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In-Vivo Anti-Hypertensive Activity of *Peganum Harmala* Experimentally Induced Hypertension in Rats

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Conflict of interest

The authors declare that they have no conflict of interest.

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Abstract

Background: Hypertension is a significant global health burden. Current pharmacotherapies have limitations, including side effects and cost. Peganum harmala, a traditionally used medicinal plant, may offer a safer alternative.

Objective: To evaluate the antihypertensive activity of the methanolic extract of Peganum harmala seeds in glucose-induced hypertensive rats and assess its in vitro ACE inhibition potential.

Methods: Extraction was done using a Soxhlet apparatus. Hypertension was induced in Wistar rats with 10% glucose. Rats were grouped and treated with standard (Nifedipine) and P. harmala extract (100 & 300 mg/kg). Blood pressure was measured using NIBP on days 0, 7, 14, and 21. In vitro ACE inhibition was also performed.

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Results: The methanolic extract significantly reduced diastolic and mean arterial pressure in glucose-induced hypertensive rats. It also showed potent ACE inhibition, comparable to that of Nifedipine.

Conclusion: Peganum harmala exhibits promising antihypertensive potential, likely through ACE inhibition. Further studies are warranted to isolate the active compounds and validate the underlying mechanisms.

Keywords: Peganum harmala, nifedipine, hypertension, methanolic, antihypertensive.

Abbreviation	Full Form
ACE	Angiotensin-Converting Enzyme
ARBs	Angiotensin II Receptor Blockers
BP	Blood Pressure
CCBs	Calcium Channel Blockers
DBP	Diastolic Blood Pressure
MAP	Mean Arterial Pressure
NaCMC	Sodium Carboxymethyl Cellulose
NIBP	Non-Invasive Blood Pressure
RAAS	Renin-Angiotensin-Aldosterone System
ROS	Reactive Oxygen Species
SBP	Systolic Blood Pressure
WHO	World Health Organization

INTRODUCTION

Cardiovascular diseases (CVDs) have become a major global health issue and are expected to be the leading cause of death by 2020. According to the National Health Survey of Pakistan, about 100,000 deaths each year are due to these conditions. Despite the widespread availability of synthetic drugs, many people in developing countries still depend on traditional herbal remedies for primary healthcare. Medicinal plants are culturally important and also offer promising opportunities for new drug development because they are accessible and affordable. Many ethnobotanical studies

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have documented the extensive use of herbal therapies in managing cardiovascular disorders. Peganum harmala (Family: Nitrariaceae), a locally available plant, has been traditionally used to treat various ailments affecting the liver, lungs, heart, and kidneys. It is also recommended for wounds, gastrointestinal infections, diabetes, heart problems, jaundice, and even some types of cancer. This study aims to investigate the effects of Peganum harmala on blood pressure in both normal and diet-induced hypertensive rats, providing scientific support for its traditional medicinal use.

Plant Profile

Peganum harmala

Figure : *Peganum harmala*

Table 1: Plant Description

Kingdom	Plantae
Order	Sapindales
Family	Nitraiaceae
Genus	*Peganum*
Species	*P.harmala*
Binomial name	*Peganum harmala L.*

Scientific name: *Peganum Harmala*

Family: Nitraiaceae

Common name: Wild Rue, Syrian Rue, African Rue, Harmel

Synonyms: *Peganum Dauricum, Peganum Crithmifolium, Peganum Rothschildianum, Peganum Crantz*

Chemical composition & pharmacological properties

Mostly β-carboline alkaloids, including harmine, harmaline, tetrahydroharmine, and harmalol—known for their hallucinogenic, neuroprotective, and antibacterial properties—are found in harmala seeds, which contain several bioactive compounds. They also include quinazoline alkaloids like vasicine and vasicinone, which have bronchodilatory and uterotonic effects, as well as flavonoids like quercetin and kaempferol that enhance antioxidant activity. Additionally, the seeds contain sterols such as β-sitosterol, fatty acids, and phenolic compounds that contribute to their anti-inflammatory, antibacterial, and antioxidant effects. The components of harmala seeds make them pharmacologically active, aiding in the treatment of oxidative stress, bacterial infections, cancer, and diabetes; however, caution is advised due to their potential toxicity and interactions with medications.

MATERIALS & METHODS

Plant material

The fresh seeds of *Peganum harmala* will be collected from local gardens of Gwalior, Madhya Pradesh. The seeds of *Peganum harmala* will be dried in shade & then grind to a coarse powder**.**

Preparation of ethanol extracts

The shade-dried seeds of Peganum harmala were pulverized. The coarse powder underwent sequential extraction with alcohol in the Soxhlet apparatus at temperatures ranging from 60 to 80°C. The residue acquired post-ethanolic extraction was macerated with water to get an aqueous extract. The concentrated extract was stored in amber bottles & refrigerated. The drug extract was suspended in 0.5% sodium carboxymethyl cellulose (NaCMC, w/v).

Experimental animals

Healthy Wistar albino rats were used for the study. They were maintained at standard laboratory conditions & fed a commercial pellet diet & water ad libitum. The animals were acclimatized to laboratory conditions for one week before the experiment began**.**

Experimental design

Experimental Protocol (*In vivo* method) Glucose-induced hypertension.

Animal Grouping & Experimental Design

Male Wistar rats (weighing 200–250 g) were randomized & divided into five groups, with 5–6 animals in each group:

- **Group 1 (Control):** Animals received no medication & were provided with distilled water for drinking.
- **Group 2 (G-10):** Animals were given a 10% glucose solution ad libitum as a replacement for drinking water for 21 days.
- **Group 3 (G-10 + CAP-20):** Animals were given a 10% glucose solution ad libitum & Nifedipine (20 mg/kg/day, orally) for 21 days.
- **Group 4 (G-10 + ME-100):** Animals received a 10% glucose solution ad libitum, along with a methanolic extract of *Peganum harmala* (100 mg/kg/day, orally) for 21 days.
- **Group 5 (G-10 + ME-300):** Animals were given a 10% glucose solution ad libitum, along with a methanolic extract of *Peganum harmala* (300 mg/kg/day, orally) for 21 days.

Hypertension Induction

Hypertension was induced in male Wistar rats by providing a 10% glucose solution ad libitum as drinking water for 5–6 weeks. The glucose solution was freshly prepared every two days by dissolving glucose in distilled water. Control animals were given ordinary tap water throughout the experimental period.

Mechanism of Hypertension Induction

Chronic consumption of a glucose solution induces hypertension through multiple mechanisms, including:

Activation of the sympathetic nervous system.

Increased salt retention.

Enhanced renin-angiotensin system activity.

This experimental setup was designed to evaluate the antihypertensive effects of *Peganum harmala* methanolic extract & its potential mechanisms of action.

Antihypertensive action in vitro

Reagent preparation

Reagent A: 100 mM sodium borate buffer with 300 mM sodium chloride at pH 8.3

Reagent B: Buffer substrate solution with 5 mM hippuryl-L-histidyl-L-leucine (HHL)
Reagent C: A solution of angiotensin converting enzyme (ACE) at 0.1 units/ml. Sample & standard stock solutions are prepared.

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One milligram of each extract was dissolved in one milliliter of sodium borate buffer at pH 8.3 to create sample solutions of n-hexane, chloroform, methanol, ethanol, & water extracts. One milligram of nifedipine was dissolved in one milliliter of sodium borate buffer at a pH of 8.3 to create a reference standard solution.

Assessment of inhibition of the angiotensin-converting enzyme (ACE)

With minor adjustments, the angiotensin converting enzyme (ACE) inhibition assay was carried out, which was first reported by Cushman & Cheung (1971). Each experimental setup required the following preparations:

• Test Solution: 40 µl of extract solution, 20 µl of ACE solution (Reagent C), & 100 µl of buffer substrate solution (Reagent B).

• Control Solution: 40 µl of deionized water, 20 µl of ACE solution (Reagent C), & 100 µl of buffer substrate solution (Reagent B).

• Blank Solution: 60 µl of deionized water & 100 µl of buffer substrate solution (Reagent B).
• Standard Solution: 40 µl of Nifedipine solution, 20 µl of ACE solution, & 100 µl of buffer substrate solution (Reagent B).

Every solution was incubated for 30 minutes at 37°C. Each sample received 250 µl of 1M HCl to stop the reaction. One milliliter of ethyl acetate was used to extract hippuric acid, which is a byproduct of the interaction between ACE & hippuryl-L-histidyl-L-leucine (HHL). The mixture was centrifuged for 10 minutes after being violently vortexed for 15 seconds.

To evaporate the solvent, the top organic layer (1 ml) was carefully placed in a test tube & heated to 100°C for 30 minutes. One milliliter of deionized water was used to dissolve the leftover residue. Using a spectrophotometer, the absorbance of each sample test, blank, control, & standard—was determined at 228 nm. Comparisons across experimental groups were made easier by the accurate quantification of ACE inhibitory activity provided by this refined methodology.

The following formula (Eq. F.1) was used to determine the percentage of inhibition: (Control test - solution test) / (control test - blank control) × 100 is the percentage inhibition (%).

The Documentation Principle Blood Pressure:

The animal was placed in the NIBP restrainer, & its tail was fitted with a suitable cuff equipped with a sensor. The temperature was raised to about 33 to 35 °C. The Power Lab data gathering system & computer were used to monitor the pulse as the tail cuff was gradually deflated after being inflated to a pressure far higher than the

anticipated systolic blood pressure, specifically 250 mm Hg. Each rat's mean arterial pressure (MAP), diastolic, & systolic blood pressure (SBP) were measured. A more accurate measure of perfusion in the kidneys, brain, & coronary arteries is mean arterial pressure, which is the average arterial pressure for a single cardiac cycle.

The formula MAP = SBP + 2(DBP) is used to determine the mean arterial pressure. On days 0, 7, 14, & 21, the tail cuff method was used using non-invasive blood pressure (NIBP) equipment to measure the animal's systolic blood pressure (SBP), diastolic blood pressure (DBP), & mean arterial pressure (MAP).

RESULTS

Extraction & Proximate Analysis

The outcomes of the proximate analysis of Peganum harmala are displayed in the table below. The moisture content of Peganum harmala seeds was 9.1%. The powdered roots demonstrated a moisture content of 6.48 ± 0.45%, but the total ash content in the seeds of Peganum harmala was 18%. The acid-insoluble ash included 5.7%, the water-soluble ash 5.20%, & the sulfated ash 21.60%.

Table 2: Proximate analysis of extracts of Peganum harmala seed powder

S.No	Physicochemical parameters	Percentage content ±SD (%w/w)
1	Moisture	8.2±0.2
2	Ash (total)	19.20±0.5
3	Ash (acid insoluble)	4.70±.02
4	Ash (water soluble)	6.20±0.3
5	Sulfated ash	20.65±0.6
6	Extractive (alcohol soluble)	5.39±0.2
7	Extractive (water soluble)	1.2±0.4

Determination of phytochemicals

Determination of primary metabolites

Table 3 Primary metabolites (mg/g) of powdered seeds of Peganum harmala

S .no	Primary metabolite	mg/g ±SD
1	Total protein content	34.90±0.8
2	Total lipid content	3.68±0.5
3	Total carbohydrate content	11.75±1.2

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Determination of secondary metabolites

Table 4: Secondary metabolites (mg/g) of extracts of powdered seeds of Peganum harmala

Extract	Total Protein (mg/g)	Total Polyphenols (mg/g)	Total Flavonoids (mg/g)	Total Polysaccharides (mg/g)	Total Glycosaponins (mg/g)
n-Hexane	9.60 ± 1.3	15.80 ± 0.8	28.50 ± 0.6	21.50 ± 0.5	Negative
Chloroform	12.70 ± 1.3	74.60 ± 0.7	150.90 ± 1.1	26.35 ± 0.6	Negative
Methanol	56.40 ± 1.2	93.60 ± 0.6	258.10 ± 0.7	56.60 ± 1.5	60.10 ± 1.5
Ethanol	36.50 ± 0.7	37.40 ± 1.2	173.70 ± 0.5	43.15 ± 1.1	53.25 ± 0.7
Water	38.30 ± 0.8	46.70 ± 0.6	106.10 ± 0.6	19.00 ± 0.4	70.10 ± 1.4

Assessment of the ACE inhibitory effect of Peganum harmala seed extract

The angiotensin-converting enzyme (ACE) inhibitory activity of a 1 mg/ml concentration of different seed extracts of Peganum harmala was evaluated. Figure displays the % inhibition of each solution. The results indicate that the methanolic extract of Peganum harmala seed powder exhibits the maximum percentage of angiotensin-converting enzyme inhibition. Consequently, the methanolic extract exhibits antihypertensive activity, is analysed with the ACE inhibition efficacy of the conventional medication Nifedipine. Conversely, n-hexane exhibits a 35% inhibitory effect, which is the least equivalent to the reference standard. Additional in vivo research with alternative models may be performed on the seed extract of Peganum harmala to explore the plant's antihypertensive effect.

Glucose-induced hypertension:

The methanolic extract of Peganum harmala exhibited a significant ($p<0.05$) decrease in systolic blood pressure (SBP), diastolic blood pressure (DBP), & mean arterial pressure (MAP) antihypertensive effects on day 0 & day 7 at doses of 100 & 300 mg/kg, in comparison to glucose-induced hypertensive control groups (tables 10 & 11). On the 14th day, the test extracts at a dosage of 300 mg/kg significantly reduced

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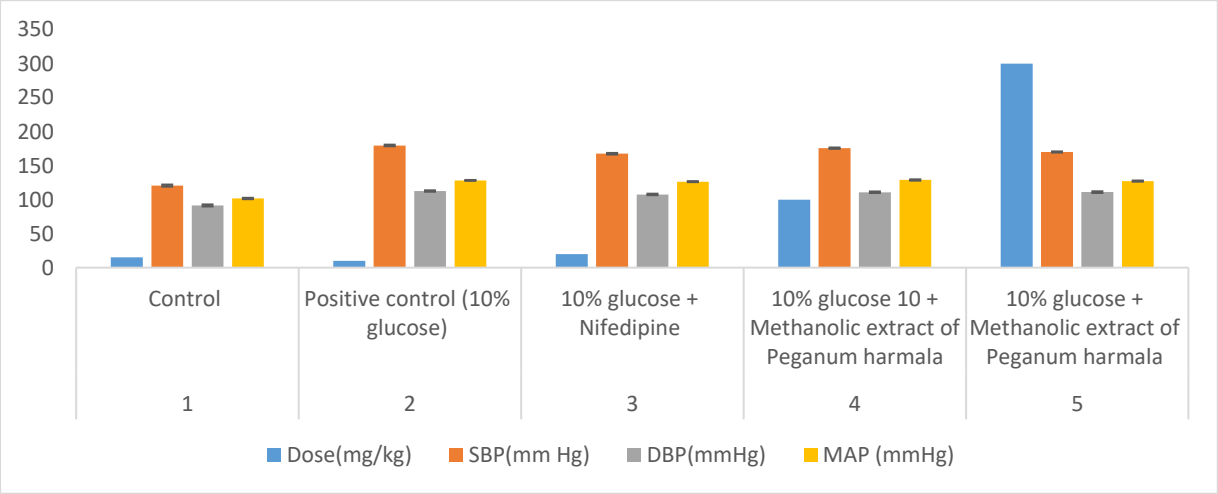
only diastolic blood pressure (DBP) & mean arterial pressure (MAP) ($p<0.05$). On the 21st day of treatment, a reduction in diastolic blood pressure (DBP) was observed; however, despite ongoing medication, no substantial benefits were detected on systolic blood pressure (SBP) & mean arterial pressure (MAP) in the hypertensive rats. The antihypertensive effect was maintained on the 14th & 21st days, indicating that the test extracts diminished all parameters in a dose-dependent manner within the hypertension control group.

Table 5: Effect of *Peganum harmala* on blood pressure in Glucose-induced hypertensive rats on 0 days.

Groups	Treatment	Dose(mg/kg)	SBP(mm of Hg)	DBP(mm of Hg)	MAP (mm of Hg)
1	Control	15	120.6±1.53	91.4±1.50	101.6±1.02
2	Positive control (10% Glucose)	10	179.6±1.20	112.6±1.02	128.2±0.66
3	10% Glucose + Nifedipine	10+20	167.4±1.20	107.6±1.12	126.4±0.74
4	10% Glucose 10 + Methanolic extract of Peganum harmala	100	175.6±0.97*	110.8±1.15*	128.8±0.96*
5	10% Glucose + Methanolic extract of Peganum harmala	300	170±0.83*	111±1.22*	127.2±0.86*



Graph 1: SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean Arterial blood pressure.

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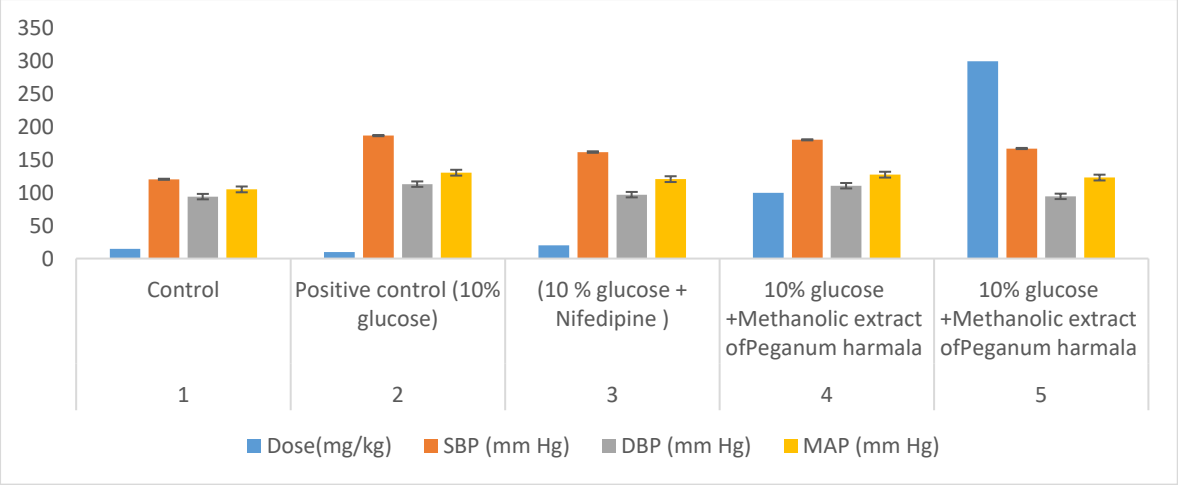
Table 6: Effect of *Peganum harmala* on blood pressure in Glucose induced hypertensive rats on 7th day.

Groups	Treatment	Dose(mg/kg)	SBP (mm Hg)	DBP (mm Hg)	MAP (mm Hg)
1	Control	15	120.6±0.81	94.2±1.35	105.2±1.71
2	Positive control (10% Glucose)	10%	187±0.89	113.2±1.01	130.6±0.97
3	(10 % Glucose + Nifedipine)	10+20	162±1.14	97.2±1.01	120.8±0.96
4	10% Glucose + Methanolic extract of Peganum harmala	100	180.6±0.81*	110.8±0.96*	127.6±0.81*
5	10% Glucose + Methanolic extract of Peganum harmala	300	167.4±0.87*	94.6±1.02*	123.2±1.01*



Graph 2: Effect of *Peganum harmala* on glucose-induced hypertensive rats, comparing the effectiveness of the extract across different animal groups.

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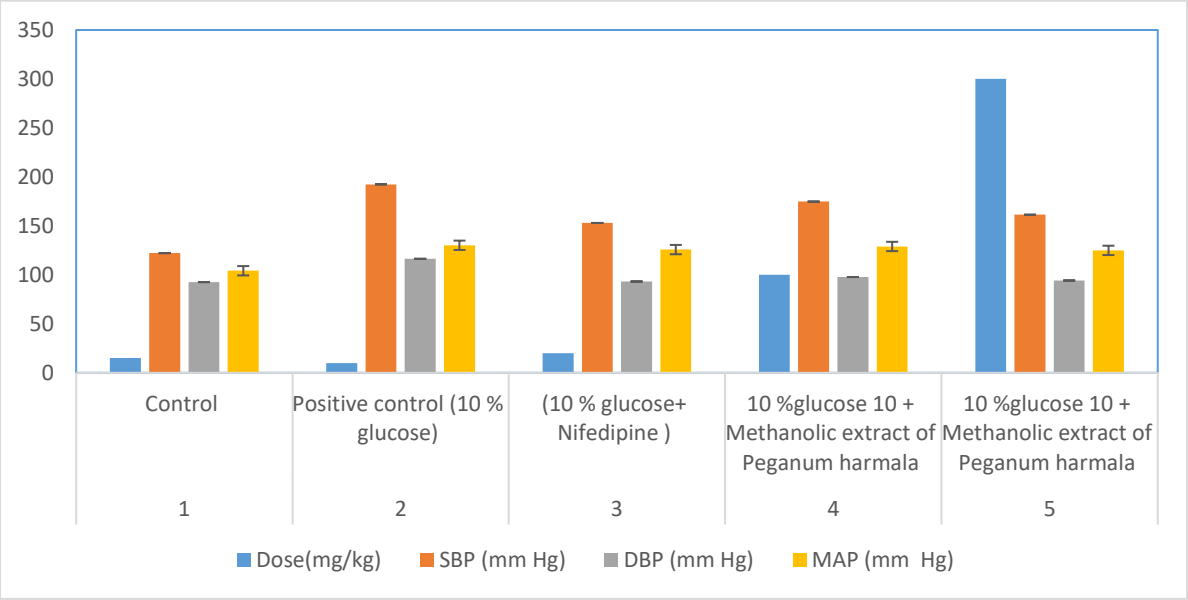
Table 7: Effect of *Peganum harmala* on blood pressure in glucose-induced hypertensive rats on 14th day.

Groups	Treatment	Dose(mg/kg)	SBP (mm Hg)	DBP (mm Hg)	MAP (mm Hg)
1	Control	15	122.2±1.49	92.6±1.16	104.2±1.28
2	Positive control (10 % Glucose)	10	192.4±0.97	116.4±1.12	130.2±1.11
3	(10 % Glucose Nifedipine)	10+20	153±1.14	93.2±0.73	125.8±0.66
4	10 %Glucose 10 + Methanolic extract of Peganum harmala	100	174.8±1.06	97.8±0.66*	129±0.99*
5	10 % Glucose + Methanolic extract of Peganum harmala	300	161.4±0.97	94.2±0.66*	125±0.70*



Graph 3: Effect of *Peganum harmala* on Glucose induced hypertensive rats taking groups of animals against effectiveness of the extract.

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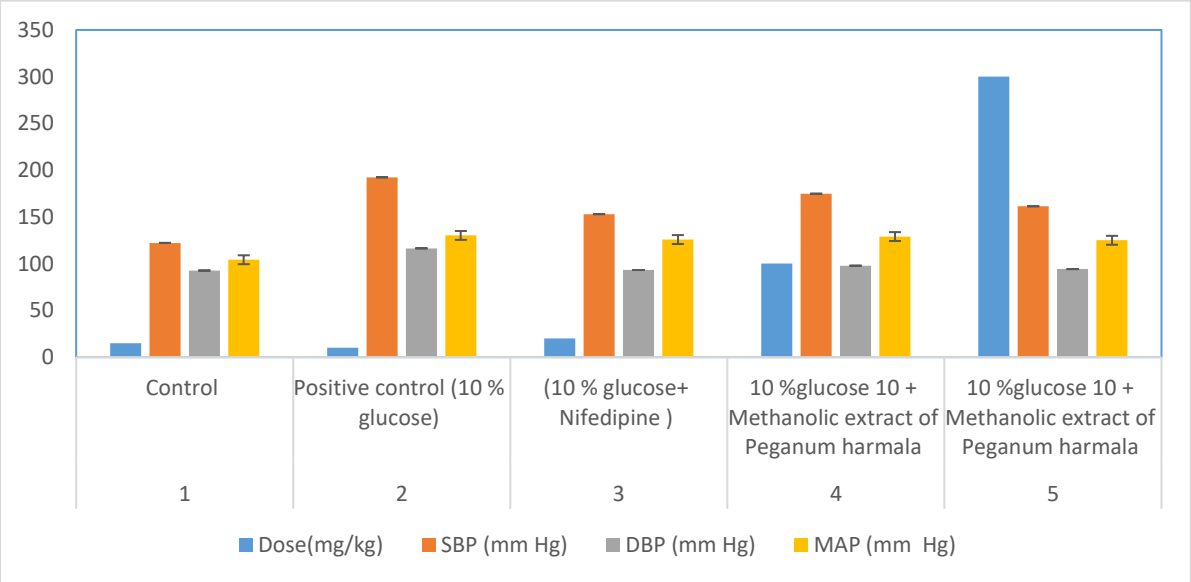
Table 8: Effect of *Peganum harmala* on blood pressure in glucose-induced hypertensive rats on the 21st day.

Groups	Treatment	Dose(mg/kg)	SBP (mm Hg)	DBP (mm Hg)	MAP (mm Hg)
1	Control	15	120.6±1.88	91.6±1.20	104.8±0.96
2	Positive control (10% Glucose)	10	194.2±0.66	114.4±1.16	129.6±0.50
3	10% Glucose+ Nifedipine	10+20	145.6±0.81	90.4±1.20	119±0.83
4	10% Glucose10 +Methanolic extract of Peganum harmala	100	170.8±1.15	94.6±0.74*	125±0.89
5	10% Glucose + Methanolic extract of Peganum harmala	300	153.2±1.01	91±0.99*	120.6±1.16



Graph 4: Effect of *Peganum harmala* on glucose-induced hypertensive rats taking groups of animals against effectiveness of the extract.

DISCUSSION

Hypertension is the predominant clinical symptom linked to numerous cardiovascular diseases. It is seen as both a precursor & a result of acute coronary artery disease & congestive heart failure, rendering it a vital element in assessing cardiovascular function. The World Health Organization (WHO) has identified hypertension as a primary risk factor for worldwide morbidity & mortality, responsible for almost nine million deaths per year. The management of hypertension primarily entails synthetic medications, utilizing various pharmacological classes over the past forty years, such as diuretics, beta-blockers (β-blockers), calcium channel blockers (CCBs), and, more recently, angiotensin-converting enzyme (ACE) inhibitors & angiotensin II receptor blockers (ARBs).

This study sought to assess the antihypertensive effects of Peganum harmala via its methanolic extract in a glucose-induced hypertension paradigm using male Wistar rats weighing 200–250 grams. Hypertension was elicited by a glucose-loading technique. The botanical material was meticulously pulverized & underwent cold maceration with hexane & methanol solvents. The resultant extracts were preserved at 40°C for subsequent analysis. The phytochemical analysis of the extract verified the existence of significant bioactive components, including carbohydrates, proteins, alkaloids, saponins, terpenoids, & glycosides.

The noted decrease in blood pressure in hypertensive rats administered ethanolic & aqueous extracts of Peganum harmala is probably due to many processes. Prior research indicates that excessive glucose consumption leads to heightened blood pressure, chiefly due to augmented sympathetic nervous system activity. This increased sympathetic activity usually leads to a higher heart rate & blood pressure. The extracts evaluated in this study exhibited a notable hypotensive impact, indicating their potential utility in alleviating hypertension.

Considered as main causes of hypertension development are endothelial dysfunction and oxidative stress. Excessive glucose intake has been linked to the overproduction of reactive oxygen species (ROS) in tissues, together with a concurrent drop in antioxidant levels observed in hypertension patients. Furthermore, connected to lower nitric oxide (NO) levels and consequently aggravation of hypertension is higher blood glucose. The results of this study imply that Peganum harmala's antihypertensive properties might be related to its potential to reduce underlying processes, like oxidative stress and endothelial dysfunction.

CONCLUSION

The results of this work show that the methanolic extract of Peganum harmala

probably consists of active molecules with antihypertensive effects in rats generated from glucose. Moreover, the present work shows that Peganum harmala is safe for use. Alkaloids present in the methanolic extract of Peganum harmala might be responsible for its antihypertensive action by perhaps altering the RAAS system. Still unknown is the exact mode of action. An extensive investigation is needed to pinpoint the main molecule, separate the phytoconstituents, and prove their exact antihypertensive mechanism.

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