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PHARMACOLOGICAL EVALUATION OF ANTIHYPERTENSIVE EFFICACY OF ELATHI CHOORNAM IN RENAL ARTERY LIGATION INDUCED HYPERTENSIVE RATS

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ABSTRACT

Hypertension is a leading cause of cardiovascular disease. Impairment of the vascular relaxation process occurs primarily as a result of endothelial dysfunction and oxidative stress. Due to the fact that hypertension is a silent disease, it significantly raises the risk of consequences. Through blood pressure control, the optimal therapy of hypertension should result in protection from tissue damage, most notably to the heart, arteries, brain, and kidneys. As a result, drug development efforts are centered on identifying and creating compounds that might ameliorate this pathophysiological situation by acting on targets that govern the contraction and relaxation of vascular smooth muscle. Herbal medicines contribute significantly to world healthcare, both as a traditional and complementary type of therapy, and as a source of novel conventional pharmaceuticals. Elathi Chooranam (EC) is a traditional siddha preparation which encompasses versatile herbal ingredients indicated for its wide safety and therapeutic window as listed in the literatures. The main objective of the present study is to evaluate the anti-hypertensive potential of the siddha formulation EC in renal artery ligation induced hypertensive rats. Treatment with EC at the dose of 250 and 500 mg/kg has shown dose dependent decrease in mean arterial pressure of rats belongs to group III and IV. There was significant increase in systolic blood pressure observed in rats belongs to group II. Treatment with EC at the dose of 250 and 500 mg/kg have shown marked decrease in systolic BP of rats belongs to group III and IV. Further it was also noticed that profound increase in the heart rate of rats belongs to group II when compare to group I sham operated animals, Treatment with trial drug EC have shown marginal decrease in the heart rate at both the dose level of 250 and 500 mg/kg. It was concluded from the observation of the present investigation that the trial drug Elathi Chooranam reveals significant anti-hypertensive activity in the tested animal model. Further recommendation may be ascertained for the clinical management of the hypertensive with prior clinical safety in near future.

KEY WORDS: ***Hypertension, Siddha, Elathi Chooranam, Renal artery ligation, Mean arterial pressure, Clinical safety***

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1. Introduction

Hypertension is a chronic illness that affects the whole world, and uncontrolled hypertension frequently progresses to chronic renal disease and eventually to kidney failure [1]. Renal impairment caused by hypertension is a substantial source of morbidity and death in hypertensive individuals and has developed into a major public health concern [2]. The understanding of the processes generating hypertensive renal damage, as well as the discovery of innovative therapeutics to slow its progression, are critical [3].

Growing number of antihypertensive medicines available, practitioners must become informed with the possible adverse effects of these medications. Several things must be kept in mind in order to limit the prevalence of drug-induced adverse effects: (a) The most serious adverse effect of diuretics is hypokalemia, which can result in cardiac arrhythmias and is potentially dangerous in patients taking digitalis, those with chronic arrhythmias, and those with acute myocardial infarction; (b) -blockers (-B) can cause bronchoconstriction, peripheral vasoconstriction, glycogenolysis, and insulin secretion inhibition, and can occasionally result in severe bradycardia [4].

Phytocomponents commonly known as secondary metabolites are a diverse set of naturally occurring substances that have been utilised to treat a wide range of ailments [5]. The biochemistry of medications based on traditional natural ingredients has made a significant contribution to public healthcare and has accelerated the development of cheap medicines throughout the world [6]. Secondary metabolites have been intensively studied since the 1850s [7].

Siddha is an old traditional practise that arose from the southern zone of India. The ultimate philosophy of siddha has been defined by the siddhar, also known as ancient physicians, who methodically categorise medications based on their nature, necessity, and other distinguishing traits. Disease may arise as a result of an imbalance of essential humours such as vatham, pitham, and kabam, according to siddha terminology. The reversal of balance would significantly treat the sickness and benefit humanity. The majority of siddha preparations operate on this basis, making the possibility of illness recurrence largely speculative. The main objective of the present study is to evaluate the anti-hypertensive potential of the siddha formulation Elathi Chooranam in renal artery ligation induced hypertensive rats.

2. Materials and Methods

2.1. Animals

Healthy adult male wistar albino rats weighing between 260-280 g were used for the study. The animals were housed in poly propylene cages and were kept in well ventilated with 100% fresh air by air handling unit. A 12 light / dark cycle were maintained .Room temperature was maintained between 22 ¬+ 2o C and relative humidity 50–65%. They were provided with food (Sai feeds, Bangalore, India) and water ad libitum. All the animals were acclimatized to the laboratory for 7 days prior to the start of the study. The experimental protocol was approved by The Institutional Animal Ethics Committee of Sathyabama Institute of science and technology, Chennai, Tamil Nadu, India. SU/CLATR/IAEC/XVII/178/2021

2.2. Experimental Methodology

The animals were grouped into four groups of 6 animals each. Group I (Sham Operated group) – Surgically exposed renal artery without ligation. Group II – Rats underwent surgical renal artery ligation served as hypertension control. Group III – Rats underwent surgical renal artery ligation prior treatment with low dose of EC 250 mg/kg,(p.o). Group IV – Rats underwent surgical renal artery ligation prior treated with high dose of EC 500 mg/kg (p.o).

2.3. Induction of hypertension [8,9]

The hypertension was induced in experimental animals by ligation of left renal artery. Rats were anaesthetised by 30–40 mg/kg pentobarbital sodium. A 3 cm retroperitoneal flank incision was done. The left kidney was exposed and the renal artery were carefully separated free of the renal vein. The renal artery was then ligated by sterile surgical silk thread.

2.4. Study Protocol [10]

All the experimental animal belongs to group III and IV were treated with 250 and 500 mg/kg of EC orally for the period of four weeks followed by this on the 29th day of experiment the renal artery was occluded for 6 h (ischemia) following the surgery; the animals than anesthetized by intraperitoneal injection of 30–40 mg/kg pentobarbital sodium. After 6 h the renal arterial ligation was removed (reperfusion). This leads

to a rise in blood pressure as a consequence of elevated plasma renin level. Within 15 min a stable hypertension is achieved. Kidney being placed back in its original position. All rats were observed for 4 h following surgery, then individually housed for 24 h and allowed access to standard rat chow and water ad libitum. The test substance EC was then administered orally at the doses of 250 mg/kg and 500 mg/kg to the animal belongs to treatment group. Hemodynamic change in the Blood pressure were monitored using non-invasive blood pressure monitoring instrument with Powerlab data acquisition system. After measurement of blood pressure, the left kidney was removed and stores at 10% formalin saline for histopathological analysis.

2.5. Sample Collection [11]

At the end of the study, before sacrifice, the animals were fasted for overnight with free access to water. Animals were sacrificed with excess anesthesia. Blood samples were collected from retro orbital and cardiac puncture and stored in clot activator coated test tubes for serum biochemical analysis. Kidney sample were harvested and carefully investigated for gross lesions.

2.6. Histopathology [12]

A portion of pancreatic tissue was dissected out and fixed in 10% buffered neutral formal saline and processed. After fixation, tissues were embedded in paraffin. Fixed tissues were cut at 10 µm and stained with hematoxylin and eosin. The sections were examined under light microscope for histological changes.

2.7. Statistical Method

The statistical analysis was carried by one-way analysis of variance ANOVA. Results are expressed as ±SEM. The data were statistically analyzed by ONE WAY ANOVA followed by Dunnett's multiple comparison test. Probability P values < 0.05 were considered as significant.

3. Results

3.1. Effect of EC on Blood pressure and Heart rate of renal Artery ligation induced hypertensive rats

Elevated mean arterial pressure in ligated rats belongs to group II signifies the induction of hypertension in the experimental animals. Treatment with EC at the dose of 250 and 500 mg/kg has shown dose dependent decrease in mean arterial pressure of rats belongs to group III and IV. There was significant increase in systolic blood pressure observed in rats belongs to group II. Treatment with EC at the dose of 250 and 500 mg/kg have shown marked decrease in systolic BP of rats belongs to group III and IV. The data's obtained from the present investigation indicates the anti-hypertensive potential of the trial drug in the treated rats. Further it was also noticed that profound increase in the heart rate of rats belongs to group II when compare to group I sham operated animals, Treatment with trial drug EC have shown marginal decrease in the heart rate at both the dose level of 250 and 500 mg/kg. As show in Table 1.

Table 1: Effect of EC on Blood pressure and Heart rate of renal Artery ligation induced hypertensive rats

Group	Systolic BP (mm Hg)	Mean arterial pressure in (mm Hg)	Heart Rate (Beats /Min)
Group I – Sham operated	115.7 ± 2.94	121.5 ± 2.094	320.7 ± 6.438
Group II – Renal Artery ligation Hypertensive	201.7 ± 3.947**	183.8 ± 4.293**	392 ± 6.836**
Group III – Renal Artery ligation + 250 mg/kg of EC.,p.o	177 ± 0.7491*	155 ± 0.8333**	376.7 ± 12.2*
Group IV – Renal Artery ligation + 500 mg/kg of EC.,p.o	156.8 ± 4.722*	135.5 ± 2.335*	348.8 ± 8.203**

Values represent mean ± SEM of 6 experimental animals. * P< 0.05; ** P< 0.01; *** P < 0.001.

3.2. Effect of EC on Histopathological analysis of Rat Kidney

Microscopic observation of samples belongs to group I rats reveals normal appearance of proximal and distal convolutes tubules with no evidence of atrophy, further no evidence of lymphocytic infiltrate and inflammation were observed in group I rats. Section shown shrunken glomeruli (G) with widen capsular Bowman's space. Vascular, degenerative with significant inflammatory changes were been observed in specimen belongs to group II. In group III some renal tubules are hypertrophic, others are dilated. The dilated tubules are lined by flattened epithelium and their lumen, Widen capsular morphology observed in comparison with group II. Prominent histology of glomeruli with mild vascular congestion were observed in the sample belongs to group IV. As show in Figure 1.

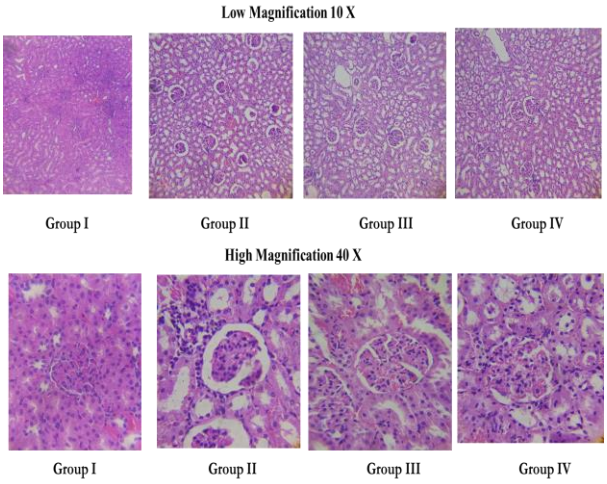

Figure 1: Effect of EC on Histopathological analysis of Rat Kidney

4. Discussion

Cardiovascular dysfunction is associated with an increased risk of developing heart failure, stroke, and hypertension. Fortunately, hypertension is the most preventable risk factor for cardiovascular disease [13,14]. Hypertension is related with a variety of disorders, including metabolic, renal, and endothelial dysfunctions [15]; it is also responsible for sympathetic nerve activation, which can result in a variety of difficulties when it is excessive [16]. Endothelial cells play a critical role in blood circulation, the production of vasoactive factors, and vascular activation [17]. Nitric oxide is generated in endothelial cells by nitric oxide synthase (NOS) and is a significant endothelium-derived relaxing factor. Reduced NO activity has a detrimental effect on endothelial function and also has an effect on the cardiovascular system [18,19].

Renal artery ligation model employed in this investigation is a well-established model of renovascular hypertension that has been used in several studies [20]. The activation of the renin-angiotensin-aldosterone system (RAAS) is required for the onset and progression of hypertensive kidney injury. Renal arteryligation model exhibits such hypertension as a result of RAAS overactivation, resulting in renal-heart injury [21]. By raising the angiotensin (Ang) II and aldosterone levels, the RAAS imbalance may result in renovascular hypertension and a variety of cardiovascular diseases, as well as renal failure [22]. RAAS plays a critical role in the regulation of renal blood flow, salt reabsorption in the tubules, and Ang II activation. After clipping the left renal artery, dysregulation of the RAAS results in an abrupt spike in Ang II levels. Such an aberrant rise in Ang II concentration leads in excessive sympathetic nerve activity, which acts as a vasoconstrictor [23]. Additionally, the 2K1C model is strongly related with increased NO generation and oxidative stress, which is shown by the presence of fibrosis and a decline in kidney structure and function [24,25].

In the present study elevated mean arterial pressure in ligated rats belongs to group II signifies the induction of hypertension in the experimental animals. Treatment with EC at the dose of 250 and 500 mg/kg has shown dose dependent decrease in mean arterial pressure of rats belongs to group III and IV. There was significant increase in systolic blood pressure observed in rats belongs to group II. Treatment with EC at the dose of 250 and 500 mg/kg have shown marked decrease in systolic BP of rats belongs to group III and IV. The data's obtained from the present investigation indicates the anti-hypertensive potential of the trial drug in the treated rats. Further it was also noticed that profound increase in the heart rate of rats belongs to group II when compare to group I sham operated animals, Treatment with trial drug EC have shown marginal decrease in the heart rate at both the dose level of 250 and 500 mg/kg.

Renal hypertrophy, which is a necessary component of hypertensive renal injury, is one of the pathological alterations that occur. Microscopic observation of samples belongs to group I rats reveals normal appearance of proximal and distal convolutes tubules with no evidence of atrophy, further no evidence of lymphocytic infiltrate and inflammation were observed in group I rats. Section shown shrunken glomeruli (G) with widen capsular Bowman's space. Vascular, degenerative with significant inflammatory changes were been observed in specimen belongs to group II. In group III some renal tubules are hypertrophic, others are dilated. The dilated tubules are lined by flattened epithelium and their lumen, Widen capsular morphology observed in comparison with group II. Prominent histology of glomeruli with mild vascular congestion were observed in the sample belongs to group IV.

5.Conclusion

Hypertension is a highly widespread cardiovascular risk factor for cardiovascular disease, affecting a large number of people worldwide. Hypertension reduces people's life expectancy owing to heart disease, stroke, eye impairment, and renal damage. Exploration of drugs from complementary source will be highly appreciated due to its efficacy and safety upon long term usage. It was concluded from the observation of the present investigation that the trial drug Elathi Chooranam reveals significant anti-hypertensive activity in the tested animal model. Further recommendation may be ascertained for the clinical management of the hypertensive with prior clinical safety in near future.

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