

Nephroprotective Potential of *Zanthoxylum Acanthopodium*: Phytochemical Basis, Antioxidant, and Anti-Inflammatory Mechanisms

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ABSTRACT

Kidney injury develops through interconnected oxidative, inflammatory, mitochondrial, microvascular, and tubular mechanisms, while pharmacological strategies that directly prevent renal cellular damage remain limited. *Zanthoxylum acanthopodium* DC., locally known as Andaliman, is an aromatic Rutaceae plant used as a culinary spice and traditional medicinal resource in North Sumatra, Indonesia. Published phytochemical studies identify flavonoids, phenolics, alkaloids, lignans, monoterpenes, and sesquiterpenes with renal-relevant antioxidant and anti-inflammatory properties. Quantitative signals are notable, an alkaloid fraction of Andaliman fruit produced a DPPH IC₅₀ of 23.15 ± 0.01 µg/mL, while Chinese fruit essential oil containing 29.78% limonene and 26.65% β-myrcene inhibited nitric oxide production with an IC₅₀ of 16 µg/mL, close to the reference inhibitor L-NMMA (12.2 µg/mL). Direct renal evidence remains limited. In a benzopyrene-associated model, overall renal tubular narrowing and renal-cell necrosis differed across groups, while pairwise treatment effects were more consistent for renal-cell necrosis at 200 and 400 mg/kg than for tubular narrowing. A preeclampsia study that included nano-Andaliman showed an overall between-group difference in renal necrosis but no significant difference in kidney weight. A recent 2026 DMBA-associated rat study further extends the renal, inflammatory, and histopathological evidence base. This narrative review integrates phytochemical composition, antioxidant capacity, inflammatory modulation, and direct renal studies while separating demonstrated plant-level effects from constituent-derived mechanistic hypotheses. Current evidence supports Andaliman as a promising source of nephroprotective pharmacophores, but extract standardization, renal pharmacokinetics, dose-response characterization, direct pathway validation, and human safety data remain major translational gaps.

Keywords: Andaliman; antioxidant; inflammation; nephroprotection; oxidative stress; *Zanthoxylum acanthopodium*

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INTRODUCTION

Acute kidney injury (AKI) and progressive renal damage remain major clinical problems because renal cellular injury is generated by interacting rather than isolated pathways. Hemodynamic disturbance, mitochondrial dysfunction, excessive reactive oxygen species (ROS), lipid peroxidation, endothelial activation, inflammatory-

cell recruitment, and tubular epithelial injury can reinforce one another and propagate renal dysfunction. Redox-targeted therapy is therefore conceptually attractive, but indiscriminate antioxidant supplementation has important limitations; restoration of redox homeostasis is more relevant than complete suppression of physiologic ROS signaling.^{1,2} Natural products continue to provide lead

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molecules and complex pharmacological scaffolds for drug discovery.³ Among Indonesian medicinal plants, *Zanthoxylum acanthopodium* DC. (Andaliman) is particularly interesting because its fruit combines culinary exposure with a chemically diverse profile. Broad reviews have described antioxidant, anti-inflammatory, antimicrobial, anticancer, wound-healing, and organ-protective activities.^{4,5} However, another general inventory would add limited novelty. A renal-focused synthesis is warranted because the kidney is especially vulnerable to oxidative and inflammatory amplification, and several published Andaliman studies now provide direct or supporting renal evidence. The central question of this review is therefore not whether Andaliman is “antioxidant,” but whether its phytochemical composition and experimentally observed biological effects form a coherent pharmacological basis for nephroprotection. We distinguish direct renal evidence from plant-level mechanistic evidence and from supportive evidence derived from individual constituents. This hierarchy is important because pathways such as Nrf2/HO-1, NF- κ B, NLRP3, apoptosis, and ferroptosis are biologically plausible but should not be assigned to a crude extract unless directly demonstrated in the relevant renal model.

MATERIALS AND METHODS

Literature search strategy

A structured narrative search was performed using PubMed/MEDLINE, Google Scholar, publisher databases, and reference lists of relevant publications. Searches were updated through 20 September 2026, with no lower publication-date restriction. Search terms combined “*Zanthoxylum acanthopodium*,” “Andaliman,” “kidney,” “renal,” “nephroprotective,” “nephrotoxicity,” “acute kidney injury,” “oxidative stress,” “antioxidant,” “inflammation,” “anti-inflammatory,” “phytochemical,” “flavonoid,” “alkaloid,” “terpenoid,” “essential oil,” “TNF- α ,” “NF- κ B,” and “Nrf2.” English-language original studies and reviews addressing Andaliman phytochemistry, antioxidant or anti-inflammatory activity, renal outcomes, pharmacokinetics, or safety were eligible. Conference proceedings were retained only when they contained directly relevant renal data not available as a full journal article. Original studies of Andaliman were prioritized;

studies of isolated constituents were used only to support biological plausibility. Evidence was categorized as direct renal evidence, plant-level mechanistic evidence, or constituent-level mechanistic evidence. Scopus-indexed publications were prioritized when available. Only published evidence was used in the present synthesis.

Phytochemical Profile and Quantitative Pharmacological Signals

Phytochemical investigations demonstrate that Andaliman is not a single-compound intervention. Ethanol extracts and solvent fractions contain alkaloids, flavonoids, glycosides, tannins, saponins, steroids or triterpenoids, and other phenolic constituents.^{6,7} Volatile fractions contain a broad group of mono- and sesquiterpenes whose relative abundance varies with geography, plant part, and extraction method. In a Vietnamese study, leaf oil contained dehydroaromadendrane (23.4%) and (E)-carpacin (17.6%), whereas stem oil was dominated by γ -gurjunene (51.1%), demonstrating marked plant-part-dependent variation.⁸ This chemical variability is not a minor analytical issue; it directly affects the interpretation and reproducibility of pharmacological experiments. A particularly informative essential-oil study compared fruit samples from China and Myanmar. The Chinese oil was dominated by limonene (29.78%) and β -myrcene (26.65%), whereas the Myanmar oil contained 43.35% terpinen-4-ol. Thirty-six compounds were identified, with overall identification rates of 96.96% and 98.17%, respectively. The Chinese oil inhibited nitric oxide production in RAW 264.7 macrophages with an IC₅₀ of 16 μ g/mL, close to the reference inhibitor L-NMMA (12.2 μ g/mL).⁹ These data simultaneously demonstrate anti-inflammatory activity and the magnitude of chemotypic variation between Andaliman preparations. The antioxidant signal is also quantitative. In a DPPH study, the ethanol extract and alkaloid fractions produced IC₅₀ values ranging from 23.15 $\pm$ 0.01 to 273.24 $\pm$ 0.12 μ g/mL; the most active fraction reached 23.15 $\pm$ 0.01 μ g/mL.¹⁰ Chemical radical-scavenging assays cannot establish in-vivo renal efficacy, but they provide a useful foundation for prioritizing fractions for mechanistic testing. The principal quantitative phytochemical and pharmacological signals are summarized in Table 1.

Table 1. Selected quantitative phytochemical and pharmacological findings relevant to the nephroprotective hypothesis

Study/preparation	Dominant or active chemical signal; Quantitative finding	Interpretation for renal pharmacology
Rosidah et al., 2018; fruit alkaloid fractions	Alkaloid-enriched fractions; Best DPPH IC ₅₀ 23.15 $\pm$ 0.01 μ g/mL	Strong chemical antioxidant signal; requires cellular and renal confirmation
Yang et al., 2022; Chinese fruit essential oil	Limonene 29.78%; β -myrcene 26.65%; NO inhibition IC ₅₀ 16 μ g/mL; L-NMMA reference 12.2 μ g/mL	Plant-level anti-inflammatory signal relevant to renal inflammatory amplification

Study/preparation	Dominant or active chemical signal; Quantitative finding	Interpretation for renal pharmacology
Yang et al., 2022; Myanmar fruit essential oil	Terpinen-4-ol 43.35%; Markedly different chemotype from Chinese sample	Shows why dose expressed only as crude extract mass is not pharmacologically equivalent across preparations
Megawati et al., 2023; fruit ethanol extract/fractions	Alkaloids, flavonoids, glycosides, tannins, saponins, steroid/triterpenoid-related groups; Multiple classes confirmed by phytochemical and FTIR analysis	Supports multi-component pharmacology but highlights need for quantitative marker standardization
Diep et al., 2023; Vietnamese leaf and stem essential oils	Leaf: dehydroaromadendrane 23.4%, (E)-carpacin 17.6%; stem: γ -gurjunene 51.1%; Marked plant-part-dependent compositional divergence	Reinforces the need for plant-part and chemotype-specific standardization

Antioxidant Mechanisms Relevant to Nephroprotection

The kidney has high metabolic demand and abundant mitochondria, particularly in tubular segments. In nephrotoxic and ischemic injury, excessive ROS can disrupt mitochondrial membrane potential, oxidize lipids and proteins, damage DNA, deplete glutathione-dependent defenses, and promote regulated or unregulated cell death. Superoxide dismutase, catalase, glutathione peroxidases, and low-molecular-weight antioxidants form an integrated defense system rather than isolated biomarkers.^{1,2} The antioxidant properties of Andaliman are therefore pharmacologically relevant, but two levels of evidence must be separated. The first is direct chemical reducing or scavenging capacity, as demonstrated by DPPH experiments.¹⁰ The second is intracellular redox signaling. Nrf2-Keap1 is a central regulator of cytoprotective genes, including heme oxygenase-1, NAD(P)H quinone dehydrogenase 1, glutathione-related enzymes, and other antioxidant systems.¹¹ Several flavonoids and terpenoids identified in Andaliman are capable of modulating redox-sensitive pathways in other systems, but direct renal demonstration that a chemically standardized Andaliman extract activates Nrf2 remains insufficient. This distinction matters for publication quality. A defensible review can state that Andaliman has antioxidant capacity and contains compounds compatible with Nrf2-related pharmacology; it should not state that Andaliman “works through Nrf2” until renal nuclear translocation, downstream gene induction, or target-engagement experiments are available. Future studies should therefore pair renal function and histology with Nrf2 nuclear localization, Keap1, HO-1, NQO1, glutathione status, catalase, superoxide dismutase, lipid peroxidation products, and mitochondrial endpoints.

Anti-inflammatory Mechanisms Relevant to Renal Injury

Oxidative and inflammatory injury are mutually reinforcing. Damaged renal epithelium and endothelium release danger signals that activate resident and recruited immune cells; TNF- α , IL-1 β , IL-6, inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and chemokine networks then amplify tubular and

microvascular damage. Plant-level evidence shows that Andaliman can suppress inflammatory mediator expression. In fibroblast models, Andaliman fruit extract reduced inflammatory mediators including TNF- α and IL-6.¹² In macrophages, essential oil from Chinese fruit strongly suppressed nitric oxide generation, with an IC₅₀ of 16 μ g/mL.⁹ A systematic review of plant essential oils further supports inflammation-related signaling as a recurrent target of terpene-rich preparations, but this evidence is supportive rather than Andaliman-specific.¹³ NF- κ B is an obvious mechanistic candidate because it regulates many of the cytokines and enzymes altered in inflammatory renal injury. Likewise, the NLRP3 inflammasome is relevant to mitochondrial stress, IL-1 β and IL-18 maturation, and several forms of AKI.¹⁴ However, direct renal NF- κ B or NLRP3 target engagement after standardized Andaliman exposure remains limited. The correct interpretation is therefore that the observed cytokine and nitric-oxide effects make these pathways plausible targets rather than confirmed mechanisms. Similar caution is appropriate for apoptosis, necroptosis, pyroptosis, and ferroptosis, which are interconnected forms of cell death with substantial relevance to renal injury.¹⁵

Direct Experimental Evidence of Renal Protection

The direct renal evidence base is substantially smaller than the broader Andaliman pharmacology literature, but several studies provide signals that are more informative than generic antioxidant assays. In benzopyrene-exposed rats, methanolic Andaliman fruit extract was administered at 100, 200, or 400 mg/kg/day for 30 days. Overall group differences were significant for renal tubular narrowing ($p < 0.001$) and renal-cell necrosis ($p < 0.01$). Pairwise analysis showed that tubular narrowing in the treatment groups did not differ significantly from the positive control, whereas renal-cell necrosis differed significantly from the positive control at 200 and 400 mg/kg ($p < 0.05$).¹⁶ The strength of this experiment is the use of direct renal tissue outcomes; its limitation is that it was embedded in a carcinogen-associated model and did not comprehensively

connect structural findings with renal function, tubular biomarkers, extract chemistry, or renal target engagement.

A separate preeclampsia model compared pregnant controls, preeclamptic controls, extra virgin olive oil, nano-Andaliman at 100 mg/200 g body weight from gestational days 13-19, and the combination intervention. Kidney weight did not differ significantly across groups ($p>0.05$), whereas renal necrosis showed an overall between-group difference ($p<0.05$).¹⁷ The study therefore supports renal biological activity in a pregnancy-specific model, but the overall group comparison does not by itself quantify the magnitude of the Andaliman-alone effect, and functional renal endpoints were limited.

The most recent addition to the evidence base is a 2026 study evaluating *Z. acanthopodium* in a DMBA-induced rat model with renal, inflammatory, and histopathological endpoints.¹⁸ Its importance lies less in establishing a definitive nephroprotective indication than in expanding the number of independent renal-relevant models. Together, these studies suggest that renal histological protective signals are reproducible enough to justify dedicated nephroprotection programs, but not yet broad enough to establish clinical or mechanistic certainty. Direct renal-relevant studies and their principal limitations are summarized in Table 2.

Table 2. Direct published evidence relevant to renal protection by *Zanthoxylum acanthopodium*

Model; Intervention	Renal endpoints; Key finding	Interpretive limitation
Benzopyrene-exposed rats; Simanullang et al., 2021; Methanol fruit extract 100-400 mg/kg/day for 30 days	Tubular narrowing; renal-cell necrosis; histology; Overall: tubular narrowing $p<0.001$; renal-cell necrosis $p<0.01$. Versus positive control, necrosis differed at 200 and 400 mg/kg ($p<0.05$), whereas tubular narrowing did not.	Carcinogen-associated model; limited renal function, tubular biomarker, extract-standardization, and target-engagement data
Preeclampsia rat model; Situmorang et al., 2019; Nano-Andaliman 100 mg/200 g BW on gestational days 13-19; separate EVOO and combination groups	Kidney weight; renal necrosis; tubular histology; Kidney weight was not significantly different ($p>0.05$), whereas renal necrosis showed an overall between-group difference ($p<0.05$).	Pregnancy-specific model; limited functional renal endpoints; the overall necrosis comparison does not by itself quantify the magnitude of the Andaliman-alone effect
DMBA-induced rat model; Simanullang et al., 2026; Andaliman-based experimental intervention	Renal, inflammatory and histopathological outcomes; Recent study reports a protective renal-inflammatory-histopathological signal	Toxicant/carcinogenesis context; requires independent replication in dedicated AKI models

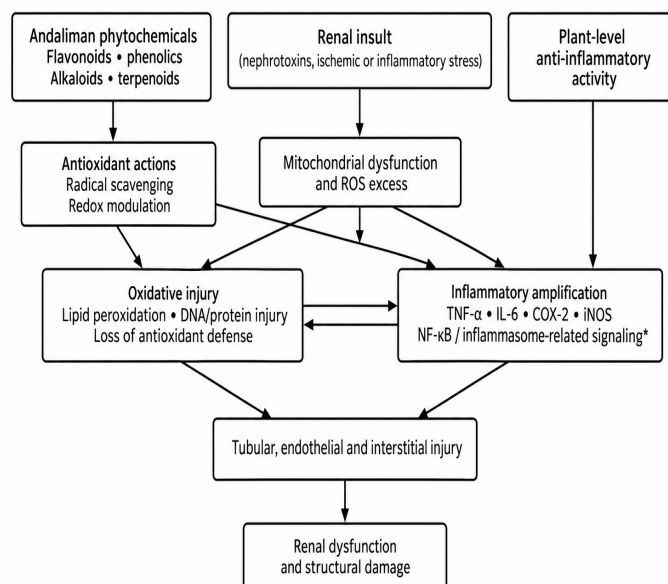
Integrating Phytochemistry with Renal Protection

The strongest pharmacological interpretation is that Andaliman is a multi-component system rather than a single-agent antioxidant. Its phenolics and flavonoids can contribute electron-donating and redox-modulating effects, while volatile terpenoids may influence inflammatory signaling, membrane biology, and cellular stress responses.^{19,20} The broader *Zanthoxylum* literature similarly supports the presence of pharmacologically active terpenoids and phenolic compounds across the genus.²¹

Supporting organ-protection studies strengthen biological plausibility but should remain secondary to direct kidney data. Hydroalcoholic Andaliman fruit extract has recently shown cardioprotective activity in doxorubicin-exposed

rats, while other formulations have demonstrated wound-healing and cytokine-modulating effects.^{22,23} These findings suggest that the plant can modify oxidative-inflammatory injury in several tissues, but they cannot substitute for renal target-engagement studies.

The most useful working model is therefore an oxidative-inflammatory amplification loop: renal stress increases mitochondrial ROS, oxidative damage activates inflammatory transcription and immune signaling, and inflammatory mediators generate additional oxidant burden. A standardized Andaliman preparation could theoretically interrupt this loop at multiple points. Figure 1 illustrates this proposed framework while explicitly marking signaling pathways that remain mechanistically plausible rather than directly proven.



*Proposed signaling targets require direct validation in renal tissue after standardized Andaliman exposure.

Figure 1. Proposed pharmacological framework linking *Zanthoxylum acanthopodium* phytochemistry with renal protection. Asterisks denote pathways that remain mechanistically plausible but require direct validation in renal tissue.

Standardization, Dose-Response, and Pharmacokinetic Gaps

For translational pharmacology, the greatest barrier may be reproducible product identity rather than absence of biological activity. Published studies use ethanol, methanol, aqueous, ethyl acetate, n-hexane, essential-oil, nanoformulated, and combination preparations. These are chemically different interventions and should not be compared solely by crude-extract mg/kg. The pronounced chemotypic difference between Chinese and Myanmar fruit essential oils demonstrates this problem directly.⁹

A standardized nephroprotective candidate should document botanical authentication, voucher specimen, geographic origin, plant part, harvest and drying conditions, extraction solvent and ratio, extraction yield, chromatographic fingerprint, quantitative marker compounds, contaminants, residual solvents, stability, and batch-to-batch reproducibility. Essential-oil molecular docking and profiling work further illustrates the richness of the volatile fraction but also the need to distinguish computational plausibility from experimentally achieved systemic exposure.²⁴

Dose-response also deserves specific attention. Multi-component extracts may exhibit non-linear pharmacology because different constituents have different absorption, metabolism, target affinities, and toxicity thresholds. Higher crude-extract doses cannot be assumed to provide greater protection. Future studies should therefore use multiple doses, prespecified pharmacodynamic outcomes, and exposure-response modelling rather than a single arbitrary dose.

Pharmacokinetic information is especially sparse. The field needs data on oral absorption, plasma concentration,

metabolites, renal tissue exposure, elimination, and interactions with drug-metabolizing enzymes or transporters. These questions are essential because patients at risk of AKI frequently receive antimicrobials, chemotherapy, cardiovascular agents, analgesics, or immunosuppressive drugs.

Safety and Toxicological Considerations

Traditional culinary exposure provides useful context but is not equivalent to safety at pharmacological doses. Acute and subacute toxicological studies of methanolic and nano-herbal Andaliman preparations have been reported, but the available evidence does not yet define a robust therapeutic index for chronic nephroprotective use.^{25,26} This is particularly important because a product intended for patients with impaired renal function must demonstrate that neither the parent compounds nor their metabolites increase renal burden or alter concomitant drug exposure.

Future safety programs should include repeated-dose toxicity, renal and hepatic chemistry, complete blood count, electrolytes, urinalysis, renal histopathology, organ weights, reproductive and genotoxic assessments when appropriate, and targeted herb-drug interaction studies. Toxicity should be linked to quantified phytochemical exposure rather than only to crude extract mass.

Research Gaps and Translational Roadmap

The current literature supports a testable nephroprotective hypothesis, but publication-quality progress will require moving beyond descriptive antioxidant claims. Four priorities are particularly important: chemical standardization, dedicated renal models, direct pathway validation, and pharmacokinetic-pharmacodynamic integration. Dedicated models should include cisplatin nephrotoxicity, ischemia-reperfusion, sepsis-associated

AKI, and selected chronic or metabolic injury models. Renal outcomes should combine serum creatinine and urea with urine output or clearance measures, kidney injury molecule-1, neutrophil gelatinase-associated lipocalin, urinary biomarkers, and quantitative histopathology.

Mechanistic experiments should test Nrf2/Keap1/HO-1, NF- κ B, NLRP3/caspase-1/IL-1 β /IL-18, apoptosis, and ferroptosis only when accompanied by actual target-

engagement measurements. Constituent-level or in-silico evidence may guide selection of pathways, but cannot substitute for renal tissue validation. Once a reproducible active preparation has been identified, plasma and kidney concentrations of marker compounds and metabolites should be related to pharmacodynamic effects. The current evidence gaps and priorities for translational development are summarized in Table 3.

Table 3. Evidence framework for development of Andaliman as a nephroprotective pharmacological candidate

Development domain	Current evidence	Priority evidence needed
Phytochemical identity	Multiple metabolite classes and variable essential-oil chemotypes identified	Quantitative marker panel, chromatographic fingerprint and batch reproducibility
Antioxidant activity	Strong chemical radical-scavenging signal; active alkaloid fraction IC ₅₀ 23.15 μ g/mL	Cellular and renal redox validation; Nrf2 target engagement; mitochondrial endpoints
Anti-inflammatory activity	NO inhibition and cytokine-modulating activity demonstrated	Renal NF- κ B/NLRP3 target engagement and immune-cell phenotyping
Direct renal protection	Renal histological protective signals in several toxicant/pregnancy-associated models	Independent replication in dedicated AKI models with functional, biomarker and structural endpoints
Dose-response	Heterogeneous dosing across crude and nano preparations	Multi-dose exposure-response experiments and identification of therapeutic window
Pharmacokinetics	Very limited	Plasma and renal tissue concentrations of marker compounds and metabolites
Safety	Preliminary acute/subacute data	Repeated-dose toxicology, renal safety, genotoxicity and interaction studies
Clinical translation	No established nephroprotective efficacy in humans	Phase I safety/PK only after standardized preclinical efficacy and toxicology

CONCLUSION

Zanthoxylum acanthopodium possesses a phytochemical and pharmacological profile that provides a credible basis for further nephroprotective development. The most persuasive current evidence is the convergence of strong antioxidant capacity, plant-level anti-inflammatory activity, and renal histological protective signals across several experimental contexts. Quantitative findings—including a highly active antioxidant alkaloid fraction, nitric-oxide inhibition by a limonene-rich essential oil, and significant renal histological effects in benzopyrene and preeclampsia models—make the hypothesis more substantial than a generic traditional-medicine claim.^{9,10,16,17} Nevertheless, the evidence remains preclinical and chemically heterogeneous. Nrf2, NF- κ B, NLRP3, apoptosis, and ferroptosis should currently be regarded as candidate pathways rather than established renal mechanisms of Andaliman. Standardized extracts, direct renal target engagement, pharmacokinetic-pharmacodynamic integration, rigorous dose-response analysis, and modern toxicology are required before human nephroprotection can be meaningfully considered. Andaliman may ultimately prove valuable either as a

standardized phytopharmaceutical or as a source of nephroprotective lead compounds, but the next phase of research must be pharmacologically precise rather than simply descriptive.

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Author Contributions

ELRS: Conceptualization, Methodology, Literature search, Evidence screening, Writing – original draft, and Project administration.

NNS: Supervision, Methodology, Interpretation of evidence, and Writing – review & editing.

RAM: Literature search, Evidence screening, Interpretation of evidence, and Writing – review & editing.

YM: Methodology, Supervision, Interpretation of evidence, and Writing – review & editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability

All data discussed in this narrative review are available in the cited publications.

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