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# Antihypertensive effect of *Plantago major* Linn. whole plant (Ahkyawpaung-tahtaung) on mild to moderate hypertensive patients

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A clinical trial to determine the antihypertensive effect of medicinal plant, *Plantago major* Linn. (Ahkyawpaung-tahtaung) (whole plant) crude powder tablet was carried out on 10 mild to moderate hypertensive patients attending the out patient department (OPD) of Thingungyun Sanpya Hospital, Yangon and Traditional Medicine Hospital, Yangon. After washout period of 3 days, patients were treated orally with *Plantago major* Linn. whole plant crude powder tablet 3 g three times daily for 12 weeks. Blood pressure was monitored at 0 hr, 0.5hr, 1hr, 2 hr, 3 hr after first dose of trial drug. Monitoring of blood pressure and vital signs were done on day 1, day 2, day 3 and weekly up to 12 weeks. Laboratory investigations such as blood for complete picture, platelet count, random blood sugar level, liver function test, renal function test and ECG were done before and after the study. The results showed that reduction of blood pressure from baseline level was found at (0.5 hr-1 hr) after the first dose of the trial drug and was maintained up to 3 hr post dose. After 12 weeks of treatment with this trial drug, it was observed that significant reduction of mean blood pressure was from 150 ± 2.58/98 ± 1.33 mmHg (baseline blood pressure) to 129 ± 2.77/86 ± 1.63 mmHg ($P<0.001$). This trial drug decreased the mean systolic blood pressure and diastolic blood pressure from baseline level by 21 mmHg ($p<0.001$) and 12 mmHg ($p<0.001$) respectively. No side effects were observed. Therefore, it can be concluded that *Plantago major* Linn. showed significant antihypertensive effect on mild to moderate hypertensive patients with no side effects.

## INTRODUCTION

Globally, hypertension is a common health problem found in both developed and developing countries [1]. There are many complications of hypertension principally involved the central nervous system, the retina, the heart, the vessels and the kidneys. Hypertension is a common cause of death in cardiovascular disease [2]. Today, the management of hypertension is a challenge to the medical profession. There has been a continuous search for a remedy which produces the least side effects and cost effectiveness. In Myanmar traditional medicine and Ayurvedic medicine of India, there are many medicinal plants which are known to have antihypertensive activity. People have used many antihypertensive plants even though they have not been investigated scientifically. *Plantago major* Linn. (Family - Plantaginaceae) (Fig.1) commonly known as (Ahkyawpaung-tahtaung) in Myanmar is a perennial herb with erect stout root stock which grows wild along streams, river banks and moist places

in Shan State, Maymyo, and the Kachin State [3]. This medicinal plant has been widely used in traditional medicines of Myanmar and India for many years. The leaves have been known to be useful in fever, cuts and wounds and arthritis. Whole plant decoction has been used as diuretic [4, 5].

Fig. 1. *Plantago major* Linn. (Ahkyawpaung-tahtaung)

It was found that a soluble pectin polysaccharide, isolated from leaves of this plant had antibacterial effect [6]. It was also reported that pectin substance, plantaglucide isolated from the leaves has been effectively used in the treatment of peptic ulcer [7].

In the review article of Samuelsen (2000) [8] it was reported that a range of biological activities has been found from this plant extracts including wound healing activity, antiinflammatory activity, antioxidant activity, immunomodulatory activity and anti-ulcerogenic activity.

Myanmar people traditionally use this plant in the belief that it produces a fall in blood pressure [3]. Khin Kyi Kyi *et al*. (1971) [9] and Aye Than *et al.* (1977) [10] reported that this medicinal plant, *Plantago major* Linn. whole plant extract had shown hypotensive effect in dog model. It was also reported that this plant showed no acute toxic effect on mice. Thaung Hla *et al.* (2000) [11] stated that this plant had no sub-acute toxic effect on rats.

It has also been characterized physico-chemically and botanically [12]. Tin May Nyunt and Ohnmar May Tin Hlaing *et al.* (2003) [13] reported that in the clinical trial of short-term antihypertensive efficacy of crude powder of this whole plant in mild to moderate hypertensive patients, this plant showed significant antihypertensive effect with no side effects . In view of the above findings, this study was performed to determine the long-term antihypertensive effect of this medicinal plant on mild to moderate hypertensive patients.

*Objectives*

(1) To investigate the long-term antihypertensive effect of medicinal plant, *Plantago major* Linn. (whole plant) on mild to moderate hypertensive patients.

(2) To determine the side effects of this trial drug.

## MATERIALS AND METHODS

*Plant collection and preparation of Plantago major* Linn. *tablet*

The mature fresh *Plantago major* Linn. whole plants collected from Shan State (Taunggyi) were carefully washed with tap water to remove dust and foreign material and dried under shade at room temperature. The air dried whole plants were powdered with electric grinder and made tablets with 500 mg each.

*Patients selection*

After ethical clearance from Department of Medical Research (LM), eligible patients from out patient department of Thingun-gyun Sanpya Hospital and Traditional Medicine Hospital were selected according to the criteria. Only those patients who gave the voluntary informed consents were allowed to participate in this study and they had the right to withdraw at any stage.

*1. Inclusion criteria*

(i) Established essential hypertensive patients who had supine systolic blood pressure (SBP) ranged (140-170mmHg) and supine diastolic blood pressure (DBP) ranged (90-110 mmHg) were selected.

(ii) Both sexes of age between 30-70 years

*2. Exclusion criteria*

(i) Subjects who were not included in above inclusion criteria

(ii) Subjects with severe hypertension and hypertension with target organ damages

(iii) Patients taking regular treatment with long acting antihypertensive drugs (e.g. Amlodipine, Enalapril, Lisinopril etc)

(iv) Patients with other diseases (such as infectious diseases, central nervous system disease, heart disease, lung disease, liver disease, renal disease and endocrine organ diseases)

(v) Pregnancy, lactating mothers and children

(vi) Patients with regular consumption of alcohol

*3. Withdrawal criteria*

(i) Subject's request

(ii) Patients developing uncontrolled blood pressure

(iii) Attending physician's recommen-dation because of side effects of the trial drug

(iv) Patients with no response to the trial drug

*Study design*

The study design was an open typed (single arm) clinical trial. Ten mild to moderate hypertensive patients of both sexes were selected from out patient department of Traditional Medicine Hospital, Yangon and Thingungyun Sanpya Hospital, Yangon.

*Trial procedure*

After getting the informed consent from each patient, history taking, physical examination and laboratory investigations such as blood for complete picture, platelet count, ECG, LFT (Liver Function Test), renal function test (ie. urine RE, blood urea and serum creatinine) and random blood sugar level were done before the trial drug study.

Ten established hypertensive patients with supine blood pressure ranged from 140/90 mmHg to 160/100 mmHg of both sexes took part in this study. Any previous anti-hypertensive therapies were stopped and wash out period for 3 days was done before entry into the trial. The patients were also advised not to take alcohol, smoking and salty diet during the study period.

As a preliminary study, 7 mild hypertensive patients with the blood pressure ranged from 140/90 mmHg to 150/100 mmHg were treated orally with trial drug 1.5 g (3 tablets) and blood pressures were measured before giving the trial drug and at 30 min, 1hr, 2hr, 3hr after taking the first dose. Then, the trial drug 1.5 g per dose for 3 times per day daily was administered to the patients. Follow up was done on day 2 and day 3. Blood pressure and vital signs such as heart rate, pulse rate and respiratory rate were monitored at each follow up. It was found that there were no changes in blood pressure up to 3 days. So, on the $4^{th}$ day, the dose was increased to 3 g (6 tablets) per dose and the patients were treated with the trial drug 3 g three times daily. Then, blood pressure measurement and monitoring of vital signs were done as described above. Follow up was done on $2^{nd}$ day and $3^{rd}$ day of this dose. If there were reductions in blood pressure with 3 g three times daily dose, the patients were treated

daily with this dose up to 12 weeks. Then, follow up was done weekly up to 12 weeks. Blood pressure and vital signs such as heart rate, pulse rate and respiratory rate were monitored at each follow up.

The remaining subjects with moderate hypertension were also treated with the trial drug 3 g three times daily for 12 weeks. Follow up and monitoring of blood pressure, heart rate, pulse rate and respiratory rate at each visit were also done as described above up to 12 weeks. Dosage adjustment was done according to the patient's response. Side effects were recorded at each visit.

Blood pressure was measured on the right forearm by a standardized mercury sphyg-momanometer and stethoscope by the same observer. Supine BP and standing BP were measured in this study. Supine BP was measured after the patient was in recumbent position for 10 minutes and standing BP was measured after patient had been standing for 2 minutes. Blood pressure was monitored in duplicate. Under each condition, the average of two measurements was taken [14]. Laboratory investigations such as blood for complete picture, platelet count, ECG, LFT (Liver Function Test), renal function test (ie. urine RE, blood urea and serum creatinine) and random blood sugar level were done again at the end of the study.

*Data analyses*

The results were shown in mean ± standard error and compared statistically with baseline levels applying student paired't' test.

## RESULTS

Ten mild to moderate hypertensive patients of mean age 51.3years (ranged from 40-70 years) of both sexes with mean blood pressure ($\bar{X}$±SE), 150±2.58/98 ± 1.33mmHg (ranged from 140/90 to 160/100mmHg) took part in this study. The results of reduction of mean systolic and diastolic blood pressure from baseline levels after the first dose on the first day of the trial drug and day 2, day 3 and at each week are shown in Table 1.

Table 1. The effect of *Plantago major* Linn. on mean lying systolic and diastolic blood pressure in mild to moderate hypertensive patients (n=10)

| Time | Systolic blood pressure (mmHg) | | | Diastolic blood pressure (mmHg) | | |
|---|---|---|---|---|---|---|
| | Mean (± SE) | Mean differ-ence from baseline | P value | Mean (± SE) | Mean differ-ence from baseline | P value |
| Baseline | 150 (2.58) | | | 98 (1.33) | | |
| 30min | 140.5 (3.69) | 9.5 | <0.001 | 91.5 (2.36) | 6.5 | <0.01 |
| 1 hr | 140.5 (3.37) | 9.5 | <0.001 | 91 (2.33) | 7 | <0.01 |
| 2 hr | 139 (3.79) | 11 | <0.01 | 90.5 (2.41) | 7.5 | <0.01 |
| 3 hr | 135.5 (3.2) | 14.5 | <0.001 | 87.5 (2.01) | 10.5 | <0.001 |
| Day 2 | 140 (3.33) | 10 | <0.001 | 90 (2.58) | 8 | <0.001 |
| Day 3 | 138.5 (2.99) | 11.5 | <0.001 | 90 (2.58) | 8 | <0.001 |
| 1st wk | 137.5 (2.71) | 12.5 | <0.001 | 88 (2) | 10 | <0.01 |
| 2nd wk | 134.5 (3.37) | 15.5 | <0.001 | 88 (2.5) | 10 | <0.001 |
| 3rd wk | 136 (3.06) | 14 | <0.001 | 89 (1.8) | 9 | <0.001 |
| 4th wk | 134 (3.06) | 16 | <0.001 | 89 (2.33) | 9 | <0.001 |
| 5$^{t}$th wk | 134 (3.06) | 16 | <0.001 | 85.5 (2.63) | 12.5 | <0.01 |
| 6th wk | 133.5 (2.12) | 16.5 | <0.001 | 86.5 (1.5) | 11.5 | <0.001 |
| 7th wk | 131.5 (2.36) | 18.5 | <0.001 | 84 (1.63) | 14 | <0.001 |
| 8th wk | 132 (3.35) | 18 | <0.001 | 86 (2.67) | 12 | <0.001 |
| 9th wk | 131 (3.15) | 19 | <0.001 | 85 (2.11) | 13 | <0.001 |
| 10th wk | 129 (2.33) | 21 | <0.001 | 84.5 (1.57) | 13.5 | <0.001 |
| 11th wk | 131 (2.33) | 19 | <0.001 | 86.5 (1.5) | 11.5 | <0.001 |
| 12th wk | 129 (2.77) | 21 | <0.001 | 86 (1.63) | 12 | <0.001 |

wk = week hr = hour

Statistical comparisons were made between mean baseline blood pressure and mean blood pressure at different times, days and weeks.

The results of mean hourly systolic and diastolic blood pressure changes after treatment with the first dose of the trial drug on the first day of the study and weekly blood pressure changes up to 12 weeks

treatment with the trial drug are shown in Fig 2 & 3.

Mean pulse rates ($\overline{X}$ ± SE) were 81 ± 2.3 pulses /min at baseline and 75.2 ± 1.72 pulses/min at the end of 12 weeks treatment. Mean heart rates ($\overline{X}$ ± SE) were 81.2 ± 2.29 beats/min at the baseline and 76.2 ± 2.1 beats/min at the end of 12 weeks treatment. Mean respiratory rates ($\overline{X}$ ± SE) were 23 ± 2.11 times/min at the baseline and 20.8 ± 2.26 times/min at the end of 12 weeks treatment. It was found that at the end of the 12 weeks treatment with the trial drug, there were no significant changes in mean pulse rate, heart rate and respiratory rate from baseline levels (p >0.1).

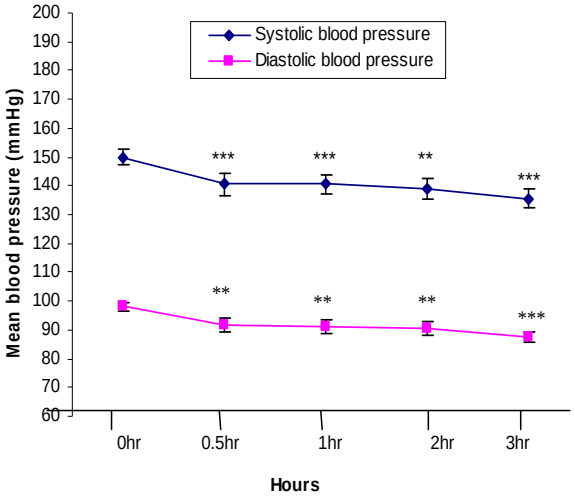


Fig 2. Effect of *Plantago major* Linn. (whole plant crude powder tablet ) on mean systolic and diastolic blood pressure ( hourly changes) after the first dose of trial drug ($\overline{X}$± S.E) *p<0.05, *p<0.01, ***p<0.001.

## DISCUSSION

Khin Kyi Kyi *et al.* (1971)[9] reported that hypotensive screening tests of various extracts of this plant on dog model showed hypotensive activity in some extracts. Aye Than *et al.* (1977) [10] reported that the various extracts of this plant had been screened for their hypotensive activity on dog model. PM-9 fraction possessed the most effective hypotensive activity. No

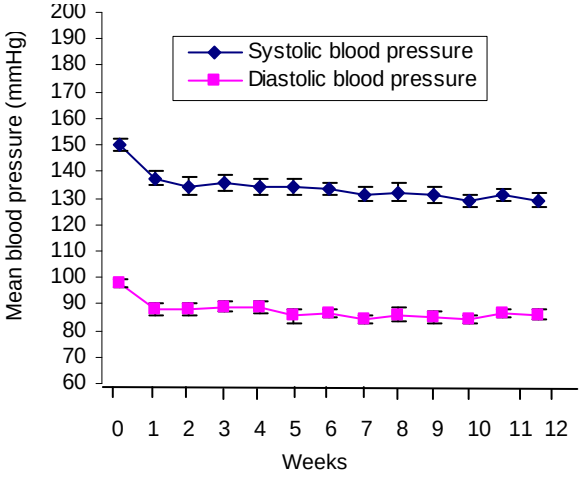


Fig. 3. Effect of *Plantago major* Linn.(whole plant crude powder tablet) on mean weekly systolic and diastolic blood pressure up to 12 weeks (n=10)X± SE.

evidence of the hypotensive action was detected directly at the vascular smooth muscle, at the adrenergic neurone and at the sympathetic ganglion. The fact that PM-9 caused hypotension by acting centrally was confirmed in experiment with dogs.

Tin May Nyunt and Ohnmar May Tin Hlaing *et al.* (2003) [13] carried out the clinical trial of antihypertensive effect of *Plantago major* Linn. whole plant (crude powder tablet) in 10 mild to moderate hypertensive patients for one month. They reported that this plant showed significant antihypertensive effect on mild to moderate hypertensive patients and side effects were not detected.

This study was the 3 months clinical trial of antihypertensive effect of *Plantago major* Linn. whole plant (crude powder tablet) on 10 mild to moderate hypertensive patients.

In this study, the results showed that the significant reduction of blood pressure from baseline level was found at 0.5 hr–1hr after first dose and was maintained up to 3 hr post dose. Weekly blood pressure was maintained at less than 140/90 mmHg. After the 12 weeks treatment with this trial drug, it was observed that significant reduction of mean lying blood pressure was from 150 ± 2.58/98 ± 1.33 mmHg (baseline

blood pressure) to 129 ± 2.77/86 ± 1.63 mmHg ($p<0.001$). This trial drug decreased the mean lying systolic blood pressure and diastolic blood pressure from baseline level by 21 mmHg ($p<0.001$) and 12 mmHg ($p<0.001$) respectively.

It was observed that initial blood pressure between 140/90 mmHg – 150/100 mmHg could be controlled with the trial drug dose of 3 g three times daily and for control of initial blood pressure 160/100 mmHg, 3.5 g three times daily was needed. Throughout the study period, no significant changes in mean pulse rate, heart rate and respiratory rate from baseline levels and no side effects were found. At the end of 12 weeks, it was found that there were no changes in laboratory investigations described above.

In conclusion, *Plantago major* Linn. (whole plant) showed significant antihypertensive effect on mild to moderate hypertensive patients with cost effectiveness and no side effects. In future, this herbal drug may be useful in the treatment of mild to moderate hypertensive patients.

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