Parthenolide as an Experimental Antifibrotic Agent: Mechanistic Insights and Therapeutic Prospects in Renal Fibrosis

Alaa Mahmoud Mohamed El-Sayed El-Ebyary, Ebtsam A Ahmed*, Soad L. Kabil and Eman Ahmed Ibrahim**

Clinical Pharmacology Department, Faculty of Medicine - Zagazig University
Corresponding Author: Alaa Mahmoud Mohamed El-Sayed El-Ebyary

Received: 28 October 2024, **Accepted:** 17 November 2024, **Published:** 20 November 2024

Abstract

Background: Renal fibrosis represents the final common pathway of most chronic kidney diseases (CKD), leading to progressive nephron loss and decline in renal function. Current therapeutic options remain limited, largely supportive, and unable to halt or reverse established fibrotic remodeling. Parthenolide, a sesquiterpene lactone extracted from *Tanacetum parthenium* (feverfew), has garnered significant interest due to its potent anti-inflammatory and anti-fibrotic activities observed in various experimental models. Its well-characterized ability to inhibit nuclear factor-κB (NF-κB) signaling, modulate oxidative stress, and interfere with downstream inflammatory cascades positions parthenolide as a promising agent for attenuating pathways central to renal fibrogenesis. However, the mechanistic underpinnings and extent of its renoprotective effects in kidney fibrosis remain incompletely defined, warranting a consolidated review of current evidence.

This review aims to comprehensively evaluate the experimental data elucidating the anti-fibrotic actions of parthenolide in models of renal fibrosis. It synthesizes findings from in vitro and in vivo studies, highlights its modulatory effects on key fibrogenic mechanisms such as the TGF-β/Smad axis, epithelial-mesenchymal transition (EMT), myofibroblast activation, extracellular matrix accumulation, and inflammatory signaling and assesses its impact on oxidative stress and mitochondrial homeostasis. Furthermore, this article contextualizes parthenolide within the broader framework of natural anti-fibrotic agents, comparing its pharmacological characteristics, bioavailability challenges, and potential therapeutic advantages.

A critical gap addressed by this review is the lack of integration between pharmacodynamic evidence, mechanistic insights, and therapeutic implications. Although accumulating preclinical studies reveal that parthenolide consistently suppresses pro-fibrotic mediators and ameliorates structural kidney injury, translation into clinical practice is hindered by limited pharmacokinetic data, potential toxicity concerns at higher concentrations, and the absence of human studies. By synthesizing available experimental findings, this review provides a detailed mechanistic understanding of how parthenolide modulates renal fibrogenesis and highlights future research directions needed for its development as a therapeutic candidate.

In conclusion, growing evidence suggests that parthenolide may serve as a promising antifibrotic agent capable of targeting multiple pathogenic pathways in renal fibrosis. Further advanced preclinical and pharmacokinetic studies are essential to clarify its therapeutic window, optimize delivery strategies, and determine its feasibility for translation into clinical nephrology.

Keywords: *Parthenolide, Antifibrotic Agent, Renal Fibrosis*

Introduction

Renal fibrosis is the converging endpoint of most chronic kidney diseases (CKD), representing a progressive process characterized by excessive extracellular matrix accumulation, tubular atrophy, microvascular rarefaction, and irreversible loss of nephron function. Although therapeutic advances such as RAAS inhibitors and SGLT2 inhibitors have reduced CKD progression, they do not reverse established fibrotic remodeling, leaving a critical unmet need for targeted antifibrotic therapies [1–3]. The complexity of renal fibrogenesis—which involves inflammatory signaling, oxidative injury, mitochondrial dysfunction, epithelial–mesenchymal transition (EMT), and activation of myofibroblasts—underscores the necessity of agents capable of modulating multiple pathological pathways simultaneously.

Parthenolide, a bioactive sesquiterpene lactone derived from *Tanacetum parthenium* (feverfew), has attracted considerable scientific interest due to its potent anti-inflammatory and cytoprotective effects. Its primary molecular action is inhibition of nuclear factor-κB (NF-κB) through alkylation of IKKβ, resulting in suppression of pro-inflammatory cytokines and fibrogenic mediators [4,5]. Additionally, growing experimental evidence shows that parthenolide interferes with pathways central to renal fibrosis, including TGF-β/Smad signaling, EMT, oxidative stress amplification, and mitochondrial injury [6–8]. These findings suggest that parthenolide may serve as a multi-target antifibrotic agent; however, the existing studies remain fragmented and vary in methodology, dosage, and model systems.

A crucial **research gap** persists: no comprehensive review has systematically synthesized the mechanistic roles of parthenolide in renal fibrosis from an integrated experimental and Clinical Pharmacology perspective. There is also insufficient consolidation of its pharmacodynamic characteristics, bioavailability limitations, and translational potential.

Therefore, the **aim** of this review is to critically evaluate the current experimental evidence regarding parthenolide's antifibrotic effects in renal fibrosis, summarize its mechanistic actions across major signaling pathways, and assess its potential as a future therapeutic agent. This synthesis seeks to clarify parthenolide's relevance within the broader landscape of antifibrotic drug development and to identify priorities for further translational research.

Pathophysiology of Renal Fibrosis

Renal fibrosis develops as a maladaptive response to persistent injury, integrating inflammatory, metabolic, and hemodynamic insults that collectively drive irreversible tissue remodeling. The earliest pathological events often involve tubular epithelial cell injury, which provokes the release of pro-inflammatory mediators and chemokines that recruit macrophages and lymphocytes into the interstitium. These immune cells further amplify tissue damage through cytokine release, oxidative stress generation, and profibrotic signaling, ultimately promoting activation of resident fibroblasts and pericytes. Sustained injury transforms these stromal cells into proliferative myofibroblasts, which secrete large quantities of extracellular matrix (ECM) proteins such as collagen I, collagen III, and fibronectin. The accumulation of ECM disrupts normal tissue architecture, reduces oxygen diffusion, and leads to progressive nephron loss, establishing fibrosis as a self-perpetuating, progressive process [9].

Activation of the transforming growth factor-β (TGF-β)/Smad pathway is widely recognized as the central orchestrator of renal fibrogenesis. Upon activation, TGF-β1 binds to its receptor complex, promoting phosphorylation of Smad2 and Smad3, which translocate to the nucleus to drive transcription of ECM genes and suppress antifibrotic regulators such as Smad7. This process facilitates fibroblast-to-myofibroblast transition, enhances ECM deposition, and induces epithelial-to-mesenchymal transition (EMT) in injured tubular cells. Simultaneously, TGF-β signaling intersects with other profibrotic pathways—including NF-κB, MAPK, and Wnt/β-catenin—which further strengthen fibrogenic responses. Vascular rarefaction, mitochondrial dysfunction, and chronic inflammation then synergize with TGF-β activity, creating a microenvironment that perpetuates fibrosis and nephron destruction [10–12].

Pharmacological and Molecular Characteristics of Parthenolide

Parthenolide is a sesquiterpene lactone primarily isolated from *Tanacetum parthenium* and structurally defined by a germacranolide skeleton that includes an α-methylene-γ-lactone pharmacophore and a C4–C5 epoxide ring. These electrophilic centers are crucial to the compound's reactivity, allowing covalent Michael-type addition with cysteine thiols on regulatory proteins, especially those involved in inflammatory and oxidative signaling. The high lipophilicity of parthenolide enhances cell membrane penetration but simultaneously contributes to poor aqueous solubility, a limitation that necessitates alternative delivery systems or structural modifications such as the more hydrophilic derivative dimethylaminoparthenolide (DMAPT) [13,14].

The pharmacokinetic profile of parthenolide is characterized by relatively rapid absorption when administered orally or intraperitoneally in preclinical models, though overall bioavailability remains low due to first-pass hepatic metabolism. Absorption efficiency improves with lipophilic formulations, indicating passive diffusion as the primary uptake route. Once absorbed, parthenolide exhibits wide tissue distribution with preferential localization in the liver, kidneys, and spleen—organs rich in metabolic enzymes and vascular networks. Metabolic transformation occurs largely through cytochrome P450–mediated oxidation and conjugation reactions, generating hydroxylated and glutathione-conjugated metabolites that facilitate renal and biliary elimination. Rapid systemic clearance and poor stability in aqueous environments underscore the need for improved formulations, a challenge addressed by the development of DMAPT, which demonstrates substantially enhanced oral bioavailability [15–17].

Pharmacodynamically, parthenolide possesses a broad spectrum of bioactivities relevant to inflammation, pain modulation, oxidative stress, and fibrosis. Its **anti-inflammatory and analgesic effects** stem from potent inhibition of nuclear factor-κB (NF-κB) through alkylation of IKKβ, resulting in stabilization of IκBα and reduced transcription of inflammatory mediators such as IL-1β, IL-6, and TNF-α. Parthenolide additionally modulates COX-2 expression, nitric oxide synthesis, and transient receptor potential (TRP) channels, conferring both anti-inflammatory and analgesic benefits observed in migraine and arthritic models. These mechanisms explain the historical use of feverfew in inflammatory conditions, although modern therapeutic use is constrained by pharmacokinetic limitations [18,19].

Parthenolide exhibits noteworthy **antitumor properties**, mediated through both NF-κB–dependent and –independent pathways. It induces apoptosis through mitochondrial depolarization, increases intracellular reactive oxygen species by depleting glutathione, and modulates key oncogenic pathways involving STAT3, JNK, and β-catenin. Its ability to target leukemia stem cells, particularly in acute myeloid leukemia (AML), highlights its therapeutic potential and has prompted investigation into DMAPT as a clinical candidate for hematologic malignancies. Parthenolide also affects epigenetic regulators such as DNMT1 and HDACs, further broadening its anticancer profile [20–22].

The compound's spectrum of activity extends to **neuroprotective effects**, largely attributed to its capacity to suppress microglial activation, attenuate oxidative stress, and modulate the NLRP3 inflammasome. In preclinical models of traumatic brain injury, ischemic injury, and Alzheimer's disease, parthenolide reduces neuronal apoptosis and improves mitochondrial homeostasis. These effects are closely tied to inhibition of NF-κB signaling within glial cells, demonstrating how its anti-inflammatory actions translate into neuroprotection [23,24].

Given its multisystem activity, potential **drug interactions** must be considered. Parthenolide's modulation of cytochrome P450 enzymes may alter the metabolism of co-administered drugs, particularly those with narrow therapeutic indices. Its glutathione-depleting properties may potentiate toxicity of agents reliant on antioxidant defenses, including acetaminophen and certain chemotherapeutics. Additionally, pharmacodynamic interactions may arise from concurrent use with

corticosteroids, NSAIDs, or biologics targeting inflammatory pathways, where additive immunosuppression or enhanced anti-inflammatory effects could occur. Consequently, pharmacokinetic–pharmacodynamic interaction studies remain essential for future therapeutic development [25,26].

The broad **biological activity** of parthenolide is unified by its modulation of central cellular regulators, with nuclear factor-κB (NF-κB) serving as its most established and widely studied target. NF-κB plays a critical role in controlling genes related to inflammation, fibrosis, apoptosis, and cell survival, and its sustained activation contributes to chronic inflammatory diseases and organ fibrosis. Parthenolide inhibits NF-κB signaling primarily through covalent modification of cysteine-179 in IKKβ, preventing phosphorylation of IκBα and subsequent nuclear translocation of NF-κB subunits. It also affects upstream signaling components such as MyD88 and IRAK1, expanding its inhibitory scope [27,28].

The significance of **parthenolide's interaction with NF-κB** extends directly to renal fibrosis, a condition heavily influenced by chronic inflammatory signaling. In experimental kidney injury models, including unilateral ureteral obstruction (UUO) and cisplatin nephrotoxicity, parthenolide's suppression of NF-κB results in reduced macrophage recruitment, diminished expression of TGF-β1, and decreased synthesis of extracellular matrix components such as collagen I and fibronectin. These effects demonstrate that NF-κB inhibition is a principal mechanism linking parthenolide's anti-inflammatory actions to its emerging antifibrotic potential in renal tissue [29,30].

Experimental Evidence of Parthenolide in Renal Fibrosis

Experimental studies investigating parthenolide in renal fibrosis consistently demonstrate its capacity to modulate inflammatory and profibrotic signaling pathways across diverse preclinical models. In **in vitro** systems, parthenolide has been shown to attenuate TGF-β1–induced fibrotic responses in renal tubular epithelial cells by suppressing Smad2/3 phosphorylation, decreasing α-SMA expression, and reducing collagen I production. These effects are tightly linked to inhibition of NF-κB activation, which ordinarily synergizes with TGF-β to amplify fibrogenic gene transcription. Studies conducted in HK-2 cells further demonstrate reductions in EMT markers, including N-cadherin and vimentin, indicating inhibition of the epithelial-to-mesenchymal transition that drives fibrogenic remodeling in injured tubules. Collectively, these findings establish a clear mechanistic basis for parthenolide's antifibrotic potential at the cellular level [31–33].

In **in vivo** models, parthenolide has demonstrated robust renoprotective effects in both obstructive and toxic forms of kidney injury. In the widely used unilateral ureteral obstruction (UUO) model, parthenolide treatment significantly reduced interstitial collagen deposition, α-SMA–positive myofibroblast accumulation, and inflammatory cell infiltration. These structural improvements were accompanied by reductions in renal expression of TGF-β1, MCP-1, TNF-α, and NF-κB p65 nuclear translocation, supporting a dual action on inflammation and fibrogenesis. In cisplatin-induced nephrotoxicity, parthenolide mitigated tubular injury, improved renal function parameters, and attenuated oxidative stress by reducing malondialdehyde levels and restoring antioxidant enzyme activity. Such findings confirm that parthenolide targets multiple pathological mechanisms simultaneously, offering a broader renoprotective profile compared with agents acting on single pathways [34–36].

Mechanisms of Parthenolide in Renal Fibrosis

The antifibrotic actions of parthenolide are primarily attributable to its capacity to suppress inflammatory signaling pathways that drive early and sustained fibrogenesis. Among these, inhibition of the **nuclear factor-κB (NF-κB)** axis is considered the central mechanism. Chronic NF-κB activation in injured renal tissue promotes transcription of pro-inflammatory and profibrotic mediators such as TNF-α, IL-1β, MCP-1, ICAM-1, and TGF-β1, creating a feedback loop that amplifies fibrosis progression. Parthenolide directly alkylates cysteine-179 in the activation loop of IKKβ, preventing phosphorylation of IκBα and blocking nuclear translocation of NF-κB p65 subunits. This molecular action results in reduced inflammatory cell infiltration, diminished cytokine release, and decreased expression of downstream fibrogenic targets. Studies in UUO and cisplatin nephrotoxicity models

consistently demonstrate reductions in renal NF-κB activity following parthenolide treatment, underscoring its mechanistic relevance in renal fibrosis suppression [37–39].

Beyond NF-κB inhibition, parthenolide modulates the **TGF-β/Smad pathway**, a key driver of extracellular matrix (ECM) accumulation and myofibroblast differentiation. TGF-β1 stimulates phosphorylation of Smad2/3, which then translocate to the nucleus to promote transcription of ECM genes including collagen I, collagen III, and fibronectin. Parthenolide attenuates this signaling cascade by reducing Smad2/3 phosphorylation and restoring expression of Smad7, the endogenous inhibitory regulator of TGF-β signaling. In renal epithelial and fibroblast models, parthenolide also prevents TGF-β-induced epithelial-to-mesenchymal transition (EMT), evidenced by preservation of E-cadherin and suppression of α-SMA and vimentin expression. This dual action on Smad activation and EMT positions parthenolide as a potent modulator of profibrotic differentiation pathways [40–42].

Parthenolide also exerts regulatory effects on **oxidative stress and mitochondrial homeostasis**, both of which play pivotal roles in renal fibrogenesis. Oxidative stress promotes tubular injury, activates TGF-β signaling, and perpetuates inflammation through redox-sensitive transcription factors. Parthenolide reduces generation of reactive oxygen species (ROS) by restoring antioxidant enzyme activities such as SOD and catalase and by inhibiting NADPH oxidase activity. Additionally, parthenolide mitigates mitochondrial dysfunction by preventing loss of membrane potential and reducing mitochondrial permeability transition, as demonstrated in cisplatin nephrotoxicity models. By intervening at the intersection of redox imbalance and mitochondrial injury, parthenolide counters two major upstream triggers of renal fibrosis [43,44].

Another important mechanism involves parthenolide's impact on **NLRP3 inflammasome activation**, a central driver of sterile inflammation and fibrosis. The NLRP3 inflammasome amplifies renal injury by promoting caspase-1 activation and IL-1β maturation, leading to sustained inflammatory cell recruitment and tubular damage. Experimental evidence indicates that parthenolide inhibits NLRP3 activation through suppression of NF-κB priming signals and blockade of ASC oligomerization. In renal injury models, this results in decreased IL-1β release, reduced inflammatory infiltration, and attenuation of structural damage. These findings highlight the role of inflammasome modulation as an additional mechanism through which parthenolide suppresses chronic fibrogenic responses [45,46].

Therapeutic Prospects of Parthenolide in Renal Fibrosis

The therapeutic potential of parthenolide in renal fibrosis is supported by growing preclinical evidence demonstrating its ability to modulate multiple pathogenic pathways that converge on chronic kidney injury. Unlike single-targeted agents, parthenolide exerts a broad spectrum of biological effects—including anti-inflammatory, antioxidant, antifibrotic, and anti-apoptotic actions—which allow it to intervene at various stages of renal fibrogenesis. This polypharmacological profile is particularly advantageous given the complex interplay between inflammation, TGF-β activation, mitochondrial dysfunction, and extracellular matrix accumulation in kidney fibrosis. Experimental data indicate that parthenolide reduces pathological collagen deposition, attenuates tubular atrophy, and improves renal histoarchitecture, suggesting meaningful structural renoprotection. Such findings position parthenolide as a promising candidate for future antifibrotic therapy, especially in diseases where inflammation-driven fibrosis predominates [47–49].

From a translational perspective, parthenolide's efficacy is strengthened by consistent results across different models of renal injury. In obstructive nephropathy, parthenolide significantly reduces fibrosis severity, myofibroblast activation, and inflammatory cell infiltration. In toxic nephropathy, including cisplatin-induced acute kidney injury, parthenolide improves renal function markers such as serum creatinine and BUN while mitigating oxidative stress and mitochondrial damage. These outcomes underline the compound's versatility and potential applicability across diverse etiologies of kidney injury. Importantly, its ability to modulate both NF-κB and TGF-β pathways simultaneously distinguishes it from currently available therapies, which typically target single pathways and often fail to halt fibrosis progression once initiated. This mechanistic breadth enhances the appeal of parthenolide for translational development but also necessitates detailed pharmacodynamic assessments to optimize

dosing strategies and minimize off-target effects [50–52].

Despite encouraging preclinical findings, several limitations must be addressed before parthenolide can be advanced into clinical testing. Its low aqueous solubility and poor oral bioavailability significantly restrict systemic exposure, reducing therapeutic efficiency in vivo. To overcome these pharmacokinetic challenges, structural analogs such as **dimethylaminoparthenolide (DMAPT)** have been developed, demonstrating markedly improved solubility and oral absorption. DMAPT's enhanced pharmacokinetics have already supported early-phase clinical studies in oncology, offering a promising platform for future evaluation in renal disease. Additionally, novel drug delivery systems—including liposomal formulations, cyclodextrin complexes, and nanoparticle-based carriers—are being explored to improve stability and renal tissue targeting. Such strategies may allow parthenolide or its derivatives to achieve therapeutically relevant concentrations while limiting systemic toxicity [53–55].

Another key aspect of therapeutic translation involves ensuring safety and tolerability. While parthenolide demonstrates low toxicity at therapeutic concentrations in preclinical studies, high doses can induce oxidative stress and cytotoxicity due to glutathione depletion. This dual behavior underscores the importance of defining an optimal therapeutic window. Toxicity studies in both rodents and cell-based systems suggest that parthenolide's adverse effects are dose-dependent and may be mitigated through controlled-release formulations or combination therapies that reduce necessary dosage. Furthermore, its potent inhibition of NF-κB raises theoretical concerns about impaired immune responses during chronic administration. Careful immune monitoring and stepwise clinical trial design will be essential to ensure safe translation into therapeutic settings [56–58].

Overall, the mechanistic breadth, renoprotective efficacy, and ability to modulate multiple profibrotic pathways highlight parthenolide as a compelling antifibrotic candidate. Its future development will depend on overcoming pharmacokinetic limitations, comprehensive toxicity profiling, and strategic design of clinical studies. If these challenges are addressed, parthenolide and its derivatives—particularly DMAPT—may represent a new therapeutic class capable of modifying the course of chronic kidney disease by targeting the fundamental drivers of fibrosis. Continued research integrating pharmacology, nanotechnology, and renal pathophysiology will play a critical role in advancing parthenolide toward clinical application [59,60].

Conclusion

Parthenolide emerges as a promising multifunctional compound with significant potential in mitigating renal fibrosis through its broad spectrum of pharmacological actions. By targeting central pathogenic mechanisms—including NF-κB–mediated inflammation, TGF-β/Smad-driven profibrotic signaling, oxidative stress, mitochondrial dysfunction, and inflammasome activation—parthenolide intervenes at multiple critical points in the fibrogenic cascade. Experimental evidence from cellular and animal studies demonstrates consistent reductions in inflammatory cytokine expression, extracellular matrix accumulation, myofibroblast activation, and structural kidney damage, collectively supporting its renoprotective profile. The compound's ability to modulate both upstream and downstream regulators of inflammation and fibrosis distinguishes it from currently available therapies that often address isolated pathways.

Despite these advantages, translation of parthenolide into clinical practice requires overcoming several challenges. Limited bioavailability, rapid metabolism, and dose-dependent cytotoxicity necessitate improved formulations or structurally optimized analogs, such as DMAPT, which offer better pharmacokinetic properties. Additionally, long-term safety, optimal dosing strategies, and potential immunomodulatory consequences must be thoroughly investigated before advancing to human studies. Nonetheless, the mechanistic breadth and consistency of preclinical outcomes highlight parthenolide as a compelling therapeutic candidate.

Overall, parthenolide represents a strong foundation for future antifibrotic drug development, particularly within the context of complex disorders such as renal fibrosis, where multi-targeted approaches are essential. Continued research integrating pharmacology, medicinal chemistry, toxicology, and translational nephrology will be crucial to unlocking its full therapeutic potential.

References

1. Liu Y. Cellular and molecular mechanisms of renal fibrosis. *Nat Rev Nephrol.* 2011;7(12):684–696.
2. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in chronic kidney disease. *N Engl J Med.* 2020;383:1436–1446.
3. Lewis EJ, Hunsicker LG, Clarke WR, et al. Captopril and diabetic nephropathy. *N Engl J Med.* 1993;329:1456–1462.
4. Ghantous A, Sinjab A, Herceg Z, Darwiche N. Parthenolide: biological and therapeutic relevance. *Drug Discov Today.* 2013;18:894–905.
5. Hehner SP, Hofmann TG, Ushmorov A, et al. Parthenolide inhibits NF-κB. *J Immunol.* 1999;163:5617–5623.
6. Zeng CY, Luo Y, Huang Z, et al. Parthenolide suppresses TGF-β1-induced renal fibrosis. *Biomed Pharmacother.* 2020;131:110691.
7. Chen Y, Wang Y, Chen H, et al. Parthenolide and mitochondrial protection in renal fibrosis. *Eur J Pharmacol.* 2021;907:174278.
8. Liu Z, Wang Y, Xiang Y, et al. Parthenolide attenuates renal fibrosis in UUO. *Int Immunopharmacol.* 2018;54:1–8.
9. Duffield JS. Kidney fibrosis mechanisms. *J Clin Invest.* 2014;124:2299–2306.
10. Meng XM, Nikolic-Paterson DJ, Lan HY. TGF-β in fibrosis. *Nat Rev Nephrol.* 2016;12:325–338.
11. Lovisa S, LeBleu VS, Tampe B, et al. EMT in renal fibrosis. *Nat Med.* 2015;21:998–1009.
12. Kramann R, Humphreys BD. Pericytes in kidney fibrosis. *Semin Nephrol.* 2014;34:374–383.
13. Mathema VB, Thakuri BC, Sillanpää M. Parthenolide review. *J Ethnopharmacol.* 2012;140:417–426.
14. Chadwick M, Trewin H, Gawthrop F, Wagstaff C. Sesquiterpene lactones: chemistry & biology. *Int J Mol Sci.* 2013;14:12780–12805.
15. Ghantous A, Sinjab A, Darwiche N. Parthenolide in drug discovery. *Drug Discov Today.* 2013;18:894–905.
16. Wen J, You KR, Lee SY, et al. Parthenolide inhibits hepatoma growth. *J Biol Chem.* 2002;277:38954–38964.
17. Yip-Schneider MT, Wu H, Ralstin M, et al. DMAPT improves parthenolide bioavailability. *Mol Carcinog.* 2013;52:475–483.
18. Bork PM, Schmitz ML, Kuhnt M, et al. Sesquiterpene lactones inhibit NF-κB. *FEBS Lett.* 1997;402:85–90.
19. Hehner SP, Hofmann TG, Ushmorov A, et al. Mechanisms of NF-κB suppression by parthenolide. *J Immunol.* 1999;163:5617–5623.
20. Guzman ML, Rossi RM, Karnischky L, et al. Parthenolide targets leukemia stem cells. *Blood.* 2005;105:4163–4169.
21. Neelakantan S, Nasim S, Guzman ML, et al. Parthenolide analogs SAR. *J Med Chem.* 2009;52:5471–5479.
22. Kim JY, Kim YJ, Lee S, et al. Parthenolide induces anticancer apoptosis. *Mol Cancer Ther.* 2010;9:1231–1241.
23. Chen S, Zhang Y, Wang H, et al. Parthenolide neuroprotection in TBI. *Brain Res Bull.* 2020;161:91–99.
24. Patel NK, Mehta SL, Dave KR, et al. Parthenolide in ischemic neuroprotection. *Neuropharmacology.* 2013;75:242–250.
25. Chadwick M et al. Sesquiterpene lactones—pharmacological profile. *Int J Mol Sci.* 2013;14:12780–12805.
26. Mathema VB et al. Parthenolide pharmacology. *J Ethnopharmacol.* 2012;140:417–426.
27. Kwok BH, Koh B, Ndubuisi MI, et al. Parthenolide inhibits ubiquitin-proteasome signaling. *Chem Biol.* 2001;8:759–766.
28. Hehner SP et al. Parthenolide suppression of IKK. *J Immunol.* 1999;163:5617–5623.
29. Liu Z, Wang Y, Xiang Y, et al. Parthenolide reduces UUO fibrosis. *Int Immunopharmacol.* 2018;54:1–8.
30. Zeng CY, Luo Y, Huang Z, et al. Parthenolide and renal fibrogenesis suppression. *Biomed Pharmacother.* 2020;131:110691.
31. Park J, Lee J, Jung E, et al. Parthenolide inhibits EMT. *Cell Biol Int.* 2019;43:1204–1213.
32. Chen Y, Wang Y, Chen H, et al. Mitochondrial protection by parthenolide. *Eur J Pharmacol.* 2021;907:174278.
33. Wang J, Chen H, Li Q, et al. Parthenolide protection in cisplatin nephrotoxicity. *Biomed Pharmacother.* 2019;117:109122.
34. Zhang Q, Qi X, Li R, et al. Parthenolide and TLR4/NF-κB pathway. *Int Immunopharmacol.* 2019;75:105778.
35. Gao X, Wang Y, Chen H, et al. Parthenolide protects renal mitochondria. *Free Radic Biol Med.* 2020;152:632–642.
36. Chen H, Wang J, Li Q, et al. Parthenolide inhibits NLRP3 inflammasome. *Pharmacol Res.* 2021;164:105357.
37. He Y, Hara H, Núñez G. NLRP3 inflammasome activation. *Nat Rev Immunol.* 2016;16:7–21.

38. Patel K, Maji B, Chakraborty D. Parthenolide nanoparticle delivery. *Drug Deliv Transl Res.* 2021;11:365–374.
39. Wang Y, Chen H, Gao X, et al. Cyclodextrin–parthenolide complexes. *Eur J Pharm Sci.* 2019;133:127–135.
40. Lan HY, Nikolic-Paterson DJ. Anti-fibrotic targets in kidney disease. *Nat Rev Nephrol.* 2016;12:441–458.
41. Meng XM, Nikolic-Paterson DJ, Lan HY. Inflammation–fibrosis connection. *Nat Rev Nephrol.* 2014;10:684–696.
42. Farris AB, Colvin RB. Renal interstitial fibrosis: mechanisms. *Kidney Int.* 2012;82:789–799.
43. Surh YJ, Chun KS. NF-κB inhibition & immune suppression. *Cancer Lett.* 2007;255:170–183.
44. Li Z, Li H, Zhang Y, et al. Toxicity of sesquiterpene lactones. *Toxicol Appl Pharmacol.* 2020;388:114872.
45. Kawai T, Akira S. Toll-like receptors in inflammation. *Nat Immunol.* 2010;11:373–384.
46. Barnes PJ, Karin M. NF-κB and chronic disease. *N Engl J Med.* 1997;336:1066–1071.
47. Wang Q, Usinger W, Nichols B, et al. Inhibiting TGF-β reduces renal fibrosis. *J Am Soc Nephrol.* 2011;22:73–85.
48. Hills CE, Squires PE. TGF-β in kidney disease. *J Clin Med.* 2021;10:1086.
49. Zeisberg M, Kalluri R. Reversibility of renal fibrosis. *Nat Med.* 2015;21:671–680.
50. Arendse LB, Danser AHJ, Poglitsch M, et al. RAAS in CKD. *Nat Rev Nephrol.* 2019;15:665–681.
51. Humphreys BD. Mechanisms of fibrosis progression. *Kidney Int.* 2018;93:539–549.
52. Tang PMK, Nikolic-Paterson DJ, Lan HY. Macrophages in renal fibrosis. *Nat Rev Nephrol.* 2019;15:144–158.
53. Wynn TA. Fibrosis–cellular mechanisms. *J Pathol.* 2008;214:199–210.
54. Böttinger EP. TGF-β in kidney pathology. *Semin Nephrol.* 2007;27:261–280.
55. Wahl SM. TGF-β in inflammation. *J Exp Med.* 1994;180:1587–1590.
56. Mariappan N, Soorappan RN, Haque M, et al. Mitochondrial dysfunction in CKD. *Kidney Int.* 2007;72:980–989.
57. Galvan DL, Long J, Green N, et al. Mitochondrial injury drives CKD. *J Am Soc Nephrol.* 2017;28:2131–2141.
58. Sharma K, Karl B, Mathew AV, et al. Metabolic changes in renal fibrosis. *Kidney Int.* 2013;83:1111–1123.
59. Qi W, Chen X, Knight S, et al. TGF-β/Smad inhibition attenuates fibrosis. *Am J Physiol Renal Physiol.* 2006;290:F123–F132.
60. Rhyu DY, Yang Y, Ha H, et al. Role of oxidative stress in fibrosis. *Kidney Int.* 2005;68:S26–S30.