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Pre-Clinical Validation of Anti-Hypertensive Activity of Potential Siddha formulation *Paruthi Chooranam* in Spontaneous hypertensive rats

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Abstract

Hypertension (HTN) or high blood pressure (BP) is a chronic medical condition in which the BP in the arteries is elevated. It is classified as either primary (essential) or secondary.Persistent HTN is one of the risk factors for strokes, heart attacks, heart failure, and arterial aneurysm, and is a leading cause of chronic kidney failure. Several categories of anti-hypertensive agents have been widely used for treating the elevated BP whereas most of these agents offer greater side effects upon long term usage. Herbs play a vital role in nearly 80% of the siddha formulations. Since plant-derived medicines have a long history of use for the prevention and treatment of CVDs. Industries are now examining sources of alternative medicine that are more natural and environmentally friendly. Medicinal plants have provided a good source of a wide variety of compounds, such as phenolic compounds, nitrogen compounds, vitamins, terpenoids, and other secondary metabolites, which are rich in valuable bioactivities. Our previous investigation on phytochemical analysis of *PC* revealed the presence of active phytocomponents such as alkaloid, flavonoid, saponin, triterpenoids and polyphenols.The main aim of the present study is to evaluate the anti-hypertensive potential of the formulation *PC* in In-vivo spontaneous hypertensive ratsmodel. From the result analysis of the present investigation it was t there was significant increase in the systolic blood pressure 240.3±6.15 mm Hg of the Deoxycorticosterone acetate (DOCA) salt treated group, whereas treatment with *PC* at the dose of 100 mg/kg has shown marked decrease in SBP of about 188.4±4.24 mm Hg. Further treatment with *PC* at the dose of 200 mg/kg has shown significant decrease in SBP of about 162.2±2.42 mm Hg when compare to that of the standard drug Verapamil hydrochloride treated group with the SBP of 125.2±2.28 mm Hg. Similar type of dose dependent decrease in heart rate were observed in both treatment and standard drug treated group when compare to control group rats. Hence it was concluded from the data's of the present study that siddha drug *PC* may be considered for treating hypertensive patients with proper clinical justification.

Keywords: Hypertension, Siddha, Paruthi Chooranam,*Gossypium herbaceum*, Anti-hypertensive.

1. Introduction

Hypertension is a global public health issue and is associated with increased risk of cardiovascular disease, stroke, and kidney disease. The disease is regarded as a "silent killer" as it rarely produces symptoms in its early stages and as a result many people go undiagnosed [1]. Hypertension has a huge economic impact, and in both developed and developing countries, including those in Eastern Europe and Central Asia, the disease accounts for almost 23% of health care expenditure [2].

Hypertension is one of the most popular risk factors affecting cardiovascular disease. Blood pressure (BP) sustaining high systolic pressure ≥140 mmHg or diastolic pressure ≥90 mmHg may be defined as hypertension [3]. According to epidemiology research, the occurrence of hypertension is persistent and shows an increasing trend. The global population suffering from hypertension is predicted to reach 1.56 billion by 2025 [4].

Although common hypertension treatments, such as calcium-channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers (ARB), diuretics, and β-blockers are indeed helpful in controlling blood pressure (BP), each comes with its own limitations. Only approximately 30-40% of hypertensive patients taking an antihypertensive drug benefit from BP-lowering effects and about 70% of patients must combine two types or more different drugs to see their BP reach the standard level [5]. Drugs currently used to lower blood pressure have some adverse effects including orthostatic hypotension, hypercholesterolemia, depression and impotency [6]. So, it is necessary to search for drugs derived from nature that are more potent but have fewer negative side effects. Recently, herbal medicines are being used for the treatment of a variety of disorders including cardiovascular diseases because of their safety, efficacy, cultural acceptability and lesser side effects [7].

Gossypium spp was one of the earliest herbs that have been cultivated by mankind and it has been used for over 4,000 historic years. It was evident through several research that Gossypium possess several significant pharmacological activities such as neurotonic for memory and learning [8], Anti-epileptic [9], Anti-oxidant [10], Anti-diabetic [11], Anti-hyperlipidemic [12],wound healing [13],Anti-Microbial [14], Diuretic [15], Ulcer healing [16]. Medicinally, cotton seeds were used as pain reliever, as a nervine tonic in treating of headache and migraine; the decoctions of the seed were given in intermittent fever. The seeds and flowers in the form of poultice were applied to burns. Seeds were also used in epilepsy and as an antidote to snake poison. The juice of the leaves and the decoctions of the seed were used in dysentery [17-19].

Siddha system medicines have certain unique formulation which has a tendency to reduce hypertension through its versatile mechanism. One such formulation is *Paruthi Chooranam (PC)* which consists of *Gossypium herbaceum* as a major ingredient. *PC* is already proven for its potential anti-oxidant activity in our previous research but still now there is no proper documentary evidence with respect to the anti-hypertensive potential *PC* this prompted us to pursue the present investigation on evaluating the anti-hypertensive potential of *PC* in in-vivo model.

2. Materials and Methods

2.1. Extraction of *Paruthi chooranam*

Paruthi chooranam (*Gossypium herbaceum*) dry leaves were finely powdered and triturated in house hold mixer grinder without adding water. Then the powdered leaves were made aqueous decoction into sterile distilled water in water both 100 ^{0}C for 20 minutes. The extracts were filtered and evaporated to dryness and kept for further studies.

2.2. Animals

Spontaneous hypertensive rats (SHR male; weight: 200–250 g; age: 8 weeks) were purchased from NIN, Hyderabad. All procedures involving animals were conducted according to the animal welfare guidelines and the study protocol was approved by the IAEC of C.L. BaidMetha College of Pharmacy, Chennai, Tamil Nadu, India. The rats were housed under controlled conditions (22 ± 2°C; lighting, 07:00–19:00), and food and water were available ad libitum.

2.3. Treatment

The drug *PC* was administered orally and once daily for 4 weeks. In this study, the effect of a four weeks chronic administration of daily oral doses of 100 and 200 mg/kg body weight, The stock solution was prepared once every three days. Extract suspensions were stored at 4ºC and were allowed to reach room temperature before administration.

2.4. Measurement of systolic blood pressure

The systolic blood pressure (SBP) was recorded by non-invasive tail-cuff method at the first day and the last day of the experiment in conscious rats. Before the measurements, the rats were restrained in heated chambers at 38 ± 1 °C for 10 min. A training period of one week was established before initiation of the experiment to allow the rats to become acclimated to the procedure. Three blood pressure measurements were taken for each rat and their averages were used to obtain a mean SBP [20].

2.5. Statistical analysis

All values were represented as the mean ± SEM. For statistical analysis, a one-way analysis of variance (ANOVA) followed by Tukey post-hoc test was used (SPSS software version 16.0). P values <0.05 were considered significant.

3. Results

3.1. Effect of *PC* on systolic blood pressure and heart rate of Rats

From the result analysis of the present investigation it was t there was significant increase in the systolic blood pressure 240.3±6.15 mm Hg of the DOCA salt treated group, whereas treatment with *PC* at the dose of 100 mg/kg has shown marked decrease in SBP of about 188.4±4.24 mm Hg. Further treatment with *PC* at the dose of 200 mg/kg has shown significant decrease in SBP of about 162.2±2.42 mm Hg when compare to that of the standard drug Verapamil hydrochloride treated group with the SBP of 125.2±2.28 mm Hg. As shown in table 1 and figure 1.Similar type of dose dependent decrease in heart rate were observed in both treatment and standard drug treated group when compare to control group rats. As shown in table 2 and illustrated in figure 2.

Table 1. Effect on *PC* on Systolic Blood Pressure (SBP) on rats

S.no	Treatment group	SBP (mm Hg)
1	Control	240.3±6.15
2	*Paruthi chooranam* (*Gossypium herbaceum*) (*PC*) 100mg/kg b.w	188.4±4.24**
3	*Paruthi chooranam* (*Gossypium herbaceum*) (*PC*) 200mg/kg b.w	162.2±2.42***
4	Verapamil hydrochloride 12.5 mg/kg b.w	125.2±2.28***

Values represent mean ± SEM of 6 experiments. * P< 0.05; ** P< 0.01; *** P < 0.001, treatment versus control group

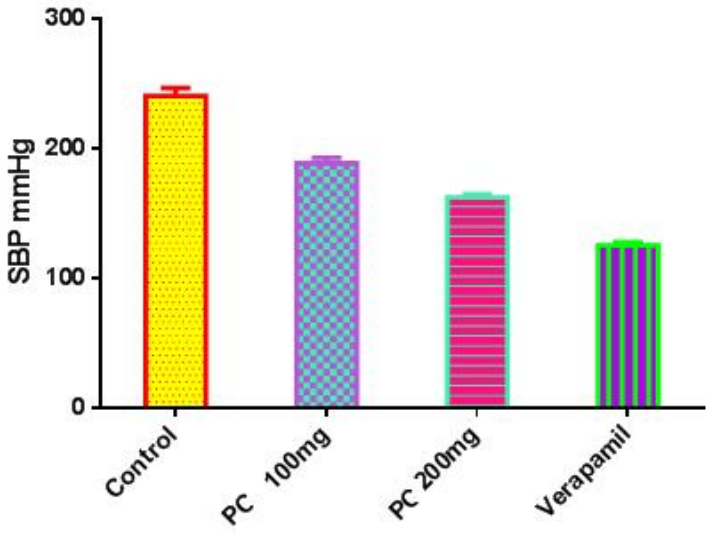

Figure 1: Effect of *PC* on systolic blood pressure

Table 2: Effect on *PC* on Hear rate of control and treated rats

S.no	Treatment group	Heart rate (beats/min)
1	Control	520.2±4.21
2	*Paruthi chooranam* (*Gossypium herbaceum*) *(PC)* 100mg/kg b.w	474.4±1.22**
3	*Paruthi chooranam (Gossypium herbaceum) (PC)* 200mg/kg b.w	420.2±1.11***
4	Verapamil hydrochloride 12.5 mg/kg b.w	330.1±3.34***

Values represent mean ± SEM of 6 experiments. * P< 0.05; ** P< 0.01; *** P < 0.001, treatment versus control group

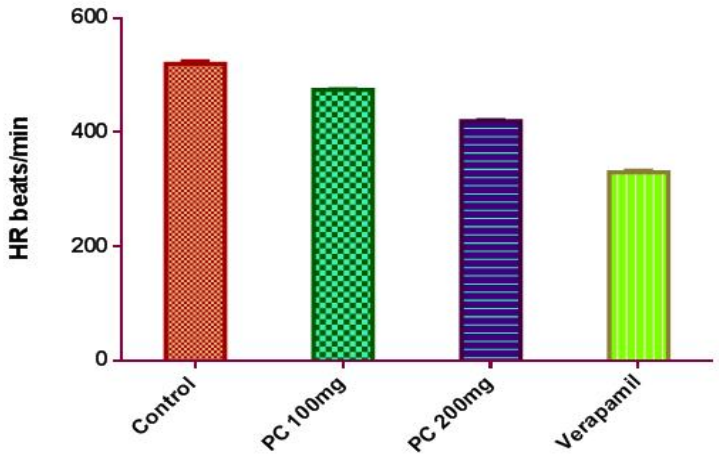

Figure 2: Effect of *PC* on Hear rate

4. Discussion

Hypertension is one of the most critical concerns for human health that nearly influences 40% of people in the world [21]. The prevalence of hypertension rises with advancing age and more than half of people aged 60 to 69 years are affected by this disease [22]. Elevated arterial pressure causes pathological changes in the vasculature and is a major risk factor for life-threatening cardiovascular diseases such as myocardial infarction, stroke, heart and renal failure [23]. Several mechanisms are known to participate in the pathogenesis of this disease including disruption of the autonomic nervous system, activation of the renin-angiotensin-aldosterone system, oxidative stress, inflammation, immune system disorder, endothelial dysfunction and imbalance between vasoconstrictor and dilator factors [24-27].

Elevated blood pressure is categorized into types: primary (essential) and secondary hypertension. Secondary hypertension, which affects 5–10% of hypertensive individuals, is due to identifiable causes, such as diabetes and renal damage, and thus has a relatively higher chance of being treated. On the other hand, essential hypertension is acquired by multiple factors such as diet, age, lifestyle, neurohumoral activity, and interactions. Since its etiology may be more difficult to ascertain or establish, essential hypertension is more difficult to manage. Interestingly, the percentage of patients with essential hypertension (90–95%) far exceed those with secondary hypertension [28].

As anti -hypertensive drugs have some side effects, many studies have been conducted to find more suitable antihypertensives from natural sources, such as herbal medicine or components derived from food. Numerous epidemiologic studies have indicated that high intake of fruits and vegetables reduce the risk of cardiovascular diseases [29].The use of herbal therapies for treatment and management of cardiovascular diseases (CVDs) is increasing. Plants contain a bounty of phytochemicals that have proven to be protective by reducing the risk of various ailments and diseases.

Approximately two-thirds of the world's plant species are widely used in medicines, and almost all of these exhibit excellent antioxidant potential [30]. The antioxidant potential of plants has received a great amount of attention for increased oxidative stress has been identified as a major causative factor of CVD. Approximately 80% of the world population uses herbal medicines due to their low toxicity and better acceptability by the human body [31-32].

From the result analysis of the present investigation it was t there was significant increase in the systolic blood pressure 240.3±6.15 mm Hg of the DOCA salt treated group, whereas treatment with *PC* at the dose of 100 mg/kg has shown marked decrease in SBP of about 188.4±4.24 mm Hg. Further treatment with *PC* at the dose of 200 mg/kg has shown significant decrease in SBP of about 162.2±2.42 mm Hg when compare to that of the standard drug Verapamil hydrochloride treated group with the SBP of 125.2±2.28 mm Hg. Similar type of dose dependent decrease in heart rate were observed in both treatment and standard drug treated group when compare to control group rats.

5. Conclusion

In conclusion from the results of the present research work it was observed that the treatment of experimental rats with *PC* causes progressive decrease in the systolic blood pressure. *PC* being a potential antioxidant suggesting that reducing oxidative stress in the circulation may also play a role as part of the mechanisms. Further this result provides evidence-based data on beneficial effect of *PC* on cardiovascular function.

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