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RESEARCH ARTICLE OPEN ACCESS

Thymol attenuates carboplatin-induced nephrotoxicity in male rats by suppressing oxidative stress and NF-κB-mediated inflammation: A biochemical and histopathological study

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Abstract
Objective: Carboplatin, a platinum-based chemotherapeutic agent, often causes dose-limiting nephrotoxicity. Thymol, a natural monoterpene phenol, has antioxidant and anti-inflammatory properties. This study aimed to determine whether thymol protects against carboplatin-induced kidney injury in male rats.
Methods: Fifty adult male albino rats were randomly divided into five groups (n=10 each): control (distilled water), olive oil (vehicle), thymol alone (40 mg/kg/day orally), carboplatin alone (50 mg/kg single intraperitoneal), and carboplatin plus thymol (same doses, thymol started 24 hours after carboplatin). After three months, serum renal function markers, oxidative stress indices (malondialdehyde [MDA], 8-hydroxy-2′-deoxyguanosine [8-OHdG]), circulating Nrf2, antioxidant enzymes (superoxide dismutase [SOD], catalase [CAT], glutathione peroxidase [GPx], reduced glutathione [GSH]), pro-inflammatory cytokines (NF-κB p65, TNF-α, IL-6, IL-1β), and renal histopathology were assessed. Data were analysed by one-way ANOVA with Tukey's post hoc test ($p<0.05$).
Results: Carboplatin significantly increased serum creatinine, urea, and uric acid; elevated MDA, 8-OHdG, and circulating Nrf2; depleted SOD, CAT, GSH, and GPx; and raised NF-κB, TNF-α, IL-6, and IL-1β ($p<0.05$). Renal histology showed tubular degeneration, vascular congestion, and inflammatory infiltration. Co-administration of thymol reversed most of these changes towards control values and markedly improved histological architecture.
Conclusion: Thymol attenuates carboplatin-induced nephrotoxicity in male rats, likely by reducing oxidative damage and suppressing inflammatory signalling. These findings support further investigation of thymol as a potential adjunct to platinum-based chemotherapy.

Keywords: Thymol, Carboplatin, Nephrotoxicity, Oxidative stress, NF-κB; Antioxidant enzymes

Plain English Summary

Chemotherapy with drugs like carboplatin can harm the kidneys, limiting their use. This study tested whether thymol – a natural compound found in thyme oil – could protect the kidneys of male rats given carboplatin. Rats that received carboplatin alone developed kidney damage, shown by blood tests and microscope examination. When thymol was given together with carboplatin, kidney function and structure improved significantly. Thymol reduced harmful chemicals (oxidative stress) and lowered inflammation in the kidneys. These results suggest that thymol might one day be used alongside chemotherapy to protect patients' kidneys, but more research is needed.

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Introduction

Cancer remains a leading cause of death worldwide, and platinum-based chemotherapy is a mainstay of systemic treatment (1, 2). Carboplatin, a second-generation platinum analogue, is widely used because it causes less neurotoxicity and nephrotoxicity than cisplatin; nevertheless, it can still damage the kidneys through mechanisms beyond DNA cross-linking (3, 4).

The kidney's proximal tubules are particularly vulnerable because they concentrate circulating drugs and have high metabolic activity (5). Inside tubular cells, carboplatin generates reactive oxygen species (ROS), leading to lipid peroxidation, DNA damage, depletion of endogenous antioxidants, and activation of redox-sensitive inflammatory pathways (6, 7). Excess ROS triggers nuclear factor-kappa B (NF-κB), which upregulates pro-inflammatory cytokines (tumour necrosis factor-α [TNF-α], interleukin-6 [IL-6], interleukin-1β [IL-1β]) and amplifies tissue injury (8). Concurrently, the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway is activated as an adaptive response (9).

Thymol (2-isopropyl-5-methylphenol) is a phenolic monoterpene with documented antioxidant and anti-inflammatory effects (10, 11). It has protected against nephrotoxicity induced by gentamicin, glycerol, vancomycin, and cisplatin in animal models (12, 13, 14, 15). However, its potential to ameliorate carboplatin-induced renal injury has not been thoroughly explored. Therefore, this study was designed to evaluate whether thymol could mitigate carboplatin-induced nephrotoxicity in rats, using biochemical markers of renal function, oxidative stress, inflammation, and histological examination.

Materials and Methods

Animals and ethical approval

Fifty adult male albino rats (Sprague-Dawley strain, 3–4 months old, weight 200–260 g) were obtained from the animal facility of the Department of Biology, University of Anbar. They were housed in polypropylene cages under standard conditions (22±2°C, 13:11 h light-dark cycle) with free access to standard pellet diet and water. All animals were acclimatised for two weeks before the experiment. The study protocol was approved by the Institutional Animal Care and Use Committee of the University of Anbar (approval number: UoA-IACUC-2024-023, date not specified). All procedures complied with the institutional guidelines for the care and use of laboratory animals, and every effort was made to minimise suffering.

Chemicals and reagents

Thymol (purity ≥99%), olive oil, and histological stains were purchased from Sigma-Aldrich (USA). Carboplatin was supplied by Ebewe Pharma (Austria). Diagnostic kits for creatinine, urea, uric acid, superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH) were obtained from Linear (Spain). Enzyme-linked immunosorbent assay (ELISA) kits for 8-hydroxy-2′-deoxyguanosine (8-OHdG), Nrf2, glutathione peroxidase (GPx), NF-κB p65, TNF-α, IL-6, and IL-1β were purchased from Elabscience (USA). Malondialdehyde (MDA) assay kits were also from Elabscience.

Experimental design

Rats were randomly assigned to five groups (n=10 each) after stratification by body weight to ensure baseline homogeneity. The groups were:

Control group: Received 5 mL of distilled water orally twice daily for three months.

Olive oil group: Received 2 mL of extra virgin olive oil orally once daily for three months (vehicle control).

Thymol-alone group: Received thymol (40 mg/kg body weight) dissolved in olive oil, orally once daily for three months.

Carboplatin-alone group: Received a single intraperitoneal injection of carboplatin (50 mg/kg body weight) on day 1, then no further treatment.

Carboplatin + thymol group: Received the same single carboplatin injection (50 mg/kg i.p.) on day 1 and, starting 24 hours later, received thymol (40 mg/kg/day orally) for three months.

The dose of carboplatin (50 mg/kg) was chosen based on published ranges (40–256 mg/kg) that induce significant oxidative renal damage without excessive mortality (16, 17). The thymol dose (40 mg/kg) was selected from previous nephroprotection studies (12, 13). All treatments were administered between 8:00 and 9:00 AM.

Sample collection

After three months of treatment (or three months after carboplatin injection), rats were fasted overnight (12 hours) with free access to water. They were then anaesthetised with ketamine (60 mg/kg) and xylazine (10 mg/kg) intraperitoneally. Blood was collected by cardiac puncture, allowed to clot, and centrifuged at 3000 rpm for 15 minutes. Serum was separated and stored at −20°C until analysis. Both kidneys were rapidly excised, rinsed with ice-cold 0.9% saline, and fixed in 10% neutral buffered formalin for histopathology.

Biochemical assays

Serum concentrations of creatinine, urea, and uric acid were measured colourimetrically using

a UV-visible spectrophotometer (Shimadzu, Japan) according to the manufacturer's protocols. MDA was measured by the thiobarbituric acid reactive substances (TBARS) method at 532 nm. SOD, CAT, and GSH were determined using commercial colourimetric kits. ELISA was used to quantify 8-OHdG, Nrf2, GPx, NF-κB p65, TNF-α, IL-6, and IL-1β; absorbance was read at 450 nm on a microplate reader (Bio-Rad, USA). All samples were run in duplicate, and concentrations were calculated from standard curves.

Histopathological examination

Formalin-fixed kidney tissues were dehydrated through graded ethanol, cleared in xylene, embedded in paraffin, sectioned at 4–5 µm thickness, and stained with haematoxylin and eosin (H&E) [18]. Slides were examined under a light microscope (Olympus BX43) by a pathologist blinded to the group allocation. Renal injury was assessed semi-quantitatively using a scoring system adapted from previous studies (14): 0 = no damage; 1 = mild (tubular degeneration affecting <25% of tubules); 2 = moderate (25–50% tubular degeneration, focal necrosis); 3 = severe (>50% tubular degeneration, widespread necrosis, cast formation, interstitial inflammation). At least ten non-overlapping fields per section (×400 magnification) were evaluated, and the mean score was calculated for each animal. Representative images were captured at ×400.

Statistical analysis

Statistical analyses were performed using GraphPad Prism version 8.0 (San Diego, CA, USA). Data are expressed as mean ± standard deviation (SD). Normality was checked using the Shapiro-Wilk test, and homogeneity of variances was assessed by Levene's test. Between-group differences were analysed by one-way analysis of variance (ANOVA) followed by Tukey's post hoc test for multiple comparisons. A p-value <0.05 was considered statistically significant.

Results

Thymol improved renal function in carboplatin-treated rats

Carboplatin alone caused a marked increase in serum creatinine, urea, and uric acid compared to the control group (all p<0.05; Table 1, Figure 1A–C). The thymol-only group showed slightly lower values than controls, but the difference was not consistent across all parameters. Co-administration of thymol with carboplatin significantly reduced all three markers to levels that did not differ from controls (p<0.05 vs carboplatin group). Olive oil alone had no effect compared to controls, confirming that the vehicle did not influence renal function.

Table 1: Serum renal function biomarkers

Group	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)
Con	0.517 ± 0.045^a	16.929 ± 1.392^a	4.051 ± 0.294^a
OO	0.487 ± 0.048^a	16.050 ± 1.121^a	3.906 ± 0.336^a
THY	0.450 ± 0.035^a	13.450 ± 1.397^b	3.324 ± 0.445^b
CAR	0.804 ± 0.044^b	24.328 ± 1.114^b	6.014 ± 0.369^b
CAR+THY	0.486 ± 0.034^a	14.776 ± 1.492^a	4.125 ± 0.347^a

Data are mean ± SD (n=10). Different superscript letters (a, b) indicate significant differences between groups (p<0.05, one-way ANOVA with Tukey's test). Groups: Con, control; OO, olive oil; THY, thymol alone; CAR, carboplatin alone; CAR+THY, carboplatin plus thymol

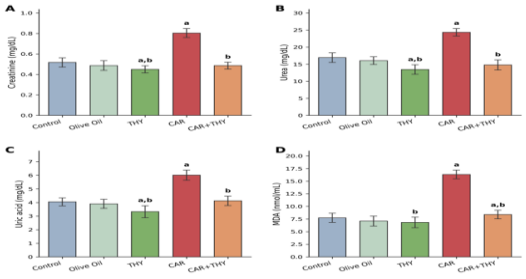


Figure 1. Effect of thymol on (A) creatinine, (B) urea, (C) uric acid, and (D) malondialdehyde (MDA) in carboplatin-treated rats

Bars represent mean ± SD (n=10). Groups with different letters are significantly different (p<0.05, one-way ANOVA with Tukey's test). (Insert figure as in original, but ensure consistent labelling.)

Thymol reduced oxidative stress and DNA damage

Carboplatin significantly increased serum levels of MDA (lipid peroxidation) and 8-OHdG (oxidative DNA damage) compared to controls

(p<0.05; Table 2). Surprisingly, circulating Nrf2 levels were also elevated in the carboplatin group. Co-administration of thymol brought MDA and 8-OHdG back to near-control levels and reduced Nrf2 to values even slightly below control in the thymol-only group. The decrease in Nrf2 after thymol co-treatment is interpreted as a reduction in the compensatory antioxidant response because of lower oxidative stress.

Table 2: Oxidative stress and DNA damage markers.

Group	MDA (nmol/mL)	8-OHdG (ng/mL)	Nrf2 (ng/mL)
Con	7.738 ± 0.915^a	1.929 ± 0.210^a	0.176 ± 0.013^a
OO	7.102 ± 0.994^a	1.904 ± 0.243^a	0.174 ± 0.011^a
THY	6.833 ± 1.045^a	1.485 ± 0.173^b	0.149 ± 0.011^b
CAR	16.330 ± 0.857^b	3.672 ± 0.224^b	0.235 ± 0.013^b
CAR+THY	8.384 ± 0.854^a	2.263 ± 0.180^c	0.188 ± 0.011^c

Data are mean ± SD (n=10). Groups: Con, control; OO, olive oil; THY, thymol alone; CAR, carboplatin alone; CAR+THY, carboplatin plus thymol. Different superscript letters denote significant differences (p<0.05)

Thymol restored antioxidant enzyme activities

Carboplatin severely depleted all measured antioxidants: SOD, CAT, GSH, and GPx (p<0.05 vs control). Thymol alone significantly increased these enzymes above control levels. When given with carboplatin, thymol restored SOD, CAT, GSH, and GPx to values not significantly different from controls (Table 3; p<0.05 vs carboplatin alone). This suggests that thymol not only prevented antioxidant depletion but also boosted endogenous defence capacity.

Table 3: Antioxidant parameters

Group	SOD (U/L)	CAT (U/mL)	GSH (mg/L)	GPx (pg/mL)
Con	13.080 ± 0.814^a	38.117 ± 2.408^a	10.667 ± 0.932^a	24.644 ± 1.625^a
OO	14.312 ± 0.884^a	39.254 ± 1.611^a	11.180 ± 0.891^a	25.432 ± 1.420^a
THY	15.076 ± 1.068^b	42.465 ± 2.275^b	14.232 ± 0.839^b	28.585 ± 2.167^b
CAR	8.222 ± 0.810^c	19.692 ± 2.439^c	6.777 ± 0.666^c	18.769 ± 1.593^c
CAR+THY	12.330 ± 0.800^a	34.724 ± 1.930^d	11.999 ± 0.911^a	23.676 ± 1.501^a

Data are mean ± SD (n=10). Groups: Con, control; OO, olive oil; THY, thymol alone; CAR, carboplatin alone; CAR+THY, carboplatin plus thymol. Different superscript letters indicate significant differences (p<0.05)

Thymol suppressed pro-inflammatory cytokines

Carboplatin induced a robust inflammatory response, as evidenced by significantly elevated serum levels of NF-κB p65, TNF-α, IL-6, and IL-1β (p<0.05 vs control; Table 4). Co-treatment with thymol substantially reduced all four inflammatory markers to values close to those of controls. Thymol alone did not alter inflammatory markers, indicating no intrinsic pro-inflammatory effect.

Table 4: Inflammatory markers

Group	NF-κB p65 (ng/mL)	TNF-α (pg/mL)	IL-6 (pg/mL)	IL-1β (pg/mL)
Con	0.257 ± 0.015^a	33.347 ± 2.430^a	45.268 ± 3.289^a	64.653 ± 6.879^a
OO	0.250 ± 0.012^a	32.905 ± 2.761^a	44.286 ± 2.921^a	61.246 ± 6.072^a
THY	0.225 ± 0.016^a	33.048 ± 3.297^a	41.922 ± 4.562^a	57.668 ± 5.936^a
CAR	0.401 ± 0.021^b	57.159 ± 4.281^b	67.450 ± 3.366^b	122.800 ± 6.461^b
CAR+THY	0.261 ± 0.018^a	36.331 ± 3.801^c	45.576 ± 3.496^a	71.814 ± 5.661^c

Data are mean ± SD (n=10). Groups: Con, control; OO, olive oil; THY, thymol alone; CAR, carboplatin alone; CAR+THY, carboplatin plus thymol. Different superscript letters denote significant differences (p<0.05)

Thymol improved renal histology

Representative photomicrographs of H&E-stained renal cortex are shown in Figure 2. The control, olive oil, and thymol-alone groups displayed normal glomeruli, intact Bowman's capsules, and well-preserved convoluted tubules with healthy epithelial cells. In contrast, the carboplatin-alone group showed widespread tubular degeneration, cytoplasmic vacuolation, cell swelling, marked vascular congestion, and interstitial inflammatory infiltration, consistent with acute tubular injury. The semi-quantitative injury score was significantly higher in the carboplatin group (mean score 2.8 ± 0.4) compared to controls (0.1 ± 0.1; p<0.001). Co-administration of thymol markedly attenuated

these changes: tubular architecture was largely preserved, congestion and inflammation were reduced, and the injury score fell to 0.6 ± 0.3, which was not statistically different from controls ($p>0.05$). Some residual mild tubular degeneration remained in a few fields.

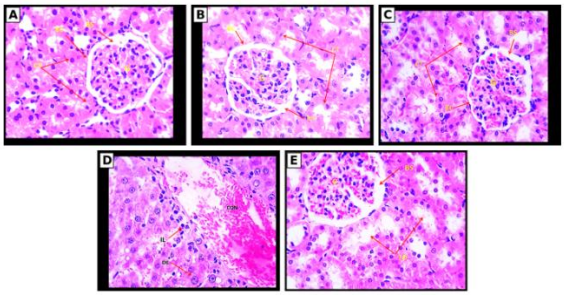


Figure 2: Photomicrographs of renal cortex (H&E, ×400)
(A) Control, (B) olive oil, (C) thymol alone: normal glomeruli (G), Bowman's capsule (BC), and tubules (CT). (D) Carboplatin alone: severe tubular degeneration (DE), vascular congestion (CON), and inflammatory infiltration (IL). (E) Carboplatin + thymol: near-normal architecture with only mild tubular changes (TD). Scale bar = 50 µm.

Discussion

This study demonstrates that thymol, a naturally occurring monoterpene, provides substantial protection against carboplatin-induced nephrotoxicity in male rats. The protective effect was evident across multiple domains: renal function, oxidative stress, antioxidant defence, inflammation, and histology. These findings align with previous reports on thymol's renoprotective actions against other nephrotoxicants (12, 13, 14, 15) and extend them to carboplatin.

The kidney is particularly susceptible to platinum-induced injury because proximal tubular cells actively take up circulating drugs and have high oxygen consumption, making them vulnerable to mitochondrial ROS generation (5, 6). Here, carboplatin alone caused significant increases in serum creatinine and urea – classical markers of reduced glomerular filtration – as well as uric acid, which can further promote oxidative damage and inflammation via the NLRP3 pathway (19). Thymol co-treatment reversed these functional abnormalities, suggesting preservation of glomerular and tubular integrity. The thymol-only group exhibited slightly lower renal markers than controls, possibly due to mild antioxidant upregulation, but this did not reach pathological significance.

The oxidative burden induced by carboplatin was evident from marked elevations in MDA (lipid peroxidation) and 8-OHdG (DNA oxidation). These results are consistent with the well-established ability of platinum drugs to generate ROS (6, 7). Thymol significantly reduced both markers, likely through its hydrogen-donating phenolic ring, which terminates free radical chain reactions (10, 11). The circulating Nrf2 data require careful interpretation. Nrf2 is a transcription factor that resides primarily in the cytoplasm and translocates to the nucleus upon oxidative stress; its presence in serum is unconventional and likely reflects leakage from damaged tissues or measurement of fragmented protein. Nevertheless, the elevation of Nrf2 in the carboplatin group is consistent with a compensatory stress response, and its reduction after thymol treatment suggests that thymol lowers the oxidative load, thereby diminishing the need for Nrf2 activation. This interpretation is supported by the restoration of downstream antioxidants (SOD, CAT, GSH, GPx) in the combined treatment group.

The inflammatory cascade initiated by carboplatin was clearly demonstrated by the upregulation of NF-κB p65 and its target cytokines TNF-α, IL-6, and IL-1β. ROS can activate NF-κB by causing degradation of its inhibitor IκB, leading to nuclear translocation and pro-inflammatory gene transcription (8). Thymol suppressed these inflammatory markers, which is consistent with previous studies showing that thymol can inhibit NF-κB signalling (13, 14). The histological finding of reduced interstitial inflammatory infiltration in the thymol-treated group corroborates the biochemical data.

The histological analysis using a blinded semi-quantitative scoring system strengthens the conclusion. Carboplatin induced severe tubular damage, vacuolation, and congestion – features typical of acute kidney injury. Thymol co-treatment preserved normal architecture, with only occasional mild tubular changes. This structural protection underlies the functional improvements seen in serum markers.

Several limitations must be acknowledged. First, this study used only male rats; sex differences in drug metabolism and nephrotoxicity have been reported, so future studies should include females. Second, while we measured circulating

Nrf2, the exact cellular localisation and functional status of Nrf2 were not determined (e.g., nuclear translocation in kidney tissue). Third, the carboplatin dose (50 mg/kg) is higher than human equivalent doses; however, it is within the range used in rodent toxicity models to produce a clear phenotype. Fourth, we did not include a group receiving thymol alone for three months without carboplatin to assess long-term safety, although the three-month thymol-only group showed no adverse effects. Fifth, the absence of a tumour model means we cannot comment on whether thymol interferes with carboplatin's anticancer efficacy – this is a critical gap before any translational claim. Finally, the three-month duration is unusual for acute nephrotoxicity models; however, it reflects a chronic exposure scenario that may be relevant to repeated chemotherapy cycles. Future directions should include: (i) measurement of Nrf2 and NF-κB in kidney tissue nuclear extracts; (ii) assessment of mitochondrial function and apoptosis markers; (iii) co-treatment studies in tumour-bearing animals; and (iv) dose-response studies to establish the minimal effective thymol dose.

Despite these limitations, the data consistently support that thymol mitigates carboplatin-induced renal injury through combined antioxidant and anti-inflammatory actions. These findings are in line with other natural products that have shown nephroprotection via similar mechanisms (20, 21).

Study limitations

The main limitations are: exclusive use of male rats, the unconventional measurement of circulating Nrf2 without tissue nuclear localisation, the high carboplatin dose, lack of a tumour model to assess chemotherapeutic interference, and the extended three-month protocol that may not reflect acute clinical nephrotoxicity. Additionally, the sample size was modest, and no blinding was performed for the biochemical assays (though histology was blinded).

Conclusion

Thymol significantly attenuates carboplatin-induced nephrotoxicity in male rats, as evidenced by improved renal function, reduced oxidative stress and DNA damage, restoration of antioxidant enzymes, suppression of pro-inflammatory cytokines, and preservation of normal renal histology. The protective effects are likely mediated by the scavenging of reactive oxygen species and the inhibition of NF-κB-driven inflammation.

List of Abbreviations

8-OHdG: 8-hydroxy-2′-deoxyguanosine
ANOVA: Analysis of variance
CAT: Catalase
ELISA: Enzyme-linked immunosorbent assay
GPx: Glutathione peroxidase
GSH: Reduced glutathione
H&E: Haematoxylin and eosin
IL: Interleukin
MDA: Malondialdehyde
NF-κB: Nuclear factor-kappa B
Nrf2: Nuclear factor erythroid 2-related factor 2
ROS: Reactive oxygen species
SD: Standard deviation
SOD: Superoxide dismutase
TNF-α: Tumour necrosis factor-alpha

Declarations

Ethics Approval and Consent to Participate

The Institutional Animal Care and Use Committee of the University of Anbar (approval no. UoA-IACUC-2024-023) approved all animal procedures. The study complied with the ARRIVE guidelines and institutional regulations for the care and use of laboratory animals. Consent to participate is not applicable.

Consent for Publication

All authors have read and approved the final manuscript and give their consent for publication under the Creative Commons Attribution Non-Commercial 4.0 license.

Data Availability

The datasets generated and analysed during the current study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare no competing interests.

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Author Contributions (CRediT Taxonomy)

HRA worked on the conceptualisation, investigation, methodology, writing the original draft and visualisation.

AHL worked on the conceptualisation, methodology, formal analysis, supervision, project administration, writing the review and editing.

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