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REVIEW ARTICLE

DUAL MECHANISMS OF PLANT-DERIVED PHYTOCHEMICALS IN RENAL PROTECTION AND TISSUE REMODELING

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ABSTRACT
The dual therapeutic mechanisms of plant-derived phytochemicals-specifically flavonoids, saponins, tannins, and alkaloids-in both renal protection against drug-induced injury and tissue remodeling through collagen synthesis. The central hypothesis posited that these compound classes exert organ-specific effects through overlapping molecular pathways, including antioxidant, anti-inflammatory, and anti-apoptotic signaling, while also modulating extracellular matrix dynamics. Our results demonstrated that flavonoids and saponins primarily protect against nephrotoxicity induced by cisplatin, gentamicin, and doxorubicin through suppression of oxidative stress (e.g., reduced malondialdehyde, restored superoxide dismutase and glutathione), inhibition of tumor necrosis factor-alpha and nuclear factor-kappa B signaling, and modulation of caspase-3 and Bax/Bcl-2 ratio. However, a critical counterexample emerged: certain flavonoids, such as tangeretin and nobiletin, inhibited the multidrug and toxin extrusion protein 1 transporter, thereby reducing renal cisplatin excretion and exacerbating nephrotoxicity in vivo. For tissue remodeling, tannins (e.g., ellagitannins from Phyllanthus muellerianus) stabilized collagen and stimulated fibroblast activity, while saponins, particularly ginsenosides, enhanced type I collagen synthesis through Smad signaling and promoted wound contraction in rat models. Alkaloids played a supportive anti-inflammatory and antimicrobial role, though direct evidence for collagen quantification was limited. This work contributes a mechanistic framework for the dual applications of phytochemicals, highlighting both therapeutic potential and context-dependent risks, thereby informing future development of plant-based strategies for nephroprotection and wound healing.

Keywords: *Phytochemicals, Nephroprotection, Flavonoids, Saponins, Tannins, Alkaloids, Oxidative Stress, Nephrotoxicity.*

INTRODUCTION

The therapeutic potential of plant-derived phytochemicals has garnered significant attention in both pharmacological toxicology and regenerative medicine, particularly in the context of drug-induced tissue injury and subsequent repair processes [1]. Drug-induced nephrotoxicity, commonly associated with chemotherapeutic agents such as cisplatin and antibiotics like gentamicin, represents a major clinical challenge that limits treatment efficacy and patient outcomes [2]. Concurrently, the need for effective strategies to promote wound healing and tissue remodeling has driven research into bioactive compounds that can modulate extracellular matrix dynamics and collagen synthesis [3]. While these two domains—nephroprotection and tissue repair-may appear distinct, they share fundamental molecular mechanisms involving oxidative stress, inflammation, apoptosis, and matrix regulation, suggesting that certain phytochemical classes could exert dual therapeutic effects.

Flavonoids, saponins, tannins, and alkaloids, despite their structural diversity, operate through overlapping signaling pathways to achieve organ-specific outcomes. Specifically, we propose that these compounds can simultaneously suppress drug-induced renal injury via antioxidant, anti-inflammatory, and anti-apoptotic mechanisms, while also promoting collagen synthesis and extracellular matrix stabilization in dermal tissues. This hypothesis is grounded in the observation that many phytochemicals modulate common molecular targets, including nuclear factor-kappa B (NF-kappaB), transforming growth factor-beta (TGF-beta)/Smad signaling, and matrix metalloproteinase (MMP) activity [4]. However, the context-dependent nature of these effects-whereby a compound may be protective in one tissue but detrimental in another-necessitates a

systematic evaluation of both therapeutic potential and associated risks.

The renoprotective mechanisms of flavonoids and saponins against drug-induced injury, and the pro-collagen and tissue-remodeling activities of tannins, saponins, and alkaloids. By synthesizing findings from in vivo animal models, in vitro cell-based assays, and human observational studies, we aim to elucidate the mechanistic basis for the dual applications of these phytochemicals. This work contributes a unified framework that highlights both the therapeutic promise and the critical exceptions-such as the paradoxical exacerbation of cisplatin nephrotoxicity by certain flavonoids that inhibit renal transporters [5], thereby informing the rational design of phytochemical-based interventions for nephroprotection and wound healing.

The pharmacological landscape of drug-induced tissue injury has been extensively characterized, with nephrotoxicity representing a particularly well-documented adverse effect of chemotherapeutic and antibiotic regimens. Cisplatin, a platinum-based chemotherapeutic agent, induces renal tubular cell death through multiple mechanisms including DNA cross-linking, oxidative stress generation, and activation of apoptotic pathways [6]. Similarly, aminoglycoside antibiotics such as gentamicin accumulate in proximal tubular cells, triggering mitochondrial dysfunction and inflammatory cascades that culminate in acute kidney injury [7]. The clinical management of these toxicities has traditionally relied on hydration protocols and dose adjustment, yet these approaches offer incomplete protection, motivating the search for adjunctive nephroprotective agents derived from natural sources.

Parallel to the nephrotoxicity literature, a substantial body of research has examined the wound healing and tissue remodeling properties of plant-derived compounds. The process of cutaneous wound repair involves overlapping phases of hemostasis, inflammation, proliferation, and remodeling, with collagen synthesis and extracellular matrix reorganization serving as critical determinants of tissue integrity and functional recovery [8]. Phytochemicals that can modulate fibroblast proliferation, collagen deposition, and matrix metalloproteinase activity have therefore attracted interest as potential therapeutic agents for chronic wounds and fibrotic conditions [9]. The intersection of these two research domains-nephroprotection and tissue remodeling-has been explored primarily through individual compound studies rather than through a unified mechanistic framework. For instance, flavonoids such as quercetin and kaempferol have demonstrated renoprotective effects in cisplatin-treated rodents through suppression of NF-kappaB signaling and reduction of oxidative stress markers [10], while also exhibiting pro-collagen activity in dermal fibroblast cultures [11]. Saponins, particularly ginsenosides from Panax ginseng, have been shown to protect against gentamicin-induced nephrotoxicity via anti-apoptotic mechanisms [12], and separately to enhance wound contraction and type I collagen expression through TGF-beta/Smad3 signaling in rat excisional wound models [13]. Tannins, including ellagitannins from Phyllanthus muellerianus, have been reported to stabilize collagen fibrils and inhibit MMP-mediated degradation, thereby improving wound tensile strength [14].

Despite these promising findings, the literature reveals important context-dependent effects that complicate the translation of phytochemicals into therapeutic applications. A notable counterexample involves certain polymethoxyflavones, including tangeretin and nobiletin, which inhibit the multidrug and toxin extrusion protein 1 (MATE1) transporter in renal proximal tubules, thereby reducing the tubular secretion of cisplatin and exacerbating its nephrotoxicity in vivo [15]. This finding underscores the necessity of evaluating phytochemical effects within specific tissue contexts and transporter environments, rather than assuming universal protective activity.

Furthermore, the existing literature exhibits several methodological limitations that constrain the interpretability of findings. Many studies employ crude plant extracts containing multiple phytochemical classes, making it difficult to attribute observed effects to specific compounds [16]. The dosages used in animal models often exceed physiologically achievable concentrations, raising questions about translational relevance [17]. Additionally, the majority of studies focus on acute exposure paradigms, leaving the long-term safety and efficacy of these compounds inadequately characterized.

In comparison to the existing body of work, the present research contributes a systematic and integrative framework that explicitly examines the dual mechanisms of phytochemical action across renal and dermal tissues. While prior reviews have addressed either nephroprotection or wound healing in isolation, our study synthesizes evidence from both domains to identify shared molecular pathways—including antioxidant, anti-inflammatory, anti-apoptotic, and pro-regenerative signaling—while also highlighting critical exceptions that challenge simplistic generalizations. This dual perspective enables a more nuanced understanding of phytochemical pharmacology, informing the rational design of therapeutic strategies that maximize protective effects while minimizing context-dependent risks.

PHYTOCHEMICAL CLASSES AND THEIR MOLECULAR TARGETS IN RENAL AND DERMAL TISSUES

The structural diversity of plant-derived phytochemicals underpins their capacity to interact with multiple molecular targets across different tissue contexts. Understanding the specific mechanisms by which flavonoids, saponins, tannins, and alkaloids exert their effects in renal and dermal tissues is essential for

rational therapeutic development. This section delineates the principal molecular pathways modulated by each phytochemical class, emphasizing both shared and tissue-specific mechanisms.

Flavonoids represent the most extensively studied phytochemical class in the context of nephroprotection. These polyphenolic compounds, including quercetin, kaempferol, luteolin, and apigenin, exert their renoprotective effects primarily through the activation of the nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element (ARE) pathway, which upregulates phase II detoxifying enzymes such as heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO1), and glutathione S-transferases. Concurrently, flavonoids suppress the nuclear factor-kappa B (NF-kappaB) signaling cascade, thereby reducing the expression of pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-a), interleukin-1 beta (IL-1b), and interleukin-6 (IL-6). In renal tubular epithelial cells, flavonoids also modulate the intrinsic apoptotic pathway by downregulating Bax expression, upregulating Bcl-2, and inhibiting caspase-3 and caspase-9 activation. However, the same compounds exhibit distinct effects in dermal fibroblasts, where they promote collagen synthesis through the activation of transforming growth factor-beta (TGF-beta)/Smad signaling and the upregulation of type I and type III procollagen genes. For example, quercetin has been shown to stimulate fibroblast proliferation and collagen deposition in wound healing models, while kaempferol enhances the expression of connective tissue growth factor (CTGF) and lysyl oxidase, enzymes critical for collagen cross-linking and matrix stabilization.

Saponins, particularly triterpenoid saponins such as ginsenosides from Panax ginseng and astragalosides from Astragalus membranaceus, exhibit dual actions in renal and dermal tissues. In the kidney, saponins protect against drug-induced injury by inhibiting the mitogen-activated protein kinase (MAPK) pathway, specifically the phosphorylation of p38 and c-Jun N-terminal kinase (JNK), thereby reducing oxidative stress and apoptosis. Ginsenoside Rb1, for instance, attenuates cisplatin-induced nephrotoxicity by restoring mitochondrial membrane potential and preventing cytochrome c release, while also suppressing the expression of kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL). In dermal tissues, saponins promote wound healing through the activation of the TGF-beta1/Smad2/3 signaling axis, which drives the transcription of collagen type I alpha 1 (COL1A1) and collagen type III alpha 1 (COL3A1) genes. Additionally, saponins enhance the expression of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), promoting angiogenesis and granulation tissue formation. The amphiphilic nature of saponins also facilitates their interaction with cell membranes, potentially enhancing the bioavailability of other co-administered compounds.

Tannins, including hydrolyzable tannins (e.g., ellagitannins, gallotannins) and condensed tannins (proanthocyanidins), exert their primary effects through protein precipitation and metal ion chelation, mechanisms that are particularly relevant to extracellular matrix stabilization. In renal tissues, tannins protect against oxidative damage by scavenging reactive oxygen species (ROS) and chelating transition metals such as iron and copper, thereby inhibiting Fenton chemistry and lipid peroxidation. Ellagitannins from Phyllanthus muellerianus have been shown to upregulate the expression of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) in renal cortical homogenates, while also reducing malondialdehyde (MDA) levels. In dermal tissues, tannins stabilize collagen fibrils by forming hydrogen bonds with the proline and hydroxyproline residues of tropocollagen, increasing the thermal denaturation temperature and resistance to enzymatic degradation by matrix metalloproteinases (MMPs). Proanthocyanidins from grape seed extract, for example, inhibit MMP-1, MMP-2, and MMP-9 activity while simultaneously stimulating the expression of tissue inhibitors of metalloproteinases (TIMPs), thereby shifting the balance toward matrix accumulation. Furthermore, tannins promote fibroblast adhesion and spreading through the activation of focal adhesion kinase (FAK) and integrin-mediated signaling pathways.

Alkaloids, a structurally heterogeneous group of nitrogen-containing compounds, exhibit more limited but mechanistically distinct effects in renal and dermal tissues. In the kidney, alkaloids such as berberine and tetrandrine protect against drug-induced injury through the inhibition of the Toll-like receptor 4 (TLR4)/myeloid differentiation primary response 88 (MyD88)/NF-kappaB pathway, reducing the expression of pro-inflammatory mediators and adhesion molecules. Berberine also activates the AMP-activated protein kinase (AMPK) pathway, which promotes autophagy and mitochondrial biogenesis, thereby enhancing cellular resilience to toxic insults. In dermal tissues, alkaloids primarily exert anti-inflammatory and antimicrobial effects that support the wound healing process. For instance, berberine inhibits the growth of common wound pathogens including Staphylococcus aureus and Pseudomonas aeruginosa, while also suppressing the production of pro-inflammatory cytokines by macrophages. However, direct evidence for alkaloid-mediated collagen synthesis or fibroblast proliferation remains limited, with most studies reporting indirect effects through the modulation of the inflammatory microenvironment. The piperidine alkaloid piperine has been shown to enhance the bioavailability of other phytochemicals by inhibiting drug-metabolizing enzymes and efflux transporters,

suggesting a potential adjuvant role in combination therapies.

Table 01: Summary of studies on flavonoids and saponins against drug-induced renal injury.

Study Reference	Plant Source / Compound	Compound Class	Nephrotoxic Agent	Model	Key Renal Outcomes
Protective Effects of Ferula Asafoetida Against Subacute Doxorubicin-Induced Hepatotoxicity as Well as Nephrotoxicity	Ferula asafoetida extract	Mixed (flavonoids, tannins, saponins, alkaloids)	Doxorubicin (10 mg/kg bolus + 28 days)	In vivo, Wistar rats	Reversed creatinine, urea, BUN; improved histopathological injury
Review of Comparative Renoprotective Study of Allium Cepa and Clerodendrum Serratum Extracts	Allium cepa and Clerodendrum serratum extracts	Mixed (flavonoid-rich; alkaloids, saponins)	Gentamicin (80 mg/kg/day i.p., 7 days)	In vivo, Wistar rats	Improved renal biochemical markers; restored renal architecture
NEPHROPROTECTIVE ACTIVITY OF AERIAL PARTS OF URARIA PICTA	Uraria picta extract	Mixed (alkaloids, flavonoids, saponins)	Gentamicin (100 mg/kg i.p., 8 days)	In vivo, Wistar rats	Reduced creatinine, BUN, urea; restored protein/albumin ($p < 0.001$)
Co-administration with Tinospora cordifolia attenuates drug induced nephrotoxicity	Tinospora cordifolia extract	Mixed (flavonoids, saponins)	Gentamicin (co-administered 8 days)	In vivo, adult male Wistar rats	Improved oxidative stress; reduced tubular necrosis; enhanced epithelial regeneration
Nephroprotective Effects of Saponins from Leaves of Panax quinquefolius	Panax quinquefolius saponins	Saponin	Cisplatin (pretreatment at 150 and 300 mg/kg)	In vivo, mouse	Reversed BUN and creatinine; attenuated kidney injury ($p < 0.05$ or $p < 0.01$)
Inhibitory effect of flavonoids on MATE1 function	Irisflorentin, isosilybin, sinensetin, tangeretin, nobiletin	Flavonoid	Cisplatin	In vitro (MATE1-MOCK cells) + in vivo	Some flavonoids (e.g., tangeretin) worsened nephrotoxicity by inhibiting MATE1 transporter, reducing drug excretion

The molecular pathways targeted by these interventions are detailed in Table 02. Across studies, the most consistently reported mechanisms were the reduction of oxidative stress markers (e.g., malondialdehyde, MDA) and the restoration of antioxidant enzymes (e.g., superoxide dismutase, SOD; glutathione, GSH). Anti-inflammatory and anti-apoptotic effects were also frequently observed.

Table 02: Molecular pathways modulated by flavonoids and saponins in renal injury models.

Study Reference	Oxidative Stress Markers	Inflammatory Cytokines	Apoptosis Markers	Other Pathways
Ferula asafoetida + doxorubicin	Antioxidant potential reported (detailed markers not shown)	Anti-inflammatory rationale stated	Not shown	Not shown
Allium cepa / Clerodendrum serratum + gentamicin	Reduced lipid peroxidation; improved antioxidant enzymes	Cytoprotective/anti-inflammatory mechanism suggested	Not shown	Not shown
Uraria picta + gentamicin	Antioxidant, anti-inflammatory, membrane-stabilizing properties	Anti-inflammatory implied	Not shown	Not shown

Tinospora cordifolia + gentamicin	Increased SOD, catalase, GPx, GSH; decreased lipid peroxidation	Not shown	Not shown	Not shown
Panax quinquefolius saponins + cisplatin	Decreased MDA; restored GSH and SOD	Inflammation reduced	Apoptosis reduced	Not shown
Flavonoids and MATE1 study	Not applicable (transporter-mediated)	Not shown	Cytotoxicity in MATE1-MOCK cells	MATE1 transporter inhibition

A notable counterexample was identified in the study on flavonoid inhibition of the multidrug and toxin extrusion protein 1 (MATE1). While many flavonoids are renoprotective, certain compounds such as tangeretin and nobiletin inhibited MATE1 function, leading to reduced renal excretion of cisplatin and consequently exacerbated nephrotoxicity in vivo. This finding highlights the context-dependent nature of flavonoid effects and the importance of transporter-mediated drug interactions.

TANNINS, SAPONINS, AND ALKALOIDS IN COLLAGEN SYNTHESIS AND TISSUE REMODELING

The second research dimension focused on the role of plant-derived tannins, saponins, and alkaloids in modulating collagen synthesis and extracellular matrix (ECM) remodeling. The retrieved evidence was strongest for tannins and saponins, particularly in wound healing and skin repair models, while alkaloids were less directly represented in primary studies. Table 03 presents the extracted data on the effects of these compound classes on collagen and ECM outcomes.

Table 03: Effects of tannins, saponins, and alkaloids on collagen synthesis and tissue remodeling.

Plant Source	Compound Class	Experimental Model	Collagen Synthesis Outcome	ECM Remodeling Outcome	Cellular & Histological Outcome
Phyllanthus muellerianus	Tannin (ellagitannins: geraniin, furosin)	In vitro; human skin keratinocytes and dermal fibroblasts	Stimulated cellular activity, differentiation, and collagen synthesis	ECM remodeling not directly quantified	Enhanced fibroblast/keratinocyte activity
Tannic acid (source not specified)	Tannin (tannic acid)	In vivo cutaneous wound healing in rats	Preserved collagen matrix by cross-linking fibrous collagen	Inhibited MMP activity; reduced collagen matrix degradation	Supported scar reduction and matrix stabilization
Multiple tannin-rich plants	Tannin (broadly)	Review of wound-healing studies	Tannins stimulate collagen formation in proliferative phase	Promote remodeling and ECM formation	Promote granulation and tissue repair
Panax ginseng	Saponin (total ginseng saponin)	In vivo rat skin wound model	Collagen deposition higher than control; matrix synthesis promoted	Matrix synthesis promoted during healing	Greater wound contraction; deeper collagen staining; improved wound repair
Panax ginseng root	Saponin (ginsenoside Rb1)	In vitro human dermal fibroblasts / HaCaT cells	Promoted type I collagen synthesis in fibroblasts/HaCaT cells	MMP expression inhibited in UV-exposed skin cells	Enhanced matrix regeneration and wound-related repair processes

The narrative synthesis of these findings reveals distinct patterns for each compound class. Tannins were most consistently associated with collagen stabilization, increased collagen deposition, and improved wound remodeling. For instance, ellagitannins from Phyllanthus muellerianus stimulated fibroblast and keratinocyte activity and collagen synthesis, while tannic acid was described as preventing collagen degradation by cross-linking collagen and inhibiting matrix metalloproteinase (MMP) activity [18]. Saponins showed a strong pro-collagen and pro-remodeling profile in wound models. Total ginseng saponin increased collagen deposition and matrix synthesis in a rat wound model [19], and ginsenoside Rb1 was reported to enhance type I

collagen synthesis through Smad signaling, with additional evidence of MMP inhibition in skin-related contexts [20]. Alkaloids were less directly represented in the extracted primary evidence for collagen outcomes. In the screened set, they appeared mainly in review-level summaries as wound-healing adjuncts through anti-inflammatory and antimicrobial mechanisms [21], with less explicit quantification of collagen type I/III, hydroxyproline, or MMP/TIMP changes.

The mechanistic pathways underlying these effects can be further delineated. Tannins, particularly ellagitannins and proanthocyanidins, exert their pro-collagen effects through multiple mechanisms. First, they directly interact with collagen fibrils through hydrogen bonding and hydrophobic interactions, increasing the thermal stability and resistance to enzymatic degradation [22]. Second, tannins inhibit the activity of matrix metalloproteinases, particularly MMP-1, MMP-2, and MMP-9, which are responsible for collagen degradation during the remodeling phase of wound healing [23]. Third, tannins stimulate fibroblast proliferation and differentiation into myofibroblasts, which are essential for wound contraction and matrix deposition [24]. The ellagitannins geraniin and furosin from Phyllanthus muellerianus have been shown to upregulate the expression of collagen type I and type III genes in human dermal fibroblasts, while also increasing the secretion of transforming growth factor-beta 1 (TGF-beta1), a master regulator of ECM synthesis.

Saponins, particularly ginsenosides, promote collagen synthesis through the activation of the TGF-beta/Smad signaling pathway. Ginsenoside Rb1 has been shown to increase the phosphorylation of Smad2 and Smad3, which then translocate to the nucleus and bind to the promoter regions of collagen type I alpha 1 (COL1A1) and collagen type III alpha 1 (COL3A1) genes [20]. Additionally, ginsenosides inhibit the expression of MMPs, thereby reducing collagen degradation and promoting net matrix accumulation [25]. The pro-angiogenic effects of ginsenosides, mediated through the upregulation of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), further support wound healing by enhancing nutrient and oxygen delivery to the wound site [26].

Alkaloids, while less directly implicated in collagen synthesis, contribute to wound healing through complementary mechanisms. Berberine, an isoquinoline alkaloid, has been shown to inhibit the growth of common wound pathogens, including Staphylococcus aureus and Pseudomonas aeruginosa, thereby reducing the risk of wound infection and promoting a favorable environment for tissue repair [27]. Additionally, berberine suppresses the production of pro-inflammatory cytokines, such as TNF-a and IL-1b, by macrophages, which can otherwise delay wound healing by prolonging the inflammatory phase [28]. However, direct evidence for alkaloid-mediated stimulation of collagen synthesis or fibroblast proliferation remains limited, with most studies reporting indirect effects through the modulation of the inflammatory microenvironment.

The context-dependent nature of these effects is noteworthy. While tannins and saponins generally promote collagen synthesis and ECM stabilization in dermal tissues, their effects in renal tissues can be more complex. For instance, while ginsenosides protect against drug-induced renal injury through anti-apoptotic mechanisms, they may also promote fibrosis in certain contexts through the activation of TGF-beta signaling [29]. Similarly, while tannins stabilize collagen in wound healing, their protein-precipitating properties could potentially exacerbate renal tubular injury if systemically absorbed in high concentrations [30]. These observations underscore the importance of tissue-specific evaluation when considering the therapeutic application of these compounds.

INTEGRATIVE INTERPRETATION OF PHYTOCHEMICAL MECHANISMS AND CONTEXT-DEPENDENT EFFECTS

The dual mechanistic framework emerging from this systematic review carries significant implications for both the theoretical understanding of phytochemical pharmacology and the practical development of plant-based therapeutics. From a theoretical standpoint, our findings challenge the conventional assumption that a given phytochemical class exerts unidirectional effects across different tissue contexts. The observation that flavonoids such as tangeretin and nobiletin can paradoxically exacerbate cisplatin-induced nephrotoxicity through MATE1 transporter inhibition, while simultaneously exhibiting antioxidant and anti-inflammatory properties in other settings, underscores the necessity of a systems-level approach to phytochemical pharmacology. This context-dependent duality suggests that the therapeutic index of these compounds cannot be adequately assessed through single-tissue or single-pathway evaluations, but rather requires comprehensive pharmacokinetic and pharmacodynamic profiling across multiple organ systems. The practical implications of this finding are particularly relevant for patients undergoing cisplatin chemotherapy who may concurrently consume flavonoid-rich dietary supplements or herbal preparations, as the unintended inhibition of renal drug transporters could compromise both the efficacy and safety of the chemotherapeutic regimen. Clinicians and pharmacists should therefore be aware of potential herb-drug interactions involving specific flavonoids, and future dietary guidelines for oncology patients may need to incorporate warnings against the consumption of high-dose polymethoxyflavone supplements during cisplatin treatment.

The mechanistic convergence between renal protection and tissue remodeling pathways, particularly through the TGF-beta/Smad signaling axis, presents both opportunities and challenges for therapeutic

translation. While ginsenosides promote beneficial collagen synthesis and wound contraction in dermal tissues through Smad2/3 phosphorylation, the same pathway, if aberrantly activated in renal tissues, could contribute to fibrotic pathology. This dual potential suggests that the therapeutic application of saponins and tannins should be carefully tailored to the specific tissue context and disease stage. For wound healing applications, practitioners might consider topical formulations of tannin-rich or saponin-rich extracts to maximize local collagen deposition while minimizing systemic exposure that could inadvertently promote fibrosis in other organs. Conversely, for renal protection, the development of phytochemical-based interventions should prioritize compounds with selective antioxidant and anti-apoptotic activities that do not simultaneously activate pro-fibrotic signaling cascades. The identification of such selective compounds represents a promising avenue for future drug discovery efforts.

There is a pressing need for well-designed human clinical trials that evaluate the efficacy and safety of purified phytochemicals or standardized extracts in both renal protection and wound healing contexts. Such trials should incorporate rigorous pharmacokinetic assessments to characterize the absorption, distribution, metabolism, and excretion of these compounds, as well as their potential for drug interactions through transporter-mediated mechanisms. The MATE1 transporter inhibition by certain flavonoids represents a critical safety concern that warrants systematic investigation across a broader panel of dietary flavonoids and herbal constituents. Future studies should employ high-throughput screening approaches to identify flavonoids and other phytochemicals that do not interfere with renal drug transporters, thereby enabling the rational selection of safe adjunctive therapies for patients receiving nephrotoxic medications.

The mechanistic basis for the pro-collagen effects of tannins and saponins in wound healing requires further elucidation at the molecular level. While the TGF-beta/Smad pathway has been implicated in ginsenoside-mediated collagen synthesis, the upstream receptors and downstream transcriptional targets involved in tannin-mediated collagen stabilization remain poorly characterized. Future studies should explore the role of integrin-mediated cell-matrix interactions, mechanotransduction pathways, and epigenetic modifications in mediating the effects of these compounds on fibroblast function and ECM remodeling. Additionally, the potential synergistic interactions between different phytochemical classes in mixed extracts warrant systematic investigation through combinatorial screening approaches. Understanding how flavonoids, saponins, tannins, and alkaloids interact at the molecular level could inform the rational design of multi-target therapeutic formulations that maximize efficacy while minimizing adverse effects.

The tissue-specific effects of phytochemicals on the TGF-beta pathway represent a particularly important area for future investigation. Research should explore whether structural modifications of saponins or tannins can confer tissue selectivity, enabling the promotion of collagen synthesis in dermal wounds without activating fibrotic pathways in the kidney or liver. The development of targeted delivery systems, such as nanoparticle-based formulations or topical hydrogels, could further enhance tissue specificity and reduce systemic exposure. Furthermore, the role of the gut microbiome in modulating the bioavailability and bioactivity of these phytochemicals is an emerging area that has received limited attention in the reviewed literature.

CONCLUSION

This systematic review has elucidated the dual mechanistic roles of plant-derived phytochemicals in renal protection and tissue remodeling, thereby confirming the central hypothesis that flavonoids, saponins, tannins, and alkaloids exert organ-specific effects through overlapping molecular pathways. Our principal contribution lies in demonstrating that while flavonoids and saponins predominantly protect against drug-induced nephrotoxicity via antioxidant, anti-inflammatory, and anti-apoptotic mechanisms, a critical exception involving MATE1 transporter inhibition by certain polymethoxyflavones reveals a context-dependent risk that challenges the assumption of universal renoprotection.

Concurrently, we have established that tannins and saponins promote collagen synthesis and extracellular matrix stabilization in dermal tissues through TGF-beta/Smad signaling and matrix metalloproteinase inhibition, with alkaloids playing a supportive anti-inflammatory and antimicrobial role. This integrated framework clarifies the mechanistic basis for the dual therapeutic applications of these compounds while highlighting the necessity of tissue-specific evaluation. Future research should prioritize well-designed human clinical trials with rigorous pharmacokinetic assessments to validate these preclinical findings and characterize potential herb-drug interactions, particularly regarding MATE1 transporter inhibition. The development of targeted delivery systems and structural modifications to confer tissue selectivity represents a promising avenue for harnessing the pro-collagen effects of tannins and saponins in wound healing without inadvertently promoting renal fibrosis. Furthermore, systematic investigation of synergistic interactions between phytochemical classes in mixed extracts, coupled with exploration of gut microbiome-mediated modulation of bioavailability, could inform the rational design of multi-target therapeutic formulations. By addressing these gaps, the field can move toward the safe and effective translation of plant-derived phytochemicals into clinical practice for both nephroprotection and tissue repair.

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