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# Antihypertensive Effect of *Allium sativum* Linn. (Garlic) Bulb Tablets on Stage 1 Hypertensive Patients

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This study was performed to investigate the antihypertensive effect of dried bulb powder tablet of *Allium sativum* Linn. (garlic) on 15 stage 1 hypertensive patients attending the Out-patient Department of Traditional Medicine Hospital, Yangon. Garlic bulb tablets were prepared by tableting dried powder of bulbs with adhesive materials. After wash-out period of 3 days, the patients were treated orally with the dried bulb powder tablets (400 mg), 800 mg two times per day daily for 4 weeks. Blood pressure was monitored at baseline, 0.5 hr and hourly for 6 hrs after the first dose of the trial drug. Monitoring of blood pressure and vital signs was done on day 1, day 2, day 3 and weekly up to 4$^{th}$ week. Side effects were monitored on each patient follow-up. Investigations on biochemical and hematological parameters (blood for complete picture, random blood sugar, liver function test, renal function test) and ECG were done before and at the end of the study. The results showed that there were no reductions in blood pressure from baseline levels with the first dose of the trial drug. At the end of the trial, mean supine systolic pressure was significantly decreased from 140.33±1.29 mmHg (baseline) to 130±5.35 mmHg ($p<0.001$) whereas mean diastolic blood pressures was significantly decreased from 90.67±2.58 mmHg (baseline) to 82.33±4.17 mmHg ($p<0.001$). The results of laboratory investigations were within the reference normal ranges. No side effects were observed. It can be concluded that the dried powder of *Allium sativum* Linn. bulb had significant antihypertensive effect on stage 1 hypertensive patients.

*Key words*: Garlic, Antihypertensive activity

## INTRODUCTION

Hypertension is an important health problem in the world. It was reported that in 2000, about one billion people worldwide had hypertension and the researchers predict that by 2025, the number will climb to 1.56 billions people worldwide.[1] Hypertension can cause many complications and it is a common cause of death in cardiovascular diseases.[2] Today, the management of hypertension is a challenge to the medical profession. There has been a continuous search for a remedy which produces least side effects and cost effectiveness. In Myanmar traditional medicine and Indian system of medicine, there are many medicinal plants which have been used to lower the blood pressure in human. However, many of them have not been established scientifically to lower the blood pressure. *Allium sativum* Linn. (Kyet Thun Phyu) (Family - Liliaceae) is a medicinal plant which is widely cultivated in Shan State in Myanmar. Its English name is garlic. The bulbs of *Allium sativum* Linn.

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have been commonly used throughout the world for culinary and medicinal purposes since ancient times.

In traditional medicine, the bulb of *Allium sativum* Linn. is known to be useful for hypertension, diabetes mellitus, fever, cough, asthma, flatulence, arthritis, skin disease, etc.[3, 4]

The bulbs of garlic have been reported to have many medicinal activities such as hypolipidemic, antimicrobial, anti-hypertensive, antihyperglycemic, hepato-protective, antioxidant and anticoagulant activities.[5, 6]

It was found that oral administration of garlic extract decreased the blood pressure in spontaneously hypertensive rats.[7] In the anaesthetized dogs, it was found that oral administration of garlic powder reduced the arterial blood pressure.[8]

Raman, *et al*.[9] reported that garlic capsule administration to hypertensive patients decreased blood pressure level. It was reported that in a meta-analysis of the effect of garlic on blood pressure of hypertensive patients, the results showed a significant reduction in blood pressures.[10]

Bulbs of the garlic have been used traditionally by Myanmar people to treat hypertension.[3] It is included in some Myanmar Traditional Medicine Formulations for hypertension. In chronic toxicity study, when the rats were fed up to 2 g/kg of ethanol garlic extract for 6 months, no serious toxicity was demonstrated. Garlic is generally recognized as safe and most people enjoy garlic. It is known to cause heart burn and gastric irritation if it is taken in high dose. Garlic can also cause skin allergy in sensitive people.[11]

In Myanmar, there is no scientific report of antihypertensive effect of the dried bulb powder of *Allium sativum* Linn. (garlic) in human. This study was performed to find out the antihypertensive effect of *Allium sativum* Linn. bulb tablets and their side effects in stage 1 hypertensive patients.

## MATERIALS AND METHODS

Pre-test and post-test study design was used on stage 1 hypertensive patients. Sample size was calculated by using the following formula. (Hypothesis tests for two paired means "two-sided test"). The required sample size was 16.

$$N = \frac{2\,SD^2\,(Z_{\alpha}+Z_{\beta})}{(M_0-M_1)^2}$$

Stage 1 hypertensive patients of both sexes were recruited from Traditional Medicine Hospital, Yangon.

The study site was Pharmacology Research Division, Department of Medical Research and Out patient Department (OPD) of Traditional Medicine Hospital, Yangon.

*Tests for quality control parameters on the dried bulb powder tablet of Allium sativum Linn.*

Tests for quality control parameters included phytochemical study and physico-chemical study. Phytochemical tests of the dried bulb powder tablet of *Allium sativum* Linn. were done qualitatively for the detection of alkaloids, flavonoids, glycosides, etc by using the method of Harborne.[12] The physicochemical study of the dried bulb powder tablet was done by using the method of WHO.[13]

*Plant collection and preparation of Allium sativum Linn. (garlic) dried bulb powder tablets*

*Allium sativum* Linn. (garlic) bulbs from Shan State were collected from herbal shop from Yangon. The bulbs were firstly air-dried at room temperature. The air-dried bulbs were powdered by using grinding machine and the dried bulb powder was made into tablets of 400 mg each. WHO (2010) recommended daily dose of dried garlic powder for adult patients is 0.4-1.2 g per day in divided dose.[11]

*Patient selection*

Eligible patients were selected from OPD of Traditional Medicine Hospital according to

the criteria set. Only those patients who gave voluntary written informed consent were included in this study. They were informed about the nature and purpose of the study and the right to withdraw at any stage of the study.

Inclusion criteria

- Established hypertensive patients (i.e. essential hypertension patients) who had supine systolic blood pressure (140-159 mmHg) and supine diastolic blood pressure (90-99 mmHg) were selected. (According to JNC VII, 2003 blood pressure classification)[14]
- Age between 30-65 years of both sexes.

Exclusion criteria

- Subjects with stage 2 hypertension and hypertension with target organ damages.
- Patients taking regular treatment with long-acting antihypertensive drugs (eg. amlodipine, enalapril, lisinopril, etc).
- Patients with other diseases such as infectious diseases, other organ diseases (like central nervous system, heart, liver, lung, renal, endocrine organ diseases, etc).
- Pregnancy, lactating mothers and children.
- Patient with regular consumption of alcohol
- Patient with history of hypersensitivity to garlic

Withdrawal criteria

- Subject's request
- Patients who showed no blood pressure reduction with two-week treatment of this trial drug (i.e. garlic powder tablet)
- Attending physician's recommendation because of side effects of the trial drug.

*Procedure*

Baseline paramters

After getting the informed consent from each patient, history taking, physical examination and laboratory investigations such as ECG, blood for complete picture, platelets count, liver function test (serum bilirubin, SGOT, SGPT, serum alkaline phosphatase), renal function test (urine for routine analysis, blood urea and serum creatinine) and random blood sugar level test were done on each subject as stated in Proforma A before the clinical study.

Clinical study

Any previous antihypertensive drugs were stopped and wash-out period for 3 days was done before entry into the study. During the wash-out period, blood pressures were measured. Moreover, the patients were not allowed to alcohol drinking, smoking, salty diet and other antihypertensive drug during wash-out period and throughout the study period.

Fifteen stage 1 hypertensive patients were included in this study. On the first day of trial study, blood pressure was measured before giving the trial drug. Then, 800 mg of the trial drug [i.e. two tablets of dried garlic bulb powder tablet (400 mg)] were given orally and the blood pressures were monitored at 30 min, 1 hr, 2 hr, 3 hr, 4 hr, 5 hr and 6 hr after taking the trial drug. Vital signs such as heart rate, pulse rate, and respiratory rate were also monitored.

Then, the trial drug (800 mg) was given two times per day daily for 4 weeks. Upper limit of the trial drug for each dose was not be more than 800 mg per dose and total daily dose was not be more than 1.6 gm per day. Follow-up was done on day 2, day 3 for first week and weekly up to $4^{th}$ week. Blood pressure and vital signs were monitored on each follow-up. Side effects were recorded at each follow-up as stated in Proforma.[15]

The blood pressure was measured from the right forearm by a standardized mercury sphygmomanometer and stethoscope by same observer. Supine blood pressure (BP) was measured after patient was in recumbent position for 10 minutes. On the first day of the treatment, both supine BP and standing BP were measured. Standing BP was measured after patient had been standing for 2 minutes to detect postural hypotension.

Blood pressures were monitored in duplicate. Under each condition, the averages of the 2 measurements were taken. The disappearances of sound so called Korotkoff phase V were taken as the diastolic blood pressure, not phase IV.[16] In this study, reduction of blood pressure due to the treatment was defined as a reduction in systolic or diastolic blood pressure by 10 mmHg or more than 10 mmHg from baseline levels. At the end of the clinical study (i.e. at the end of 4th week) laboratory investigations described above were done again.

*Data management and analysis*

The results were shown as mean±S.D. The results of blood pressure and the parameters of vital signs after treatment with the trial drug were compared statistically with baseline levels by applying paired 't' test. 95% confidence intervals (CI) for reduction of blood pressure from baseline levels were also calculated. A difference at $p<0.05$ was considered statistically significant.

*Ethical consideration*

Ethical approval for this study was obtained from Ethical Review Committee of Department of Medical Research.

## RESULTS

*Tests for quality control parameters on the dried bulb powder tablets of Allium sativum Linn.*

The phytochemical tests of dried bulb power tables of *Allium sativum* Linn. showed the presence of alkaloids, steroids/terpenes, flavonoids, polyphenol, tannin, saponin, amino acid, glycosides and carbohydrate. Cyanogenic glycoside was not detected. The results of physicochemical tests are shown in Table 1.

*Clinical study*

Regarding the clinical study, a total of 15 stage 1 hypertensive patients of both sexes (mean age 49.6±5.47 years) completed this study. It was observed that mean pulse rate was 76.33±8.52 pulse/minutes at baseline and 76.53±6.12 pulse/minutes at the end of the trial study (4th week). Mean heart rate was 76.67±9.02 beats/minutes at baseline and 76.53±6.12 beats/minutes at the end of 4th week treatment. Mean respiratory rate was 15.47±4.5 times/minutes at baseline and 15.33±2.58 times/minutes at the end of 4th week treatment.

Table 1. Quality control parameters for dried bulb powder tablets of *Allium sativum* Linn.

| Tests | Results |
|---|---|
| Colour | Pale yellow |
| Smell | Alliaceous odour |
| Taste | Pungent |
| Uniformity of weight | Not more than 7% |
| PH 1% | 5.196 |
| Swelling index | 5.5 ml |
| Foaming index | <100 cm |
| Water and volatile matters | 9% |
| *Ash values* | |
| Total ash value | 6.53% |
| Water soluble ash | 4.83% |
| Acid insoluble ash | 0.66% |
| *Extractive values* | |
| Watery extract | 87.55% |
| Ethanol extract | 12.33% |
| Petroleum ether extract | 2.08% |

Table 2. The effect of dried bulb powder tablets of *Allium sativum* Linn. on mean supine systolic pressures in stage 1 hypertensive patients (n=15)

| Time | A (mmHg) | B (mmHg) | P value | 95%CI |
|---|---|---|---|---|
| (0 hour)# | 140.33±1.29 | | | |
| 0.5 hour | 139.67±4.81 | 0.67 | 0.004 | -2.08-3.41 |
| 1 hour | 136±5.07 | 4.33 | 0.001 | 7.45-1.21 |
| 2 hour | 134.67±6.39 | 6.33 | 0.01 | 9.72-2.94 |
| 3 hour | 136±5.07 | 5 | 0.09 | 8.14-1.86 |
| 4 hour | 138±4.14 | 3 | 0.33 | 5.93-0.07 |
| 5 hour | 140 | 0.33 | 0.33 | 0.38-1.05 |
| 6 hour | 140 | 0.33 | 0.07 | -0.38-1.05 |
| 2nd day | 137.33±5.94 | 3 | 0.17 | -0.28-6.28 |
| 3rd day | 138.67±5.17 | 1.67 | 0.18 | -0.83-4.16 |
| 1st week | 131.33±9.15 | 9 | 0.0002 | 3.85-14.15 |
| 2nd week | 133.67±4.81 | 6.67 | <0.0001 | 3.77-9.57 |
| 3rd week | 130.67±5.94 | 9.67 | <0.0001 | 6.28-13.06 |
| 4th week | 130±5.35 | 10.33 | <0.0001 | 7.29-13.38 |

A=Systolic blood pressure, B=Mean blood pressure decrease from baseline, CI=Confidence Interval, #=Baseline

Statistical comparisons were made between systolic blood pressures at baselines and systolic blood pressures after treatment with trial drug at different time intervals ($p<0.05$=slightly significant, $p<0.01$=moderately significant, $p<0.001$=highly significant).

Table 3. The effect of dried bulb powder tablets of *Allium sativum* Linn. on mean supine diastolic blood pressures (n=15)

| Time | A | B | P value | 95 % CI |
|---|---|---|---|---|
| (0 hour)# | 90.67±2.58 | | | |
| 0.5 hour | 89.33±4.58 | 1.33 | 0.16 | -0.62-3.28 |
| 1 hour | 86±4.71 | 4.67 | 0.002 | 2-7.33 |
| 2 hour | 85.67±4.95 | 5 | 0.002 | 2.23-7.77 |
| 3 hour | 87.67±5.63 | 3 | 0.07 | -0.28-6.28 |
| 4 hour | 89.33±4.58 | 1.33 | 0.33 | -1.53-4.2 |
| 5 hour | 90.67±2.58 | 0 | 1 | -2.09-2.09 |
| 6 hour | 90.67±2.58 | 0 | 1 | -2.09-2.09 |
| 2nd day | 88.67±3.52 | 2 | 0.08 | -0.29-4.29 |
| 3rd day | 89.33±2.58 | 1.33 | 0.16 | -0.62-3.29 |
| 1st week | 85.33±5.16 | 5.33 | 0.001 | 2.47-8.20 |
| 2nd week | 86.33±4.81 | 4.33 | 0.004 | 1.59-7.08 |
| 3rd week | 84.67±5.16 | 6 | 0.0004 | 3.19-8.81 |
| 4th week | 82.33±4.17 | 8.33 | <0.0001 | 6.33-10.34 |

A=Diastolic blood pressure, B=Mean blood pressure, decrease from baseline, CI=Confidence Interval, #=Baseline

Statistical comparisons were made between diastolic blood pressures at baselines and diastolic blood pressures after treatment with trial drug at different times intervals ($p<0.05$=slightly significant, $p<0.01$=moderately significant, $p<0.001$=highly significant).

Table 4. Effect of dried bulb powder tablets of *Allium sativum* Linn. on laboratory parameters of the patients (n=15)

| Biochemical parameters | Before treatment# | After treatment | P value |
|---|---|---|---|
| Total serum bilirubin (µmol/L) | 10.77±5.2 | 9.1±5.35 | NS |
| Serum aspartate amino transferase (AST) (U/L) | 31.7±8.67 | 27.36±8.54 | NS |
| Serum alanine amino transferase (ALT) (U/L) | 28.86±8.52 | 24.9±9.55 | NS |
| Serum alkaline phosphatase (ALP) (U/L) | 48.23±21.59 | 50.9±18.37 | NS |
| Serum creatinine (µmol/L) | 68.4±16.85 | 67.79±17.58 | NS |
| Blood urea (mmol/L) | 4.2±1.26 | 4.02±1.19 | NS |
| Random blood sugar (mg/dl) | 103.53±17.86 | 110.53±13.61 | NS |

NS=Not significant, #=Baseline

The data were expressed in mean±SD. Statistical comparisons were made between laboratory parameters at baseline and at the end of trial study (4th week).

It was observed that there were no significant changes in mean pulse rates, heart rates and respiratory rates from baseline levels. It was observed that mean body weight was 133.87±19.46 lbs at baseline and 135.27±18.89 lbs at the end of 4th week. No side effects were noted. The results of mean supine blood pressures after giving treatment with the trial drugs are shown in Table 2 and Table 3. The results of the effect of trail drug on laboratory parameters of the patients are shown in Table 4.

At the end of the study (4th week), it was observed that there were no significant changes in the results of biochemical parameters when compared with those of the baseline and hematological parameters (blood for complete picture and platelet count) were within the reference normal ranges. There were no changes in ECG finding between the baselines and at the end of treatment.

## DISCUSSION

*Allium sativum* Linn. bulb (garlic) is one of the most commonly used medicinal plants for the treatment of hypertension in traditional medicine of Myanmar and other countries. In the literature of Myanmar and Indian traditional medicine, it is described to have antihypertensive activity. It is also present in TMF 23 produced by Department of Traditional Medicine, Myanmar.[3]

In one study, the aqueous extracts of garlic were given orally to rats (two kidney-one-clip Goldblatt model in rats) (2 K-1C). The data showed the single dose of garlic had antihypertensive effect.[17] In a meta analysis of the effect of dried garlic powder tablet on blood pressure of hypertensive patients, three of the trial study reported a decrease in both systolic and diastolic blood pressures.[10] Khine Khine Lwin, *et al.* (2011) reported that in the toxicity study, dried bulb powder of *Allium sativum* Linn. possessed no acute and sub-acute toxic effects in mice and rat models.[18]

It was reported that bulb of *Allium sativum* Linn. may increase production of nitric oxide (potent vasodilator) which is associated with a decrease in blood pressure. *In vitro* studies using watery or alcohol extracts of garlic or garlic powder activated nitric-oxide synthase and these results have been confirmed by in *vivo* studies.[19, 20]

In the present study, the results showed that there were no significant reductions of mean supine systolic and diastolic blood pressures from baseline levels after first dose of the trial drugs on the first day of the trial study. But, the significant reductions of mean supine systolic blood pressures from baseline levels were found after one week of the trial drug treatment. Weekly mean blood pressures were maintained from 131.33 mmHg to 130 mmHg up to 4-week treatment period.

At the end of $4^{th}$ week treatment with the trial drug, it was observed that the trial drug significantly decreased the mean supine systolic blood pressure from 140.33±1.29 mmHg (baseline) to 130±5.35 mmHg ($p<0.001$) and mean supine diastolic blood pressure from 90.66±2.58 mmHg (baseline) to 82.33±4.17 mmHg ($p<0.001$). Therefore, this trial drug reduced the mean supine systolic and diastolic blood pressures from baselines by 10.33 mmHg (95% CI=7.29 to 13.38) ($p<0.001$) and 8.33 mmHg (95% CI 6.33 to 10.34) ($p<0.001$), respectively. In the present study, the dosage of the trial drug 800 mg two times daily was needed to control the blood pressure of these stage 1 hypertensive patients.

Throughout the study period, there were no significant changes in vital signs from baseline levels and no side effects were found. At the end of $4^{th}$ week treatment, there were no changes in laboratory investigations. In conclusion, dried bulb powder tablets of *Allium sativum* Linn. possessed mildly antihypertensive effect on stage 1 hypertensive patients with no side effects.

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