

# Antihypertensive activities of processed garlic on spontaneously hypertensive rats and hypertensive humans

Chuan-Hsiao HAN<sup>1,9</sup>, Ju-Chi LIU<sup>2,3,9</sup>, Kwan-Han CHEN<sup>4,5,9</sup>, Yin-Shiou LIN<sup>1</sup>, Ching-Tan CHEN<sup>5</sup>, Chien-Teng FAN<sup>5</sup>, Hu-Lun LEE<sup>5</sup>, Der-Zen LIU<sup>6</sup>, and Wen-Chi HOU<sup>7,8,\*</sup>

<sup>1</sup>School of Pharmacy, Taipei Medical University, Taipei, Taiwan

<sup>2</sup>Department of Internal Medicine, School of Medicine, Taipei Medical University, Taipei, Taiwan

<sup>3</sup>Department of Internal Medicine, Taipei Medical University-Shuang Ho Hospital, Zhonghe City, Taiwan

<sup>4</sup>Institute of Food Science and Technology, National Taiwan University, Taipei, Taiwan

<sup>5</sup>AGV Food & Health Research Institute, AGV Products Co., Chia-Yi, Taiwan

<sup>6</sup>Institute of Biomedical Materials and Engineering, Taipei Medical University, Taipei, Taiwan

<sup>7</sup>Traditional Herbal Medicine Research Center, Taipei Medical University Hospital, Taipei, Taiwan

<sup>8</sup>Graduate Institute of Pharmacognosy, Taipei Medical University, Taipei, Taiwan

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**ABSTRACT.** This study evaluated the effects of processed garlic (PG) on the systolic blood pressure (SBP) and the diastolic blood pressure (DBP) of spontaneously hypertensive rats (SHR) and on the BP of hypertensive humans. The color of raw garlic changed to black through enzymatic browning over two-week processing periods, and the active compound *S*-allyl-L-cysteine was analyzed and calculated as 75.3 mg/100 g in PG. PG was found to effectively reduce the blood pressure of SHR after 4, 6, and 8 weeks with a single daily dose of 30 and 50 mg/kg. We conducted a placebo-controlled trial to test the efficacy of PG on lowering SBP and DBP of 44 hypertensive subjects over a period of 8 weeks. PG significantly lowered SBP after only 2 weeks ( $p < 0.01$ ), while a significant reduction in DBP ( $p < 0.05$ ) took 8 weeks. This significant DBP reduction was also found in the placebo group ( $p < 0.05$ ), which might be attributed to a placebo effect. After 8 weeks, PG lowered SBP by 8.05 mmHg. In conclusion, taking two 500 mg capsules of PG for 8 weeks can significantly lower blood pressure in hypertensive subjects.

**Keywords:** Antihypertensive; Blood pressure; Feeding trial; Processed garlic (PG); Spontaneously hypertensive rats (SHR).

**Abbreviations:** PG, processed garlic; DBP, diastolic blood pressure; NO, nitric oxide; SBP, systolic blood pressure; SHR, spontaneously hypertensive rat.

## INTRODUCTION

A number of risk factors are associated with stroke, including age, gender, elevated cholesterol, smoking, alcohol consumption, excessive weight, race, family history and hypertension (Mark and Davis, 2000). Although some of these risk factors cannot be modified, the controllable factor that has the greatest impact on the etiology of stroke is high blood pressure (Dunbabin, 1992). A recent review paper (Chen et al., 2009) pointed out that nutraceuticals and functional foods might have blood pressure-lowering abilities. The endogenous molecule nitric oxide (NO), which is released by endothelial cells through NO synthesis, is a major factor in blood vessel relaxation,

which may result in lowering blood pressure (Chalupsky et al., 2004; Bruckdorfer, 2005; Moon et al., 2006). Spontaneously hypertensive rats (SHR) are the most acceptable animal model for evaluating the antihypertensive effects of natural products or functional foods (Lin et al., 2006; Liu et al., 2007; Lin et al., 2008; Liu et al., 2009a; Liu et al., 2009b; Huang et al., 2010).

Garlic (*Allium sativum*) is reported to have many biological activities, including protective roles in cardiovascular function (Rahman and Lowe, 2006; Yeh and Yeh, 2006; Mukherjee et al., 2009), as an antihypertensive (Harauma and Moriguchi, 2006; Reinhart et al., 2008; Ried et al., 2008), an antioxidant (Dhawan and Jain, 2005), and for hypocholesterolemia (Stevinson et al., 2000; Yeh and Liu, 2001). Aged garlic extracts are considered superior to those of raw garlic in terms of their anti-oxidation properties and for ameliorating physiological and psychological stress (Imai et al., 1994; Harauma and Moriguchi, 2006; Morihara et al., 2006). In the present

<sup>9</sup>These authors contributed equally to this study.

\*Corresponding authors: E-mail: wchou@tmu.edu.tw; Fax: +886-2-2378-0134.

study, the goals were first, to evaluate the antihypertensive effects of processed garlic powder (PG) on SHRs, and second, to conduct a feeding trial in hypertensive subjects. In SHR, PG significantly lowered SBP and DBP after 8 weeks ( $p < 0.05$ ). In human subjects, taking two daily 500 mg capsules of PG for 8 weeks also lowered BP.

## MATERIALS AND METHODS

### Materials

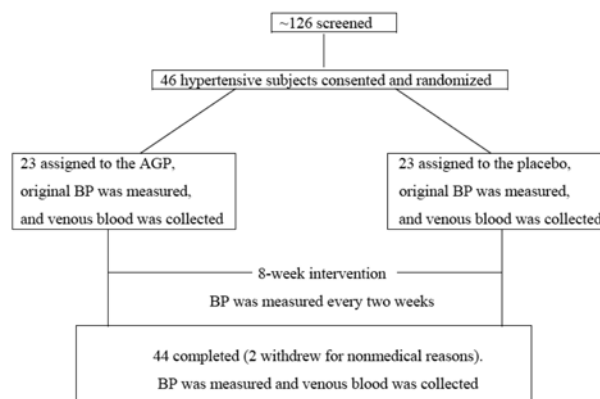
PG powders, PG capsules and the placebo were provided by AGV Products Co. (Chia-Yi, Taiwan) for the animal and clinical trials. PG was manufactured as follows: raw garlic was washed then put in a reactor for two weeks. After completion of the enzymatic reaction process, the processed garlic was de-hulled, lyophilized and then powdered. The active components of *S*-allyl-L-cysteine were determined to be 75.3 mg/100 g in PG, and total phenolics were 775 mg/100 g. Other chemicals were from Sigma Chemical Co. (St. Louis, MO, USA).

### Effects of antihypertensive activity of PG on SHR

Before the rat feeding trial, effects of PG on the SBP and DBP of SHR were determined using the method of Liu et al. (2009a, b). All animal experimental procedures were approved by the Institutional Animal Care and Use Committee and followed published guidelines (National Science Council, 1994). The male SHRs (5 weeks of age, National Laboratory Animal Center, Taipei) were housed individually in steel cages kept at 24°C with a 12-h light-dark cycle and had free access to a standard mouse/rat chow (Prolab® RMH2500, 5P14 Diet, PMI Nutrition International, Brentwood, MO) and water. After being housed up to 14 weeks, they were randomly divided into three groups (eight rats per group), one of these the control group. All were given 30 mg of PG/Kg and 50 mg of PG/Kg (suspended in 0.5 ml water) once a day for 8 weeks, and the control group was then orally administered 0.5 ml water. SHR tail blood pressure was measured once every 2 weeks before each oral administration. Before each blood pressure measurement, SHRs were warmed for 10 min in a 39°C thermostated box. SHR tail blood pressure was measured every two weeks. An indirect blood pressure meter (BP-98A, Softron Co. Ltd. Tokyo, Japan) was used to measure SBP and DBP four times in each determination for each treatment.

### Subjects and clinical trials

The Institutional Review Board of Taipei Medical University approved the clinical trial design (approval number P970401). Subjects were males and females aged 20 to 60 years with pre-hypertension (SBP, 130 to 140 mmHg and DBP, 85 to 90 mmHg) or hypertension (SBP, 140 mmHg or higher and DBP, 90 mmHg or higher) that was confirmed by an internal medicine physician at Taipei Medical University Hospital. Exclusion criteria included pregnant



**Figure 1.** Summary of subject trials experimental design.

and lactating women, people who had received trace element supplements in the previous three months, people receiving gastric or diuretic treatments, patients with acute renal failure, or people with recent history of surgery or acute infections. All subjects were informed of the purposes of the study, were free to ask questions throughout the study, and signed an informed consent form witnessed by one of the investigators. This clinical trial was designed as a randomized, placebo-controlled parallel feeding trial (Figure 1). Forty-six subjects (35 males and 11 females) were randomly assigned to either control or treatment groups. GP or placebo capsules kept in a dark bottle were then given to subjects. They were instructed to take two 500 mg capsules of PG or placebo daily, together with 200 ml of water, 30 min after breakfast for 8 weeks. Eating habits were not restricted during the treatment. However, to avoid possible interference with the effects of PG, the consumption of vitamin supplements and functional foods was prohibited during the trial. Each subject's BP was measured at the beginning of the trial, then once every two weeks during the trial. Their BP was measured using a digital BP analyzer (ES-P110, Terumo Corp., Tokyo, Japan) and recorded as the average of two measurements. Measurements were always made at the same place and time after 15 min of rest. Venous blood was also collected from each subject before and after the trial. Blood samples were assayed for serum lipid profiles and for other biochemical cardiovascular risk markers (e.g., total cholesterol (TC), triglyceride (TG), glutamate oxaloacetate transaminase (GOT), low density lipoproteins (LDL), high density lipoproteins (HDL), and blood urea nitrogen (BUN)) in the Department of Laboratory Medicine, Taipei Medical University Hospital.

### Statistical analysis

Each data was expressed as mean  $\pm$  S.D. Effects of PG on SHR BP were assessed by a one-way ANOVA followed by a post hoc Tukey's test to compare SBP or DBP between PG (30 and 50 mg/Kg) and the control group at the fixed week, and values at the same time point not sharing an alphabetic letter are significantly different ( $P < 0.05$ ). Effects of the PG on BP of subjects or serum lipid profiles

and other biochemical measurements from venous blood collection of subjects were assessed by a paired *t*-test to compare SBP or DBP before and after the feeding trial with PG and the placebo at 2, 4, 6, 8 weeks. A difference was considered statistically significant when  $P < 0.05$  (\*) or  $P < 0.01$  (\*\*).

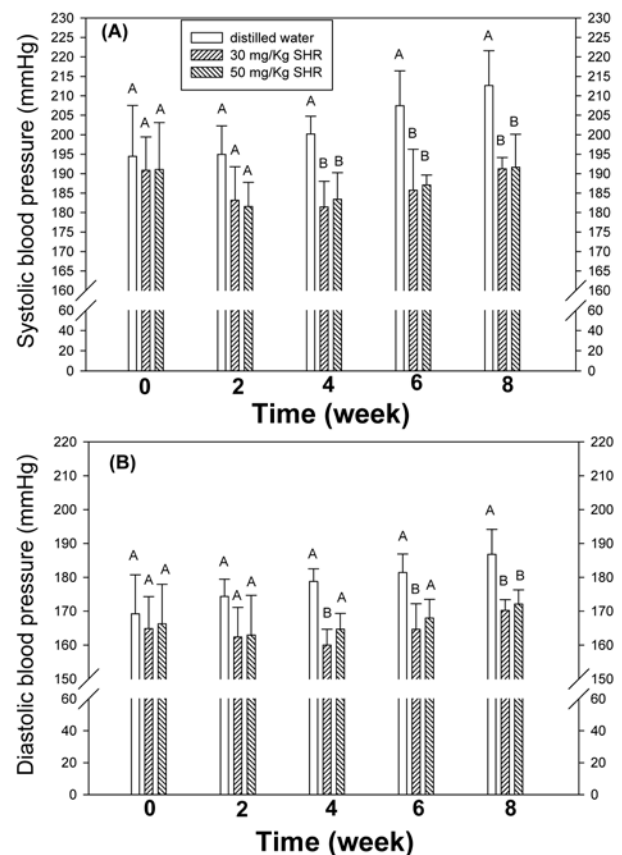
## RESULTS AND DISCUSSION

Potential drawbacks to using fresh garlic in the experiment were the possibility of subject indigestion and its unacceptable odors, which are mainly from alliin (*S*-allyl-L-cysteine sulfoxide). Instead, a process that combined aging at 37°C and water extraction for over 20 months produced aged garlic extracts which contained *S*-allyl mercaptocysteine and *S*-allyl-L-cysteine. The *S*-allyl-L-cysteine was reported to have a 98% absorption rate into the blood system and was used for standardizing aged garlic extracts (Nagae et al., 1994).

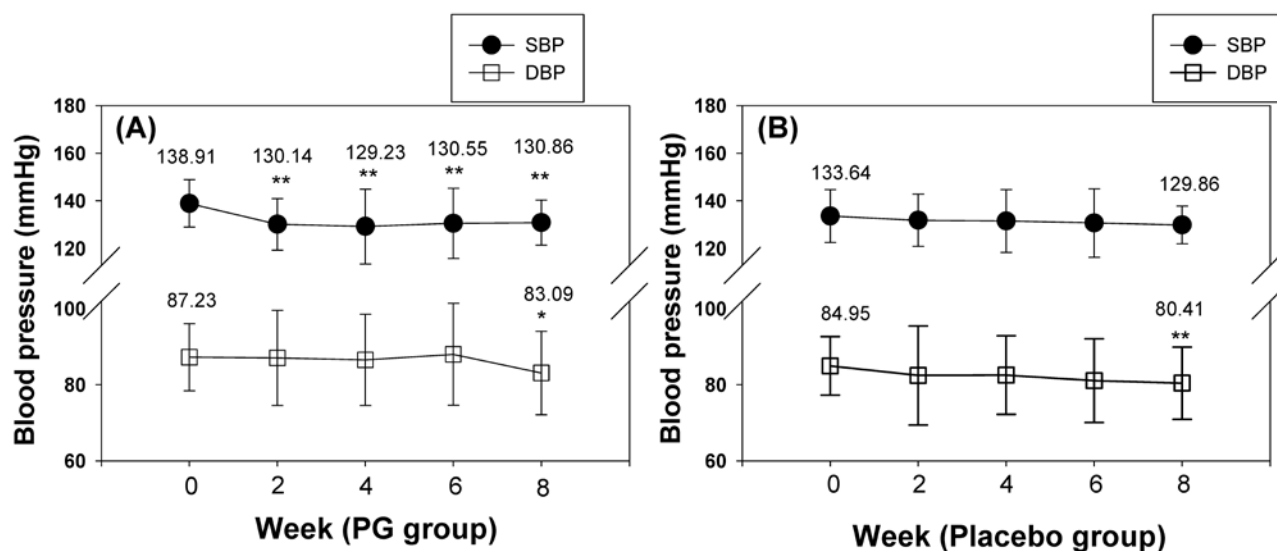
Before investigating the long-term effects of PG on the SHR BP, a 24 h BP change was performed by a single oral administration. A single dose of 30 or 50 mg/Kg of PG was orally administered to SHR, and the BP was then measured after 2, 4, 6, and 24 h. PG significantly lowered SBP and DBP ( $P < 0.05$ ) at four time points (data not shown). On the basis of this result, a long-term study (8 weeks) of the effects of PG on SBP (Figure 2A) and DBP (Figure 2B) was performed. At the beginning of the experiment, the average SBPs of the control and the two treatment groups (30 and 50 mg/Kg of PG) were  $194.5 \pm 13.1$ ,  $190.9 \pm 8.6$ , and  $191.1 \pm 12.1$  mmHg, respectively. The corresponding mean DBPs were  $169.2 \pm 11.5$ ,  $164.8 \pm 9.5$ , and  $166.3 \pm 11.7$  mmHg, respectively. During the test period, the control showed a continuous increase (Harauma and Moriguchi, 2006; Liu et al., 2009a) of SBP and DBP, respectively, up to  $212.6 \pm 9.0$  and  $186.8 \pm 7.3$  mmHg after 8 weeks' administration. In contrast, PG significantly decreased the SBP (Figure 2A) and DBP (Figure 2B) of SHR at these two doses. This effect was not dose-dependent but was statistically significant, except for DBP at 50 mg/Kg for 4 and 6 weeks, when compared with the control group at 4, 6, and 8 weeks. Therefore, a clinical trial was performed to evaluate the effects of PG on hypertension in humans.

Forty-four subjects were divided into control (17 males and 5 females) and treatment (16 males and 6 females) groups (Figure 1). The effects of PG on the BPs of hypertensive subjects are shown in Figure 3. For the PG group, the initial mean SBP and DBP measurements were  $138.91 \pm 9.95$  and  $87.23 \pm 8.83$  mmHg, respectively (Figure 3A). The corresponding values for the placebo group were  $133.64 \pm 11.11$  and  $84.95 \pm 7.69$  mmHg, respectively (Figure 3B). There were no significant differences in the initial SBP and DBP measurements in the placebo or PG groups as shown by *t*-test. Figure 3A shows the changes in BP after PG treatment for 8 weeks. The mean SBPs were  $130.14 \pm 10.77$ ,  $129.23 \pm 15.68$ ,  $130.55 \pm 14.73$ , and  $130.86 \pm 9.45$  mmHg after 2, 4, 6, and 8 weeks, re-

spectively. The corresponding mean DBPs were  $87.05 \pm 12.51$ ,  $86.55 \pm 12.01$ ,  $88.00 \pm 13.43$ , and  $83.09 \pm 10.98$  mmHg, respectively. All reductions in SBP were significant ( $P < 0.01$ ), as shown by paired *t*-test, whereas only the reduction in DBP after 8 weeks was statistically significant ( $P < 0.05$ ). Figure 3B shows the changes in BP for the control group. The reductions in SBP were not statistically significant ( $P > 0.05$ ), as shown by paired *t*-test. However, the reduction in DBP after 8 weeks was statistically significant ( $P < 0.05$ ). Thus, daily consumption of PG produces a statistically significant reduction in SBP that can be sustained for 8 weeks. Figures 2 and 3 show that PG has a long-term antihypertensive effect in both SHR and hypertensive human subjects. Venous blood collection was performed for each subject after the assigned feeding and at the end of 8 week PG or placebo intervention. There were no significant differences in TC, TG, GOT, LDL, HDL, or BUN levels ( $P > 0.05$ ) after 8 weeks between the PG treatment group (Figure 4A) and the placebo group (Figure 4B), as shown by paired *t*-test. Thus, PG did not have any



**Figure 2.** Effects of processed garlic powders at concentrations of 30 mg/Kg and 50 mg/Kg SHR (suspended in 0.5-mL water) on systolic blood pressure (A) and diastolic blood pressure (B) of SHR (N=8) over eight weeks. 0.5-mL water was orally administered to the control group. A one-way ANOVA followed by a post hoc Tukey's test to compare SBP or DBP between PG (30 and 50 mg/Kg) and the control group at the fixed week, and values at the same time point not sharing an alphabetic letter are significantly different ( $P < 0.05$ ).



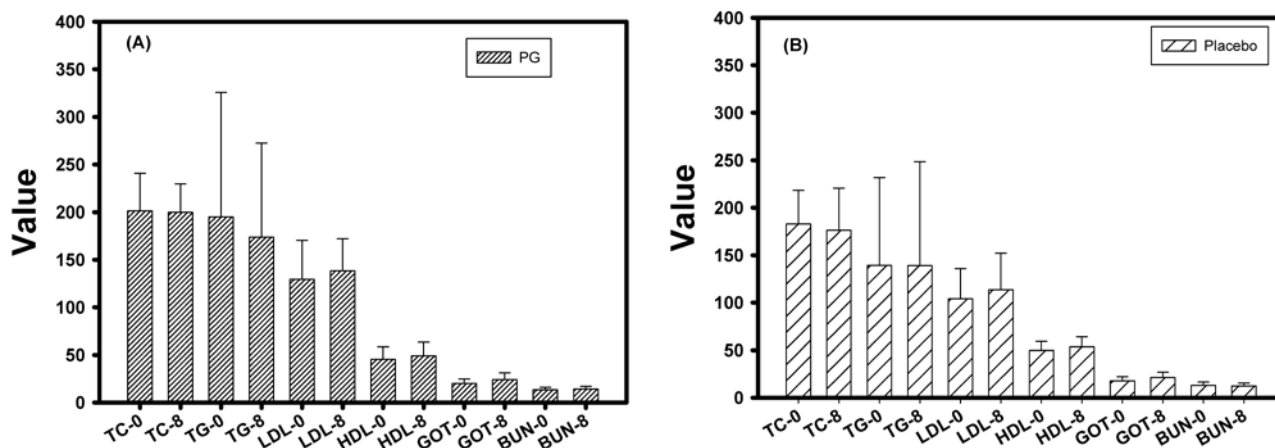
**Figure 3.** Effects of the processed garlic powder (A) and the placebo (B) on the systolic blood pressure (SBP) and diastolic blood pressure (DBP) of hypertensive subjects in the feeding trial. Two capsules (each 500 mg) together with 200-mL water were administered daily for 8 weeks. The paired *t*-test was performed to compare the changes of the blood pressure (SBP and DBP) between the originals vs. processed garlic powder or placebo at 2, 4, 6, and 8 week intervals, and a difference was considered statistically significant when  $P < 0.05$  (\*) or  $P < 0.01$  (\*\*) or  $P < 0.001$  (\*\*\*)

effect on serum lipid profiles or on other biochemical cardiovascular risk markers.

Our stepwise results showed that PG had antihypertensive activities in SHR animal models and hypertensive subjects. This is the first report to use processed garlic, PG, to conduct simultaneous antihypertensive studies in animals and human subjects. The antihypertensive activities against SHR were the same as those of a previous study using aged garlic extract (Harauma and Moriguchi, 2006), however, the advantage of aged garlic powder in this report was the timesaving

fermentation (two weeks) and the simple processing, rather than the several months required of aged garlic extracts. There were several reports concerning the placebo group with statistical effects in nutrient supplements (Venn et al., 2003; Binkoski et al., 2004; Theobald et al., 2007; Edwards et al., 2007; Liu et al., 2009a). The placebo was shown to lower DBP in this feeding trial, which might be attributed to a placebo effect.

Oxidative stresses might be involved in hypertension (Dhawan and Jain, 2005). Various kinds of processed garlic are reported to have radical scavenging activities



**Figure 4.** Effects of (A) the processed garlic powder (PG) and (B) the placebo on serum lipid profiles and other biochemical measurements of total cholesterol (TC), triglyceride (TG), glutamate oxaloacetate transaminase (GOT), low density lipoproteins (LDL), high density lipoproteins (HDL), and blood urea nitrogen (BUN) of clinical trials. The paired *t*-test was performed, and a difference was considered statistically significant when  $P < 0.05$ .

(Imai et al., 1994; Borek, 2001; Banerjee et al., 2003) and the ability to elevate the antioxidant status of hypertensive subjects (Dhawan and Jain, 2005), which might explain the antihypertensive mechanism of garlic products. One water-soluble component, *S*-allyl-L-cysteine, the represented compound derived from  $\gamma$ -glutamyl-*S*-allylcysteine in aged garlic preparations (Lawson and Gardner, 2005; Harauma and Moriguchi, 2006; Borek, 2006) was reported to increase the antioxidant status of MCD-induced hepatotoxic mice (Lin et al., 2008), to prevent CCl<sub>4</sub>-induced acute liver injury and reduce hepatic lipid peroxidation in rats (Kodai et al., 2007), to inhibit the formation of advanced glycation end products (Ahmad et al., 2007) and to increase the antioxidant status of cyclosporine-induced nephrotoxicity in Wistar rats (Magendramani et al., 2009). Kim et al. (2001) reported that garlic extract and *S*-allyl-L-cysteine could significantly increase NO production in endothelial cells. The NO is a major endogenous factor in blood vessel relaxation which may result in lowering blood pressure (Chalupsky et al., 2004; Bruckdorfer, 2005; Moon et al., 2006). Our present results showing antihypertensive activities in SHR and in hypertensive subjects might partially be due to the high contents of *S*-allyl-L-cysteine (753  $\mu$ g/g) in the processed garlic powders. Though garlic has been reported to have hypocholesterolemia activities (Stevinson et al., 2000; Yeh and Liu, 2001) the clinical trial did not appear to effect serum lipid profiles or other biochemical measurements for cardiovascular risk in the present feeding trial. It was proposed that the criteria of enrolled subjects focused primarily on blood pressure and they were thus not as aware of the other reported activities.

In conclusion, the timesaving (two-week) and simply-processed garlic products, PG, could effectively lower the SBP and DBP of SHR during the 8 week treatment period, and this effect was statistically significant compared to the control group. Furthermore, daily consumption of two 500 mg PG capsules over 8 weeks had regulatory effects on the SBP of hypertensive subjects.

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## 加工大蒜對於自發性高血壓鼠與高血壓民眾降血壓活性研究

韓傳孝<sup>1</sup> 劉如濟<sup>2,3</sup> 陳冠翰<sup>4,5</sup> 林音秀<sup>1</sup> 陳鏡譚<sup>5</sup>  
樊謙騰<sup>5</sup> 李惠倫<sup>5</sup> 劉得任<sup>6</sup> 侯文琪<sup>7,8</sup>

<sup>1</sup> 臺北醫學大學 藥學系

<sup>2</sup> 臺北醫學大學 內科學科

<sup>3</sup> 雙和醫院 心臟內科

<sup>4</sup> 臺灣大學 食品科技研究所

<sup>5</sup> 愛之味股份有限公司

<sup>6</sup> 臺北醫學大學 生醫材料暨工程研究所

<sup>7</sup> 臺北醫學大學 附設醫院中草藥研究中心

<sup>8</sup> 臺北醫學大學 生藥學研究所

本研究評估加工大蒜對於自發性高血壓鼠與高血壓民眾降血壓活性研究。生大蒜經過兩週酵素褐變，將原本白色變成黑色。活性成分，S-allyl-L-cysteine，經分析與測定，含量為 753  $\mu\text{g/g}$  加工大蒜在 30 與 50 mg/Kg 劑量下，每天餵食一次，在第四、六與八週能有效降低高血壓鼠的血壓。以安慰劑控制組平行進行加工大蒜對於 44 位高血壓民眾降血壓之人體試驗，總共進行八週，血壓每兩週於固定時間與地點，以電子血壓計進行血壓量測。結果顯示，每天吞食 500 毫克膠囊兩顆之加工大蒜，在兩週後具有顯著性差異 ( $P < 0.01$ ) 降低收縮壓，降幅達 8.05 毫米汞柱。

**關鍵詞：**加工大蒜；降壓；血壓；人體試驗；自發性高血壓鼠。

