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Antihypertensive Activity of Aqueous Extract of *Adhatoda Vasica* in Hypertensive Rats.

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Abstract: *The present study involved the evaluation of effectiveness of aqueous extract of Adhatoda Vasica on blood pressure, Systolic blood pressure, diastolic blood pressure and mean arterial blood pressure in the hypertensive rats. The result of present study was shown that the pretreatment with aqueous extract of adhatoda vasica (100, 200 & 400mg/Kg p.o) for six week and on the day of experiment after administration of aqueous extract of adhatoda Vasica (10, 20 & 40mg/kg i.v.) produced significant reduction in BP, SBP, DBP and MABP at different time interval in dose dependant manner. The positive control, Captopril at the dose of 1mg/kg was shown significant decrease in the elevated blood pressure in Goldblatt model. It reveals that antihypertensive effect observed for aqueous extract of adhatoda vasica in present study due to decrease rennin release and angiotensin II levels: AT1 and AT2 receptors antagonism: inhibition of aldosterone secreation: increased prostaglandin synthesis or inhibition of ACE that is involved in angiotensin II from angiotensin I.*

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I. Introduction

Cardiovascular disease (CVD) is leading and major contributor to the global disease burden. Importantly, (CVD) is eminently preventable to large extent. In order to achieve significant reduction in the avoidable (CVD) burden, a combination of population-based and high risk strategy is necessary. These strategies should target life-style related risk factor such as un healthy diet, physical inactivity and tobacco misuse as well as the intermediate manifestation of these lifestyle; e.g. hypertension glucose intolerance, and hyperlipidemia. In addition, the strategies, aimed at improving management of those already affected by CVD should be an integral component of a comphrensive approach, for the prevention and control of CVD **(1)**. Hypertension (HT) has been evidently, the most important contributing factor to cardiovascular disease, the leading causes of morbidity and untimely death. Sustained hypertension damage heart,kidney, blood vessel and brain which lead to ischemic heart disease, congestive heart failure, renal failure and stroke. Hypertension, therefore, is one of the most serious concerns of modern medical practice **(2).**

Many synthesis drugs have been developed for the treatment of hypertension because of the severity and prevalence of the disease. Herbal medicine have been regaining importance because of their ease of availability less side effect and cost effective **(3).** Adhatoda vasica belonging to family Acanthaceae. Leaves are 9-24 cm in length, opposite, lanceolate, Acuminate, minutely puberulous when young, glabrous hen mature, entire dark green, paler beneath, base tapering **(4).** Adhatoda vasica nees is an important medicinal plant widely employed for a variety of ailment in ancient Indian medicine . Recent investigation has reaffirmed the versatile activities of vasicine, the major alkaloid in the plant, as a highly potent expectorant, oxytocic and an abotificient agent **(5).** The literature survey reveals that the plant Adhatoda vasica having Anticestodal activity **(6)**, Antiulcer activity **(7)**, Antitussive activity **(8)**, Antituberculosis activity **(9)**, Hepatoprotective activity **(10)**, Modulatory influence activity **(11)**, Anti-inflammatory activity **(12)**, Anthelmintic activity **(13)**, inhibitory effect **(14)** and antidiabetic activity **(15)**.

II. Material And Method

2.1 Materials

2.1.1 Collection and Identification of plant material

The leaves of Adhatoda Vasica was collected from Bhor (Dist – Pune, Maharastra, India) in the month of October 2012 and were authenticated by the Agharkar research institute, Pune.

2.1.2 Extraction of Leaves

The leaves were dried under shade and powdered by using grinder mixture. For the prepration of aqueous extracts powdered material (1000gm) was extracted with distilled water at 100º C for 8-10 hour by using soxhlet apparatus. Extraction was done under reflux with an appropriate volume of distilled water. Extract was dried at 60º C on water bath, yielding a reddish coloured dry mass of 28gm (2.80% w/w). The extract was then preserved in the desiccators **(16).**

2.1.3 Preparation of drug solution

Accurately weighed quantity of extract was dissolved in the distilled water to prepare the appropriate stock solution of the extract. The doses administered orally by selecting the appropriate concentration of the stock solution. Aciten dispersible tablet (Captopril 25mg) was dispered in distilled water . The doses were administered by selecting the appropriate concentration (100ml/kg) of the stock solution

2.1.4 Animal

Male wistar albino rats of weighing between (200-250 g) were used. They were maintained at 25ºc ± 2ºc and relative humidity of 45 to 55% and under standard environmental condition (12 hours light/12 hours dark cycle). The animal had free access to food (pranav Agro Industries Ltd Sangli india) and water. Animal were obtained from Yash farm, Pune, Maharastra, India and national toxicological centre, Pune, Maharastra, India. All the experiment Protocol was approved by institutional Animal Ethics Committee (IAEC)

2.1.5 Daily acclimatization of animal

The animals were shifted from animal house to the laboratory one hour prior to the experiment. The respective apparatus were cleaned with hydrogen peroxide or damp cloth wherever necessary to avoid possible bias due to odour trials left by the previous animal.

2.1.6 Storage condition

All the solutions were prepared freshly and use on the day of dosing. The solution were stored, if required, in airtight amber colored vials in the refrigerator.

2.2 Methods

2.2.1 Acute toxicity studies

In order to decide the dose, toxicity study was carried out as per OECD guidelines No. 423; CPCSEA for acute oral toxicity.

Female mice were randomly selected and marked for individual identification. Animal were fasted 24 h prior to dosing of aqueous extract of A. Vasica were administered in a single dose orally. Toxicity study was carried out using a starting dose of 2000 mg/kg body weight. Animal were observed individually after dosing once during the first 30 min. periodically during the first 24 hr with special attention given during first 4 h. OECD guidelines, No. 423.

2.2.2 Effect of AEAV on renal artery-occluded hypertensive rats (17).

Male Wister rats were divided into the 6 groups each group consisting six animals. Animals in normal control and negative control groups received distilled water. Aqueous extract of A. Vasica was administered orally at the dose level of 100,200 and 400 mg/kg to the treatment groups for six week. At the end of the day treatment, animal were anesthetized by intraperitoneal injection of 1.25 gm/kg of urethane. A small incision was given on the left side of peritoneal cavity of the animal to expose left kidney. The renal artery was occluded for the 4 h by using renal bulldog clamp. The jugular vein was cannulated for the administration of test drug. The carotid artery was cannulated to measure the blood pressure and connected to the blood pressure transducer of power lab eight channel recorders. After stablisation blood pressure, the renal bulldog clamp was removed. this lead to rise in blood pressure as a consequence of elevated plasma rennin level. After bulldog clamp was removed the std. and test drug were administered immediately, $1/10^{th}$ of the oral administered dose of the A. Vasica aqueous extract i.e. 10, 20 and 40 mg/kg was given respective group through jugular vein and parameter like BP, SBP, DBP and MABP were measured at different time intervals (10, 15,30,45,60 min.) all parameter for each animal were recorded in normal group without clamping renal artery. Captopril (1 mg/kg, i.v.) was used as a positive control. Changes in the parameter of treated groups were compared with negative control.

III. Statistical Analysis

The statistical significance was assessed using one way analysis of variance (ANOVA) followed by Dunnet comparison test. The values were expressed as mean ± SEM and $p<0.05$ was considered significant**.**

IV. Result & Discussions

4.1 Acute toxicity study

No mortality and no signs of toxicity were found after administration of a limit dose of 2000 mg/kg body weight of extract of Adhatoda Vasica leaves in acute toxicity test carried as per the OECD guidelines no. 423. The substance might be considered to have an LD50 value above 2000mg/kg body weight. Hence for administration the doses selected were 100mg/kg and 400mg/kg and for intravenous administration the doses were 10, 20 and 40 mg/kg.

4.2 Effect of AEAV on renal artery-occluded hypertensive rats.

4.2.1 Effect of AEAV on BP in retail artery-occluded hypertensive rats

Removal of bulldog clip in ligated control group resulted in significant ($p<0.05$) increase in BP. pretreatment with AEAV 100,200 and 400 mg/kg, p.o. for six weeks and 10,20, and 40 mg/kg , i.v. on the day of experiment showed significant ($p<0.05$) decrease in BP in dose dependent manner at different time intervals when compared with ligated control group. In addition Captopril (1 mg/kg) produced significant ($p<0.05$) reduction in BP as compared to ligated control group.

S. No.	Treatment (Mg/Kg)	Stabilization	BP(In mmHg)			
			Post Treatment			
			15 Min	30 Min	45 Min	60 Min
1	Normal Control	84.13±7.559	84.07±8.851	83.26±9.221	83.40±8.429	84.45±8.739
2	Ligated Control	98.67±3.176	118.18±2.282@	111.74±2.431@	109.20±3.461@	108.77±2.550@
3	Captopril (1)	79.23±3.188	64.21±5.339*	62.30±3.662*	60.88±2.491*	60.41±3.479*
4	AEAV 1	86.21±6.287	84.66±5.915*	83.03±3.584*	80.01±3.876*	72.07±4.518*
5	AEAV 2	86.56±8.026	84.95±7.629*	80.41± 8.306*	72.79± 12.132*	71.10±9.364*
6	AEAV 4	82.40±4.593	79.36±5.392*	79.89±8.691*	72.47±8.209*	70.56±5.882*

Table: 1 Effect of AEAV on BP in retail artery-occluded hypertensive rats

Values are expressed as mean ± SEM, (n=6), $^{@}p<0.05$ as compared with Normal control, *$p<0.05$ as compared with Ligated control. Data analyzed by one way ANOVA followed by Dunnet test. Stabilization of BP before the treatments for 10 min; AEAV 1, AEAV 2 & AEAV 4: AEAV 100, 200 & 400 mg/Kg. p.o. for six week and 10, 20 and 40, mg/Kg, i.v. on the day of experiment respectively.

4.2.2 Effect of AEAV on SBP in renal artery-occluded hypertensive rats

Removal of bulldog clip in ligated control group resulted in significant ($p<0.05$) increase in SBP. pretreatment of animal with AEAV 100, 200 and 400 mg/kg p.o. for six week and 10,20, and 40 mg/ kg i.v. on the day of experiment showed significant ($p<0.05$) decrease in SBP in dose dependent manner at different time intervals, when compared with ligated control group . in addition , Captopril (1mg/ kg i.v.) produced significant ($p<0.05$) reduction in SBP as compared to ligated control group.

S. No.	Treatment (Mg/Kg)	Stabilization	SBP(In mmHg)			
			Post Treatment			
			15 Min	30 Min	45 Min	60 Min
1	Normal Control	92.16±5.563	89.96±7.196	90.09±7.654	90.09±87.497	92.79±8.011
2	Ligated Control	97.91±2.846	119.64±2.349@	111.74±2.431@	109.20±3.461@	108.77±2.550@
3	Captopril (1)	91.12±2.868	77.53±1..803*	74.913±4.075*	73.26±4.744*	69.32±1.914*
4	AEAV 1	89.28±5.567	88.83±4.175*	84.25±4.582*	80.14±4.285*	80.74±3.419*
5	AEAV 2	94.39±7.768	87.70±5.854*	83.92± 6.034*	76.96± 7.740*	72.74±9.883*
6	AEAV 4	90.08±4.343	84.49±4.038	80.80±3.676*	76.22±1.595*	71.52±2.890*

Table: 2 Effect of AEAV on SBP in retail artery-occluded hypertensive rats

Values are expressed as mean ± SEM, (n=6), $^{@}p<0.05$ as compared with Normal control, *$p<0.05$ as compared with Ligated control. Data analyzed by one way ANOVA followed by Dunnet test. Stabilization of SBP before the treatments for 10 min; AEAV 1, AEAV 2 & AEAV 4: AEAV 100, 200 & 400 mg/Kg. p.o. for six week and 10, 20 and 40, mg/Kg, i.v. on the day of experiment respectively.

4.2.3 Effect of AEAV on DBP in renal artery-occluded hypertensive rats

Removal of bulldog clip in ligated control group resulted in significant ($p<0.05$) increase in DBP. pretreatment of animal with AEAV 100, 200 and 400 mg/kg p.o. for six week and 10,20, and 40 mg/ kg i.v. on the day of experiment showed significant ($p<0.05$) decrease in DBP in dose dependent manner at different time intervals, when compared with ligated control group . in addition, captopril (1mg/ kg i.v.) produced significant ($p<0.05$) reduction in DBP as compared to ligated control group.

S. No.	Treatment (Mg/Kg)	Stabilization	DBP(In mmHg)			
			Post Treatment			
			15 Min	30 Min	45 Min	60 Min
1	Normal Control	73.39±8.582	76.25±10.998	71.40±10.135	69.05±8.845	68.91±9.233
2	Ligated Control	79.37±6.436	106.32±2.908@	93.87±2.440@	89.23±3.779@	85.41±4.099@
3	Captopril (1)	68.99±4.239	47.66±4.446*	47.26±2.536*	53.12±2.491*	47.95±2.199*
4	AEAV 1	79.16±6.633	70.25±5.696*	68.74±6.173*	62.40±5.885*	62.86±3.703*
5	AEAV 2	75.39±7.480	71.49±6.132*	66.18± 3.819*	59.61± 8.971*	57.57±8.340*
6	AEAV 4	71.83±4.921	71.05±5.880*	63.40±3.471*	58.43±3.124*	56.86±2.253*

Table: 3 Effect of AEAV on DBP in retail artery-occluded hypertensive rats

Values are expressed as mean ± SEM, (n=6), $^{@}p<0.05$ as compared with Normal control, *$p<0.05$ as compared with Ligated control. Data analyzed by one way ANOVA followed by Dunnet test. Stabilization of

DBP before the treatments for 10 min; AEAV 1, AEAV 2 & AEAV 4: AEAV 100, 200 & 400 mg/Kg. p.o. for six week and 10, 20 and 40, mg/Kg, i.v. on the day of experiment respectively.

4.2.4 Effect of AEAV on MABP in renal artery-occluded hypertensive rats

Removal of bulldog clip in ligated control group resulted in significant ($p<0.05$) increase in **MABP**. pretreatment of animal with AEAV 100, 200 and 400 mg/kg p.o. for six week and 10,20, and 40 mg/ kg i.v. on the day of experiment showed significant ($p<0.05$) decrease in **MABP** in dose dependent manner at different time intervals, when compared with ligated control group . in addition , captopril (1mg/ kg i.v.) produced significant ($p<0.05$) reduction in **MABP** as compared to ligated control group.

S. No.	Treatment (Mg/Kg)	Stabilization	MABP(In mmHg)			
			Post Treatment			
			15 Min	30 Min	45 Min	60 Min
1	Normal Control	83.09±8.109	81.93±9.326	81.19±9.696	80.62±8.620	77.99±9.156
2	Ligated Control	86.33±5.116	115.26±3.911@	108.73±3.799@	105.68±2.801@	101.81±4.457@
3	Captopril (1)	75.43±3.450	59.41±5.101*	59.11±2.163*	57.44±2.053*	54.63±3.625*
4	AEAV 1	79.97±6.547	76.23±4.333*	75.86±4.657*	73.84±4.296*	69.26±4.514*
5	AEAV 2	83.77±8.815	74.17±4.689*	72.96± 5.034*	70.42± 4.921*	67.34±4.664*
6	AEAV 4	79.03±4.611	73.59±4.084*	70.25±5.568*	68.08±5.650*	68.30±6.031*

Table: 4 Effect of AEAV on MABP in retail artery-occluded hypertensive rats.

Values are expressed as mean ± SEM, (n=6), @$p<0.05$ as compared with Normal control, *$p<0.05$ as compared with Ligated control. Data analyzed by one way ANOVA followed by Dunnet test. Stabilization of MABP before the treatments for 10 min; AEAV 1, AEAV 2 & AEAV 4: AEAV 100, 200 & 400 mg/Kg. p.o. for six week and 10, 20 and 40, mg/Kg, i.v. on the day of experiment respectively.

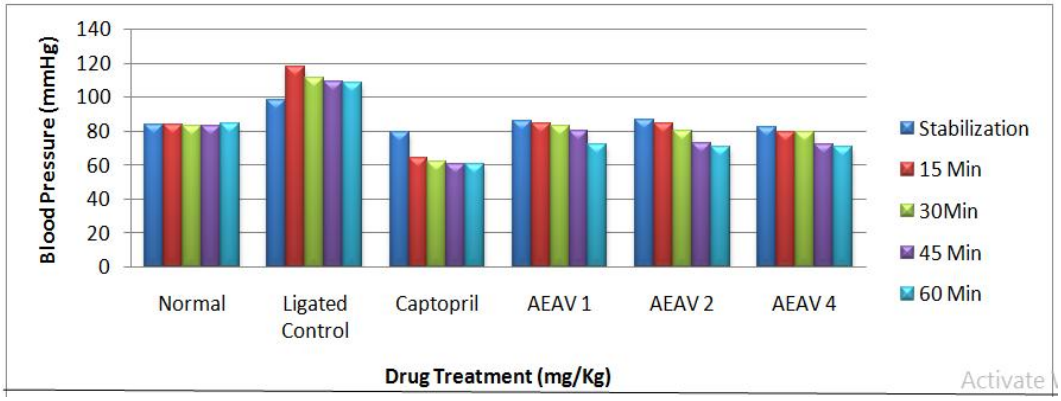


Figure: 1 Effect of AEAV on BP in Renal artery – occluded hypertensive rats

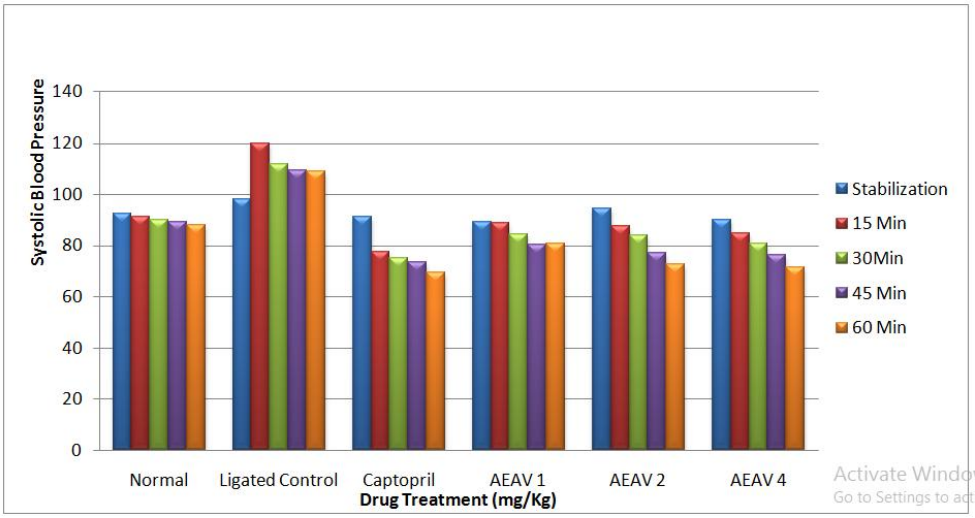


Figure: 2 Effect of AEAV on SBP in Renal artery – occluded hypertensive rats

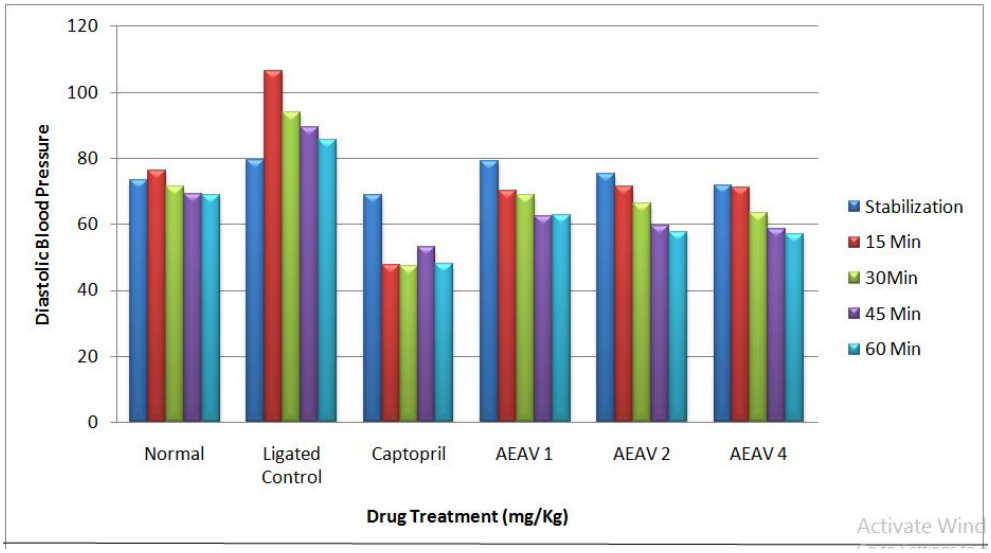
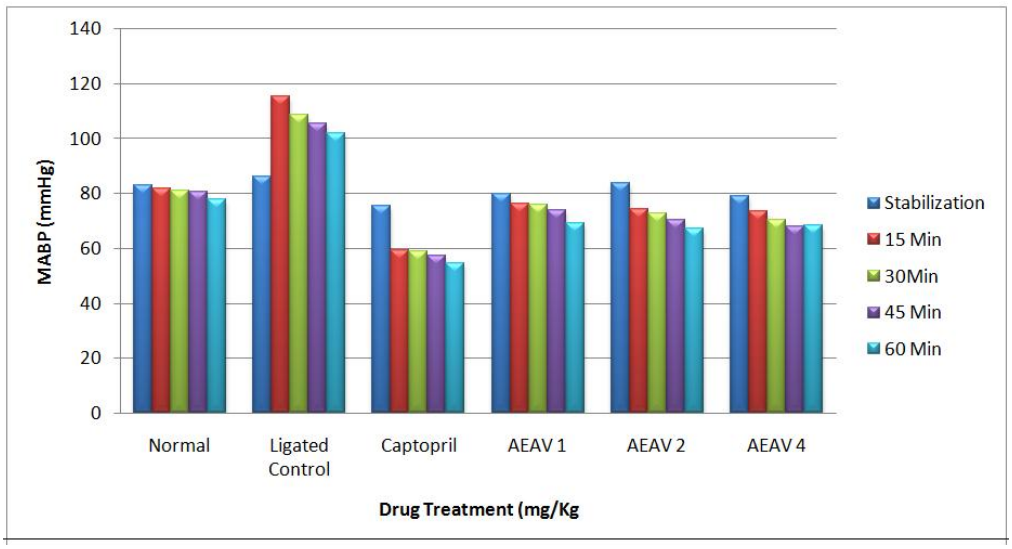


Figure: 3 Effect of AEAV on DBP in Renal artery – occluded hypertensive rats



V. Conclusion

Hypertension is major risk factor for stroke, myocardial infaraction, and heart and kidney failure. Worldwide hypertension is estimated to cause 7.1 million premature deaths and 4.5% of the disease burden. Treating hypertension has been associated with about a 40% reduction in the risk of stroke and about a 15% reduction in the of myocardial infaraction. In consequence, current clinical practice guidelines identify lowering blood pressure as a priority in the treatment of people with hypertension **(magos et al., 2008).** The result of present study showed that the AEAV extract had produced significant reduction in BP, SBP, DBP, and MABP at different time interval in dose dependant manner. From the result of present study and mechanism involve in the induction of hypertension in goldblatt model, it was revealed that antihypertensive effect observed for AEAV may possibly be due to decrease in rennin release and angiotensin II levels; AT 1 & AT2 receptors antagonism; inhibition of aldosterone secretion; increase prostaglandin synthesis or inhibition of ACE that is involve in synthesis of angiotensin II from angiotensin I.

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