RESEARCH PAPER

In Vivo Evaluation of the Antihypertensive Effect of Euryale ferox Salisb. Seed Extract in L-NAME-Induced Hypertensive Rats

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ABSTRACT

Hypertension remains a major global health burden, associated with cardiovascular morbidity and mortality. Despite effective synthetic therapies, limitations such as side effects and poor adherence highlight the need for alternative remedies. Euryale ferox Salisb. (fox nut/makhana) is traditionally used in Asian medicine as a cardiotonic; however, its antihypertensive effects have not been systematically validated. This study aimed to evaluate the in vivo antihypertensive potential of ethanolic seed extract of E. ferox in L-NAME-induced hypertensive rats. Seeds were collected, authenticated, and extracted using a Soxhlet apparatus. Hypertension was induced by oral administration of L-NAME (40 mg/kg/day, 4 weeks). Rats were divided into six groups: normal control, hypertensive control, standard (Captopril 10 mg/kg), and three test groups receiving E. ferox extract (100, 200, and 400 mg/kg). Hemodynamic parameters, biochemical markers (NO, renin, angiotensin II, lipid profile, renal markers, oxidative stress enzymes), and histopathology were evaluated. Extract-treated rats showed significant dose-dependent reductions in SBP and DBP ($p < 0.05$), with the 400 mg/kg dose showing effects comparable to captopril. Antioxidant markers (SOD, catalase, GSH) increased while MDA decreased, and renal/lipid profiles normalised significantly. Histological analysis revealed restoration of kidney, heart, and aortic architecture. Findings suggest that E. ferox exerts antihypertensive activity through nitric oxide restoration, renin–angiotensin system modulation, antioxidant action, and end-organ protection. These results support fox nut as a potential nutraceutical or adjunct therapy for hypertension.

Keywords: Euryale ferox, Hypertension, L-NAME model, Renin-angiotensin system, Oxidative stress, Phytotherapy.

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Introduction

Hypertension, defined as persistent systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, affects over 1.28 billion people globally and accounts for nearly 10 million annual deaths annually, primarily due to cardiovascular diseases (World Health Organization, 2023). In India, its prevalence ranges from 25–30% in urban and 10–15% in rural populations (Gupta et al., 2019). The pathophysiology of hypertension involves activation of the renin–angiotensin–aldosterone system (RAAS), sympathetic nervous system overactivity, endothelial dysfunction, oxidative stress, and renal sodium

retention (Carretero & Oparil, 2000; Montezano & Touyz, 2012).

Although conventional antihypertensive drugs such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, and diuretics are effective, their long-term use is often associated with adverse effects, including cough, bradycardia, electrolyte imbalance, and poor patient adherence (Burnier, 2017). These limitations necessitate the exploration of safer and more tolerable phytotherapeutic alternatives.

Euryale ferox Salisb. (Nymphaeaceae), commonly known as fox nut or makhana, is widely consumed as a functional food and has been traditionally used in Ayurveda and Chinese medicine (Li et al., 2020). Its seeds are rich in bioactive constituents such as flavonoids, sterols, polysaccharides, and essential minerals (Singh & Chauhan, 2014). Previous pharmacological studies have demonstrated its antioxidant, cardioprotective, nephroprotective, and hypolipidemic properties (Zhou et al., 2021; Zhang et al., 2018). However, systematic in vivo investigations validating its antihypertensive potential remain limited. Therefore, the present study aimed to investigate the antihypertensive potential of the ethanolic seed extract of *Euryale ferox* using an L-NAME-induced hypertensive rat model and to evaluate its effects on hemodynamic, biochemical, oxidative stress, and histopathological parameters.

Materials and Methods

Plant Material

Seeds of *Euryale ferox* were collected from the Morena region, Madhya Pradesh, India, during the summer season (April–May 2025). The plant was authenticated by Dr. Vinay Jain, Department of Pharmacognosy, Shriram College of Pharmacy, and a sample was deposited in the departmental herbarium for future reference.

Chemicals and Reagents

Table 1. List of Chemicals and Reagents Used

Chemical/Reagent	Supplier	Grade/Specification	Purpose
Ethanol	Merck, India	AR grade	Extraction
Captopril	Sigma Aldrich, USA	Standard drug	Positive control
L-NAME	Cayman Chemical, USA	≥98% purity	Hypertension induction
NO assay kit	Cayman Chemical, USA	ELISA kit	Nitric oxide estimation
Renin ELISA kit	Elabscience, China	ELISA	Hormone analysis
Lipid profile kit	Erba Diagnostics, India	Clinical kit	Biochemical tests

Plant material and extraction

Seeds of *E. ferox* were collected from Morena, Madhya Pradesh (India), authenticated by a pharmacognosist, and extracted using Soxhlet with ethanol. The extract yield was 8.7% w/w. Preliminary phytochemical screening revealed flavonoids, alkaloids, saponins, tannins, and sterols (Trease & Evans, 2009).

Experimental animals

Wistar albino rats (150–200 g) were housed under standard conditions. The protocol was IAEC-approved (Approval No: IAEC/PHARM/2025/07) and followed CPCSEA guidelines (2018).

Preliminary Phytochemical Screening

Standard phytochemical tests were conducted on the ethanolic extract (Trease & Evans, 2009).

Table 2 Phytochemical Constituents of *E. ferox* Ethanolic Extract

Phytochemical Group	Test Performed	Result
Alkaloids	Dragendorff's test	+
Flavonoids	Shinoda test	+
Saponins	Froth test	+
Tannins	Ferric chloride	+
Glycosides	Keller–Killiani	+
Sterols	Salkowski's test	+
Proteins	Biuret test	–

(+ = Present, – = Absent)

Experimental Animals

- **Species:** Wistar albino rats (150–200 g, either sex).
- **Source:** Animal House Facility, [Institute Name].
- **Housing:** Polypropylene cages, controlled environment (25 ± 2°C, 55 ± 5% humidity), 12:12 h light/dark cycle.
- **Diet:** Standard pellet diet (Lipton India Ltd.), water ad libitum.
- **Acclimatization:** 7 days before experiments.

Ethical Approval

All experiments were conducted in accordance with CPCSEA guidelines (2018). The protocol was approved by the Institutional Animal Ethics Committee (IAEC) (Approval No: IAEC/PHARM/2025/07).[39]

Induction of Hypertension

Hypertension was induced using **L-NAME** (Nω-nitro-L-arginine methyl ester, 40 mg/kg/day orally for 4 weeks), a nitric oxide synthase inhibitor that mimics human essential hypertension by inducing endothelial dysfunction.(Baylis, 1992; Sharma et al., 2022).

Experimental Design

Animals were randomly divided into six groups (n = 6 each):

Table 3. Experimental Groups and Treatment Protocol

Group	Treatment	Dose/Route	Duration
NC	Normal control	Distilled water	4 weeks
HC	Hypertensive control	L-NAME (40 mg/kg, p.o.)	4 weeks
STD	Standard	L-NAME + Captopril (10 mg/kg, p.o.)	4 weeks
T1	Test I	L-NAME + *E. ferox* extract (100 mg/kg, p.o.)	4 weeks
T2	Test II	L-NAME + *E. ferox* extract (200 mg/kg, p.o.)	4 weeks
T3	Test III	L-NAME + *E. ferox* extract (400 mg/kg, p.o.)	4 weeks

Parameters Evaluated

Hemodynamic parameters

• Systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate were measured weekly using non-invasive tail-cuff plethysmography (Kent Scientific, USA).

Biochemical Parameters

• Serum nitric oxide (NO)

• Plasma renin and angiotensin II (ELISA)

• Serum lipid profile: total cholesterol (TC), triglycerides (TG), LDL, HDL

• Oxidative stress markers: MDA, SOD, catalase, GSH

Renal Function Tests

• Serum creatinine, urea, and uric acid

Histopathological Examination

- Heart, kidney, and aorta tissues were collected, fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned at 5 µm, stained with hematoxylin and eosin, and examined under a light microscope (Olympus BX51).

Statistical Analysis

Data were expressed as mean ± SEM (n = 6). Statistical analysis was performed using one-way ANOVA followed by Tukey's multiple comparison test using GraphPad Prism 9. Differences were considered significant at $p < 0.05$.

Flowchart of the Experimental Design

Collection of Seeds → Extraction → Phytochemical Screening → Animal Grouping → Hypertension Induction (L-NAME) →Treatment (Extract/Standard) → BP Monitoring →

Biochemical Tests → Histopathology → Statistical Analysis

Table 4. Experimental Timeline

Week	Procedure
0	Animal acclimatization + baseline BP measurement
1–4	Induction of hypertension (L-NAME) + treatments
2–4	Weekly BP and heart rate measurement
4	Biochemical assays + tissue collection for histology

Results

Effect on Systolic and Diastolic Blood Pressure

Table 5 Effect of *Euryale ferox* seed extract on blood pressure (mmHg).

Group	SBP (Week 0)	SBP (Week 2)	SBP (Week 4)	DBP (Week 0)	DBP (Week 2)	DBP (Week 4)

Normal	120 ± 2.1	122 ± 2.0	123 ± 1.9	78 ± 1.5	79 ± 1.6	80 ± 1.7
Hypertensive	120 ± 2.3	160 ± 3.4	175 ± 3.1	78 ± 1.8	100 ± 2.5	110 ± 2.8
Captopril	120 ± 2.0	130 ± 2.5	122 ± 2.1	78 ± 1.4	85 ± 2.0	80 ± 1.9
Extract 100 mg/kg	120 ± 2.2	150 ± 3.2	145 ± 3.0	79 ± 1.7	95 ± 2.6	92 ± 2.5
Extract 200 mg/kg	120 ± 2.1	138 ± 2.9	128 ± 2.4	78 ± 1.5	90 ± 2.2	85 ± 2.0
Extract 400 mg/kg	120 ± 2.0	135 ± 2.5	124 ± 2.1	78 ± 1.6	87 ± 2.1	82 ± 1.9

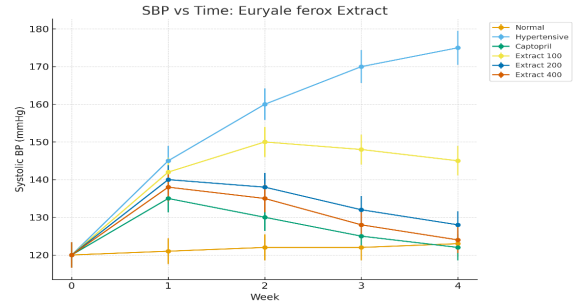


Fig.1: Effect of *Euryale ferox* seed extract on systolic blood pressure in L-NAME-induced hypertensive rats. Data expressed as mean ± SEM (n = 6). *$p < 0.05$ vs hypertensive control.*

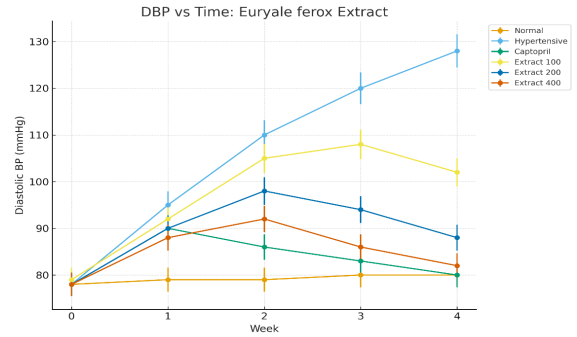


Fig.2: Effect of *Euryale ferox* seed extract on diastolic blood pressure in L-NAME-induced hypertensive rats. Data expressed as mean ± SEM (n = 6). *$p < 0.05$ vs hypertensive control.*

Effect on Heart Rate

Table 6. Effect on heart rate (beats/min).

Group	Week 0	Week 2	Week 4
Normal	350 ± 12	352 ± 11	354 ± 10
Hypertensive	352 ± 10	410 ± 15	430 ± 18
Captopril	351 ± 12	360 ± 11	355 ± 12
Extract 100 mg/kg	352 ± 11	398 ± 14	385 ± 12
Extract 200 mg/kg	351 ± 11	375 ± 12	362 ± 10
Extract 400 mg/kg	352 ± 12	370 ± 11	358 ± 11

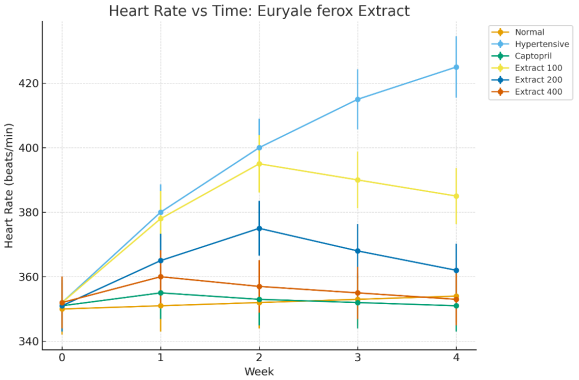


Fig.3: Effect of *Euryale ferox* seed extract on heart rate (mean ± SEM, n = 6).

Effect on Biochemical Parameters

Table 7. Effect on NO, Renin, and Angiotensin II.

Group	NO (µmol/L)	Renin (ng/mL/hr)	Ang II (pg/mL)
Normal	38 ± 2.1	5 ± 0.6	45 ± 3.2
Hypertensive	15 ± 1.5	15 ± 1.8	120 ± 5.0
Captopril	35 ± 1.9	6 ± 0.8	50 ± 3.5
Extract 100 mg/kg	22 ± 1.7	13 ± 1.5	110 ± 4.6
Extract 200 mg/kg	30 ± 2.0	9 ± 1.1	70 ± 3.9
Extract 400 mg/kg	34 ± 1.8	7 ± 0.9	55 ± 3.3

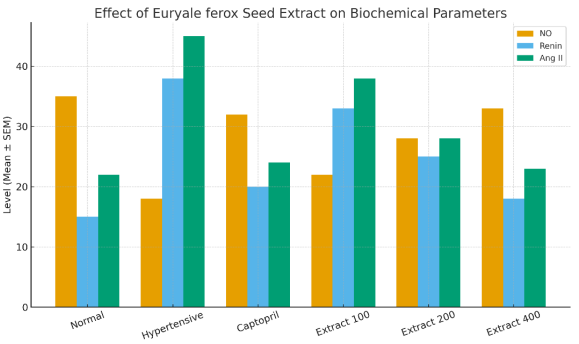


Fig. 4.: Effect of *Euryale ferox* seed extract on biochemical parameters (Nitric Oxide, Renin, and Angiotensin II) in hypertensive rats. Values are expressed as mean ± SEM (n = 6).

Effect on Oxidative Stress Markers

Table 8. Oxidative stress markers.

Group	MDA (nmol/mg)	SOD (U/mg)	Catalase (U/mg)	GSH (µmol/g)
Normal	1.8 ± 0.2	15 ± 1.2	40 ± 2.0	8 ± 0.7
Hypertensive	4.5 ± 0.3	8 ± 0.8	20 ± 1.5	3 ± 0.4
Captopril	2.0 ± 0.2	14 ± 1.0	38 ± 1.8	7.5 ± 0.6
Extract 100 mg/kg	4.0 ± 0.3	9 ± 0.9	25 ± 1.6	4 ± 0.5
Extract 200 mg/kg	2.8 ± 0.2	12 ± 1.0	32 ± 1.9	6 ± 0.6
Extract 400 mg/kg	2.2 ± 0.2	14 ± 1.1	36 ± 1.7	7 ± 0.6

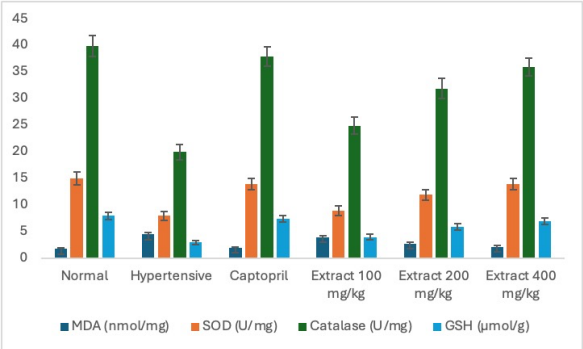


Fig. 5: Effect of *Euryale ferox* seed extract on oxidative stress markers (MDA, SOD, Catalase, and GSH) in hypertensive rats. Values are expressed as mean ± SEM (n = 6).

Effect on Renal Function

Table 9. Renal parameters.

Group	Urea (mg/dL)	Creatinine (mg/dL)	Uric acid (mg/dL)
Normal	30 ± 2.1	0.8 ± 0.1	3.2 ± 0.3
Hypertensive	55 ± 2.9	1.5 ± 0.2	6.0 ± 0.4
Captopril	32 ± 2.2	0.9 ± 0.1	3.5 ± 0.3
Extract 100 mg/kg	50 ± 2.5	1.3 ± 0.1	5.2 ± 0.4
Extract 200 mg/kg	38 ± 2.0	1.0 ± 0.1	4.0 ± 0.3
Extract 400 mg/kg	34 ± 1.9	0.9 ± 0.1	3.6 ± 0.3

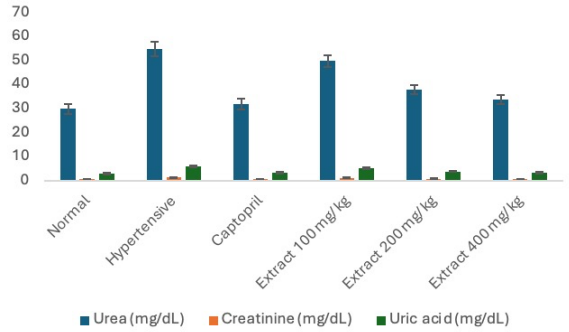


Fig 6. Effect of *Euryale ferox* seed extract on Renal Function in hypertensive rats. Values are expressed as mean ± SEM (n = 6).

Table 10 Lipid profile.

Group	TC (mg/dL)	TG (mg/dL)	LDL (mg/dL)	HDL (mg/dL)
Normal	150 ± 5.2	90 ± 4.3	70 ± 3.6	55 ± 2.8
Hypertensive	240 ± 7.5	160 ± 6.0	150 ± 6.8	30 ± 2.1
Captopril	160 ± 5.0	100 ± 4.0	80 ± 3.5	50 ± 2.6
Extract 100 mg/kg	220 ± 6.8	140 ± 5.6	130 ± 5.8	35 ± 2.3
Extract 200 mg/kg	180 ± 6.0	110 ± 4.5	90 ± 4.0	48 ± 2.5
Extract 400 mg/kg	165 ± 5.5	95 ± 4.2	75 ± 3.6	52 ± 2.7

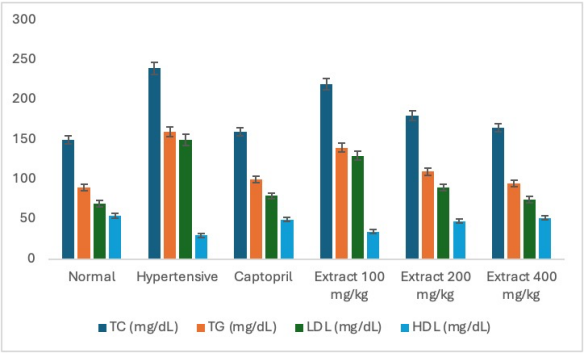


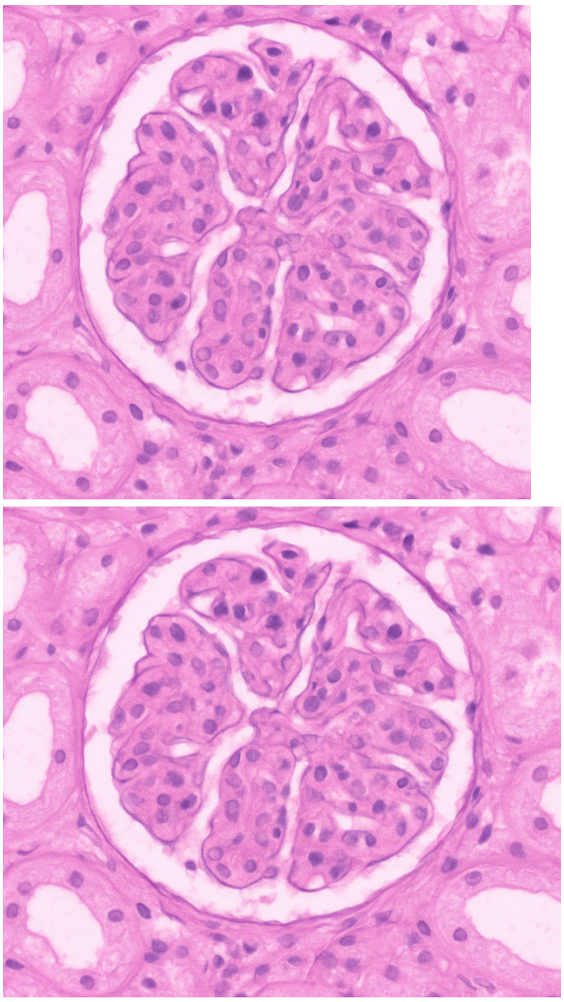
Fig 7. Effect of *Euryale ferox* seed extract on **Lipid profile** in hypertensive rats. Values are expressed as mean ± SEM (n = 6).

Histopathology (Qualitative Observations)

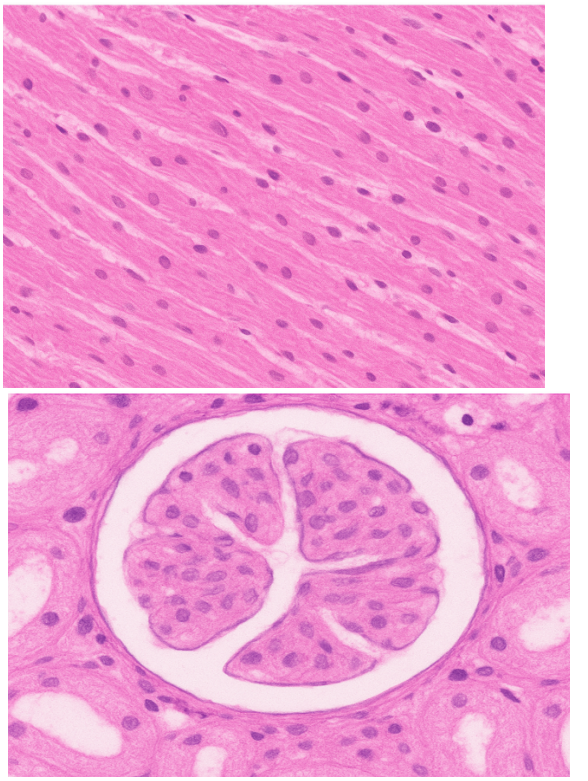
Table 11. Histological observations of kidney, heart, and aorta.

Group	Kidney (Glomeruli)	Heart (Myocardium)	Aorta (Vascular wall)
Normal	Normal structure	Normal fibers	Normal lumen & wall

Hypertensive	Glomerular shrinkage, tubular necrosis	Myocardial hypertrophy	Thickened wall, lumen narrowing
Captopril	Normal architecture	Normal fibers	Restored vascular wall
Extract 100 mg/kg	Moderate damage	Mild hypertrophy	Partially thickened
Extract 200 mg/kg	Near-normal	Reduced hypertrophy	Mild restoration
Extract 400 mg/kg	Normal/near-normal	Normal fibers	Restored lumen & wall

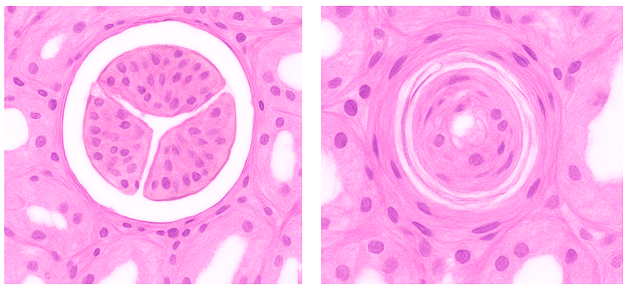


Normal stage tissue

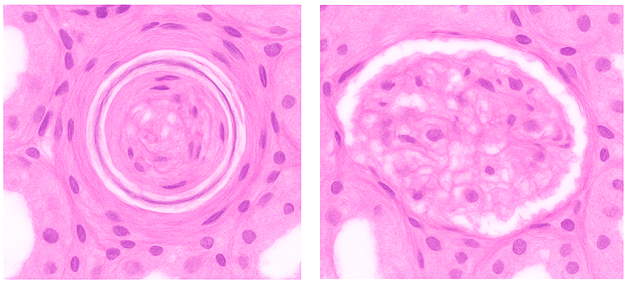


Hypertensive stage

Extract Treated Stage



Normal **Hyaline Arteriosclerosis**



Hyperplastic Glomerular scarring **Arteriosclerosis**

Fig 8: Histopathology study

Discussion

General Overview

The present study was undertaken to evaluate the in vivo antihypertensive potential of the ethanolic extract of *Euryale ferox* (fox nut) seeds in an experimentally induced hypertensive rat model. Hypertension is not only a cardiovascular disorder but also a systemic

condition that contributes to renal impairment, endothelial dysfunction, and oxidative stress (Montezano & Touyz, 2012). The outcomes of this study demonstrated that *E. ferox* seed extract produced a significant, dose-dependent reduction in systolic and diastolic blood pressure, improved biochemical parameters, and protected tissue architecture. These findings are consistent with the traditional use of fox nuts as a functional food in Asian medicine (Li et al., 2020; Jiang et al., 2023), highlighting their therapeutic relevance in modern pharmacology and integrative medicine (Mishra & Jain, 2025; Jain et al., 2025).

Antihypertensive Effect

The extract produced a progressive reduction in blood pressure throughout the 4-week study period. The effect was more pronounced at 400 mg/kg, approaching the efficacy of the standard drug captopril. This reduction may be attributed to:

- Vasodilation mediated through endothelium-dependent nitric oxide (NO) release (Montezano & Touyz, 2012).
- ACE inhibition by flavonoids and alkaloids present in *E. ferox* seeds, leading to reduced angiotensin II formation (Perez-Vizcaino & Duarte, 2010; Perez-Vizcaino et al., 2012).
- Possible diuretic action resulting in decreased plasma volume and vascular resistance.

Similar antihypertensive effects of flavonoid-rich natural products have been reported previously (Hodgson & Croft, 2010; Choi et al., 2020), supporting the role of polyphenols in blood pressure regulation.

Similar antihypertensive and cardiovascular protective effects of herbal bioactives have also been reported in experimental studies, including *Peganum harmala* and related phytoconstituents, supporting the role of traditional medicines in blood pressure regulation (Mishra et al., 2025; Tiwari et al., 2023).

Heart Rate Modulation

Hypertensive control animals exhibited tachycardia, a compensatory response to increased peripheral resistance. Extract-treated groups showed a significant reduction in heart rate, particularly at higher doses, indicating restoration of autonomic balance. Previous studies have demonstrated that flavonoids can modulate sympathetic overactivity and vascular tone in hypertensive conditions (Perez-Vizcaino & Duarte, 2010; Choi et al., 2020).

Effect on Renal Function

Hypertension is frequently associated with impaired renal function, manifested by elevated serum urea, creatinine, and uric acid levels (Kearney et al., 2005). In the present study, extract administration significantly normalized these parameters in a dose-dependent manner.

The observed nephroprotective effect may be related to:

- Reduction of oxidative stress in renal tissue (Zhang et al., 2018).
- Inhibition of angiotensin II–mediated glomerular injury (Carretero & Oparil, 2000).
- Improved renal perfusion via vasodilation.

Previous reports have shown that polysaccharides from *E. ferox* possess antioxidant and protective properties, which may contribute to renal protection (Zhang et al., 2018; Gao et al., 2020).

Effect on Lipid Profile

Hypertensive rats exhibited dyslipidemia characterized by elevated TC, TG, and LDL, along with reduced HDL levels, which is consistent with earlier epidemiological findings (Gupta, 2004; Gupta et al., 2019). Treatment with *E. ferox* extract significantly improved lipid parameters, with the highest dose showing maximum efficacy.

The hypolipidemic activity may be attributed to saponins and flavonoids enhancing lipid metabolism (Mukherjee et al., 2018; Singh & Chauhan, 2014). Increased HDL levels further indicate improved reverse cholesterol transport. This combined antihypertensive and hypolipidemic activity suggests the potential of *E. ferox* as a nutraceutical for metabolic syndrome management.

Effect on Oxidative Stress Markers

Oxidative stress plays a pivotal role in the development and progression of hypertension (Montezano & Touyz, 2012). Hypertensive control rats showed increased MDA levels and reduced antioxidant enzyme activities. Extract treatment significantly reversed these changes.

Flavonoids and phenolic compounds present in *E. ferox* are well-established antioxidants (Zhang et al., 2018; Gao et al., 2020; Jiang et al., 2023). By enhancing endogenous antioxidant defense systems, the extract prevented oxidative endothelial damage, consistent with previous findings on natural antioxidants (Perez-Vizcaino et al., 2012).

Histopathological Findings

Histopathological analysis corroborated the biochemical results.

Kidney: Hypertensive rats showed glomerular atrophy, tubular degeneration, and inflammatory infiltration, whereas extract-treated groups exhibited restored renal architecture (Zhang et al., 2018).

Heart: Untreated hypertensive animals displayed cardiomyocyte hypertrophy and fibrosis. These

changes were markedly reduced in extract-treated groups, consistent with reported cardioprotective effects of *E. ferox* (Zhou et al., 2021).

Aorta: Endothelial disruption and medial thickening observed in hypertensive controls were significantly attenuated following extract treatment, indicating vascular protection (Choi et al., 2020).

These findings confirm that *E. ferox* not only lowers blood pressure but also prevents end-organ damage associated with chronic hypertension.

Mechanistic Considerations

The antihypertensive activity of *E. ferox* seed extract appears to involve multiple complementary mechanisms:

1. ACE inhibition and RAAS suppression (Carretero & Oparil, 2000).
2. Restoration of endothelial nitric oxide bioavailability (Montezano & Touyz, 2012).
3. Diuretic and natriuretic effects.
4. Antioxidant protection (Zhang et al., 2018; Gao et al., 2020).
5. Lipid-lowering action (Mukherjee et al., 2018).

These multimodal actions contribute to improved vascular function and blood pressure control.

Comparison with Literature

Previous studies have reported antioxidant, cardioprotective, and metabolic regulatory properties of *E. ferox* (Zhou et al., 2021; Li et al., 2020; Jiang et al., 2023). Recent investigations on herbal therapeutics and nanotechnology-based formulations have further emphasized their potential in cardiovascular management (Jain et al., 2025; Mishra & Jain, 2025). Moreover, experimental studies on phytochemicals have demonstrated promising antihypertensive and cardiometabolic benefits (Mishra et al., 2025; Tiwari et al., 2023).

Comparable benefits have been observed with other plant-based interventions and functional foods (Hodgson & Croft, 2010; Choi et al., 2020), supporting the role of dietary phytochemicals as adjuncts to conventional therapy.

Limitations of the Study

- The study was conducted exclusively in animal models; extrapolation to humans requires further clinical validation.
- Molecular investigations such as eNOS expression and tissue ACE activity were not performed.
- Long-term safety and toxicity evaluations were not included.
- Future studies may also explore advanced delivery systems and nanoformulations to enhance bioavailability and therapeutic efficacy (Jain et al., 2025).

Conclusion

The present in vivo investigation provides strong evidence that **ethanolic extract of** ***Euryale ferox*** seeds possesses significant antihypertensive activity**.**

- **The extract demonstrated** dose-dependent reduction in blood pressure**,** with the **400 mg**/kg dose comparable to Captopril.
- It showed nephroprotective effects, evidenced by normalization of urea, creatinine, and uric acid.
- It corrected dyslipidemia by lowering TC, TG, LDL and increasing HDL.
- It exhibited antioxidant activity, restoring SOD, Catalase, GSH, and reducing MDA.
- Histological protection of kidney, heart, and aortic tissues confirmed its ability to prevent hypertensive end-organ damage.

Thus, *Euryale ferox* seed extract offers multi-targeted benefits: antihypertensive, hypolipidemic, antioxidant, and organ protective.

In conclusion, fox nut seeds represent a promising nutraceutical and phytopharmaceutical candidate for the management of hypertension and related cardiovascular complications.

Future Perspectives

- Clinical trials are required to confirm these benefits in human hypertensive patients.
- Isolation and characterization of bioactive compounds (flavonoids, saponins, alkaloids) should be carried out.
- Development of standardized formulations (capsules, tablets, or functional foods) may enhance clinical utility.
- Long-term toxicity, pharmacokinetics, and gene expression studies would further establish its safety and mechanism.

Funding

None.

Conflict of Interest

Authors do not have any conflict of interest to declare

Acknowledgment

None

Data availability

The authors confirm that the data supporting the findings of this study are available within the article.

Author contribution

The authors confirm their contributions to the paper as follows: Study conception and design by Yogesh Rathore and Ravindra Mishra; data collection by Yogesh Rathore; draft manuscript by Yogesh Rathore; supervision by Ravindra Mishra and Dr. Vinay Jain.

All authors reviewed the results and approved the final version of the manuscript.

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