10.21608/avmj.2025.365998.1612 Assiut University web-site: www.aun.edu.eg

THERAPEUTIC POTENTIAL OF THYMOL-RICH *THYMUS VULGARIS* ESSENTIAL OIL IN MITIGATING HYPERTENSION AND ASSOCIATED ORGAN DAMAGE

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Received: 29 April 2025; **Accepted:** 21 June 2025

ABSTRACT

Hypertension is a significant global health issue that contributes to various cardiovascular and renal diseases. This study investigated the therapeutic potential of *Thymus vulgaris* essential oil, specifically its primary component, thymol, in mitigating hypertension and related complications. Thirty-two male Sprague-Dawley rats were divided into four groups: normal control, L-NAME-induced hypertension (40mg/kg), L-NAME + high-dose thymol oil (10 mg/kg), and L-NAME + low-dose thymol oil (5 mg/kg). Blood pressure, lipid profiles, renal function markers, inflammatory cytokines (TNF-α, IL-6), apoptosis markers (Annexin-V, Bcl-2), and histopathological changes were evaluated. GC–MS analysis of *Thymus vulgaris* essential oil confirmed thymol was the dominant compound (34.21%), suggesting its substantial pharmacological role. In hypertensive rats induced by L-NAME (40 mg/kg), the administration of high-dose thymol oil (10 mg/kg) significantly reduced the systolic and diastolic blood pressures, supporting its antihypertensive efficacy. Additionally, thymol improved lipid profiles by lowering triglyceride, total cholesterol, and LDL levels, while increasing HDL levels. Thymol oil also had protective effects on renal function, as evidenced by decreased levels of urea and creatinine, which are markers of renal dysfunction. Moreover, it reduced the levels of inflammatory markers such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) in the heart, aorta, and kidneys, indicating its anti-inflammatory properties. Flow cytometry and histopathological analysis revealed that thymol oil significantly reduced apoptosis, as evidenced by decreased Annexin-V expression and increased levels of the anti-apoptotic protein Bcl-2. Tissue damage in the heart, aorta, and renal tissues was markedly restored after administration of high-dose thymol, highlighting its potential for reversing hypertension-induced organ damage. These findings suggest that thymol-rich *Thymus vulgaris* essential oil offers a multifaceted approach for managing hypertension and its complications, providing both cardiovascular and renal protection.

Keywords: Hypertension, L-NAME, Thymus vulgaris, Apoptosis, Annexin-V

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INTRODUCTION

Cardiovascular diseases, particularly hypertension, remain a major factor impacting people's lives, despite considerable progress in diagnostic and therapeutic tools. Hypertension leads to damage in critical organs, eventually resulting in conditions such as heart failure, vascular injury, microvascular dysfunction, atherosclerosis, and renal impairment (Poznyak *et al.,* 2022). Evidence suggests that vascular remodelling, ultrastructural damage, and apoptosis in the heart, kidneys, and aorta contribute significantly to end-organ damage and failure, making hypertension a growing global health issue. Hypertensive vascular injury is strongly associated with the overexpression of inflammatory modulators, such as reactive oxygen species, while growth, inflammation, and fibrosis also contribute to arterial remodelling. Therefore, preventing arterial remodelling should be a key target in antihypertensive therapy (Li *et al.,* 2023).

The traditional use of medicinal plants has long been practiced worldwide for preventing and treating chronic conditions, including cardiovascular diseases, inflammatory diseases, arthritis, diabetes, and hypertension. The study aims to investigate the pharmacological properties of thymol, a bioactive compound in thyme that has shown promising effects in reducing blood pressure (Rahmani *et al.,* 2014). Thymol, chemically identified as 2-isopropyl-5-methylphenol, is a colourless crystalline monoterpene phenol (Pandey *et al.,* 2014). Its beneficial effects are largely attributed to its antioxidant, free radical-scavenging, antihyperlipidemic, and ionic homeostasis-maintaining properties. These pharmacological effects stem from the phenolic hydroxyl group in thymol's chemical structure, which allows it to neutralize free radicals and enhance endogenous antioxidant defenses (Lalhminghlui and Jagetia 2018).

Studies have demonstrated thymol's vasorelaxant activity in isolated rat aorta, showing that it induces endothelium-independent relaxation by releasing Ca^{2+} from the sarcoplasmic reticulum, reducing the sensitivity of contractile elements to Ca^{2+}, and preventing Ca^{2+} influx across the membrane (Peixoto-Neves *et al.,* 2010). Thymol also exerts anti-inflammatory effects by inhibiting cytokine and chemokine recruitment. Previous studies have revealed that thymol (1 - 10 mg/kg) can significantly lower blood pressure and heart rate in Wistar rats and rabbits, while decreasing the atrial contraction force and rate of spontaneous beating atria (Nagoor Meeran *et al.,* 2017). Its hypotensive and bradycardiac effects are linked to its Ca^{2+} channel-blocking properties.

This study investigated the therapeutic potential of *Thymus vulgaris* essential oil, specifically its primary component, thymol, in mitigating hypertension and related complications.

MATERIALS AND METHODS

Experimental animals

Thirty-two male adult Sprague–Dawley rats, aged 6–7 weeks and weighing between 200–220 g. The rats were housed individually in stainless steel cages under controlled conditions, maintaining a 12-hour light/dark cycle, a temperature of 24 ± 1°C, and a relative humidity of 52 ± 12%. Food and water were provided ad libitum, and the animals were acclimated for two weeks before the start of the experiment.

Ethics approval statement:

The experimental protocol adhered to the guidelines set by the Institutional Animal Care and Use Committee and was approved by the Research Ethics Committee (Approval no BUFVTM12-10-24).

Chemicals and natural agents

The chemicals and antioxidants used in this study include the following:
L-NAME (N(gamma)-nitro-L-arginine methyl ester hydrochloride, purity: 98%) was obtained from Sigma–Aldrich, USA. A freshly prepared L-NAME solution was administered orally at a dose of 40 mg/kg, three times per week, for six weeks (Altangerel *et al.,* 2024). Other reagents included Folin-Ciocalteu reagent (FCR), Trolox. ABTS and DPPH were procured from *Sigma–Aldrich*, USA. Additionally, 98% gallic acid was purchased from *Acros Organics*, Belgium. All other chemicals and solvents used were of high analytical grade and were supplied by *Fisher Scientific UK* (Bishop Meadow Road, Loughborough) (Mohammed *et al.,* 2020). *Thymus vulgaris L.* was obtained from Al-Harraz Co. for Agriculture Seeds, Herbs, and Medicinal Plants, Cairo, Egypt.

Thymus vulgaris L. thymol oil extraction:
This study focused on the extraction and analysis of thymol oil from *Thymus vulgaris L*., which was authenticated, followed by an estimation of its volatile content. A 50 g sample of dried leaves was subjected to water distillation for 4 hours via a Clevenger apparatus, as described previously (El-Gengaihi *et al.,* 2013). The extracted thymol oil was dehydrated using anhydrous sodium sulfate and stored in a deep freezer until analysis. Each extraction was performed in triplicate, and the mean oil yield was recorded as 10.2 ± 0.9 ml.

Gas chromatography–mass spectrometry analysis (GC–MS) conditions:
The chemical composition of the thymol oil was determined via gas chromatography-mass–mass spectrometry (GC–MS). The analysis was carried out via an Agilent Technologies GC–MS system equipped with a gas chromatograph (7890B) and a mass spectrometer detector (5977A). The identification of individual components was performed by comparing the fragmentation patterns of the compounds with those in the Wiley and NIST mass spectral libraries (Apel *et al.,* 2003).

Antioxidant activity of *Thymus vulgaris* thymol oil (In vitro study).

The antioxidant activity of *Thymus vulgaris* thymol oil was assessed via DPPH (1,1-diphenyl-2-picrylhydrazyl) and ABTS (2,2′-azinobis-3-ethylbenzothiazoline-6-sulfonate) free radical scavenging procedures. Various concentrations of thymol oil (10, 5, 2.5, 1.5, 1, 0.45, 0.3, 0.15, and 0.075 µg/mL) were tested, with ascorbic acid and Trolox serving as positive controls. The preparation of the DPPH and ABTS solutions followed the methods outlined by, with slight modifications. The reduction in the absorbances of DPPH and ABTS, and the calculation of the percentage of antioxidant activity were used to determine the antioxidant activity (Baliyan *et al.,* 2022).

Experimental design

Thirty-two rats were randomly and blindly assigned to four groups (8 rats per group) as follows:

- **(Normal Control):** Rats were provided a standard diet with no treatment for 28 days.
- **(L-NAME):** Rats were given daily oral doses of L-NAME (40 mg/kg) for 28 days **(Altangerel et al., 2024)**.

(L-NAME + high-dose volatile oil): Rats were received daily oral doses of L-NAME (40 mg/kg) combined with *Thymus vulgaris* thymol oil (10 mg/kg body) for 28 days **(Nagoor Meeran et al., 2017)**.

(L-NAME + low-dose volatile oil): Rats were given daily oral administration of L-NAME (40 mg/kg body weight/day) along with *Thymus vulgaris* thymol oil (5 mg/kg) for 28 days (Elshopakey *et al.,* 2021).

Throughout the experiment, doses were adjusted weekly on the basis of changes in body weight to ensure consistent dosing per kilogram of body weight across the entire study period for all groups.

Hypertension measurement:

A BP-2010 AUL non-invasive blood pressure monitoring system was utilized to measure the blood pressure from different animal groups (Su-Hong *et al.,* 2015). First, the airtightness of the instrument monitoring channel was verified, and the incubator temperature was set to 37°C and maintained at room temperature. The rats were then placed in a monitoring environment for 15 minutes within a fixed bag. During this time, the BP monitoring sensors were positioned around the root of the rats' tails. Once the signal became stable, the systolic blood pressure (SBP) and diastolic blood pressure (DBP) data were recorded and collected, with the volume adjusted to 1 ml/100 g based on the weight of the rats.

Blood samples and **tissue specimens**

Blood samples were taken from the eyes of the rats' retro-orbital plexus following anaesthesia with ketamine (100 mg/kg) and xylazine (10 mg/kg) (Soliman et al., 2025). Sera were separated using centrifugation at 3000 rpm for 15 minutes at 4 °C (Labore-zentrifuger, cooling centrifuge, 2k15, Sigma, Germany) and stored at -20°C for further lipid profile analysis. The rats were euthanized in accordance with the Animal Ethics Committee's guidelines following the collection of blood samples. The heart, aorta, and kidney tissues were dissected and cut into two sections. The initial portion was homogenized after being washed with sterile physiological saline and stored at -80°C for analysis via flow cytometry and ELISA. The second portion of each tissue sample was fixed in 10% formalin for histopathological analysis.

Biochemical analysis

The manufacturer's instructions were followed to measure urea and creatinine levels via colorimetric assays from Bio Diagnostic Company (Dokki, Giza, Egypt) (Cat. NO. UR2110 for urea and Cat. No. CR1250 for creatinine). Triglycerides were evaluated via the lipase technique, whereas cholesterol levels were determined via the cholesterol esterase method. Cholesterol was separated into HDL and LDL via phosphotungstic acid precipitation. (Apel *et al.,* 2003).

Enzyme-Linked Immunosorbent Assay (ELISA)

IL-6 and TNF-α levels were quantified via ELISA kits from CUSABIO (Cat. No: CSB-E04640r and CSB-E11987r, China) in accordance with the manufacturer's protocols (Çetin *et al.,* 2018).

Flow cytometry analysis

Flow cytometry was employed to detect apoptotic markers via the FITC Annexin V Apoptosis Detection Kit I (catalogue no. 556547) according to the propidium iodide (PI) staining method. This methodology was implemented to ascertain the number of necrotic and apoptotic cells (Wuputra *et al.,* 2022). The tissue samples were processed via

incubation with appropriate amounts of diluted enzymes in PBS, followed by cell filtration and centrifugation to remove clumps and debris. The cells were then resuspended in staining buffer for viability and cell count analysis (Sedik *et al.,* 2023). For anti-apoptotic marker analysis, a Bcl-2 monoclonal antibody (Bcl-2-100, Catalogue No. 13-8800) was used at a concentration of 0.5 mg/mL, with the immunogen being a synthetic peptide corresponding to residues 41- 54 of the human Bcl-2 protein (Sedik A *et al.,* 2023).

Histopathological examination

Heart, aorta, and kidney tissue samples were preserved in 10% neutral buffered formalin and then serially sectioned at 5 µm. Hematoxylin and eosin (HE) staining was used, and the tissue samples were examined under a light microscope. (Afifi *et al.,* 2017) (Altangerel *et al.,* 2024).

Statistical analysis

The statistical analysis was carried out using Two-way ANOVA using SPSS, ver. 27 (IBM Corp. Released 2013). Data were treated as a complete randomization design, according to Steel et al. (1997). Multiple comparisons were carried out applying the Duncan test. The significance level was set at $P<0.05$

RESULTS

GC–MS analysis

GC–MS analysis of the thymol oil from *Thymus vulgaris* revealed 18 components, representing 100% of the total composition. The results revealed the presence of various monoterpenes and phenolic compounds, with thymol as the dominant constituent (34.21%). Other significant components included γ-terpinene, terpinen-4-ol, α-terpinene, and p-cymene. Fewer constituents include compounds such as α-pinene, β-myrcene, and caryophyllene.

The qualitative analysis highlights a rich profile of bioactive compounds, including both oxygenated and hydrocarbon monoterpenes, contributing to the characteristic aroma and potential therapeutic properties of the oil. The high content of thymol (34.21%) aligns with previous findings that thymol has principal bioactive and antioxidant properties. Its dominance suggests significant therapeutic potential for pharmaceutical and cosmetic applications. The presence of γ-terpinene and p-cymene is noteworthy, as they are precursors in the biosynthetic pathway of thymol and carvacrol, indicating the biosynthetic efficiency of the plant in producing phenolic compounds. Terpinen-4-ol and α-terpinene also contribute to the antimicrobial and anti-inflammatory activities of the oil, increasing its medicinal value. Identification of minor constituents, such as α-pinene and β-myrcene **(Table 1)**.

Table 1: Chemical composition (%) of *Thymus vulgaris* thymol oil (GC–MS qualitative analysis)

Peak	RT	Name	Area %
1	4.31	Thujene	2.52
2	4.41	α-Pinene	0.74
3	5.02	β-Sabinene	0.66
4	5.29	β-Myrcene	1.26
5	5.74	α-Terpinene	7.61
6	5.88	p-Cymene	7.48
7	5.93	D-Limonene	0.77
8	5.95	p-Mentha-1	0.77
9	6.44	γ-Terpinene	17.95
10	6.58	trans-4-Thujanol	1.10
11	6.79	α-Terpinolene	1.44
12	7.09	cis-4-Thujanol	5.23
13	7.39	4-Isopropyl-1-methylcyclohex-2-enol	0.46
14	8.30	Terpinen-4-ol	8.3
15	8.48	Alpha. -Terpineol	2.58
16	9.98	Thymol	34.21
17	10.06	2,5-Diethylphenol	5.38
18	11.50	Caryophyllene	1.54
		Total Identification	100%

GC–MS qualitative analysis was used to identify the chemical composition (%) of *Thymus vulgaris* thymol oil

Antioxidant activity

DPPH and ABTS+ Radical Scavenging Activity

The in vitro DPPH and ABTS+ antioxidant activities of the standards (vitamin C and Trolox) and Thymus vulgaris thymol oil extracts were evaluated at various concentrations, as shown in. At higher concentrations, all samples exhibited 100% scavenging activity, indicating strong antioxidant potential. At lower concentrations, the activity varied significantly. At 0.45 µg/mL, vitamin C had the highest activity, outperforming Trolox and thymol oil. Interestingly, *Thymus vulgaris* thymol oil exhibited a better scavenging ability than did Trolox at 0.3 µg/mL and 0.15 µg/mL. The IC50 values, which reflect the concentration required to inhibit 50% of the radicals, revealed that *Thymus vulgaris* thymol oil outperformed Trolox and vitamin C **(Table 2)**.

Table 2: In vitro DPPH and ABTS radical scavenging assays of *Thymus vulgaris* volatile oil

Sample DPPH and ABTS Conc µg/ml)	Vit C		trolox		*Thymus vulgaris* Volatile Oil	
	DPPH	**ABTS**	**DPPH**	**ABTS**	**DPPH**	**ABTS**
10	100 ± 0	100 ± 0	100 ± 0	100 ± 0	100 ± 0	100 ± 0
5	100 ± 0	100 ± 0	100 ± 0	100 ± 0	90.36 ± 2.1	96 ± 0.56
2.5	90.23 ± 1.25	90.23 ± 0.85	92.36 ± 0.36	83.55 ± 0.81	80.36 ± 3	85 ± 0.87
1.5	78.8 ± 0.56	83.63 ± 0.86	80.35 ± 0.52	80.77 ± 1.02	70.65 ± 0.26	80 ± 0.65
1	70.91 ± 0.89	70.03 ± 0.99	75.58 ± 0.75	73.42 ± 0.85	65.73 ± 0.56	73.82 ± 0.34
0.45	65.62 ± 0.94	56.19 ± 0.25	60.59 ± 0.85	45.21 ± 0.89	50.45 ± 0.11	49.33 ± 0.11
0.3	24.93 ± 0.33	20.52 ± 0.65	37.2 ± 0.42	30.55 ± 0.85	45.84 ± 0.45	43.48 ± 0.79
0.15	20.51 ± 0.52	20.51 ± 0.52	30.55 ± 0.96	24.2 ± 0.96	46.44 ± 6.51	45.96 ± 6.24
0.075					12.81 ± 0.78	25.62 ± 2.72
IC_{50}	0.5186	0.4196	1.544	0.5468	1.630	0.7398

The data are presented as the means ± SEM. The antioxidant activity of *thymol* oil was evaluated via DPPH and ABTS radical scavenging assays. The radical scavenging activity was expressed in terms of the IC_{50} value.

Biochemical parameter

Compared with normal rats, L-NAME-induced hypertensive rats presented significantly elevated systolic and diastolic pressures. Thymol oil treatment (10 mg/kg) significantly reduced the systolic and diastolic pressures, which approached normal values. Thymol oil treatment (5 mg/kg) was less effective, but still improved the parameters, compared with those of the L-NAME group. Hypertension was associated with dyslipidaemia, as evidenced by elevated triglyceride, total cholesterol, and LDL levels and reduced HDL levels in the L-NAME group. Thymol oil treatment (10 mg/kg) resulted in pronounced improvement, normalizing triglyceride and total cholesterol levels. LDL was reduced, and HDL improved. Thymol oil treatment (5 mg/kg) also improved lipid parameters, but was less effective than the high dose. The hypertensive rats suffered from a significant renal impairment, as indicated by elevated urea and creatinine levels. High-dose thymol effectively reduced the urea and creatinine levels, indicating renal protection. Low-dose thymol oil resulted in moderate improvement **(Figure 1) (Table 3).**

Table 3: Effect of administration of thymol oil on the lipid profile in hypertensive rats

Parameters / Groups	Creatinine (mg/dL)	Urea (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)	HDL (mg/dL)	LDL (mg/dL)
Normal control	0.35±0.027	39.20±0.99	88.67±2.03	115.30±2.91	46.67±1.45	8.33±0.88
L-NAME (40mg/kg)	0.86±0.02*	67.00±1.16*	154.10±2.01*	158.00±2.89*	24.33±1.76*	26.67±1.45*
L-NAME (40mg/kg) + Thymol oil (10)	0.81±0.01* #	42.00±1.16* #	97.00±3.22* #	99.33±3.18* #	32.00±1.16* #	13.67±0.33* #
L-NAME (40mg/kg) + Thymol oil (5)	0.64±0.03* #	54.33±0.67* #	136.30±2.33* #	140.30±2.03* #	40.00±0.58* #	18.33±0.67* #

Hypertension was induced by daily intake of L-NAME (40 mg/kg) for 28 days. Rats received two doses from thymol oil (high dose 10 mg/kg) low dose; 5 mg/kg) concurrently with L-NAME for 28 days. After the last doses of the drugs, levels of creatinine, urea, triglycerides, total cholesterol, HDL and LDL were measured in the serum samples from different experimental groups. Results are expressed as means ± SEM (n=8). * Significant difference from normal group (P<0.05). # Significant difference from L-NAME group (P<0.05).

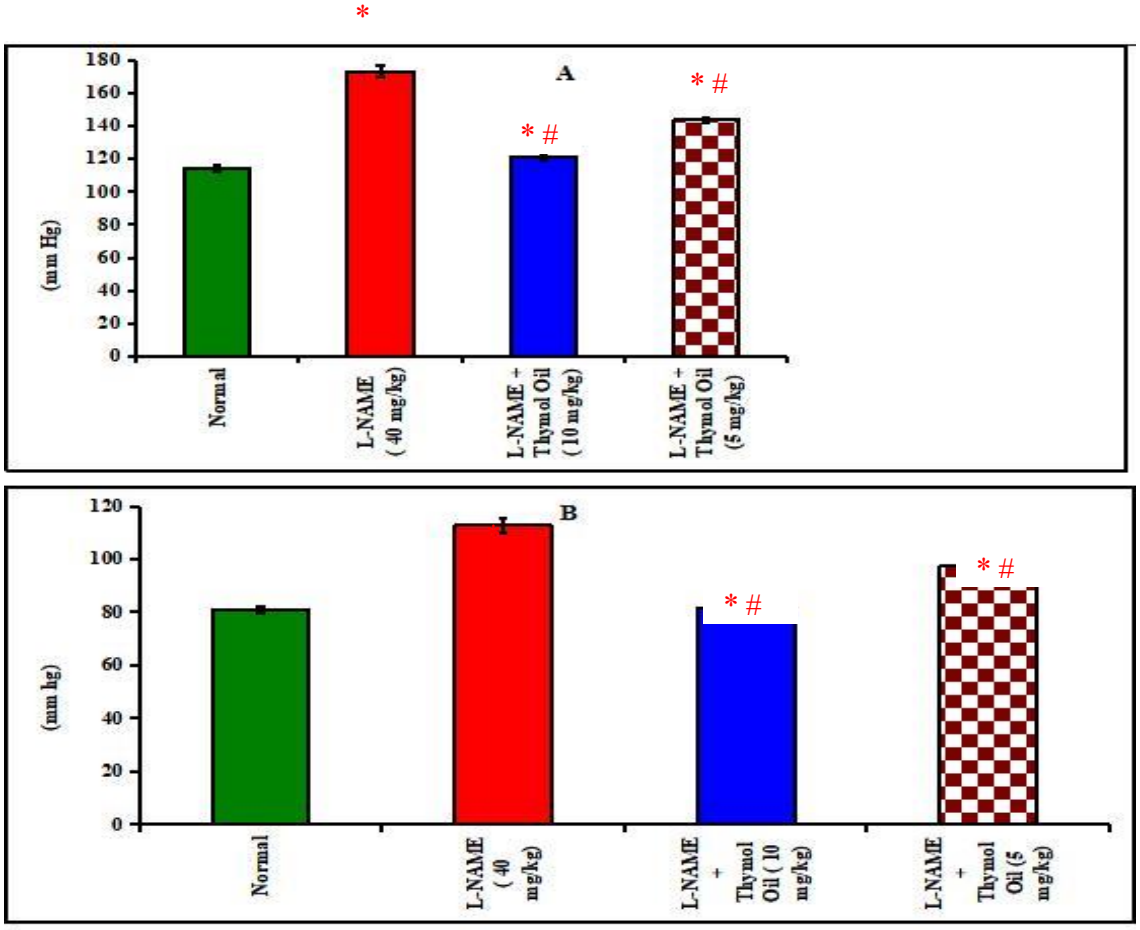

Figure 1: Effect of thymol oil administration on the Systolic and diastolic blood pressure changes in hypertensive rats. Hypertension was induced by daily intake of L-NAME (40 mg/kg) for 28 days. Rats received two doses from thymol oil (high dose 10 mg/kg) low dose; 5 mg/kg) concurrently with L-NAME for 28 days. After the last doses of the drugs, systolic and diastolic blood pressure (mm Hg) was measured from different animal groups. (A) Changes in systolic blood pressure (SBP). (B) Changes in diastolic blood pressure (DBP). Data are presented as means ± SEM (n=8). * Significant difference from normal group (P<0.05). # Significant difference from L-NAME group (P<0.05).

ELISA findings

The administration of L-NAME (40 mg/kg) resulted in a significant increase (P< 0.05) in the levels of TNF-α and IL-6 in the heart, aorta, and kidney compared with those in normal rats. Additionally, compared with L-NAME, thymol (10 mg/kg and 5 mg/kg) significantly (P< 0.05) reduced the levels of TNF-α and IL-6 in the heart, aorta, and kidney in a dose-dependent manner **(Table 4).**

Table 4: Effect of administration of thymol oil on TNF-α and IL-6: Cardiac, Aorta and kidney levels in hypertensive rats.

Organ	Normal	L-NAME (4/kg)	L-NAME (40 mg/kg) + Thymol oil (10 mg/kg)	L-NAME (40 mg/kg) + Thymol oil (5 mg/kg)
TNF-α (Pg /mg)				
Heart	85.32±1.453	1076±30.69*	436±4.359* #	755.7±2.963* #
Aorta	47.29±3.182	434.7±2.333*	133.7±2.028* #	173.3±1.453* #
Kidney	98±2.309	984.7±2.333*	330.7±1.453* #	390.7±4.055* #
IL-6 (Pg /mg)				
Heart	62.33± 2.963	1324±2.333*	394.7±2.404* #	694.7±2,333* #
Aorta	24±1.732	394.3±2.333*	99.67±2.333* #	197.3±2.028* #
Kidney	76.67±1.764	1111±2.333*	282 ±2.646* #	355±2.887* #

Hypertension was induced by daily intake of L-NAME (40 mg/kg) for 28 days. Rats received two doses from thymol oil (high dose 10 mg/kg) low dose; 5 mg/kg) concurrently with L-NAME for 28 days. After the last doses of the drugs, TNF-α and IL-6 were evaluated in the heart, aorta and kidneys from different experimental groups. Results are expressed as means ± SEM (n=8). * Significant difference from normal group (P<0.05). # Significant Difference from L-Name group (P<0.05).

Flow cytometry

Apoptosis Analysis: L-NAME treatment led to a marked increase in apoptotic cell populations in cardiac, aortic, and renal tissues, indicating significant cellular damage. The treatment with thymol oil (10 mg/kg and 5 mg/kg) led to a significant reduction (P<0.05) in Annexin V expression compared with that in the L-NAME control rats. The high dose of thymol oil resulted in values close to normal, indicating its anti-apoptotic effects. The reduction in apoptosis suggests that thymol oil helped mitigate oxidative stress and inflammatory-mediated cell death **(Figure 2, Table 5)**.

Anti-Apoptotic Effects: L-NAME treatment was associated with a decrease in BCL-2 expression, an essential anti-apoptotic protein, indicating increased susceptibility to apoptosis. Thymol oil treatment restored BCL-2 levels, with the higher dose providing stronger protection. These findings suggest thymol oil enhances cell survival signaling, which may contribute to its overall protective effects **(Figure 3) (Table 6)**.

Histopathological findings

Heart Tissue Histology, the control group revealed intact and normal myocardial fibers (M) with normal staining properties and structure. Moreover, the cardiac tissue of L-NAME-exposed rats exhibited loss of cellular normal morphology, a small cluster of inflammatory cells (black arrow), and widening of myofibrils. The L-NAME and Thymol oil at 10 mg/kg group exhibited improvements in cardiac tissue histoarchitecture, with fine waviness of few myofibers and no separation of myocardial fibers. The L-NAME and thymol oil (5 mg/kg) groups presented mildly wavy myocardial fibers, high separation, and loss of cellular constituents (Mag 40X). The findings suggest that thymol oil mitigates L-NAME-induced

cardiac damage, with a higher dose showing better preservation of tissue integrity. **(Figure 4)** highlights the impact of L-NAME and thymol oil on cardiac tissue structure.

Table 5: Effect of administration of thymol oil on Annexin-V values: Cardiac, Aorta and kidney levels in hypertensive rats

Groups	Heart tissue	Aorta	Kidney
Normal	0.02±0.02	0.35±0.05	0±0
L-NAME (40 mg/kg)	71.83±1.27*	84.42±1.25*	55.27±1.56*
L-NAME (40 mg/kg) + Thymol oil (10 mg/kg)	13.50±0.78* #	13.55±0.68* #	14.52±0.56* #
L-NAME (40 mg/kg) + Thymol oil (5 mg/kg)	23.65±0.98* #	22.53±1.06* #	23.70±1.55* #

Hypertension was induced by daily intake of L-NAME (40 mg/kg) for 28 days. Rats received two doses from thymol oil (high dose 10 mg/kg) low dose; 5 mg/kg) concurrently with L-NAME for 28 days. After the last doses of the drugs, rats were sacrificed and their heart, aorta and kidneys were excised to evaluate Annexin-V values in different experimental groups. Results are expressed as means ± SEM (n=8). * Significant difference from normal group (P<0.05). # Significant Difference from L-Name group (P<0.05).

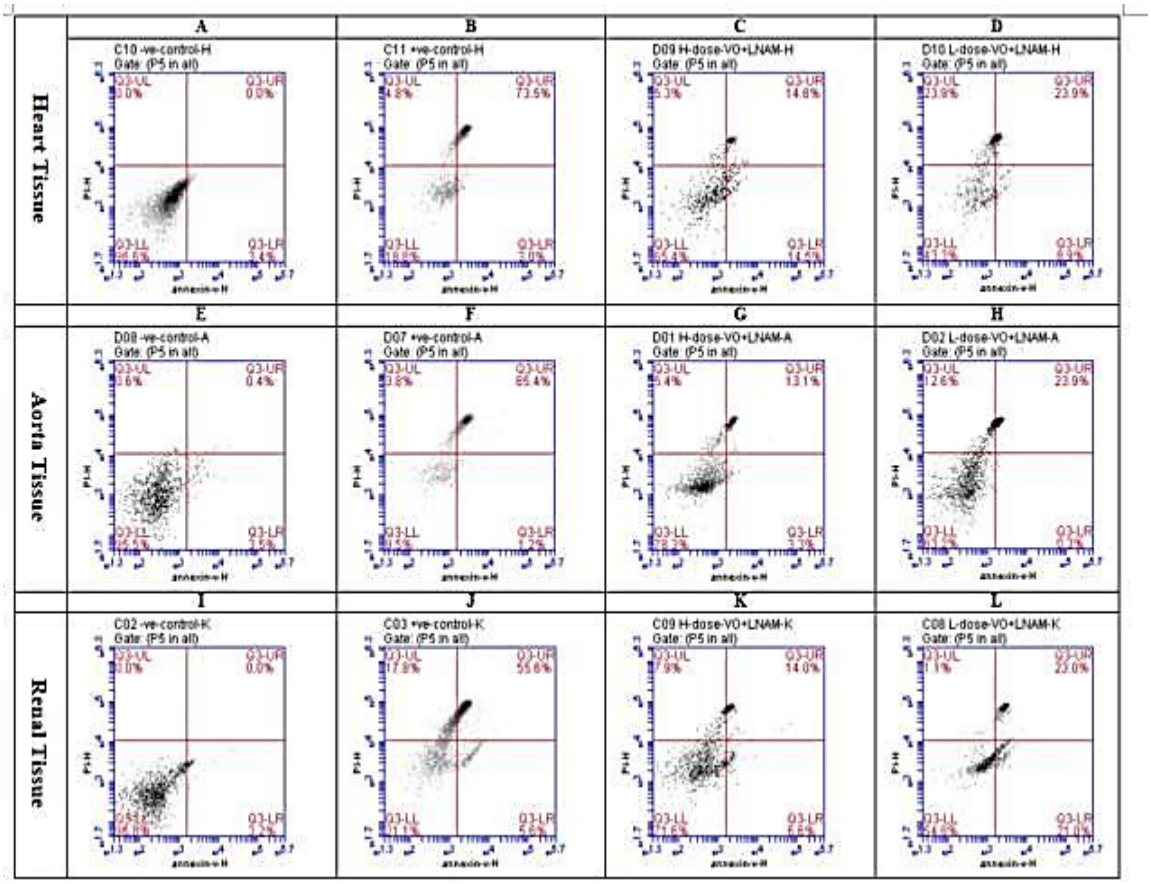

Figure 2: Effect of thymol oil administration on Annexin-V expression in cardiac, aortic, and renal tissues in hypertensive rats. Flow cytometry charts showing the effect of administration of thymol oil on Annexin-V expression. Hypertension was induced in rats by daily intake of L-NAME (40 mg/kg) for 28 days. The rats were then administered two doses of thymol oil (10 or 5 mg/kg) concurrently with L-NAME for 28 days. After the final doses, the heart, aorta, and kidney tissues were dissected for flow cytometry analysis of Annexin-V expression. . Results are expressed as means ± SEM (n=8). * Significant difference from normal group (P<0.05). # Significant Difference from L-Name group (P<0.05).

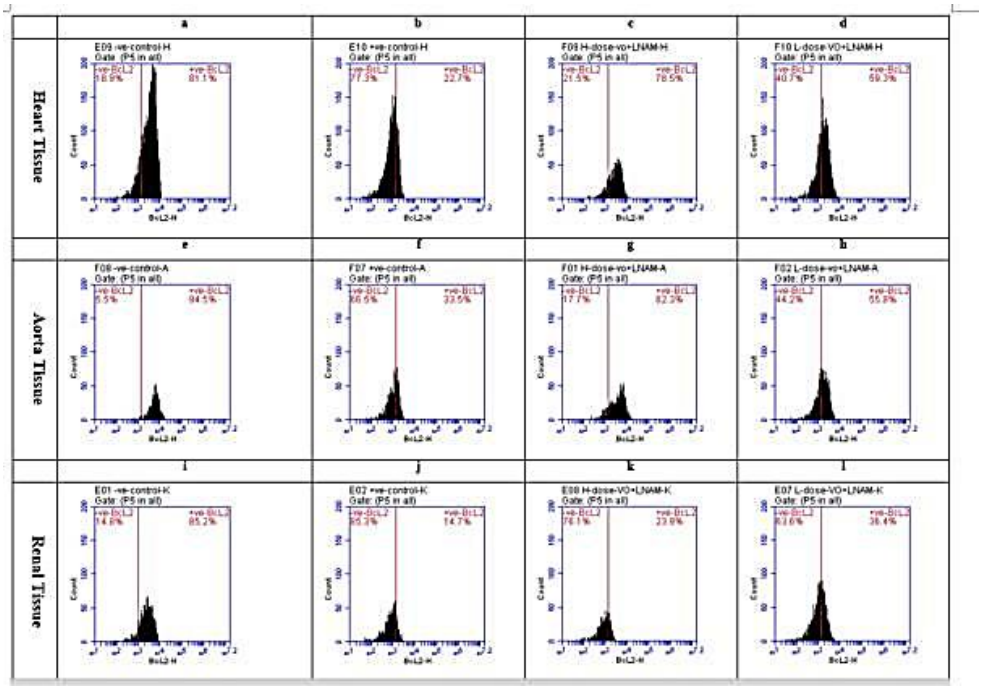

Figure 3: Effect of thymol oil administration on Bcl-2 levels in heart, aorta, and kidney tissues in hypertensive rats. Flow cytometry charts showing the effect of thymol oil on BCL-2 expression. Hypertension was induced in rats by daily intake of L-NAME (40 mg/kg) for 28 days. The rats were then administered two doses of thymol oil (10 or 5 mg/kg) concurrently with L-NAME for 28 days. After the final doses, the heart, aorta, and kidney tissues were dissected for flow cytometry analysis of BCL-2 expression. . Results are expressed as means ± SEM (n=8). * Significant difference from normal group (P<0.05). # Significant Difference from L-Name group (P<0.05).

Table 6: Effect of administration of thymol oil on BcL-2: Cardiac and Renal levels in hypertensive rats

Groups	Aorta	Heart	Kidney
Normal	94.27±0.44	80.35±1.24	86.83±1.02
L-NAME (40 mg/kg)	34.52±0.80*	23.23±0.63*	15.47±0.34*
L-NAME (40 mg/kg) + Thymol oil (10 mg/kg)	83.82±1.97* #	77.83±1.56* #	23.93±0.23* #
L-NAME (40 mg/kg) + Thymol oil (5 mg/kg)	55.33±0.89* #	59.05±0.62* #	37.90±0.85* #

Hypertension was induced by daily intake of L-NAME (40 mg/kg) for 28 days. Rats received two doses from thymol oil (high dose 10 mg/kg) low dose; 5 mg/kg) concurrently with L-NAME for 28 days. After the last doses of the drugs, rats were sacrificed and their heart, aorta and kidneys were excised to evaluate BcL-2 values in different experimental groups. Results are expressed as means ± SEM (n=8). * Significant difference from normal group (P<0.05). # Significant Difference from L-Name group (P<0.05).

Aorta Tissue Histology The control group revealed normal tunica adventitia TA with normal fibroblasts F, normal tunica intima TI, and tunica media TM, which contain normal smooth muscle cells Sc. Meanwhile, the Aorta of L-NAME-exposed rats showed thickening of the tunica media (TM) with increased numbers of smooth muscle cells (S) and alterations in the tunica intima (TI). The L-NAME and thymol oil (10 mg/kg) groups presented improvements in the aorta, and the layers appeared more or less normal in the control group. Comparable to the group of rats treated with L-NAME. Moreover, the L-NAME and thymol oil (5 mg/kg) groups presented minimal to mild

thicknesses of the TM layer with increasing amounts of smooth muscle Sc cells. Mag. 40X This indicates a dose-dependent protective effect of thymol oil against vascular remodeling. **(Figure 5**) illustrates structural changes in the aorta.

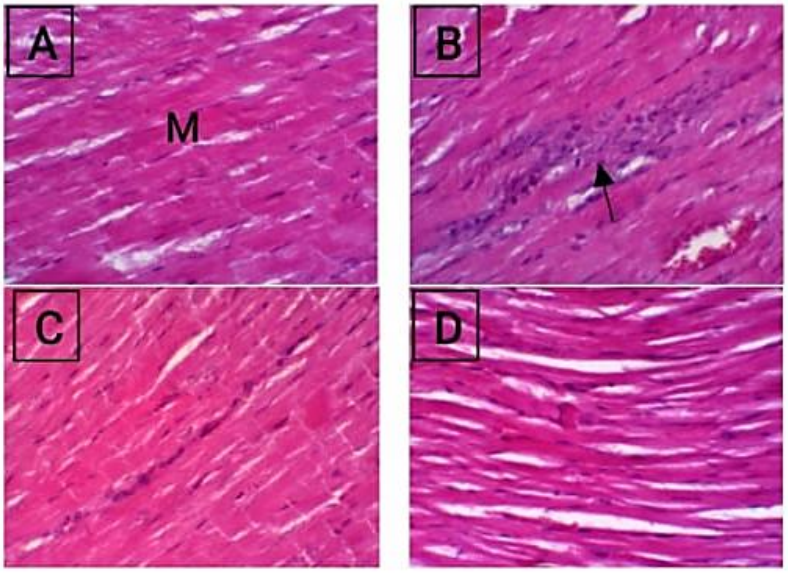

Figure 4: Effect of thymol oil administration on the histopathological changes in the heart tissue of hypertensive rats. The control group (A) exhibits intact myocardial fibers, while L-NAME treatment (B) shows morphological loss, inflammatory cell infiltration, and widening of myofibrils. The thymol group (10 mg/kg) (C) demonstrates a notable improvement in histoarchitecture, while the thymol group (5mg/kg) (D) shows mild improvement but with some fiber separation. The findings suggest that thymol oil mitigates L-NAME-induced cardiac damage, with a higher dose showing better preservation of tissue integrity.

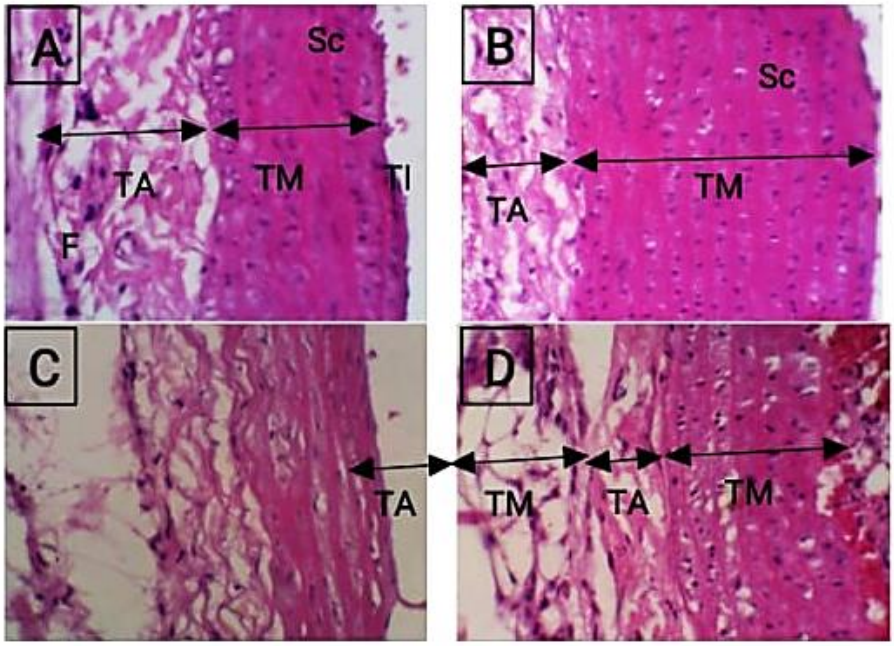

Figure 5: Effect of thymol oil administration on the histopathological changes in the aorta of hypertensive rats. The control group (A) has normal tunica layers, while L-NAME treatment (B) results in tunica media thickening and tunica intima alteration. The thymol group (10 mg/kg) (C) restores near-normal structure, whereas the thymol group (5mg/kg) (D) reduces thickening but still shows an increase in smooth muscle cells. This indicates a dose-dependent protective effect of thymol oil against vascular remodeling.

Kidney Tissue Histology The control group showed normal structure of the kidney with normal glomerulus (G) surround by its glomerular capsule (c) and capsular space (S) with its vascular pole (P), normal proximal convoluted tubule (PCT) and normal distal convoluted (DCT). Meanwhile, Kidney of L- NAME exposed rats Note marked hypertrophy and glomerular collapse (G*), with inflammatory infiltrate (white arrow), tubulointerstitial fibrosis (#) with blood cells infiltration (black arrow). The L-NAME and Thymol oil (10 mg /kg) group appears nearly normal with fine blood infiltration (white arrow). In the meantime, the kidneys of the rats in the L-NAME and Thymol oil (5 mg /kg) group showed swelling and shrinking of glomeruli. Renal injury appears as prominent renal tubules, interstitial expansion where renal tubules appear collapsed, and some are normal (Mag. 40 X). These observations indicate that thymol oil, particularly at the higher dose, preserves kidney integrity against L-NAME-induced damage **(Figure 6**). demonstrates kidney structural alterations due to L-NAME and the potential protective role of thymol oil.

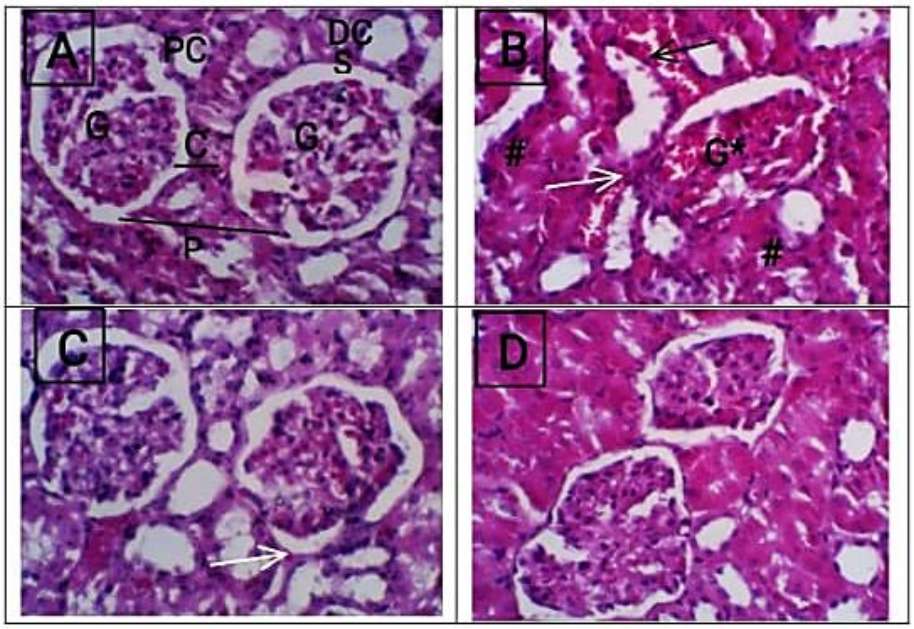

Figure 6: Effect of thymol oil administration on the histopathological changes in the kidney tissue of hypertensive rats. The control (A) has normal kidney architecture, while L-NAME treatment (B) causes glomerular hypertrophy, collapse, inflammation, and tubulointerstitial fibrosis. The thymol group (10mg/kg) (C) shows a near-normal kidney structure with mild blood infiltration, whereas, the thymol group (5mg/kg) (D) presents renal injury signs, including glomerular swelling and tubule collapse. These observations indicate that thymol oil, particularly at the higher dose, preserves kidney integrity against L-NAME-induced damage.

DISCUSSION

This study revealed that the activity of thymol oil can be attributed to its phytochemical composition, particularly the presence of flavonoids, tannins, and other phenolic compounds, which are known for their free radical scavenging properties. (Mohammed *et al.,* 2021, Rhimi *et al.,* 2022). Both the DPPH and ABTS+ assays demonstrated that the antioxidant potential of thymol oil extract suggests potential synergistic effects with major components, enhancing the overall bioactivity of the oil (Piasecka *et al.,* 2015).

In our study, hypertensive rats induced by L-NAME presented significant elevations in systolic and diastolic blood pressures (Li *et al.,* 2023), which were reduced following treatment with thymol oil (10, 5 mg/kg). This anti-hypertensive effect was accompanied by improved lipid profiles (Kohlert et al., 2002), significantly reduced triglyceride and cholesterol levels, increased HDL, and significant decreases in urea and creatinine levels, aligning with its effectiveness as an agent for managing lipid metabolism and hypertension, and has renal protective effects (Bacova et al., 2020). Compared with L-NAME, thymol significantly decreased the release of the inflammatory markers, TNF-α and IL-6, in hypertensive rats, and previous studies supported the anti-inflammatory properties of thymol (Escobar *et al.,* 2020, Horváth et al., 2021).

This reduction in inflammation was accompanied by a significant anti-apoptotic effect, as evidenced by decreased Annexin-V and increased Bcl-2 levels. Our results revealed that Annexin V levels were elevated in the L-NAME group, which is consistent with previous findings documenting apoptosis in cardiac, aortic, and renal tissues. In contrast, the dose-dependent effects of thymol oil were associated with a significant reduction in Annexin V levels (Henry *et al.,* 2013, Tanaka *et al.,* 2016).

The expression of Bcl-2 plays a crucial role in regulating apoptosis, with its overexpression promoting cell survival both in vitro and in vivo (Huang *et al.,* 2012). Our results indicated that the expression of the anti-apoptotic protein Bcl-2 was substantially elevated in the thymol group compared with the L-NAME group. These findings suggest that thymol may offer protection against cardiac hypertrophy by increasing the expression of anti-apoptotic factors (Safari *et al.,* 2021).

Histopathological examinations provided further support for the biochemical results and validated the current findings. Microscopic analysis revealed that the L-NAME group presented widespread inflammatory damage and a loss of normal cellular morphology. However, treatment with thymol oil helps restore nearly normal tissue structure in the heart, aorta, and kidney (Kensara et al., 2013).

CONCLUSION

Thymol oil effectively reduces L-NAME-induced hypertension, as demonstrated by blood pressure normalization, enhancing lipid profiles, and decreasing inflammatory markers. It protects against apoptosis and enhances cell survival, as shown by Annexin-V and BCL-2 analyses. Histological analysis confirms its protective effects on the heart, aorta, and kidneys, with higher doses providing superior protection.

Clinical Implications and Future Directions

These findings suggest that thymol oil has a potential therapeutic value in managing hypertension and its complications. Future research should explore its mechanistic pathways, pharmacokinetics, and long-term efficacy in clinical settings. The dose-dependent effects highlight the importance of optimal dosing strategies

for therapeutic applications. In conclusion, thymol oil demonstrates promising antihypertensive and organ-protective properties, warranting further investigation as a natural therapeutic agent against hypertension-induced cardiovascular and renal damage.

Funding: There is no funding.

Acknowledgement: None

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إمكانيات زيت الزعتر الأساسي الغني بالثيمول في التخفيف من ارتفاع ضغط الدم والأضرار المرتبطة بالأعضاء

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يعتبر ارتفاع ضغط الدم قضية صحية عالمية هامة تسهم في الإصابة بالعديد من الأمراض القلبية الوعائية والكلوية. استهدفت هذه الدراسة استكشاف الإمكانيات العلاجية لزيت الزعتر (*Thymus vulgaris*) الأساسي، وخاصة مكونه الرئيسي، الثيمول، في التخفيف من ارتفاع ضغط الدم والمضاعفات المرتبطة به .أظهرت تحليلاتGC–MS لزيت الزعتر الأساسي أن الثيمول هو المركب الرئيسي (٣٤,٢١٪)، مما يشير إلى دوره الصيدلاني الكبير. في الفئران المصابة بارتفاع ضغط الدم بواسطة (L-NAME 40 ملغ/كغ)، أدت الجرعة العالية من زيت الثيمول (١٠ ملغ/كغ) إلى انخفاض كبير في ضغط الدم الانقباضي والانبساطي، مما يدعم فعاليته في خفض ضغط الدم. بالإضافة إلى ذلك، حسن الثيمول مستويات الدهون من خلال خفض مستويات الدهون الثلاثية والكوليسترول الكلي وLDL، بينما زادت مستويات HDL. كما أن زيت الثيمول له تأثيرات واقية على وظائف الكلى، والذي اتضح من انخفاض مستويات اليوريا والكرياتينين، وهما علامتان لفشل الكلى. علاوة على ذلك، خفض الزيت مستويات المؤشرات الالتهابية مثل عامل نخر الورم-ألفا (TNF-α) والإنترلوكين-٦ (IL-6) في القلب والأبهر والكلى، مما يشير إلى خصائصه المضادة للالتهابات. أظهرت تحليلات التدفق الخلوي والفحص النسيجي أن زيت الثيمول قلل بشكل كبير من موت الخلايا المبرمج ، كما يتضح من انخفاض تعبير Annexin-V وزيادة مستويات البروتين المضاد لموت الخلايا المبرمج Bcl-2. تم استعادة الأنسجة في القلب والأبهر والأنسجة الكلوية بشكل ملحوظ بواسطة زيت الثيمول عالي الجرعة، مما يبرز إمكانياته في عكس التلف العضوي الناتج عن ارتفاع ضغط الدم .تشير هذه النتائج إلى أن زيت الزعتر الأساسي الغني بالثيمول يقدم نهجًا متعدد الجوانب لإدارة ارتفاع ضغط الدم ومضاعفاته، مما يوفر حماية لكل من الجهازين القلبي الوعائي والكلى.