RESEARCH PAPER

Isopulegol Ameliorates Hypertension-Associated Oxidative Stress and Cardiovascular Dysfunction in L-NAME-Induced Hypertensive Rats

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ABSTRACT

Background: Hypertension, a major contributor to cardiovascular morbidity and death, is directly linked to endothelial dysfunction and oxidative stress. Although Isopulegol, a naturally occurring monoterpene, has antioxidant properties, its ability to decrease blood pressure is unknown. Objective: This study assessed Isopulegol's cardioprotective and antihypertensive properties in rat model of hypertension brought on by L-NAME.

Methods: hypertension was induced in male Wistar rats by conduct of Nω-nitro-L-arginine methyl ester in their drinking water for four weeks. Isopulegol was supplied once daily for 30 days. Systolic and diastolic blood pressures were measured using a tail-cuff plethysmography system. Cardiac function was measured via the Langendorff isolated perfused heart preparation. Histopathological changes in the heart and aorta, oxidative stress markers, and levels of enzymatic and non-enzymatic antioxidant were assessed. Enalapril (0.5 mg/kg) was employed as the reference drug.

Results: L-NAME markedly lowered antioxidant defenses, increased lipid peroxidation, decreased cardiac function, and raised blood pressure. Treatment with Isopulegol enhanced heart function, reduced oxidative stress, raised antioxidant levels, and significantly lowered systolic and diastolic blood pressure. Cardiac and aortic histopathological changes were significantly reduced. Isopulegol has effects similar to those of enalapril.

Conclusion: Isopulegol has notable cardioprotective and antihypertensive benefits in rats with L-NAME-induced hypertension, which are probably mediated by endothelial-protective and antioxidant mechanisms.

Keywords: Oxidative Stress; Isopulegol; L-Name; Hypertension; Antioxidant; Cardio protection

How to cite this article: Ragul K, Dhakshinamoorthi R, Raja B. Isopulegol Ameliorates Hypertension-Associated Oxidative Stress and Cardiovascular Dysfunction in L-NAME-Induced Hypertensive Rats. Int J Drug Deliv Technol. 2026;16(63s):1328-1337. DOI: 10.25258/ijddt.16.63s.132

Source of support: Nil

Conflict of interest: None

1.INTRODUCTION

Hypertension is a major worldwide public health concern and a major contributor to cardiovascular deaths and disabilities.[1] Persistently high blood pressure greatly increases the risk of myocardial infarction, stroke, heart failure, and chronic renal disease[2]. It has been repeatedly demonstrated that effective blood pressure management improves clinical outcomes and lowers cardiovascular events[3]. Endothelial dysfunction has a major impact on the development and course of hypertension. Through vasodilation, reduction of smooth muscle proliferation, and regulation of platelet aggregation, nitric oxide (NO), a calming agent generated by the endothelium, is crucial for preserving vascular tone and homeostasis[4,5] Reduced NO bioavailability leads to chronic hypertension and increased vascular resistance[6]. Endothelial dysfunction, oxidative stress, and cardiovascular remodeling are characteristics of a reproducible model of hypertension that closely reflects clinical essential hypertension when nitric oxide synthase is experimentally suppressed via L-NAME[7]. Terpenoids are naturally occurring phytochemicals having a multiplicity of biological response, including cardioprotective and antioxidant properties[8]. The monoterpene alcohol Isopulegol, which is present in the essential oils of a number of therapeutic plants, has been shown to strengthen the body's natural defenses against oxidative damage[9]. Despite these characteristics, not enough research has been done on its impact in hypertension and related cardiovascular dysfunction[10].

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The current study sought to evaluate the antihypertensive and cardioprotective effects of Isopulegol in a rat model of hypertension caused by L-NAME, with an emphasis on hemodynamic metrics, cardiac function, oxidative stress markers, antioxidant status, and histological abnormalities.

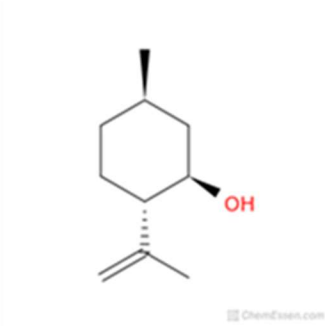


Figure 1. structure of Isopulegol

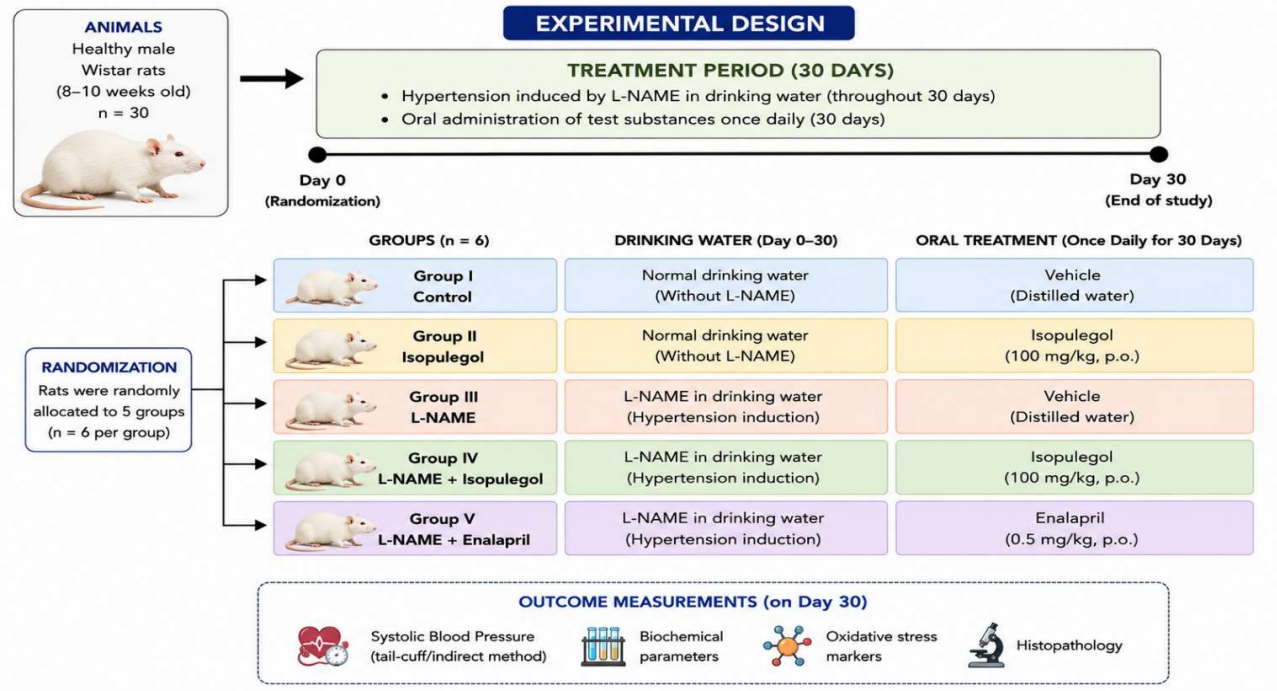
2. MATERIALS AND METHODS

Male Wistar albino rats (180–220 g, 8–10 weeks old) were maintained under standard laboratory conditions, including pelleted diet, ad libitum water access, a 12:12 h light/dark cycle, and temperature of 25 ± 2 °C. All experimental protocols were approved by the Institutional Animal Ethics Committee of Annamalai University, adhering to CPCSEA guidelines (Proposal No. 1355/2023).

2.1 Drugs and chemicals

Isopulegol and L-NAME were supplied by Sigma Chemical Co. (USA). All of the remaining reagents were of analytical quality and were acquired from reliable commercial suppliers.

2.2 Experimental design



2.3 Blood pressure measurement

Systolic and diastolic blood pressure was recorded using a non—invasive tail-cuff plethysmography device following acclimatization. Mean values were calculated using accurate readings.

2.4 Langendorff isolated heart preparation

Heart function was measured using the Langendorff technique. The left ventricular pressure parameters (+dp/dt, -dp/dt, and LVEDP) were recorded using a pressure transducer and data collection system.

2.5 Biochemical analyses

Markers of lipid peroxidation, as well as enzymatic and non-enzymatic antioxidants, were quantified in plasma and tissue samples using established standard protocols.

2.6 Histopathological examination

Heart and aortic tissues were processed, sliced, and kept in neutral buffered formalin before being stained with hematoxylin and eosin under a microscope.

2.7 Statistical analysis

Duncan multiple range test was used to assess the outcomes of a one way ANOVA. The results are shown as mean ± SD, and $P<0.05$ is considered statistically significant.

3. RESULTS

3.1 BLOOD PRESSURE MEASUREMENTS

Isopulegol (100 mg/kg) modulated systolic and diastolic blood pressure in rats with L-NAME induced hypertension, as depicted in Figures 2 and 3. Chronic L-NAME administration markedly elevated systolic and diastolic blood pressures relative to control rats ($P < 0.05$). Treatment with enalapril or Isopulegol substantially mitigated the L-NAME induced hypertension. The antihypertensive effects of Isopulegol and enalapril did not differ significantly ($P<0.05$).

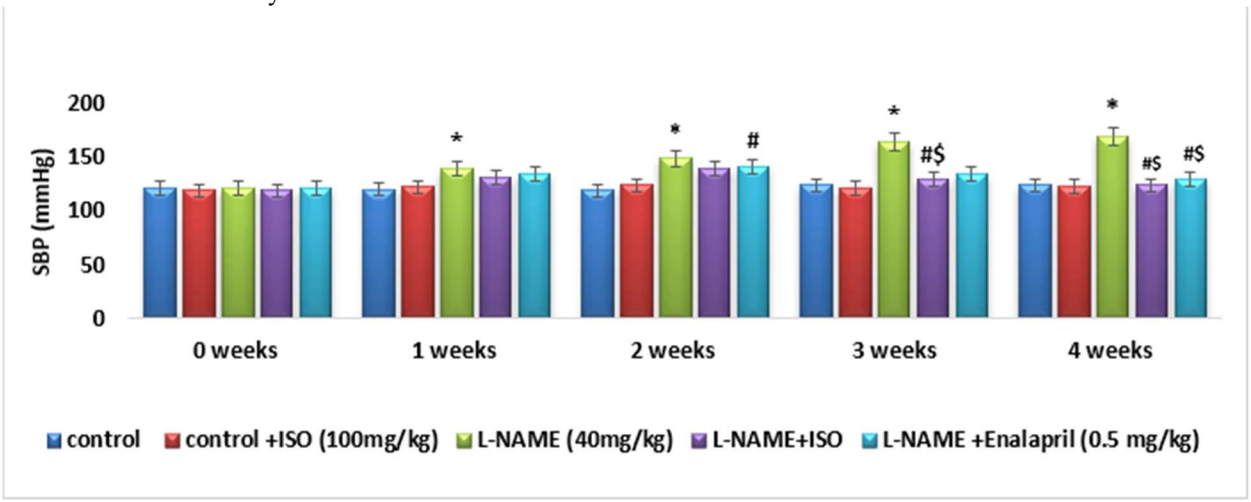


Figure 2. systolic blood pressure levels in control rats, those with L-NAME-induced hypertension, and Isopulegol-treated groups(n = 6). Values are expressed as mean ± standard deviation from six animals per group. DMRT's was employed for statistical analysis. Bars without a shared superscript letter represent significant differences ($P<0.05$) Asterisks (*) signify differences from the control group, whereas hashtags (#) denote differences from the L-NAME-treated group.

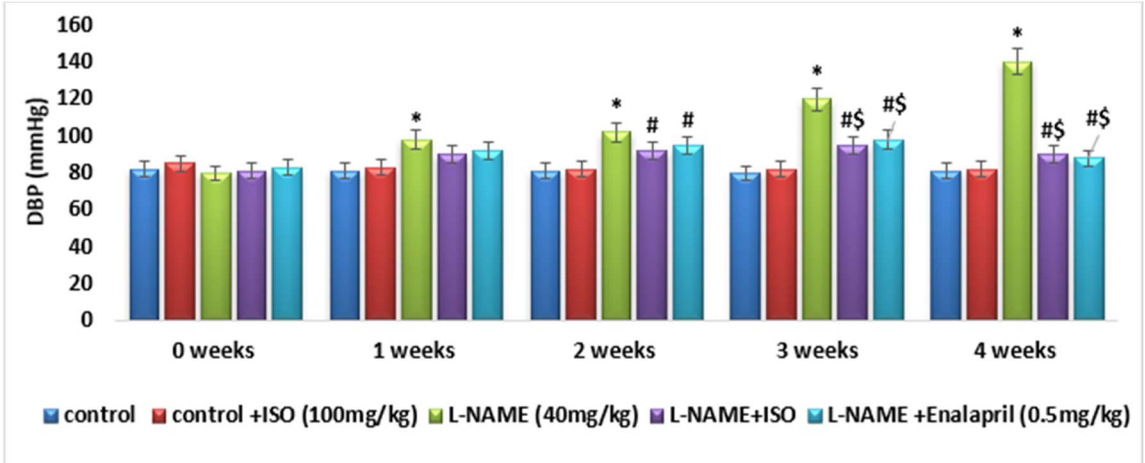


Figure 3. Diastolic blood pressure in control and L-NAME induced hypertensive rats, with or without Isopulegol administration. Values are presented as mean ± standard deviation from six animals per group(n = 6). Statistical

significance was assessed via Duncan's multiple range test. Bars lacking a shared superscript letter reflect significant differences($P<0.05$). Asterisks (*) denote significance versus controls, while hashes (#) denote significance versus L-NAME-treated rats.

3.2 Cardioprotective Effects of Isopulegol

The Langendorff isolated heart preparation was utilized to assess cardiac function. Rats administered L-NAME demonstrated significantly reduced maximal rates of left ventricular pressure development (+dp/dt) and relaxation (−dp/dt) compared to control animals ($P < 0.05$), suggesting compromised diastolic and systolic function. Following Isopulegol treatment, the +dp/dt and −dp/dt values were considerably recovered to normal levels ($P < 0.05$), indicating improved ventricular performance (Figure 4A).

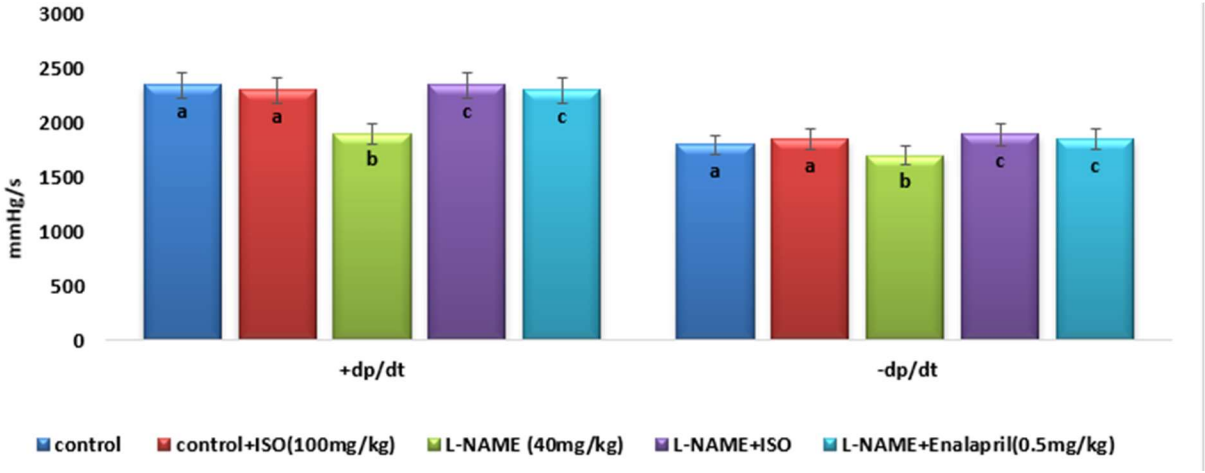


Figure 4A. Cardiac ventricular function in rats with hypertension. Data represent mean values for six animals per group (n = 6), with vertical bars indicating standard deviation. Statistical significance was determined using DMRT ($P < 0.05$).

The left ventricular end-diastolic pressure (LVEDP) of rats treated with L-NAME was significantly greater than that of controls ($P < 0.05$). Treatment with Isopulegol considerably reduced LVEDP, indicating improved diastolic function. Similar to enalapril, Isopulegol decreased LVEDP (Figure 4B).

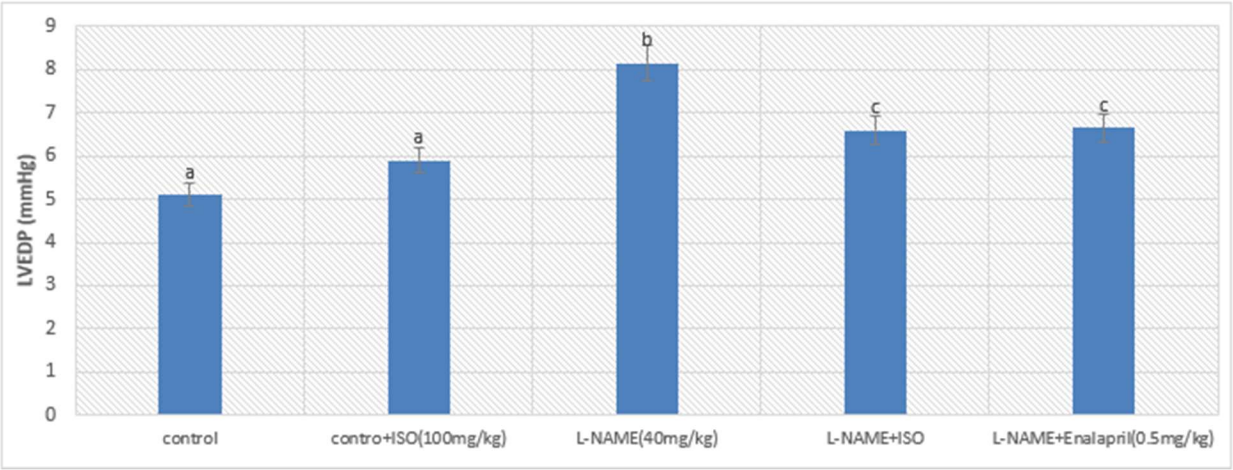


Figure 4B: illustrates the impact of Isopulegol on left ventricular end-diastolic pressure in control and L-NAME-induced hypertensive rats. Values are reported as mean ± standard deviation from animals per group(n = 6). Bars lacking a shared superscript letter indicate significant differences, as evaluated by Duncan's multiple range test($P < 0.05$).

3.3 Lipid Peroxidation Biomarkers

Lipid hydroperoxides (LOOH) and thiobarbituric acid–reactive compounds (TBARS) were determined in

plasma and cardiovascular tissues to assess lipid peroxidation. TBARS and LOOH levels were substantially elevated by L-NAME administration, suggesting increased oxidative stress ($P < 0.05$). Treatment with Isopulegol or enalapril significantly reduced these lipid peroxidation markers ($P < 0.05$). Dramatically, Isopulegol (100 mg/kg) substantially reduced oxidative stress markers, indicating strong antioxidant action.

Parameter	Groups					
	Sample	Control	Control+ Isopulegol	L-NAME	L-NAME+ Isopulegol	L-NAME+ Enalapril
TBARS	Plasma(mmol/d)	0.16±0.01[a]	0.15±0.01[a]	0.41±0.03[b]	0.24±0.02[c]	0.21±0.02[c]
	Heart	0.60±0.05 [a]	0.56±0.04 [a]	2.56±0.19 [b]	0.95±0.07[c]	0.94±0.07[c]
	Aorta	0.54 ±0.04[a]	0.51±0.04 [a]	1.80±0.14 [b]	0.76±0.06[c]	0.78±0.06[c]
LOOH	Plasma(mmol/d)	9.3±0.70[a]	9.54±0.73 [a]	21.25±1.62 [b]	13.12±1.00[c]	11.50±0.88[c]
	Heart	63.35±4.82[a]	61.59±4.71[a]	121.47±9.25[b]	77.60±5.94[c]	78.22±5.96[c]
	Aorta	74.56±5.68[a]	72.33±5.54[a]	107.25±8.17[b]	83.45±6.39[c]	84.12±6.41[c]

Table 1: effects on Isopulegol on lipid hydroperoxide and TBARS levels in tissues and plasma of control and L-NAME induced hypertensive rats. Data are expressed as mean ± SD. Statistical significance was determined using DMRT ($P<0.05$).

3.4 Effects on Enzymatic Antioxidants

Table 2 summarizes the activities of glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) in erythrocytes and cardiovascular tissues. Rats treated with L-NAME had substantially reduced levels all enzymatic antioxidant activities than controls ($P < 0.05$), suggesting a compromised antioxidant defense. Following treatment with either Isopulegol or enalapril, SOD, CAT, and GPx activity considerably recovered ($P < 0.05$), with Isopulegol demonstrating a significant recovery of enzymatic antiodidant status

Parameter	Groups					
	Sample	Control	Control+ Isopulegol	L-NAME	L-NAME+ Isopulegol	L-NAME+ Enalapril
Superoxide dismutase	Erythrocyte	8.12±0.62[a]	8.07±0.62 [a]	4.75±0.36 [b]	7.08±0.54[c]	7.95±0.61[c]
	Heart	8.21±0.63 [a]	8.02±0.61 [a]	4.67±0.36 [b]	6.42±0.49[c]	7.12±0.54 [c]
	Aorta	13.11±1.0 [a]	13.76±1.05 [a]	8.61±0.66 [b]	9.11±0.70[c]	10.45±0.80 [c]
Catalase	Erythrocyte	171.1±13.03[a]	173.2±13.26[a]	102.2±7.78[b]	151.37±11.59[c]	151.35±11.75[c]
	Heart	51.24±3.90 [a]	52.24±4.0 [a]	35.26±2.68[b]	45.19±3.46 [c]	47.20±3.59[c]
	Aorta	54.51±4.15[a]	55.24±4.23[a]	36.46±2.78[b]	48.24±3.69[c]	49.56±3.77[c]
Glutathione peroxidase	Erythrocyte	15.9±1.21[a]	15.31±1.17[a]	7.15±0.54 [b]	12.91±0.99[c]	13.5±1.03[c]
	Heart	7.89±0.6 [a]	7.45±0.57[a]	5.12±0.39 [b]	6.39±0.49[c]	7.29±0.56[c]

	Aorta	8.29±0.63 [a]	8.45±0.65 [a]	6.22±0.47 [b]	8.05±0.62[c]	9.02±0.69[c]

Table 2: Effects of Isopulegol on CAT, GPx, and SOD activities in tissues and erythrocytes of normotensive and L-NAME-induced hypertensive rats. Data are expressed as mean ± SD. Statistical significance determined using DMRT ($P < 0.05$).

3.5 Effects on non-enzymatic antioxidants

Table 3 displays the concentrations of vitamin C, vitamin E, and reduced glutathione in tissues and plasma, in the L-NAME induced hypertension model, non-enzymatic antioxidant were substantially ($P<0.05$) depleted. Treatment with Isopulegol or enalapril resulted in markedly elevated levels of GSH, vitamin C, and vitamin E pertaining to the L-NAME group ($P< 0.05$). Notably, Isopulegol at 100 mg/kg substantially augmented non-enzymatic antioxidant levels, thereby effectively alleviating oxidative stress.

Parameter	**Groups**					
	Sample	Control	Control+ Isopulegol	L-NAME	L-NAME+ Isopulegol	L-NAME+ Enalapril
Vitamin- C	Plasma(mg/dl)	3.22±0.25[a]	3.45±0.26 [a]	0.89±0.07 [b]	3.04±0.23[c]	4.15±0.32[c]
	Heart	0.61±0.05 [a]	0.63±0.05 [a]	0.39±0.03 [b]	0.53±0.04[c]	0.65±0.05[c]
	Aorta	0.69±0.05 [a]	0.72±0.06 [a]	0.48±0.04[b]	0.60±0.05[c]	0.70±0.05[c]
Vitamin- E	Plasma(mg/dl)	3.15±0.24 [a]	3.49±0.27 [a]	0.98±0.07 [b]	2.79±0.21[c]	3.15±0.24[c]
	Heart	5.12±0.39 [a]	5.45±0.42 [a]	3.87±0.29 [b]	4.72±0.36[c]	5.77±0.44[c]
	Aorta	4.51±0.34 [a]	5.11±0.39 [a]	4.17±0.32 [b]	5.00±0.38[c]	5.55±0.42[c]
Reduced glutathione	Plasma(mg/dl)	33.11±2.52[a]	34.72±2.66[a]	21.20±1.61[b]	31.24±2.39[c]	32.51±2.48[c]
	Heart	7.78±0.59 [a]	7.53±0.58[a]	4.22±0.32 [b]	6.06±0.46[c]	7.01±0.53[c]
	Aorta	6.45±0.49 [a]	6.33±0.48[a]	3.34±0.26 [b]	6.12±0.47[c]	6.21±0.47[c]

Table 3. Concentrations of vitamin-C, vitamin-E, and GSH in plasma from control and L-NAME induced hypertensive rats treated with Isopulegol. Values are reported as mean ± standard deviation. Statistical significance was elevated using DMRT ($P<0.05$).

3.6 Histopathology of Heart and Aorta

Histopathological examination of cardiac tissue revealed well-organized myocardial fibers in control and Isopulegol-alone treated rats. In contrast, L-NAME-induced hypertensive rats exhibited myocardial hypertrophy, fiber disarray, and inflammatory cell infiltration. Treatment with Isopulegol or enalapril markedly attenuated these pathological changes and preserved myocardial architecture (Figure 5A–E).

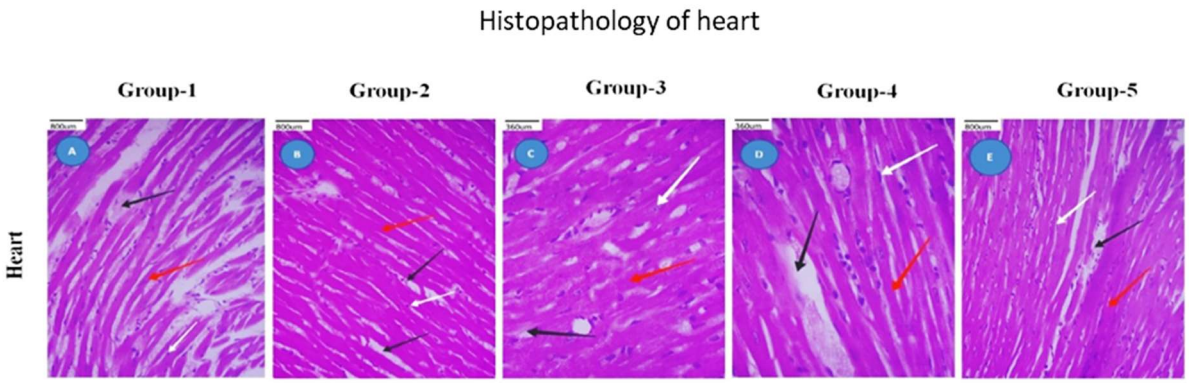


Figure 5. Myocardial slices from rats with L-NAME-induced hypertension and control that were stained with H&E. (A) Group I control rats with undamaged cardiac fibers. (B) Group II control rats that received 100 mg/kg of Isopulegol had preserved architecture. (C) Group III rats treated with L-NAME exhibit hypertrophy and fiber disruption. (D) Partial restoration with L-NAME + Isopulegol (100 mg/kg; Group IV). (E) Group V, L-NAME + enalapril (0.5 mg/kg), demonstrates enhanced myocardial integrity.

Similarly, aortic sections from L-NAME-treated rats showed increased adventitial fat deposition and mild sub-intimal fatty infiltration. Isopulegol and enalapril treatments substantially restored normal aortic structure, with preservation of the intima, media, and adventitia (Figure 6A–E).

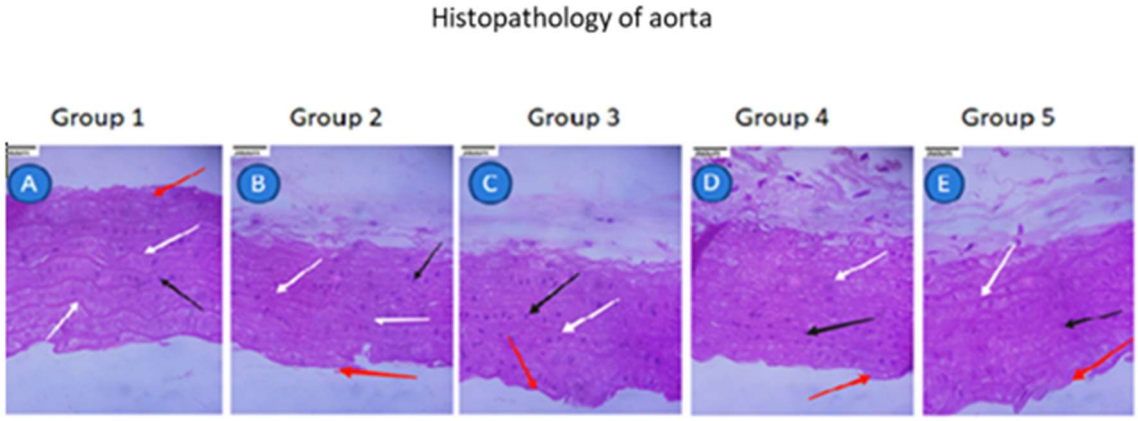


Figure 6. Aortic sections from rats with control and L-NAME-induced hypertension stained with H&E. (A) Control (Group I) using standard media, intima, and adventitia. (B) Control + Isopulegol (Group II) demonstrates structural preservation. (C) L-NAME (Group III) demonstrating sub-intimal lipid infiltration and adventitial fat buildup. (D) L-NAME + partial restoration Isopulegol (Group IV). (E) Near-normal aortic morphology is displayed by L-NAME + enalapril (Group V).

4. DISCUSSION

Hypertension, a major risk factor for the development of cardiovascular diseases, is strongly linked with endothelial dysfunction, vascular remodeling, and oxidative stress[11]. Nitric oxide (NO) is vital for maintaining vascular homeostasis because of its anti-inflammatory, anti-proliferative, and vasodilatory characteristics. L-NAME reveals an established experimental model that closely mimics human essential hypertension by continuously blocking nitric oxide synthase.[12] As a result, peripheral resistance rises, vasoconstriction persists, and hypertension emerges[13].

In the rat model of hypertension established by L-NAME administration, oral Isopulegol substantially reduced rises in both systolic and diastolic blood pressure in a recent research.[14] Enalapril, a popular ACE inhibitor used in clinical settings, had similar effects in lowering blood pressure. These results reveal that Isopulegol has potent antihypertensive properties,

most likely via regulating oxidative stress pathways and improving endothelial function[10].

Oxidative stress has a major impact on the pathogenesis of hypertension and associated cardiovascular remodeling[13]. Overproduction of reactive oxygen species (ROS) increases vascular damage, promotes lipid peroxidation, and decreases NO bioavailability. TBARS and LOOH, two markers of lipid peroxidation in in plasma and cardiovascular tissues, were markedly elevated by L-NAME administration in the current investigation, demonstrating increased oxidative stress under hypertension conditions[15]. Treatment with Isopulegol significantly reduced these lipid peroxidation products, indicating its potent antioxidant activity and ability to reduce oxidative tissue damage[16].

The antioxidant defense system is formed by enzymatic antioxidants like SOD,CAT,GPX which are crucial for eliminating ROS and maintaining redox equilibrium. Due to L-NAME-induced hypertension, these enzymes' activity dramatically dropped in this study, indicating a reduced potential for antioxidant defense[17]. In erythrocytes and cardiovascular tissues, Isopulegol supplementation significantly increased SOD, CAT, and GPx activities, indicating an improvement in endogenous antioxidant defenses Blood pressure could return to normal as a result of improved NO bioavailability and vascular relaxation brought on by this repair[18].

In addition to antioxidant enzymes, non enzymatic compounds such vitamin-vitamin E, and reduced glutathione(GSH) are crucial for lowering free radicals and halting oxidative damage to cell membranes[19]. The major decrease in these antioxidants in rats given L-NAME provided extra proof of oxidative stress. After Isopulegol was administered, the concentrations of vitamin-C, vitamin-E, GSH tissue and plasma were successfully returned to normal, highlighting its role in preserving redox equilibrium[20]. Isopulegol's potential as a naturally occurring antioxidant was highlighted by the fact that its antioxidant activity was notably comparable to, and occasionally superior to, that of the reference medication enalapril[21].

Myocardial fibrosis, increased ventricular stiffness, and reduced systolic and diastolic performance are the main symptoms of cardiac dysfunction, a significant side effect of long-term hypertension[22]. According to the current study, L-NAME-induced hypertension considerably reduced the rates of left ventricular pressure development (+dp/dt) and relaxation (−dp/dt), but raised left ventricular end-diastolic pressure (LVEDP), indicating decreased myocardial contractility and relaxation[23]. These functional parameters were significantly improved by Isopulegol therapy, suggesting increased ventricular function and decreased myocardial stiffness. The reduction of oxidative stress and maintenance of the structural integrity of the heart are probably responsible for these gains[24].

Histopathological analysis provided additional evidence of Isopulegol's cardioprotective benefits. Rats with L-NAME-induced hypertension showed vascular structural changes in the aorta, myocardial dysfunction, and inflammatory cell infiltration[25]. These pathological alterations were significantly reduced by Isopulegol treatment, which restored vascular integrity and myocardial architecture to almost normal[26]. The observed histological improvements, which further emphasize Isopulegol's protective effect against hypertension-induced cardiovascular remodeling, corroborate the functional and biochemical results[27].

The study's overall findings suggest that Isopulegol's antioxidant properties, which reduce oxidative stress, preserve endothelial function, and prevent the structural and functional deterioration of cardiovascular tissues, are primarily responsible for its antihypertensive and cardioprotective effects. Although the current study offers strong preclinical data, more research examining molecular signaling pathways and long-term safety is necessary to completely clarify Isopulegol's therapeutic potential in the treatment of hypertension.

5. CONCLUSION

Isopulegol exhibited significant antihypertensive and cardioprotective effects in L-NAME-induced hypertensive rats by lowering blood pressure, improving cardiac function, reducing oxidative stress, enhancing antioxidant defenses, and attenuating histopathological alterations in the heart and aorta. These findings suggest that Isopulegol may serve as a promising natural therapeutic agent for the management of hypertension and its associated cardiovascular complications.

Author contributions

This concept, design, experimentation, data analysis, and manuscript preparation were all done by the authors.

Conflict of interest

The authors declare no conflict of interest.

Funding

No external funding was received for this study.

Ethical approval

All animal treatments were carried out in compliance with CPCSEA norms and approved by Annamalai University's Institutional Animal Ethics Committee (Proposal No. 1355/2023).

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