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ANTIHYPERTENSIVE ACTIVITY OF *Nardostachys jatamansi* IN HYPERTNSIVE RATS FOLLOWING RENAL GOLD BLATT OCCLUSION METHOD.

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ABSTRACT

Siddha drugs are gaining popularity in recent years and there is a significant increase in scientific researches on traditional Siddha drugs because of theirs potent effects with no or less adverse effects.One of the safest and potent anti-hypertensive drug from the reservoir in Siddha system of medicine is Sadamanjil Chooranam (*Nardostachys jatamansi*). Hence an attempt was made to validate the anti-hypertensive potential of Sadamanjil Chooranam in hypertensive rats following renal Goldblatt occlusion method. After induction, hypertensive rats were randomly divided into four groups each consists of five rats. All the groups were categorized into normal control, hypertension control, SMC 500 (500mg/kg) and SMC 1000 (1000mg/kg). The test drug Sadamanjil Chooranam was administered (500mg/1000mg/kg) orally from the next day for 10 days. The systolic (SBP) and diastolic (DBP) blood pressure of the animals were recorded with tail cuff BP apparatus. Administration of SMC at the dose levels of 500mg and 1000mg /kg b.w. for 10 days significantly decreases the Systolic BP and Diastolic BP as compared with hypertensive animal group. Decrease in systolic and diastolic BP was more pronounced in high dose level (1000mg/kg) than low dose (500mg/kg) indicated the dose dependent activity of Sadamanjil Chooranam. The results concluded the anti-hypertensive potential of Sadamanjil Chooranam in a scientific way.

KEY WORDS : *Nardostachys jatamansi*, Sadamanjil Chooranam, Siddha, anti-hypertensive, Gold Blatt method.

INTRODUCTION

High blood pressure, or hypertension, is a serious medical condition, if untreated it can lead to myocardial infarction, heart failure, renal failure, retinal damage, stroke and even death. Globally cardiovascular disease accounts for approximately 17 million deaths a year, nearly one third of the total.[1] Of these, complications of hypertension account for 9.4 million deaths worldwide every year.[2]

In India, hypertension is a major public health issue due to its mortality rate. Several surveys have been conducted in recent years and was reported that hypertension is the leading NCD risk and estimated to be attributable for nearly 10 per cent of all deaths.[3] The number of hypertensive individuals is anticipated to nearly 213 million by 2025.[4]Treating hypertension has been associated with about a 40% reduction in the risk of stroke and about a 15% reduction in the risk of myocardial infarction.[5] Therefore it is necessary to detect, treat, control and prevent hypertension.

Even though different groups of anti-hypertensive drugs available in the market that significantly reduce the blood pressure, unfortunately most of the anti-hypertensive may have different side effects and may interact with other substances. So that,Siddha drugs are gaining popularity in recent years and there is a significant increase in scientific researches on traditional Siddha drugs because of theirs potent effects with no or less adverse effects. Siddha system of medicine has an extensive medical history with its phytochemical reservoir.

One of the safest and potent anti-hypertensive drug from the reservoir is Sadamanjil Chooranam (*Nardostachys jatamansi*). It is used traditionally in the treatment of nervous headache,hypertension, epilepsy, intestinal colic, hysteria and depressive illness.[6] More than 25 active principles havebeen isolated from the rhizome part of this plant which includes alkaloids jatamansone, nardostachone, jatamansicacid, coumarins, lignan, neolignans and sesquiterpenes.[7-8] Hence an attempt was made to validate the anti-hypertensive potential of Sadamanjil Chooranam (*Nardostachys jatamansi*) in hypertensive rats following renal Goldblatt occlusion method.

MATERIALS AND METHODS

Preparation of the trial drug Sadamanjil Chooranam

The plant material Sadamanjil (*Nardostachys jatamansi*) was obtained from the Country drug shop at Parrys, Chennai, Tamilnadu, India and the same was authenticated by Botanist, Government Siddha Medical College, Arumbakkam, Chennai. The specimen sample has been kept in the department for future reference.

After identification and authentication of the plant material, it was first decontaminated by removal of the dust particles which was performed by washing the plant with plenty of water. Then the plant material was allowed to complete drying at room temperature. The dried plant material was finely powdered by pulverizer and sieved through white cloth and the subjected to further study.

Animal Experimental Design

Drug, Reagents and Stock solution preparation

Since the test drug is partially soluble in distilled water and hence the test drug was mixed uniformly in 2% CMC solution to achieve 100mg/ml of suspension as main stock solution and used in this study.

Animals

Wistar rats of either sex weighing 150-200g were selected for the screening of acute toxicity and anti-hypertensive studies. Animals were fed on conventional diets and water ad libitum and they were maintained under standard conditions of humidity, temperature (20-24°C) and 12 hour light and dark cycle. Then the rats were randomly assigned to control and different treatment groups, six animals per group. The present experimental study was approved by the Institutional Animal Ethical Committee (IAEC) and the study was conducted in accordance with CPCSEA guidelines.

Acute toxicity study

Acute oral toxicity test was carried out as per OECD Guidelines 425 up and down method.[9-10]The food was withdrawn 12 hours before starting the experiment and again 3 hours after providing administration.Animals were observed individually for the first 30 minutes after drug administration in a single dose and periodically during the first 24 hours, with particular care during the first 4 hours.All the animals were monitored and observed any signs and symptoms of toxicity, including the onset of duration, changes in the skin, eyes, mucous

membrane, respiratory system, circulatory system , CNS and changes in general behaviour and mortality. All observations are systematically recorded.

Dosing levels

The tolerable dose levels 500 and 1000mg/kg were taken for further pharmacological study.

Induction of hypertension in rats - Goldblatt method

The Goldblatt et al in 1934 introduced the first animal model of hypertension in dogs evoked by unilateral constriction of the renal artery (2K1C – two kidney one clip model).[11]This type of hypertension has also been followed by similar method in rabbits, rats and monkeys.[12].Later on this method was modified by constriction of the renal artery is done on one side and contralateral kidney is removed. There is an increase in BP within a few hours due to rapid salt and water retention.[13-14]This surgical method in rodents is well-validated model and which mimic the rennin-angiotensin induced hypertension.

Animals are anaesthetized with ketamine + xylazine (75 +25 mg/kg i.p). Small 1 cm incision was made near lumbar region and left kidney and left renal artery was identified and occluded with surgical thread 4-0 silk suture.[15] The occluded kidney is replaced in its original position and wound is closed with surgical catgut. All the animals are allowed to free access to food and *ad libitum* and the rats were housed individually. All the rats were allowed to recover from the surgical wound.The animal is considered hypertensive if systolicBP is more than 160 mm Hg for two consecutive days after 4 weeks of ligation.[16]

Then hypertensive rats were randomly divided into four groups each consists of five rats.All the groups were categorized into normal control, hypertension control, SMC 500 (500mg/kg) and SMC 1000 (1000mg/kg). The test drug Sadamanjil Chooranam was administered (500mg/1000mg/kg) orally from the next day for 10 days. The systolic (SBP) and diastolic (DBP) blood pressure of the animals were recorded with tail cuff BP apparatus.

STATISTICAL ANALYSIS

All data were expressed as mean±SEM. Systolic blood pressure and diastolic blood pressure values obtained from two doses of test drug were compared with the hypertensive control group by analysis of variance (ANOVA) followed by Dunnet's test. **P*<0.05, ***P*<0.01 vs HT group and ‡P< 0.001 vs control group.

RESULTS AND DISCUSSION

Table 1.Showing the effect of *SMC* on Systolic and Diastolic blood pressure

Groups	Systolic BP (mm/Hg) (Mean±SEM)	Diastolic BP (mm/Hg) (Mean±SEM)
Control	117.4±2.79	77.0 ± 3.41
HT	159.4 ±5.71ǂ	90.0 ±4.15ǂ
SMC 500	132.0 ± 4.34**	79.2 ±3.07*
SMC 1000	119.2 ±3.70**	74.2 ± 1.69*

*Values are expressed in Mean ± SEM (n=5)1Way ANOVA followed by Dunnett's Multiple comparison test. Where *P< 0.05, **P< 0.01 vs HT group and ‡P< 0.001vs control group.*

Acute toxicity study

In this study, the trial drug Sadamanjil Chooranam with doses of 2000mg/kg and 5000mg/kg mixed with CMC administered in animals were survived after 48 hrs. showing good response in Alertness, Aggressive earlier and settle down lately, Touch response, Gripping, Increased motor activity, and Normal respiration.The trial drug did not show any adverse effects or mortality even at the dose of 5000mg/kg.From the result, it was proved that Sadamanjil Chooranam is so safe.

Anti-hypertensive study

In the present study, renal Goldblatt occlusion method of hypertensive model was examined. We measured the arterial BP and the heart rate of both the normotensive and hypertensive rats, with a view to validate the anti-hypertensive potential of Siddha traditional drug Sadamanjil Chooranam by scientific basis in renal hypertensive rats.

Table.1 and Fig.1 represented the effect of SMC on systolic BP on hypertensive rats. There is a significant (P<0.001) increase in systolic BP was noted in renal hypertensive rats (RHR) as compared with the normal control group. Administration of SMC at the dose levels of 500mg and 1000mg /kg b.w. for 10 days significantly decreases the Systolic BP (132 ± 4.34 and 119.2 ±3.72 mm Hg respectively) as compared with hypertensive animal group (159.4 ±5.71 mm Hg) (P < 0.01). Decrease in systolic BP was more pronounced in high dose level (1000mg/kg) than low dose (500mg/kg) indicated the dose dependent activity of Sadamanjil Chooranam.

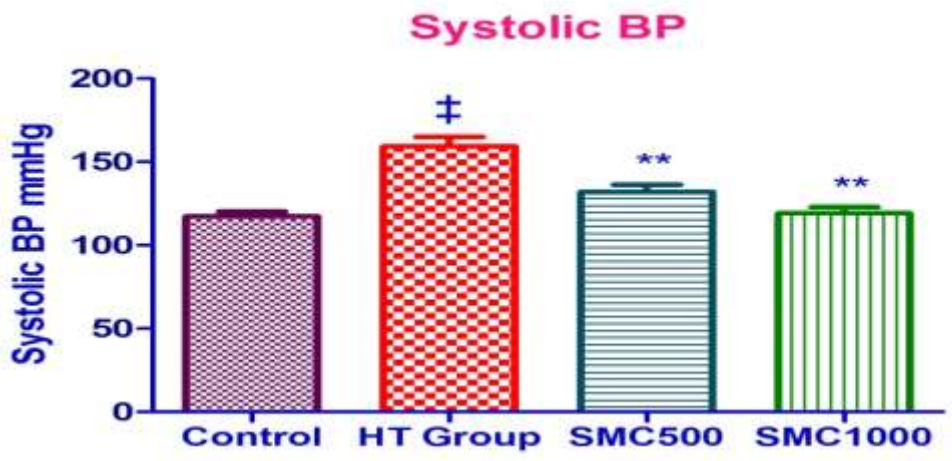

Fig No.1. Effect of SMC on systolic BP on renal hypertensive rats. ‡*p<0.001* versus control; ** *p<0.01* versus HT group.

Table.1 and Fig.2 represented the effect of SMC on diastolic BP on hypertensive rats. There is a significant (P<0.05) increase in diastolic BP was noted in renal hypertensive rats (90 ±4.15) as compared with the normal control group (77 ±3.41 mm Hg). Administration of SMC at the dose levels of 500mg and 1000mg /kg b.w. for 10 days significantly decreases the diastolic BP (79.2 ±3.07 and 74.2 ±1.69 mm Hg respectively) as compared with the Hypertensive animal group (P < 0.05). Decrease in diastolic BP was more pronounced in high dose level (1000mg/kg) than low dose (500mg/kg) indicated the dose dependent activity of Sadamanjil Chooranam.

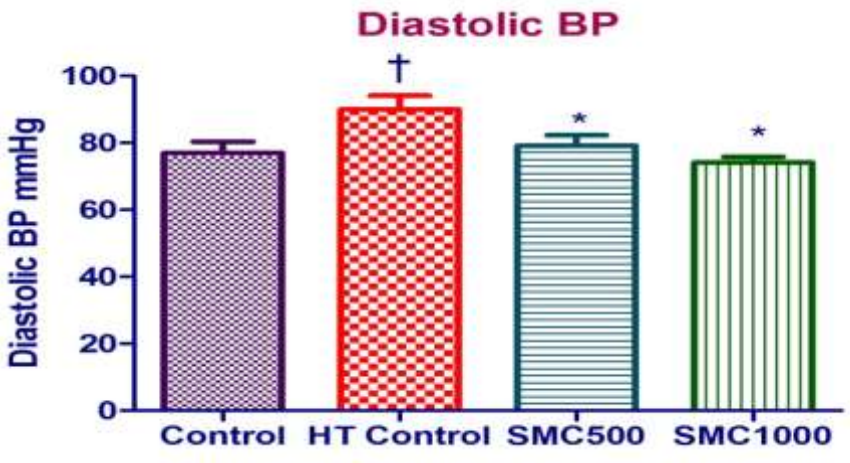

Fig No.2. Effect of SMC on diastolic BP on renal hypertensive rats. † *p<0.05 versus* control; * *p<0.05* versus HT group.

The renal artery stenosis is a clinical entity, because due to stenosis of one or more of the renal arteries become narrowed which leads to the decrease in renal perfusion pressure and

increases the secretion of mineralocorticoid aldosterone which activates the renin-angiotensin system mediated by salt and water retention result in hypertension.

Hypertension is also induced by unilateral stenosis of the renal artery due to the so-called gold leaf mechanism. Because of the reduced renal perfusion pressure, the kidney responds with an increased renin synthesis. As a consequence, renin-angiotensin-aldosterone system is activated which leads to hypertension.

The results from the present investigation reveals that the test drug at the dose of 1gm/kg body weight administered orally for 10 days to the hypertensive rats significantly ($p<0.05$) decrease the systolic and diastolic Blood pressure.

The exact mechanism through which they produce beneficial effects remain unclear, but it has been found that the use of inhibitors of the renin-angiotensin-aldosterone (RAA), usually associated with diuretics, which has been very effective in reducing the blood pressure. The trial drug Sadamanjil Chooranam is proved to be effective hypernatremic, hyperchloremic and hyperkalemic diuretic potential by previous research in animal model.[17]Its oily extract has also been found to have an anti-oxidant[18]and anti-arrhythmic properties.[19]Jatamansone is one of the main sesquiterpene found in *Nardostachys jatamansi* which has been reported as antihypertensive through animal studies.[20]

In relation to the aforementioned could be considered that the antihypertensive effect of Sadamanjil Chooranam (*Nardostachys jatamansi*) may be because it acts as a diuretic or ACE inhibition or central depressant property and or an antioxidant in renovascular hypertension.

CONCLUSION

The antihypertensive activity of Sadamanjil Chooranam (*Nardostachys jatamansi*) may be resulted through the action on renin angiotensin system. The oral administration of Sadamanjil Chooranam with two dose level (500mg and 1000mg/kg body weight) produces a statistically significant decrease in systolic and diastolic blood pressure in renovascular hypertensive rats. marked hypotensive response was observed in hypertensive rats treated with 1000 mg/kg dose than 500mg/kg dose level which showed the dose dependent activity. It is not clear that the anti-hypertensive effect of the Sadamanjil Chooranamis due to ACE inhibition or diuretic or central depressant property. Further experiments will clarify the exact pharmacological mechanism of the drug.

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