SBP and MAP significantly, but its effect on HR was not significant. In addition, an effective dose of asafoetida on cardiovascular responses was 10 mg/kg.

The RAS via AngII, its main product, has an important physiologic and pathological effect on the cardiovascular system. The AngII has two AT1 and AT2 receptors, and it has been documented that the cardiovascular effect of AngII is mediated by AT1 receptor. Important cardiovascular effects of AT1 are vasoconstriction, aldosterone synthesis and secretion, and increased secretion of vasopressin. Due to the cardiovascular effects of AngII, mainly mediated by AT1, we used Los as an antagonist of AT1, before AngII to confirm this effect of AngII. Pretreatment of Los significantly attenuated the effect of AngII on cardiovascular responses.
that confirm the cardiovascular effect of AT1. Pretreatment with three doses of asafoetida could significantly amend the effects of AngII on the SBP and MAP that was comparable with Los. Based on these results, we suggested that the hypotensive effect of asafoetida extract is partly mediated by AT1 receptor. It has been indicated that hypertension induced by AngII is mediated through numerous mechanisms. Vasoconstriction is one of mechanisms that mediated by signaling pathways such as stimulation of phospholipase C that by increased intracellular free calcium as a key factor in contraction elicit vascular smooth muscle cell (VSMC) contraction. Because asafoetida extract has calcium channel blocking effect, we suggest that the antihypertensive effect of asafoetida is mediated by an effect on signaling pathways activated by AngII. The extract has several compounds, and each one of them may be involved in this effect of AngII. The umbelliferone (7-hydroxycoumarin) is one of the main compounds of the asafoetida that its inhibitory effects on ACE have been reported. Another compound of asafoetida is luteolin (3′,4′,5,7-tetrahydroxyflavone). The previous studies indicated that luteolin ameliorated hypertensive vascular remodeling by inhibiting the proliferation and migration of AngII-induced VSMCs. Therefore the effect of AngII may be mediated by these compounds. The vascular endothelium has an important role in regulation of vasomotor tone. It should be mentioned that this effect is mostly mediated by balance between AngII and nitric oxide (NO). In hypertension, balance of between AngII (vasoconstrictor) and NO (vasodilator) due to over activity of RAS or decrease of bioavailability of NO perturbed and effect of AngII as an important factor in pathogenesis of hypertension predominates than NO and hypertension induced. Furthermore, it has been shown that increased of AngII lead to decreased bioactivity of NO by formation of reactive oxygen species (ROS) that are oxidant and can induce stress oxidative and as a result lead to endothelium dysfunction and decreased bioavailability of NO. It has been shown that umbelliferone and ferulic acid compounds of asafoetida have an antioxidant effect. Therefore, these compounds can ameliorate the effect of AngII on NO production and by an increase in bioavailability of NO reduced hypertension induced by AngII. The cardioprotective effect of another compound of asafoetida such as monoterpenes of it (α-pinene, p-cymene, and limonene) in the improve
cardiovascular diseases including hypertension have been indicated.\cite{31,32} Therefore, a part of hypotensive effects of asafoetida in AngII-induced hypertension may reflect the presence of these monoterpenes.\cite{28}

In this experiment, we used three doses of asafoetida extract, and the lower dose had the best effect, but the high dose (60 mg/kg) has less effect on cardiovascular responses induced by AngII. Indeed, our study did not explain this effect of extract, and more research is needed to elucidate this effect. However, the previous studies have shown that AngII via AT\textsubscript{1} increases prostaglandin E2 and prostaglandin I\textsubscript{2} synthesis that are vasodilator agents and oppose the vasoconstriction role of AngII\cite{33}. Therefore, we suggest that, in a lower dose, vasodilatory effect of extract is predominant, but in a higher dose, asafoetida can impair the balance between vasoconstriction and vasorelaxation with tendency to affect vasoconstriction effect of AngII. In addition, we show that asafoetida contains anthocyanin (1.9 mg/g crude extract). Anthocyanin based on its dose has a biphasic effect;\cite{34} In low dose has a cardiovascular protective effect but in high dose shows a toxic effect. It seems that low dose of asafoetida (10mg/kg) due to having values less than anthocyanin has a beneficial effect on cardiovascular parameters but high dose of asafoetida (60 mg/kg) has the opposite effect that that could increase blood pressure and bradycardia, although future studies are needed to evaluate this effect of extract.

AngII in the dose that we use (50 ng/kg) reduces the HR, and this effect probably is a baroreflex response. In this reflex, an increase of the blood pressure is detected by baroreceptors and centrally caused bradycardia.\cite{35} Pretreatment with Los as an antagonist of AT\textsubscript{1}, significantly attenuated bradycardia induced by AngII. Furthermore, AngII can via AT\textsubscript{2} receptor that has a negative chronotropic effect,\cite{36} lead to bradycardia. A lower dose of extract also decreased bradycardia induced by AngII that is comparable with Los. Moreover, at a higher dose (60 mg/kg), the extract did not attenuate bradycardia induced by AngII, so it was no considerable respect to AngII. It is possible that a lower dose via the antagonistic effect on AT, decreased bradycardia. However, in the higher dose, concentration compounds of extract such as anthocyanin and monoterpenes\cite{32} increased bradycardia. It is also probable that extract in a higher dose by increased parasympathetic activity induces bradycardia.

**Conclusion**

Our results indicated that aqueous extract of asafoetida has an inhibitory effect on cardiovascular responses in acute hypertension induced by AngII. This effect in the lower dose (10 mg/kg) was more effective and comparable with Los. According to this finding, we suggest that the antihypertensive effect of asafoetida is partly mediated through inhibition cardiovascular effect of AngII.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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