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Original Article

The Cardioprotective Effect of the Hydroalcoholic Extract of Ginger in Renovascular Hypertension Model in Male Rats

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Abstract

Background and Aim: Many studies have been conducted worldwide to control blood pressure through herbal medicines. The present study was conducted to investigate ginger's role in the treatment of hypertension.
Materials and Methods: Fifty-four male Wistar rats weighing about 200 to 250 grams were randomly divided into 6 groups (3 groups of ten, and 3 groups of eight rats) for in vivo investigation. The left renal artery was blocked using a non-allergenic stainless-steel clamp to create hypertension. Then, the hydroalcoholic extract of ginger was prepared using distilled water in three doses of 100, 200, and 300 mg/kg. Oral gavage administration was used for the rats daily for 42 days using the hydroalcoholic extract of ginger. Pulmonary blood pressure was assessed using a cuff sphygmomanometer. Electrocardiogram (EKG or ECG) and echocardiogram (echo) tests were also performed after the end of the gavage on the 42nd day. Moreover, the amount of nitric oxide (NO) in serum samples was measured using the Griess reagent system. After categorizing raw data in Excel, they were analyzed using analysis of variance (ANOVA) by SPSS software.
Results: In this study, it was observed that ginger could notably decrease blood pressure. This decrease in blood pressure is due to the diuretic effect of the ginger's extract. Consequently, the use of ginger decreases the amount of NO. Furthermore, these data revealed that ginger had no toxic effect on the heart, and using this plant in hypertensive heart disease patients is safe.
Conclusion: Considering the positive effects of ginger in decreasing blood pressure and its non-toxicity for the heart, it is recommended to conduct further specialized studies and clinical trials in this regard.
Keywords: Ginger, Hypertension, Rat, Nitric oxide (NO)

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Introduction

Hypertension is a chronic disease in which blood pressure in the arteries increases (1). After the increment of blood pressure, the heart must work harder than normal to maintain blood circulation in the blood vessels (1). Hypertension is a severe disorder that increases the possibility of the risk of heart, brain, kidney, and other diseases (2). It is one of the main causes of premature death throughout the world with 1

in 4 men and 1 in 5 women (more than one billion people) suffering from this disease (3). Previous studies have shown that nearly 50% of hypertensive people are not aware of their disease and many patients accidentally notice their hypertension (4). To diagnose hypertension, blood pressure is taken on different days. If the systolic blood pressure is higher than 140 mm Hg on both days and the diastolic blood pressure is higher than 90 mm Hg on both days, hypertension is diagnosed (5).

In addition to making positive changes in their lifestyle, people with hypertension should take medications to control their blood pressure. Blood pressure medications act in different ways and keep blood pressure at a healthy level (6). Recent publications from the latest clinical trials have shown that antihypertensive drugs are effective and can control additional risk factors (7). The main risk factor of current medications is their role in decrement of kidney function, a clinical condition which is often encountered when taking an ACE inhibitors and/or ARBs (8). These medications, which are usually combined with a calcium antagonist and a diuretic treatment, are effective in 86-92% of patients with renal hypertension (7). In addition to using medications, other treatments such as revascularization procedure are also used. Currently, renovascular surgery is rarely performed due to the increment of number of angioplasty procedures (9) Moreover, many studies have been done around the world on controlling blood pressure using herbal medicines. These studies have shown that a large number of plants in their right doses can be effective in the reduction of blood pressure (10).

One of these plants is ginger (Zingiberaceae from the family of flowering plants), which is commonly used in many regions of the world as a part of the diet. Recent studies have shown that ginger has a role in stimulating blood pressure. Ginger is a very strong antioxidant that hinders the production of free radicals (11). There have not been many studies on the effect of ginger on renal hypertension. Moreover, its effects on different aspects of blood pressure as well as factors influencing blood pressure have rarely been investigated. The results of the study conducted by Shaban *et al*. (12) regarding the effect of ginger on blood pressure in hypertensive patients revealed that there was a significant difference between the control group and the experimental groups in terms of systolic and diastolic blood pressure. Considering the prevalence of hypertension all over the world and the importance of treating and controlling this disease, we decided to take a step towards controlling and treating this disease by investigating the protective effect of the hydroalcoholic extract of ginger via inducing hypertension in male Wistar rats. Thus, this study aimed to determine the protective effect of the hydroalcoholic extract of ginger in renal hypertension cases in male rats.

Materials and Methods

Animals

Fifty-four male Wistar rats weighing from 200 to 250 grams were randomly divided into 6 groups (three groups of ten and three groups of eight rats) for in vivo investigation. All laboratory protocols were included according to the NREC.IR.LUMS.REC.1400.0099 ethics code. The studied groups were as follows:

Group 1: The sham group (control group) in which the rats were without induction of hypertension or any treatment. However, the animals in this group were subjected to surgical stress by opening and closing the surgical site (n=8).

Group 2: The control group (hypertension group) included rats with hypertension whose blood pressure was induced by surgery (n=8).

Group 3: Rats with hypertension who received the hydroalcoholic extract of ginger (100 mg/kg, n=10).

Group 4: Rats with hypertension who received the hydroalcoholic extract of ginger (200 mg/kg, n= 10).

Group 5: Rats with hypertension who received the hydroalcoholic extract of ginger (300 mg/kg, n=10).

Group 6: Rats were subjected to surgical stress by opening and closing the surgical site, and then received the hydroalcoholic extract of ginger (200 mg/kg, n=8).

Induction of Hypertension

The rats were anesthetized by intraperitoneal injection of ketamine and Xylazine at a dose of 8 and 60 mg/kg (13). After shaving the surgical site and placing the animal on the surgical bed, a 2 cm vertical incision was made on the left side of the rat with a surgical Scalpel Blade No.11. After accessing the kidney, the left renal artery was blocked using a small clamp made of stainless steel with a glass wall (plexiglass). After surgery, the

surgical site was sutured using absorbable thread and the surgical site was disinfected using tetracycline ointment. Consequently, artificial hypertension was made due to the narrowing of the renal artery of the rats.

Measurement of NOx in Heart Tissue

The NOx concentration in heart tissue was determined using the Griess method as described by Miranda *et al*. (2001). To provide a brief overview, 100 mg of heart tissue was homogenized in 200 µL of phosphate-buffered saline (100 mM, pH 7.4) and then centrifuged at 10,000 g for 10 minutes at 4°C. The resulting supernatants were utilized for NOx measurement with the NOx assay kit obtained from Pazhohesh KavAfagh Co., located in Tehran, Iran. The obtained data are presented as nmol/mg protein (14).

Preparing the Hydroalcoholic Extract of Ginger

After obtaining ginger rhizomes from local stores and accurate recognition of them, any possible impurities were separated. The ginger was carefully cleaned and cut into smaller pieces. Then, using a drying machine, all the parts were dried over a full day. Subsequently, the dried rhizome was completely ground into powder. Then, the ginger powder was kept in a dark environment for 3 days with 700 ccs of 96% methyl alcohol and 200 ccs of water. Subsequently, fine filtration was done using large and small filter papers. The pure extract was placed and heated in tissue bath system to 50°C until its alcohol was almost completely evaporated. The hydroalcoholic extract of ginger was prepared using distilled water in three doses of 100, 200, and 300 mg/kg. Gavage oral administration was used once daily for 42 days (103,104) using the hydroalcoholic extract of ginger.

Electrocardiogram

After the end of gavage on the 42nd day, the rats were anesthetized for electrocardiogram examination by the intraperitoneal injection of ketamine and Xylazine at a dose of 60 and 8 mg/kg. The rats were placed in a supine position, and a subcutaneous needle electrode was used to record II-lead electrocardiogram (ECG). Thus, the negative electrode in the right hand, the positive one in the left leg, and the neutral electrode in the left hand were placed subcutaneously, and then the electrocardiogram was recorded.

Echocardiography

After inducing blood pressure in the rats and giving them drugs at the end of the 42nd day, they were anesthetized by the intraperitoneal injection of ketamine and xylazine at a dose of 60 and 8 mg/kg and then were placed in a supine position. Ultrasound gel was applied to the rat's chest that had already been shaved. Ultrasound was performed based on the method provided by the American Society of Echocardiography (ASE) as a guide for evaluating the heart.

Blood Sampling and Tissue Separation

After performing the mentioned tests, blood was taken from the heart with a blood collection needle. The blood was poured into gel separator tubes and then centrifuged at 4000 rpm for 15 minutes to separate the serum. The isolated serum was separated using a sampler and placed in a microtube to be frozen at -80°C. This serum was used in further experiments to measure nitric oxide (NO) metabolites. After blood sampling, the animal's body was cut from the abdomen, and the tissues of the left kidney, right kidney, and heart were separated. Then, these tissues were cut horizontally and placed in 10% formalin. The rest of the tissues were placed in a microtube and put in a -80 freezer for further research projects.

Statistical Analysis

Statistical analyses were performed using the statistic package for social science (SPSS) software (18.0, SPSS Inc., Chicago, IL). One-way analysis of variance (ANOVA) was used to determine the significance level among different groups. Post-hoc analysis was performed using Tukey's test. Hemodynamic parameters were analyzed with repeated measures of analysis of variance. Mean ± standard error of the mean (SEM) was used to show the results of each group. $p < 0.05$ was considered statistically significant.

Results and Discussion

The Effect of Ginger on Average Blood Pressure, Electrocardiography, Echocardiography and NO

During testing, at the end of the first, second, and third weeks, the blood pressure of all the groups was measured. Table 1 represents the obtained results. The obtained results have been presented in Table 1. In relation to the NO variable, the samples with induced blood pressure who received ginger at a dose of 100 were equal to 24.20 ± 2.22 ng/dl.

Table 1: The average blood pressure (mmHg) of the studied groups.

Group	End of first week	End of second week	End of third week	P- Value Intragroup
Control	128.48 ± 7.54	123.08 ± 9.72	136.12 ± 11.36	0.197
zo 200	123.1 ± 19.56	139.84 ± 16.45	140.39 ± 8.85	0.072
Hyp	151.26 ± 10.07 *##	150.84 ± 31.24	152.03 ± 19.44	0.417
Hyp + zo 100	141.58 ± 7.35	153.14 ± 21.37 *	144.1 ± 20.25	0.273
Hyp + zo 200	144.51 ± 6.29 #	151.56 ± 19 *	154.14 ± 9.57	0.368
Hyp + zo 300	146.58 ± 12.56	146.05 ± 34.28	142.05 ± 35.33 $	0.236
P- Value intergroup	P<0.0001	0.002	0.01	--

Control groups (without extract and without blood pressure), zo 200 (samples with ginger extract but without induced blood pressure), Hyp (with blood pressure without ginger extract), Hyp + zo 100 (samples with induced blood pressure while receiving ginger in a dose of 100), Hyp + zo 200 (samples with induced blood pressure while receiving ginger in a dose of 200), Hyp + zo 300 (samples with induced blood pressure while receiving ginger at a dose of 300). The results have been presented as mean ± standard deviation * The difference with the control group was significant at the 0.01 level. # The difference with zo 200 was significant at the 0.05 level. ## The difference with zo 200 was significant at the 0.01 level. $ The difference with Hyp + zo 200 was significant at the 0.05 level.

Table 2: Averaged electrocardiography results of the studied groups.

Variable	Control	zo 200	Hyp	Hyp + zo 100	Hyp + zo 200	Hyp + zo 300	P-value
QT (m/s)	0.05±0.01	0.07±0.05	0.06±0.02	0.07±0.01	0.07±0.02	0.12±0.17	0.50
QTc (m/s)	0.12±0.03	0.14±0.05	0.12±0.03	0.14±0.03	0.12±0.06	0.12±0.03	0.93
T amplitud (µv)	0.12±0.04	0.10±0.05	0.11±0.07	0.20±0.09	0.12±0.07	0.15±0.09	0.10
ST (µv)	0.69±0.03	0.05±0.03*	0.06±0.04	0.12±0.08	0.06±0.05	0.08±0.04	0.04

The results have been written as mean standard± deviation. There is a significant difference with group *Hyp + zo at the level of 0.05.

The samples with induced blood pressure who received ginger at a dose of 200 were equal to 24.32 ± 2.38. The samples with induced blood pressure who received ginger at a dose of 300 were equal to 25.59 ± 1ng/dl. The samples without induced blood pressure and treated with ginger extract were equal to 23.22 ± 3.01ng/dl. The samples with blood pressure without ginger extract were equal to 24.60 ± 2.86 and the control group was equal to 24.23 ± 1.5. The ANOVA results indicated that there were no statistically significant differences in the average levels of NO among the studied groups, with a p-value of 0.752 (Figure 1). The results of electrocardiography and echocardiography have been presented in Tables 2 and 3, respectively.

The Effect of Ginger on Average Blood Pressure

During testing, at the end of the first, second, and third weeks, the blood pressure of all the groups was measured. The results have been presented in Table 1. In relation to the NO variable, the samples with induced blood pressure who received ginger at a dose of 100 were equal to 24.20 ± 2.22 ng/dl. The samples with induced blood pressure who received ginger at a dose of 200 were equal to 24.32 ± 2.38. The samples with induced blood pressure who received ginger at a dose of 300 were equal to 25.59 ± 1 ng/dl. The samples without induced blood pressure and treated with ginger extract were equal to 23.22 ± 3.01 ng/dl. The samples with blood pressure without ginger extract were equal to 24.60 ± 2.86 and the control group was equal to 24.23 ± 1.5. The results of ANOVA indicated that there was no significant difference between the average NO of the studied groups (p=0.752). The results of electrocardiography and echocardiography have been presented in Tables 2 and 3, respectively.

Our data revealed that despite the role of ginger in the decrement of blood pressure, this plant did not show any significant effect over time in the intragroup analysis. However, our data showed that ginger had a positive role with a significant effect in different measurements in comparison between the groups.

Table 3: Averaged echocardiography results of the studied groups.

Variable	Control	zo 200	Hyp	Hyp + zo 100	Hyp + zo 200	Hyp + zo 300	P value
EF (%)	51.98±8.69	40.09±7.77##	63.43±9.71	82.33±8.07	37.05±23.79##	56.07±23.96	<0.0001
FS (%)	76.15±8.24	63.61±9.45#	85.87±6.8$	96.36±3.01	55.86±23.19##	75.7±23.57	0.003
LVED (mm)	7.06±2.07	7.63±0.55#	9±2.31	13.86±4.02**	5.6±1.93###	11.81±4.14$	<0.0001
LVES (mm)	3.26±0.28	4.5±0.28	3.25±0.36	3.31±2.73	3.5±1.15	3.9±0.8	0.576
STIME (s)	0.12±0.008	0.1±0.009	0.11±0.01	0.12±0.02	0.138±0.06	0.135±0.08	0.870
SD (mm)	1.68±0.12	1.82±0.19	1.43±0.27##	2.22±0.59	1.68±0.17	1.51±0.18	0.009

The results have been written as mean standard± deviation. There is a significant difference with group *control, # Hyp + zo and $Hyp + zo 20 at the level of 0.05 and a significant difference with group **control, ## Hyp + zo at the level of 0.01. and a significant difference with group ### Hyp + zo at the level of 0.001.

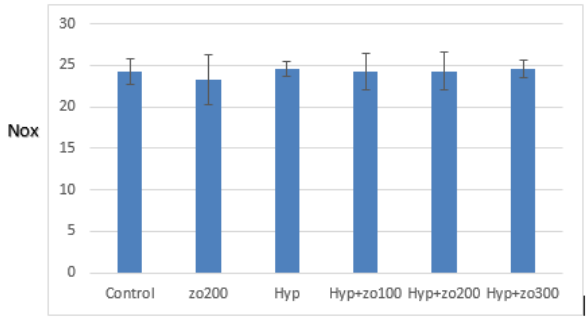

Figure 1. The effect of ginger on NO metabolites (NOx) levels. Mean± SD, the results of one-way analysis of variance showed that there was no significant difference between the NOx levels of the studied groups (P=.752).

In the study conducted on rats in 2021 by Hanifah *et al.* (15), the results revealed the significant effect of nanoparticles coated with ginger. In our study, systolic and diastolic blood pressure significantly decreased as a result of ginger extract administration. In a study conducted by Ghayur *et al.* (16) on the impact of ginger on blood pressure, the data showed that ginger had a positive effect on blood pressure and decreased the blood pressure of the tested rats. Moreover, in a clinical trial conducted by Azimi *et al.* (17) in 2016, effects of various herbal medicines including ginger, cardamom, cinnamon, and saffron on various factors of 208 patients were examined. It was reported in their studies that ginger, cinnamon, saffron, and cardamom with significance levels of 0.39, 0.7, 0.6, and 0.66 did not have any significant effect on blood pressure respectively. Based on these studies and their reported data, ginger could have a significant effect on the decrement of blood pressure in studies conducted on rats and other studies on laboratory animals. However, in a clinical trial conducted in 2016, ginger reduced blood pressure in a group of patients, but the reduction was not statistically significant (17). As it has been shown in many studies that examined the effects of ginger and other medicinal plants on blood pressure in different methods from one side, and according to many agreements and objections in this regard, it seems that further research is required to determine the definitive effect of this plant on blood pressure.

In this study, there was no change in NO level in any of the studied groups. In a study conducted by Ferrini *et al.* (18) in 2018, it was reported that ginger could increase NO production in the smooth muscles of the studied rats by activating the Nitric oxide-cyclic GMP pathway which prevents ischemia. The results of their study conducted at the genetic level are in contrast with the findings of our study, in which the final amount of NO measured in the blood of the tested rats was investigated. In 2016, Naderi *et al.* studied the effects of ginger on CRP and NO levels in cases with osteoarthritis. The results showed that ginger could decrease the amount of NO. Naderi *et al.* also mentioned many studies that reported the same results as ours (9). It seems that the mechanism of ginger in the reduction of blood pressure is a mechanism other than increasing the amount of NO.

This study investigated four factors in relation to electrocardiography, including QT, QTc, T, and ST. It seems that ginger and artificially induced blood

pressure had no significant effect on the electrocardiogram factors through narrowing the renal artery. This may be due to the limitation of the study period to create electrocardiographic changes in the heart, which requires more investigations in this regard (19). It was revealed in this study that consumption of ginger for three weeks had no significant effects on electrocardiographic changes. Moreover, in association with echocardiographic changes, ginger consumption was able to prevent the increment of EF and FS caused by single kidney hypertension and increased left ventricular assist device (LVAD). In general, according to the results of our study and those described in other studies such as the study of Fakhri *et al*, it seems that ginger has a positive effect on the heart (20). Moreover, this plant not only has no negative effect on the heart but also increases the life span of heart cells, increases heart health, and reduces cardiac remodeling (21,22). To sum up, the data achieved from our study showed that ginger can be used in hypertensive patients who also suffer from heart disease, and heart disease is generally not a contraindication for the administration of ginger.

Based on the results of this study and also findings of recently published articles, the possible mechanisms are as follows. 1) Ginger contains compounds like gingerols and shogaols that have vasodilatory effects. They relax and widen blood vessels, decreasing peripheral resistance and improving blood flow. This vasodilatory action can help lower blood pressure (23). 2) Ginger has been found to inhibit the activity of angiotensin-converting enzyme (ACE), an enzyme involved in the regulation of blood pressure. ACE inhibitors are commonly used medications for the treatment of hypertension. By inhibiting ACE, ginger may exert similar blood pressure-lowering effects (24). 3) Ginger contains various antioxidants that can help combat oxidative stress and inflammation, both of which are associated with the development of hypertension. By reducing oxidative damage and inflammation, ginger may contribute to improved blood pressure control (25). 4) It has been shown that ginger can improve endothelial function, which refers to the health and proper functioning of the inner lining of blood vessels (26). Endothelial dysfunction is a key factor in the development of hypertension. By improving endothelial function, ginger may help maintain healthy blood pressure levels.

While these mechanisms suggest the potential of ginger in improving high blood pressure, it is should be noted that further research is required to fully understand the impacts and optimal dosage of ginger for this purpose. The use of ginger as a natural remedy by hypertensive patients needs consultation with a healthcare professional to ensure its safety and effectiveness in individual cases.

Conclusion

This article investigated the role of ginger in the treatment of hypertension. The study was conducted on male rats, where the left renal artery was blocked to induce hypertension. The rats were then given the hydroalcoholic extract of ginger for 42 days. The results showed that ginger significantly decreased blood pressure and had a diuretic effect. It was also found that ginger had no toxic effect on the heart, making it safe to be used in hypertensive heart disease patients. The authors recommend further specialized studies and clinical trials to explore the potential benefits of ginger in controlling blood pressure.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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