



Research Article

Protective Effects of *Pistacia terebinthus* in Isotretinoin-Induced Experimental Kidney Injury: Evaluation of Oxidative Stress, Inflammation, and KIM-1-Mediated Tubular Damage

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Abstract: Isotretinoin is an effective retinoid widely used in acne vulgaris treatment; however, systemic administration may induce renal injury. This study investigated the protective effects of *Pistacia terebinthus* fruit and resin extracts against isotretinoin-induced kidney damage through the evaluation of oxidative stress, inflammation, and Kidney Injury Molecule-1 (KIM-1) levels. Sixty-four male Wistar albino rats were allocated into eight groups: Control, ISO, SIL, PT-M, PT-R, ISO+PT-M, ISO+PT-R, and ISO+SIL. Levels of Kidney Injury Molecule-1 (KIM-1), malondialdehyde (MDA), glutathione (GSH), catalase (CAT), superoxide dismutase (SOD), tumor necrosis factor-alpha (TNF- α), interleukin-1 beta (IL-1 β), interleukin-6 (IL-6), and nuclear factor-kappa B (NF- κ B) were determined using the enzyme-linked immunosorbent assay (ELISA) method. Isotretinoin administration statistically significantly increased ($p<0.05$) NF- κ B, MDA, IL-1 β , IL-6, and TNF- α levels, while statistically significantly decreasing GSH, SOD, and CAT levels ($p<0.05$). In the groups treated with both *P. terebinthus* fruit and resin extracts, the elevated inflammatory markers, oxidative stress markers, and KIM-1 levels were significantly reduced ($p<0.05$). In light of these findings, both *P. terebinthus* fruit and resin extracts may exhibit antioxidant and anti-inflammatory properties, demonstrating protective effects against isotretinoin-induced renal injury

Keywords: Isotretinoin, *Pistacia terebinthus*, Nephrotoxicity, Oxidative stress, Inflammation, Kidney injury molecule-1

İzotretinoin Uygulanan Sıçan Modelinde Böbrek Dokusunda *Pistacia terebinthus*'un Oksidatif Stres, İnflamasyon ve KIM-1 Ekspresyonu Üzerindeki Modülatör Etkileri

Öz: İzotretinoin, akne vulgaris tedavisinde yaygın olarak kullanılan etkili bir retinoiddir; ancak sistemik uygulanması böbrek hasarına neden olabilmektedir. Bu çalışmada, *Pistacia terebinthus* meyve ve reçine ekstraktlarının izotretinoin kaynaklı böbrek hasarı üzerindeki koruyucu etkileri; oksidatif stres, inflamasyon ve Böbrek Hasar Belirteci-1 (Kidney Injury Molecule-1, KIM-1) düzeyleri değerlendirilerek araştırılmıştır. Çalışmada altmış dört erkek Wistar albino sıçan; Kontrol, ISO, SIL, PT-M, PT-R, ISO+PT-M, ISO+PT-R ve ISO+SIL olmak üzere sekiz gruba ayrılmıştır. Böbrek Hasar Belirteci-1 (KIM-1), malondialdehit (MDA), glutatyon (GSH), katalaz (CAT), süperoksit dismutaz (SOD), tümör nekroz faktörü-alfa (TNF- α), interlökin-1 beta (IL-1 β), interlökin-6 (IL-6) ve nükleer faktör-kappa B (NF- κ B) düzeyleri enzim bağlantılı immünoresorbent analiz (ELISA) yöntemi kullanılarak belirlenmiştir. İzotretinoin uygulaması NF- κ B, MDA, IL-1 β , IL-6 ve TNF- α

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düzeylerinde istatistiksel olarak anlamlı artışa ($p<0.05$), GSH, SOD ve CAT düzeylerinde ise istatistiksel olarak anlamlı azalmaya ($p<0.05$) neden olmuştur. *P. terebinthus* meyve ve reçine ekstraktı uygulanan gruplarda ise artmış inflamatuvar belirteçler, oksidatif stres belirteçleri ve KIM-1 düzeyleri anlamlı düzeyde azalmıştır ($p<0.05$). Elde edilen bulgular doğrultusunda, *P. terebinthus* meyve ve reçine ekstraktlarının antioksidan ve antiinflamatuvar özellikler göstererek izotretinoin kaynaklı böbrek hasarına karşı koruyucu etki gösterebileceği sonucuna varılmıştır.

Anahtar Kelimeler: İzotretinoin, *Pistacia terebinthus*, Nefrotoksisite, Oksidatif stres, İnflamasyon, Böbrek hasar belirteci-1 (KIM-1).

1. Introduction

Isotretinoin (13-cis retinoic acid) is frequently administered in cases of severe and treatment-resistant acne vulgaris. Owing to its ability to suppress sebaceous gland activity, regulate keratinocyte differentiation, reduce follicular hyperkeratinization, and modulate inflammatory responses, isotretinoin is considered one of the most effective therapeutic options in dermatology (Bagatin & Costa, 2020; Paichitrojjana, 2023; Kandhari et al., 2026). Nevertheless, despite its remarkable clinical efficacy, systemic isotretinoin therapy has been associated with a broad spectrum of adverse reactions affecting multiple organs and physiological systems (Vallerand et al., 2018). In addition to its well-known teratogenic potential, isotretinoin has been linked to neuropsychiatric alterations, gastrointestinal complications, hepatotoxicity, and nephrotoxic effects (Karadağ, 2020; Nuriyeva et al., 2024).

Recent experimental and clinical studies indicate that isotretinoin-related tissue damage is closely associated with disturbed oxidant–antioxidant balance and inflammatory reactions. Increased formation of reactive oxygen-derived compounds can weaken endogenous antioxidant capacity, enhance membrane lipid peroxidation, and lead to cellular injury in several organs, particularly the kidneys (Daye et al., 2020; Miqdad et al., 2022; Pile et al., 2025; Altınöz Güney & Koç, 2026). In renal tissue, alterations in redox balance may facilitate tubular damage, activation of inflammatory pathways, and gradual deterioration of kidney function.

Kidney injury molecule-1 (KIM-1) has attracted considerable attention as a valuable indicator of early tubular impairment in the kidney. Under normal physiological conditions, its expression in renal tissue is scarcely detectable; however, damage to tubular epithelial cells leads to a substantial rise in KIM-1 expression, particularly in the proximal tubules (Sies, 2019; Størjerd et al., 2023). It has been reported that KIM-1 levels indicate kidney damage earlier and more effectively than biomarkers routinely assessed in kidney damage (Vaidya et al., 2010; Yin & Wang, 2016). Increased KIM-1 expression has been reported to be an indicator of acute kidney injury as well as being associated with permanent and serious damage to kidney tissue.

Pistacia terebinthus L. (*P. terebinthus*), a plant indigenous to the Mediterranean basin and the Middle East, has traditionally been employed by local populations for the management of numerous health conditions (Erişir et al., 2022; Fırat et al., 2024). The therapeutic effect of *P. terebinthus* is reported to be due to its biologically active substances such as rich phenolics, flavonoid compounds, and terpenoid components. Earlier investigations on different *Pistacia* species have reported free radical-scavenging, antibacterial, inflammation-modulating, and cell-protective effects (Fırat et al., 2024; Haşimi & Algan, 2025). Traditionally, *P. terebinthus* has been preferred for conditions involving the respiratory and gastrointestinal systems, skin-related disorders, and several inflammatory complaints (Fırat et al., 2024).

Studies on *P. terebinthus* have primarily focused on its antioxidant properties. However, no studies have been found that evaluate the effects of *P. terebinthus* on oxidative stress and inflammatory processes in kidney tissue, in conjunction with KIM-1, a key biomarker of kidney damage. Furthermore, the relationship between changes in KIM-1 levels and *P. terebinthus* application has not been sufficiently clarified. Therefore, this study aims to investigate the potential effects of *P. terebinthus* on oxidative stress, inflammation, and KIM-1 responses in kidney tissue.

Based on these considerations, the present study aimed to investigate the possible renoprotective effects of *P. terebinthus* fruit and resin extracts against isotretinoin-induced experimental kidney injury. The novelty of this study lies in the comprehensive evaluation of both fruit and resin extracts through the simultaneous assessment of oxidative stress, antioxidant defense, inflammatory mediators, and KIM-

1 in renal tissue. Therefore, oxidative stress markers, antioxidant defense parameters, inflammatory mediators, and KIM-1 levels were evaluated to clarify the potential mechanisms underlying the protective effects of *P. terebinthus*.

2. Materials and Methods

2.1. Sample Collection

P. terebinthus fruits used in the present study were gathered from Çukurca (Hakkâri, Türkiye) during the autumn season of 2023 (September–October). Resin samples belonging to the same plant were obtained later, between November and December 2023. Species confirmation was conducted at the Herbarium of Van Yüzüncü Yıl University, Department of Biology, Faculty of Education, and the authenticated samples were preserved as reference material. Until extraction procedures were initiated, resin specimens were maintained under cold storage conditions at 0–8 °C.

2.2. Preparation of Extracts

P. terebinthus fruit and resin samples were shade-dried and then ground into powder using a mechanical grinder. The powdered materials were extracted for 48 h in a hydroalcoholic solvent consisting of 70% ethanol and 30% distilled water. At the end of the extraction period, the mixtures were filtered, and the solvent phase was removed using a rotary evaporator (Abubakar & Haque, 2020). The extracts thus obtained were kept at –18 °C pending subsequent analysis.

2.3. Experimental Animals and Experimental Design

The experimental study was carried out using 64 male Wistar albino rats aged approximately 2–3 months, with body weights ranging from 190 to 220 g. All animals were provided by the Experimental Medicine Application and Research Center of Van Yüzüncü Yıl University. Animals were housed under standard laboratory conditions (22 ± 2 °C, 50–60% humidity, 12 h light/12 h dark cycle) with free access to standard pellet diet and tap water. Permission for the animal protocol was received from the Van Yüzüncü Yıl University Local Ethics Committee for Animal Experiments (Protocol No: 2026/04-42, 30 April 2026). The animals were randomly divided into eight groups of eight rats each: Control, isotretinoin (ISO), silymarin (SIL), *P. terebinthus* fruit extract (PT-M), *P. terebinthus* resin extract (PT-R), isotretinoin + *P. terebinthus* fruit extract (ISO+PT-M), isotretinoin + *P. terebinthus* resin extract (ISO+PT-R), and isotretinoin + silymarin (ISO+SIL). Control group: received an oral gavage of 0.9% NaCl.

- ISO group: oral isotretinoin at a dose of 40 mg/kg/day (Kumaş et al., 2018).
- SIL group: oral silymarin at a dose of 200 mg/kg/day (Kumaş et al., 2018).
- PT-M group: oral *P. terebinthus* fruit extract at a dose of 200 mg/kg/day (Bakırel et al., 2003; Bozorgi et al., 2013).
- PT-R group: oral *P. terebinthus* resin extract at a dose of 200 mg/kg/day (Bakırel et al., 2003; Bozorgi et al., 2013).
- ISO+PT-M group: oral isotretinoin (40 mg/kg/day) and *P. terebinthus* fruit extract (200 mg/kg/day).
- ISO+PT-R group: oral isotretinoin (40 mg/kg/day) and *P. terebinthus* resin extract (200 mg/kg/day).
- ISO+SIL group (positive control): oral isotretinoin (40 mg/kg/day) and silymarin (200 mg/kg/day).

All treatments were freshly prepared in 0.9% NaCl and administered orally by gavage (2 mL/kg) once daily for 42 consecutive days. In the combination groups, isotretinoin was administered together with either *P. terebinthus* fruit extract, *P. terebinthus* resin extract, or silymarin once daily for 42 consecutive days. At the end of the 42-day experimental period, the animals were anesthetized with

ketamine (90 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.), sacrificed by decapitation, and both kidneys were immediately collected and stored at -80°C until biochemical analyses.

Kidney tissue concentrations of interleukin-6 (IL-6; ELK1158), interleukin-1 beta (IL-1 β ; ELK1272), tumor necrosis factor-alpha (TNF- α ; ELK1396), catalase (CAT; ELK5986), nuclear factor-kappa B (NF- κ B; ELK7219), superoxide dismutase (SOD; ELK8178), glutathione (GSH; ELK8577), malondialdehyde (MDA; ELK8612), and Kidney Injury Molecule-1 (KIM-1; ELK11099) were quantified using enzyme-linked immunosorbent assay (ELISA) kits. All analytical kits were purchased from ELK Biotechnology (Wuhan, China), and the assays were carried out in accordance with the manufacturer's instructions.

2.4. Statistical Analysis

Statistical evaluation of the data was conducted using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Distribution normality was assessed with the Shapiro–Wilk test. Results are presented as mean $\pm$ standard deviation (SD). Intergroup comparisons were carried out using one-way analysis of variance (ANOVA), followed by Duncan's multiple comparison test. Statistical significance was accepted at $p < 0.05$.

3. Results

Renal tissue levels of TNF- α , IL-1 β , NF- κ B, and IL-6 showed a statistically significant elevation in the isotretinoin-administered group compared to the control group ($p < 0.05$) (Table 1). Inflammatory levels in the ISO+PT-M and ISO+PT-R groups treated with PT-M and PT-R were similar to each other ($p > 0.05$). In the ISO+PT-M group, NF- κ B and TNF- α levels were statistically significantly higher compared with the positive control group (ISO+SIL) ($p < 0.05$), while IL-1 β and IL-6 levels were also elevated, although the differences were not statistically significant ($p > 0.05$). In the ISO+PT-R group, IL-1 β and IL-6 levels were significantly higher than those in the positive control group (ISO+SIL) ($p < 0.05$), whereas NF- κ B and TNF- α levels were elevated but did not reach statistical significance ($p > 0.05$) (Table 1).

Table 1. Effects of *Pistacia terebinthus* treatment on renal TNF- α , IL-1 β , IL-6, and NF- κ B levels in isotretinoin-induced kidney injury in rats.

Groups	NF- κ B (pg/mL)	TNF- α (pg/mL)	IL-1 β (pg/mL)	IL-6 (pg/mL)
Control	38.85 $\pm$ 3.75 ^d	1218.37 $\pm$ 164.96 ^d	47.62 $\pm$ 9.36 ^c	372.37 $\pm$ 85.36 ^c
ISO	98.42 $\pm$ 23.22 ^a	2314.87 $\pm$ 374.22 ^a	121.37 $\pm$ 24.76 ^a	719.50 $\pm$ 123.17 ^a
ISO+PT-M	64.86 $\pm$ 12.85 ^b	1672.25 $\pm$ 248.71 ^b	82.50 $\pm$ 19.90 ^{b,c}	521.87 $\pm$ 73.91 ^{b,c}
ISO+PT-R	62.36 $\pm$ 17.86 ^{b,c}	1546.50 $\pm$ 226.18 ^{b,c}	89.75 $\pm$ 22.36 ^b	563.12 $\pm$ 110.02 ^b
ISO+SIL	51.43 $\pm$ 9.53 ^{c,d}	1398.37 $\pm$ 205.44 ^c	68.37 $\pm$ 14.93 ^{c,d}	464.12 $\pm$ 80.15 ^{c,d}
SIL	42.67 $\pm$ 6.63 ^d	1226.50 $\pm$ 151.06 ^{c,d}	43.12 $\pm$ 9.18 ^c	319.37 $\pm$ 48.83 ^c
PT-M	42.83 $\pm$ 4.60 ^d	1264.37 $\pm$ 170.74 ^d	51.75 $\pm$ 11.18 ^{d,e}	360.12 $\pm$ 57.46 ^c
PT-R	42.35 $\pm$ 7.23 ^d	1246.37 $\pm$ 162.52 ^d	56.25 $\pm$ 11.70 ^{d,e}	398.62 $\pm$ 73.58 ^{d,e}

Each value in the table reflects the mean and corresponding standard deviation (mean $\pm$ SD) for that group. Where group values within a given column lack a shared superscript letter (a–e), the difference between them is regarded as statistically significant ($p < 0.05$).

In the isotretinoin-treated ISO group, renal tissue MDA levels were significantly higher than those of the control group ($p < 0.05$), while GSH, SOD, and CAT levels were significantly lower ($p < 0.05$) (Table 2).

In the *P. terebinthus*-treated groups, a significant improvement in oxidative stress parameters was observed compared with the ISO group. In the ISO+PT-M and ISO+PT-R groups, MDA levels were significantly reduced ($p < 0.05$), whereas GSH, SOD, and CAT levels were significantly increased ($p < 0.05$). However, no statistically significant differences were detected between the ISO+PT-M and ISO+PT-R groups regarding the evaluated parameters ($p > 0.05$).

Compared with the positive control group (ISO+SIL), the ISO+PT-M group exhibited significantly higher MDA levels ($p < 0.05$) and lower SOD and CAT levels ($p < 0.05$), whereas GSH levels were comparable ($p > 0.05$). In contrast, oxidative stress parameters in the ISO+PT-R group were comparable to those of the ISO+SIL group ($p > 0.05$) (Table 2).

Table 2. Renal oxidative stress markers in isotretinoin-induced kidney injury following *Pistacia terebinthus* administration.

Groups	MDA (pg/mL)	GSH (pg/mL)	SOD (pg/mL)	CAT (pg/mL)
Control	18.37 ± 3.73 ^d	9.08 ± 1.76 ^a	72.63 ± 9.86 ^a	41.27 ± 6.19 ^a
ISO	46.87 ± 10.04 ^a	3.11 ± 1.41 ^c	31.42 ± 7.97 ^e	17.52 ± 4.62 ^d
ISO+PT-M	31.50 ± 6.32 ^b	5.86 ± 1.96 ^b	49.36 ± 8.04 ^d	28.63 ± 5.70 ^c
ISO+PT-R	29.87 ± 9.17 ^{b,c}	6.23 ± 2.33 ^b	53.41 ± 8.86 ^{c,d}	30.41 ± 7.07 ^{b,c}
ISO+SIL	24.12 ± 5.89 ^{c,d}	7.36 ± 1.51 ^{a,b}	61.57 ± 7.98 ^{b,c}	35.86 ± 6.90 ^{a,b}
SIL	19.37 ± 5.01 ^d	8.42 ± 3.30 ^{a,b}	69.42 ± 8.67 ^{a,b}	39.26 ± 5.75 ^a
PT-M	20.87 ± 5.24 ^d	8.16 ± 2.87 ^{a,b}	67.35 ± 11.15 ^{a,b}	38.41 ± 5.67 ^a
PT-R	21.37 ± 6.69 ^d	7.93 ± 2.59 ^{a,b}	65.83 ± 12.70 ^{a,b}	37.63 ± 6.63 ^a

Each value in the table reflects the mean and corresponding standard deviation (mean ± SD) for that group. Where group values within a given column lack a shared superscript letter (a–e), the difference between them is regarded as statistically significant ($p < 0.05$).

Isotretinoin administration caused a significant increase in renal tissue KIM-1 levels compared with the control group ($p < 0.05$) (Table 3). In the *P. terebinthus*-treated groups, the elevated KIM-1 levels observed in the ISO group were significantly reduced compared with the ISO group ($p < 0.05$). Renal tissue KIM-1 levels were similar between the ISO+PT-M and ISO+PT-R groups ($p > 0.05$), but remained higher than those of the positive control group (ISO+SIL) ($p < 0.05$). Renal tissue KIM-1 levels in the ISO+SIL, PT-M, and PT-R groups were comparable to those of the control group ($p > 0.05$) (Table 3).

Table 3. Renal KIM-1 levels following *Pistacia terebinthus* treatment in rats with isotretinoin-induced kidney injury.

Groups	KIM-1 (pg/mL)
Control	1.84 ± 0.50 ^d
ISO	6.92 ± 1.49 ^a
ISO+PT-M	4.58 ± 1.03 ^{b,c}
ISO+PT-R	4.16 ± 1.18 ^{b,c}
ISO+SIL	3.02 ± 0.78 ^{c,d}
SIL	1.96 ± 0.57 ^d
PT-M	2.14 ± 0.66 ^{c,d}
PT-R	2.28 ± 0.99 ^{c,d}

Each value in the table reflects the mean and corresponding standard deviation (mean ± SD) for that group. Where group values within a given column lack a shared superscript letter (a–e), the difference between them is regarded as statistically significant ($p < 0.05$).

4. Discussion

This study demonstrated that isotretinoin administration increased levels of KIM-1, MDA, TNF- α , IL-1 β , and IL-6 in kidney tissue, while decreasing levels of GSH, CAT, and SOD. These changes triggered inflammation and oxidative stress, leading to kidney damage. Additionally, both fruit and resin forms of *P. terebinthus* were found to suppress the NF- κ B signaling pathway, thereby reducing the inflammatory response and alleviating oxidative stress, which may confer protective effects against kidney damage.

Although isotretinoin is one of the most effective agents used in the treatment of severe acne vulgaris, increasing scientific evidence indicates that its systemic use, especially in long-term or high-dose applications, may cause toxic effects in various organs (Armaly et al., 2013). Recently, renal side effects associated with isotretinoin have attracted growing attention, with oxidative stress considered one

of the main mechanisms underlying this toxicity (Forouzani-Haghighi & Karimzadeh, 2020; Akbey et al., 2026). Oxidative stress results from an increase in reactive oxygen species such as hydrogen peroxide and superoxide anion, leading to the production of peroxyl radicals through the reduction of molecular oxygen. It causes membrane lipid peroxidation and cellular DNA damage, which can lead to mutation and cell death (Daye et al., 2020). Studies have reported that isotretinoin induces oxidative stress in various tissues (Daye et al., 2020). The increase in oxidative stress levels caused by isotretinoin occurs through alterations in the transcription of genes regulating cellular differentiation, proliferation, apoptosis, and inflammatory responses via all-trans retinoic acid (ATRA), retinoid X receptors (RXR), and retinoic acid receptors (RAR) (Georgala et al., 2005; Ozkol et al., 2015; Xu, 2024). These changes in gene expression affect mitochondrial functions, DNA methylation, and inflammatory signaling pathways, thereby increasing lipid peroxidation and contributing to oxidative damage development (Feszak et al., 2025).

Experimental evidence from different tissues indicates that isotretinoin promotes oxidative stress. Daye et al. (2020) and Taziki et al. (2022) reported disruptions in the antioxidant defense system accompanied by increased MDA levels in liver tissue. Al-Shahed et al. (2022) observed elevated MDA levels and decreased SOD activity in testicular tissue. Similarly, Akbey et al. (2026) found increased MDA levels alongside decreased GSH and SOD levels in kidney tissue. The findings of the present study are consistent with the literature. In the isotretinoin-treated group, MDA levels were elevated, whereas significant reductions in GSH, SOD, and CAT levels were observed. These results suggest that isotretinoin disrupts the balance between oxidant and antioxidant systems in kidney tissue, contributing to the development of oxidative damage.

When ROS are generated in excessive amounts, the equilibrium between oxidant and antioxidant systems is disturbed, thereby triggering oxidative stress and promoting tissue inflammation (Tawanwongsri et al., 2025). Overproduction of ROS plays a significant role in initiating and progressing kidney damage by activating proinflammatory cytokines (Tucker et al., 2015). Studies have reported that isotretinoin treatment induces oxidative stress, thereby intensifying the inflammatory response (Georgala et al., 2005; Ozkol et al., 2015). Although Forouzani-Haghighi and Karimzadeh (2020) reported that isotretinoin inhibits the NF- κ B signaling pathway, reducing proinflammatory cytokine levels, Armaly et al. (2013) described a case of acute interstitial nephritis in a patient using isotretinoin, with renal function returning to normal after discontinuation of treatment. Similarly, Kaya Aksoy et al. (2016) reported a case of eosinophilic tubulointerstitial nephritis in a 16-year-old patient treated with isotretinoin. The presence of eosinophil and mononuclear cell infiltration, confirmed by biopsy in this case, suggests that isotretinoin may cause kidney damage through immune and inflammatory mechanisms. Furthermore, excessive ROS production activates the NF- κ B signaling pathway, resulting in increased expression of multiple proinflammatory cytokines, including TNF- α , IL-1 β , and IL-6 (Lingappan, 2018). In the present study, isotretinoin administration increased oxidative stress in kidney tissue, accompanied by elevated NF- κ B levels and increased proinflammatory cytokines TNF- α , IL-1 β , and IL-6. These findings suggest that the NF- κ B-mediated inflammatory response triggered by oxidative stress may play a critical role in the development of isotretinoin-induced nephrotoxicity.

Silymarin refers to a standardized extract isolated from *Silybum marianum* seeds, which is made up of roughly 70–80% flavonolignans together with various polyphenolic substances (Abenavoli et al., 2018). Due to its rich and potent phenolic content, silymarin is noted for its strong antioxidant properties, which provide protective effects against toxic agents (Federico et al., 2017). In rats with experimentally induced nephrotoxicity by cisplatin, silymarin treatment was reported to increase the decreased levels of GSH, CAT, and SOD in kidney tissue while reducing elevated MDA levels (Karimi et al., 2005). Sengul et al. (2021) demonstrated in an experimental rat model of nephrotoxicity and hepatotoxicity that silymarin reduced MDA levels and increased GSH, SOD, and CAT levels in kidney tissue, showcasing strong antioxidant effects. The potent antioxidant activity of silymarin has been attributed not only to its direct neutralization of free radicals but also to the inhibition of enzymes involved in their formation (Surai, 2015). In the present study, the ISO+SIL group, evaluated as a positive control, exhibited oxidative stress marker levels comparable to those of the control group. These oxidative stress values obtained with silymarin treatment align with the findings of the aforementioned researchers. Studies on various disease models have reported that the anti-inflammatory properties of silymarin arise from its inhibition of the NF- κ B signaling pathway (Surai, 2015; Biedermann et al., 2017). In rats with experimentally induced liver toxicity, silymarin treatment significantly reduced both TNF- α gene expression and serum TNF- α

levels (Soto et al., 2010). Bannwart et al. (2026) demonstrated that silymarin exhibited strong anti-inflammatory effects by inhibiting the NF- κ B signaling pathway and significantly reducing IL-1 β levels in blood mononuclear cells isolated from preeclamptic women. The strong anti-inflammatory properties of silymarin observed in the present study are consistent with these prior findings.

P. terebinthus, a member of the Anacardiaceae family, is a deciduous tree known for its abundance of bioactive phenolic constituents including tannins, flavonoid derivatives, as well as omega-3 fatty acids — compounds associated with antioxidant and anti-inflammatory activities (Bozorgi et al., 2013). Traditionally used in the treatment of kidney and liver diseases, *P. terebinthus* is considered a natural source with high therapeutic potential due to its elevated oleic acid content (Duru et al., 2003). Türkoğlu et al. (2017) reported that *P. terebinthus* extract demonstrated antioxidant effects by reducing MDA levels and increasing GSH and SOD levels in kidney tissue in an experimental oxidative stress model induced by H₂O₂. Orhan et al. (2015) found that *P. terebinthus* coffee reduced MDA levels and inhibited the NF- κ B signaling pathway, thereby decreasing TNF- α and IL-6 levels in a thioacetamide-induced liver injury model. The plant exhibited both antioxidant and anti-inflammatory properties, reducing fibrosis and necrosis levels in the liver and providing protective effects against tissue damage (Orhan et al., 2015). In experimentally induced ulcerative colitis in rats, *P. terebinthus* fruit was reported to reduce TNF- α , MDA, IL-6, and IL-1 β levels while increasing GSH and SOD levels in colon tissue, demonstrating both antioxidant and anti-inflammatory activities (Kaya et al., 2018). Previous studies have demonstrated that *P. terebinthus* extracts possess strong antioxidant properties due to their high phenolic and flavonoid contents, exhibiting potent free radical scavenging activity and contributing to cellular protection against oxidative stress (Topçu et al., 2007; Özcan et al., 2020; Uysal et al., 2022). In the present study, both fruit and resin extracts of *P. terebinthus* decreased the elevated levels of TNF- α , MDA, IL-6, NF- κ B, and IL-1 β caused by isotretinoin administration, while increasing SOD, GSH, and CAT levels, thereby exhibiting anti-inflammatory and antioxidant effects in kidney tissue. The anti-inflammatory and antioxidant properties of this plant are believed to arise from its rich content of bioactive compounds. The abundant bioactive constituents in *P. terebinthus* have been reported to exert anti-inflammatory and antioxidant effects by modulating biochemical pathways such as cyclooxygenase, lipoxygenase, and NF- κ B, which play key roles in the inflammatory process (Bozorgi et al., 2013; Haşimi & Algan, 2025).

KIM-1 represents a type I transmembrane glycosylated protein whose expression is upregulated within proximal tubular epithelial cells subsequent to renal injury, and it is regarded as the most important biomarker for assessing renal tubular damage (Vaidya et al., 2010). The specificity of KIM-1 as a biomarker is enhanced by its exclusive expression in kidney tissue and its significant elevation after kidney injury, distinguishing it from other biomarkers used in renal damage evaluation (Yin & Wang, 2016). Numerous experimental studies inducing kidney injury have reported increased KIM-1 expression (Prozialeck et al., 2009; Vaidya et al., 2010). In the present study, isotretinoin administration was found to significantly increase KIM-1 expression in kidney tissue, leading to renal damage. Elevated KIM-1 expression approached control levels following treatment with silymarin, the positive control. Additionally, both fruit and resin extracts of *P. terebinthus* reduced the increased KIM-1 levels induced by isotretinoin treatment. The reduction in KIM-1 levels observed following *P. terebinthus* treatment may be associated with the antioxidant and anti-inflammatory properties of its bioactive constituents, including phenolic compounds, flavonoids, and terpenoids. By attenuating oxidative stress and suppressing inflammatory signaling pathways, these compounds may alleviate tubular epithelial cell injury, thereby reducing KIM-1 expression. In the present study, the concomitant decrease in MDA, TNF- α , IL-1 β , IL-6, and NF- κ B levels, together with the restoration of GSH, SOD, and CAT activities, supports the hypothesis that the reduction in KIM-1 reflects an overall attenuation of renal tubular injury rather than an isolated biomarker change.

Isotretinoin administration was found to significantly increase oxidative stress, inflammatory response, and KIM-1 levels in kidney tissue, leading to renal damage. Both the fruit and resin of *P. terebinthus* demonstrated protective effects in kidney tissue by reducing isotretinoin-induced oxidative damage, inflammation, and KIM-1 expression. Furthermore, this protective effect was observed to be comparable to the improvements seen in the silymarin-treated positive control group.

5. Conclusion

The biochemical findings of the present study demonstrated that isotretinoin disrupted the renal oxidant–antioxidant balance, increased lipid peroxidation and inflammatory responses, and elevated KIM-1 levels, indicating marked renal tubular injury. The increases in MDA, TNF- α , IL-1 β , IL-6, and NF- κ B levels, together with the reductions in GSH, SOD, and CAT levels, confirmed the involvement of oxidative stress and inflammation in isotretinoin-induced nephrotoxicity. Treatment with both *Pistacia terebinthus* fruit and resin extracts significantly attenuated these alterations by improving antioxidant defense, reducing lipid peroxidation, suppressing inflammatory mediators, and decreasing KIM-1 levels. These findings suggest that the renoprotective effects of *P. terebinthus* may be associated with its antioxidant and anti-inflammatory bioactive constituents and their ability to limit renal tubular damage. Notably, the resin extract produced improvements that were generally comparable to those observed in the silymarin-treated positive control group, suggesting a potentially stronger protective effect than the fruit extract for some parameters. However, since the present findings are based primarily on biochemical analyses, further studies incorporating histopathological, immunohistochemical, molecular, and gene-expression evaluations are required to clarify the underlying mechanisms and confirm the therapeutic potential of *P. terebinthus* against isotretinoin-induced kidney injury.

The limitation of this study is that the changes occurring in kidney tissue were demonstrated through biochemical analyses but were not supported by immunohistochemical or molecular methods. Additionally, the signaling pathways and gene expression changes potentially involved in the protective effects of *P. terebinthus* were not evaluated in detail. Future studies are recommended to include immunohistochemical, histopathological, and molecular analyses for a more comprehensive assessment.

Declaration of Authors' Contribution

Nur Akman: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. Canan Demir: Formal Analysis, Validation, Statistical Analysis, Writing – Review & Editing. Gökhan Oto: Investigation, Methodology, Resources, Data Curation. Semih Yaşar: Investigation, Methodology, Validation, Resources. Yusuf Sevinç: Supervision, Project Administration, Validation, Writing – Review & Editing.

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The authors declare that they have no conflict of interest.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Research and Publication Ethics Statement

The authors declare that this study was conducted in accordance with the principles of research and publication ethics.

Ethics Committee Approval Statement

Ethical approval for this study was obtained from the Van Yüzüncü Yıl University Animal Experiments Local Ethics Committee (Approval No: 2026/04-42; Date: 30 April 2026).

Artificial Intelligence Use Statement

The authors declare that they did not use any generative artificial intelligence in the writing of this article, or in the creation of the tables.

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