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Research Article

# Antihypertensive effect of Ethanolic Extract of Indian *Carica papaya l. Root bark* (caricaceae) in Renal Artery Occluded Hypertensive Rats.

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**ABSTRACT:** Ethanolic extract of *Carica papaya*L. root bark powder (Family: Caricaceae) was evaluated for its antihypertensive activity in renal artery occluded hypertensive rats. Male Wistar rats (180-200g) were pretreated with ethanolic extract of *Carica papaya*L. root barkfor 6 weeks. Hypertension was induced in animals by clamping the renal artery with renal bulldog clamp for 4 h. Ischemia of the kidneys causes elevation of blood pressure by activation of the renin-angiotensin system. Elevated blood pressure of the animals was significantly (*P<0.001*) decreased by the ethanolic extract of *Caricapapaya*L. Root bark at the dose levels of 25 , 50 and 100mg/kg, *i.v* .Also Captopril, angiotensin converting enzyme inhibitor (ACE-I) at the dose of 1 mg/kg,*i.v.* resulted significant (*P<0.001*) reduction in the elevated blood pressure, in different time intervals. Among all the doses of extract, 100mg/kg was comparable and equipotent as that of the Captopril. The antihypertensive activity of ethanolic extract of *Carica papaya*L. root bark may be due to the action on rennin – angiotensin system.

**Key words**: Caricapapaya, Antihypertensive activity, Rennin – Angiotensin system, Captopril

## INTRODUCTION

Cardiovascular diseases account for 12 million deaths, annually worldwide and are known to be number one group of 'killer disease'. Hypertension is one of the leading causes of disability, mortality, and morbality along the population. It is the most common chronic illness among the world faces.[1,2] Hypertension is the most common cardiovascular diseases and constituents a major factor for several cardiovascular pathologies including atherosclerosis, coronary artery disease, myocardium infraction, heart failure, renal insufficiency, stroke and dissecting aneurysm of aorta.[3] An elevated arterial pressure is an important public health issue in developed countries. Although it is common, asymptomatic and readily detectable but it can often lead to lethal complication, if left untreated. Because of high incidence and morbidity, various drugs and regimes have been advocated for the control of hypertension. Many new drugs have been introduced which may demonstrate better efficacy but posses side effects. Recently attention has been focused towards herbal and mineral preparations which are traditionally used as potential therapeutic agents in the prevention and management of cardiovascular diseases[4].

*Carica papaya* (Family-Caricaceae), in English commonly known as pawpaw .It is a small herbaceous, fast growing short lived laticiferous tree. Papaya is now grown in all tropical countries and many sub – tropical regions of the world. Root extract of plant *Caricapapaya* gave similar effect of excretion of urinary electrolytes to that of the standard drugs . The determination of the osmolality of urine and electrolyte perunit time suggests that the extracts of *C. Papaya* exhibit such effect due to its high salt contents[5]. Various pharmacological action (s) and medicinal uses of different parts of papaya are well reported in the ancient literature, among all parts root is used for abortifacient, diuretic, checking irregular bleeding from the uterus, piles, anti-fungal activity.[6,7,8] Papaya leaves decoction can be used as an anti-hypertentive agent. A study on villagers of Agboville Department located at 80 km of Abidjan (West Africa), showed the hypotentive activity of Papaya plant when administered orally.[9] However, crude extracts of different parts of papaya have been used as traditional medicine for the treatment of various diseases. Though there were scanty reports available on its antihypertensive activity, its mechanism was still unknown. Hence, present work was undertaken to investigate its mechanism of action of antihypertensive effect of ethanolic extract of *Carica papaya*L. in renal artery occluded hypertensive rats.

## MATERIALS AND METHOD

Plant materials and preparation of test sample: The mature root bark of *Carica papaya*L. was collected from the Himachal Pradesh Distt. Mandi, India in October month Herbarium specimen was deposited in Botany Department of Abhilashi College of Life Sciences, where it was identified. Root bark was

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Table No.1: Effect of Ethanolic extract of *Carica papaya*L. root bark (EECP) on renal artery - occluded hypertensive rats.

| Groups | Mean Arterial Blood Pressure Groups (MABP) in mmHg at different time interval | | | | | |
|---|---|---|---|---|---|---|
| | Treatment (mg/kg) | MABP after removing clip | 5 min | 15 min | 30 min | 60 min |
| Normal Control | Distilled water, *p.o.* | -------- | 84.56±4.31 | 86.78±9.01 | 87.92±6.12 | 88.70±2.22 |
| Positive control | Distilled water, *p.o.* | 128.56±5.23 | 118.20±5.65 | 115.00±6.02 | 108.34±4.02 | 106.02±5.62 |
| EECP | 25, *i.v.* | 122.79±2.24 | 81.43±6.25** | 76.02±5.25*** | 70.01±3.33*** | 69.00±5.21** |
| EECP | 50, *i.v.* | 113.83±4.68 | 72.43±4.65*** | 70.24±1.35*** | 64.89±2.09*** | 60.01±6.25*** |
| EECP | 100, *i.v.* | 112.53±2.28 | 66.54±2.24*** | 63.02±1.64*** | 55.03±1.25*** | 40.88±1.09*** |
| Captopril | 1, *i.v.* | 123.06±5.45 | 64.39±4.39*** | 46.08±3.09*** | 39.09±2.02*** | 24.95±1.02*** |

Values in the results are expressed as mean ± SEM, (n=6), ***$p$<0.001 significantly different in comparison with positive control

washed with tap water and then shade dried at room temperature. The dried root bark was then grinded in mixer grinder to make powder, which was then sieved to get fine powder. The grinded and sieved product around 500gm of coarsely powdered root bark of the plant was packed in a soxhlet apparatus and extracted with the solvent ethanol. The extract so obtained were concentrated under vacuum, using rotary vacuum evaporator and dried in dessicator until use. Product was utilized for *in vivo* biological studies.

Experimental animals: Male Wistarrats (180–200g) and Swiss albino mice (20-22g) of either sex were obtained from the animal house of Nandha College of Pharmacy, Erode, Tamilnadu. They were housed in polypropylene cages with paddy husk bedding in a controlled room temperature 22±1°C and relative humidity of 60–70%. They were kept under standard conditions of 12/12 h light and dark cycle. The animals were maintained with standard commercial pellet diet, rat chaw (M/S Hindustan Lever Ltd., Mumbai) and water*ad libitum* . The animals were acclimatized to laboratory condition for seven days before commencement of experiment. All studies were carried out using 6 rats in each group .Ethical clearance was obtained from Institutional Animal Ethical Committee (IAEC). All the experimental procedures and protocols used in this study were reviewed by the Institutional Animal Ethical Committee (688/2/C-CPCSEA) Proposal No.: NCP / IAEC / PG/2010-19 and were in accordance with the guidelines of the IAEC.

Chemicals and instrument: Urethane was purchased from Hi media Pvt. Ltd. India. Captopril (ACETEN, WOCKHARDT), 12.5 mg tablet was procured from local market. All the chemicals used for the study were of analytical grade. Eight – channel recorder powerlab (AD Instruments) system was used for the measurement of blood pressure.

Phytochemical evaluation: Ethanolic extract of *Carica papaya*L. root bark was studied for its phytoconstituents such as alkaloids, steroid and/or triterpenoids and their glycosides, tannins, flavonoids and their glycosides and carbohydrates using different phytochemical tests.[10]

Acute oral toxicity study: Acute oral toxicity study of Ethanolic extract of *Carica papaya*L. root bark was carried out in Swiss albino mice of either sex (20-22g) according to OECD guidelines no 423. Extract at different doses up to 2000 mg/kg, *p.o.* was administered and animals were observed for behavioural changes, toxicity and mortality up to 48 hours.[11,12]

Antihypertensive activity: Male wistar rats were divided into the 6 groups each group had six animals. Animals in normal control and positive control groups received distilled water. Ethanolic extract of *Carica papaya*L. root bark was administered orally at the dose levels of 250, 500 and 1000mg/kg to the treatment groups for six week. At the end day of treatment, animals were anaesthetized 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 eight channel recorder powerlab. After stabilized blood pressure, the renal bulldog clip was removed. Then $1/10^{th}$ of the administered dose of the Ethanolic extract of *Carica papaya*L. root bark , i.e. 25, 50, and 100 mg/kg was given respectively through jugular vein and mean arterial blood pressure (MABP) was measured at different time intervals (5,15,30,60 min). MABP of normal control groups were recorded without clamping the renal artery. Captopril 1 mg/kg, *i.v.* was used as a standard. Changes in blood pressure of treated groups were compared with positive control[13,14].

**STATISTICAL ANALYSIS**

The results were expressed as the mean ± SEM for each group. Statistical differences were evaluated using a one way analysis of variance (ANOVA)

**Figure No.1:**Effect of Ethanolic extract of *Carica papaya*L. root bark (EECP) and standard drugon renal artery-occluded hypertensive rats.

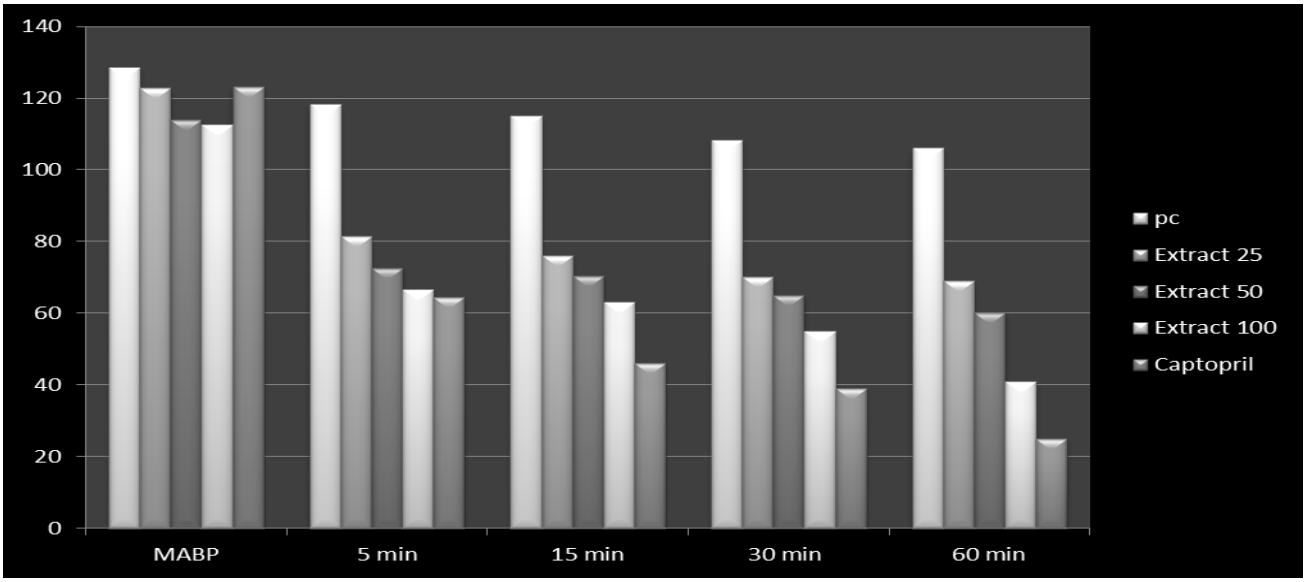
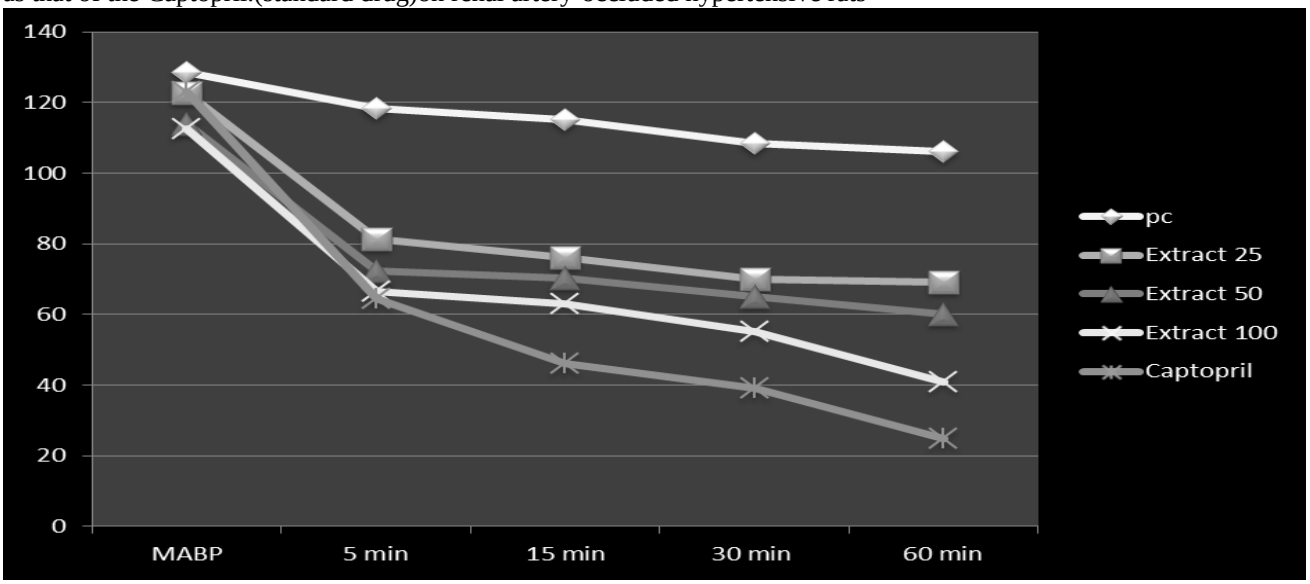



**Figure No.2:**Effect of Ethanolic extract of *Carica papaya* L. root bark (EECP)100mg/kg was comparable and equipotent as that of the Captopril.(standard drug)on renal artery-occluded hypertensive rats




followed by Dunnett´s test. Results were considered to be statistically significant at $p<0.05$.

**RESULTS**

The phytochemical evaluation of Ethanolic extract of *Carica papaya*L. root bark revealed the presence of alkaloids, glycosides, steroids and flavonoids. Animals treated with Ethanolic extract of *Carica papaya*L. root bark didn't showed any behavioural changes, toxic reaction or mortality. The extract was found to be safe at the dose of 2000 mg/kg. Removal of renal bulldog clip in the positive controlgroup resulted in significant ($p<0.05$) increase in MABP (Table 1). Pretreatment of animals with Ethanolic extract of *Carica papaya*L. root bark ,25, 50 and 100 mg/kg *i.v* .showed significant decrease ($p<0.001$) in the MABP at different time intervals (Table1). Captopril (1mg/kg *i.v.*) produced significant ($p<0.001$) reduction in MABP. The hypotensive effect was found maximum after 60 min, but among all captopril showed marked decrease in MABP.

**DISCUSSION**

Present study revealed the significant antihypertensive activity of Ethanolic extract of *Carica papaya*L. root bark in renal artery occluded hypertensive rats. The occlusion of renal artery upto 4 hour, leads to cause kidney ischemia. Ischemia of the kidneys causes elevation of blood pressure by activation of the rennin - angiotensin system. The procedure can be

used for acute and chronic hypertension. Acute renal hypertension can be induced in rats, by clamping the left renal artery for 4 h. After reopening of the vessel, accumulated rennin is released into circulation[5]. Renin acts on angiotensinogen (rennin substrate), a α2- globulin to release the decapeptide angiotensin-I. This decapeptide is cleaved by angiotensin converting enzyme (ACE) to yield the active angiotensin-II (octapeptide) which is a potent vasoconstrictor leading to hypertension. Angiotensin-II undergoes hydrolysis by an aminopeptidase to yield the heptapeptide angiotensin-III which is also active. Further cleavage yields to peptides with little activity[15]. The protease rennin catalyzes the first and rate - limiting step in the formation of angiotensin-II leading to acute hypertension. The test is used to evaluate antihypertensive activities of drugs[13]. The results showed that, intravenous injection of Ethanolic extract of *Carica papaya*L. root bark significantly ($p$<0.001) decreased the elevated blood pressure in dose dependent manner. Captopril, ACE-I at the dose of 1 mg/kg, *i.v.* showed the significant ($p$<0.001) decrease in the elevated blood pressure. The extract differed from captopril in respect of the potency. After a sharp fall in MABP at 5 minute a stable baseline was observed where as progressive decrease in MABP was shown by captopril. The drastic fall in MABP after 1 hour may precipitate reflex tachycardia and compensatory increase in sympathetic tone. The extract appears to be free from such hypertensive effect. The antihypertensive activity of Ethanolic extract of *Carica papaya*L. root bark may be resulted through the action on rennin – angiotensin system.

## CONCLUSION

Thus it can be concluded that, ethanolic extract of *Carica papaya L.* root bark has promising antihypertensive effect in renal artery occluded hypertensive rats model and the results showed that, intravenous injection of Ethanolic extract of *Carica papaya*L. root bark significantly ($p$<0.001) decreased the elevated blood pressure in dose dependent manner, which was mediated by the rennin - angiotensin system. Quite a significant amount of work has been done on the anti - hypertensive and diuretic properties of *Carica papaya* L. root bark extract and hence extensive investigation on its biological activities, proper standardization and clinical trials is needed to exploit their therapeutic utility to combat cardiovascular diseases

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