

Role of garlic in treatment of constrictive renovascular hypertension

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- Objective** : *To study the role of garlic in treatment of constrictive renovascular hypertension (RVH)*
- Design** : *Animal experiment study*
- Setting** : *Department of Physiology, Department of Medicine, Faculty of Medicine, Chulalongkorn University.*
- Animal** : *11 male dogs weighing 10-12 kg, 5 normotensive and 6 hypotensive dogs*
- Method** : *Hypertensive dogs caused by unilateral constriction of the renal artery with a 60-80 % reduction in renal blood flow. The acute effects of garlic extract were performed in 11 anesthetized dogs by oral administration, via gastric tube, of garlic extract at the dose of 50 mg/kg. bw. Systemic and renal hemodynamics, blood and urine samples were determined before and after garlic treatment.*
- Result** : *In dog with RVH, at 2 hour after garlic administration, the garlic extract could cause decreases in systolic arterial pressure and renal vascular resistance but induced increases in renal blood flow. Garlic extract treatment also resulted in increases of urine flow rate, free water clearance, urinary fractional excretion of sodium, potassium and chloride. In normotensive dogs no significant changes in the*

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hemodynamics and urinary parameters mentioned above were observed following garlic treatment.

Conclusion : *The garlic extract would lower blood pressure in an RVH model by systemic and renal vasodilatation as well as by acting on renal tubules as a loop diuretic-like agent. All these effect of garlic extract are silimilar to the vascular and tubular effects of prostaglandin E₂.*

Key words : *Garlic , Renovascular hypertension, Loop diuretics, Prostaglandin E₂.*

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- วัตถุประสงค์** : เพื่อศึกษาบทบาทของกระเทียมในการรักษาภาวะความดันโลหิตสูงที่เกิดจากการตีบของหลอดเลือดแดงที่ไปเลี้ยงไต
- รูปแบบการวิจัย** : การศึกษาในสัตว์ทดลอง
- สถาบันการศึกษา** : ภาควิชาสรีรวิทยา ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
- สัตว์ทดลอง** : สุนัขตัวผู้ 11 ตัว หนักประมาณ 10 - 12 กิโลกรัม 5 ตัวมีภาวะความดันโลหิตปกติ ส่วนอีก 6 ตัวมีภาวะความดันโลหิตสูง
- วิธีการศึกษา** : สุนัขที่มีความดันโลหิตสูง ทำให้โดยทำให้หลอดเลือดแดงที่ไปเลี้ยงไตข้างหนึ่งตีบลงจนลดอัตราการไหลของเลือดลงประมาณ 60 - 80 เปอร์เซ็นต์ ทำการศึกษาผลของสารสกัดกระเทียมในสุนัข 11 โดยการให้สารสกัดกระเทียมทางปากผ่านทางท่อเข้ากระเพาะอาหาร ในความเข้มข้น 50 มิลลิกรัมค่อน้ำหนักตัว 1 กก. ค่าพลศาสตร์ของระบบไหลเวียนส่วนกาย และของไต ตัวอย่างเลือดและปัสสาวะ จะทำการวัดก่อน และหลังการให้สารสกัดกระเทียม
- ผลการศึกษา** : ในสุนัขที่เป็นความดันโลหิตสูง หลังจากได้รับสารสกัดกระเทียม 2 ชม. พบว่าสารสกัดกระเทียมสามารถลดความดันโลหิตซิสโตลิกลดลง ค่าของความต้านทานของหลอดเลือดแดงของไตลดลง แต่มีการเพิ่มขึ้นของปริมาณเลือดเลี้ยงไต สารสกัดกระเทียมยังมีผลเพิ่มอัตราการไหลของปัสสาวะ อัตราการขจัดสารน้ำอิสระ อัตราส่วนการขับโซเดียม ไปแดงซึมและคลอไรด์ด้วย ไม่พบการเปลี่ยนแปลงดังกล่าวในสุนัขที่มีความดันโลหิตปกติ
- วิจารณ์และสรุป** : กระเทียมสามารถลดความดันโลหิตที่เกิดจากการตีบของหลอดเลือดแดงที่ไปเลี้ยงไต โดยกลไกการขยายตัวของหลอดเลือดแดง ทั้งภายในและภายนอกไต และโดยกลไกการออกฤทธิ์เหมือนกับยาขับปัสสาวะชนิดที่ออกฤทธิ์ที่ท่อไต ส่วนเช่นเลอูป กลไกการออกฤทธิ์ ดังกล่าวของกระเทียมเหมือนกับฤทธิ์ของพรอสตาแกลนดินอีสอง

Garlic, the scientific name of which is *Allium sativum*, has been commonly used since ancient time as a spice in food and as a folk medicine in various parts of the world. Modern scientific research has proven many useful medicinal properties of garlic including antifatulent, stimulant, hypolipemia, inhibition of platelet aggregation, and antiatherosclerotic and hypotensive effects.⁽¹⁻⁶⁾ Early studies have shown the hypotensive effects of tincture of garlic in experimental animals.⁽⁷⁾ Most, but not all, of the following referenced studies in both animals and humans have also supported the antihypertensive action of garlic.⁽⁸⁻²⁰⁾

In essential hypertension, the proposed mechanisms of the hypotensive effects of garlic include vasorelaxation and diuretic-like action.^(16,21-24) Various endogenous hypotensive substances, including histamine and prostaglandin E_2 (PGE_2), have been demonstrated to play roles in the hypotensive effects of garlic.

There is, however scarce data regarding the hypotensive role of garlic in renovascular hypertension (RVH). The present studies were, therefore, performed in order to examine the antihypertensive effect of garlic extract in dogs with RVH. Systemic and renal hemodynamics and urinary parameters of the animals were determined in order to delineate the mechanism of the hypotensive action of the garlic extract.

Animal preparation and methods

1. Preparation of hypertensive dogs

Unilateral RVH was induced in experimental animals by the methods previously described by Lupu et al.⁽²⁵⁾ With aseptic precautions, male mongrel dogs were anesthetized with sodium pentobarbital at a dose

of approximately 30 mg./kg. body weight (b.w.). Arterial pressure was measured by a medicut punctured into one femoral artery. The medicut was connected to a pressure transducer (Harvard Universal, model EM 750) which could continuously record the arterial pressure in an oscillograph. A left flank incision was made to expose the left renal artery. An electromagnetic flow probe was then applied around the left renal artery. Partial constriction of the left renal artery was performed until the renal blood flow was reduced by 60 - 80 percent of the value of which had been previously obtained.⁽²⁵⁾

The arterial pressure of each animal was remeasured at 3 weeks after the operation. The dogs which developed at least 20 percent higher systolic blood pressures than that of the control animals were defined as hypertensive animals and was enrolled in the experiment.

2. Preparation of garlic extract powder

The procedures of garlic preparation followed those described by Poolsanong.⁽²⁶⁾ In brief, 100 grams of garlic cloves were washed and dried. After the addition of 120 ml of chloroform, the cloves were processed in a blender until a good mixture was obtained. The mixture was then filtered. The chloroform was separated out from the filtrate by rota vaporization at 55° C, leaving behind a yellowish oily liquid residue. The extract was then preserved with 1.2 gram of providone and stored in refrigerator. For subsequent use, the garlic extract was diluted in normal saline solution to make a concentration of 50 mg/ml.

3. Experimental procedure

The experiments were performed in both

normotensive and hypertensive dogs. The animals were anesthetized with sodium pentobarbital. A tracheostomy was performed in each dog and the animals allowed to ventilate room air. Arterial blood pressure and heart rates were continuously monitored and recorded via the right femoral artery. For maintaining hydration, 0.9 per cent of normal saline solution 0.9 % NSS was continuously infused into the right femoral vein, which was also used for supplemental doses of anesthesia when required. The left femoral vein was cannulated for infusion of insulin.

To circumvent the local confounding effects caused by the operation process in the left kidney area, the data of renal hemodynamics and urinary parameters in pre-and post-garlic treatment periods were determined by collecting urinary samples from the right kidney. Thus, a right flank incision was made operated to expose the right kidney. The right ureter was cannulated for collecting urinary samples. The electromagnetic flow transducer (Nihon Kohden, model MFV 3200) was placed around the right renal artery adjacent to the aorta and renal blood flow was recorded on an oscillograph (Harward Universal).

During the surgical and experimental periods, 0.9 % NSS was infused at a rate of 1.0 - 1.5 ml./min to maintain body hydration. For the measurement of glomerular filtration rate, a priming dose of inulin, 50 mg./kg body weight, was administered and this was followed by a sustaining infusion sufficient to maintain the plasma inulin concentrations at approximately 20 mg./dl.

A period of 60 min was allowed to elapse for stabilization of plasma inulin concentrations. Two timed collections of urine (30 min/sample) along with blood samples at the midpoint of each urine collection

were taken for the baseline data.

The garlic water extract at a dose of 50 mg./kg. b.w. was intragastrically administered as a single dose. Blood and urinary samples were collected at 1,2,3, and 4 hours after garlic treatment. The concentrations of sodium and potassium, chloride, and inulin were determined by a flame photometry (Corning model 410 C), chloride analyzer (Corning model M 92 S), and photometry (Biosystems, model BTS 320). Plasma osmolality was measured by osmometer (Advanced Digi Matic Osmometer, model 3 D 2).

At the end of the experiment the right kidney was excised, stripped off of surrounding fat and tissue, blotted dry, and weighted. The results in all figures and tables were expressed as mean \pm SE. The statistical significance, a P value of less than 0.05, was assessed by using the Student's paired t-test or Analysis of Variance where appropriate.

Results

Table 1 demonstrated the effects of garlic extract on systemic hemodynamics in normal and hypertensive dogs. The hypertensive dogs had significantly higher baseline values of systolic blood pressure and heart rate than the normotensive ones ($P < 0.05$). Although the hypertensive dogs had a tendency to have higher diastolic and mean arterial blood pressure, the statistical significances were not attained. In the hypertensive group, at 2 hours after oral administration of garlic extract, garlic extract could produce a significant decrease in systolic blood pressure. Such hypotensive action of garlic was persistently observed for the whole duration of the experiment. Of note, the hypotensive effect of garlic was apparent even though the value of heart rate was

still high and not significantly altered by garlic treatment. Garlic water extract had no effects on diastolic blood pressure and mean arterial pressure. In the normotensive group, there were no significant changes in systemic hemodynamics following garlic treatment.

Table 2 showed the effects of garlic extract on renal hemodynamics in normal and hypertensive dogs. At baseline period, the hypertensive dogs had higher values of glomerular filtration rate (GFR), filtration fraction (FF), and renal vascular resistance (RVR) than the normotensive dogs. The baseline values of renal blood flow (RBF) were not significantly different between the two groups. In the hypertensive group, after 2 hours of garlic treatment, garlic induced increased RBF and decreased RVR but had no effects on GFR and FF. Garlic water extract had no significant effects on renal hemodynamics in the normotensive animals.

Table 3 detail the effects of garlic extract on urinary parameters in normal and hypertensive dogs. There were no significant differences in the values of all parameters at baseline period between the two groups. Following 2 hours after garlic treatment, there were significant increases in urine flow rate (v), fractional excretion of sodium, potassium, and chloride (FE_{Na} , FE_K , and FE_{Cl} respectively), and free water clearance in the hypertensive animals. In the normotensive group, garlic extract treatment could not produce significant alteration in any of these urinary parameters.

Discussion

Hypertension also often results when the artery to one kidney is constricted, whereas the artery to the

other kidney is normal. This hypertension results from increase in renin release by the ischemic kidney. This renin causes the formation of angiotensin II, which facilitated the activity of sympathetic nervous system and also salt and water retention.⁽²⁵⁾

The results of the present studies have shown that 1) Garlic extract could significantly lower systolic blood pressure in renovascular hypertension. 2) The hypotensive effect of garlic extract is mediated by systemic as well as renal vasodilatation and also by the loop diuretic-like action on renal tubule.

The hypotensive effect of tincture of garlic was described in experimental animals as early as 1921 by Loeper and Debray.⁽⁷⁾ Following studies in various animals also showed the antihypertensive properties of aqueous extracts of garlic and freeze-dried garlic.^(11,16,21-24) Several clinical studies in patients with essential hypertension could demonstrated the hypotensive effect of garlic.^(8-10,12,13,15,18,19) In a following study, however, no significant change in blood pressure could be observed after giving garlic powder to hypertensive and hyperlipidemic patients.⁽¹⁷⁾ There was also a report regarding the ineffectiveness of dried garlic in the treatment of patients with essential hypertension.⁽¹⁴⁾ Recently, there has been a meta-analysis of clinical studies regarding the effect of garlic on blood pressure.⁽¹⁸⁾ The results suggest that garlic may be of some clinical use in subjects with mild hypertension. However, there is still insufficient evidence to recommend it as a routine clinical therapy for the treatment of hypertensive subjects. More rigorously designed and analysed trial are needed.

The discrepancies in the results of these previous studies might be caused by differences in the garlic components, garlic strains, and animal species.

Indeed, various preparations garlic and components: such as garlic powder, aqueous extracts of garlic, garlic extract, and allicin, the most active ingredient of garlic, were used in previous studies. It appears that garlic extract contains a higher amounts of allicin than garlic powder and aqueous extracts of garlic. Besides allicin, garlic also contains substantial amount of other components including Ajoene Vinylthiins and other thiosulfinates.⁽²⁷⁻²⁹⁾ Whether these substances have contributory roles in the hypotensive action of garlic is presently unknown.

The results of the present study help demonstrate the hypotensive effects of garlic, previously shown in essential hypertension, in renovascular hypertension (RVH) (Table 1). Garlic could reduce systolic, diastolic, and mean arterial pressure as in the former group. As seen in table 1, however, garlic could lower only systolic blood pressure in the RVH model. Of interest, the hypotensive action

of garlic in RVH observed in the present work is apparent without changes in heart rate. In a recent study in anaesthetized dogs, garlic powder at the dose of 15 mg./kg. b.w. reduced the systolic pressure and also cause initial bradycardia.⁽¹⁶⁾

The basic mechanisms of the hypotensive effects of garlic are still not well established. The proposed mechanisms include vasodilatation and diuretic-like actions.⁽²¹⁻²⁴⁾ The vasorelaxant effect of garlic is mediated neither by depression of the vasomotor center and heart nor by stimulation of the parasympathetic nervous system.⁽²¹⁾ Thus, endogenous circulating vasodilators have been postulated as the proximate causes in lowering blood pressure. An earlier study showed that the hypotensive effect of garlic extract is due to release of histamine,⁽²¹⁾ the observation of which is not confirmed by the our study.⁽²²⁾ Furthermore, administrations of antagonists of other common endogenous hypotensive substances

Table 1. Effects of garlic extract^a on systemic hemodynamics in normal and hypertensive dogs.

Parameters	Normal dogs (5) ^b		Hypertensive dogs (6) ^b	
	Baseline	Garlic	Baseline	Garlic
Ps (mmHg)	126.00 ± 7.81	122.00 ± 7.68	140.83 ± 3.01*	125.33 ± 4.94**
Pd (mmHg)	90.00 ± 7.58	86.00 ± 5.18	97.50 ± 6.42	94.17 ± 7.89
MAP (mmHg)	105.20 ± 19.93	101.80 ± 19.33	110.00 ± 16.58	105.17 ± 16.29
HR (beat/min)	127.00 ± 16.59	122.50 ± 21.44	149.17 ± 27.62*	142.17 ± 35.74

^a At 2 hours after oral administration of garlic extract.

^b The figure in the parasentesis represents the number of animals used in the experiments.

Abbreviations : Ps = systolic blood pressure, Pd = diastolic blood pressure,

MAP = mean arterial pressure [= Pd + 1/3 (Ps-Pd)], HR = heart rate,

* = P < 0.05 compared to the value of normal dogs.

** = P < 0.01 compared to the baseline value of the same group.

including acetylcholine, serotonin, and kinin also could not abrogate the hypotensive action of garlic. Recently, prostaglandin E₂ (PGE₂) has been demonstrated as a possible vasodilator to produce the hypotensive effect of garlic.⁽²²⁻²⁴⁾ PGE₂ may be derived directly by chemical conversion of fatty acids contained in garlic or indirectly by the action of garlic of various cell types. Garlic juice could induce direct relaxant effects on smooth and cardiac muscles.⁽³⁰⁾ On the other hand, a recent work has shown that the vasorelaxant effect of garlic is mediated by the production of endothelium-derived relaxing factors (EDRF), including PGE₂.⁽²⁴⁾

More recently, garlic has been demonstrated to activate nitric oxide synthase, one of the most important enzymes in the production of EDRF.⁽³¹⁾

Indeed, PGE₂ exerts both vasodilatation and tubular effects. The vasorelaxant action of PGE₂ occurs at systemic as well as renal levels. The tubular actions of PGE₂ resemble those of loop diuretics which consist of natriuresis, diuresis, and kaliuresis. In the present work, garlic treatment resulted in decreased RVR and increased RBF, suggesting a renal vasodilating action of garlic (Table 2). Administration of garlic to animals with RVH could cause diuresis,

Table 2. Effects of garlic extract^a on renal hemodynamics in normal dogs and dogs with renovascular hypertension.

Parameters	Normal dogs (4) ^b		Hypertensive dogs (5) ^b	
	Baseline	Garlic	Baseline	Garlic
RBF ml./(min/gm kidney wt.)	4.34 ± 1.08	4.49 ± 0.94	3.71 ± 1.17	4.14 ± 1.40**
GFR ml./(min/gm kidney wt.)	1.02 ± 0.24	1.03 ± 0.21	1.47 ± 0.30*	1.52 ± 0.35
FF (%)	31.09 ± 7.08	30.35 ± 7.43	46.58 ± 9.58*	43.82 ± 10.44
RVR (mmHg)	21.16 ± 4.79	22.71 ± 5.76	30.81 ± 5.14*	23.18 ± 3.98**

^a At 2 hours after oral administration of garlic extract.

^b The figure in the parenthesis represents the number of animals used in the experiments.

Abbreviations : RBF = renal blood flow,

GFR = glomerular filtration rate

$$\left[= \frac{U_{\text{inulin}}}{P_{\text{inulin}}} \times V, = \text{urine flow rate (ml/min/gm. Kidney wt.)} \right]$$

FF = filtration fraction

$$\left[= \frac{\text{GFR} \times 100}{\text{RPF}}, \text{ where RPF} = \text{renal plasma flow} = \text{RBF (1-hem)} \right]$$

RVR = renovascular resistance (= MAP/RBF),

* = P < 0.05 compared to the value of normal dogs.

** = P < 0.05 compared to the baseline value of the same group.

natriuresis kaliuresis, and chlориuresis (Table 3). The hemodynamic and tubular effects of garlic treatment obtained in the present study are quite similar to all of the effects of PGE₂ stated above (Tables 1, 2, and 3). Although the levels of PGE₂ or its metabolites were not measured in the present work, it is likely that garlic would express hypotensive effects by direct or indirect stimulation of PGE₂ levels.

In summary, garlic extract could lower the blood pressure in renovascular hypertension. The

mechanisms of the hypotensive action of garlic include systemic as well as renal vasodilatation, and the loop diuretic-like action on renal tubule. On the basis of the relative absence of side effects, garlic and its compounds might be an attractive therapeutic tool in treating cardiovascular diseases, including hypertension. The development of drugs containing specifically defined compounds of garlic might be a huge step forward in designing efficient garlic-based treatments.

Table 3. Effect of garlic extract^a on urinary parameters in normal dogs and dogs with renovascular hypertension.

Parameters	Normal dogs (4) ^b		Hypertensive dogs (5) ^b	
	Baseline	Garlic	Baseline	Garlic
V [ml/(min/ gm kidney wt.)]	0.48 ± 0.34	0.34 ± 0.23	0.61 ± 0.38	1.05 ± 0.42*
CH ₂ O μl/(min/gm kidney wt.)	-2.41 ± 1.65	-1.54 ± 1.98	-1.80 ± 1.35	3.45 ± 1.72*
FE _{Na} (%)	0.82 ± 0.21	0.90 ± 0.24	0.71 ± 0.20	1.24 ± 0.41*
FE _K (%)	9.61 ± 1.84	10.05 ± 3.17	8.84 ± 2.12	13.86 ± 3.8*
FE _{Cl} (%)	0.60 ± 0.27	0.71 ± 0.24	0.49 ± 0.19	0.81 ± 0.23*

^aAt 2 hours after oral administration of garlic extract.

^bThe figure in the parenthesis represents the number of animals used in the experiments.

Abbreviations : V = urine flow rate, FE_{Na} = fractional excretion of sodium (= $\frac{U/P_{Na}}{U/P_{Cr}} \times 100\%$)

FE_K = fraction excretion of potassium (= $\frac{U/P_K}{U/P_{Cr}} \times 100\%$)

FE_{Cl} = fractional excretion of chloride (= $\frac{U/P_{Cl}}{U/P_{Cr}} \times 100\%$)

CH₂O = free water clearance (V - C_{osm}, where C_{osm} = $\frac{U_{osm} \cdot v}{P_{osm}}$)

* = P < 0.05 compared to the baseline value of the same group.

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