Uttar Pradesh Journal of Zoology

Volume 45, Issue 19, Page 388-399, 2024; Article no.UPJOZ.4176
ISSN: 0256-971X (P)

Ameliorative Effects of Phyto-estrogen 'Genistein', Homeopathic Combination 'R-85'and Captopril on Body Weight, Organ Weight, Feed and Water Intake in L-NAME Induced Hypertensive Wistar Rats

Ankit Kumar Singh [a*], Shahid Prawez [a], Manish Kumar [b], Dhananjay Kumar [c], Vineeth M.R. [d] and Priyanka Narwade [e]

[a] Department of Veterinary Pharmacology and Toxicology, Faculty of Veterinary and Animal Sciences, RGSC, Banaras Hindu University, Barkachha, Mirzapur, 231001, Uttar Pradesh, India.
[b] Department of Veterinary Physiology and Biochemistry, Faculty of Veterinary and Animal Sciences, RGSC, Banaras Hindu University, Barkachha, Mirzapur, 231001, Uttar Pradesh, India.
[c] Department of Livestock Products Technology, Faculty of Veterinary and Animal Sciences, RGSC, Banaras Hindu University, Barkachha, Mirzapur, 231001, Uttar Pradesh, India.
[d] Department of Animal Genetics and Breeding, Faculty of Veterinary and Animal Sciences, RGSC, Banaras Hindu University, Barkachha, Mirzapur, 231001, Uttar Pradesh, India.
[e] Department of Veterinary Gynaecology and Obstetrics, Faculty of Veterinary and Animal Sciences, RGSC, Banaras Hindu University, Barkachha, Mirzapur, 231001, Uttar Pradesh, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.56557/upjoz/2024/v45i194542

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://prh.mbimph.com/review-history/4176

**Corresponding author: Email: ankitsingh.r7@gmail.com;*

Cite as: *Singh, Ankit Kumar, Shahid Prawez, Manish Kumar, Dhananjay Kumar, Vineeth M.R., and Priyanka Narwade. 2024. "Ameliorative Effects of Phyto-Estrogen 'Genistein', Homeopathic Combination 'R-85'and Captopril on Body Weight, Organ Weight, Feed and Water Intake in L-NAME Induced Hypertensive Wistar Rats". UTTAR PRADESH JOURNAL OF ZOOLOGY 45 (19):388-99. https://doi.org/10.56557/upjoz/2024/v45i194542.*

Original Research Article

Received: 02/08/2024
Accepted: 06/10/2024
Published: 14/10/2024

ABSTRACT

Hypertension is associated with the development and progression of severe damage to organs. Meager studied has been found on the effect of Phyto-estrogen 'genistein' and homeopathic combination 'R-85' as antihypertensive action which may aid in main therapy of hypertension. Thus, present study aims to evaluate the effect of 'genistein', 'R-85' and 'captopril' on body weight, organ weight feed and water intake in N^{ω}-Nitro-L-arginine methyl ester hydrochloride (L-NAME) induced hypertensive male wistar rats. After acclimatization, the male wistar rats were divided into 5 groups of 5 rats in each group. The rats except control group (group-I) were treated with L-NAME (@50mg/kg, in drinking water, group-II), L-NAME + Genistein (@50mg/kg, *per os*, group-III), L-NAME + R-85 (@ 5 drops, twice daily, group-IV) and L-NAME + Captopril (@50 mg/kg, *per os,* group-V) daily for 42 days. The study was conducted for a period of 42 days. During the experimental period, weight of rats, feed intake and water intake was measured weekly. At the end of the experimental period, rats were sacrificed andheart, kidneys and liver were weighed. After treatment with genistein, R-85 and captopril an increase in body weight was found as compared to L-NAME group. On similar treatment there was an increase in feed intake per 100 g of rat was found compared to L-NAME hypertensive group per week. Unlike feed intake, treatments decrease the water intake per 100 g of rat compared to L-NAME group per week. A significant increase in the relative weights of the liver and kidney was found in L-NAME group compared to control. Whereas, treatment with R-85 and captopril significantly decreased the relative weight of liver and kidney as compared to L-NAME group. Thus finding of the present study discloses ameliorative effect of genistein, R-85 and captopril on hypertensive rats.

Keywords: Genistein; hypertension; L-NAME; R-85; wistar.

1. INTRODUCTION

Hypertension is a key indicator of cardiovascular dysfunction and overall health in mammals [1]. The rising global morbidity and mortality rates are largely attributed to hypertension. Epidemiological studies have consistently shown a strong relation between hypertension in both fatal and non-fatal health events. The rising prevalence of hypertension is linked to factors such as population growth, aging, behavioral risks, unhealthy diets, harmful alcohol consumption, lack of physical activity, excess weight and chronic exposure to stress [2]. Global urbanization, a sedentary lifestyle and a lack of social support contribute to increased anxiety and uncertainty, which ultimately leads to chronic mental and emotional stress [3].

N^{ω}-Nitro-L-arginine methyl ester hydrochloride (L-NAME) is a nitric oxide synthase (NOS) inhibitor and used in research to induce hypertension in rat models [4]. L-NAME treatment leads to down-regulation of endothelial nitric oxide synthase (eNOS) in blood vessels, depletion of plasma nitric oxide (NO) levels, systemic vasoconstriction, increased vascular resistance and high blood pressure [5].

For thousands of years, plants have served a vital role as source of medicinal remedies and have been instrumental in the discovery of new drugs for managing various disorders. Phytoestrogens, a class of plant compounds, have structures similar to estrogenand have ability to bind to estrogen receptors. Among these phytoestrogens, genistein stands out for its potential role in managing certain diseases including hypertension pharmacological and physiological qualities [6].

Complementary and alternative medicine therapies are gaining popularity for managing chronic diseases, including hypertension [7]. In recent years, there have been increasing numbers of pre-clinical studies, including *in vitro* and animal research, aimed at assessing efficacy of certain homeopathic medicines.Therefore, it is crucial to evaluate the various effects of genistein on cardiovascular diseases *viz* hypertension.

There are scanty of scientific literatures available to disclose the antihypertensive role of phytoestrogen 'genistein' and homeopathic combination 'R-85'. In this notion, the present study was designed to investigate the efficacy of genistein and R-85 on body weight, organ weight (liver, heart and kidney) feed and water intake of hypertensive rats induced by L-NAME.

2. MATERIALS AND METHODS

2.1 Chemicals and Reagents

L-NAME, Genistein and Captopril were procured from Tokyo Chemical Industry (TCI, Japan). Homeopathic drug R-85 was procured from Dr. Reckeweg R 85. Urethane was purchased from Sigma Aldrich (Germany).

2.2 Animals

Male wistar (*Rattus norvegicus*) rats (180-220 gm) were procured from the Central Drug Research Institute (CDRI), Lucknow. After an acclimatization the animals were randomly divided into five groups containing five rats in each group and housed in cages. The cages are made up of standard polypropylene cages (32.5 × 21 × 14cm) padded with straw husk housed in the laboratory animal house of the Faculty of Veterinary and Animal Sciences, RGSC, Banaras Hindu, Barkachha, University at room temperature of 22-25°C with alternate 12 hr light/dark cycle. The experimental rats were allowed to eat standard pelleted feed of VRK nutritional solutions, Maharashtra and provided drinking water *ad libitum*. All the experimental protocols were carried as per the guidelines provided by Committee for Control and Supervision of Experiments on Animals (CCSEA), New Delhi, Government of India, and experimental protocol of the present study was approved by the Institutional Animal Ethics Committee of RGSC bearing ref. no. RGSC-BHU/IAEC/2021-22/91 dated 09/03/2022.

2.3 Experimental Design

The experimental period of the present study was of 42 days. The first group (control) received only distilled water (*per os*), while the second group (L-NAME group) was treated with L-NAME (@50 mg/kg/day, in drinking water) [8]. The third group received a combination of both L-NAME (@50 mg/kg/day) and genistein (@50 mg/kg/day, *per os*). The fourth group received L-NAME (@50 mg/kg/day) and homeopathic medicine R-85, administered at dose of 5 drops *per os* (1 drop = 0.06 ml) to each rat twice daily [9] and the fifth group received L-NAME (@50 mg/kg/day) with captopril (@50 mg/kg/day, *per os*) [10]. Drugs were prepared in distilled water for oral dose (*per os*) at a dosage volume of 1 ml/100 g body weight for 42 days.

2.4 Measurements of Body Weight, Feed and Water Intake

Body weight, feed consumption and water intake of each group were measured once in a week till the completion of experimental period of 42 days. The amount of feed consumed was recorded daily by measuring the quantity of the feed provided and the left over. After each day, the volume of water remaining in the water bottle was deducted from the initial volume to obtain the average daily consumption of water per rat [11] and the data analysis was done on once per week basis.

2.5 Organ Collection

The heart, liver, and kidneys were quickly removed, cleaned off adipose tissues, washed with 0.9% normal saline, blotted dried and weighed.

2.6 Statistical Analysis

Data were analyzed using One-Way Analysis of Variance (ANOVA). Results were expressed as mean ± SEM (Standard Error of Mean)**.** Statistical analysis of the data was performed using suitable statistical methods [12] and considered statistically significant had analyzed at $P< 0.05$. Post hoc analysis was not possible in feed and water intake due to the unavailability of variance data.

3. RESULTS AND DISCUSSION

3.1 Effects of the Genistein, R-85 and Captopril on Body Weight (g) on L-NAME Induced Hypertensive Male Wistar Rats

During the experimental period weight of rats of each group was measured weekly and the mean body weight of different groups of rats showed in Table 1 and Fig. 1. There was a progressive weekly increase in the mean body weight of rats found in each group during the experimental period of 42 days. After the completion of 42 days of experiment, a significant decrease in

Table 1. Effects of the Genistein, R-85 and Captopril on body weight (g) onL-NAME induced hypertensive male wistarrats

	Control (n=5)	L-NAME (n=5)	L-NAME + Genistein (n=5)	L-NAME + R-85 (n=5)	L-NAME + Captopril (n=5)
0 day	202 ± 3.97	198 ± 6.16	201 ± 5.93	196 ± 7.13	204 ± 3.83
1st week	212 ± 3.47^{a}	202 ± 4.68^{b}	203 ± 5.2^{ab}	203 ± 7.38^{ab}	204 ± 1.85^{ab}
2nd week	221 ± 3.43^{a}	205 ± 5.62^{b}	215 ± 3.71^{ab}	213 ± 8.38^{ab}	216 ± 0.81^{ab}
3rd week	231 ± 4.04^{a}	212 ± 5.12^{b}	226 ± 2.44^{ab}	223 ± 10.86^{ab}	226 ± 0.58^{ab}
4th week	242 ± 3.30^{a}	216 ± 4.62^{b}	237 ± 2.75^{ab}	232 ± 10.97^{ab}	236 ± 1.11^{ab}
5th week	251 ± 3.20^{a}	224 ± 4.50^{b}	245 ± 2.07^{ab}	246 ± 9.78^{ab}	246 ± 1.53^{ab}
6th week	263 ± 3.79^{a}	231 ± 4.20^{b}	254 ± 2.77^{ab}	255 ± 9.79^{ab}	258 ± 1.17^{ab}

Values are expressed as means ± S.E.M.
Groups showing different superscript letters ^{a,b} are significantly different at P<0.05 and n represent number of animals

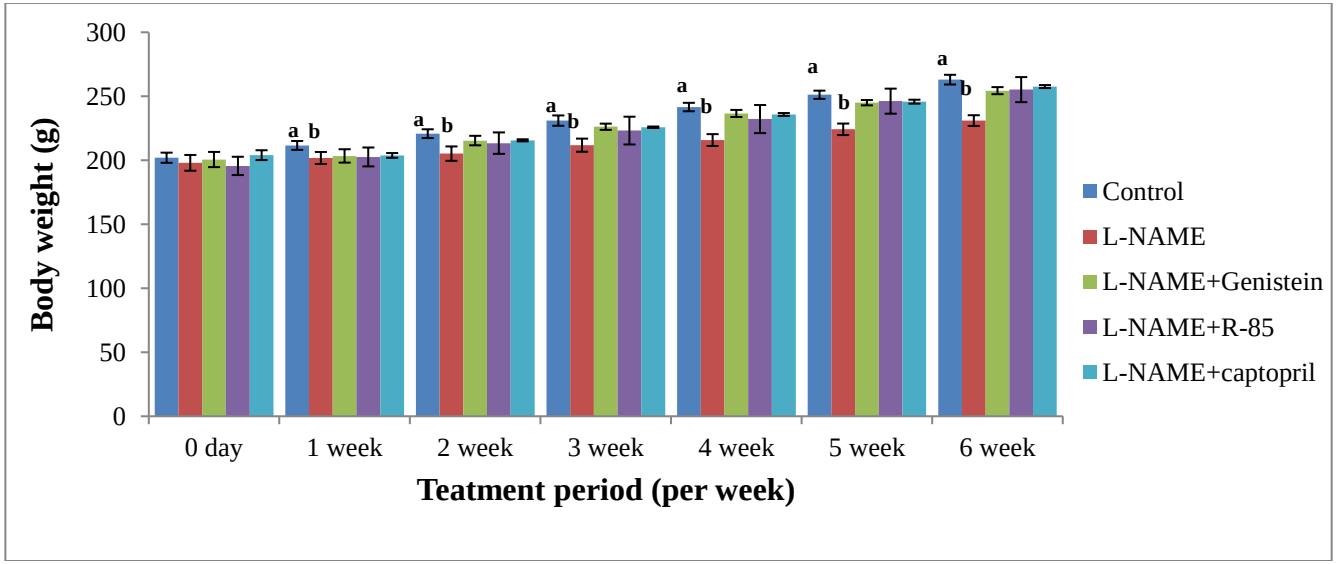

Fig. 1. Effects of the Genistein, R-85 and Captopril on body weight (g) on L-NAME induced hypertensive male wistar rats

Table 2. Effects of the Genistein, R-85 and Captopril on feed intake per 100 g on L-NAME induced hypertensive male wistar rats

	Control (n=5)	L-NAME (n=5)	L-NAME + Genistein (n=5)	L-NAME + R-85 (n=5)	L-NAME + Captopril (n=5)
1st week	239.40	146.23	206.92	196.35	197.89
2nd week	241.22	157.15	211.96	202.93	208.74
3rd week	243.88	158.41	208.32	200.20	208.67
4th week	246.05	160.09	192.22	187.04	187.60
5th week	261.52	160.30	202.72	191.24	195.30
6th week	267.96	162.89	230.02	209.02	220.01

Values are expressed as sum of feed intake per 100 g rat per week
n represent number of animals

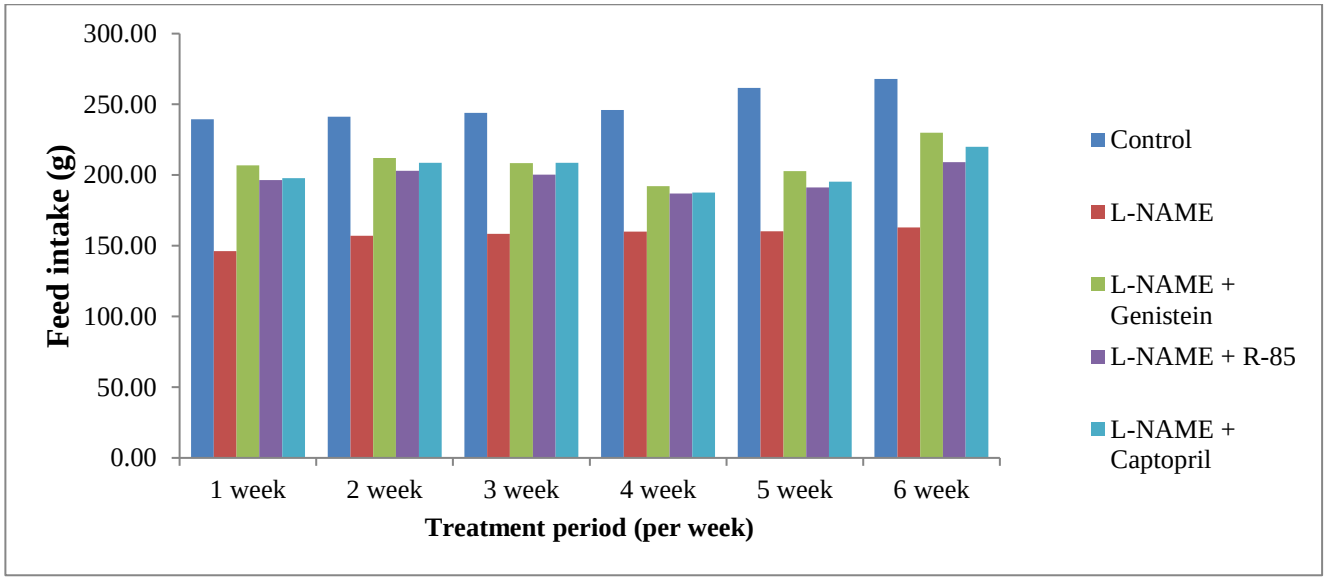

Fig. 2. Effects of the Genistein, R-85 and Captopril on feed intake per 100 g/day on L-NAME induced hypertensive male wistarrats

Table 3. Effects of the Genistein, R-85 and Captopril on water intake per 100 g on L-NAME induced hypertensive male wistar rats

	Control (n=5)	L-NAME (n=5)	L-NAME + Genistein (n=5)	L-NAME + R-85 (n=5)	L-NAME + Captopril (n=5)
1st week	366.80	420.91	357.98	382.34	370.02
2nd week	367.88	444.87	361.70	380.41	355.92
3rd week	369.81	451.57	366.78	366.13	342.54
4th week	366.73	459.83	385.56	355.67	377.16
5th week	376.11	460.60	384.37	376.46	381.29
6th week	378.37	475.18	385.72	388.75	393.88

Values are expressed as sum of water intake per 100 g rat per week
Groups showing significant different at P <0.05 and n represent number of animals

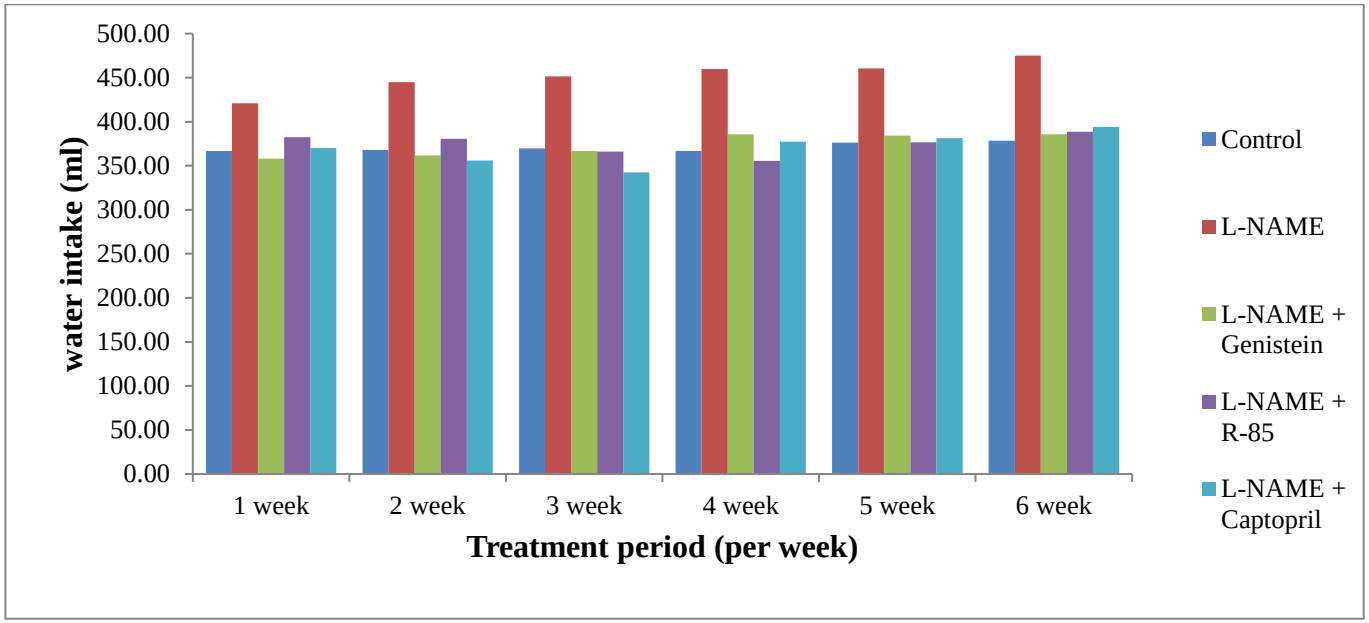

Fig. 3. Effects of the Genistein, R-85 and Captopril on water intake per 100 g/day on L-NAME induced hypertensive male wistar rats

Table 4. Effects of the Genistein, R-85 and Captopril onrelative weight of liver, heart and kidneyg/100 g rat on L-NAME induced hypertensive male wistar rats

Organs	Control (n=5)	L-NAME (n=5)	L-NAME + Genistein (n=5)	L-NAME + R-85 (n=5)	L-NAME + Captopril (n=5)
Liver	2.50 ± 0.04^{a}	3.03 ± 0.01^{b}	2.59 ± 0.02^{ab}	2.37 ± 0.02^{a}	2.49 ± 0.02^{a}
Heart	0.34 ± 0.01^{a}	0.39 ± 0.01^{a}	0.35 ± 0.02^{a}	0.33 ± 0.02^{a}	0.34 ± 0.03^{a}
Kidney	0.41 ± 0.02^{a}	0.56 ± 0.04^{b}	0.44 ± 0.02^{a}	0.42 ± 0.03^{a}	0.43 ± 0.03^{a}

Values are expressed as means ± S.E.M.

Groups showing different superscript letters ^{a,b} are significantly different at P <0.05 and n represent number of animals

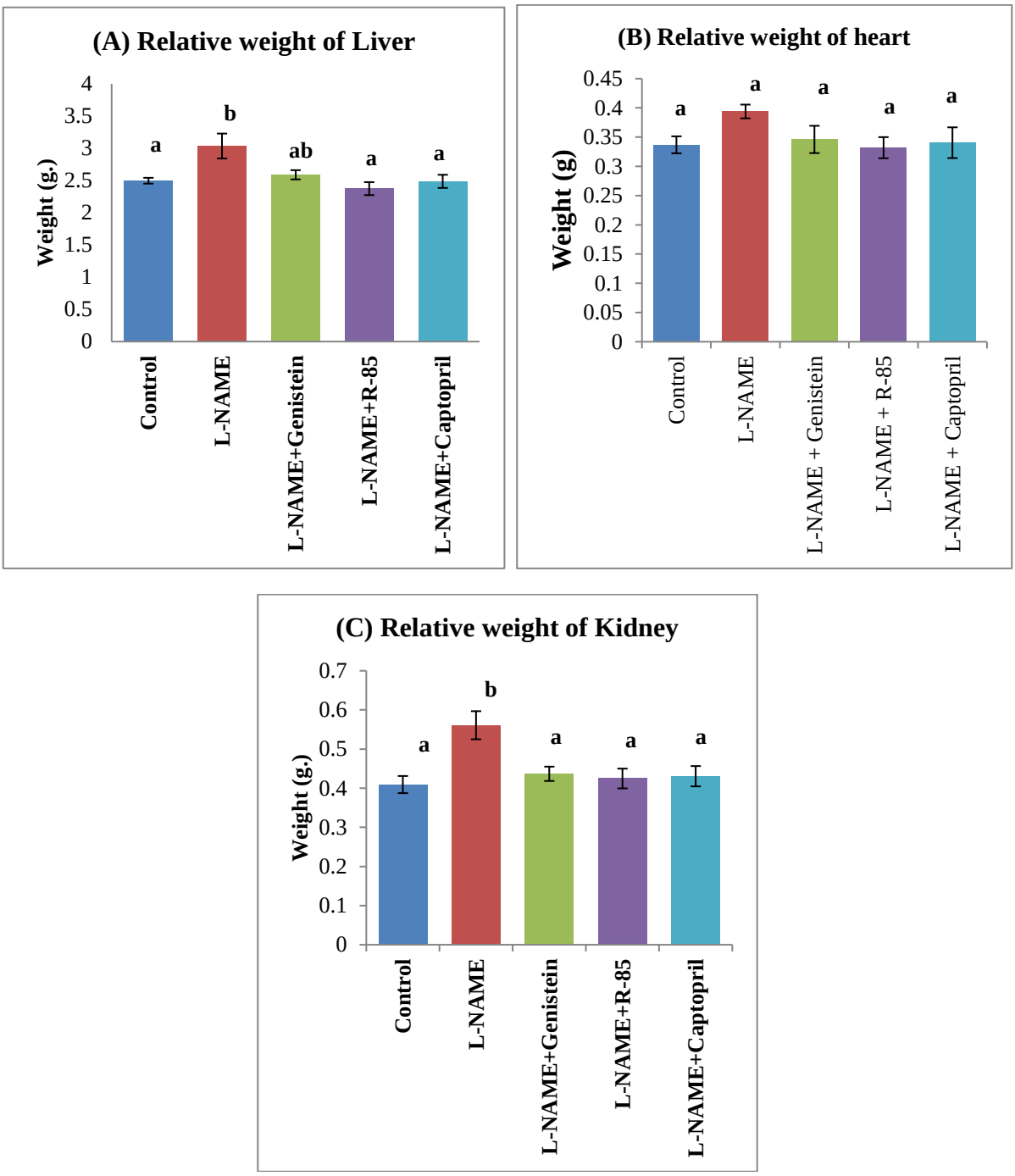

Fig. 4 (A) (B) (C). Effects of the Genistein, R-85 and Captopril onrelative weight of liver, heart and kidneyin g/100 g rat of L-NAME induced hypertensive male wistarrats

body weight was observed in first, second, third, fourth, fifth and sixth weeks in rats treated with L-NAME compared with control. However, 42 days of treatment period with genistein, R-85 and captopril, a non-significant increase in the body weight per week was found (first, second, third, fourth, fifth and sixth) compared with L-NAME group.

3.2 Effects of the Genistein, R-85 and Captopril on feed Intake on L-NAME Induced Hypertensive Male Wistar Rats

Table 2 and Fig. 2, showing the effect of genistein, R-85 and captopril on feed

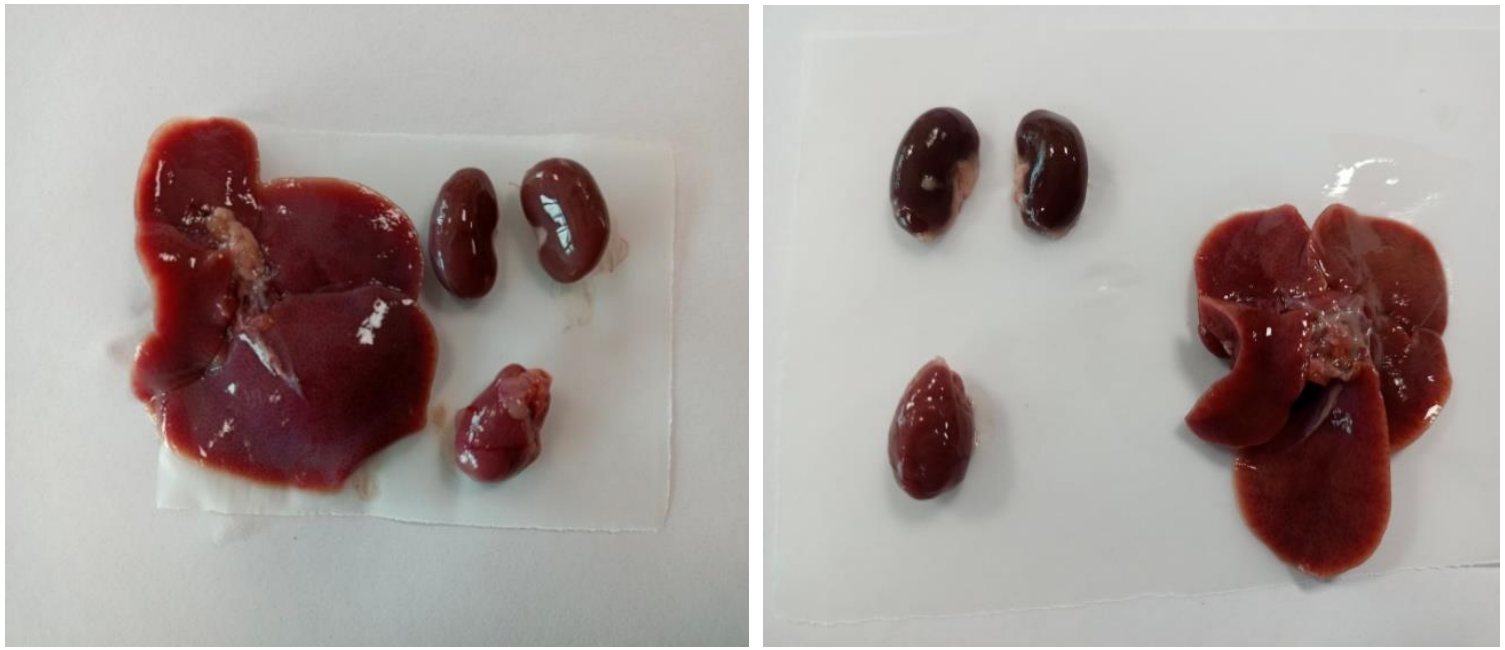

Image 1. Images of liver, heart and kidney

consumption per 100 g rat in L-NAME induced hypertensive male wistar rats. There was a remarkable decrease in feed consumption per 100 gm rat was found in L-NAME induced hypertensive rats as compared to control rat, between the groups per week. However, after 42 days of treatment with genistein, R-85 and captopril, a non-significantly increase in the feed consumption per 100 g rat was found as compared to L-NAME induced hypertensive rats per week.

3.3 Effects of the Genistein, R-85 and Captopril on Water Intake on L-NAME Induced Hypertensive Male Wistar Rats

Table 3 and Fig. 3 showing the effect of genistein, R-85 and captopril on water consumption per 100 g rat in L-NAME induced hypertensive male wistar rats. There was a significant difference in water intake per 100 g rat was found in third, fifth and sixth week between groups, however an increase in water intake observed in L-NAME hypertensive rats. Treatment withgenistein, R-85 and captopril reduces the water intake starting from the second week to sixth week. In the third, fifth and sixth week of treatment, water intake of rats treated with genistein, R-85 and captopril produces significant difference. The changes with treatment of genistein, R-85 and captopril are comparable with water intake of control group.

3.4 Effects of the Genistein, R-85 and Captopril Onrelative Weight of Liver, Heart and Kidney on L-NAME Induced Hypertensive Male Wistar Rats

The effects of the drugs on the relative weight of liver, heart and kidney after 42 days of treatment period are summarized in Table 4, Fig. 4 (A,B,C). A significant ($P < 0.05$) increase in the relative weights of the liver wasfound inL-NAME hypertensive groupcompared to control rats. In treatment group R-85 and captopril significantly decrease in the relative weight of liver was found compared to L-NAME.
However relative weight of heart was non-significantly increased in rats treated with L-NAME compared to control.

A significant increase in the relative weight of kidney was observed in L-NAME treated rats compared to control. In treatment group of genistein, R-85 and captopril, relative weight of kidney was decreased significantly in rats as compared to L-NAME hypertensive rats.

The macroscopic examination of organs of control and treated animals did not show remarkable changes in color and texture (Image 1).

There was scanty literature available on antihypertensiveaction of phytoestrogen ‘genistein’ and homeopathic combination ‘R-85’ and hence the present study conducted to analyze their antihypertensive action in NO deficient hypertensive model. L-NAME is a nitric oxide synthase (NOS) inhibitor which is commonly used in research to induce hypertension in rat [13]. Studies have showed that NO is involved in the regulation of feed and water consumption [14]. The present study showed there was an improvement in body weight of rats treated with genistein, R-85and captopril compared to L-NAME hypertensive rats, which is comparable to control group.

This increase in body weight of treated rats was found in consonance to the increase in feed intake particularly at sixth week of experimental period similarly. A decrease in water intake representing thirst was also observed in the rat treated with genistein, R-85and captopril compared to L-NAME, deducing that said treatments helping to decrease the water intake of hypertensive rats. Earlier study hasshown that increased nitric oxide level can stimulate feed intake by influencing brain appetite center [15] and reduces Angiotensin II levels [16], which lead to decrease in feed intake and increased intake of water.In present study outcome may be because of the rise in nitric oxide levels in hypertensive rats following treatment with genistein, R-85and captopril.

Hypertension is responsible for serious tissue damages which are characterized by endothelial dysfunction [17], cardiac alteration and renal functions [18]. Thepresent study revealed that weight of liver, heart and kidney of rats were increased may be to combat the detoriating effect of hypertension produced by L-NAME. Genistein, R-85 and captoprilinhibitsthe weight gain of organs as observed in L-NAME treated group. Increased in heart weight can be linked to fibrosis and cardiomyocyte remodeling due to constant high pressure and a low concentration of nitric oxide [19]. In response to chronic

pressure or volume overload seen in hypertension, triggers the excessive production of angiotensin II [20]. Angiotensin II, in turn, promotes cardiomyocyte growth, leading to an increase in cardiac mass [20]. Kidney plays a critical role in the maintaining balance between body's water and electrolyte. Hypertension is a significant risk factor that predisposes both the liver, kidneys [6,21] and heart dysfunction. Inhibition of nitric oxide causes microvascular changes which impairs hepatic and renal perfusion, leading to damage of organs [22]. Macroscopic analysis of target organs (liver, heart and kidney) of treatment of rats did not showed changes in colour and texture compared with the control group. The result of present findings suggests that the treatment with genistein, R-85 and captopril may help in the reduction in organ damage, by an increase in NO levels.

4. CONCLUSION

The present study finding discloses that genistein, R-85and captoprileffectively helped to combat theadverse effects of hypertension induced by L-NAME in male wistar rats. Their long term antihypertensive effect can attribute to the ability to improve arterial wall structure and endothelial function. Thus, present study demonstrates that genistein, R-85 and captopril can bepotential candidates for the treatment of related pathologies develops during hypertension and can be used as adjunct in the main antihypertensive therapy.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

ACKNOWLEDGEMENT

The author is grateful to The Department of Veterinary Pharmacology and Toxicology, Faculty of Veterinary and Animal Science, RGSC-Banaras Hindu University, Barkachha, Mirzapur-231001 (Uttar Pradesh) for providing necessary research facilities to carry out the research activities.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Al Ghorani H, Gotzinger F, Bohm M, Mahfoud F. Arterial hypertension-Clinical trials update. Nutrition, Metabolism, and Cardiovascular Diseases NMCD. 2021;32 (1):21–31
2. A Global Brief on Hypertension. Silent Killer, Global Public Health Crisis. World Health Day. World Health Organisation; 2013.
Available:https://apps.who.int/iris/bitstream/handle/10665/79059/WHO_DCO_WHD_2013.2_eng.pdf?sequence=1&isAllowed=y.
(Last accessed on 2020 Mar 27).
3. Ushakov AV, Ivanchenko VS, Gagarina AA. Psychological stress in pathogenesis of essential hypertension. Curr Hypertens Rev. 2016;12:203–214.
4. Kopincova J, Puzserova A, Bernatova I. L-NAME in the cardiovascular system—Nitric oxide synthase activator? Pharmacological Reports. 2012;64:511–520.
Available:https://doi.org/10.1016/j.pharep.2012.05.008
5. Silambarasan T, Manivannan J, Krishna Priya M, Suganya N, Chatterjee S., Raja B. Sinapic acid prevents hypertension and cardiovascular remodeling in a pharmacological model of nitric oxide inhibited rats. PLoS One. 2014;9 (e115682).
Available:https://doi.org/10.1371/journal.pone.0115682
6. Sureda A, Sanches Silva A, Sánchez-Machado DI, et al. Hypotensive effects of genistein: From chemistry to medicine. Chemico-Biological Interactions. 2017;268: 37–46.
Available:https://doi.org/10.1016/j.cbi.2017.03.007
7. Kretchy IA, Owusu-Daaku F, Danquah S. Patterns and determinants of the use of complementary and alternative medicine: A cross-sectional study of hypertensive patients in Ghana. BMC Complementary and Alternative Medicine. 2014;14:44.
Available:https://doi.org/10.1186/1472-6882-14-44
8. Abdel-Rahman RF, Hessin AF, Abdelbaset M, Ogaly HA, Abd-Elsalam RM, Hassan SM. Antihypertensive effects of roselle-olive combination in L-NAME-induced hypertensive rats. Journal of Hypertension Research; 2017. Article 9460653.
Available:https://doi.org/10.1155/2017/9460653

9. Maiti S, Ali KM, Jana K, Chatterjee K, De D, Ghosh D. Ameliorating effect of mother tincture of *Syzygium jambolanum* on carbohydrate and lipid metabolic disorders in streptozotocin-induced diabetic rat: Homeopathic remedy. Journal of Natural Science, Biology, and Medicine. 2013;4: 68–73.
10. Wu H, Lam TYC, Shum TF, Tsai T, Chiou J. Hypotensive effect of captopril on deoxycorticosterone acetate-salt induced hypertensive rat is associated with gut microbiota alteration. Hypertension Research. 2022;45:270–282.
11. Akhigbe RE, Ige SF, Afolabi AO, Oyeyipo PI, Ajao FO, Ajayi FA. Water balance and serum levels of some electrolytes in oral contraceptive treated female wistar rats. The Journal of Medical Sciences. 2008;8 (6):591–594.
12. Snedecor GW, Cochran WG. Statistical methods, 8th Edition, Iowa State University Press, Ames; 1994.
13. Kho J, Tian X, Wong WT, et al. Argininosuccinate lyase deficiency causes an endothelial-dependent form of hypertension. The American Journal of Human Genetics. 2018;103(2):276–287.
14. Furstenau CR, Ramos DB, Vuaden FC, et al. L-NAME treatment alters ectonucleotidase activities in kidney membranes of rats. Life Sciences. 2010;87(9-10):325–332.
15. McGavin JJ, Cochkanoff NL, Poole EI, Crosby MK. 2-arachidonylglycerol interacts with nitric oxide in the dorsomedial hypothalamus to increase food intake and body weight in young male rats. Neuroscience Letters. 2019;698: 23–32.
Available:https://doi.org/10.1016/j.neulet.2019.01.042
16. Saad WA, Guarda IFMS, De Arruda Camargo LA, et al. Lateral hypothalamus lesions influence water and salt intake, and sodium and urine excretion, and arterial blood pressure induced by L-NAME and FK 409 injections into the median preoptic nucleus in conscious rats. Life Sciences. (2004); 75(6): 685–697.
Available:https://doi.org/10.1016/j.lfs.2004.02.025
17. Zanfolin M, Faro R, Araujo E, et al. Protective effect of BAY 41-2272 (sGC stimulator) on hypertension and heart hypertrophy induced by chronic L-NAME treatment in rats. Journal of Cardiovascular Pharmacology and Therapeutics. 2006;47 (3):391–395.
Available:https://doi.org/10.1177/10742480604700306
18. Panchal SK, Poudyal H, Iyer A, et al. High-carbohydrate high-fat diet-induced metabolic syndrome and cardiovascular remodeling in rats. Journal of Cardiovascular Pharmacology and Therapeutics. 2011;57(1):51–64.
Available:https://doi.org/10.1177/1074248410382977
19. Jiang H, Zhang C, He W. The effects of *Dracocephalumheterophyllum* Benth flavonoid on hypertrophic cardiomyocytes induced by angiotensin II in rats. Medical Science Monitor. 2018; 24:6322–6330.
Available:https://doi.org/10.12659/MSM.910748
20. Kim JH, Jiang YP, Cohen IS, Lin RZ, Mathias RT. Pressure-overload-induced angiotensin-mediated early remodeling in mouse heart. PLoS One. 2017;12(5):1–17.
Available:https://doi.org/10.1371/journal.pone.0177461
21. Ribiere C, Jaubert AM, Gaudiot N, et al. The relationship between lipid profile and severity of liver damage in cirrhotic patients. Life Sciences. 2018;10(4):285–288.
Available:https://doi.org/10.1016/j.lfs.2017.12.022
22. Tsuchiya K, Tomita S, Ishizawa Ket al. Dietary nitrite ameliorates renal injury in L-NAME-induced hypertensive rats. Nitric Oxide. 2010;22(2): 98–103.
Available:https://doi.org/10.1016/j.niox.2009.11.005

Peer-review history:
The peer review history for this paper can be accessed here:
https://prh.mbimph.com/review-history/4176